

# Total Synthesis of Fijiolide A via an Atropselective Paracyclophane Formation

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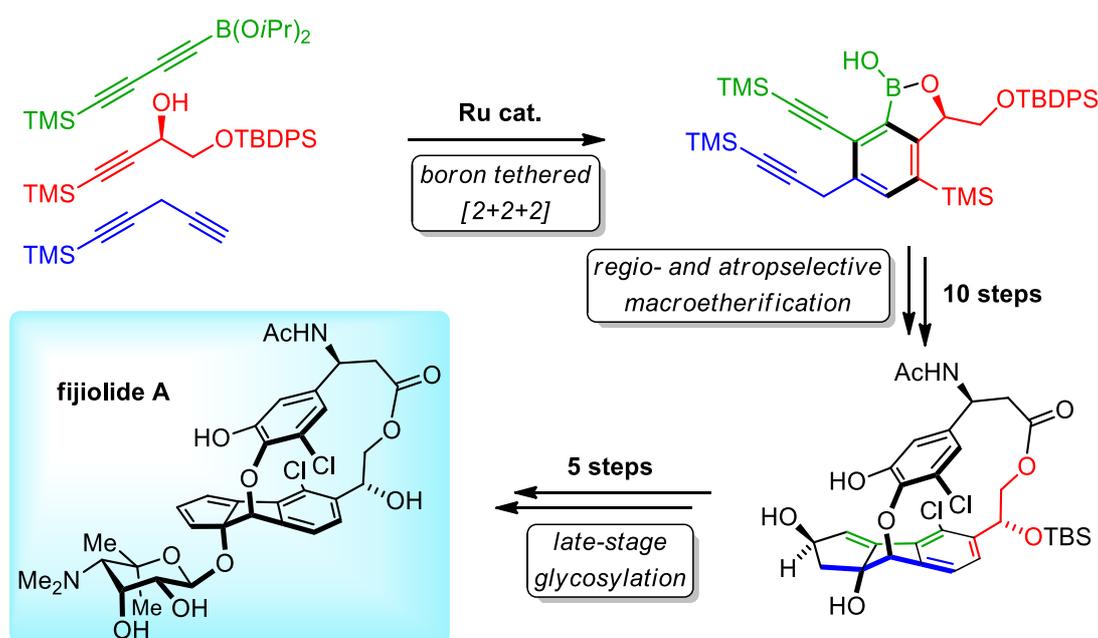
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## Abstract

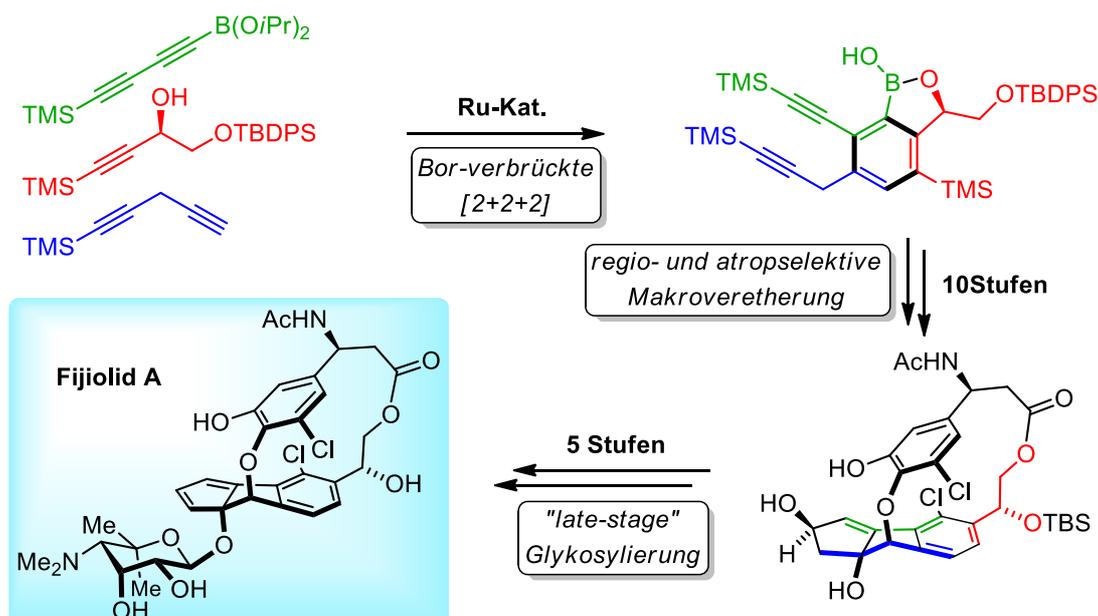
The natural product fijiolide A is a secondary metabolite isolated from a marine-derived actinomycete of the genus *Nocardopsis*. It displays inhibitory activity against TNF- $\alpha$ -induced activation of NF $\kappa$ B, an important transcription factor and a potential target for the treatment of different cancers and inflammation related diseases. Structurally, fijiolide A impresses by its highly complex molecular architecture, featuring a polychlorinated and rotationally restricted [2.6]paracyclophane core. The embedded highly unsaturated cyclopenta[*a*]indene framework is glycosylated with an amino ribopyranose unit. Fijiolide A is related to the Bergman cycloaromatization product of the C-1027 chromophore and is proposed to stem from a similar biosynthetic enediyne precursor. This thesis outlines a total synthesis of fijiolide A. Our synthetic approach features an intermolecular ruthenium-catalyzed [2+2+2] cycloaddition of three different alkynes to assemble the heavily substituted central arene core. Only 10 further steps were required to build up the strained [2.6]paracyclophane core of the fijiolide A aglycone. For this purpose we engineered an unprecedented macroetherification process that proceeds with remarkably high regio- and atropselectivity *via* a templated nucleophilic substitution. A late-stage glycosylation of the sterically encumbered tertiary alcohol enabled, for the first time, access to fijiolide A. Overall, the natural product fijiolide A was synthesized in a longest linear sequence of 18 steps from commercially available starting material.



**Keywords:** total synthesis, natural products, fijiolide, [2+2+2] cycloaddition, Pauson-Khand reaction, paracyclophane formation, atropselectivity, glycosylation.

## Kurzfassung

Der Naturstoff Fijiolid A ist ein von einem marinen Actinomyceten der Gattung *Nocardiosis* produzierter Sekundärmetabolit. Er zeigt inhibitorische Aktivität gegen TNF- $\alpha$  induzierte Aktivierung von NF $\kappa$ B. NF $\kappa$ B ist ein bedeutender Transkriptionsfaktor und potenzielles Zielmolekül für die Behandlung von verschiedenen Krebsarten und Entzündungskrankheiten. Strukturell besteht Fijiolid A durch einen hochkomplexen molekularen Aufbau und weist ein polychloriniertes, rotationseingeschränktes [2.6]Paracyclophan-Gerüst auf. Das eingebundene Cyclopenta[*a*]inden-Skelett ist mit einer Aminoribopyranose-Einheit glykosyliert. Fijiolid A ist mit dem Bergman-Cyclisierungsprodukt des C-1027 Chromophors verwandt und stammt mutmaßlich von einem vergleichbaren biosynthetischem Endiin-Vorläufer ab. Diese Dissertation beinhaltet die Entwicklung der Totalsynthese von Fijiolid A. Die Synthesestrategie zeichnet sich durch eine inter-molekulare Ruthenium-katalysierte [2+2+2]-Cycloaddition dreier verschiedener Alkine zum Aufbau des zentralen hochsubstituierten Arenkerns aus. In zehn weiteren Synthesestufen wurde das gespannte [2.6]Paracyclophan aufgebaut. Hierzu wurde eine Makroveretherungs-reaktion entwickelt, welche durch eine templat-gesteuerte nukleophile Substitution bemerkenswert hohe Regio- und Atropselektivitäten ermöglicht. Die Glykosylierung des sterisch gehinderten tertiären Alkohols erfolgte auf einer späten Synthesestufe. Dies ermöglicht erstmals den Zugang zu Fijiolid A. Insgesamt wurde der Naturstoff Fijiolide A in einer längsten linearen Sequenz 18 Synthesestufen ausgehend von kommerziell erhältlichem Startmaterial hergestellt.



**Schlagworte:** Totalsynthese, Naturstoffe, Fijiolid, [2+2+2]-Cycloaddition, Pauson-Khand-Reaktion, Paracyclophanbildung, Atropselektivität, Glykosylierung.

## *List of Abbreviations and Acronyms*

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[ $\alpha$ ] <sub>D</sub>	Specific rotation at a wavelength of 589 nm (sodium D line)
Å	Ångström
Ac	Acetyl
acac	Acetylacetonate
AD	Asymmetric Dihydroxylation
atm.	Atmosphere
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
br	Broad
BrettPhos	2-(Dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl
brsm	Based on recovered starting material
Bu	Butyl
ca.	Circa
cat.	Catalyst
(cat)	Catecholato
CDI	1,1'-Carbonyldiimidazole
<i>cf.</i>	Confer
Cl,MeOBiphep	5,5'-Dichloro-2,2'-bis(diphenylphosphino)-,6'-dimethoxy-1,1'-biphenyl
cod	1,5-Cyclooctadiene
Conv.	Conversion
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
CPME	Cyclopentyl methyl ether
CSA	Camphorsulfonic acid
d	Doublet
$\delta$	Chemical shift in ppm
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	Dichloroethane
(DHQ) <sub>2</sub> PHAL	Hydroquinine 1,4-phthalazinediyl diether
DIAD	Diisopropyl azodicarboxylate
DIPT	Diisopropyl tartrate
DM	3,5-Dimethylphenyl
DMA	<i>N,N</i> -Dimethylacetamide

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DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMI	1,3-Dimethyl-2-imidazolidinone
DMM	Dimethoxymethane
DMP	Dess-Martin periodinane
DMPU	<i>N,N'</i> -Dimethylpropyleneurea
DMSO	Dimethylsulfoxide
DMT	Dimethyl terephthalate
DpePhos	<i>Bis</i> [(2-diphenylphosphino)phenyl] ether
dppe	Ethane-1,2-diyl <i>bis</i> (diphenylphosphane)
dppf	1,1'- <i>Bis</i> (diphenylphosphino)ferrocene
dppp	1,3- <i>Bis</i> (diphenylphosphino)propane
<i>dr</i>	Diastereomeric ratio
DTBMP	2,6-Di- <i>tert</i> -butyl-4-methylpyridine
<i>E</i>	Entgegen
EDCI	<i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide hydrochloride
<i>ee</i>	Enantiomeric excess
EE	Ethoxyethyl
eq	equivalents
ESI	Electron spray ionization
Et	Ethyl
FT	Fourier transformation
h	Hour
HATU	1-[ <i>Bis</i> (dimethylamino)methylene]-1 <i>H</i> -1,2,3-triazolo[4,5- <i>b</i> ] pyridinium 3-oxid hexafluorophosphate
1 <i>H</i> -Imid.	1 <i>H</i> -Imidazole
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMPA	Hexamethylphosphoramide
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
HWE	Horner-Wadsworth-Emmons
<i>i</i> Pr	Isopropyl
IR	Infrared
<i>J</i>	Coupling constant
KHMDS	Potassium <i>bis</i> (trimethylsilyl)amide
L	Ligand
LHMDS	Lithium <i>bis</i> (trimethylsilyl)amide
2,6-lut.	2,6-lutidine

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<i>m</i>	Meta
m	Multiplet
M	Molar
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic acid
Me	Methyl
min	Minute
MNBA	2-Methyl-6-nitrobenzoic anhydride
MOM	Methoxymethyl
m.p.	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
MTBE	Methyl <i>tert</i> -butyl ether
MTPA	$\alpha$ -Methoxy- $\alpha$ trifluoromethylphenylacetic acid
MTPI	Methyltriphenoxyphosphonium iodide
MW	Microwave
NBS	<i>N</i> -Bromosuccinimide
nbd	Norbornadiene
<i>n</i> Bu	<i>normal</i> -Butyl
NCS	<i>N</i> -Chlorosuccinimide
<i>n.d.</i>	Not determined
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
NME	<i>N</i> -Methylephedrine
NMR	Nuclear magnetic resonance
<i>n.o.</i>	Not observed
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
$\nu$	Vibration frequency in $\text{cm}^{-1}$
<i>o</i>	<i>Ortho</i>
<i>p</i>	<i>Para</i>
Pe	Pentyl
pDBU	Polymer-bound 1,8-Diazabicyclo[5.4.0]undec-7-ene
PG	Protecting group
Ph	Phenyl
PhMe	Toluene
pin	Pinacol
Piv	Pivaloyl
PMB	<i>para</i> -Methoxybenzyl
ppm	Parts per million

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PPTS	Pyridinium <i>para</i> -toluenesulfonate
Pr	Propyl
<i>p</i> TSA	<i>para</i> -Toluenesulfonic acid
py	Pyridine
q	Quartet
Quinap	1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
<i>R</i>	Rectus
Rf	Retention factor
ROESY	Rotating frame nuclear Overhauser effect spectroscopy
s	Singlet
<i>S</i>	Sinister
SAD	Sharpless asymmetric dihydroxylation
sat.	Saturated
Segphos	4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphine)
Sphos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
t	Triplet
T	Temperature
<i>t</i> Bu	<i>tert</i> -Butyl
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
2,4,6-TCBC	2,4,6-Trichlorobenzoyl chloride
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFP	Tri(2-furyl)phosphine
THF	Tetrahydrofuran
TIPDS	1,1,3,3-Tetraisopropylidisiloxane
TLC	Thin layer chromatography
1,3,5-TMB	1,3,5-Trimethoxybenzene
TMS	Trimethylsilyl
TOF	Time of flight
Ts	<i>para</i> -Toluenesulfonyl
Ts-Dpen	[ <i>N</i> -[2-(Amino- $\kappa$ <i>N</i> )-1,2-diphenylethyl]-4-methylbenzenesulfonamidato- $\kappa$ <i>N</i> ]
vs.	Versus
Z	Zusammen

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# **1. Introduction**

## 1.1 General Introduction

Natural products have served as a mainstay of disease therapy throughout human history.<sup>1</sup> Until recently, traditional plant-based medicines represented the primary health care for approximately 80% of the world's inhabitants, according to a World Health Organization estimation.<sup>2</sup> Natural products also play a substantial role in modern drug discovery as lead structures for the development of new medicines for the treatment of human diseases. Nearly 50% of all novel drugs approved between 1981 and 2006 are either of natural product origin, or have been developed on the basis of natural product lead structures.<sup>3</sup> These cover a broad range of clinical application, from treatment of infectious and neurological diseases, cardiovascular and metabolic disorders, diabetes, as well as numerous applications in oncology.<sup>4</sup> The vast majority of all natural product derived therapeutics are of terrestrial origin.<sup>5</sup> However, the past decades have witnessed a decline in the discovery of unprecedented structural motifs from terrestrial sources. In this regard, the marine ecosystem has long been a underexplored source of biodiversity for the discovery of new bioactive metabolites, despite ocean covers more than 70% of the earth's surface. Not until the mid 1970's marine organisms such as algae, sponges and soft corals were more systematically investigated as purveyor of potential drug candidates.<sup>6</sup> Progress in this area culminated in eight marine derived pharmaceutical agents being marketed by 2014, and many more that entered different phases of clinical trials.<sup>6</sup> The US National Cancer Institute estimates that 1% of marine natural products exhibit anti-tumor activity, whereas only 0.01-0.1% of their terrestrial counterparts do.<sup>7</sup> This imposingly underlines the importance of marine secondary metabolites for the development of new cancer therapeutics, and their provision by the synthetic community.

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<sup>1</sup> G. M. Cragg, D. J. Newman, *Pure Appl. Chem.* **2005**, *77*, 7-24.

<sup>2</sup> N. R. Farnsworth, O. Akerele, A. S. Bingel, D. D. Soejarto, Z. Guo, *Bull. World Health Organ.* **1985**, *63*, 965-981.

<sup>3</sup> D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461-477.

<sup>4</sup> D. A. Dias, S. Urban, U. Roessner, *Metabolites* **2012**, *2*, 303-336.

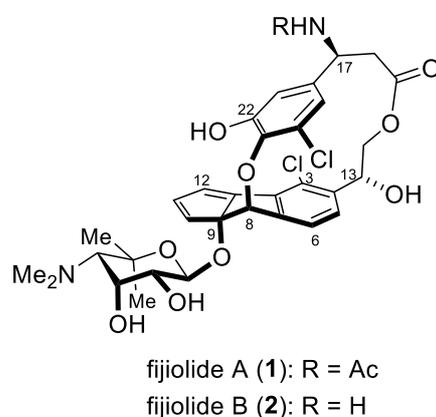
<sup>5</sup> R. Montaser, H. Luesch, *Future Medicinal Chemistry* **2011**, *3*, 1475-1489.

<sup>6</sup> A. Martins, H. Vieira, H. Gaspar, S. Santos, *Marine Drugs* **2014**, *12*, 1066-1101.

<sup>7</sup> a) M. H. G. Munro, J. W. Blunt, E. J. Dumdei, S. J. H. Hickford, R. E. Lill, S. Li, C. N. Battershill, A. R. Duckworth, *J. Biotechnol.* **1999**, *70*, 15-25; b) S. Vinothkumar, P. S. Parameswaran, *Biotechnology Advances* **2013**, *31*, 1826-1845.

## 1.2 Isolation and Structure Elucidation of Fijiolides A and B

As part of their program to explore marine bacterial metabolites as inhibitors of tumor initiation and promotion, Fenical *et al.* evaluated the marine-derived actinomycete strain CNS-653, isolated from a marine sediment sample collected from the Bequa Lagoon, Fiji. The bacterium of the genus *Nocardioopsis* was found to be the producer of two unknown secondary metabolites, fijiolide A (**1**) and B (**2**) (Figure 1).<sup>8</sup> The connectivity and relative stereochemistry of **1** and **2** were elucidated on the basis of 2D NMR spectroscopic data, while the advanced Mosher ester method and circular dichroism were used to assign the absolute configurations.



**Figure 1:** Structures of fijiolide A (**1**) and fijiolide B (**2**).

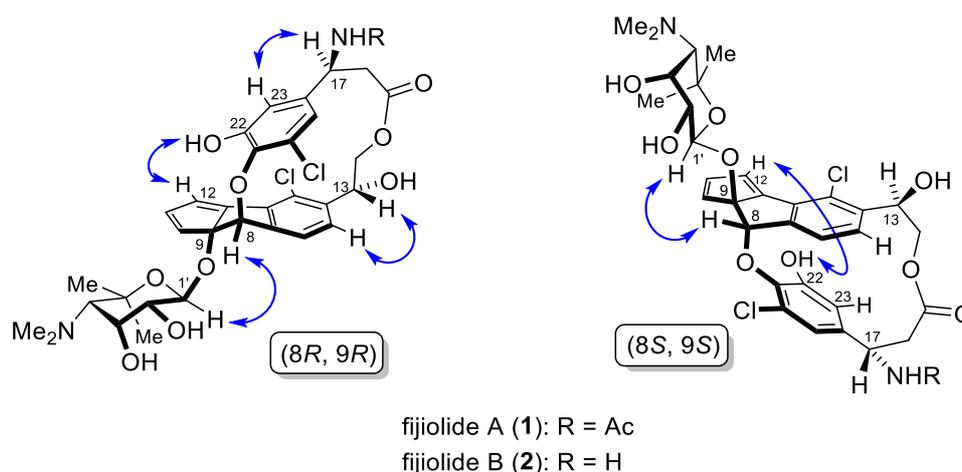
The fijiolides, which differ only by an additional acetyl group at 17-NH for fijiolide A (*cf.* **1** vs. **2**), possess several highly intriguing structural features. Specifically, **1** and **2** feature a chlorocyclopenta[*a*]indene framework, embedded into a [2.6]paracyclophane core.<sup>9</sup> In addition, the restricted rotation of the  $\beta$ -tyrosine around the ester and ether linkage between the two chlorinated aromatic portions gives rise to *non*-biaryl atropisomerism of macrolides **1** and **2**.<sup>10</sup> Linkage of the tertiary cyclopentadienol hydroxyl group at C-9 to an amino ribopyranose unit places the fijiolides in the category of glycosidic natural products.

<sup>8</sup> S.-J. Nam, S. P. Gaudêncio, C. A. Kauffman, P. R. Jensen, T. P. Kondratyuk, L. E. Marler, J. M. Pezzuto, W. Fenical, *J. Nat. Prod.* **2010**, *73*, 1080-1086.

<sup>9</sup> For recent reviews on cyclophanes, see: a) S. Kotha, M. E. Shirbhate, G. T. Waghule, *Beilstein J. Org. Chem.* **2015**, *11*, 1274-1331; b) T. Gulder, P. S. Baran, *Nat. Prod. Rep.* **2012**, *29*, 899-934.

<sup>10</sup> For a recent review on *non*-biaryl and heterobiaryl atropisomers, see: E. Kumarasamy, R. Raghunathan, M. P. Sibi, J. Sivaguru, *Chem. Rev.* **2015**, *115*, 11239-11300.

Application of the advanced Mosher method,<sup>11</sup> involving NMR analysis of the corresponding (*R*)- and (*S*)-MTPA ester derivatives of the fijiolides, enabled determination of the absolute configuration of the amino sugar unit, as well as the carbinol at C-13 and the amine at C-17. However, assignment of the complex three-dimensional structure of **1** and **2** required judicious interpretation of 2D NMR spectroscopic data. Thus, Fenical *et al.* deduced a *trans*-orientation of the C-9 glycoside and the C-8 ether bond by the presence of a NOESY correlation between H-8 and the proton H-1' of the  $\beta$ -configured anomeric center of the amino ribopyranose. This data suggested two possible stereoisomers of opposite absolute configuration at C-8 and C-9, which are depicted in Figure 2. Dipolar coupling between 22-OH and H-12 suggested a rotationally restricted  $\beta$ -tyrosine moiety, and a catechol orientation in the represented manner. Finally, a strong NOESY correlation between H-5 and H13, as well as between H-17 and H-23 prompted Fenical *et al.* to assign the structures of fijiolide A and B as the corresponding (*8R, 9R*) isomers with the depicted arene orientation.<sup>8</sup>

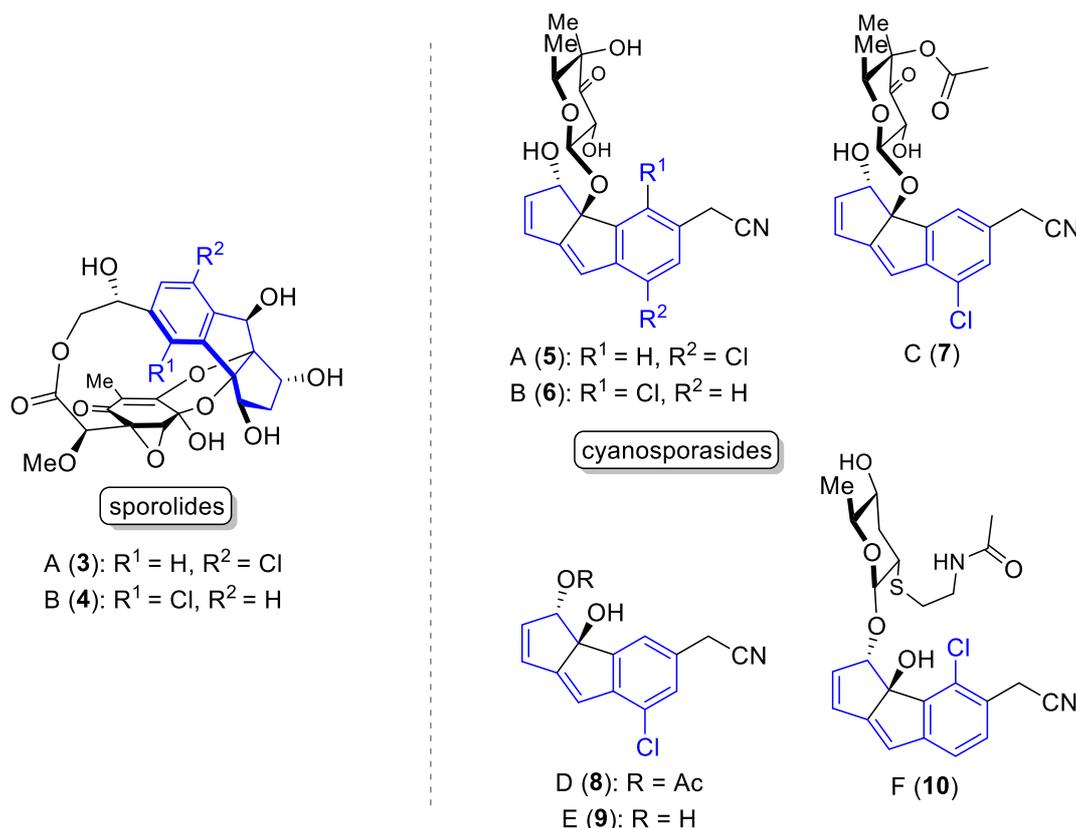


**Figure 2:** Possible stereoisomers of fijiolide A and B with opposite configuration at C-8 and C-9 and key NOESY correlations ( $\longleftrightarrow$ ).

<sup>11</sup> a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, 95, 512-519; b) T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protocols* **2007**, 2, 2451-2458.

### 1.3 Structural Relation to the Sporolides and Cyanosporasides

The chlorocyclopenta[*a*]indene core of the fijiolides is structurally related to those of the sporolides A and B<sup>12</sup> (**3** and **4**) and cyanosporasides A-F (**5-10**).<sup>13</sup> Both natural product families have also recently been isolated by Fenical *et al.* from marine actinomycete strains of the genus *Salinispora tropica* and *pacifica*, respectively.<sup>14,15</sup>



**Figure 3:** Structures of the sporolides A and B (**3** and **4**) and cyanosporasides A-F (**5-10**).

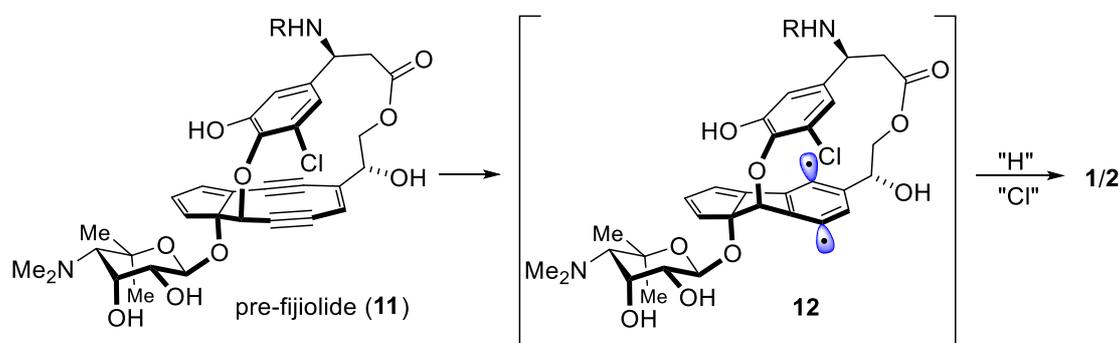
<sup>12</sup> For synthetic studies towards the sporolides, see: a) K. C. Nicolaou, J. Wang, Y. Tang, *Angew. Chem. Int. Ed.* **2008**, *47*, 1432-1435; b) K. Gademann, J.-Y. Wach, *Synlett* **2009**, *2009*, 2849-2851; c) K. C. Nicolaou, Y. Tang, J. Wang, *Angew. Chem. Int. Ed.* **2009**, *48*, 3449-3453; d) S. Bonazzi, M. Binaghi, C. Fellay, J.-Y. Wach, K. Gademann, *Synthesis* **2010**, *2010*, 631-642; e) K. C. Nicolaou, J. Wang, Y. Tang, L. Botta, *J. Am. Chem. Soc.* **2010**, *132*, 11350-11363; f) J. A. Gladding, J. P. Bacci, S. A. Shaw, A. B. Smith III, *Tetrahedron* **2011**, *67*, 6697-6706.

<sup>13</sup> For synthetic studies towards the cyanosporasides, see: a) D. Aburano, F. Inagaki, S. Tomonaga, C. Mukai, *J. Org. Chem.* **2009**, *74*, 5590-5594; b) K. Yamada, M. J. Lear, T. Yamaguchi, S. Yamashita, I. D. Gridnev, Y. Hayashi, M. Hirama, *Angew. Chem. Int. Ed.* **2014**, *53*, 13902-13906.

<sup>14</sup> G. O. Buchanan, P. G. Williams, R. H. Feling, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* **2005**, *7*, 2731-2734.

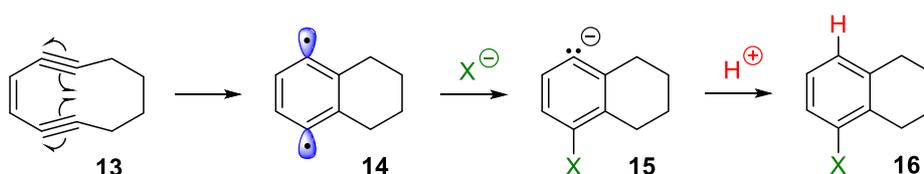
<sup>15</sup> a) D.-C. Oh, P. G. Williams, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* **2006**, *8*, 1021-1024; b) A. L. Lane, S.-J. Nam, T. Fukuda, K. Yamanaka, C. A. Kauffman, P. R. Jensen, W. Fenical, B. S. Moore, *J. Am. Chem. Soc.* **2013**, *135*, 4171-4174.

This common structural motif is believed to originate from a putative 9-membered enediyne precursor that undergoes Bergman cycloaromatization,<sup>16</sup> followed by trapping of the intermediate *p*-benzyne biradical species by chloride, as presented for the fijiolides (**Scheme 1**).<sup>17</sup>



**Scheme 1:** Formation of **1/2** from a putative enediyne precursor (**11**).

The biosynthetic incorporation of chlorine into aromatic rings has long been believed to be limited to enzymatic electrophilic substitution by chloroperoxidases or halogenases.<sup>18</sup> A fundamentally different synthetic pathway for the chlorination of *p*-benzyne biradicals was proposed by O'Connor *et al.* in 2007.<sup>19</sup> Their studies on the Bergman cycloaromatization of a model 10-membered enediyne (clodeca-1,5-diyne-3-ene, **13**) in halide containing media suggest a direct nucleophilic attack by a halide anion on biradical species **14**, and rapid protonation of haloaryl anion **15** as the most likely mechanism for *p*-benzyne halogenation.



**Scheme 2:** O'Connor's proposed mechanism for nucleophilic halogenation of *p*-benzyne biradicals.

O'Connor's mechanistic proposal is in accordance with the observed *mono*-chlorine substitution of the sporiolides and cyanosporasides at either of the two aromatic positions, whereas their dichlorinated counterparts have not been observed.

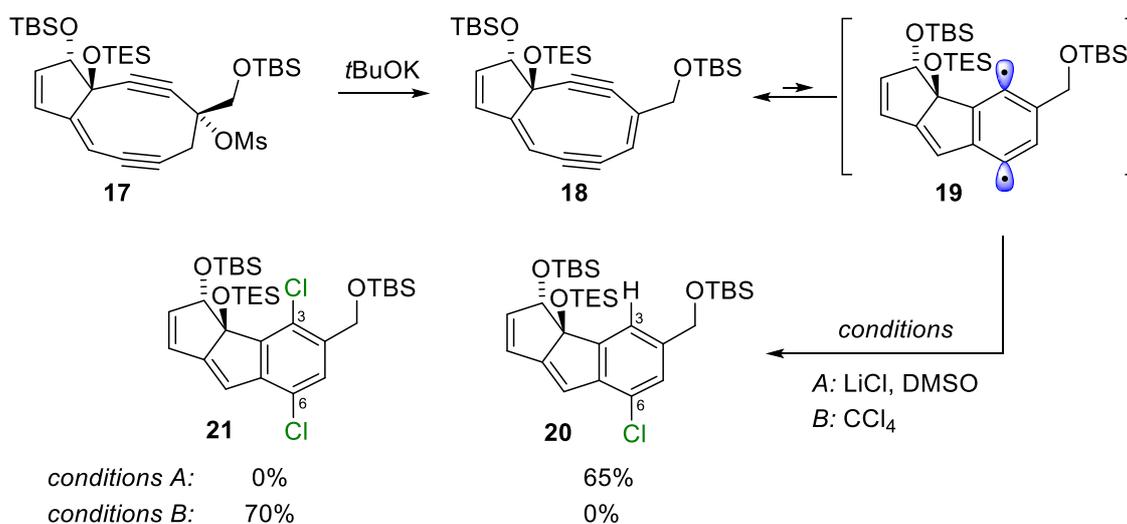
<sup>16</sup> R. G. Bergman, *Acc. Chem. Res.* **1973**, *6*, 25-31.

<sup>17</sup> M. Jean, S. Tomasi, P. van de Weghe, *Org. Biomol. Chem.* **2012**, *10*, 7453-7456.

<sup>18</sup> a) C. S. Neumann, D. G. Fujimori, C. T. Walsh, *Chem. Biol.* **2008**, *15*, 99-109; b) C. D. Murphy, *Nat. Prod. Rep.* **2006**, *23*, 147-152.

<sup>19</sup> C. L. Perrin, B. L. Rodgers, J. M. O'Connor, *J. Am. Chem. Soc.* **2007**, *129*, 4795-4799.

Further experimental evidence has recently been provided by Lear and Hiram (Scheme 3).<sup>13b</sup> Within the context of biomimetic synthetic studies towards the cyanosporaside aglycones via enediyne precursor **17**, an ionic *mono*-halogenation of *p*-benzyne **19** to form **20** was shown to be predominant in the presence of the seawater mimic LiCl/DMSO (*conditions A*). The site-selective chlorine incorporation was traced back to a sterically more accessible C-6 position of the *p*-benzyne biradical **19**. By contrast, a radical dichlorination pathway leading to **21** was active under synthetic conditions using CCl<sub>4</sub>.

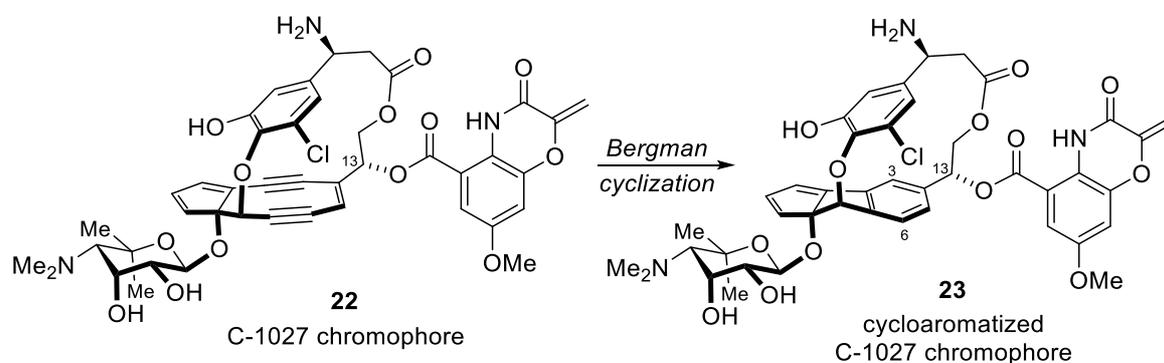


**Scheme 3:** Reported ionic *mono*- and radical dichlorination of cyanosporaside *p*-benzyne mimic **19**.

Whereas both the sporolides and cyanosporasides were originally isolated as 1:1 mixtures of positional isomers in respect to the chlorine substitution, no C-6 chlorinated regioisomer has been observed in the case of the fijiolides. On the basis of energy-minimizing modeling studies, Fenical *et al.* attributed this fact to a site selective chlorination of the *p*-benzyne biradical as a consequence of the more shielded C-6 position by the  $\beta$ -tyrosine moiety and the amino sugar side chain.<sup>8</sup>

## 1.4 Structural Relation to Eneidyne Antitumor Antibiotics

With their prominent structural features, the fijiolides possess high resemblance to the C-1027 chromophore **22**, and in particular with the corresponding Bergman cycloaromatization product **23** (Scheme 4).<sup>20</sup> In fact, **23** differs from fijiolides A and B by only the absence of a chloro substituent on the cyclopenta[*a*]indene core, and an additional benzoxazine moiety at the C-13 hydroxyl group. C-1027 is a member of the subset of chromoprotein complexes exhibiting outstanding antitumor antibiotic activity, and was isolated in 1988 from the culture broth of the terrestrial bacterium *Streptomyces globisporus*, strain C-1027.<sup>21</sup> Highly reactive chromophore **22** belongs to the enediynes structural family and naturally exists as a 1:1 complex with a stabilizing apoprotein, commonly known as the entire C-1027 natural product. The apoprotein is a single polypeptide composed of 110 amino acids to which enediynes **22** is bound in a non-covalent manner.<sup>22,23</sup> The chromophore is readily separated from its apoprotein by extraction.<sup>24</sup> However, once separated, **22** undergoes spontaneous cycloaromatization, and is the only enediynes natural product known to do so in the absence of any external activator such as nucleophiles.<sup>23</sup> Thus, the isolated C-1027 chromophore represents the most labile enediynes studied to date with a solvent dependent half-life of  $t_{1/2} = 50$  min (EtOH, 25 °C).<sup>25</sup>



**Scheme 4:** Structure of the C-1027 chromophore and its Bergman cycloaromatization product.

<sup>20</sup> For recent synthetic studies towards the C-1027 chromophore, see: a) M. Inoue, T. Sasaki, S. Hatano, M. Hiram, *Angew. Chem. Int. Ed.* **2004**, *43*, 6500-6505; b) M. Inoue, I. Ohashi, T. Kawaguchi, M. Hiram, *Angew. Chem. Int. Ed.* **2008**, *47*, 1777-1779.

<sup>21</sup> J. Hu, Y.-C. Xue, M.-Y. Xie, R. U. I. Zhang, T. Otani, Y. Minami, Y. Yamada, T. Marunaka, *J. Antibiot.* **1988**, *41*, 1575-1579; T. Otani, Y. Minami, T. Marunaka, R. Zhang, M.-Y. Xie, *J. Antibiot.* **1988**, *41*, 1580-1585.

<sup>22</sup> T. Otani, T. Yasuhara, Y. Minami, T. Shimazu, R. Zhang, M.-Y. Xie, *Agric. Biol. Chem.* **1991**, *55*, 407-417.

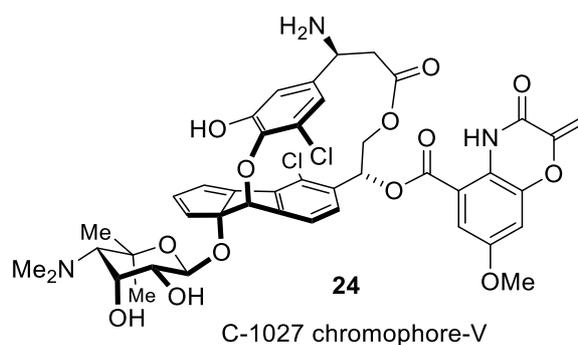
<sup>23</sup> M. Inoue, T. Usuki, N. Lee, M. Hiram, T. Tanaka, F. Hosoi, S. Ohie, T. Otani, *J. Am. Chem. Soc.* **2006**, *128*, 7896-7903.

<sup>24</sup> Y. Minami, K.-i. Yoshida, R. Azuma, M. Saeki, T. Otani, *Tetrahedron Lett.* **1993**, *34*, 2633-2636.

<sup>25</sup> K.-i. Yoshida, Y. Minami, T. Otani, Y. Tada, M. Hiram, *Tetrahedron Lett.* **1994**, *35*, 5253-5256.

Apart from the enediyne motif, the benzoxazine moiety of **22** and **23** – not present in the fijiolides – was reported to be of substantial importance for the bioactivity of antitumor antibiotic C-1027. Thus, Dedon *et al.* ascertained a ~400-fold reduced binding affinity of **23** to double-stranded DNA upon loss of the heterocyclic entity.<sup>26</sup> More precisely, the benzoxazine was proposed to function as a DNA intercalator. Once situated in the minor groove of the DNA, and following release from its apoprotein, the corresponding *p*-benzyne biradical of **22** abstracts hydrogens from the DNA backbone sugar, ultimately resulting in oxidative cleavage of the DNA double-strand.<sup>27</sup>

The close structural resemblance of the fijiolides with the C-1027 chromophore and its cyclization product suggests a common biosynthetic origin of these natural products.<sup>28</sup> A supporting piece of evidence for this assumption was recently been provided by Oh *et al.* who reported the isolation of the C-1027 Chromophore-V (**24**) in 2014 (Figure 4).<sup>29</sup> With the exception of the benzoxazine moiety, **24** is identical to fijiolide B. Moreover, C-3 chlorinated chromophore-V was isolated along with fijiolides A and B, and C-1027 chromophore cyclization product **23**, thus linking both natural product families. Interestingly, the producing bacterium is an arctic actinomycete strain (ART5), isolated from a sediment sample of the East Siberian continental margin (water depth = 352 m). Although the proposed pre-fijiolide (**11**) (*cf.* **Scheme 1**), or a complex of either **1** or **2** with an associated apoprotein could not be isolated, the fijiolides are believed to stem from the chromoprotein subfamily of 9-membered enediyne antitumor antibiotics.<sup>28</sup>



**Figure 4:** Structure of the recently isolated C-1027 chromophore-V (**24**).

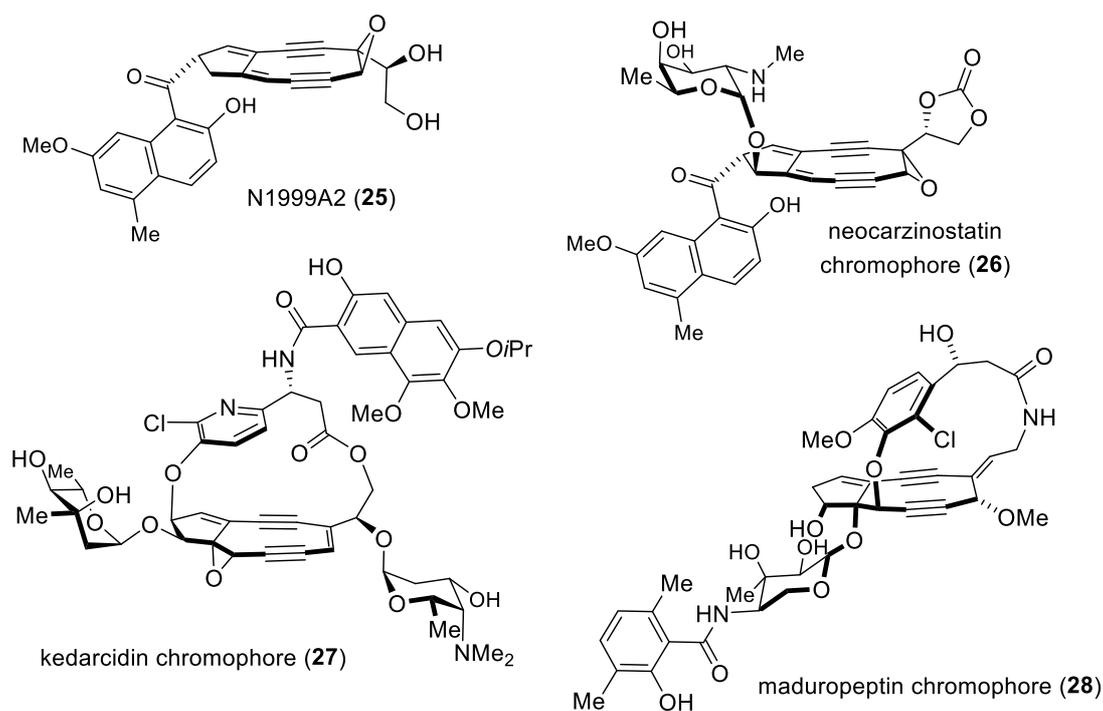
<sup>26</sup> L. Yu, S. Mah, T. Otani, P. Dedon, *J. Am. Chem. Soc.* **1995**, *117*, 8877-8878.

<sup>27</sup> a) Y. Xu, Y. Zhen, I. H. Goldberg, *Biochemistry* **1994**, *33*, 5947-5954; b) Y.-j. Xu, Z. Xi, Y.-s. Zhen, I. H. Goldberg, *Biochemistry* **1995**, *34*, 12451-12460.

<sup>28</sup> M. Jean, S. Tomasi, P. van de Weghe, *Org. Biomol. Chem.* **2012**, *10*, 7453-7456.

<sup>29</sup> K. Moon, C.-H. Ahn, Y. Shin, T. Won, K. Ko, S. Lee, K.-B. Oh, J. Shin, S.-I. Nam, D.-C. Oh, *Marine Drugs* **2014**, *12*, 2526-2538.

Prominent congeners of this subfamily are the chromophores of neocarzinostatin (**26**),<sup>30</sup> kedarcidin (**27**),<sup>31</sup> and maduropeptin (**28**) (Scheme 5).<sup>32</sup> Together with the enediyne N1999A2<sup>33</sup> (**25**) and previously discussed **22**, these secondary metabolites have received considerable attention from the synthetic community over the past two decades.<sup>34,35</sup>



Scheme 5: Naturally occurring and synthesized 9-membered enediynes.<sup>34</sup>

<sup>30</sup> a) N. Ishida, K. Miyazaki, K. Kumagai, M. Rikimaru, *J. Antibiot.* **1965**, *18*, 68-76; b) K. Edo, M. Mizugaki, Y. Koide, H. Seto, K. Furihata, N. Ōtake, N. Ishida, *Tetrahedron Lett.* **1985**, *26*, 331-334.

<sup>31</sup> a) J. E. Leet, D. R. Schroeder, S. J. Hofstead, J. Golik, K. L. Colson, S. Huang, S. E. Klohr, T. W. Doyle, J. A. Matson, *J. Am. Chem. Soc.* **1992**, *114*, 7946-7948; b) J. E. Leet, D. R. Schroeder, D. R. Langley, K. L. Colson, S. Huang, S. E. Klohr, M. S. Lee, J. Golik, S. J. Hofstead, *J. Am. Chem. Soc.* **1993**, *115*, 8432-8443.

<sup>32</sup> a) M. Hanada, H. Ohkuma, T. Yonemoto, K. Tomita, M. Ohbayashi, H. Kamei, T. Miyaki, M. Konishi, H. Kawaguchi, S. Forenza, *J. Antibiot.* **1991**, *44*, 403-414; b) D. R. Schroeder, K. L. Colson, S. E. Klohr, N. Zein, D. R. Langley, M. S. Lee, J. A. Matson, T. W. Doyle, *J. Am. Chem. Soc.* **1994**, *116*, 9351-9352.

<sup>33</sup> T. Ando, M. Ishii, T. Kajiura, T. Kameyama, K. Miwa, Y. Sugiura, *Tetrahedron Lett.* **1998**, *39*, 6495-6498.

<sup>34</sup> For recent total syntheses of nine-membered enediyne natural products, see: N1999A2: a) S. Kobayashi, S. Ashizawa, Y. Takahashi, Y. Sugiura, M. Nagaoka, M. J. Lear, M. Hirama, *J. Am. Chem. Soc.* **2001**, *123*, 11294-11295; b) S. Kobayashi, R. S. Reddy, Y. Sugiura, D. Sasaki, N. Miyagawa, M. Hirama, *J. Am. Chem. Soc.* **2001**, *123*, 2887-2888; c) N. Ji, H. O'Dowd, B. M. Rosen, A. G. Myers, *J. Am. Chem. Soc.* **2006**, *128*, 14825-14827. Neocarzinostatin chromophore: d) A. G. Myers, J. Liang, M. Hammond, P. M. Harrington, Y. Wu, E. Y. Kuo, *J. Am. Chem. Soc.* **1998**, *120*, 5319-5320; e) A. G. Myers, R. Glatthar, M. Hammond, P. M. Harrington, E. Y. Kuo, J. Liang, S. E. Schaus, Y. Wu, J.-N. Xiang, *J. Am. Chem. Soc.* **2002**, *124*, 5380-5401; f) S. Kobayashi, M. Hori, G. X. Wang, M. Hirama, *J. Org. Chem.* **2006**, *71*, 636-644. Kedarcidin chromophore: g) F. Ren, P. C. Hogan, A. J. Anderson, A. G. Myers, *J. Am. Chem. Soc.* **2007**, *129*, 5381-5383. Maduropeptin chromophore: h) K. Komano, S. Shimamura, Y. Norizuki, D. Zhao, C. Kabuto, I. Sato, M. Hirama, *J. Am. Chem. Soc.* **2009**, *131*, 12072-12073.

<sup>35</sup> For recent reviews on enediyne antitumor antibiotics, see: a) A. M. Irina, A. T. Boris, *Russ. Chem. Rev.* **2006**, *75*, 825; b) I. Sato, M. Hirama, *J. Synth. Org. Chem., Jpn* **2010**, *68*, 1123-1131.

However, enediynes **22** and **25–28** mostly lose their antibiotic and antitumoral activity upon cycloaromatization.<sup>24</sup> In contrast, the fijiolides still possess notable bioactivity, rendering them interesting for further biological evaluation, as outlined in section 1.5.

### 1.5 Biological Activity of Fijiolides A and B

In order to explore the bioactivity profile of the newly isolated secondary metabolites **1** and **2**, Fenical *et al.* investigated their inhibitory potential against transcription factor NFκB. Thus, fijiolide A was found to reduce the TNF-α induced NFκB activity by 70%. Dose-dependency experiments revealed an IC<sub>50</sub> value of 0.57 μM for **1**, while its *non*-acetylated congener fijiolide B showed diminished biological activity. In this case, TNF-α induced NFκB activity was reduced by 46% without a dose-dependent response. During additional exploration of the fijiolides' potential as cancer chemoprevention agents, they were screened as stimuli for the metabolic detoxification enzyme quinone reductase 1 (QR1). In this regard, **1** was found to enhance QR1 activity with an induction ratio of 3.5 at 20 μg/mL (28.4 μM). A concentration of 1.8 μM was determined to double the induction. In contrast, fijiolide B was not observed to induce QR1 activity, thus emphasizing the relevance of the acetamido moiety for biological activity. Fijiolides A and B, as well as the structurally related C-1027 chromophore-V (**24**), were subjected to further testing by Oh *et al.* Benzoxazine bearing **24** exhibited strong cytotoxic effects against colon cancer cell line HCT-116 and breast cancer cell line MDA-MB231 with IC<sub>50</sub> values of 0.9 and 2.7 μM, respectively.<sup>29</sup> By contrast, the fijiolides are not reported to display significant activity against these cell lines.<sup>8</sup>

## 1.6 NFκB as a Therapeutic Target in Cancer Treatment

Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) is a well-characterized transcription factor protein complex, and was first discovered in 1986 by Baltimore *et al.*<sup>36</sup> It regulates the expression of nearly 500 genes.<sup>37</sup> More than 200 of them encode proteins involved in immune and inflammation responses as well as cell growth control. In addition, the expression of tumorigenesis relevant proteins, such as cyclooxygenase (COX-2), matrix metalloproteinase (MMP-9), inducible nitric oxide synthase (iNOS) or antiapoptotic proteins bcl-2 and bcl-xl, is also mediated by NFκB.<sup>38</sup> Due to its pivotal role in immunological processes, it has been termed “central mediator of the human immune response”.<sup>39</sup> NFκB belongs to the category of rapid-acting primary transcription factors and is ubiquitously expressed in nearly all animal cell types.<sup>40,41</sup> It is ordinarily situated in the cytoplasm as a complex with the inhibitory protein IκB, suppressing the translocation of the transcription factor into the nucleus.<sup>42</sup> Hence, activation and rapid nuclear appearance of NFκB does not necessitate a *de-novo* synthesis of the protein, but merely dissociation from its inhibitor IκB, which renders NFκB a fast responder to harmful cellular stimuli. More than 150 stimuli are known to activate NFκB by phosphorylation, ubiquitination or degradation of IκB subunits.<sup>38,43</sup> These stimuli are exceedingly diverse and include stress, cytokines, free radicals, bacteria/viruses as well tumor promoters and carcinogens, such as cigarette smoke (**Figure 5A**).<sup>44</sup> Among them, the pro-inflammatory cytokine tumor necrosis factor α (TNF-α) is one of the most potent activators of NFκB. Although its activation is required for a proper immune system function and cell survival, a misregulation of the NFκB activity is linked to inflammatory and autoimmune diseases, septic shock, viral infection, arthritis and asthma.<sup>45</sup> In addition, constitutive activation of NFκB is largely observed in cancer cells.<sup>46</sup> The consequences of aberrant NFκB activation are as manifold as its triggering factors, and lead to increased expression of genes that are associated with

<sup>36</sup> R. Sen, D. Baltimore, *Cell* **1986**, *47*, 921-928.

<sup>37</sup> S. C. Gupta, C. Sundaram, S. Reuter, B. B. Aggarwal, *Biochim. Biophys. Acta* **2010**, *1799*, 775-787.

<sup>38</sup> R. J. Anto, A. Mukhopadhyay, S. Shishodia, C. G. Gairola, B. B. Aggarwal, *Carcinogenesis* **2002**, *23*, 1511-1518.

<sup>39</sup> H. L. Pahl, *Oncogene* **1999**, *18*, 6853-6866.

<sup>40</sup> M. Karin, *Nature* **2006**, *441*, 431-436.

<sup>41</sup> V. Metelev, S. Zhang, D. Tabatadze, A. Bogdanov, *Bioconjugate Chem.* **2011**, *22*, 759-765.

<sup>42</sup> A. S. Baldwin, *Annu. Rev. Immunol.* **1996**, *14*, 649-681.

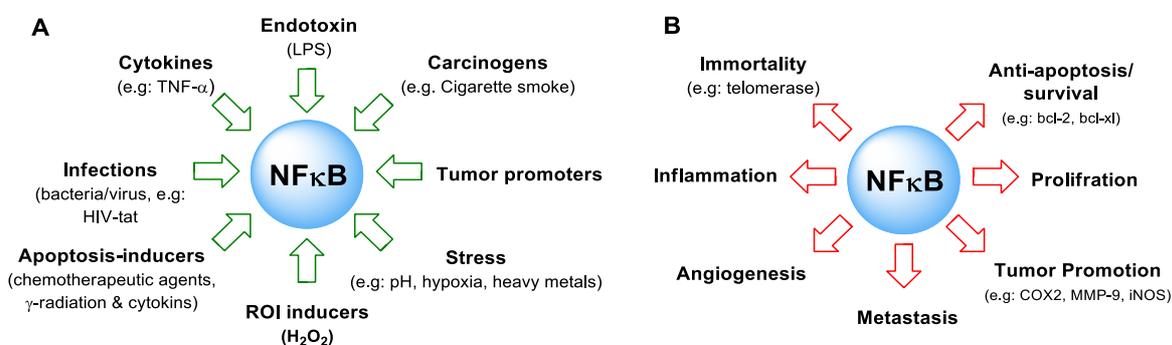
<sup>43</sup> A. C. Bharti, B. B. Aggarwal, *Biochem. Pharmacol.* **2002**, *64*, 883-888.

<sup>44</sup> B. B. Aggarwal, *Cancer Cell* **2004**, *6*, 203-208.

<sup>45</sup> S. Luqman, J. M. Pezzuto, *Phytother. Res.* **2010**, *24*, 949-963.

<sup>46</sup> T. D. Gilmore, M. Herscovitch, *Oncogene* **2006**, *25*, 6887-6899.

cell proliferation, tumor promotion, angiogenesis, metastasis, inflammation, and suppression of apoptosis (**Figure 5B**).



**Figure 5:** Inducers of NF $\kappa$ B activation (**A**) and cell processes influenced by NF $\kappa$ B (**B**).

Paradoxically, chemotherapeutic treatment of tumors or radiation - applied to induce cancer cell apoptosis - were observed to promote NF $\kappa$ B activation.<sup>47</sup> This indicates that the transcription factor is involved in the autodefense mechanism of affected cells and may result in desensitization, chemoresistance, and radioresistance.<sup>44</sup> Selective suppression of NF $\kappa$ B activation is commonly considered to inhibit proliferation and survival of the tumor cell, and either cause apoptosis directly, or render cancer cells more sensitive to the action of other antitumor agents.<sup>40,48</sup> Against this background, NF $\kappa$ B is a promising therapeutic target for the treatment of cancer and various inflammatory diseases, and inhibitors are current object of research in pharmaceutical industry.<sup>44</sup>

<sup>47</sup> C. Y. Wang, M. W. Mayo, A. S. Baldwin, Jr., *Science* **1996**, 274, 784-787.

<sup>48</sup> S. Luqman, J. M. Pezzuto, *Phytother. Res.* **2010**, 24, 949-963.



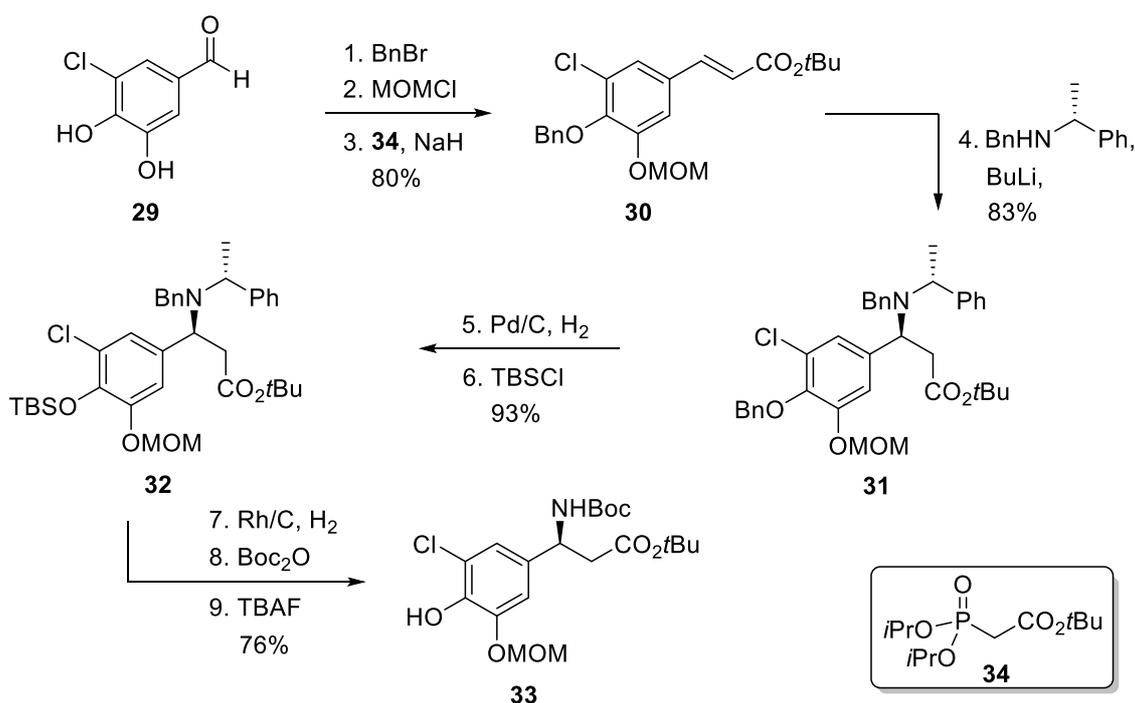
## *2. State of Research*

## 2.1 Syntheses of the $\beta$ -Amino Acid Fragment by Hirama *et al.*

In the context of synthetic studies towards the C-1027 chromophore, Hirama *et al.* disclosed a synthetic route to the  $\beta$ -amino acid fragment in 1999 (**Scheme 6**).<sup>49</sup> To date, no further synthetic approach has been published. Hirama's synthesis commences with a selective *para*-benzylation of commercially available 3-chloro-4,5-dihydroxybenzaldehyde **29**, followed by MOM-protection of the remaining hydroxyl group, and HWE-olefination to afford *tert*-butyl cinnamate **30**. Asymmetric introduction of the nitrogen atom was accomplished by conjugate addition of Davies' chiral lithium amide to furnish  $\beta$ -amino ester **31** in high diastereoselectivity (20:1).<sup>50</sup> Selective hydrogenolysis of the *O*-benzyl group was attained under Pd<sup>0</sup> catalysis and was followed by TBS protection, giving rise to silyl ether **32**. An additional hydrogenolysis employing Rh/C was required for cleavage of the *N*-benzyl and *N*- $\alpha$ -methylbenzyl groups. Boc-protection of the resulting free amine, followed by the removal of the TBS group provided  $\beta$ -amino ester **33**, which was demonstrated to be a competent substrate for aryl ether formation by nucleophilic epoxide opening. In summary, Hirama's synthesis of the C-1027  $\beta$ -amino acid fragment features 9 steps and a stereoselective conjugate addition of a chiral amine for the installation of the stereogenic center.

<sup>49</sup> I. Sato, T. Kikuchi, M. Hirama, *Chem. Lett.* **1999**, 28, 511-512.

<sup>50</sup> a) S. G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1991**, 2, 183-186; b) J. F. Costello, S. G. Davies, O. Ichihara, *Tetrahedron: Asymmetry* **1994**, 5, 1999-2008.



Scheme 6: Hirama's synthesis of the C-1027/fijiolide  $\beta$ -amino acid fragment.

## 2.2 Syntheses of the C-1027/ Fijiolide Amino Sugar

The amino sugar moiety common to both C-1027 and the fijiolides has attracted research attention by different groups. This led to the development of three synthetic approaches over the past two decades.<sup>51,52,53</sup> These will be briefly outlined in this section.

### 2.2.1 Hirama's 1<sup>st</sup> Generation Synthesis

As key contributors to the field of enediyne natural product synthesis, Hirama *et al.* published the first synthesis of methyl glycoside **42** in 1993 (Scheme 7).<sup>51</sup> The synthesis used prenol **35** as the starting material, which was converted into enantioenriched (*R*)-dimethylglycidol **36** via Sharpless asymmetric epoxidation.<sup>54</sup> **36** was subjected to benzyl protection and hydrolytic regioselective

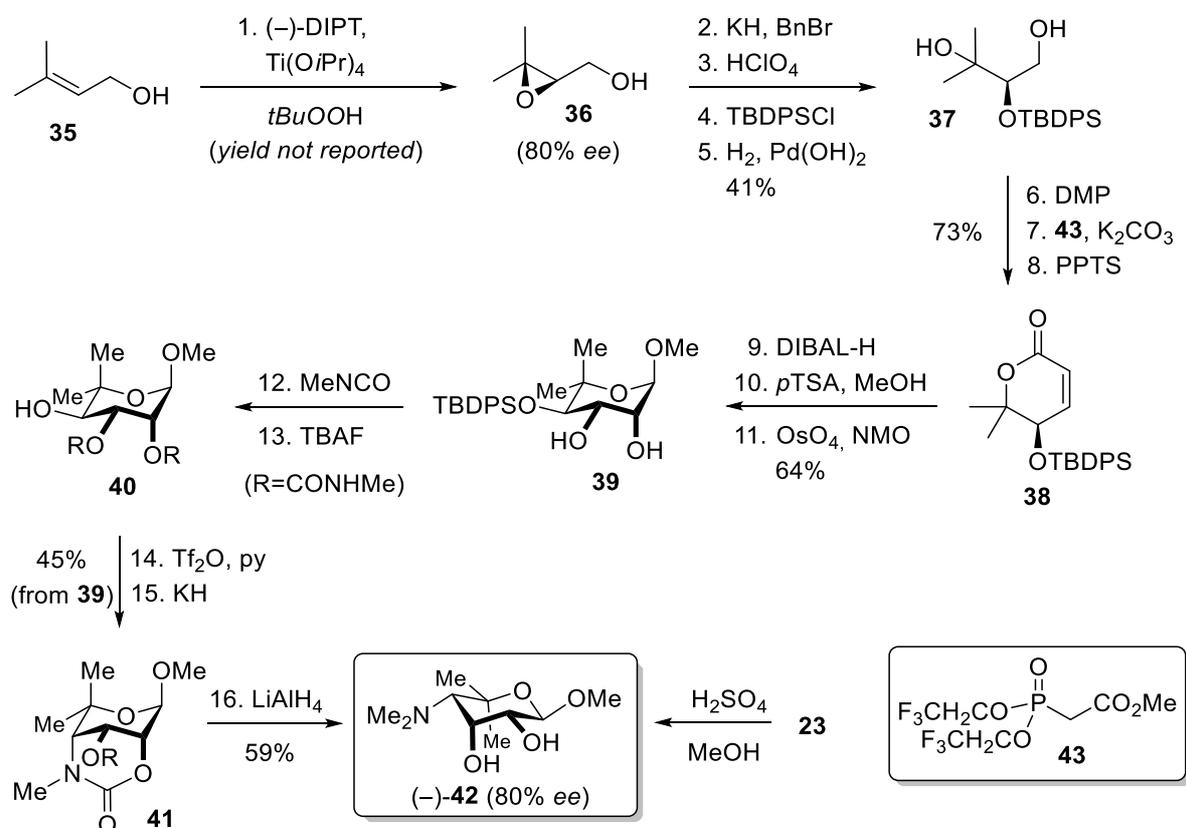
<sup>51</sup> K.-i. Iida, T. Ishii, M. Hirama, T. Otani, Y. Minami, K.-i. Yoshida, *Tetrahedron Lett.* **1993**, *34*, 4079-4082.

<sup>52</sup> M. F. Semmelhack, Y. Jiang, D. Ho, *Org. Lett.* **2001**, *3*, 2403-2406.

<sup>53</sup> K. Hirai, Y. Tamura, I. Sato, M. Hirama, *Synlett* **2010**, *2010*, 2156-2158.

<sup>54</sup> Y. Gao, J. M. Klunder, R. M. Hanson, H. Masamune, S. Y. Ko, K. B. Sharpless, *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

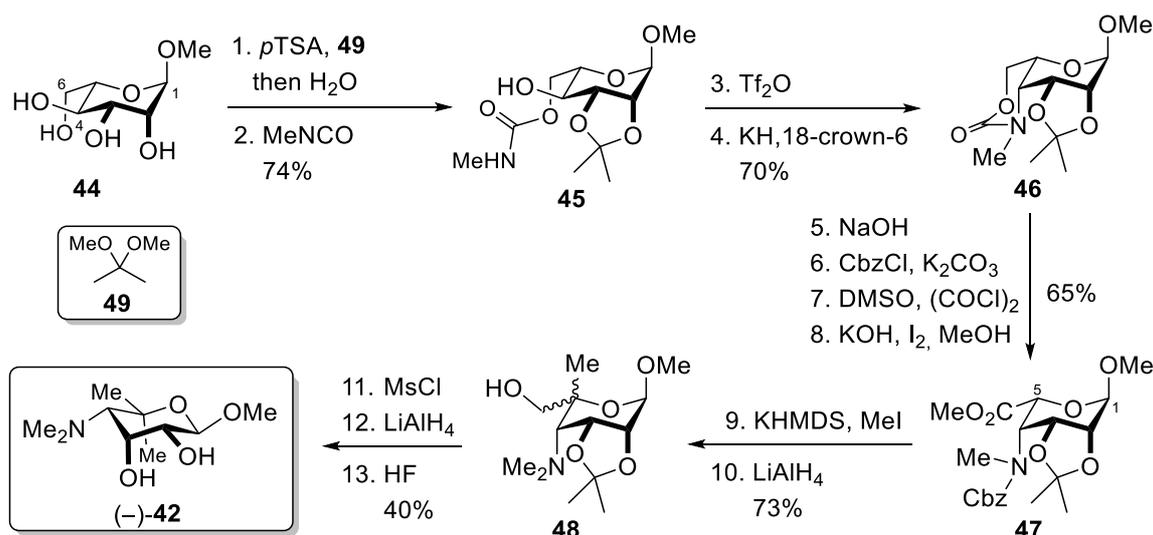
epoxide opening, followed by silyl protection and hydrogenolysis to produce diol **37** in 41% yield. Oxidation of the primary alcohol was followed by a (*Z*)-selective Still-Gennari olefination. A subsequent lactonization under acidic conditions provided **38**. Exposure to DIBAL-H and ketalization in acidic methanol prepared the substrate for an OsO<sub>4</sub> catalyzed diastereoselective dihydroxylation to afford diol **39**. Double carbamate protection of the vicinal diol prior to silyl ether cleavage with TBAF provided access to **40**. For the key step of the synthesis, the secondary alcohol was activated as the corresponding triflate, thus allowing for an intramolecular carbamate cyclization to install the nitrogen atom adjacent to the *gem*-dimethyl group in **41**. Finally, reductive cleavage of both carbamates provided methyl glycoside (–)-**42**. Acid mediated degradation of the cycloaromatized C-1027 chromophore **23** gave **42** of identical spectral data and optical rotation. In this way, Hirama *et al.* established the previously unknown absolute stereochemistry and demonstrated the C-1027 amino sugar moiety to be 4-deoxy-4-dimethylamino-5,5-dimethyl-D-ribofuranose. In summary, Hirama's synthesis requires 16 steps to provide (–)-**42** from prenosyl in a 5.1% overall yield (first step excluded).



**Scheme 7:** Hirama's first synthesis of the C-1027 amino sugar and determination of the absolute configuration.

### 2.2.2 Semmelhack's Synthesis

In 2001, a second synthesis of the C-1027 amino sugar side chain was disclosed by Semmelhack *et al.* (**Scheme 8**).<sup>52</sup> Their approach takes advantage of readily available  $\alpha$ -methyl-D-mannopyranoside (**44**) as the enantiopure starting material, which was subjected to double acetonide protection. An aqueous workup selectively hydrolyzed the 1,3-dioxane in favor of the more stable 1,3-dioxolane.<sup>55</sup> Subsequent introduction of a methyl carbamate at 6-OH delivered **45**. The synthesis continued with an activation of the C-4 hydroxyl group as the corresponding triflate. In close analogy to Hirama's synthesis, nucleophilic displacement at C-4 by intramolecular delivery of the carbamate nitrogen atom gives rise to cyclic carbamate **46**. A subsequent 4-step sequence consisting of an alkaline carbamate cleavage, a Cbz protection of the resulting secondary amine, a Swern oxidation, and an oxidative esterification provided methyl ester **47**. Alkylation at C-5 was realized by enolate generation and simultaneous trapping with methyl iodide to furnish an inconsequential 2:3 mixture of diastereomers. Further conversion into dimethylamino alcohol **48** was achieved by a one-pot reduction of both the carbamate protecting group and the methyl ester. The final stages of the synthesis involved a mesylation of the epimeric alcohol **48**, an additional reduction to generate the *gem*-dimethyl group and ketal hydrolysis providing methyl glycoside (**-**)-**42**. In summary, Semmelhack's synthesis comprises 13 steps to convert commercially available **44** into the C-1027/ fijiolide amino sugar in a 9.8% overall yield.

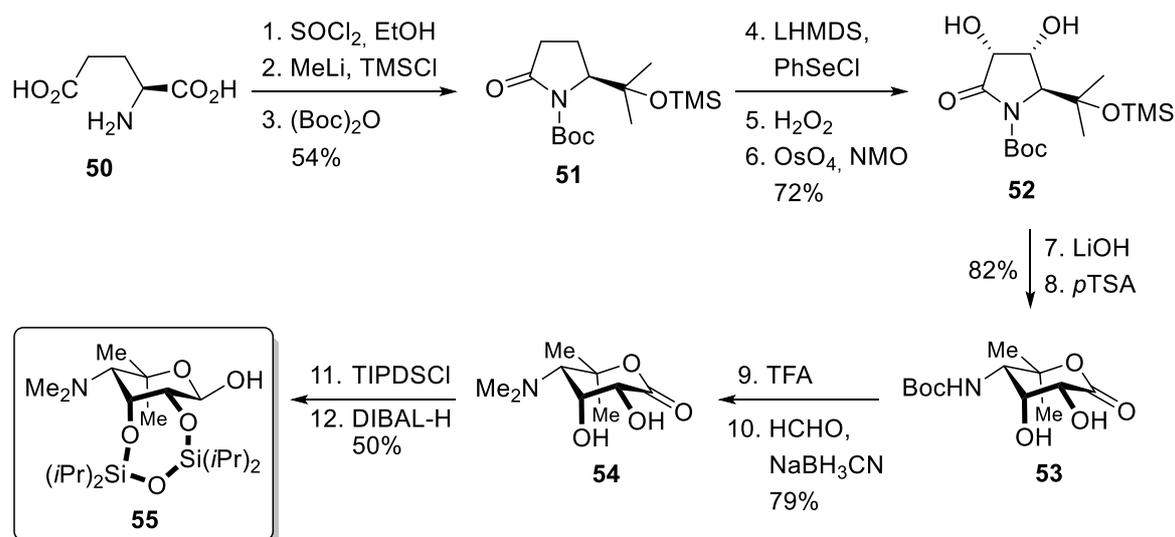


**Scheme 8:** Semmelhack's synthesis of the C-1027 amino sugar moiety.

<sup>55</sup> M. E. Evans, F. W. Parrish, *Carbohydr. Res.* **1977**, *54*, 105-114.

### 2.2.3 Hirama's 2<sup>nd</sup> Generation Synthesis

As consequence of their lasting interest in the synthesis of the C-1027 chromophore, Hirama *et al.* recently disclosed a revised synthetic approach towards the amino ribopyranose unit of **22** in 2010 (**Scheme 9**). In contrast to both syntheses discussed beforehand, this chiral pool approach elegantly forgoes stereoselective introduction of the amino group by employment of a proteinogenic  $\alpha$ -amino acid. Thus, L-glutamic acid (**50**) was first converted into ethyl L-pyroglutamate.<sup>56</sup> Twofold methylation of the ester carbonyl group, followed by trapping of the resulting lithium alkoxide with TMSCl and subsequent Boc protection provided access to **51**. With the *gem*-dimethyl group installed at the beginning of the synthesis, the stereoselective introduction of the *cis*-diol was achieved *via* elimination of the corresponding  $\alpha$ -selenoxide, followed by OsO<sub>4</sub> catalyzed dihydroxylation. Alkaline hydrolysis of the  $\gamma$ -lactam **52** with concomitant removal of the TMS group gave rise to an intermediate  $\delta$ -hydroxy acid, which was lactonized to **53** under acid conditions. Boc deprotection, followed by double reductive amination delivered tertiary amine **54**. Tetraisopropyldisiloxane (TIPDS) protection of the *cis*-diol and subsequent DIBAL-H reduction of the lactone provided the synthetically useable amino sugar **55**, compared to the previous methyl glycoside (–)-**42** (*vide supra*). In summary, Hirama's revised synthesis of the C-1027/fijiolide amino sugar features a shortened 12-step procedure for preparation of TIPDS protected amino pyranose **55** from readily available L-glutamic acid in 13% overall yield.

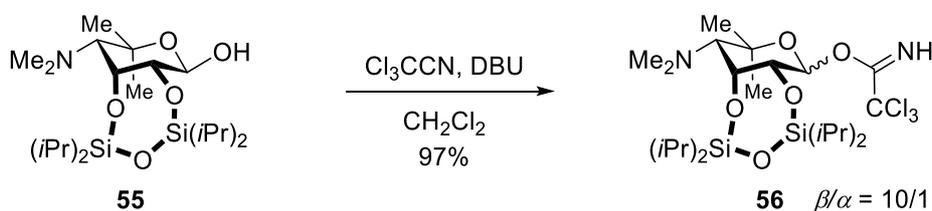


**Scheme 9:** Hirama's revised synthesis of the C-1027 amino sugar moiety.

<sup>56</sup> a) S. Saijo, M. Wada, J. Himizu, A. Ishida, *Chem. Pharm. Bull.* **1980**, *28*, 1449-1458; b) Y. Hamada, O. Hara, A. Kawai, Y. Kohno, T. Shioiri, *Tetrahedron* **1991**, *47*, 8635-8652.

### 2.3 Glycoside Synthesis with the C-1027 Amino Sugar Unit

Since the first report of a glycoside synthesis by Michael in 1879,<sup>57</sup> a vast number of glycosylation methods have become available.<sup>58,59</sup> The most prominent representatives among them are the classical Fischer glycosylation<sup>60</sup> and the Koenigs-Knorr method,<sup>61</sup> generally characterized by either acid mediated acetalization of cyclic hemiacetals or the reaction of alcohols with glycosyl halides in the presence of a halophilic promotor, typically a heavy metal salt. In 1980, Schmidt *et al.* introduced the use of anomeric trichloroacetimidates as glycosyl donors. He demonstrated their convenient preparation and remarkable scope in glycosylation of carboxylic acids, phenols, steroid alcohols and carbohydrates upon promotion by catalytic *p*TSA or BF<sub>3</sub>•OEt<sub>2</sub>.<sup>62</sup> Due to the superior stability of glycosyl trichloroacetimidates and their high reactivity under mild reaction, these now-called Schmidt donors stand out as the most popular type of glycosyl donors for the synthesis of complex glycosides including natural products. Using this method, even sterically encumbered and sensitive alcohols have been successfully glycosylated.<sup>63,64</sup> The trichloroacetimidate method has also been used by Hirama *et al.* for glycosylation of secondary and tertiary alcohols with the C-1027 amino sugar moiety after activation of hemiacetal **55** as the corresponding Schmidt donor **56** (Scheme 10).<sup>65</sup>



**Scheme 10:** Reported synthesis of Schmidt donor **56** from amino sugar **55**.

<sup>57</sup> A. Michael, *Am. Chem. J.* **1879**, *1*, 305-312.

<sup>58</sup> For recent reviews on available glycosylation methods, see: a) X. Zhu, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934; b) A. V. Demchenko, *Synlett* **2003**, *2003*, 1225-1240; c) K. J. Jensen, *J. Chem. Soc., Perkin Trans. 1* **2002**, 2219-2233; d) B. G. Davis, *J. Chem. Soc., Perkin Trans. 1* **2000**, 2137-2160.

<sup>59</sup> For reviews on synthesis of complex natural glycosides, see: Y. Yang, X. Zhang, B. Yu, *Nat. Prod. Rep.* **2015**, *32*, 1331-1355; D. P. Galonic, D. Y. Gin, *Nature* **2007**, *446*, 1000-1007; K. Toshima, *Carbohydr. Res.* **2006**, *341*, 1282-1297; H. Pellissier, *Tetrahedron* **2005**, *61*, 2947-2993; K. C. Nicolaou, H. J. Mitchell, *Angew. Chem. Int. Ed.* **2001**, *40*, 1576-1624; S. J. Danishefsky, M. T. Bilodeau, *Angewandte Chemie International Edition in English* **1996**, *35*, 1380-1419.

<sup>60</sup> E. Fischer, *Ber. Dtsch. Chem. Ges* **1893**, *26*, 2400-2412.

<sup>61</sup> W. Koenigs, E. Knorr, *Ber. Dtsch. Chem. Ges* **1901**, *34*, 957-981.

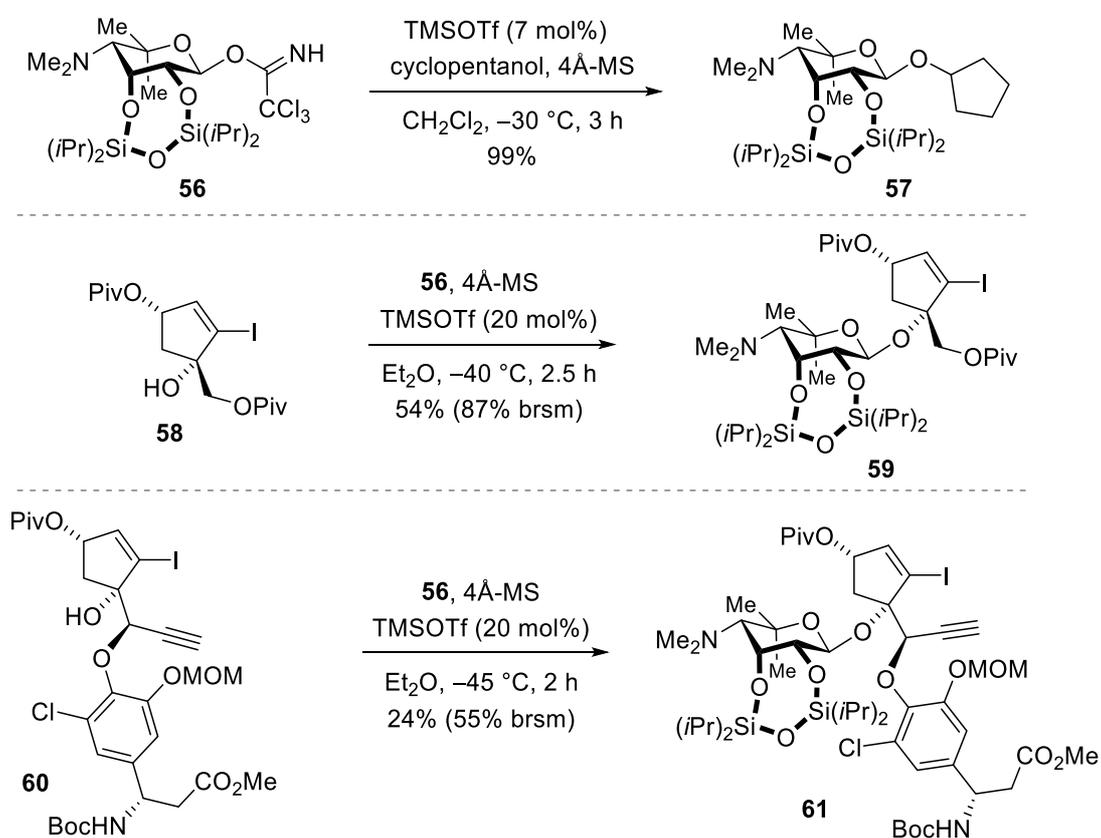
<sup>62</sup> a) R. R. Schmidt, J. Michel, *Angew. Chem. Int. Ed.* **1980**, *19*, 731-732; b) R. R. Schmidt, *Angew. Chem. Int. Ed.* **1986**, *25*, 212-235.

<sup>63</sup> Y. Yang, X. Zhang, B. Yu, *Nat. Prod. Rep.* **2015**, *32*, 1331-1355.

<sup>64</sup> A. Holkenbrink, J. B. Vicente, D. B. Werz, *Synthesis* **2009**, *2009*, 2596-2604.

<sup>65</sup> I. Sato, Y. Akahori, T. Sasaki, T. Kikuchi, M. Hirama, *Chem. Lett.* **1999**, *28*, 867-868.

A test glycosylation of cyclopentanol, employing catalytic TMSOTf as the promotor, afforded glycoside **57** in quantitative yield (**Scheme 11**). The  $\beta$ -anomer was exclusively observed. Moreover, good yields and  $\beta$ -glycosylation selectivities were achieved for early – yet sterically encumbered – synthetic intermediates **58** and **60** of the C-1027 chromophore synthesis. Hirama *et al.* attributed the observed high  $\beta$ -selectivity to the efficient shielding of the glycosyl donor's  $\alpha$ -face by the sterically demanding tetraisopropylidisiloxane protecting group.<sup>65</sup> Despite these promising glycosylation results, the reported broad variation in reaction conditions and yields/conversions, especially with respect to the temperature, suggests the need for careful adjustment of this parameter for each glycosyl acceptor.



**Scheme 11:** Reported glycosylation of secondary and tertiary alcohols with Schmidt donor **56**.

## 2.4 Aims of the Project

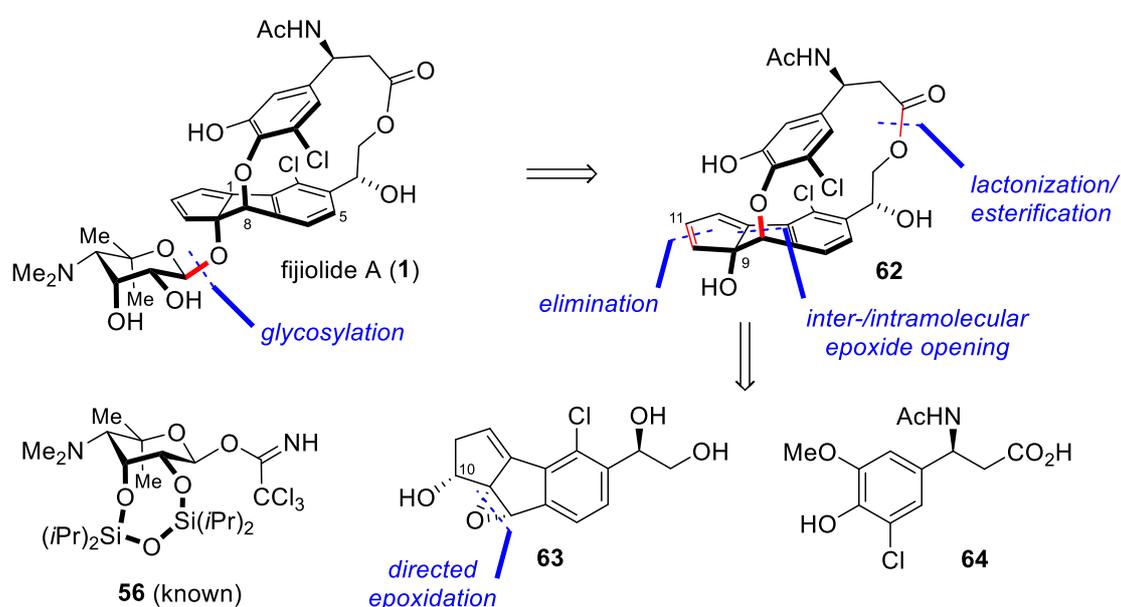
The inhibitory activity of fijiolide A with respect to the TNF- $\alpha$  induced NF $\kappa$ B activity renders **1** of therapeutic promise and a possible candidate for cancer chemoprevention and treatment. Concomitant with an intriguing molecular architecture, fijiolide A represents a formidable target for total synthesis. A modular, highly convergent, and optimally atropselective synthesis of this natural product was envisaged, allowing for ensuing extensive SAR studies. At the juncture of target selection, several synthetic studies towards related enediyne and cycloaromatized cyclopenta[*a*]indene bearing natural products had been disclosed (*cf.* chapter 1.3, 1.4 and 0). However, no synthetic studies targeting a C-3 chlorinated cyclopenta[*a*]indene skeleton for construction of the fijiolide [2.6]paracyclophane, or any other synthetic approach towards this natural product family had been published. As a result of the abovementioned facts, we felt as encouraged as challenged to elaborate a synthetic route towards fijiolide A. Our efforts towards this end will be presented in this thesis.



### ***3. General Retrosynthetic Analysis and Synthetic Challenges***

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Retrosynthetically, fijiolide A can be dissected into two fragments by scission of the glycosidic bond, yielding the fijiolide A aglycone **62**, and an amino sugar side chain (**Scheme 12**). Late-stage  $\beta$ -glycosylation of the sterically encumbered tertiary C-9 hydroxyl group of **62** represents a key transformation, and was envisioned to be realized by utilization of known Schmidt donor **56**. Regarding aglycone **62**, assembly of the strained [2.6]paracyclophane structure was considered the most challenging synthetic obstacle as rotational restriction about the ether and ester biaryl linkage demands an atropselective ring closure. This macrocycle lends itself to fission of the six-atom paracyclophane bridge at the ester, as well as retrosynthetic cleavage of the two-atom biaryl linker at the benzyl ether bond. Thus, aglycone **62** was disassembled to carbocyclic epoxide **63**, and  $\beta$ -amino acid fragment **64**.



**Scheme 12:** General retrosynthetic analysis of fijiolide A.

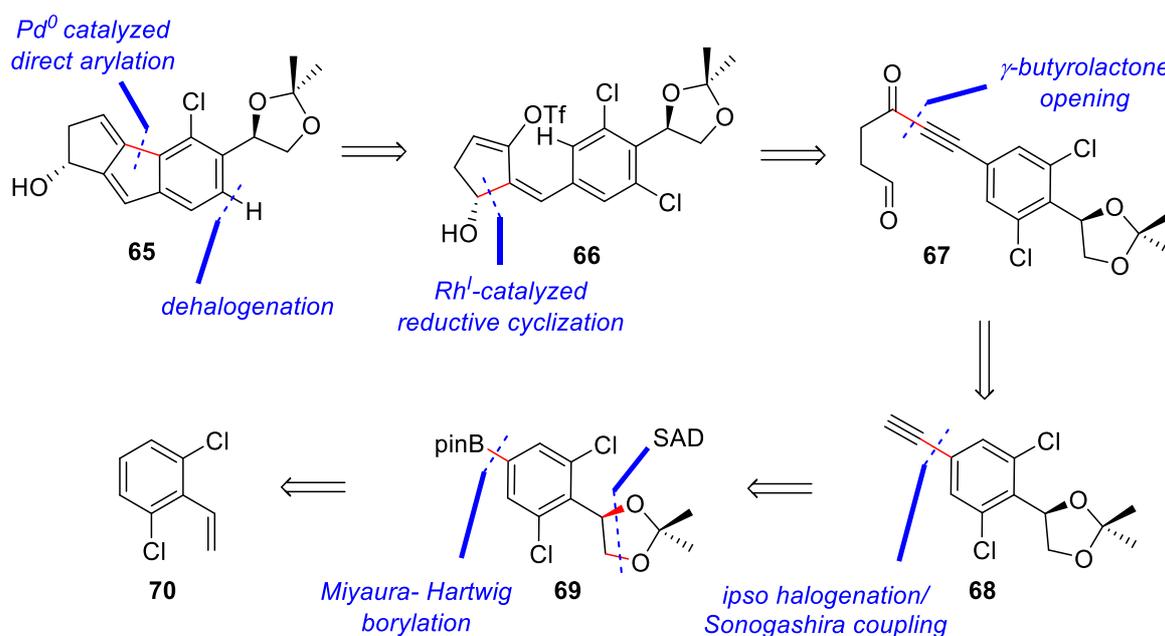
According to our proposal, identification of building blocks **63** and **64** would allow preparative evaluation of two complementary synthetic pathways towards **62**. Specifically, aryl ether formation by intermolecular nucleophilic epoxide opening, followed by macrolactonization, or reversal of these steps, *i. e.* formation of the ester linkage between **63** and **64** prior to the paracyclophane constructing intramolecular etherification. A strategically installed hydroxyl substituent at C-10 on **63** was envisaged to enable diastereoselective (directed) epoxidation, and also allow installation of the cyclopentadiene motif at late-stage of the synthesis. More detailed retrosynthetic considerations of fragments **63** and **64** will be provided in the chapters detailing synthetic approaches towards these building blocks.

*4. Studies towards the*  
*Chlorocyclopenta[a]indene Fragment*

## 4.1 Studies Involving Rh<sup>I</sup> Catalyzed Reductive Cyclization / Pd<sup>0</sup> Catalyzed Direct Arylation

### 4.1.1 Retrosynthetic Analysis

Our initial retrosynthetic analysis of the acetonide protected key fragment **65** involved a Pd<sup>0</sup> catalyzed direct arylation of vinyl triflate **66**<sup>66</sup> and a metal catalyzed dehalogenation of the sterically less encumbered C<sub>aryl</sub>-Cl bond (**Scheme 13**)<sup>67</sup>. The stereogenic center of the allylic alcohol in **66** was postulated to be introduced in a diastereoselective manner by a Rh<sup>I</sup> catalyzed reductive cyclization of 1,5-ynal **67**,<sup>68</sup> which would be in turn accessed by nucleophilic opening of  $\gamma$ -butyrolactone with terminal alkyne **68**. The latter compound could be obtained *via* a Sonogashira coupling of *ipso*-halogenated pinacol boronate **69** and trimethylsilyl acetylene.



**Scheme 13:** First retrosynthetic analysis of key fragment **65**.

<sup>66</sup> For synthesis of related indanes *via* direct arylation of vinyl triflates, see: a) M. C. Willis, C. K. Claverie, M. F. Mahon, *Chem. Commun.* **2002**, 832-833; b) A. C. F. Cruz, N. D. Miller, M. C. Willis, *Org. Lett.* **2007**, *9*, 4391-4393; c) M. R. Albicker, N. Cramer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9139-9142; d) X.-z. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5844-5847.

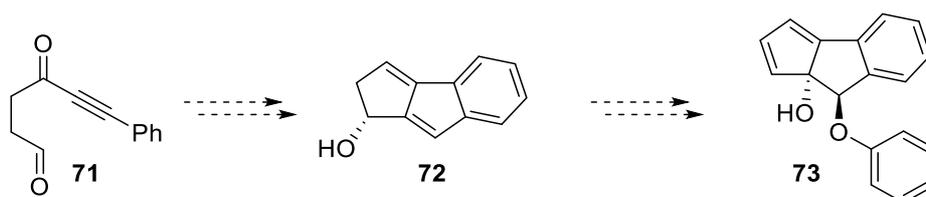
<sup>67</sup> M. S. Viciu, G. A. Grasa, S. P. Nolan, *Organometallics* **2001**, *20*, 3607-3612.

<sup>68</sup> J. U. Rhee, M. J. Krische, *J. Am. Chem. Soc.* **2006**, *128*, 10674-10675.

Finally, **69** could be synthesized *via* a Sharpless asymmetric dihydroxylation (SAD) of commercially available styrene **70**, followed by ketalization and an iridium(I) catalyzed *meta*-selective Miyaura-Hartwig borylation.<sup>69</sup>

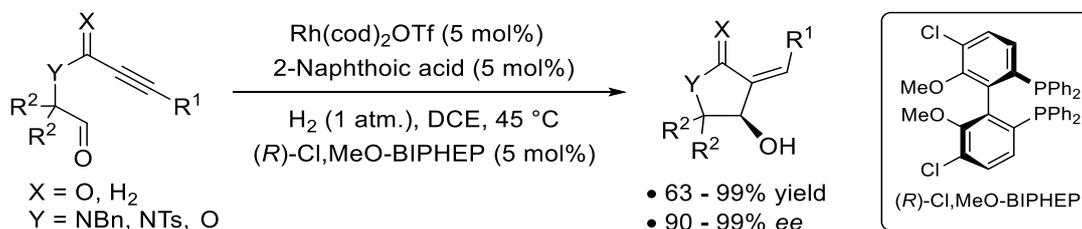
#### 4.1.2 Results

In order to assess the feasibility of this strategy, the chlorine and acetamide substituents of the arene core of **65** were initially ignored, allowing simplification of the tricyclic fragment to cyclopenta[*a*]indene **72**, which was to be synthesized from ynal **71**. (Scheme 14). With **72** in hand, model studies on a diastereoselective epoxidation and aryl ether formation by epoxide opening with phenol to synthesize **73** were envisaged.



Scheme 14: Envisaged model studies for fijiolide A.

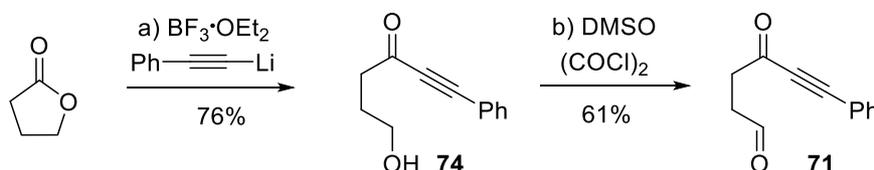
As demonstrated by Krische *et al.*,<sup>68</sup> rhodium(I) catalyzed reductive cyclization of acetylenic aldehydes provides rapid access to highly enantioenriched exomethylene cyclopentanols (Scheme 15), and was therefore elected to be investigated with 1,5-ynal **71**.



Scheme 15: Enantioselective Rh<sup>I</sup> catalyzed reductive cyclization of acetylenic aldehydes according to Krische *et al.*

<sup>69</sup> T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056-3058; J. M. Murphy, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 15434-15435.

**71** was synthesized *via* a selective *mono*-addition of *in situ* generated lithium phenylalkynyltrifluoroborate to  $\gamma$ -butyrolactone, yielding known  $\gamma$ -hydroxy ynone **74**, which provided model substrate **71** after Swern oxidation (**Scheme 16**).<sup>70</sup>

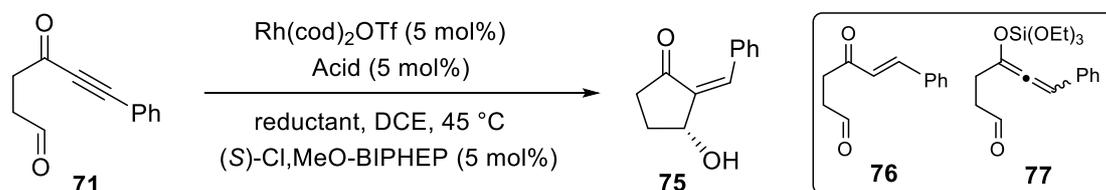


*Reagents and conditions:* a) Phenylacetylene (1.1 eq), *n*BuLi (1.1 eq), THF,  $-78\text{ }^{\circ}\text{C}$ , 1.5 h; b)  $(\text{COCl})_2$  (3.0 eq), DMSO (6.0 eq),  $\text{Et}_3\text{N}$  (1.0 eq),  $-78\text{ }^{\circ}\text{C}$ , 3 h, 61%.

**Scheme 16:** Synthesis of 1,5-ynal **71**.

Submission of **71** to Krische's cyclization conditions failed to produce  $\beta$ -hydroxy cyclopentanone **75** (**Table 1**, entry 1). *Trans* hydrogenation of the ynone moiety, giving rise to known enone **76**, was observed as the competing process.<sup>71</sup> Consequently, a reductant screen was conducted.

**Table 1:** Attempted reductive cyclization of 1,5-ynal **71**.



Entry	Acid	Reductant	T [h]	Yield of <b>75</b>
1	2-naphthoic acid	$\text{H}_2$	2	0% <sup>[a]</sup>
2	2-naphthoic acid	$\text{HCO}_2\text{H}$	22	0% <sup>[b]</sup>
3	2-naphthoic acid	$(\text{EtO})_3\text{SiH}$	4	0% <sup>[c]</sup>
4	2-naphthoic acid	$\text{Et}_3\text{SiH}$	7	0%
5	$\text{Ph}_3\text{CCO}_2\text{H}$	$\text{H}_2$	18	0% <sup>[d]</sup>

<sup>[a]</sup> Only hydrogenation to enone **76** was observed; <sup>[b]</sup> Low conversion (< 10%);

<sup>[c]</sup> Allenol silyl ether **77** was formed; <sup>[d]</sup> 22% conversion to **76**.

Whereas formic acid was found to shut down reactivity (entry 2), the use of triethoxysilane led to formation of allenol silyl ether **77** as the predominant product (entry 3).<sup>72</sup> Utilization of triethylsilane as the reductant (entry 4) or tritylformic acid in place of 2-naphthoic acid did not

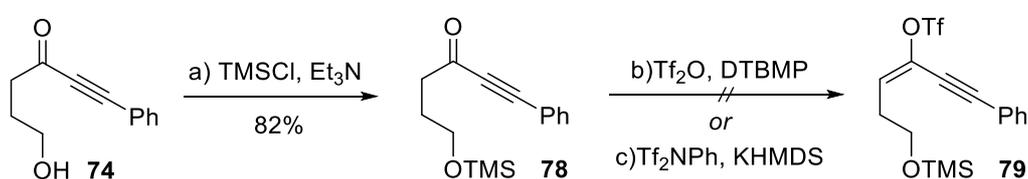
<sup>70</sup> J. Doubský, L. Streinz, L. Lešetický, B. Koutek, *Synlett* **2003**, 2003, 0937-0942.

<sup>71</sup> O. Tsuge, S. Kanemasa, T. Otsuka, T. Suzuki, *Bull. Chem. Soc. Jpn.* **1988**, 61, 2897-2908.

<sup>72</sup> Structure assignment was made on the bases of  $^1\text{H}$  NMR and HRMS data, only.

deliver the desired cyclopentanol **75** (entry 5). As ynones have not been reported to undergo this transformation, instead only propiolic esters, amides and propargyl ethers have been employed, we postulated that the adjacent ketone may render the alkyne too electron-poor, and therefore susceptible for direct hydrogenation. Modification of the ynone moiety in **71** was concluded to address this shortcoming.

Thus, primary alcohol **74** was first protected as the corresponding TMS ether (**Scheme 17**). Submission of **78** to enol triflate formation was expected to lead to a competent cyclization precursor (**79**), due to reduced reactivity of the triple bond, and the spatial proximity of the reaction sites owing to the double bond geometry of the enol triflate.

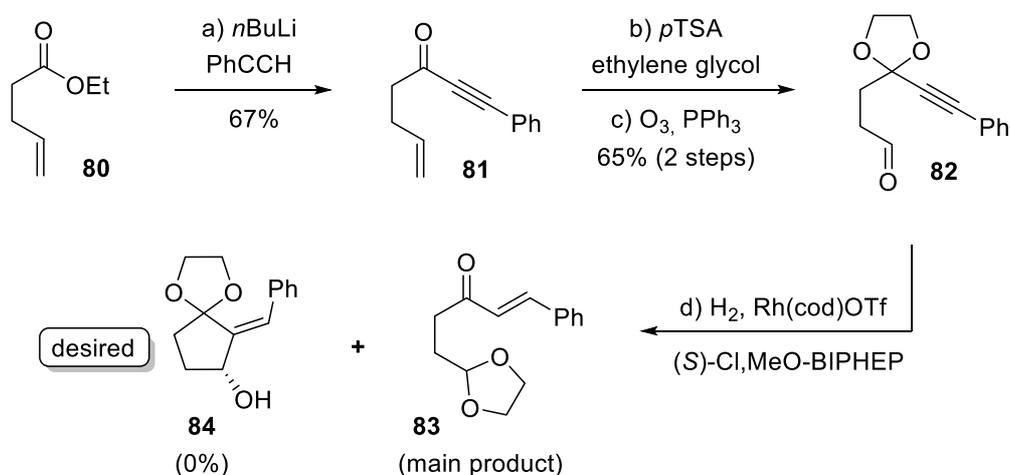


Reagents and conditions: a) TMSCl (1.1 eq), Et<sub>3</sub>N (1.5 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h; b) Tf<sub>2</sub>O (1.5 eq), DTBMP (1.3 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C or 23 °C, 2.5 h, 0%; c) Tf<sub>2</sub>NPh (1.5 eq), KHMDS (1.5 eq), THF, -78 °C, 5.5 h, 0%.

**Scheme 17:** Attempted synthesis of enol triflate **79**.

Unfortunately, enol triflate **79** could not be obtained due to product degradation upon attempts at isolation. Consequently, we proposed ketal **82** as a more stable cyclization precursor (**Scheme 18**). In addition, we anticipated increased cyclization propensity, arising from the Thorpe-Ingold effect of the 1,3-dioxolane. Starting from ethyl ester **80**, addition of lithium phenylacetylide provided the known ynone **81**,<sup>73</sup> which was subjected to ketalization and subsequent ozonolysis to furnish unstable 1,5-ynal **82** in 65% yield (**Scheme 18**).

<sup>73</sup> M. Schelwies, R. Moser, A. L. Dempwolff, F. Rominger, G. Helmchen, *Chem. Eur. J.* **2009**, *15*, 10888-10900.



*Reagents and conditions:* a) Phenylacetylene (2.0 eq),  $n\text{BuLi}$  (2.0 eq), THF,  $-78\text{ }^\circ\text{C}$ , 2 h, then  $-78\text{ }^\circ\text{C}$  to  $23\text{ }^\circ\text{C}$ , 30 min, 67%; b) ethylene glycol (10 eq),  $p\text{TSA}$  (5 mol%),  $\text{C}_6\text{H}_6$ , reflux, 3 h, 95%; c)  $\text{O}_3$ ,  $\text{PPh}_3$  (1.5 eq),  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ , 30 min, 68%; d)  $\text{Rh}(\text{cod})\text{OTf}$  (5.0 mol%),  $(S)\text{-Cl,MeO-BIPHEP}$  (5.0 mol%), 2-naphthoic acid (5.0 mol%),  $\text{H}_2$  (1 atm.), DCE,  $45\text{ }^\circ\text{C}$ .

**Scheme 18:** Synthesis of 1,5-ynal **82** and attempted reductive cyclization.

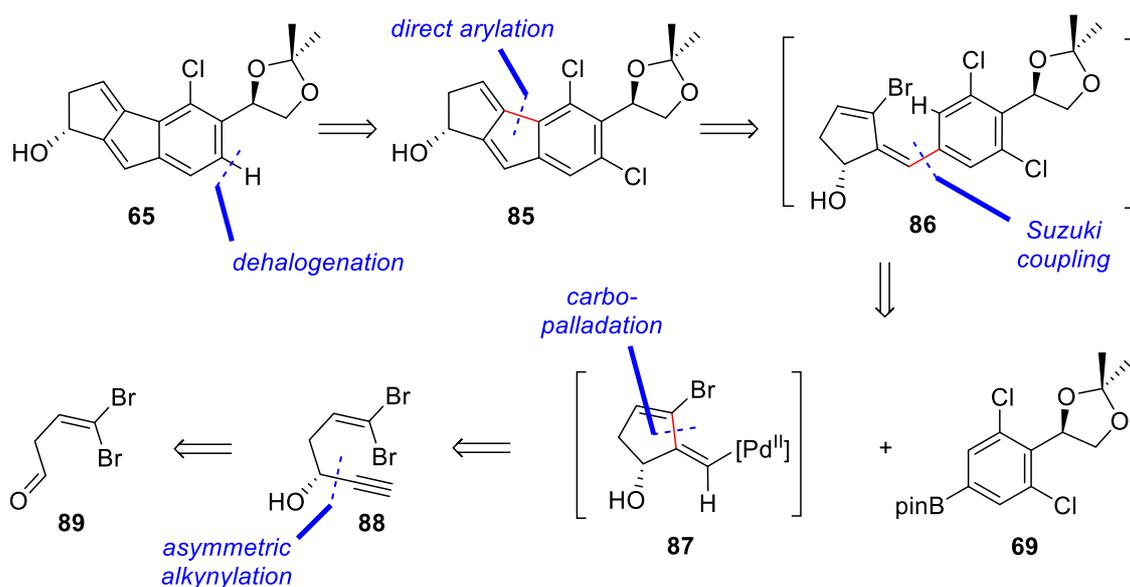
Employment of **82** as the reductive cyclization substrate did not provide desired spiro alcohol **84**. Instead, transketalization to the aldehyde under the acidic reaction conditions, followed by hydrogenation of the released ynone functionality was observed, giving rise to known enone **83**.<sup>71</sup>

In conclusion, reductive cyclization of 1,5-ynals **71** and **82** was not achieved as a result of predominant and undesired *trans* hydrogenation of the alkyne moiety. Moreover, envisaged cyclization of enol triflate **79** could not be investigated due to its inherent instability. Henceforth, we shifted our attention to an alternative synthetic approach, discussed in the following section.

## 4.2 Studies Involving Pd<sup>0</sup> Catalyzed Cascade Cyclization *via* Carbopalladation / Suzuki Coupling / Direct Arylation

### 4.2.1 Retrosynthetic Analysis

Our revised retrosynthetic analysis of **65** incorporated a selective dechlorination of **85**,<sup>67</sup> which would be accessed in a single step by a palladium(0) catalyzed cascade reaction of building blocks **88** and previously proposed pinacol boronate **69** (Scheme 19). More precisely, **85** is assumed to result from a direct arylation of intermediate vinyl bromide **86**, in turn being formed by Suzuki cross coupling of palladium(II) species **87** with boronate **69**. According to Scheme 19, species **87** arises from intramolecular carbopalladation of 1,1-dibromo-1-alkene **88**, after selective oxidative addition of Pd<sup>0</sup> into the (*Z*)-vinyl bromide.<sup>74</sup> Enantioselective access to **88** could in turn be provided by asymmetric alkynylation of dibromo aldehyde **89**.

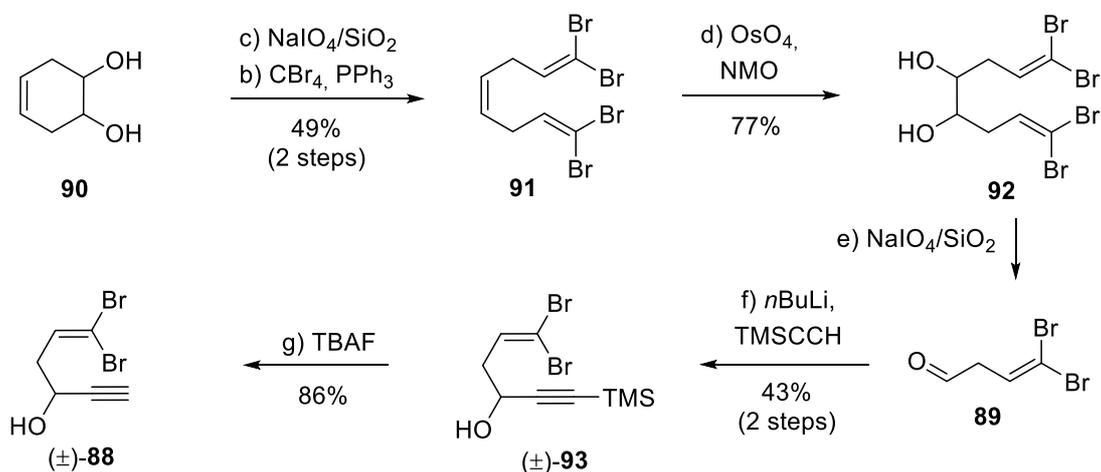


**Scheme 19:** Retrosynthetic analysis of **65**, involving a Pd<sup>0</sup> catalyzed cascade cyclization.

<sup>74</sup> a) S. Torii, H. Okumoto, T. Tadokoro, A. Nishimura, M. A. Rashid, *Tetrahedron Lett.* **1993**, *34*, 2139-2142; b) J. M. Nuss, R. A. Rennels, B. H. Levine, *J. Am. Chem. Soc.* **1993**, *115*, 6991-6992.

## 4.2.2 Results

Evaluation of this revised strategy for fragment **65** began with synthesis of racemic building block ( $\pm$ )-**88**. Glycol cleavage of **90**<sup>75</sup> with immobilized sodium periodate<sup>76</sup> cleanly furnished the corresponding *bis*-aldehyde, which was subjected to a Ramirez olefination to provide tetrabromotriene **91** (Scheme 20).<sup>77</sup> Although initially planned to be executed in one step, oxidative cleavage of the disubstituted double bond was found to proceed best *via* a stepwise oxidation to diol **92**, followed by glycol cleavage with NaIO<sub>4</sub>/SiO<sub>2</sub> to afford  $\beta,\gamma$ -unsaturated aldehyde **89** as the only alkene isomer.<sup>76</sup> Remarkably, in the absence of silica gel the undesired corresponding  $\alpha,\beta$ -unsaturated aldehyde was solely obtained. Alkyne addition to aldehyde **89** furnished propargylic alcohol ( $\pm$ )-**93** and finally 1,1-dibromoalkene ( $\pm$ )-**88** after desilylation with TBAF.



*Reagents and conditions:* a) OsO<sub>4</sub> (1 mol%), NMO (1.0 eq), acetone/H<sub>2</sub>O (v/v = 4:1), 23 °C, 13 h; 49% b) NaIO<sub>4</sub> (1.3 eq) on SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 20 min; c) CBr<sub>4</sub> (2.0 eq), PPh<sub>3</sub> (4.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 15 min, 49% (2 steps); d) OsO<sub>4</sub> (2.0 mol%), NMO (1.5 eq), 2,6-lutidine (4.0 eq), acetone/H<sub>2</sub>O (v/v = 4:1), 23 °C, 4.5 h, 77%; e) NaIO<sub>4</sub> (1.5 eq) on SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 1.5 h; f) trimethylsilylacetylene (1.2 eq), *n*BuLi (1.2 eq), THF, -78 °C to 23 °C, 2 h, 43% (2 steps); g) TBAF (1.1 eq), THF, 0 °C, 20 min, 86%.

**Scheme 20:** Synthesis of cyclization precursor ( $\pm$ )-**88**.

<sup>75</sup> T. J. Donohoe, L. Mitchell, M. J. Waring, M. Helliwell, A. Bell, N. J. Newcombe, *Org. Biomol. Chem.* **2003**, *1*, 2173-2186.

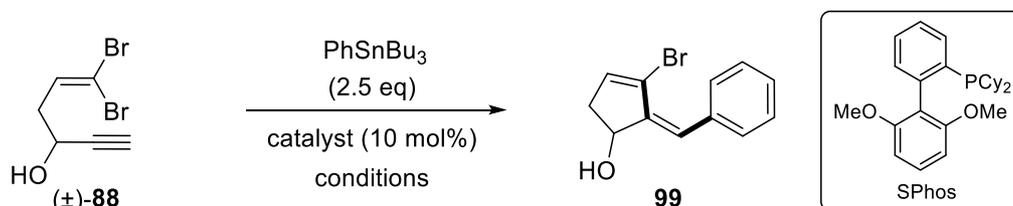
<sup>76</sup> The use of silica gel immobilized NaIO<sub>4</sub> proved superior to conventional diol cleavage conducted in aqueous media, in terms of reaction time, product purity and ease of product isolation. For a procedure for the immobilization of NaIO<sub>4</sub> on SiO<sub>2</sub>, see: Y.-L. Zhong, T. K. M. Shing, *J. Org. Chem.* **1997**, *62*, 2622-2624.

<sup>77</sup> a) N. B. Desai, N. McKelvie, F. Ramirez, *J. Am. Chem. Soc.* **1962**, *84*, 1745-1747; b) E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769-3772.



the desired vinyl bromide **99** was not observed (entries 1-3).<sup>79</sup> Similarly, neither a cyclization nor any cross coupling product was detected upon employment of *O*-benzylated ( $\pm$ )-**88** (entry 4).

**Table 2:** Attempted intramolecular carbopalladation/Stille coupling of ( $\pm$ )-**88**.



Entry	Catalyst	Ligand (eq)	Solvent (M)	T [°C]	Yield
1	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.2)	THF (0.02)	65	0% <sup>[a]</sup>
2	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.2)	PhMe (0.02)	65	0% <sup>[a]</sup>
3	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.4)	PhMe (0.1)	65	0% <sup>[a]</sup>
4 <sup>[b]</sup>	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.2)	PhMe (0.1)	60	0% <sup>[a]</sup>
5 <sup>[c]</sup>	Pd(OAc) <sub>2</sub> <sup>[d]</sup>	PPh <sub>3</sub> (0.4)	PhMe (0.1)	60	0% <sup>[a]</sup>
6	Pd(dba) <sub>2</sub>	SPhos (0.2)	PhMe (0.1)	60	0% <sup>[a]</sup>
7	Pd(OAc) <sub>2</sub>	dppe (0.2)	PhMe (0.1)	60	0% <sup>[e]</sup>
8	Pd(OAc) <sub>2</sub>	dppp (0.2)	PhMe (0.1)	60	0% <sup>[e]</sup>
9	Pd(OAc) <sub>2</sub>	dppf (0.2)	PhMe (0.1)	60	0% <sup>[e]</sup>

<sup>[a]</sup> Decomposition of ( $\pm$ )-**88**; <sup>[b]</sup> Corresponding propargylic benzyl ether was used instead of ( $\pm$ )-**88**;  
<sup>[c]</sup> Addition of CuI (0.2 eq) and CsF (2.0 eq); <sup>[d]</sup> 20 mol%; <sup>[e]</sup> No conversion.

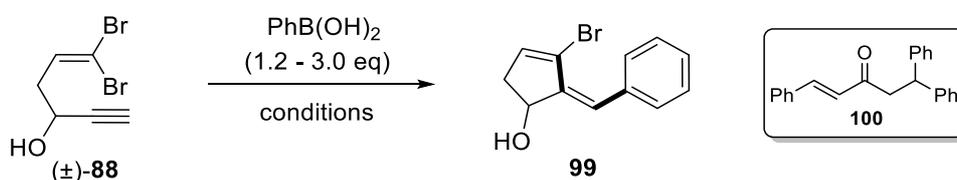
Moreover, **99** remained inaccessible by activation of the arylstannane through transmetalation to copper(I) (entry 5),<sup>80</sup> or when SPhos/Pd(dba)<sub>2</sub> was employed as the catalytic system (entry 6).<sup>81</sup> In contrast to the previous experiments, no conversion was achieved by use of bidentate ligands (entries 7-9).

Reflecting on these unpromising studies involving Stille cross coupling, we next resorted to the originally intended carbopalladation/Suzuki coupling sequence, using phenylboronic acid as the coupling partner (**Table 3**).

<sup>79</sup> Degradation of the starting material to unidentifiable products was observed.

<sup>80</sup> S. P. H. Mee, V. Lee, J. E. Baldwin, *Angew. Chem. Int. Ed.* **2004**, *43*, 1132-1136.

<sup>81</sup> C. S. Bryan, M. Lautens, *Org. Lett.* **2010**, *12*, 2754-2757.

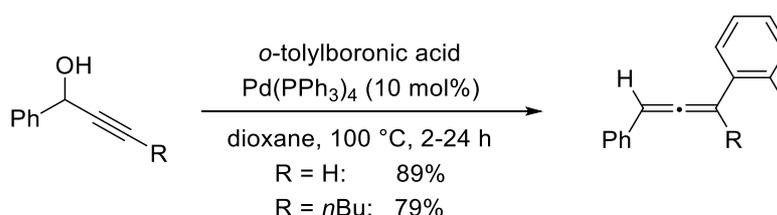
**Table 3:** Attempted intramolecular carbopalladation/Suzuki coupling of ( $\pm$ )-**88**.

Entry	Catalyst (eq)	Ligand (eq)	Solvent <sup>[a]</sup>	Additive (eq)	T [°C]	Yield
1	Pd(OAc) <sub>2</sub> (0.2)	PPh <sub>3</sub> (0.6)	PhMe	K <sub>2</sub> CO <sub>3</sub> (3.0)	60	0% <sup>[b]</sup>
2	Pd(dba) <sub>2</sub> (0.1)	SPhos (0.2)	PhMe	K <sub>3</sub> PO <sub>4</sub> (3.0)	60	0% <sup>[b,c]</sup>
3	Pd(dba) <sub>2</sub> (0.1)	-	EtOH	Cs <sub>2</sub> CO <sub>3</sub> (1.2)	25	0% <sup>[b,c]</sup>
4	Pd(OAc) <sub>2</sub> (0.2)	PPh <sub>3</sub> (0.8)	PhMe	Cs <sub>2</sub> CO <sub>3</sub> (3.0)	25	0% <sup>[b]</sup>
5	Pd(dba) <sub>2</sub> (0.1)	<i>t</i> Bu <sub>3</sub> P•HBF <sub>4</sub> (0.2)	Dioxane	Cs <sub>2</sub> CO <sub>3</sub> (4.0)	90	0% <sup>[b,c]</sup>
6	Pd(OAc) <sub>2</sub> (1.0)	PPh <sub>3</sub> (3.0)	PhMe <sup>[d]</sup>	Cs <sub>2</sub> CO <sub>3</sub> (4.0)	60	0% <sup>[b]</sup>

<sup>[a]</sup> 0.1 M; <sup>[b]</sup> Decomposition of ( $\pm$ )-**88**; <sup>[c]</sup> Formation of **100**; <sup>[d]</sup> 0.06 M.

However, none of the evaluated catalytic systems enabled the envisaged carbopalladation/cross coupling sequence. Similar to previous results, decomposition of ( $\pm$ )-**88** was observed in each case.

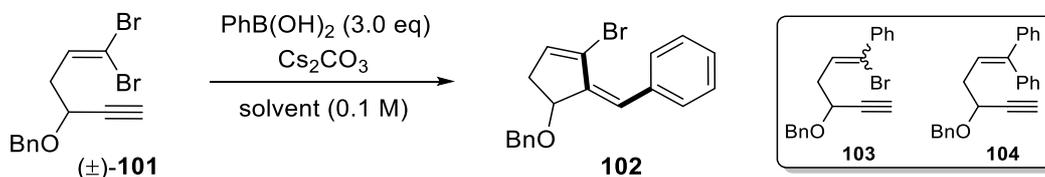
A related report of palladium catalyzed coupling of propargylic alcohols with arylboronic acids to produce aryl allenes under similar conditions (**Scheme 22**),<sup>82</sup> caused us to move away from unprotected propargylic alcohol ( $\pm$ )-**88**, and instead focused on protected derivatives.

**Scheme 22:** Reported synthesis of aryl allenes from propargylic alcohols according to Yoshida and Ihara.

Hence, we concentrated on the cascade reaction of benzyl propargyl ether ( $\pm$ )-**101** with phenylboronic acid (**Table 4**). However, the use of Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> did not provide the desired cyclic bromide **102** (entry 1). We next examined the influence of protic solvents on the reaction outcome (entries 2, 3 and 5-7), as EtOH has been employed by Oh *et al.* as the solvent of choice for cascade cyclization/cross coupling reactions of 2-bromo-1,6-enynes (**Scheme 23**).<sup>83</sup>

<sup>82</sup> M. Yoshida, T. Gotou, M. Ihara, *Tetrahedron Lett.* **2004**, *45*, 5573-5575.

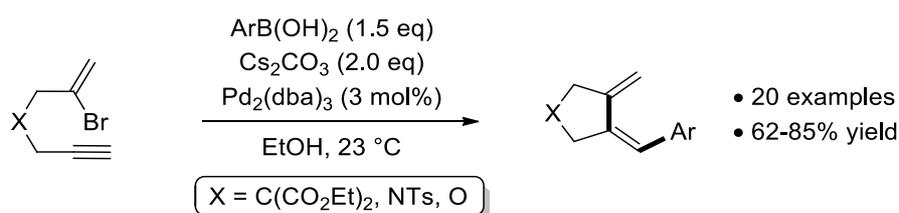
<sup>83</sup> C. H. Oh, Y. M. Lim, *Tetrahedron Lett.* **2003**, *44*, 267-270.

**Table 4:** Attempted cascade cyclization/Suzuki coupling of benzyl propargyl ether ( $\pm$ )-**101**.

Entry	Catalyst (eq)	Ligand (eq)	Solvent	Eq base	T [°C]	Yield
1	Pd(OAc) <sub>2</sub> (0.1)	PPh <sub>3</sub> (0.2)	PhMe	0	60	0%
2	Pd(dba) <sub>2</sub> (0.1)	-	EtOH	2.0	23	0%
3	Pd(dba) <sub>2</sub> (0.1)	<i>t</i> Bu <sub>3</sub> P•HBF <sub>4</sub> (0.2)	EtOH	2.2	23	0%
4	Pd(dba) <sub>2</sub> (0.1)	<i>t</i> Bu <sub>3</sub> P•HBF <sub>4</sub> (0.2)	Dioxane	4.0	70	0% <sup>[a]</sup>
5	Pd(OAc) <sub>2</sub> (0.1)	<i>t</i> Bu <sub>3</sub> P•HBF <sub>4</sub> (0.4)	EtOH	2.4	23	0%
6	Pd(OAc) <sub>2</sub> (0.2)	PPh <sub>3</sub> (0.8)	EtOH	2.0	23	0% <sup>[b]</sup>

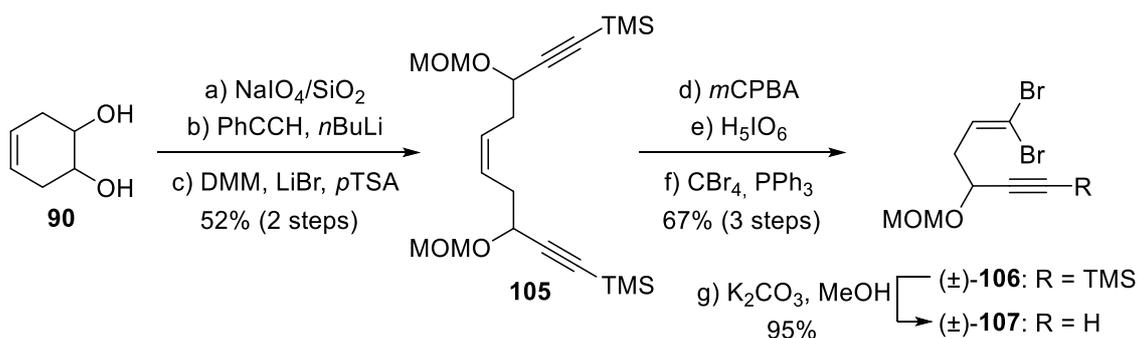
<sup>[a]</sup> Conversion of dba to **100** was observed; <sup>[b]</sup> Trace amounts of **103** and **104** were detected.

However, neither Oh's standard cyclization conditions using Pd(dba)<sub>2</sub>/Cs<sub>2</sub>CO<sub>3</sub> at ambient temperature (entry 2), nor the use of electron-rich tri-*tert*butyl phosphine resulted in formation of **102** (entries 3-5) and substrate degradation was observed in all cases. In contrast, employment of Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> afforded *mono*- and *double*-Suzuki coupling products **103** and **104** (entry 6). However, only trace amounts were detected. Thus, no information regarding the selectivity of oxidative addition into the carbon-bromide bond could be obtained.

**Scheme 23:** Cascade cyclization–coupling reaction of 2-bromo-1,6-enynes according to Oh *et al.*

It became increasingly apparent that the substitution pattern of the dibromoene two-atom linker must be judiciously chosen to enable the desired cascade cyclization/cross coupling process. Therefore, a MOM protected congener of ( $\pm$ )-**101** was elected to be investigated next, and its synthesis is presented in **Scheme 24**. Oxidative cleavage of diol **90**, followed by addition of lithium trimethylsilylacetylide and MOM protection of the resulting propargylic alcohol under acidic

conditions afforded *bis*-MOM ether **105**.<sup>84</sup> Subsequent Prilezhaev oxidation led to quantitative formation of an intermediate epoxide,<sup>85</sup> which was subsequently cleaved with periodic acid, thus breaking the C<sub>10</sub> backbone into two identical C<sub>5</sub> aldehydes. Conversion into 1,1-dibromoalkene (±)-**106** using CBr<sub>4</sub>/PPh<sub>3</sub>, followed by desilylation with potassium methanolate provided MOM protected dibromoenynne (±)-**107**.



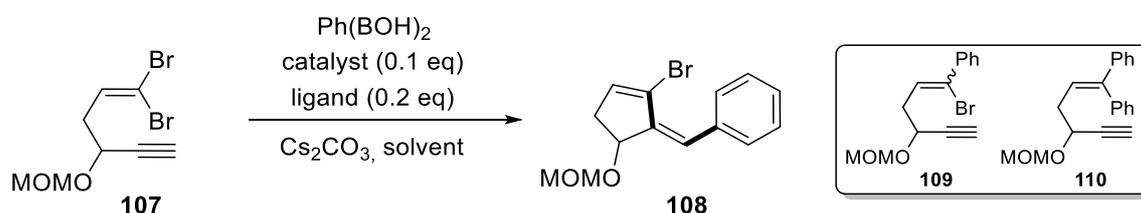
*Reagents and conditions:* a) NaIO<sub>4</sub> on SiO<sub>2</sub> (1.5 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 30 min, b) trimethylsilylacetylene (2.4 eq), *n*BuLi (2.4 eq), THF, -78 °C to 23 °C, 1.5 h; c) LiBr (0.8 eq), *p*TSA (0.2 eq), DMM, 23 °C, 36 h; d) *m*CPBA (2.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 12 h; e) H<sub>5</sub>IO<sub>6</sub> (3.0 eq), CPME, 23 °C, 7 h; f) CBr<sub>4</sub> (2.0 eq), PPh<sub>3</sub> (4.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 15 min; g) K<sub>2</sub>CO<sub>3</sub> (0.1 eq), MeOH, 23 °C, 1.5 h.

**Scheme 24:** Synthesis of MOM protected cyclization precursor (±)-**107**.

Our ensuing studies on the cascade cyclization/Suzuki coupling of (±)-**107** are summarized in **Table 5**. None of the screened reaction conditions led to formation of cyclic bromoalkene **108** or to the targeted tricyclic indene derivative by an ensuing direct arylation. Instead, *mono*-Suzuki coupling product **109** was isolated in 31% yield (entry 2). However, its double bond geometry could not be unambiguously assigned due to insufficient substance quantities.

<sup>84</sup> J.-L. Gras, Y.-Y. K. W. Chang, A. Guerin, *Synthesis* **1985**, 1985, 74-75.

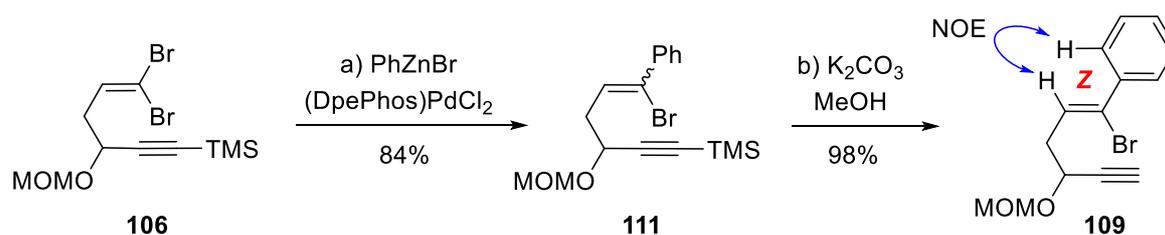
<sup>85</sup> N. Prileschajew, *Ber. Dtsch. Chem. Ges* **1909**, 42, 4811-4815.

**Table 5:** Attempted cascade cyclization/Suzuki coupling of MOM ether ( $\pm$ )-**107**.

Entry	Catalyst	Ligand	Solvent (M)	T [°C]	Result
1 <sup>[a]</sup>	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> <sup>[b]</sup>	EtOH (0.1)	25	Traces of <b>109</b>
2 <sup>[a]</sup>	Pd(dba) <sub>2</sub>	PPh <sub>3</sub>	EtOH (0.06)	60	31% <b>109</b> , 5% <b>110</b>
3 <sup>[b]</sup>	Pd(dba) <sub>2</sub>	PPh <sub>3</sub>	Dioxane (0.05)	25	Traces of <b>109</b>
4 <sup>[c]</sup>	Pd(dba) <sub>2</sub>	TFP	Dioxane/H <sub>2</sub> O (0.1)	60	Decomposition
5 <sup>[b]</sup>	Pd(dba) <sub>2</sub>	PPh <sub>3</sub>	DMF (0.1)	25	Poor conversion
6 <sup>[c]</sup>	Pd(dba) <sub>2</sub>	<i>t</i> Bu <sub>3</sub> P•HBF <sub>4</sub>	Dioxane (0.1)	60	Complex mixture
7 <sup>[a]</sup>	Pd(cin)(cp)	PPh <sub>3</sub>	EtOH (0.06)	60	Complex mixture

<sup>[a]</sup> 1.5 eq PhB(OH)<sub>2</sub>, 2.0 eq Cs<sub>2</sub>CO<sub>3</sub>; <sup>[b]</sup> 0.4 eq PPh<sub>3</sub>; <sup>[c]</sup> 1.2 eq PhB(OH)<sub>2</sub>, 4.0 eq Cs<sub>2</sub>CO<sub>3</sub>; <sup>[d]</sup> 1.0 eq PhB(OH)<sub>2</sub>, 2.0 eq Cs<sub>2</sub>CO<sub>3</sub>.

Consequently we subjected TMS protected dibromoenyne ( $\pm$ )-**106** to a Negishi cross coupling,<sup>86</sup> providing bromoalkene **111** of unknown double bond configuration in 84% yield (**Scheme 25**). Upon desilylation (K<sub>2</sub>CO<sub>3</sub>/MeOH), spectroscopically identical material to **109** was obtained in sufficiently large quantities for subsequent 1D NOE studies, revealing the depicted (*Z*)-configuration of bromoalkene **109**.



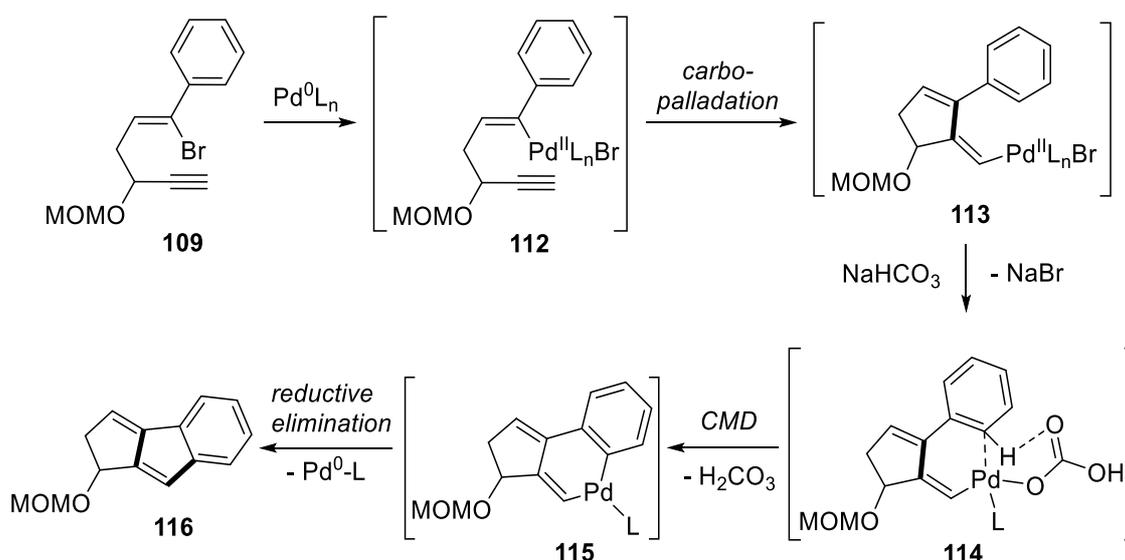
Reagents and conditions: a) PhLi (1.2 eq), ZnBr<sub>2</sub> (1.2 eq), (DpePhos)PdCl<sub>2</sub> (5 mol%) THF, 23 °C, 2 h; b) K<sub>2</sub>CO<sub>3</sub> (0.2 eq), MeOH, 23 °C, 1.5 h.

**Scheme 25:** Determination of the double bond configuration of **109**.

<sup>86</sup> J.-c. Shi, E.-i. Negishi, *J. Organomet. Chem.* **2003**, 687, 518-524.

In contrast to the dibromoenyne systems investigated by Nuss and Torii, oxidative addition of Pd<sup>0</sup> into **106** was selective for the (*E*)-carbon bromide bond, preventing the intended cascade cyclization/cross coupling sequence.

Based on this knowledge, we revised our synthetic strategy towards the tricyclic system of fijiolide A to take advantage of the observed high *trans*-selectivity for cross coupling of ( $\pm$ )-**106**. Thus, we postulated that (*Z*)-configured bromide **109** would – after oxidative addition to produce **112** – undergo intramolecular carbopalladation to form the palladium(II) species **113** (Scheme 26). This would set up the stage for a subsequent concerted metalation/deprotonation (CMD) step *via* intermediate **114** in the presence of a carbonate base, such as sodium bicarbonate.<sup>66c</sup> Reductive elimination of palladacycle intermediate **115** would close the 5-membered indene ring, and release tricyclic species **116**, as well as regenerate the palladium catalyst.

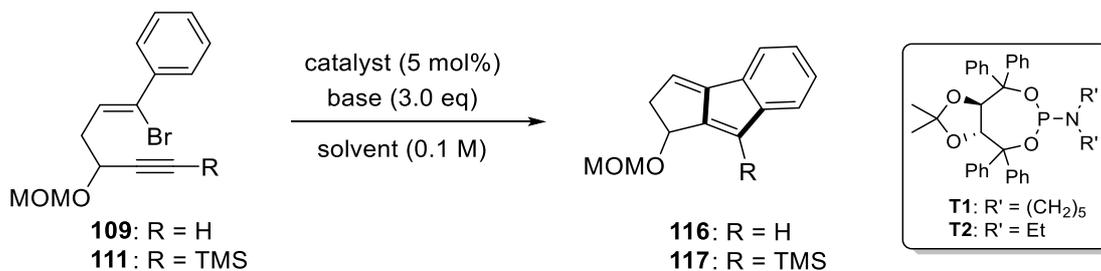


**Scheme 26:** Proposed mechanism of the envisaged cascade carbopalladation/direct arylation process.

In order to explore the proposed cascade cyclization/arylation reaction, bromide **109** and TMS protected **111** were subjected to various palladium based catalytic systems in polar aprotic solvents (Table 6).<sup>66b,c</sup> However, all evaluated conditions led to either decomposition of the employed bromoenyne starting material, complex product mixtures or poor conversions. Notably, the desired reactivity also remained elusive by use of taddol-based phosphoramidite ligands **T1** and **T2** (entries 6 and 9-11), which had previously been demonstrated to induce efficient direct arylation of enol triflates to afford indane motifs.<sup>66c</sup> Moreover, we could not enable the cascade cyclization to **117**

by protection of the terminal alkyne or by altering the reaction temperature (*cf.* entries 1-7 and 8-12).

**Table 6:** Attempted carbopalladation/direct arylation reactions of bromoalkenes **109** and **111**.



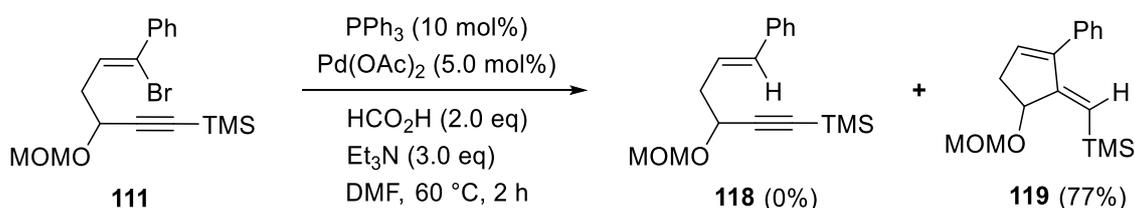
Entry	Catalyst	Ligand (eq)	Solvent	Base	T [°C]	Result
<b>R = H</b>						
1 <sup>[a,b]</sup>	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.15)	DMA	K <sub>2</sub> CO <sub>3</sub>	50	Decomposition
2 <sup>[a,b]</sup>	Pd(OAc) <sub>2</sub>	Cy <sub>3</sub> P•HBF <sub>4</sub> <sup>[c]</sup>	DMA	K <sub>2</sub> CO <sub>3</sub>	50	Decomposition
3	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.15)	DMF	K <sub>2</sub> CO <sub>3</sub>	60	Decomposition
4	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.15)	DMF	NaHCO <sub>3</sub>	60	Complex mixture
5	PdCl <sub>2</sub>	PPh <sub>3</sub> (0.2)	DMF	NaHCO <sub>3</sub>	60	Mainly decomp. <sup>[d]</sup>
6	Pd(cin)(cp)	<b>T1</b> (0.15)	DMF	NaHCO <sub>3</sub>	60	Partial decomp. <sup>[e]</sup>
7	PdCl <sub>2</sub> (DpePhos)	-	DMF	Et <sub>3</sub> N	60	Mainly decomp. <sup>[f]</sup>
<b>R = TMS</b>						
8	Pd(OAc) <sub>2</sub>	PPh <sub>3</sub> (0.15)	DMA	K <sub>2</sub> CO <sub>3</sub>	25	Decomposition
9	Pd(OAc) <sub>2</sub>	<b>T2</b> (0.15)	DMA	K <sub>2</sub> CO <sub>3</sub>	50	Complex mixture
10	Pd(OAc) <sub>2</sub>	<b>T1</b> (0.15)	DMF	K <sub>2</sub> CO <sub>3</sub>	105	Decomposition
11	CpPd(Cinnamyl)	<b>T1</b> (0.15)	DMF	K <sub>2</sub> CO <sub>3</sub>	105	Decomposition
12	CpPd(Cinnamyl)	PPh <sub>3</sub> (0.1)	DMF	Et <sub>3</sub> N	60	No conversion

<sup>[a]</sup> Identical results were obtained for vinyl bromide **111**; <sup>[b]</sup> PivOH (0.2 eq) was added; <sup>[c]</sup> 0.15 eq;

<sup>[d]</sup> 17% **109** recovered; <sup>[e]</sup> 58% **109** recovered; <sup>[f]</sup> 19% **109** recovered.

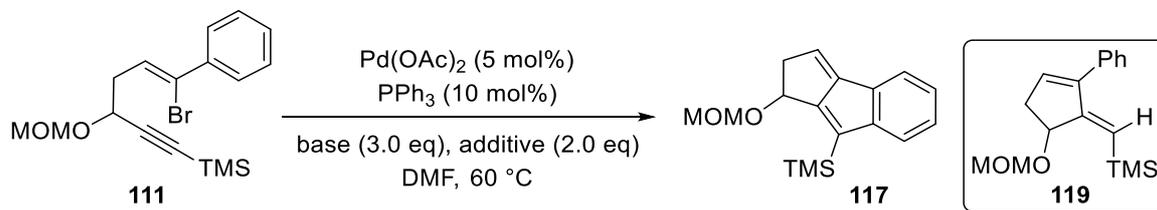
As a consequence of these results, we became increasingly concerned about the previously assigned double bond configuration of **109/111**, and aimed to obtain further proof. We proposed that a palladium catalyzed reduction of bromoalkene **111** to the corresponding disubstituted alkene would provide unequivocal evidence, as the double bond configuration could then be easily determined on the bases of the measured <sup>1</sup>H coupling constant between the olefinic protons.

Remarkably, by performing this transformation in the presence of formic acid as the reductant, and triethylamine as the base, a high yielding cyclization of **111** to reduced monocycle **119** was observed, without any traces of the expected alkene **118** (Scheme 27). Hereby, intramolecular carbopalladation was unintendedly observed for the first time and the (*Z*)-configuration of the starting vinyl bromide could unequivocally be confirmed. However, species **119** does not allow straightforward access to the desired tricyclic fragment **117** due to a lack of suitable functionalization.



Scheme 27: Unintended reductive cyclization of vinyl bromide **111**.

Encouraged by this result, we tried to exploit the newly discovered reactivity of **111** by omission of the reductant in order to allow further cyclization to carbocyclic species **117** (Table 7). However, no reaction occurred in the absence of formic acid (entry 2), and 16% of **119** was formed in the presence of sub-stoichiometric amounts of HCO<sub>2</sub>H (0.2 eq) (entry 3). Moreover, we observed almost no reactivity when alternative carboxylic acids were employed (entries 4-5). The use of triethoxysilane also resulted in reductive cyclization of **111** to afford 64% **119**, but the targeted tricycle **116** was not detected (entry 6). Interestingly, replacement of Et<sub>3</sub>N by K<sub>2</sub>CO<sub>3</sub> repressed the formation of reduced monocycle **119** to a great extent, however, formation of **117** was still not observed (entry 8). Finally, use of PivOH/K<sub>2</sub>CO<sub>3</sub> led to decomposition of the starting material (entry 8).

**Table 7:** Cascade cyclization attempts on bromoalkene **111**.

Entry	Base	Additive (eq)	Result
1	Et <sub>3</sub> N	HCO <sub>2</sub> H	77% <b>119</b>
2	Et <sub>3</sub> N	-	no conversion
3	Et <sub>3</sub> N	HCO <sub>2</sub> H <sup>[a]</sup>	16% <b>119</b>
4	Et <sub>3</sub> N	AcOH	no conversion
5	Et <sub>3</sub> N	PivOH	poor conversion <sup>[b]</sup>
6	Et <sub>3</sub> N	(EtO) <sub>3</sub> SiH	64% <b>119</b>
7	K <sub>2</sub> CO <sub>3</sub>	HCO <sub>2</sub> H	17% <b>119</b>
8	K <sub>2</sub> CO <sub>3</sub>	PivOH	decomposition

<sup>[a]</sup> 0.2 eq; <sup>[b]</sup> 85% **111** recovered.

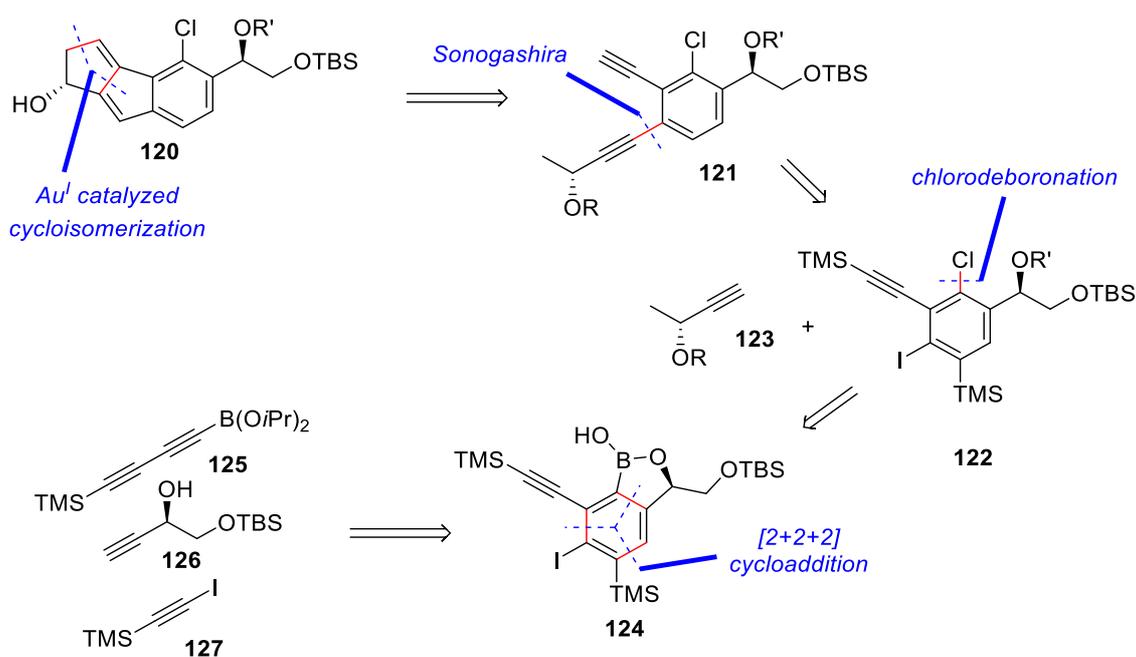
From the experiments summarized in **Table 7** it became clear that the presence of a reducing agent is essential for the observed *mono*-cyclization of precursor **111**. Omitting or replacing the reductant did not enable an intramolecular carbopalladation/direct arylation sequence.

As we were unsuccessful of cyclizing various 1,1-dibromoenynes and (*Z*)-bromoenynes to afford annulated indenenes, we revised our strategy towards fijiolide A, and studies in this direction are discussed in the following section.

### 4.3 Studies Involving Ru<sup>II</sup> Catalyzed [2+2+2] Cycloaddition / Au<sup>I</sup> Catalyzed *Bis*-Alkyne Isomerization

#### 4.3.1 Retrosynthetic Analysis

A revised strategy towards the cyclopenta[*a*]indene core of fijiolide A is presented in **Scheme 28**. Construction of carbocyclic fragment **120** is proposed to be accomplished using a gold(I) catalyzed cycloisomerization of *bis*-alkyne **121**,<sup>87</sup> which, in turn, will be accessed *via* Sonogashira coupling of aryl iodide **122** and protected propargyl alcohol **123**. A chlorodeboronation traces **122** back to heavily substituted boraphthalide species **124**. The synthesis of **124** is envisaged to be achieved in a single step from diynylboronate **125**, propargylic alcohol **126** and internal alkyne **127** *via* a temporary boron tether enabled intermolecular [2+2+2] cyclotrimerization.<sup>88</sup>



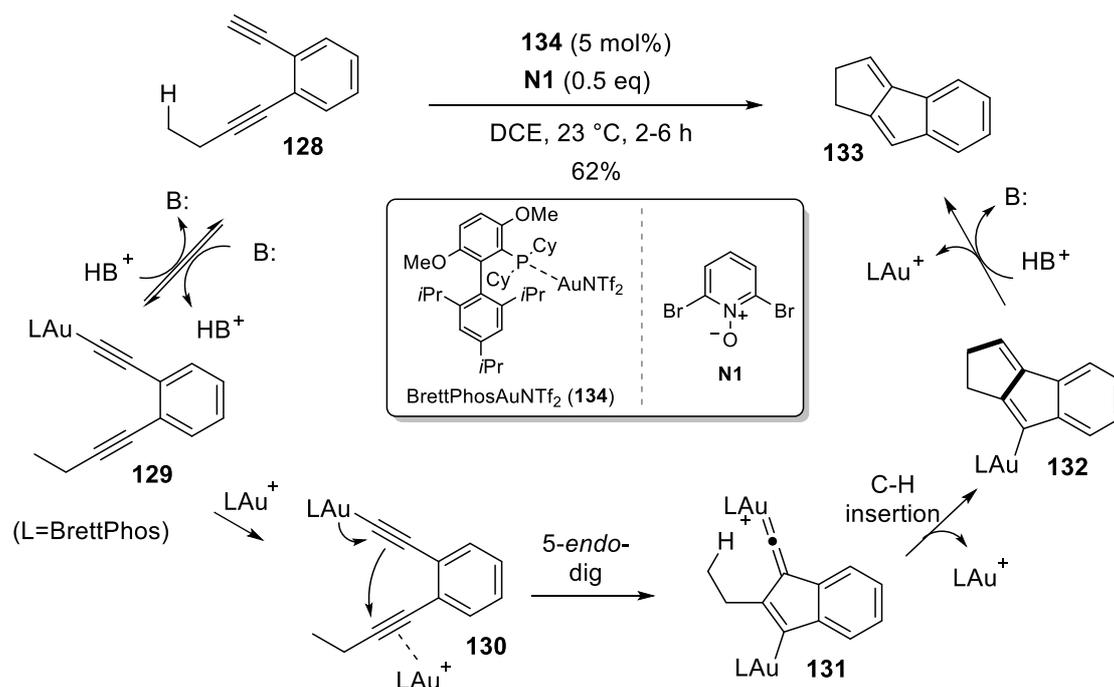
**Scheme 28:** Retrosynthetic analysis of tricyclic indene **120** involving a Au<sup>I</sup> catalyzed *bis*-alkyne cycloisomerization.

<sup>87</sup> L. Ye, Y. Wang, D. H. Aue, L. Zhang, *J. Am. Chem. Soc.* **2012**, *134*, 31-34.

<sup>88</sup> Y. Yamamoto, J.-i. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2004**, *126*, 3712-3713.

### 4.3.2 Results

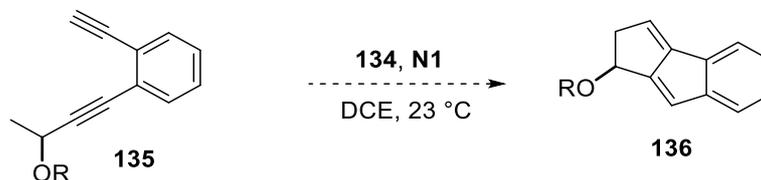
Our third generation strategy towards the fijiolide cyclopenta[*a*]indene core is based on a gold(I) catalyzed cycloisomerization process recently disclosed by Zhang *et al.* in 2012.<sup>87</sup> The authors report direct access to tricyclic indenenes from readily available 1,2-alkynylbenzenes *via* gold vinylidene species.<sup>33</sup> The proposed mechanism for this transformation, exemplified on Zhang's least substituted cyclization substrate, is provided in **Scheme 29**. Activation of the *bis*-alkyne **128** by BrettPhosAuNTf<sub>2</sub> (**134**) allows for deprotonation of the terminal alkyne by the employed pyridine *N*-oxide (**N1**) species to afford gold acetylide **129**. Another BrettPhosAuNTf<sub>2</sub> is believed to activate the second triple bond (**130**) and facilitate a 5-*endo*-dig cyclization to produce gold vinylidene intermediate **131**. This highly reactive species is proposed to undergo a C-H insertion leading to tricyclic species **132**, which releases the tricyclic indene species **133** upon protodeauration.



**Scheme 29:** Proposed mechanism for the gold(I) catalyzed *bis*-alkyne cycloisomerization.<sup>87</sup>

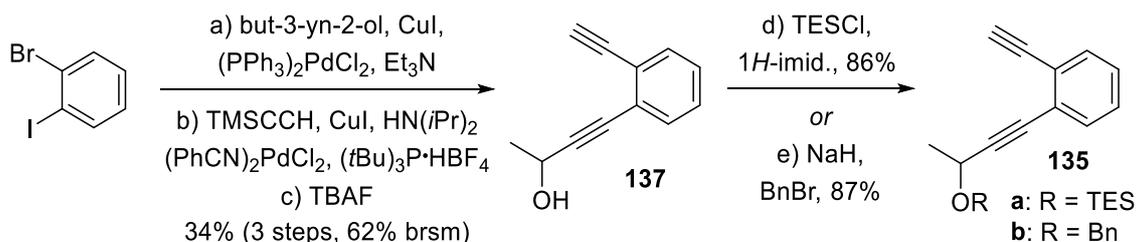
**133** completely represents the unsubstituted carbocyclic framework of the postulated synthetic intermediate **120**. To adopt this method for our synthetic target, a heteroatom-substitution of the propargylic position in **128** was required. This modification has not been reported by Zhang *et al.*

Thus, we first focused on synthesis of model substrate **135** in order to investigate the feasibility of this methodology to access **136**.



**Scheme 30:** Envisaged synthesis of model cyclopenta[*a*]indene **136**.

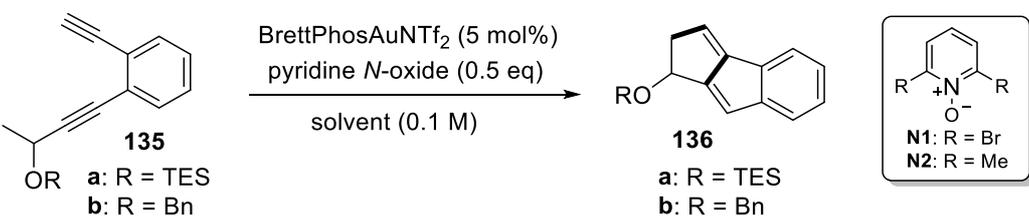
Synthesis of *bis*-alkynes **135a** (R = TES) and **135b** (R = Bn) was accomplished by successive Sonogashira coupling of 2-bromiodobenzene with methyl propargyl alcohol and trimethylsilylacetylene, followed by desilylation to afford *bis*-alkyne **137**, which was subsequently protected as its corresponding benzyl or TES ether (**Scheme 31**).



*Reagents and conditions:* a) but-3-yn-2-ol (1.2 eq), (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (1 mol%), CuI (2 mol%), Et<sub>3</sub>N, 50 °C, 54% (100% brsm); b) trimethylsilylacetylene (1.3 eq), (PhCN)<sub>2</sub>PdCl<sub>2</sub> (3 mol%), (tBu)<sub>3</sub>P•HBF<sub>4</sub> (6 mol%), CuI (3 mol%), HN(*i*Pr)<sub>2</sub> (1.3 eq), dioxane, 30 °C, 1.5 h; c) TBAF (1.2 eq), 0 °C, 20 min, 34% (2 steps); d) TESCl (4.0 eq), 1*H*-imidazole (4.0 eq), DMF, 23 °C, 13 h, 86%; e) NaH (1.5 eq), BnBr (1.3 eq), TBAI (0.3 eq), THF, 23 °C, 3 h, 87%.

**Scheme 31:** Syntheses of functionalized *bis*-alkynes **135a** and **135b**.

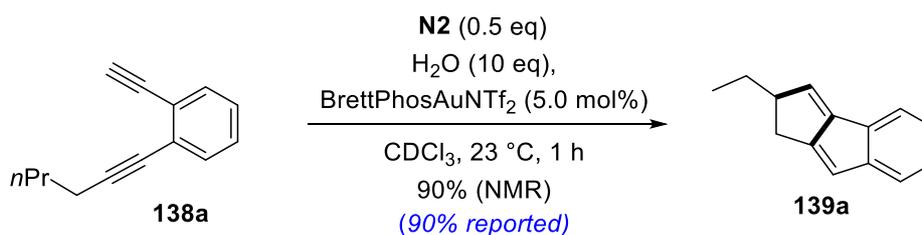
With *bis*-alkynes **135**, the BrettPhosAuNTf<sub>2</sub> catalyzed cycloisomerization was attempted under the reported conditions (**Table 8**). No formation of the targeted cyclopenta[*a*]indenes was observed (entries 1 and 7). Attempts to enhance conversion of TES ether **135a** by increasing the concentration or reaction temperature only led to desilylation (entries 2 and 3). Employment of an alternative *N*-oxide (**N2**) (entries 4 and 8), or omission of the base (entries 5-6) likewise did not provide the desired indene derivatives. Analogous experiments with the corresponding PMB propargylic ether resulted in similarly low conversions (10-32%), without any trace of the desired product (data not shown). In addition, a beneficial effect on the cycloisomerization reaction by addition of water, as reported by Zhang *et al.*, was neither observed (entry 9).

**Table 8:** Attempts at cycloisomerization of *bis*-alkynes **135a** and **135b**.


Entry	R	N-oxide	Solvent	T [°C]	T [h]	Yield / conversion [%] <sup>[a]</sup>
1	TES	<b>N1</b>	DCE	23	5	0 / 18
2	TES	<b>N1</b>	DCE <sup>[b]</sup>	23	5	48 ( <b>137</b> ) / 87
3	TES	<b>N1</b>	DCE	50	18	65 ( <b>137</b> ) / 100
4	TES	<b>N2</b>	DCE	23	5	0 / 19
5	TES	-	DCE	23	18	0 / 28
6	TES	-	DCE	50	19	0 / 29
7	Bn	<b>N1</b>	DCE	23	21	0 / 36
8	Bn	<b>N2</b>	DCE	23	7	0 / 28
9	Bn	<b>N2</b>	CDCl <sub>3</sub> <sup>[c]</sup>	23	21	0 / 43

<sup>[a]</sup> Determined by <sup>1</sup>H NMR using 1,3,5-TMB as internal standard; <sup>[b]</sup> 1.0 M in DCE; <sup>[c]</sup> 10 eq H<sub>2</sub>O were added.

Based on these results, we presumed that ether-substitution at the propargylic position may not be tolerated. To prove this assumption, and to verify the reproducibility of Zhang's method in our hands, *bis*-alkynes substrates **138a-c** were synthesized in analogy to **135**.<sup>89</sup> An excellent yield was attained for cyclopenta[*a*]indene **139a** (Scheme 32), thus proving the reproducibility of this methodology, and confirming the activity of the prepared catalyst **134**.<sup>90,91</sup>

**Scheme 32:** Verified reproducibility of the Au<sup>I</sup> catalyzed *bis*-alkyne isomerization process.

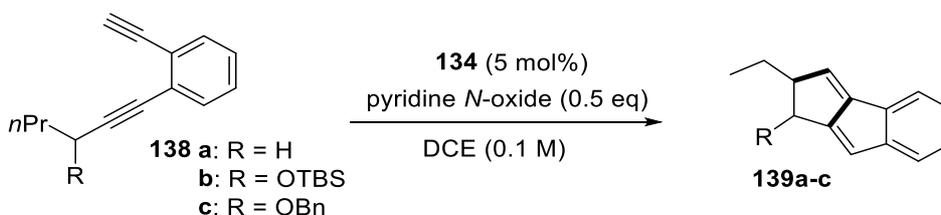
<sup>89</sup> For a synthesis of the employed propargyl alcohol, see: Jeong, E. J. Kang, L. T. Sung, S. K. Hong, E. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 14655-14662.

<sup>90</sup> a) B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552-13554; b) L. Ye, W. He, L. Zhang, *Angew. Chem. Int. Ed.* **2011**, *50*, 3236-3239.

<sup>91</sup> In contrast to the synthesis of **139a**, cycloisomerization of **128** could not be reproduced. Only low yields of 13% (62% reported) of **133** were obtained under various reaction conditions.

Active catalyst **134** was then employed in cycloisomerization attempts of *bis*-alkynes **138** (Table 9). As illustrated, the propargyl ether group completely shuts down the cyclization process (entry 1 and 2 vs. 3-5).

**Table 9:** Cycloisomerization studies on *bis*-alkynes **138a-c**.



Entry	R	<i>N</i> -oxide	T [°C]	T [h]	NMR Yield / conversion [%]
1	H	<b>N1</b>	23	4	58 <sup>[a]</sup> / 82
2	H	<b>N2</b>	23	6	85 / 88
3	OTBS	<b>N2</b>	23	4	0 / 18
4	OTBS	<b>N2</b>	50	18	0 / 33
5	OBn	<b>N2</b>	23	19	0 / 39

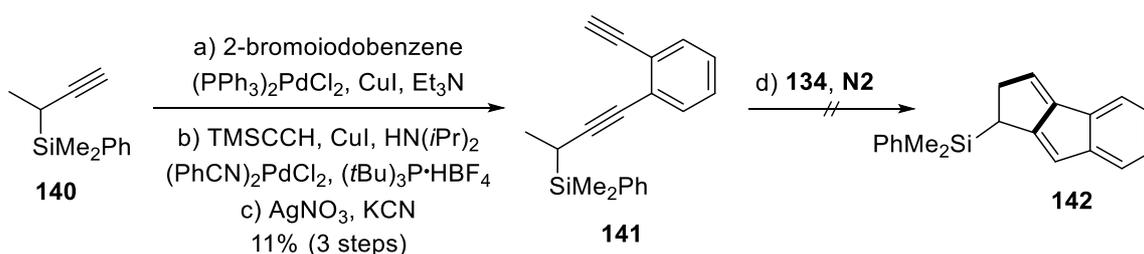
<sup>[a]</sup> Isolated yield.

As a consequence we shifted our attention to silyl-substituted cycloisomerization precursors, which we proposed to be an adequate forerunner for the desired hydroxycyclopenta[*a*]indenes by Fleming-Tamao oxidation.<sup>92</sup> Thus, propargyl silane **140** was synthesized from propionaldehyde.<sup>93</sup> Subsequent transformation into **141** was realized by a reaction sequence consisting of two Sonogashira couplings and TMS cleavage with AgNO<sub>3</sub>/KCN, according to the procedure of Rajagopalan and Zweifel (**Scheme 33**).<sup>94</sup> Unfortunately, **141** did not undergo the desired cycloisomerization reaction to provide **142**, but was slowly degraded under the reaction conditions.

<sup>92</sup> a) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694-1696; b) I. Fleming, R. Henning, H. Plaut, *J. Chem. Soc., Chem. Commun.* **1984**, 29-31.

<sup>93</sup> M. S. Betson, I. Fleming, *Org. Biomol. Chem.* **2003**, *1*, 4005-4016.

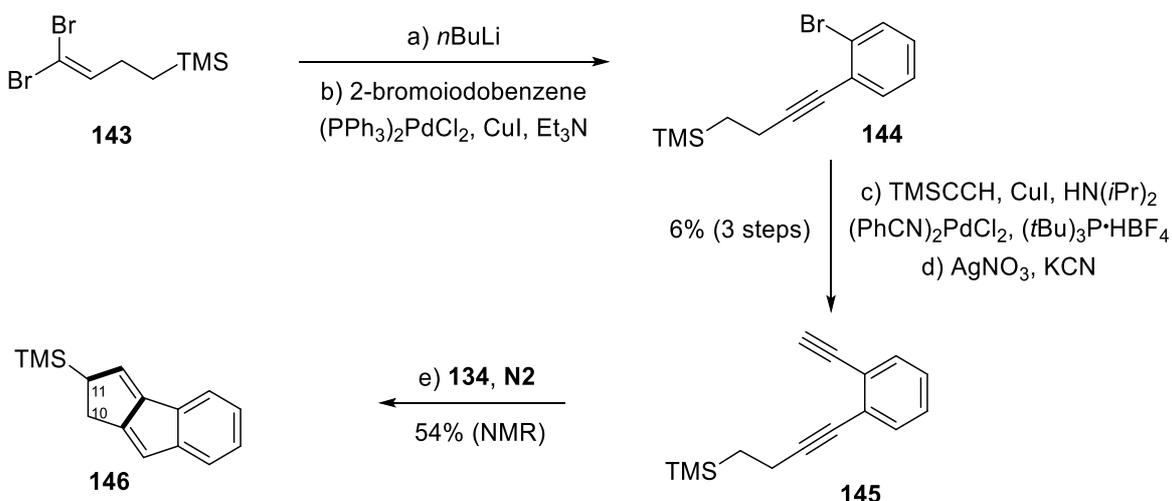
<sup>94</sup> S. Rajagopalan, G. Zweifel, *Synthesis* **1984**, *1984*, 111-112.



*Reagents and conditions:* a) 2-bromoiodobenzene (0.8 eq),  $(\text{PPh}_3)_2\text{PdCl}_2$  (3.0 mol%), CuI (6.0 mol%),  $\text{Et}_3\text{N}$  (5.0 eq), THF, 23 °C, 2 h; b) trimethylsilylacetylene (1.3 eq),  $(\text{PhCN})_2\text{PdCl}_2$  (5.0 mol%),  $(t\text{Bu})_3\text{P}\cdot\text{HBF}_4$  (10 mol%), CuI (5.0 mol%),  $\text{HN}(i\text{Pr})_2$  (1.4 eq), dioxane, 23 °C, 3 h; b)  $\text{AgNO}_3$  (1.8 eq),  $\text{EtOH}/\text{H}_2\text{O}$  (3:1), 0 °C, 1 h, then KCN (8.9 eq), 23 °C, 2 h, 11% (3 steps); d) **134** (5.0 mol%), **N2** (0.5 eq),  $\text{H}_2\text{O}$  (10 eq), DCE, 23 °C, 19 h, decomposition.

**Scheme 33:** Synthesis of silylated *bis*-alkyne **141** and attempted cycloisomerization.

An alternative cycloisomerization precursor would be TMS-substituted alkyne **145**, which was synthesized from dibromoalkene **143** in analogy to **141** (**Scheme 34**).<sup>95,96</sup> Despite the poor yield for its preparation (6% over 3 steps), **145** could be shown to cycloisomerize in the presence of BrettPhosAuNTf<sub>2</sub> to afford **146**. Thus, although silyl substitution was generally tolerated, it could not be used at the desired propargylic C-10 position.



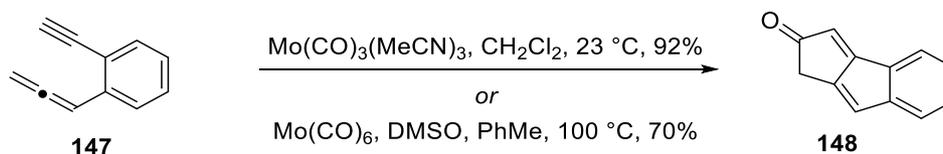
*Reagents and conditions:* a)  $n\text{BuLi}$  (2.1 eq), THF, -78 °C to 23 °C, 2.5 h; b)  $(\text{PPh}_3)_2\text{PdCl}_2$  (3.0 mol%), CuI (6.0 mol%),  $\text{Et}_3\text{N}$  (5.0 eq), THF, 23 °C, 2 h, 38%; c)  $(\text{PhCN})_2\text{PdCl}_2$  (6 mol%),  $(t\text{Bu})_3\text{P}\cdot\text{HBF}_4$  (12 mol%), CuI (6.0 mol%),  $\text{HN}(i\text{Pr})_2$  (1.4 eq), dioxane, 30 °C, 3 h; f)  $\text{AgNO}_3$  (1.8 eq),  $\text{EtOH}/\text{H}_2\text{O}$  (3:1), 0 °C, 1 h, then KCN (8.9 eq), 23 °C, 2 h; g) **134** (5 mol%), **N2** (0.5 eq),  $\text{H}_2\text{O}$  (10 eq),  $\text{CDCl}_3$ , 23 °C, 19 h.

**Scheme 34:** Synthesis of silylated *bis*-alkyne **145** and cycloisomerization to **146**.

<sup>95</sup> E. Piers, A. V. Gavai, *J. Org. Chem.* **1990**, *55*, 2374-2379.

<sup>96</sup> **145** and **146** were not fully characterized and tentatively assigned by means of <sup>1</sup>H NMR spectroscopy.

Although **146** could be used in principle to access fijiolide A, we considered an alternative strategy towards a C-11 functionalized key fragment, involving an allenic Pauson-Khand reaction, as described by Liu *et al.* (**Scheme 35**).<sup>97</sup> Results towards this end are discussed in the following section.



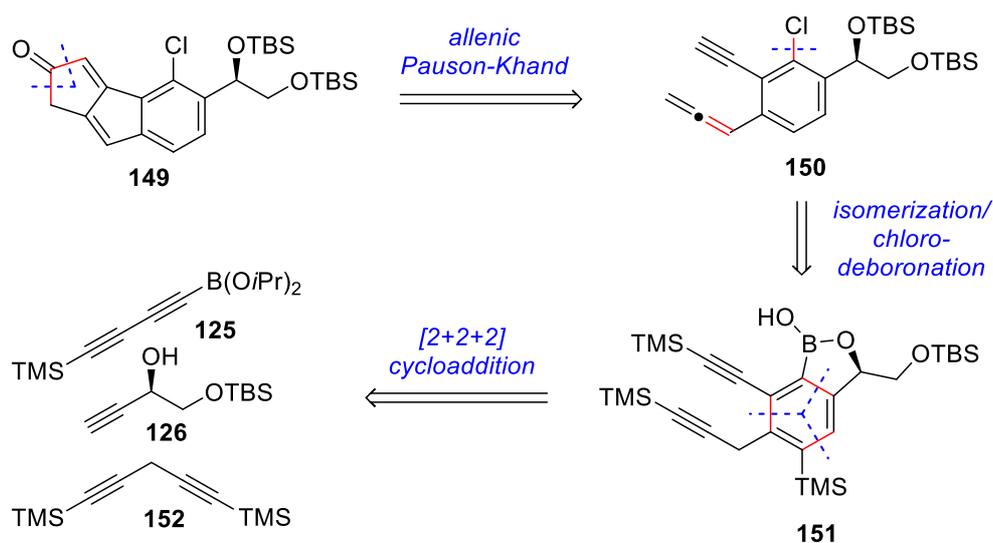
**Scheme 35:** Synthesis of cyclopenta[*a*]inden-2-one *via* an allenic Pauson-Khand reaction according to Liu *et al.*

<sup>97</sup> S. Datta, R.-S. Liu, *Tetrahedron Lett.* **2005**, 46, 7985-7988.

## 4.4 Studies Involving Ru<sup>II</sup> Catalyzed [2+2+2] Cycloaddition / Allenic Pauson-Khand Reaction

### 4.4.1 Retrosynthetic Analysis

Our fourth retrosynthetic analysis of the key fragment targets the slightly modified tricyclic indenylcyclopentenone **149** (Scheme 36). **149** was identified as the product of an allenic Pauson-Khand reaction of allene-yne **150**.<sup>98</sup> The allene handle in **150** was postulated to arise from a base-induced isomerization of a propargyl group,<sup>99</sup> while the chlorine atom was to be installed by a chlorodeboronation reaction of boraphthalide **151**. According to Scheme 36, access to the highly substituted arene core of **151** would be provided by an intermolecular Ru<sup>II</sup> catalyzed cyclotrimerization of alkynylboronate **125**, propargylic alcohol **126**, and symmetrical alkyne **152**.<sup>88</sup>



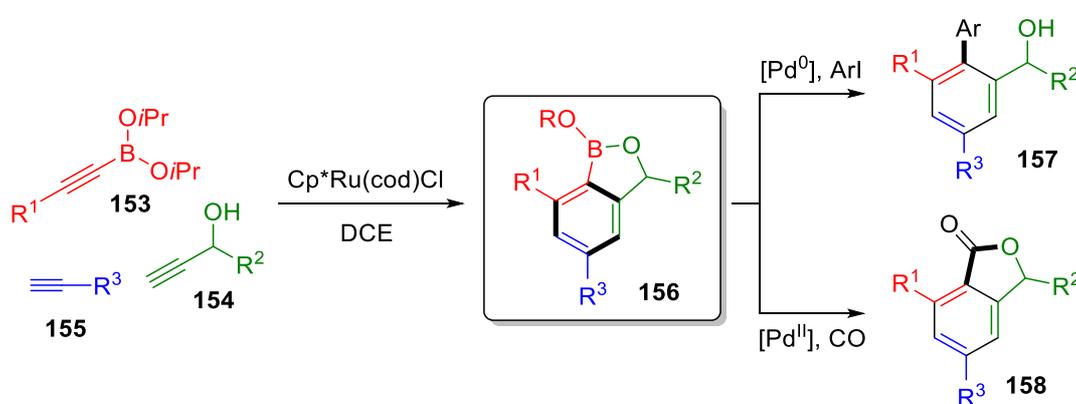
Scheme 36: Retrosynthetic analysis of the tricyclic **149** via an allenic Pauson-Khand approach.

<sup>98</sup> B. Alcaide, P. Almendros, *Eur. J. Org. Chem.* **2004**, 2004, 3377-3383.

<sup>99</sup> a) M. E. Jung, J. A. Hagenah, *J. Org. Chem.* **1987**, 52, 1889-1902; b) K.-S. Masters, M. Wallesch, S. Bräse, *J. Org. Chem.* **2011**, 76, 9060-9067; c) B. Blanco, A. Sedes, A. Peon, H. Lamb, A. R. Hawkins, L. Castedo, C. Gonzalez-Bello, *Org. Biomol. Chem.* **2012**, 10, 3662-3676.

#### 4.4.2 Results

As a synthesis of unsubstituted indenylcyclopentenone **148** has already been reported (*cf.* chapter 4.3.2, **Scheme 35**),<sup>97</sup> our revised synthetic strategy involving an allenic Pauson-Khand reaction would merely require a suitable substitution of the arene core. We proposed that an intermolecular [2+2+2] cycloaddition would be a rapid and elegant approach, in contrast to more conventional and step-extensive benzene functionalization strategies. In 2004 Yamamoto and coworkers reported a ruthenium catalyzed intermolecular [2+2+2] cycloaddition of three unsymmetrical alkynes to afford boron substituted arenes (**Scheme 37**).<sup>88</sup>



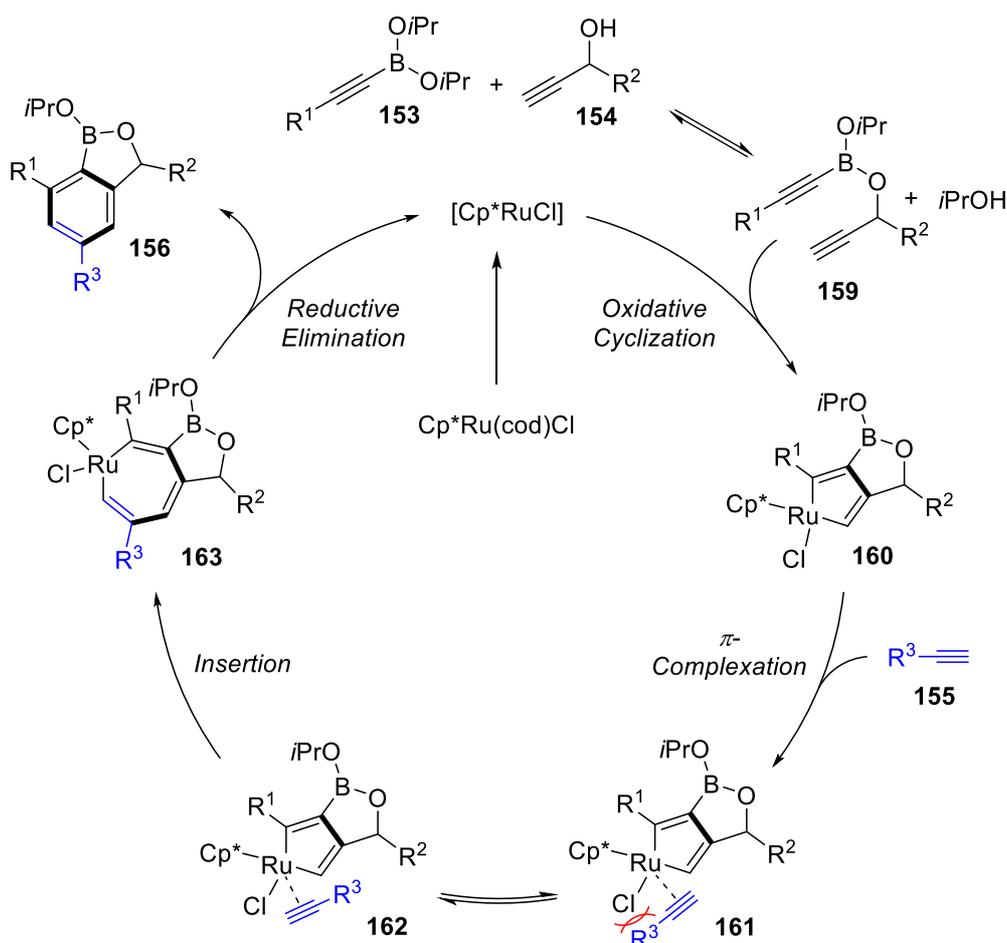
**Scheme 37:** Yamamoto's intermolecular [2+2+2] cycloaddition.

This powerful cyclotrimerization method allows a steep increase in molecular complexity, taking advantage of a temporary boron tether to control the regioselectivity of the [2+2+2] cycloaddition, and simultaneously repressing parasitic homotrimerization. The resulting boraphthalides of general structure **156**, were shown to serve as efficient coupling partners in Suzuki-Miyaura couplings with aryl halides (**157**),<sup>88,100</sup> or participate in Pd<sup>0</sup> catalyzed carbonylation reactions, leading to substituted phthalides **158**.<sup>101</sup> Mechanistically, Yamamoto *et al.* propose an initial and reversible B-O-C linkage between the alkynylboronate species **153** and the propargylic alcohol **154** (**Scheme 38**). The boron tethered 1,6-diyne **159**, is a competent substrate for oxidative cyclization with the Ru<sup>II</sup> catalyst, affording ruthenacycle **160**. Reversible coordination of the third alkyne part gives rise to  $\pi$ -complexes **161** and **162**. Insertion of the coordinated alkyne is then postulated to occur exclusively into the Ru-C bond *anti* to the boronate moiety as a consequence of the synergistic effect of both the steric influence of the substituent R<sup>1</sup> and the electronic directing effect of the

<sup>100</sup> Y. Yamamoto, J.-i. Ishii, H. Nishiyama, K. Itoh, *Tetrahedron* **2005**, *61*, 11501-11510.

<sup>101</sup> Y. Yamamoto, J.-i. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 9625-9631.

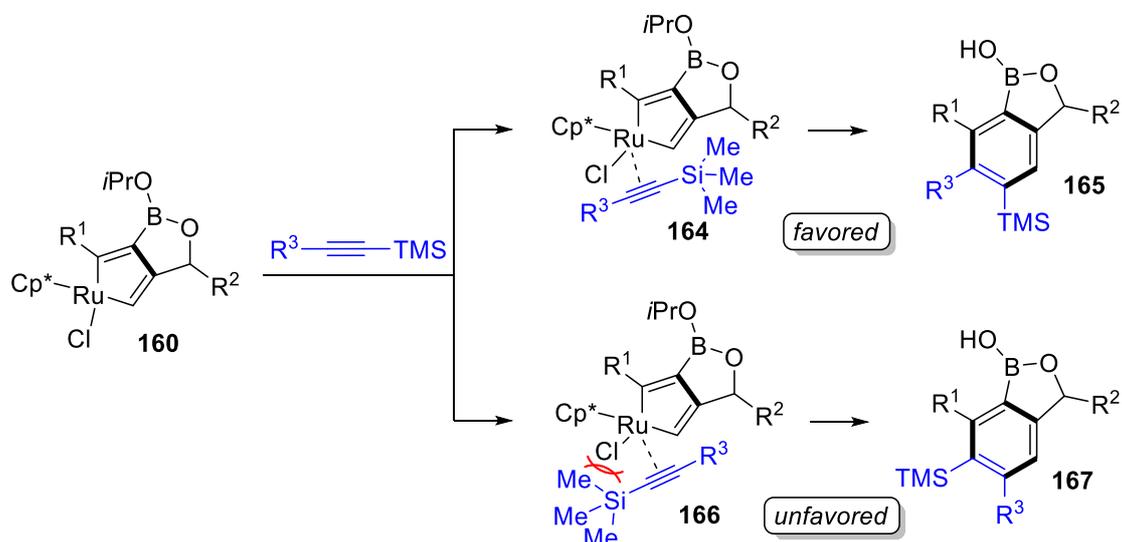
electron-deficient boron center.<sup>101</sup> Moreover, unfavorable steric repulsion between the substituent R<sup>3</sup> of the coordinated terminal alkyne and the chloro ligand of the metal center in **161** is believed to favor insertion *via* species **162**. Reductive elimination from **163** then releases the cyclotrimerization product **156** as the only observed regioisomer.



**Scheme 38:** Proposed mechanism of Yamamoto's boron tethered alkyne cyclotrimerization.

Based on Yamamoto's reports, we targeted boraphthalide **151** (**Scheme 36**), and aimed to utilize the aryl boronic acid moiety for a later incorporation of the chlorine atom *via* deborylative halogen. To realize this goal, selective formation of an arylboronic acid derivative with a *meta*-substituent would be required, as opposed to the *para*-regioselectivity observed by Yamamoto *et al.* We hypothesized that installation of a removable blocking substituent, such as a TMS group, on the third alkyne component may reverse the orientation of the alkyne with respect to the metal center, as depicted in  $\pi$ -complex **164** (**Scheme 39**). Thus, unfavored steric repulsion between the bulky TMS group and the ruthenium ligands in **166** would be avoided. Consequently, preferential alkyne

insertion *via*  $\pi$ -complex **164** would place the bulky TMS group *para* to the boronic acid, and R<sup>3</sup> at the *meta*-position, giving rise to penta-substituted benzene **165**.

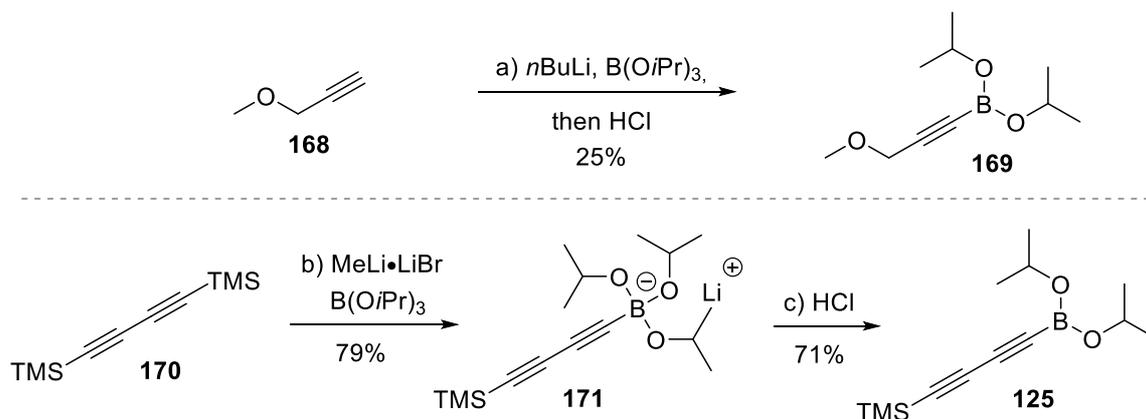


**Scheme 39:** Hypothesized preferential formation of parasilyl arylboronic acids.

In order to investigate this hypothesis, alkynylboronates **169** and **125** were synthesized from commercially available alkynes (**Scheme 40**). The preparation of known **169** from methyl propargyl ether **168** proceeded smoothly,<sup>102</sup> but in low yield. In contrast, the synthesis of required **125** following a one-pot literature procedure proved troublesome in terms of product isolation. According to Schwarz *et al.*,<sup>103</sup> **125** is obtained in up to 95% purity as the residue after distillative removal of all volatiles at 90 °C/12 mbar. In several attempts to reproduce this procedure, exposure of the crude product to heat led to severe polymerization and **125** could not be detected by <sup>1</sup>H NMR analysis. Consequently, the procedure was modified so that the intermediate lithium borate salt **171** was isolated as a solid and meticulously washed with dry Et<sub>2</sub>O to remove unreacted B(O*i*Pr)<sub>3</sub> and TMS acetylene dimer **170**. In contrast to diynylboronate **125**, **171** does not exhibit particular moisture sensitivity and does not require an inert atmosphere for handling and filtration. Nevertheless, **171** was kept at –30 °C under N<sub>2</sub> for long-term storage. Subsequent reaction of **171** with anhydrous HCl, followed by filtration under inert conditions and removal of all volatiles under high vacuum furnished diynylboronate **125** in high purity as an amber-colored liquid.

<sup>102</sup> R. Morita, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Org. Biomol. Chem.* **2005**, *3*, 1263-1268.

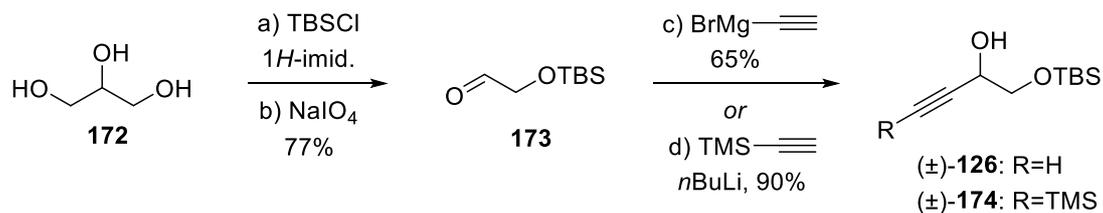
<sup>103</sup> A. M. McAnoy, S. Dua, D. Schröder, J. H. Bowie, H. Schwarz, *J. Phys. Chem. A* **2004**, *108*, 2426-2430.



Reagents and conditions: a) *n*BuLi (1.0 eq), Et<sub>2</sub>O, -78 °C, 1 h, then B(OiPr)<sub>3</sub> (1.0 eq), -78 °C, 4 h, then HCl (1.0 eq), -78 °C to 23 °C, 1 h, 25%; b) MeLi·LiBr (1.1 eq), Et<sub>2</sub>O, 23 °C, 14 h, then B(OiPr)<sub>3</sub> (1.5 eq), -78 °C to 23 °C, 3.5 h, 79%; c) HCl (1.3 eq), Et<sub>2</sub>O, -78 °C to 23 °C, 45 min, 71%.

Scheme 40: Synthesis of alkynylboronates **169** and **125**.

Known propargyl alcohols (±)-**126** and (±)-**174** were synthesized from glycerol **172** (Scheme 41),<sup>104,105</sup> and subsequently examined in the [2+2+2] cycloaddition reaction (Table 10).



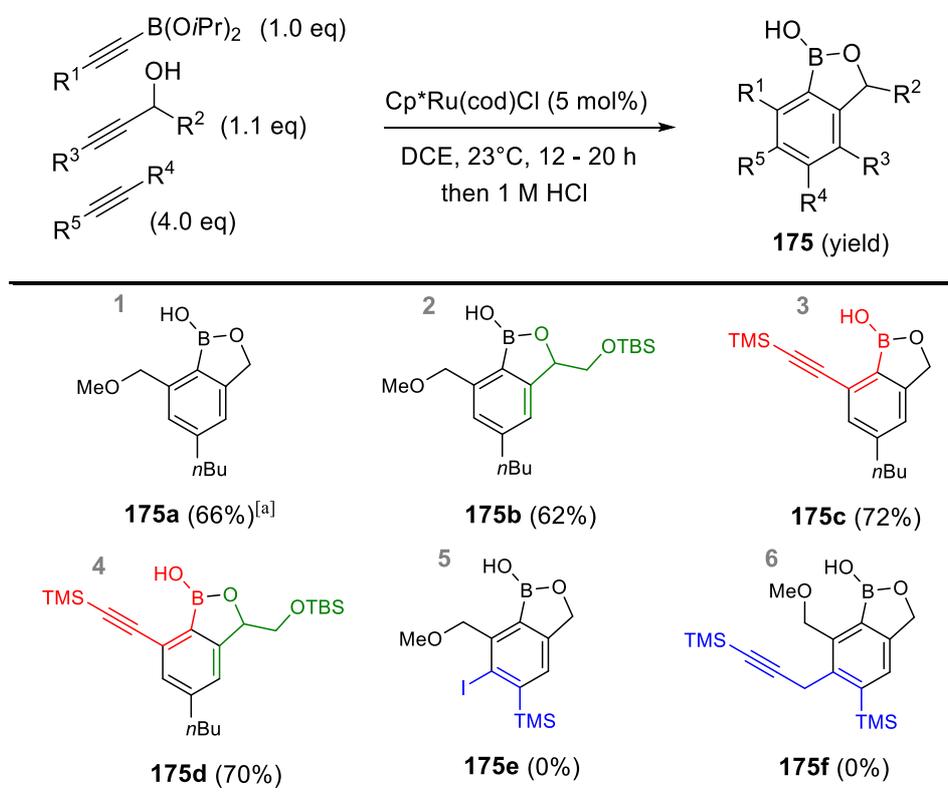
Reagents and conditions: a) TBSCl (1.0 eq), glycerin (20 eq), CH<sub>2</sub>Cl<sub>2</sub>/DMF (3:1), -18 °C, 3 h, 88%; b) NaIO<sub>4</sub> (1.8 eq), CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O (1:1), 2 h, 87%; c) ethynylmagnesium bromide (1.2 eq), 0 °C, 1 h, 65% (±)-**126**; d) trimethylsilylacetylene (1.1 eq), *n*BuLi (1.2 eq), -78 °C to 23 °C, 45 min, 90% (±)-**174**.

Scheme 41: Synthesis of propargyl alcohols (±)-**126** and (±)-**174**.

We began by reproducing Yamamoto's synthesis of boraphthalide **175a**, proceeding in 66% yield from propargyl alcohol, 1-hexyne and alkynylboronate **169** (entry 1). By consecutive substitution of the alkyne components, we discovered that utilization of either secondary propargylic alcohol (±)-**126** or diynylboronate **125**, efficiently provided the corresponding boraphthalides **175b** and **175c** in 62% and 72%, respectively (entries 2-3). Remarkably, common employment of both smoothly delivered tetrasubstituted benzene **175d** in 70% yield (entry 4).

<sup>104</sup> a) S. Kim, C. M. Cho, *Tetrahedron Lett.* **1995**, 36, 4845-4848; b) Q. Liu, G. Yue, N. Wu, G. Lin, Y. Li, J. Quan, C.-c. Li, G. Wang, Z. Yang, *Angew. Chem. Int. Ed.* **2012**, 51, 12072-12076.

<sup>105</sup> I. Paterson, O. Delgado, G. J. Florence, I. Lyothier, M. O'Brien, J. P. Scott, N. Sereinig, *J. Org. Chem.* **2005**, 70, 150-160.

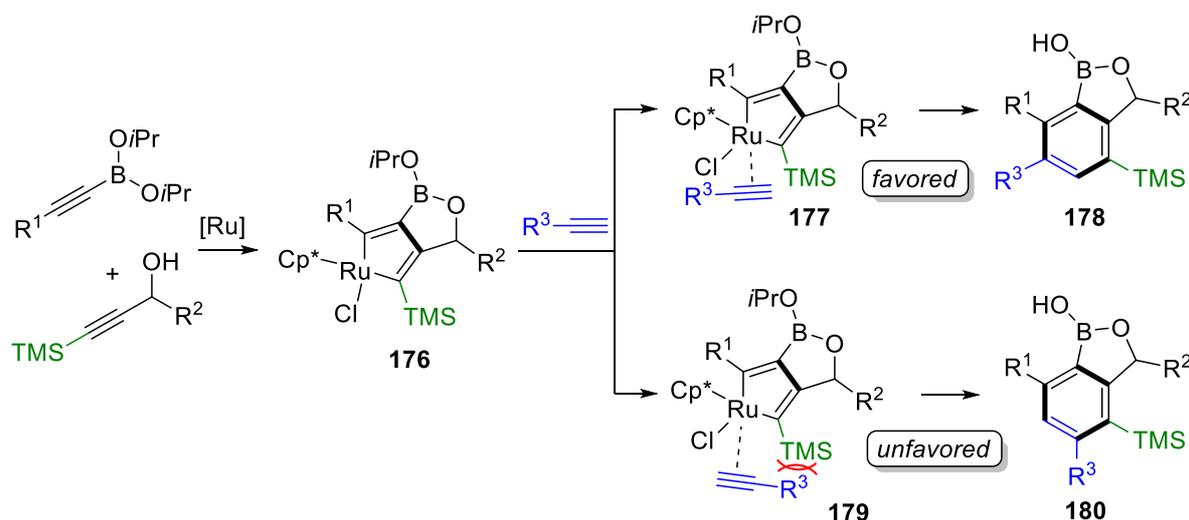
**Table 10:** [2+2+2] cycloadditions towards the fully substituted fijiolide arene core.

<sup>[a]</sup> Modifications compared to the literature compound **175** are highlighted in color; structures were tentatively assigned on the bases of  $^1\text{H}$  NMR spectroscopy.

We next replaced the third alkyne component (1-hexyne) by TMS substituted alkynes to test the desired inversion of regioselectivity. However, utilization of commercially available (iodoethynyl)trimethyl-silane resulted in marginal conversion and failed to furnish iodobenzene **175e**. Similarly, employment of known 1,5-bis(trimethylsilyl)penta-1,4-diyne<sup>106</sup> led to poor conversion, and no trace of product **175f**, bearing a TMS propargyl group as the later allene synthon (entry 6). Accordingly, the employment of TMS substituted alkynes as the third alkyne component appeared to shut down the [2+2+2] cycloaddition process. To address this shortcoming, we revised our working hypothesis, and wondered if we could invert the reported regioselectivity by the installation of a sterically demanding substituent on the terminal propargyl alcohol (**Scheme 42**). Thus, a TMS group adjacent to the metal center in ruthenacycle **176** was assumed to result in a preferential orientation of the coordinating alkyne with the substituent  $\text{R}^3$  pointing away from the guiding TMS group (**177** preferred over **179**), thus resulting in selective formation of *meta*-

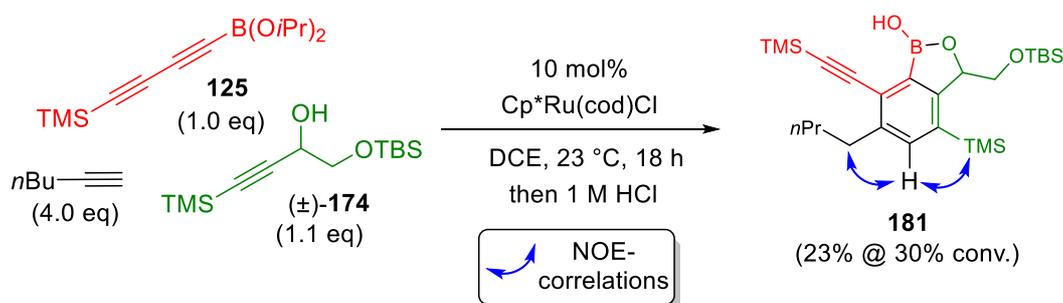
<sup>106</sup> B. Du, M. F. Faron, D. B. McConnville, W. J. Youngs, *Tetrahedron* **1995**, *51*, 4359-4370.

substituted arylboronic acid derivative **178**. Moreover, we expected the insertion rate for the third – now terminal – alkyne to be less affected by the TMS substituent, compared to our previous substitution strategy.



**Scheme 42:** Hypothesized direction of the regioselectivity by use of substituted propargylic alcohols.

Indeed, the respective experiment employing alkynylboronate **125**, propargyl alcohol ( $\pm$ )-**174** and 1-hexyne regioselectively afforded *meta*-substituted arylboronic ester **181**, as confirmed by 1D NOE studies (**Scheme 43**).

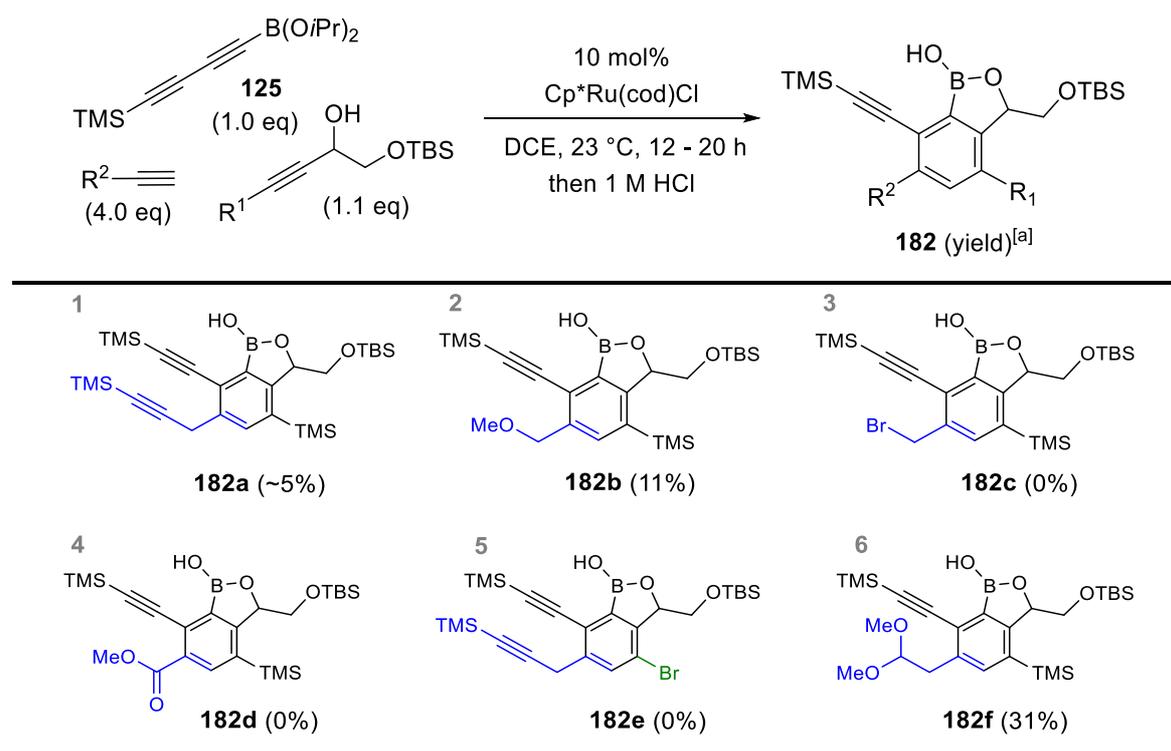


**Scheme 43:** Confirmation of the envisioned regioselectivity in the [2+2+2] cycloaddition.

With this promising result, we screened functionalized terminal alkynes that would allow preparation of an arylallene at a later stage of the synthesis (**Table 11**). As observed for the formation **181**, the reaction rates of substituted propargyl alcohols were consistently low. As a result, homotrimerization of the terminal alkyne component became a major side reaction, thus leading to consumption of the terminal alkyne before it could participate in the boraphthalide forming [2+2+2] cycloaddition. Nevertheless, formation of about 5% **182a** was observed when

commercially available trimethyl(penta-1,4-diyne-1-yl)silane was employed (**Table 11**, entry 1). The use of methyl propargyl ether provided boraphthalide **182b** in slightly increased yield of 11%, whereas no formation of **182c** was observed in the reaction with propargyl bromide (entries 2-3).

**Table 11:** Screening of functionalized terminal alkynes in the [2+2+2] cycloaddition.



<sup>[a]</sup> Determined by <sup>1</sup>H NMR using 1,3,5-TMB as internal standard; products were not isolated.

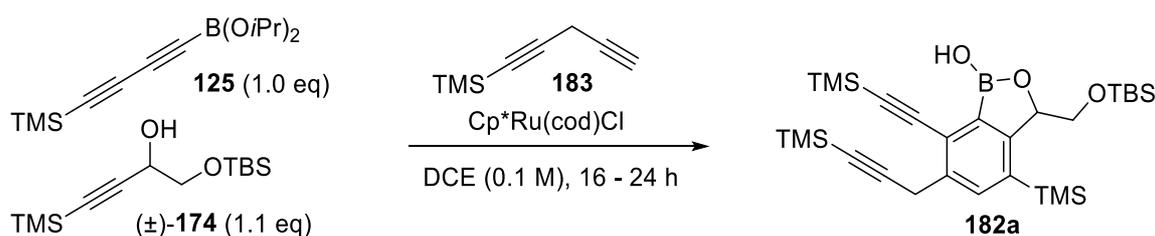
Similarly, [2+2+2] cycloadditions utilizing methyl propiolate, or bromine substituted propargyl alcohol<sup>107</sup> failed to deliver products **182d** and **182e** (entries 4-5). An increased yield of 31% **182f** was achieved by using freshly prepared homopropargylaldehyde dimethyl acetal (entry 6).<sup>108</sup>

<sup>107</sup> Y. Tang, L. Shen, B. J. Dellaria, R. P. Hsung, *Tetrahedron Lett.* **2008**, *49*, 6404-6409.

<sup>108</sup> S. Shang, H. Iwadare, D. E. Macks, L. M. Ambrosini, D. S. Tan, *Org. Lett.* **2007**, *9*, 1895-1898.

Among boraphthalides **182a-182f**, *bis*-alkyne substituted **182a** was believed to enable the most rapid access to an allene-yne species as the later allenic Pauson-Khand precursor, despite the low initial yield. Therefore, the [2+2+2] cycloaddition employing alkyne **183** was studied in greater detail (**Table 12**). Starting from an NMR yield of ~5% (entry 1), the influence of the reaction temperature and the stoichiometry of alkyne **183** was first investigated (entries 2-6). However, no increased formation of **182a** at 50 – 70 °C or in the presence of either lower or higher amounts of terminal alkyne **183** was observed, and parasitic homotrimerization of **183** persisted as the predominant process. Increased catalyst loadings of 30 mol% and 100 mol% still provided desired **182a** in low yields of 5–10%, respectively (entries 7-8.) Consequently, the homotrimerization process of **183** was hoped be slowed down by lowering its concentration by slow addition of the alkyne *via* syringe pump. However, continuous addition of **183** over 6 hours still furnished boraphthalide **182a** in an unsatisfactory low yield of 11% (entry 9).

**Table 12:** Optimization studies towards boraphthalide **182a** – Part I.

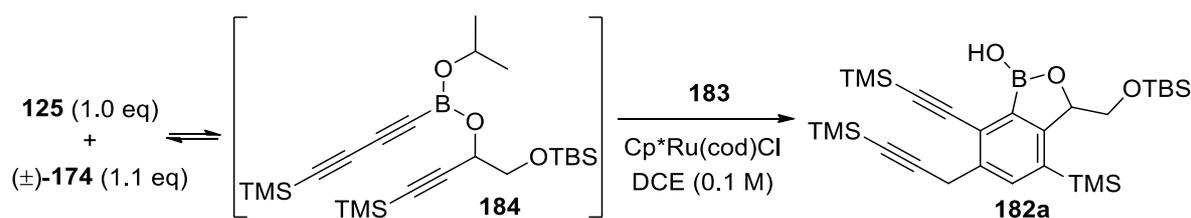


Entry	$Cp^*Ru(cod)Cl$ [mol%]	<b>183</b> [eq]	T [°C]	Yield [%] <sup>[a]</sup>
1	10	4.0	23	~5
2	10	4.0	50	traces
3	10	4.0	70	traces
4	10	1.5	70	0
5	10	1.5	23	traces
6	10	15	23	0
7	30	4.0	23	5
8	100	1.5	23	5-10
9	10	4.0 <sup>[b]</sup>	23	11

<sup>[a]</sup> Determined by  $^1H$  NMR using 1,3,5-trimethoxybenzene as internal standard; <sup>[b]</sup> Slow addition over 6 h.

We speculated that an initial transesterification, followed by removal of the released isopropanol prior to addition of the catalyst and the third alkyne, would shift the initial equilibrium towards 1,6-diyne **185**, thus allowing for higher reaction rates of the [2+2+2] cycloaddition (**Table 12**). Indeed, a major breakthrough was achieved by premixing **125** and ( $\pm$ )-**174** in DCE, and subsequent drying under high vacuum. Ensuing slow addition of the third alkyne to a solution of **184** and Cp\**Ru*(cod)Cl in DCE considerably increased the yield of **182a** to 29% (entry 1). In order to further improve this result prolonged reaction times were applied but were found to be detrimental as a result of product decomposition (entries 2-4). Slightly elevated temperature also did not improve the reaction outcome (entries 5-6). However, the manner of catalyst addition was found to have a substantial influence on the reaction yield. Slow addition of a Cp\**Ru*(cod)Cl solution increased the yield to 41% (entry 7). The yield could also be pushed to 51% by addition of all of the catalyst and alkyne at the start of the [2+2+2] cycloaddition reaction (entry 8).

**Table 13:** Optimization towards boraphthalide **182a** – Part II.



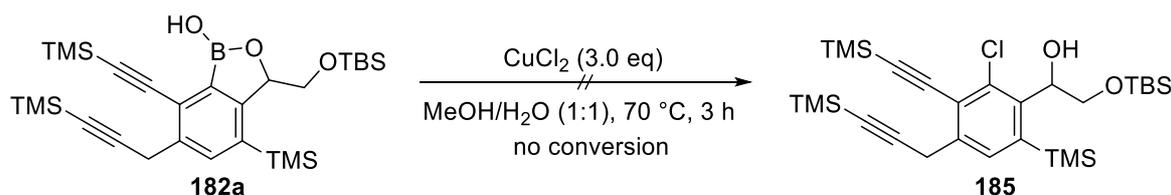
Entry	Cp* <i>Ru</i> (cod)Cl addition	Addition of <b>183</b> [eq]	T [°C]	t [h]	yield [%] <sup>[a]</sup>
1	1 x 15 mol%	4.0 over 6 h	23	19	29
2	1 x 15 mol%	4.0 over 6 h	23	60	12
3	1 x 15 mol%	4.0	23	60	20
4	1 x 15 mol%	1.5	23	60	22
5	1 x 15 mol%	4.0 over 6 h	40	19	24
6	1 x 15 mol%	4.0	40	19	25
7	15 mol% over 10 h	4.0	23	21	41
8	1 x 15 mol%	4.0	23	20	51
9	2 x 7.5 mol%	4.0	23	20	60
10	3 x 5.0 mol%	4.0	23	24	33 <sup>[b,c]</sup>
11	2 x 7.5 mol%	4.0	33	21	40 <sup>[c,d]</sup>
12	2 x 7.5 mol%	2 x 2.0	23	22	55 <sup>[c,e]</sup>

<sup>[a]</sup> Determined by <sup>1</sup>H NMR using 1,3,5-TMB as internal standard; <sup>[b]</sup> Reaction was conducted in 0.17 mmol scale; <sup>[c]</sup> Isolated yield after chromatography using a Biotage Isolera Four purification system; <sup>[d]</sup> Reaction was conducted in 12 parallel batches (67.5  $\mu$ mol each); <sup>[e]</sup> **125** and ( $\pm$ )-**174** were premixed in Et<sub>2</sub>O instead of DCE.

However, portionwise addition of the catalyst (2 x 7.5 mol%) was discovered to further boost the yield to 60% yield of **182a** (entry 9). Application of this procedure to increased reaction scales provided **182a** in acceptable preparative yields (entries 10-11). Finally, a portionwise addition of both catalyst and diyne **183** on preparative scale resulted in isolation of **182a** in 55% yield as a single regioisomer. Noteworthy, the meticulous removal of LiCl from diynylboronate **125** was found to be essential for the attainment of high reaction yields, as it interferes with the catalyst activity. Uptake of **125** in pentane and re-filtration under inert conditions provided diynylboronate **125** of highest purity.

With boraphthalide **182a** in hand, we next shifted our research focus to the installation of the required chlorine substituent. Chlorodeboronation of arylboronic acids has emerged as a promising alternative to circumvent classical arene chlorination by electrophilic aromatic substitution. The latter often suffers from limitations in terms of chemoselectivity and regioselectivity.<sup>109</sup> Several reagents, such as dichlorodimethylhydantoin,<sup>110</sup> trichloroisocyanuric acid,<sup>109</sup> *N*-chlorosuccinimide (NCS),<sup>111</sup> and copper(II) chloride<sup>112</sup> have been employed for the conversion of arylboron compounds to aryl chlorides. However, *ipso*-chlorination of boraphthalides, affording *ortho*-chlorobenzyl alcohols has not yet been reported.

Inspired by the work of Hartwig *et al.*,<sup>112c</sup> we first evaluated the transformation of **182a** with CuCl<sub>2</sub> in aqueous methanol, resulting in complete recovery of the starting material in several chlorodeboronation attempts (**Scheme 44**).



**Scheme 44:** Attempted chlorodeboronation of **182a** using CuCl<sub>2</sub>.

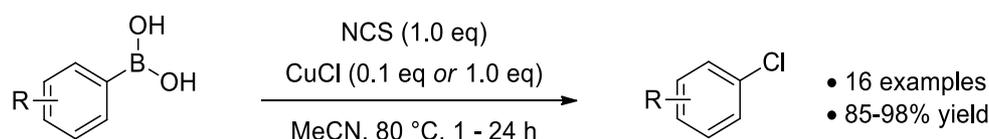
<sup>109</sup> G. A. Molander, L. N. Cavalcanti, *J. Org. Chem.* **2011**, *76*, 7195-7203.

<sup>110</sup> R. H. Szumigala, P. N. Devine, D. R. Gauthier, R. P. Volante, *J. Org. Chem.* **2004**, *69*, 566-569.

<sup>111</sup> H. Wu, J. Hynes, *Org. Lett.* **2010**, *12*, 1192-1195.

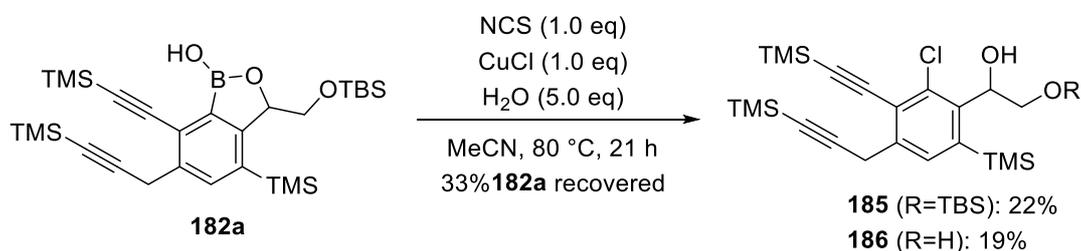
<sup>112</sup> a) A. D. Ainley, F. Challenger, *J. Chem. Soc.* **1930**, 2171-2180; b) J. W. Huffman, A. L. Thompson, G. W. Kabalka, M. R. Akula, *Synthesis* **2005**, *2005*, 547-550; c) J. M. Murphy, X. Liao, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 15434-15435.

Employment of stoichiometric amounts of NCS and copper(I) chloride in refluxing acetonitrile as reported by Hynes *et al.* (**Scheme 45**),<sup>111</sup> resulted in a complex product mixture due to unselective silyl cleavage. Still, undefined amounts of aryl chlorides were detected in the crude mixture (HRMS), showcasing the general feasibility of the intended chlorodeboronation process.



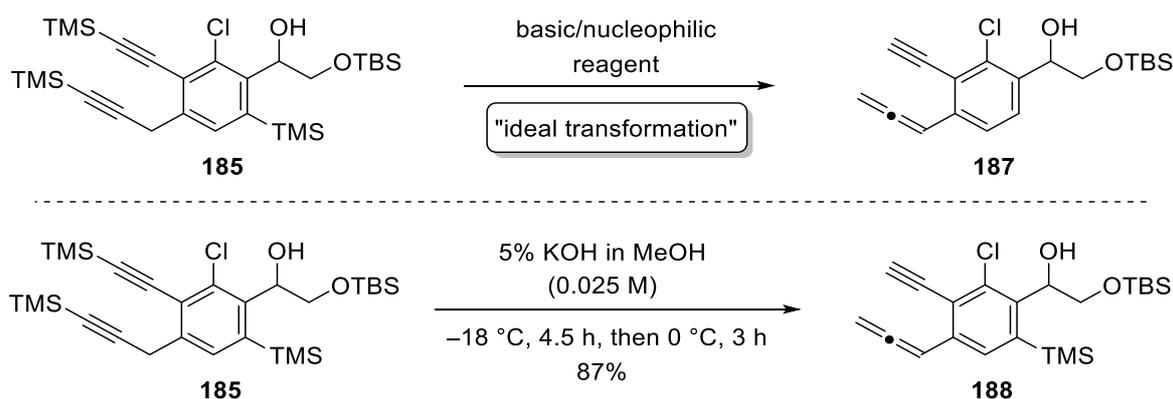
**Scheme 45:** Reported chlorodeboronation of arylboronic acids using CuCl/NCS.<sup>111</sup>

As boraphthalide **182a** was not available in high quantities, model chlorodeboronation studies were conducted on trisubstituted arylboronate ester **175d**. Importantly, our studies showed that addition of H<sub>2</sub>O to the NCS/CuCl reagent system promoted the chlorination process, and considerably enhanced the reaction rate. Two to five equivalents of water were found to be beneficial. Execution of the reaction with considerably higher loadings of water or even in MeCN/H<sub>2</sub>O (1:1) led to undesired side reactions and product degradation. We attribute the water-promoted chlorodeboronation to an *in situ* hydrolysis of the boraphthalide to the corresponding arylboronic acid. This can then undergo the desired chlorodeboronation reaction. A similar observation has been made by Hynes *et al.*, who reported a much higher chlorodeboronation reaction rate for arylboronic acids compared to their ester congeners.<sup>111</sup> As a consequence **182a** was subjected to NCS/CuCl/H<sub>2</sub>O, resulting in a 22% yield of desired arylchloride **185** (**Scheme 46**). However, silyl cleavage occurred to a considerable extent, giving rise to isolation of **186**, along with 33% unreacted starting material. Diol **186** could be converted back to the desired **185** in 84% yield by treatment with TBSCl, DMAP, and Et<sub>3</sub>N in dry CH<sub>2</sub>Cl<sub>2</sub>.



**Scheme 46:** Chlorodeboronation of **182a** using NCS/CuCl/H<sub>2</sub>O.

Having synthesized the fully substituted arene core of the fijiolides, modification of **185** for the intended allenic Pauson-Khand reaction was the next challenge to be tackled. Ideally, *bis*-alkyne **185** would simultaneously undergo global (threefold) trimethylsilyl cleavage, as well as isomerization of the propargyl group, to deliver allene-yne **187** (Scheme 47). Moreover, the TBS protecting group on the primary alcohol would be retained in this process, necessitating a chemoselective Si-C bond cleavage.



**Scheme 47:** "Ideal" and realized transformation of **185** into an allenic Pauson-Khand precursor.

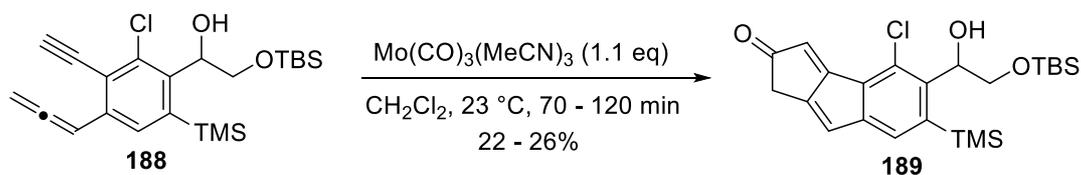
We assumed that methanolic KOH could be used to realize the intended transformation, and allene-yne **188** was isolated in high yield after optimization of the reaction conditions.<sup>99a,113</sup> However, selective cleavage of the aryl TMS group prior to TBS deprotection could not be achieved using methanolic KOH.

With very limited amounts of the unstable allene-yne **188** in hand,<sup>114</sup> we focused on realization of the allenic Pauson-Khand reaction. Treatment of **188** with freshly prepared  $\text{Mo}(\text{CO})_3(\text{MeCN})_3$ <sup>97,115</sup> provided the desired indenylcyclopentenone **189** (Scheme 48). However, low yields of 22-26%, were obtained, although the reaction appeared to proceed cleanly, as judged by TLC and <sup>1</sup>H NMR analysis. Unfortunately, we were unable to determine the fate of the missing mass balance. The crude NMR yields correspond to the isolated yields.

<sup>113</sup> a) C. Heiss, E. Marzi, M. Schlosser, *Eur. J. Org. Chem.* **2003**, 2003, 4625-4629; b) M. Tsukazaki, V. Snieckus, *Can. J. Chem.* **1992**, 70, 1486-1491.

<sup>114</sup> **188** (orange oil) was observed to decompose and form a poorly soluble red gum upon storage (even at -30 °C). The same was true for all related allene-yne species. Thus, they were immediately subjected to the Pauson-Khand reaction.

<sup>115</sup> a) K. M. Al-Kathumi, L. A. P. Kane-Maguire, *J. Inorg. Nucl. Chem.* **1972**, 34, 3759-3764; b) D. P. Tate, W. R. Knipple, J. M. Augl, *Inorg. Chem.* **1962**, 1, 433-434; c) F. Edelmann, P. Behrens, S. Behrens, U. Behrens, *J. Organomet. Chem.* **1986**, 310, 333-355.



**Scheme 48:** Allenic Pauson-Khand reaction of allene-yne **188**.

After having successfully implemented a racemic synthesis of functionalized indenyl-cyclopentenone **189**, we next focused on a scaled-up asymmetric synthesis, which required the preparation of propargyl alcohol **174** in an enantioselective manner. A variety of synthetic methods for the synthesis of enantioenriched propargylic alcohols have become available over the past two decades.<sup>116</sup> In particular, metal-mediated or catalyzed enantioselective addition of terminal alkynes to aldehydes or ketones has emerged as a very powerful tool to attain propargyl alcohols of high optical purity.<sup>117</sup> We decided to test Carreira's  $\text{Zn}(\text{OTf})_2/\text{N}$ -methylephedrine (NME)-mediated alkylation method for an asymmetric synthesis of **174** (**Table 14**).<sup>118,119</sup> Employment of TBS protected glycolaldehyde **173** in a catalytic process<sup>119</sup> furnished highly enantioenriched propargyl alcohol (+)-**174** (91% *ee*), albeit in very low yield (entry 1). Application of Carreira's stoichiometric version<sup>118</sup> of this reaction resulted in only slightly increased yields of 10% and 16% with comparable optical purity, irrespective of the aldehyde addition procedure (entries 2-3). We proposed that the poor yields may be due to low stability of the TBS group toward the reaction conditions,<sup>120</sup> thus we tested TBDPS protected glycolaldehyde **190**.<sup>121</sup> Improved, albeit still moderate yields of 35–42% were obtained for propargyl alcohol (+)-**191**, exhibiting a higher enantiomeric purity of 97% *ee* in all cases (entries 3-6).

<sup>116</sup> B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963-983.

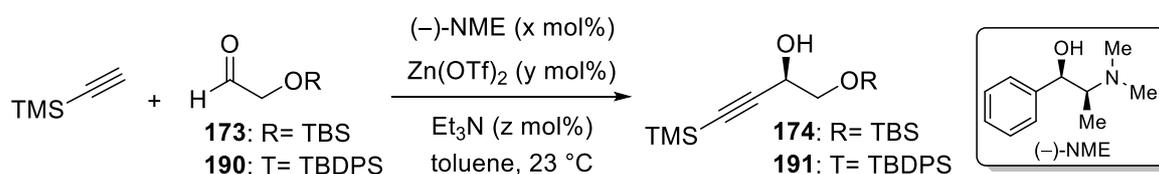
<sup>117</sup> M. Turlington, Y. Yue, X.-Q. Yu, L. Pu, *J. Org. Chem.* **2010**, *75*, 6941-6952.

<sup>118</sup> D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.

<sup>119</sup> N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687-9688.

<sup>120</sup> E. El-Sayed, N. K. Anand, E. M. Carreira, *Org. Lett.* **2001**, *3*, 3017-3020.

<sup>121</sup> L. D. Fader, E. M. Carreira, *Org. Lett.* **2004**, *6*, 2485-2488.

**Table 14:** Carreira alkynylation studies.

Entry	Aldehyde	Aldehyde addition	x / y / z [mol%]	t [h]	Yield [%]	ee [%]
1 <sup>[a]</sup>	<b>173</b>	over 3 h	22 / 20 / 50	12	4	91
2	<b>173</b>	one portion	120 / 110 / 120	3	10	92
3	<b>173</b>	over 3 h	120 / 110 / 120	3	16	93
4	<b>190</b>	over 3 h	120 / 110 / 120	2	38	97
5	<b>190</b>	over 3 h	220 / 210 / 220	2	42	97
6	<b>190</b>	one portion	220 / 210 / 220	2	35	97

<sup>[a]</sup> Reaction was conducted at 60 °C.

Since a synthesis of fijiolide A *via* **191** would not only require a highly enantioselective reaction, but also high yielding preparation of **191**, we next pursued an alternative approach toward this building block. In addition to nucleophilic addition of alkynes to carbonyls, the enantioselective reduction of ynones has been established as a reliable synthetic route to enantioenriched propargyl alcohols. High enantioselectivities have been achieved by use of Noyori's transfer hydrogenation catalyst (Ts-Dpen)Ru(*p*-cymene) in protic solvents, preferentially isopropanol.<sup>122,123</sup> In order to apply this methodology, ynone **194** was synthesized from methyl glycolate **192** *via* TBDPS protection,<sup>124</sup> followed by conversion into the corresponding commercially available Weinreb amide **193** (Scheme 49).<sup>124,125</sup> Addition of lithium trimethylsilylacetylide to **193** provided the required ynone **194** in excellent yield and purity. Noteworthy, the work-up procedure for **194** turned out to be of tremendous importance with respect to the subsequent reaction. Quenching the reaction with aqueous ammonium chloride at  $-78$  °C or  $0$  °C led to up to 25% of a TMS cleavage product, which could not be completely removed *via* flash chromatography due to the instability of **194** on silica.<sup>126</sup> This impurity was found to severely inhibit the Noyori transfer hydrogenation process.<sup>123</sup> Its formation could be avoided by quenching the reaction with acetic acid. Thus, crude

<sup>122</sup> K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, *Angew. Chem. Int. Ed.* **1997**, *36*, 285-288.

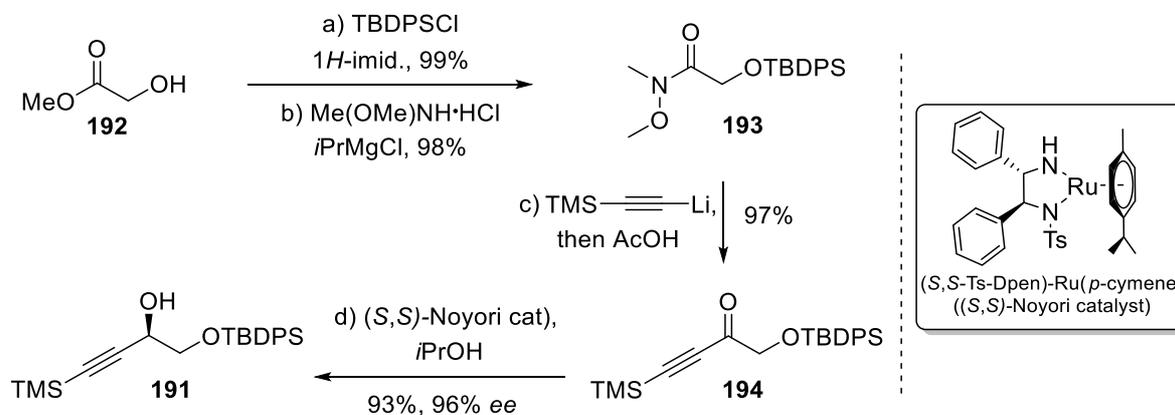
<sup>123</sup> K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739.

<sup>124</sup> H. Nemoto, M. Nagamochi, H. Ishibashi, K. Fukumoto, *J. Org. Chem.* **1994**, *59*, 74-79.

<sup>125</sup> J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 5461-5464.

<sup>126</sup> Thus impure material can still be converted to the enantioenriched **191**, provided the catalyst loading exceeds the degree of contamination.

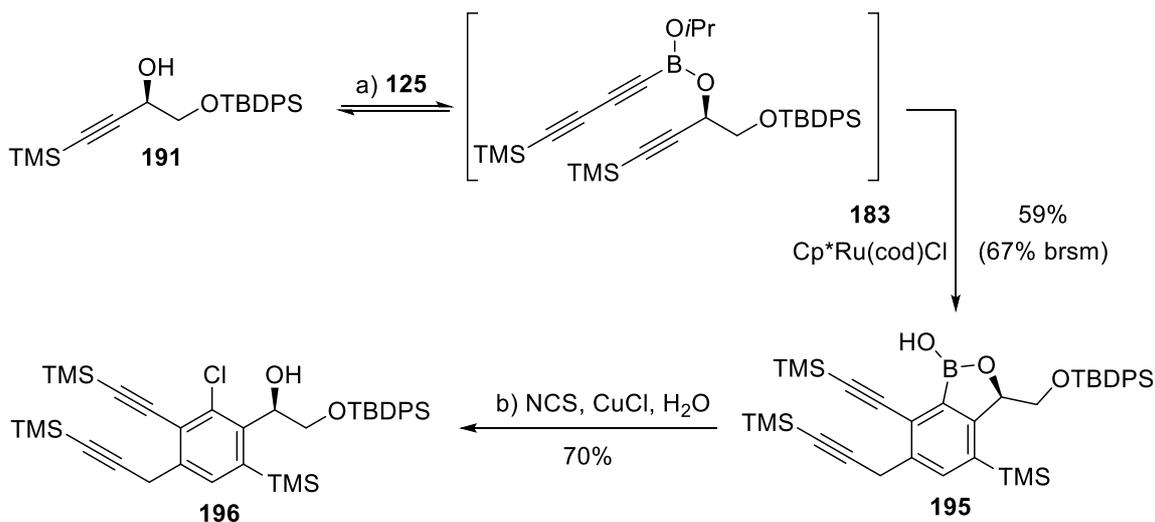
ynone **194** was directly used for the reduction step, giving propargyl alcohol **191** in 93% yield and 96% *ee*.



*Reagents and conditions:* a) **192** (1.1 eq), TBDPSCI (1.0 eq), DMAP (0.1 eq), 1*H*-imidazole (1.5 eq), DMF, 23 °C, 5 h, 99%; b) Me(OMe)NH·HCl (1.6 eq), *i*PrMgCl (3.0 eq), THF, -20 °C to 0 °C, 3 h, 98%; c) trimethylsilylacetylene (1.6 eq), *n*BuLi (1.4 eq), THF, -78 °C to -15 °C, 1.5 h, then acetic acid (1.5 eq) at -78 °C, 97%; d) *(S,S)*-Noyori catalyst (3.5 mol%), *i*PrOH, 24 °C, 4 h, 93%, 96% *ee*.

**Scheme 49:** Asymmetric synthesis of propargyl alcohol **191** via Noyori transfer hydrogenation.

Gram-quantities of enantioenriched **191** were subjected to the [2+2+2] cycloaddition with diynylboronate **125** and diyne **183** (**Scheme 50**). Remarkably, boraphthalide **195** was isolated in 59% yield (67% brsm), as a single regioisomer. Moreover, we encountered a high stability of TBDPS protected **195** in the ensuing chlorodeboronation step. Thus, unreacted starting material could be re-isolated and re-submitted to the reaction conditions. This allowed for the synthesis of the fully substituted fijiolide arene core **196** in 70% yield after 5 consecutive chlorodeboronation reactions.



*Reagents and conditions:* a) **125** (1.1 eq), Et<sub>2</sub>O, 23 °C, 4.5 h, then 1 mbar, 23 °C, 4.5 h, then Cp<sup>\*</sup>Ru(cod)Cl (3 x 4.4 mol%, **183** (3 x 1.3 eq), DCE, 23 °C, 36 h, 59% (67% brsm); b) NCS (1.0 eq), CuCl (1.0 eq), H<sub>2</sub>O (5.0 eq), MeCN, 80 °C, 22 h, 70% (after 5 consecutive reactions of re-isolated **195**).

**Scheme 50:** Synthesis of the fully substituted, enantioenriched fijiolide arene core.

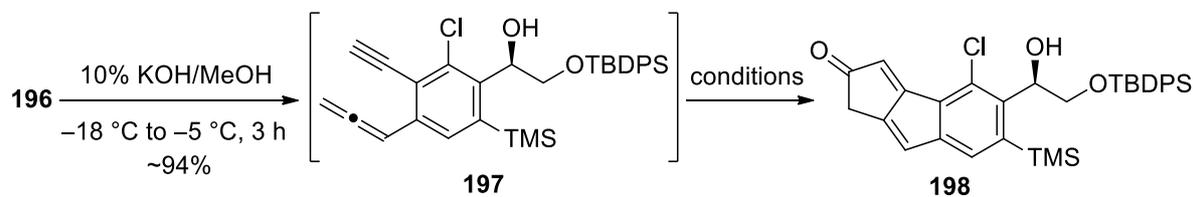
While the primary TBDPS ether appeared to be less prone to Si-O bond cleavage during chlorodeboronation, the opposite was true for the subsequent TMS cleavage/isomerization process. Hence, selective cleavage of all trimethylsilyl groups, while retaining the TBDPS ether was not achievable. Nevertheless, allene-yne **197** could be obtained in high yield, and was immediately subjected to the allenic Pauson-Khand reaction, affording indenylcyclopentenone **198** in 40% yield (**Table 15**, entry 1). However, we observed poor reproducibility of this transformation (entry 2), and therefore conducted further optimization studies. The reaction was found to proceed at 0 °C, and even at -78 °C, albeit the yield was not improved (entries 3-4). Changing from a stoichiometric molybdenum complex to catalytic [Rh(CO)<sub>2</sub>Cl]<sub>2</sub> under a CO atmosphere led to a comparable low yield of 26% (entry 5).<sup>127</sup> Reacting **197** with Mo(CO)<sub>6</sub> in toluene, activated with DMSO, enhanced the yield to over 40%, while being completely reproducible (entry 6).<sup>97,128</sup> Thus, a larger scale synthesis of **198** was carried out under these conditions, resulting in a comparable 41% yield

<sup>127</sup> a) Y. Koga, T. Kobayashi, K. Narasaka, *Chem. Lett.* **1998**, 27, 249-250; b) N. Jeong, S. Lee, B. K. Sung, *Organometallics* **1998**, 17, 3642-3644; c) K. M. Brummond, M. M. Davis, C. Huang, *J. Org. Chem.* **2009**, 74, 8314-8320.

<sup>128</sup> a) A. K. Gupta, D. I. Park, C. H. Oh, *Tetrahedron Lett.* **2005**, 46, 4171-4174; b) K. M. Brummond, D. Chen, *Org. Lett.* **2008**, 10, 705-708.

(entry 7). Finally, brief exposure (13 min) of **197** to molybdenum hexacarbonyl at 90 °C furnished **198** in an improved 50% yield (entry 8).

**Table 15:** Attempted optimization of the Pauson-Khand reaction of allene-yne **197**.

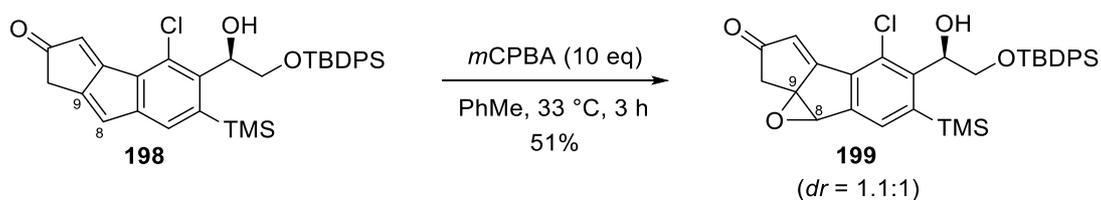


Entry	Reagent <sup>[a]</sup>	Solvent	T [°C]	t [min]	Yield
1	Mo(CO) <sub>3</sub> (MeCN) <sub>3</sub> <sup>[b]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	23	75	40
2	Mo(CO) <sub>3</sub> (MeCN) <sub>3</sub> <sup>[c]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	23	75	32
3	Mo(CO) <sub>3</sub> (MeCN) <sub>3</sub> <sup>[b]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	0	180	24 <sup>[d]</sup>
4	Mo(CO) <sub>3</sub> (MeCN) <sub>3</sub> <sup>[b]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	-78	180	21 <sup>[d]</sup>
5	[Rh(CO) <sub>2</sub> Cl] <sub>2</sub> <sup>[e]</sup>	PhMe	90	75	26
6	Mo(CO) <sub>6</sub> <sup>[f]</sup>	PhMe	100	90	41
7	Mo(CO) <sub>6</sub> <sup>[f]</sup>	PhMe	100	20	41 <sup>[g]</sup>
8	Mo(CO) <sub>6</sub> <sup>[f]</sup>	PhMe	90	13	50 <sup>[h]</sup>

<sup>[a]</sup> 1.0 – 1.1 eq were standardly employed; <sup>[b]</sup> Prepared by heating Mo(CO)<sub>6</sub> and MeCN in a sealed vial at 80 °C for 24 h; <sup>[c]</sup> Prepared by refluxing Mo(CO)<sub>6</sub> in MeCN for 1 h; <sup>[d]</sup> NMR yield; <sup>[e]</sup> Reaction was conducted under a CO atmosphere; <sup>[f]</sup> DMSO (5.0 eq) was added as the activator; <sup>[g]</sup> 10 times larger scale; <sup>[h]</sup> 30 times larger scale.

With this result in hand, focus was shifted to the conversion of **198** into the fijiolide A aglycone. As outlined in chapter 3, our synthetic strategy envisioned a nucleophilic opening of an indene epoxide by the  $\beta$ -amino acid fragment for installation of the aryl ether bond at C-8. Thus, we were keen on validating a selective epoxidation of the C-8/C-9 indenyl double bond, despite full conjugation with the enone moiety through the aromatic ring. After a brief screening of oxidation conditions, treatment of indenylcyclopentenone **198** with an excess of *m*CPBA in toluene was found to provide the desired epoxide **199** in 51% yield (**Scheme 51**). Notably, epoxidation occurred chemoselectively, albeit without facial selectivity, leaving the presumably less electron-rich enone double bond intact.

Moreover, the progress of this transformation can be followed by a change in coloration from a bright orange solution to a colorless suspension. This observation held true for most of the indenyl double bond oxidizing reactions and can be rationalized by the loss of the fulvene motif (from Latin “*fulvus*” for dull yellow, tawny) upon oxidation.<sup>129</sup>



**Scheme 51:** Epoxidation of indenylcyclopentenone **198** with *m*CPBA.

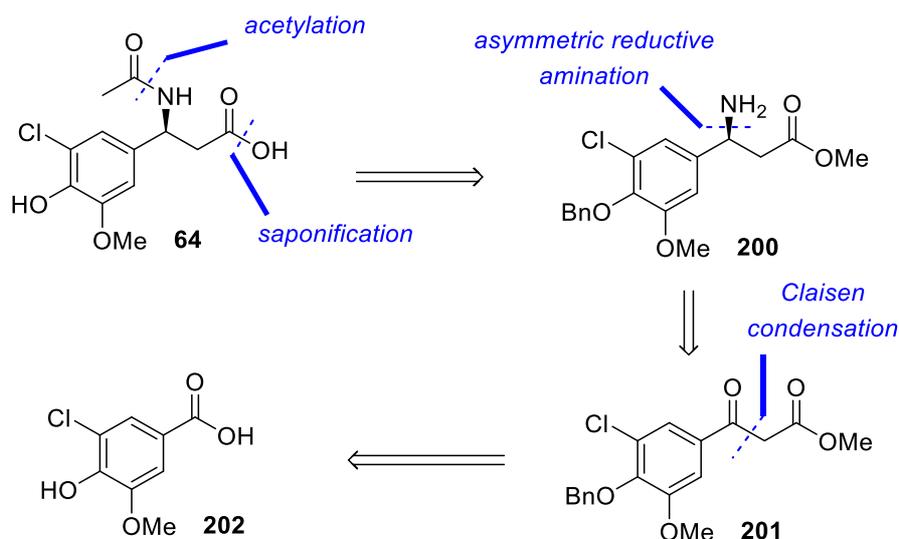
Having validated the required chemoselectivity in epoxidation of the tricyclic key fragment, synthetic access to the  $\beta$ -amino acid moiety and ensuing fragment coupling became the topic of investigation. These studies are the object of discussion in the following chapters.

<sup>129</sup> a) J. H. Day, *Chem. Rev.* **1953**, 53, 167-189; b) B. Halton, *Eur. J. Org. Chem.* **2005**, 2005, 3391-3414.

***5. Synthesis of the  
 $\beta$ -Amino Acid Fragment***

## 5.1 Retrosynthetic Analysis

Our retrosynthesis of  $\beta$ -amino acid fragment **64** features an acetylation and saponification of protected  $\beta$ -amino ester **200** (Scheme 52). Access to **200** was envisioned to be realized by a direct enantioselective reductive amination of  $\beta$ -keto ester **201**, which may be obtained by decarboxylative Claisen condensation of a malonate species with 5-chlorovanillic acid **202**.

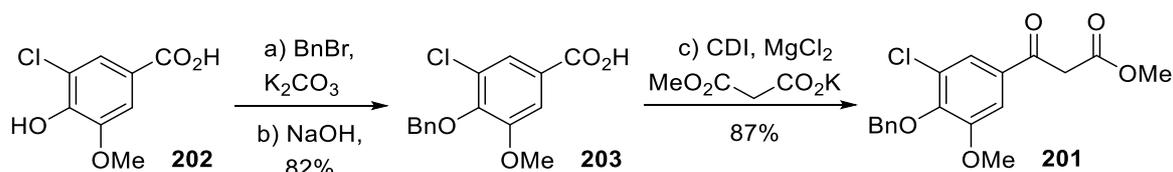


Scheme 52: Retrosynthetic analysis of the  $\beta$ -amino acid fragment.

## 5.2 Results

In the forward direction, commercially available 5-chlorovanillic acid **202** was considered as a viable starting material for the synthesis of the  $\beta$ -amino acid fragment. At the outset, we reasoned that a synthesis of **64** may not be achievable maintaining a free phenolic hydroxyl group. Therefore, **202** was first benzyl protected *via* a two-step sequence involving saponification of the intermediately formed benzyl ester affording benzoic acid **203** (Scheme 53). Elongation of the carbon chain was successfully realized *via* a decarboxylative Claisen condensation. According to the procedure of Masamune *et al.*, suspension of methyl potassium malonate and  $\text{MgCl}_2$  in THF, followed by addition of activated **203** (CDI) furnished  $\beta$ -keto ester **201** in 87% yield.<sup>130</sup>

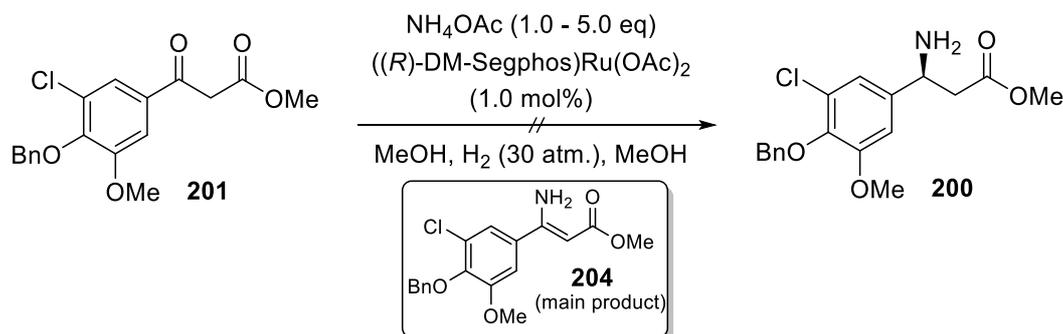
<sup>130</sup> D. W. Brooks, L. D. L. Lu, S. Masamune, *Angew. Chem. Int. Ed.* **1979**, *18*, 72-74.



Reagents and conditions: a)  $\text{K}_2\text{CO}_3$  (2.8 eq),  $\text{BnBr}$  (2.8 eq), DMF, 27 °C, 15 h; b) aq.  $\text{NaOH}$ , EtOH, 80 °C, 1 h, 82% (2 steps); c) CDI (1.2 eq),  $\text{MgCl}_2$  (1.1 eq),  $\text{MeO}_2\text{CCH}_2\text{CO}_2\text{K}$  (1.5 eq), THF, 23 °C, 17 h, 87%.

**Scheme 53:** Synthesis of  $\beta$ -keto ester **201**.

As evident by recent reports from Cooper,<sup>131</sup> Bunlaksananusorn,<sup>132</sup> de Vries,<sup>133</sup> and Matsumura,<sup>134</sup> direct enantioselective reductive amination of  $\beta$ -keto esters is a powerful tool to access highly enantioenriched  $\beta$ -amino esters. Biphep- or Segphos-derived ligands are most commonly employed for these ruthenium(II)-catalyzed high pressure transformations. We elected to examine commercially available (*R*)-DM-Segphos $\text{Ru}(\text{OAc})_2$  for the reductive amination of **201**. Experiments using ammonium acetate as the nitrogen source led to formation of anticipated enamine intermediate **204**, however, reduction to afford **200** was not observed (**Scheme 54**).



**Scheme 54:** Failed direct enantioselective reductive amination of  $\beta$ -keto ester **201**.

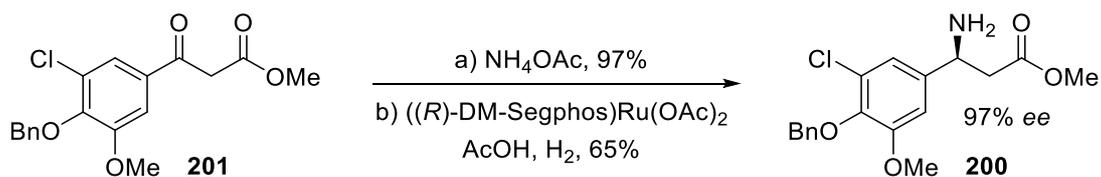
This shortcoming was overcome by realization of a two-step procedure, splitting the steps of enamine formation and enamine reduction. Thus, **204** was synthesized by refluxing **201** with ammonium acetate in methanol (**Scheme 55**). Submission of crude **204** to similar reduction conditions as before (omitting ammonia), enabled isolation of the desired  $\beta$ -amino ester **200** in good yield and an excellent enantioselectivity of 97% *ee*.

<sup>131</sup> X. Huang, E. O'Brien, F. Thai, G. Cooper, *Org. Process Res. Dev.* **2010**, *14*, 592-599.

<sup>132</sup> T. Bunlaksananusorn, F. Rampf, *Synlett* **2005**, *2005*, 2682-2684.

<sup>133</sup> G. F. Busscher, L. Lefort, J. G. O. Cremers, M. Mottinelli, R. W. Wiertz, B. d. Lange, Y. Okamura, Y. Yusa, K. Matsumura, H. Shimizu, J. G. de Vries, A. H. M. de Vries, *Tetrahedron: Asymmetry* **2010**, *21*, 1709-1714.

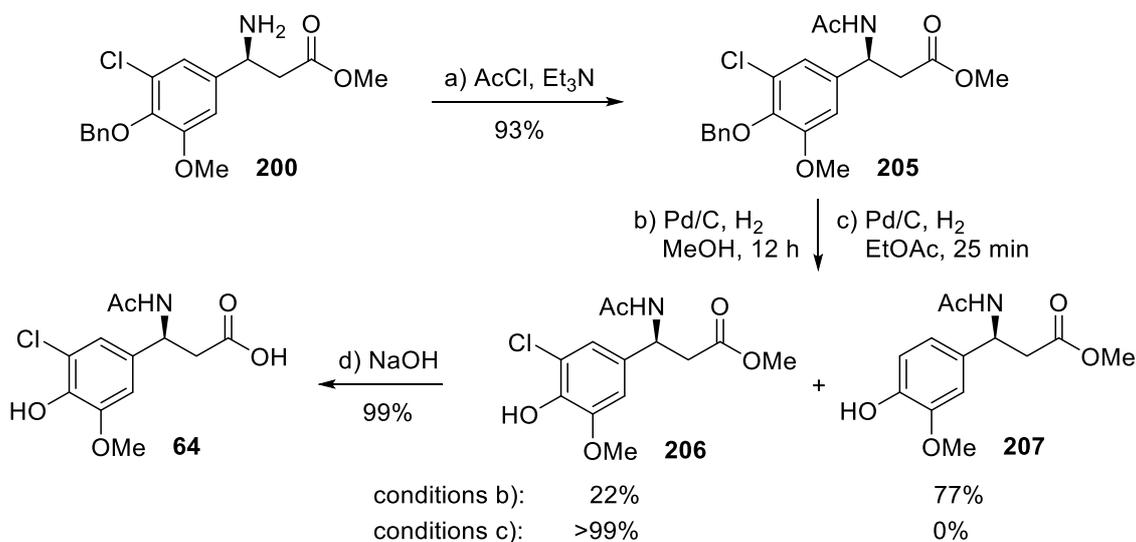
<sup>134</sup> K. Matsumura, X. Zhang, K. Hori, T. Murayama, T. Ohmiya, H. Shimizu, T. Saito, N. Sayo, *Org. Process Res. Dev.* **2011**, *15*, 1130-1137.



Reagents and conditions: a) NH<sub>4</sub>OAc (5.0 eq), MeOH, 70 °C, 9 h, 97%, b) ((*R*)-DM-Segphos)Ru(OAc)<sub>2</sub> (1.0 mol%), AcOH (2.0 eq), H<sub>2</sub> (30 atm.), MeOH, 80 °C, 5 h, 65%, 97% ee.

**Scheme 55:** Synthesis of  $\beta$ -amino ester **200**.

Acetylation of **200** proceeded smoothly to provide  $\beta$ -amido ester **205** (**Scheme 56**). The subsequent hydrogenolysis of the benzyl ether was found to be exceedingly sensitive to solvent and reaction time. Thus, employment of 10% Pd/C in MeOH gave a mixture of the desired phenol **206** (22%) and dechlorinated phenol **207** (77%) after 12 h (**Scheme 56**).<sup>49,135</sup> Altering the solvent to ethyl acetate furnished **206** in virtually quantitative yield after only 25 minutes. Further treatment of **206** with aqueous sodium hydroxide cleanly saponified the ester moiety and allowed isolation of the  $\beta$ -amino acid fragment **64** in excellent yield.



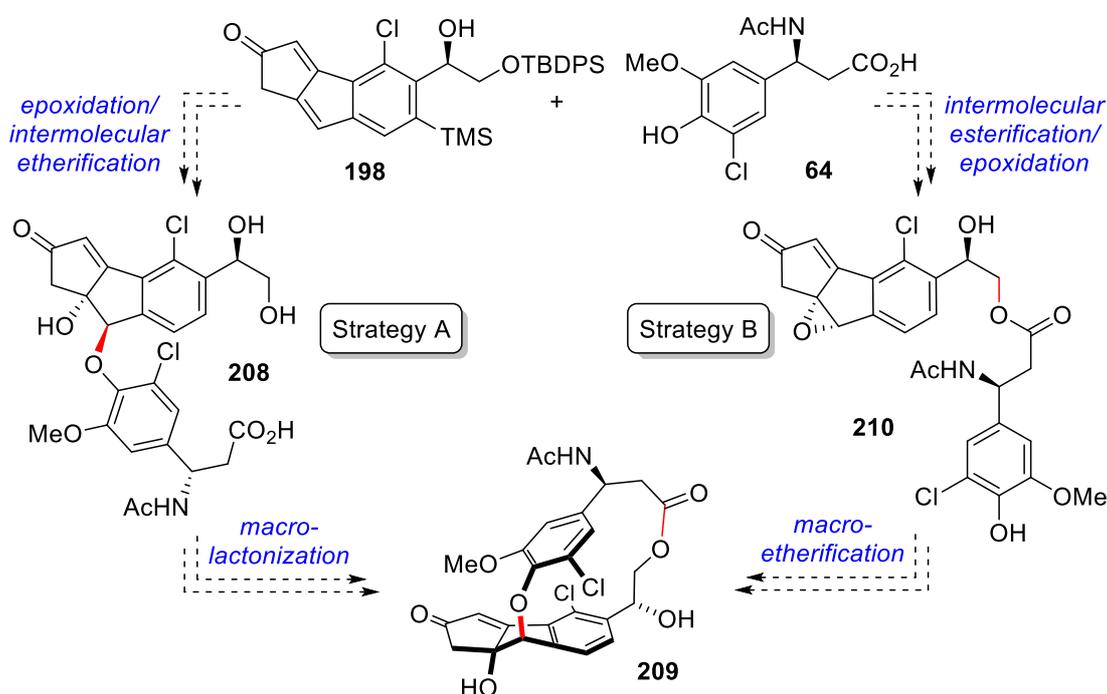
Reagents and conditions: a) AcCl (1.2 eq), Et<sub>3</sub>N (1.3 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 1 h, 93%; b) 10% Pd/C (10 mol%), H<sub>2</sub> (1 atm.), MeOH, 23 °C, 12 h, 22% **206**, 77% **207**; c) 10% Pd/C (2.5 mol%), H<sub>2</sub> (1 atm.), EtOAc, 23 °C, 25 min, >99% **206**; d) aq. NaOH (4.0 eq), THF/MeOH, 25 °C, 1.5 h, 99%.

**Scheme 56:** Completion of the  $\beta$ -amino acid synthesis.

<sup>135</sup> Dechlorinated phenol **207** was not separable from phenol **206**, but identified based on <sup>1</sup>H NMR and HRMS analysis.

***6. Studies towards the  
Fijiolide A Aglycone***

From the outset, two complementary strategies towards the fijiolide's [2.6]paracyclophane were considered, both starting from synthesized building blocks **198** and **64** (Scheme 57). In the context of strategy A, diastereoselective epoxidation of indene **198** (or a related structure), followed by intermolecular opening with an appropriate  $\beta$ -amino acid would lead to *seco*-acid **208**. Macrolactonization would then provide [2.6]paracyclophane **209**. In contrast, strategy B would proceed *via* intermolecular esterification and indene epoxidation in either order, giving cyclization precursor **210**. [2.6]Paracyclophane formation would then be realized by an unprecedented macroetherification reaction.



**Scheme 57:** Complementary strategies towards the [2.6]paracyclophane from fragments **198** and **64**.

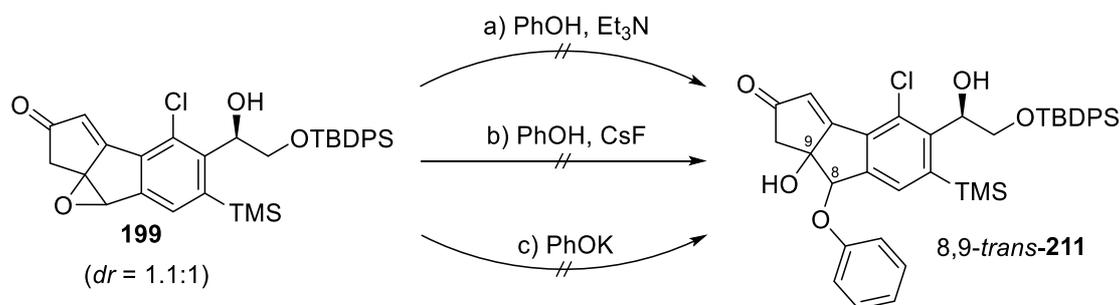
The atropselectivity of [2.6]paracyclophane formation in both strategies would be of paramount importance. Due to numerous macrolactonization methods being described,<sup>136</sup> synthetic studies following strategy A were conducted first.

<sup>136</sup> A. Parenty, X. Moreau, J. M. Campagne, *Chem. Rev.* **2006**, *106*, 911-939.

## 6.1 Intermolecular Etherification/ Macrolactonization Approach

### 6.1.1 Attempted Fragment Coupling via Nucleophilic Epoxide Opening

With indene epoxide **199** in hand (*cf.* chapter 4.4.2), we began investigating epoxide opening by the  $\beta$ -amino acid fragment to introduce the aryl ether linkage. Prior to testing the fragment coupling with advanced material, simple phenol was employed as a  $\beta$ -amino acid surrogate. As depicted in **Scheme 58**, initial trials failed under the applied reaction conditions.<sup>137,138,139</sup> It is worth mentioning that epoxide **199** appeared to be poorly stable towards base. For all executed experiments, formation of a black reaction mixture was observed immediately upon addition of all reagents into the reaction vial, and unspecific degradation of the starting material was observed in each case.<sup>140</sup>



*Reagents and conditions:* a) PhOH (2.0 eq), Et<sub>3</sub>N (2.0 eq), MeOH/H<sub>2</sub>O (v/v = 4/1), 70 °C, 1 h; b) PhOH (2.0 eq), CsF (5.0 eq), DMF, 70 °C, 18 h; c) PhOK (2.0 eq), DMF, 35 °C, 2 h.

**Scheme 58:** Attempted opening of epoxide **199** with phenol.

We reasoned that the presence of the ketone may be the origin of the encountered base sensitivity, thus interfering in the reactions described above. More precisely,  $\alpha$ -deprotonated enone species **212** (**Scheme 59**) could give rise to a fulvene *exo*-epoxide **213** (**Scheme 59**, path A), or result in formation of cyclopentadienone intermediate **214** *via* intramolecular epoxide opening (**Scheme 59**, path B). Both structural motifs are reported to be highly reactive, and rapidly undergo [4+2] cycloaddition reactions and polymerization.<sup>141</sup>

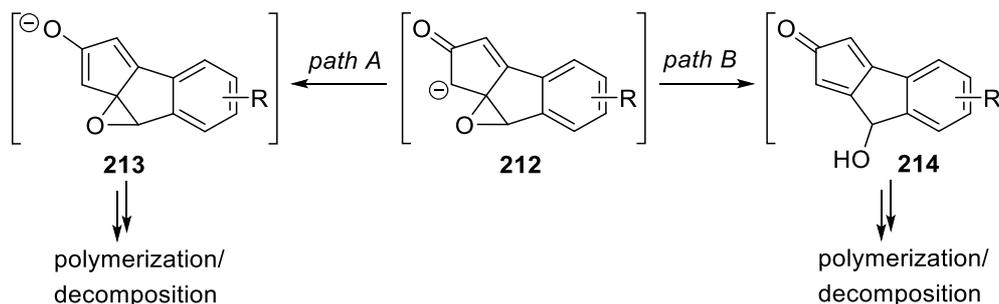
<sup>137</sup> J. R. Luly, N. Yi, J. Soderquist, H. Stein, J. Cohen, T. J. Perun, J. J. Plattner, *J. Med. Chem.* **1987**, *30*, 1609-1616.

<sup>138</sup> a) S. Kawata, M. Hirama, *Tetrahedron Lett.* **1998**, *39*, 8707-8710; b) T. Sasaki, M. Inoue, M. Hirama, *Tetrahedron Lett.* **2001**, *42*, 5299-5303.

<sup>139</sup> a) J. R. Vyvyan, J. M. Oaksmith, B. W. Parks, E. M. Peterson, *Tetrahedron Lett.* **2005**, *46*, 2457-2460; b) J. Zezula, K. C. Rice, T. Hudlicky, *Synlett* **2007**, *2007*, 2863-2867.

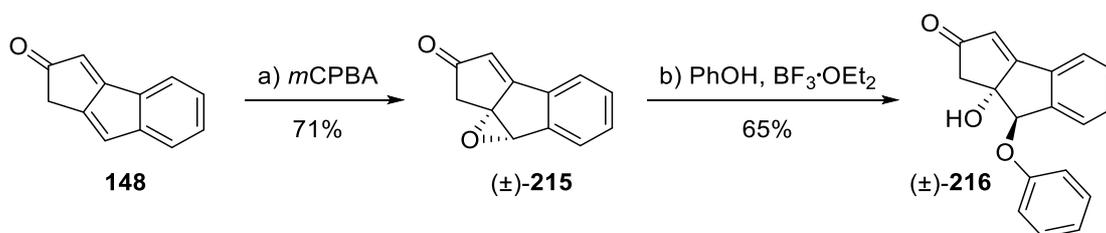
<sup>140</sup> Similarly, complete substrate degradation was observed in all attempts to convert indenylcyclopentenones into fulvene triflates by deprotonation and simultaneous trapping of the enolate with PhNTf<sub>2</sub> or Comins reagent.

<sup>141</sup> a) G. Bernardinelli, A. F. Thomas, C. Perret, *Acta Cryst. C* **1986**, *42*, 638-640; b) T. Jikyo, M. Eto, K. Harano, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3463-3470; c) Z. Xi, Q. Song, *J. Org. Chem.* **2000**, *65*, 9157-9159.



**Scheme 59:** Potential keto epoxide decomposition pathways under basic conditions.

Subsequent fragment coupling studies were conducted on a less precious epoxide. Thus, indenylcyclopentenone **148** was synthesized and converted into epoxide ( $\pm$ )-**215** using *m*CPBA (**Scheme 60**).<sup>97</sup> Pleasingly, Lewis acid mediated nucleophilic opening of epoxide ( $\pm$ )-**215** provided the target phenylether ( $\pm$ )-**216** in 65% yield.<sup>142</sup>

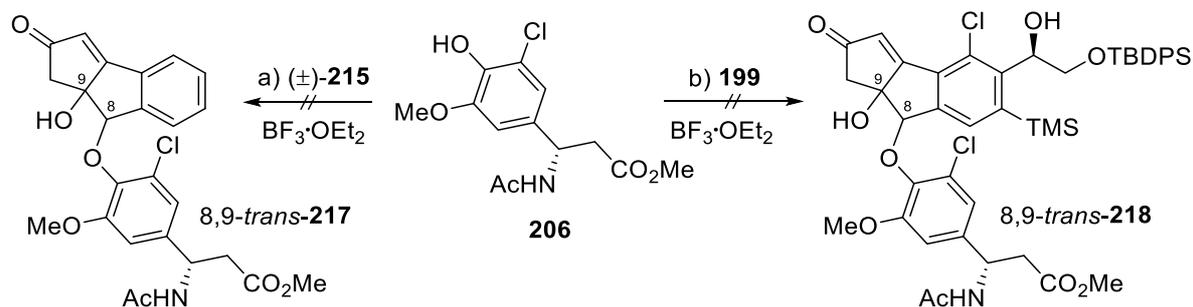


*Reagents and conditions:* a) *m*CPBA (10 eq), PhMe, 23 °C, 2.5 h, 71%; b) PhOH (10 eq), BF<sub>3</sub>·OEt<sub>2</sub> (3.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 45 min, 65%.

**Scheme 60:** Successful opening of model epoxide ( $\pm$ )-**215** with phenol.

Direct application of these conditions to the opening of epoxide ( $\pm$ )-**215** with  $\beta$ -amino ester **206** (*cf.* **Scheme 57**) predominantly led to decomposition of ( $\pm$ )-**215** (**Scheme 61**) and only trace amounts of aryether 8,9-*trans*-**217** were detected (HRMS). Conversion of fully functionalized epoxide **199** with **206** under the same conditions did not deliver any aryl ether 8,9-*trans*-**218**. Several additional coupling attempts to produce 8,9-*trans*-**217**, employing Sc(OTf)<sub>3</sub>, Al(OTf)<sub>3</sub>, CsF and CeCl<sub>3</sub>·7H<sub>2</sub>O under various conditions led to yields significantly below 10% in all cases.

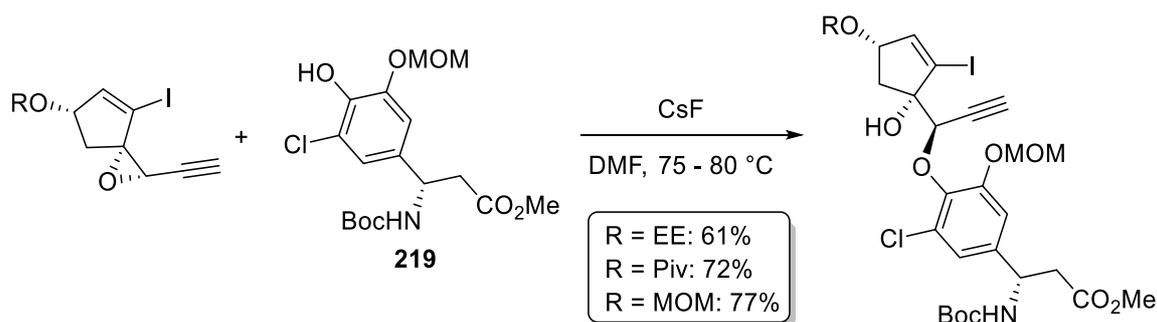
<sup>142</sup> D. Aburano, F. Inagaki, S. Tomonaga, C. Mukai, *J. Org. Chem.* **2009**, *74*, 5590-5594.



Reagents and conditions: a) **(±)-215** (1.0 eq), **206** (10 eq),  $\text{BF}_3 \cdot \text{OEt}_2$  (3.0 eq),  $\text{CH}_2\text{Cl}_2$ , 0 °C, 45 min;  
 b) **199** (1.0 eq), **206** (10 eq),  $\text{BF}_3 \cdot \text{OEt}_2$  (3.0 eq),  $\text{CH}_2\text{Cl}_2$ , 0 °C, 45 min.

**Scheme 61:** Failed coupling of  $\beta$ -amino ester **206** with epoxides **(±)-215** and **199**.

Efficient nucleophilic opening of epoxides by  $\beta$ -amino ester **219** and CsF has been reported by Hirma *et al.* (**Scheme 62**).<sup>138b,143,49</sup> In contrast to our keto epoxide systems **199** and **(±)-215**, these epoxides do not feature enone moieties, but instead protected allylic alcohols.

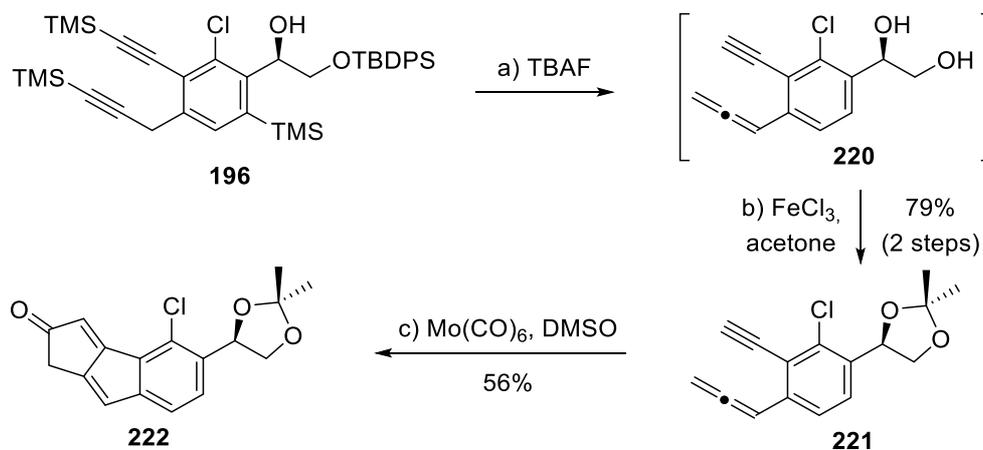


**Scheme 62:** Hirma's CsF mediated coupling of **219** to epoxides.

Guided by Hirma's work (**Scheme 62**), we aimed to prepare a protected hydroxy epoxide and re-examine the CsF mediated coupling with a phenolic nucleophile. In addition, a fluoride tolerating protecting group on the vicinal diol was envisaged. To realize this goal, acetone **222** was to be synthesized from chlorobenzene **196** (**Scheme 63**). Remarkably, addition of TBAF to **196** at room temperature resulted in a four-fold silyl cleavage and isomerization of the propargyl handle in a very clean manner.<sup>99b</sup> Subsequent exposure of allene-yne **220** to  $\text{FeCl}_3$  in acetone afforded acetone **221** in 79% yield over 2 steps.<sup>144</sup> The ensuing Pauson-Khand reaction delivered acetone **222** in 56% yield.

<sup>143</sup> M. Inoue, T. Sasaki, S. Hatano, M. Hirma, *Angew. Chem. Int. Ed.* **2004**, *43*, 6500-6505.

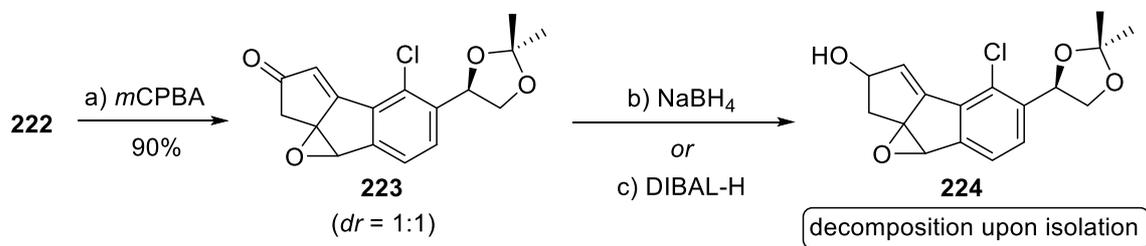
<sup>144</sup> I. Karame, M. Alame, A. Kanj, G. N. Baydoun, H. Hazimeh, M. el Masri, L. Christ, *C. R. Chim.* **2011**, *14*, 525-529.



Reagents and conditions: a) TBAF (5.0 eq), THF, 23 °C, 45 min; b) FeCl<sub>3</sub> (0.1 eq), acetone, 23 °C, 40 min, 79% (2 steps); c) Mo(CO)<sub>6</sub> (1.5 eq), DMSO (10 eq), PhMe, 90 °C, 15 min, 56%.

**Scheme 63:** Synthesis of acetonide **222**.

We then subjected **222** to epoxidation with *m*CPBA, and obtained keto epoxide **223** as a 1:1 mixture of diastereomers (**Scheme 64**). The enone was then reduced to the corresponding allylic alcohol **224**. Reduction with both NaBH<sub>4</sub> and DIBAL-H at low temperature gave rise to complex crude product mixtures. These could not be purified by flash chromatography due to decomposition upon exposure to silica gel.



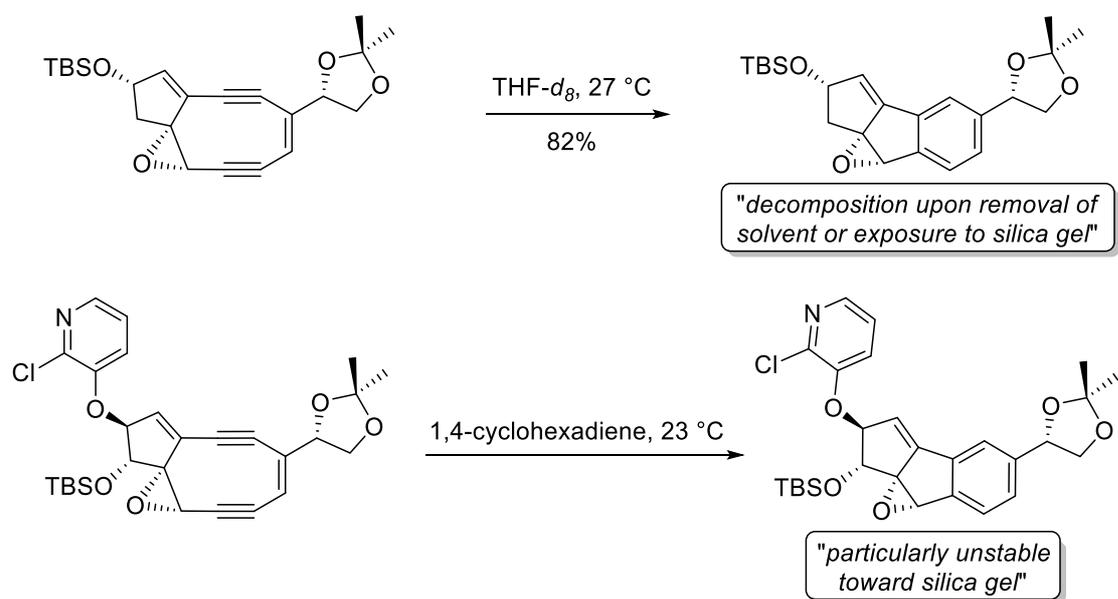
Reagents and conditions: a) *m*CPBA (10 eq), PhMe, 30 °C, 4 h, 90%; b) NaBH<sub>4</sub> (1.2 eq), EtOH, -18 °C, 2 h; c) DIBAL-H (2.2 eq), THF, -78 °C, 2 h.

**Scheme 64:** Attempted synthesis of hydroxyl epoxide **224**.

Similar observations have been made by Hirama and Myers during their studies of 9-membered cyclic epoxy enediynes (**Scheme 65**).<sup>145,146</sup> These systems spontaneously undergo Bergman cyclization to form unstable tricyclic epoxides of close structural resemblance to **224**.

<sup>145</sup> K.-i. Iida, M. Hirama, *J. Am. Chem. Soc.* **1995**, *117*, 8875-8876.

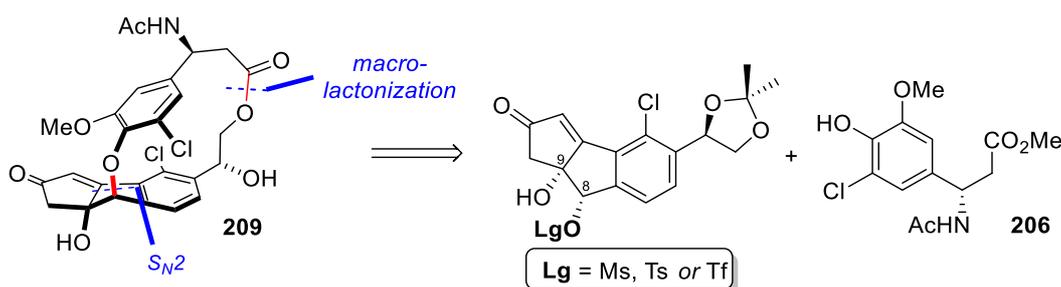
<sup>146</sup> A. G. Myers, S. D. Goldberg, *Angew. Chem. Int. Ed.* **2000**, *39*, 2732-2735.



**Scheme 65:** Reported related unstable tricyclic epoxides.

### 6.1.2 Fragment Coupling *via* Nucleophilic Substitution of Activated Alcohols

It appeared our initial strategy towards the fijiolide A [2.6]paracyclophane *via* nucleophilic epoxide opening was unfeasible due to the inherent base sensitivity of the employed keto epoxides. We hypothesized that a *mono*-activated C-8/C-9 diol would render the key fragment less susceptible towards base-induced decomposition, and consequently allow fragment coupling by an S<sub>N</sub>2 reaction. Our accordingly modified fragment coupling strategy is depicted in **Scheme 66**.

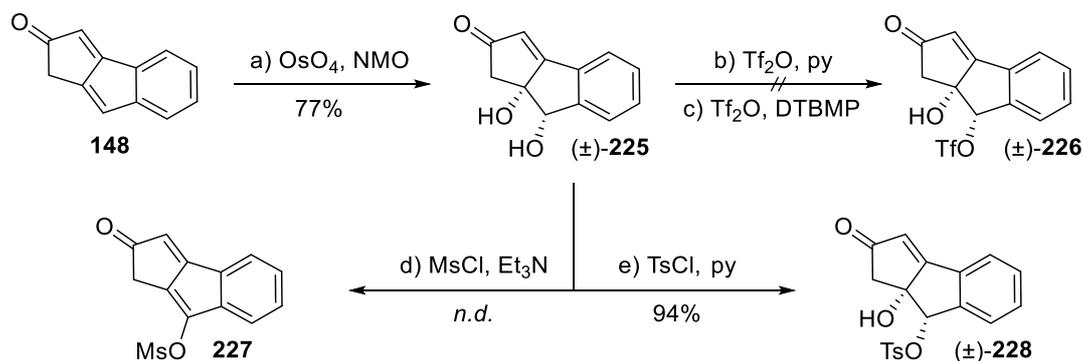


**Scheme 66:** Envisaged fragment coupling and [2.6]paracyclophane formation *via* S<sub>N</sub>2/macrolactonization.

To explore this strategy, model substrate **148** was first subjected to dihydroxylation,<sup>147</sup> followed by chemoselective activation of the benzylic hydroxyl group of *cis*-diol ( $\pm$ )-**225** (**Scheme 67**). Attempted triflation using Tf<sub>2</sub>O/pyridine or Tf<sub>2</sub>O/DTBMP led to clean conversion, as judged by TLC, followed by product degradation upon attempts at isolation. Reaction of ( $\pm$ )-**225** with MsCl and Et<sub>3</sub>N activated both hydroxyl groups, and was followed by elimination of the tertiary mesylate to give rise to indenylcyclopentenone **227**.<sup>148</sup> We found that selective tosylation at 8-OH proceeded smoothly. Therefore, model tosylate ( $\pm$ )-**228** was used as the electrophilic coupling partner in subsequent experiments towards arylether 8,9-*trans*-**217** (**Table 16**), which could not be separated from unreacted  $\beta$ -amino ester **206** *via* flash chromatography.

<sup>147</sup> L. Jørgensen, S. J. McKerrall, C. A. Kuttruff, F. Ungeheuer, J. Felding, P. S. Baran, *Science* **2013**, *341*, 878-882.

<sup>148</sup> Compound **227** was not isolated. Its structure was tentatively assigned by <sup>1</sup>H NMR analysis of the crude reaction mixture.



*Reagents and conditions:* a) OsO<sub>4</sub> (5.0 mol%), NMO (1.2 eq), citric acid (1.2 eq), *t*BuOH/H<sub>2</sub>O (1:1), 23 °C, 17 h, 77%; b) Tf<sub>2</sub>O (2.5 eq), pyridine (5.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 2 h; c) Tf<sub>2</sub>O (1.5 eq), DTBMP (3.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 2 h; d) MsCl (1.5 eq), Et<sub>3</sub>N (1.5 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to 23 °C, 20 h; e) TsCl (2.0 eq), pyridine, 23 °C, 61 h, 94%.

**Scheme 67:** Investigated activation of *cis*-diol (±)-225.

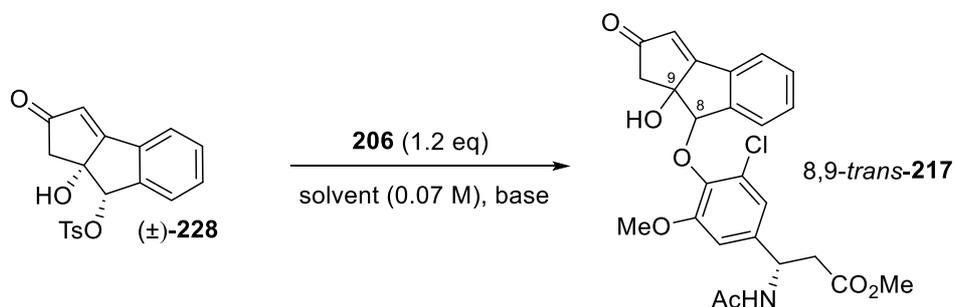
Utilization of K<sub>2</sub>CO<sub>3</sub> in MeCN, or CsF in DMF, mainly led to degradation of the starting tosylate and only trace amounts of the desired aryl ether were observed (entry 1-2).<sup>149,150</sup> Employing NaH/DMF and DBU/dioxane slightly improved the yield of 8,9-*trans*-217 to 8% and 19%, respectively (entries 3-4).<sup>151</sup> A more promising 23% yield at 45% conversion was obtained using Cs<sub>2</sub>CO<sub>3</sub> in THF under microwave irradiation (entry 5).<sup>152</sup> The reaction yield could be further increased to 42% by a prolonged reaction time (entry 6). However, more than 50% of starting tosylate was still degraded, and therefore could not be re-isolated. Altering the reaction temperature did not enable higher yields, or recovery of starting material (entries 7-8). Complete degradation of (±)-228 was observed by conducting the reaction at higher concentration (entry 9). In order to enable larger reaction scales, the reaction was performed under conventional heating to provide 8,9-*trans*-217 in 34% (THF) and 35% (dioxane, 90% conversion) yield, respectively (entries 10-11). A notable solvent dependence on arylether formation was encountered: utilization of DMF resulted in only an 8% yield, besides degradation of (±)-228 (entry 12). As DMF is known to undergo degradation to CO and dimethylamine at high temperature, especially under basic conditions, we assume that potentially formed HNMe<sub>2</sub> could undergo undesirable side reactions with the enone moiety.

<sup>149</sup> T. Ohsumi, M. Hatakoshi, H. Kisida, N. Matsuo, I. Nakayama, N. Itaya, *Agric. Biol. Chem.* **1985**, *49*, 3197-3202.

<sup>150</sup> P. Ballard, R. H. Bradbury, C. S. Harris, L. F. A. Hennequin, M. Hickinson, J. G. Kettle, J. Kendrew, T. Klinowska, D. J. Ogilvie, S. E. Pearson, E. J. Williams, I. Wilson, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4908-4912.

<sup>151</sup> J. F. Bower, P. Szeto, T. Gallagher, *Org. Lett.* **2007**, *9*, 3283-3286.

<sup>152</sup> N. K. Jobson, A. R. Crawford, D. Dewar, S. L. Pimlott, A. Sutherland, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4996-4998.

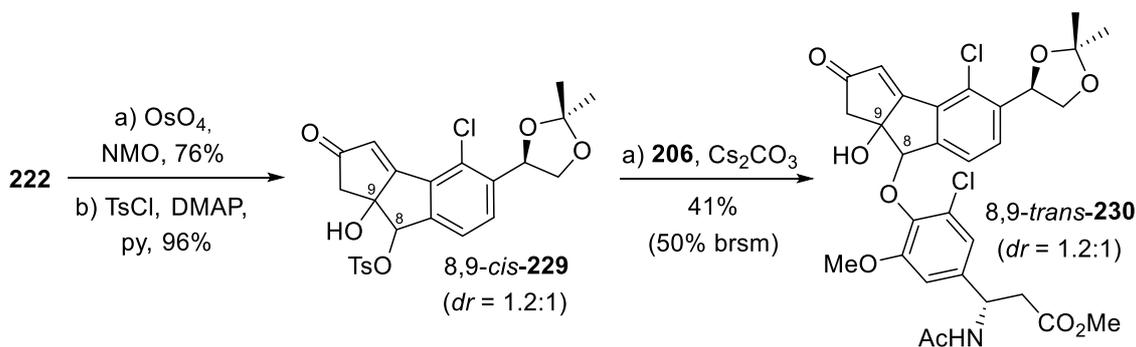
**Table 16:** Optimization table for the S<sub>N</sub>2 reaction of (±)-**228** with β-tyrosine derivative **206**.

Entry	Base (eq)	Solvent	T [°C]	t [h]	Yield / conversion <sup>[a]</sup>
1	K <sub>2</sub> CO <sub>3</sub> (7.5) <sup>[b]</sup>	MeCN	70	8	<5 / 100
2	CsF (1.5)	DMF	70 → 90	36	<5 / 84
3	NaH (1.9) <sup>[c]</sup>	DMF	45 → 80	36	8 / 100
4	DBU (1.2)	Dioxane	85	24	19 / 66
5	Cs <sub>2</sub> CO <sub>3</sub> (2.4)	THF	100 (MW)	4	23 / 45
6	Cs <sub>2</sub> CO <sub>3</sub> (2.4)	THF	100 (MW)	8	42 / 100
7	Cs <sub>2</sub> CO <sub>3</sub> (1.2)	THF	150 MW)	1	21 / 100
8	Cs <sub>2</sub> CO <sub>3</sub> (2.4)	THF	85 (MW)	6	33 / 92
9	Cs <sub>2</sub> CO <sub>3</sub> (2.4)	THF <sup>[d]</sup>	100 (MW)	8	0 / 100
10	Cs <sub>2</sub> CO <sub>3</sub> (1.2)	THF	100	6	34 / 100
11	Cs <sub>2</sub> CO <sub>3</sub> (1.2)	Dioxane	100	6	35 / 90
12	Cs <sub>2</sub> CO <sub>3</sub> (2.4)	DMF	100 (MW)	8	8 / 100

<sup>[a]</sup> Determined by <sup>1</sup>H NMR using 1,3,5-TMB as internal standard;

<sup>[b]</sup> 5.0 eq **206** were employed; <sup>[c]</sup> 2.0 eq **206** were employed; <sup>[d]</sup> reaction concentration of 0.35 M.

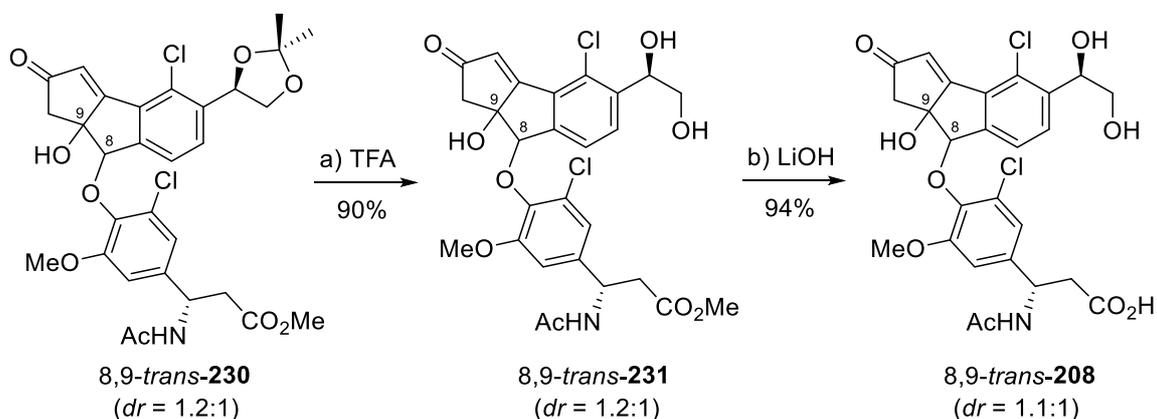
After successful realization of this model reaction, we next examined the applicability of the aryl ether forming S<sub>N</sub>2 reaction to the fully functionalized fijiolide A cyclopenta[*a*]indene core. In analogy to the synthesis of (±)-**228**, **222** was chemoselectively dihydroxylated at the indenyl double bond (*dr* = 1.2:1), and subsequently *mono*-activated with TsCl (**Scheme 68**). Submission of 8,9-*cis*-**229** to Cs<sub>2</sub>CO<sub>3</sub> in dioxane furnished aryl ether 8,9-*trans*-**230** in 41% yield, along with 18% unreacted starting material.



*Reagents and conditions:* a) OsO<sub>4</sub> (5.0 mol%), NMO (2.0 eq), THF/H<sub>2</sub>O (v/v = 9/1), 23 °C, 4 h, 76%,  $dr = 1.2:1$ ; b) TsCl (4.0 eq), DMAP (15 mol%), pyridine, 23 °C, 13 h, 96%; c) **206** (1.2 eq), Cs<sub>2</sub>CO<sub>3</sub> (1.2 eq), dioxane, 90 °C, 7.5 h, 41% (50% brsm).

**Scheme 68:** Synthesis of aryl ether 8,9-trans-230 by nucleophilic substitution.

With preparative quantities in hand, 8,9-trans-230 required modification for the crucial macrolactonization step. Pleasingly, 8,9-trans-230 proved very tolerant towards Brønsted acids, and removal of the acetonide in neat TFA proceeded smoothly (**Scheme 69**). At this stage, 8,9-trans-231 could be easily separated from unreacted  $\beta$ -tyrosine **206** that had been employed in the fragment coupling step. Saponification of the methyl ester of 8,9-trans-231 provided *seco*-acid 8,9-trans-208 in almost quantitative yield, enabling extensive studies of the subsequent macrolactonization step.



*Reagents and conditions:* a) TFA (90 mM), 0 °C, 1 h, 90%; b) LiOH (1.5 eq), MeCN/H<sub>2</sub>O (v/v = 1/1), 23 °C, 4 h, 94%.

**Scheme 69:** Synthesis of *seco*-acid 8,9-trans-208.

### 6.1.3 Macrolactonization Studies

In order to access the fully functionalized fijiolide A [2.6]paracyclophane **209** from *seco*-acid 8,9-*trans*-**208**, numerous macrolactonization methods were screened (**Table 17**). We commenced by screening Corey-Nicolaou conditions<sup>153</sup> in CH<sub>2</sub>Cl<sub>2</sub>, PhMe or THF as solvent. However, severe solubility issues were encountered for the highly polar *seco*-acid, as a result of the three unprotected hydroxyl groups, the acetamide, and the free carboxylic acid. Therefore, no conversion was achieved (entry 1). Consequently, we executed the macrolactonization in pure polar aprotic solvents, or as mixtures with more commonly employed solvents for macrocyclization. Re-examining the method of Corey and Nicolaou in DMF resulted in dissolution of the starting material. However, no conversion into the intermediate thiopyridyl ester, or to the desired **209** and its 8-*epi*-9-*epi* diastereomer **232** was observed (entry 2). A similar result was obtained using refluxing toluene as the solvent (entry 3). Attempted activation of the *seco*-acid by conversion into a mixed Yamaguchi anhydride engendered only trace conversion, with no detectable formation of **209/232** (entry 4).<sup>154</sup> The same result was obtained for attempted activation of 8,9-*trans*-**208** with Mukaiyama's reagent (entries 5).<sup>155</sup> Following this, the recently developed macrolactonization method reported by Shiina *et al.*, using 2-methyl-nitrobenzoic acid anhydride (MNBA) for carboxylic acid activation was examined. However, low conversion, and again no detectable traces of the desired macrolactone resulted from these experiments (entries 6-8).<sup>156</sup> In addition, we subjected 8,9-*trans*-**208** to Mitsunobu macrolactonization conditions and achieved full conversion after only 90 minutes. However, no formation of any [2.6]paracyclophane product was observed (entry 9). Overall, in none of these cyclization attempts, intermolecular esterification affording a *seco*-acid dimer could be ascertained by <sup>1</sup>H NMR and HRMS analysis.

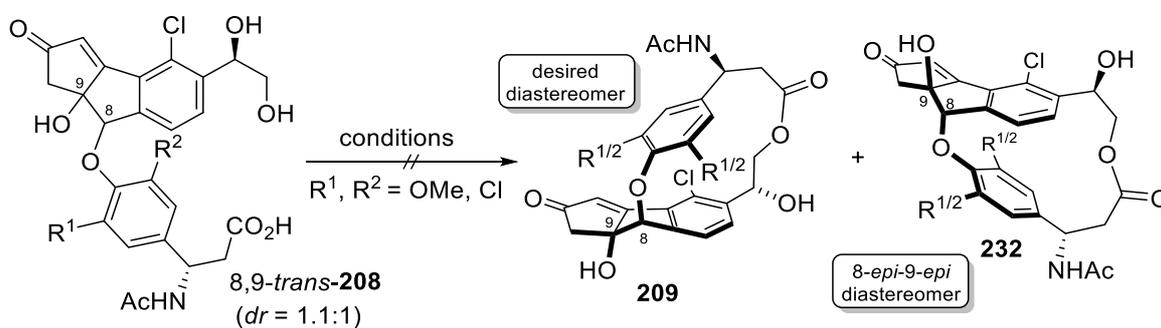
<sup>153</sup> E. J. Corey, K. C. Nicolaou, *J. Am. Chem. Soc.* **1974**, *96*, 5614-5616.

<sup>154</sup> J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993.

<sup>155</sup> T. Mukaiyama, M. Usui, K. Saigo, *Chem. Lett.* **1976**, *5*, 49-50.

<sup>156</sup> a) I. Shiina, M. Kubota, R. Ibuka, *Tetrahedron Lett.* **2002**, *43*, 7535-7539; b) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822-1830.

Table 17: Examined macrolactonization conditions.



Entry	Reagents (eq) and conditions
1	(PyS) <sub>2</sub> (1.6), PPh <sub>3</sub> (1.7), CH <sub>2</sub> Cl <sub>2</sub> , PhMe or THF, 23 °C
2	(PyS) <sub>2</sub> (2.0), PPh <sub>3</sub> (2.0), DMF, 23 °C, 24 h
3	(PyS) <sub>2</sub> (1.5), PPh <sub>3</sub> (1.5), PhMe, 110 °C, 18 h
4	2,4,6-TCBC (10), Et <sub>3</sub> N (20), DMAP (20), THF/DMF, 23 °C to 50 °C, 17 h <sup>[a]</sup>
5	1-Methyl-2-chloropyridinium iodide (5.0), Et <sub>3</sub> N (10), MeCN, 85 °C, 44 h
6	MNBA (2.4), DMAP (4.8), CH <sub>2</sub> Cl <sub>2</sub> /DMF, 40 °C, 13 h <sup>[b]</sup>
7	MNBA (2.4), DMAP (4.8), CH <sub>2</sub> Cl <sub>2</sub> /DMF, 23 °C, 19 h <sup>[c]</sup>
8	MNBA (4.0), DMAP (8.0), CH <sub>2</sub> Cl <sub>2</sub> , 23 °C, 120 h
9	DIAD (12), PPh <sub>3</sub> (12), THF/DMF, 0 °C to 10 °C, 90 min <sup>[d]</sup>

<sup>[a]</sup> Addition of 8,9-*trans*-208 over 4 h; <sup>[b]</sup> Addition of 8,9-*trans*-208 over 12 h;

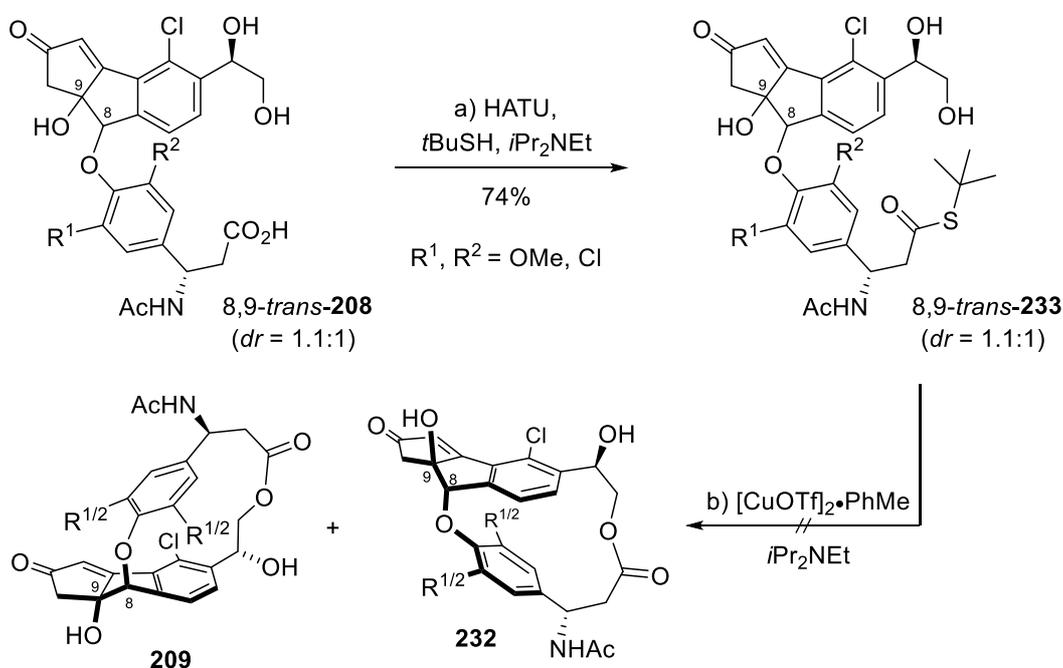
<sup>[c]</sup> Addition of 8,9-*trans*-208 over 15 h; <sup>[d]</sup> Addition of 8,9-*trans*-208 over 2 h.

We next turned to Masamune's macrolactonization method.<sup>157</sup> This features activation of an independently prepared thioester with a thiophilic metal salt, such as mercury, silver or copper.<sup>136</sup> Although this requires an additional synthetic step, we speculated that a thioester would enhance the solubility. We were therefore interested in accessing *tert*-butyl thioester 8,9-*trans*-233 (Scheme 70). Whereas submission of 8,9-*trans*-30 to Steglich esterification conditions (DCC, DMAP, *t*BuSH) did not provide the desired thioester,<sup>158</sup> 8,9-*trans*-233 could be isolated in 74% yield after activation of the *seco*-acid with HATU. Despite this pleasingly clean transformation, due to the advanced synthetic nature of 8,9-*trans*-233, only very limited quantities (2.5 mg) were obtained, still as an inseparable 1.2:1 mixture of C-8/C-9-diastereomers. Unfortunately, activation of the thioester with [CuOTf]<sub>2</sub>•PhMe in the presence of Hünig's base at 50 °C did not provide macrocycle 209, or its diastereomeric congener 232. Instead, only unreacted starting material could be detected

<sup>157</sup> S. Masamune, G. S. Bates, J. W. Corcoran, *Angew. Chem. Int. Ed.* **1977**, *16*, 585-607.

<sup>158</sup> B. Neises, W. Steglich, *Angew. Chem.* **1978**, *90*, 556-557.

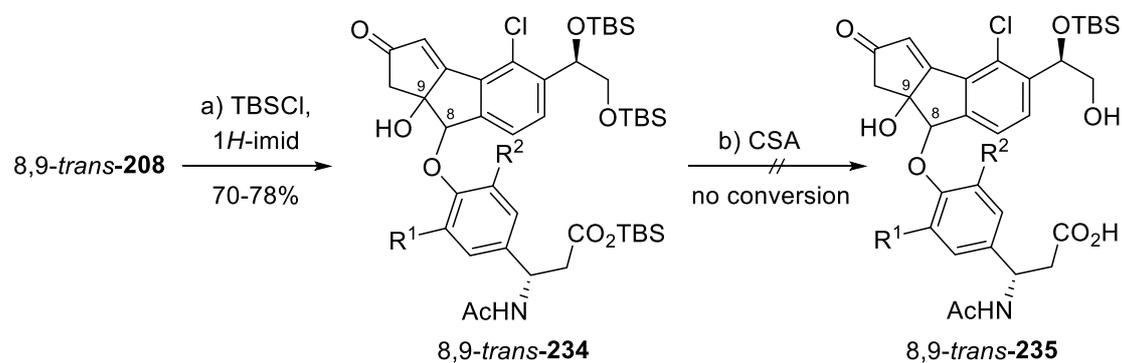
in the crude reaction mixture. An attempted HATU mediated macrocyclization of *seco*-acid 8,9-*trans*-**208** also failed to provide the desired paracyclophane.



Reagents and conditions: a) HATU (3.0 eq), *t*BuSH (6.0 eq), *i*Pr<sub>2</sub>NEt (3.0 eq), DMF, 0 °C to 23 °C, 13 h, 74%; b) [CuOTf]<sub>2</sub>·PhMe (2.5 eq), *i*Pr<sub>2</sub>NEt (10 eq), PhMe, 50 °C, 22 h.

**Scheme 70:** Attempted Masamune macrocyclization of thioester 8,9-*trans*-**233**.

Another attempt to access the fijiolide A [2.6]paracyclophane *via* a more soluble 8,9-*trans*-**208** derivative was envisaged. In this approach, silyl protection of the secondary benzylic hydroxyl group was anticipated to serve a dual purpose: improve solubility, and prevent undesired esterification. Thus, *seco*-acid 8,9-*trans*-**208** was reacted with TBSCl/*1H*-imidazole, giving rise to a mixture of *bis*- and *tris*-silylated compounds, mainly consisting of 8,9-*trans*-**234**, as judged by <sup>1</sup>H NMR (**Scheme 71**). Attempts to cleave the primary TBS ether, as well as the silyl ester of crude 8,9-*trans*-**234** with camphorsulfonic acid (CSA) in CDCl<sub>3</sub>/MeOH-*d*<sub>4</sub> were made. However, no conversion was observed for this transformation by <sup>1</sup>H NMR spectroscopy, even upon heating of the reaction mixture at 50 °C for 24 h.



Reagents and conditions: a) TBSCl (5.0 eq), 1*H*-imidazole (10 eq), DMF, 23 °C, 18 h, 70-78%; b) CSA (1.0 eq), CDCl<sub>3</sub>/MeOH-*d*<sub>4</sub>, 23 °C to 50 °C, 48 h.

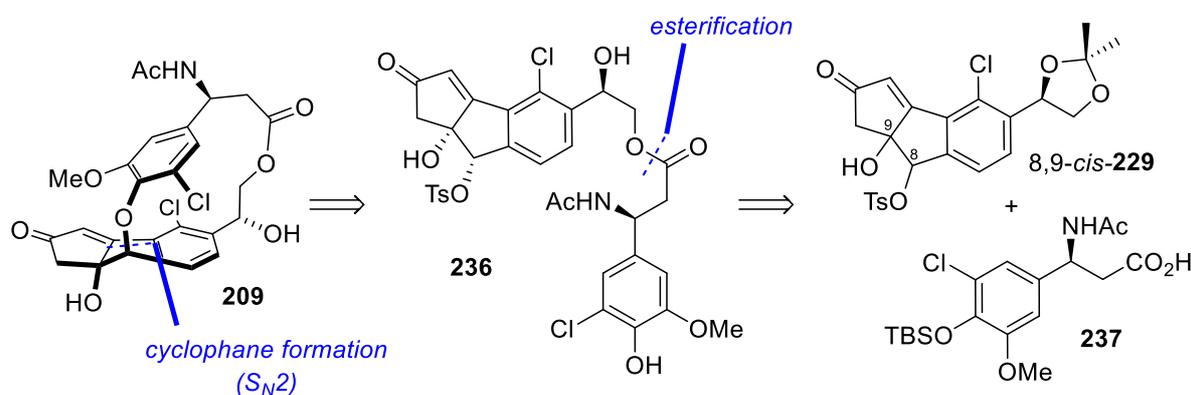
**Scheme 71:** Attempted modification of *seco*-acid 8,9-*trans*-**208**.

Based on the unsuccessful macrolactonization results discussed in this section, this strategy towards the fijiolide A [2.6]paracyclophane was abandoned in favor of a more successful synthetic approach, which was executed in parallel. This strategy is discussed in chapter 6.2.

## 6.2 Intermolecular Esterification / Macroetherification Approach

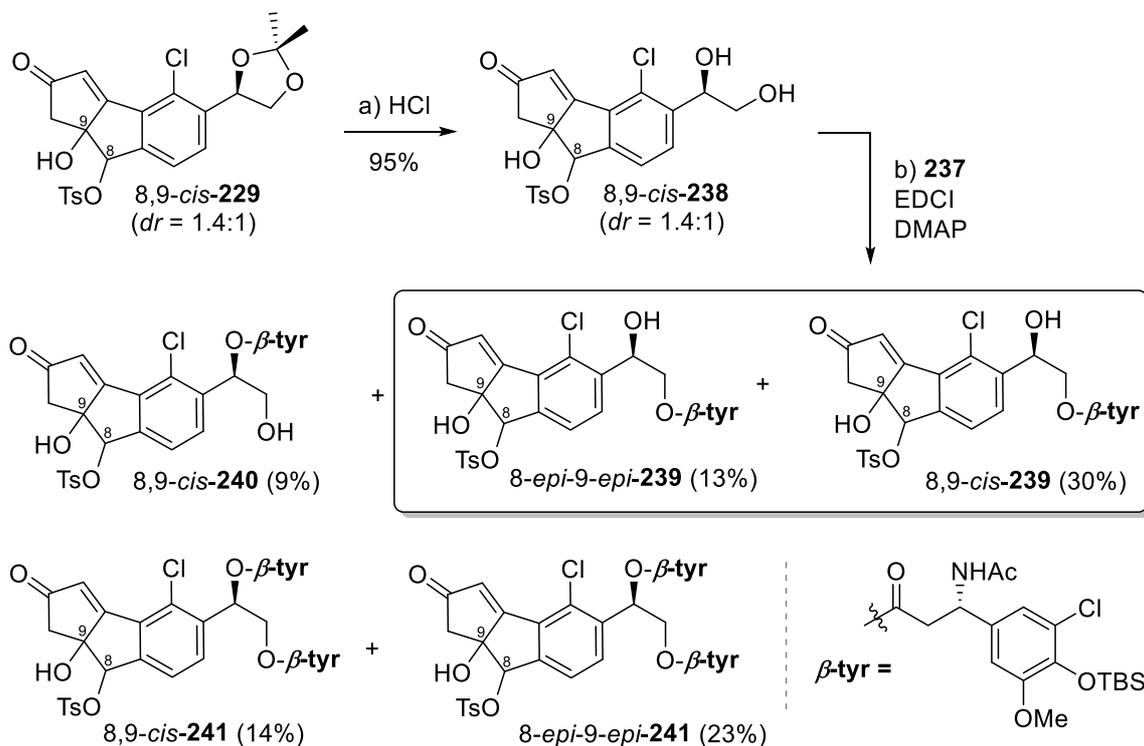
### 6.2.1 Atropselective Synthesis of the [2.6]Paracyclophane

As outlined at the beginning of chapter 6, our complementary strategy towards the fijiolides' macrocyclic aglycone bases on the synthesis of the [2.6]paracyclophane core *via* an intermolecular esterification, followed by a macrocyclic etherification (Strategy B, **Scheme 57**). Following our difficulties observed in nucleophilic epoxide opening, we planned this strategy to proceed *via* an intramolecular  $S_N2$  reaction using a tosylate leaving group (**Scheme 72**). Hence, this synthetic approach would require preparation of cyclization precursor **236**, whose synthesis was envisaged *via* ester coupling of previously synthesized tosylate 8,9-*cis*-**229** and  $\beta$ -amino acid **237**.



**Scheme 72:** Revised synthetic strategy for the fijiolide A [2.6]paracyclophane involving macroetherification.

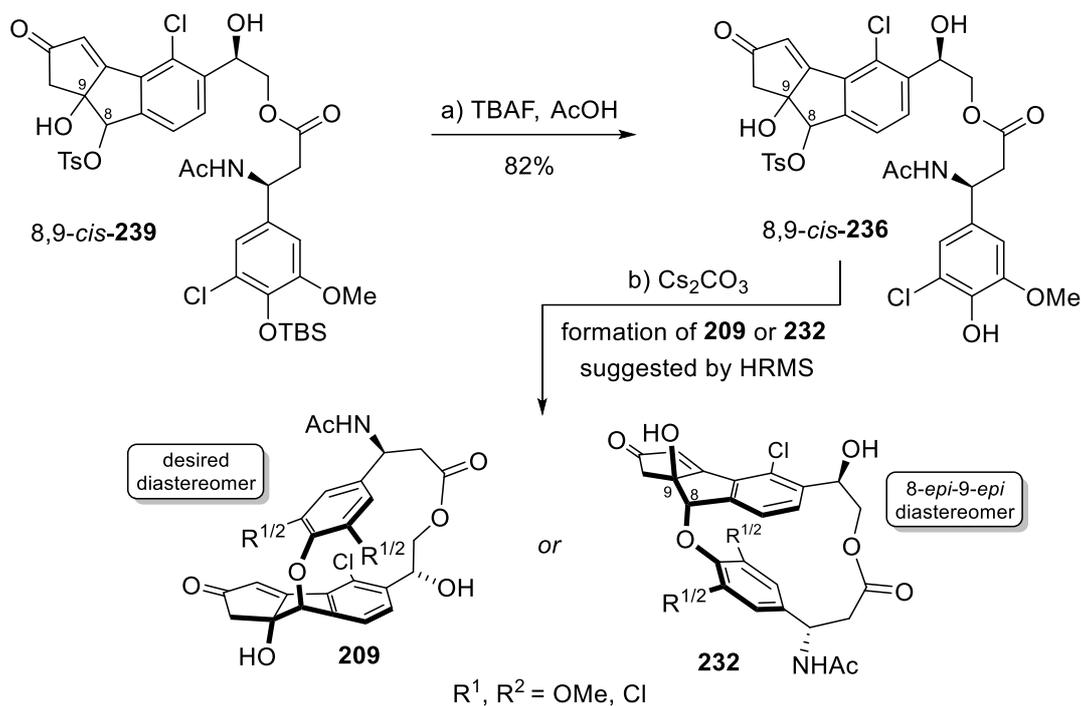
To realize this goal, the acetonide group in 8,9-*cis*-**229** was hydrolyzed with aqueous HCl, furnishing vicinal diol 8,9-*cis*-**238** in high yield (**Scheme 73**). Subsequent EDCI/DMAP mediated esterification of  $\beta$ -amino acid **237** gave rise to a variety of ester products, which could be separated by chromatographic means. *Mono*-esters 8,9-*cis*-**239** and 8-*epi*-9-*epi*-**239** were isolated in 30% and 13% yield, respectively. The absolute stereochemistry at C-8 and C-9 of both diastereomers could not be assigned on the bases of 1D and 2D NMR experiments, thus we were unaware which stereoisomer would lead to the correct paracyclophane **209**. However, both compounds could be clearly differentiated from ester 8,9-*cis*-**240**, formed in 9% yield *via* esterification of the secondary benzylic hydroxyl group. We did not observe its 8-*epi*-9-*epi* counterpart as a reaction product. However, diesters 8,9-*cis*-**241** and 8-*epi*-9-*epi*-**241** were isolated in combined 37% yield.



*Reagents and conditions:* a) 2 M HCl (30 eq), MeCN, 23 °C, 1 h, 95%; b) **237** (1.4 eq), EDCI (1.4 eq), DMAP (0.1 eq), CH<sub>2</sub>Cl<sub>2</sub>/DMF (v/v = 7/1), 0 °C, 20 h.

**Scheme 73:** Unselective fragment coupling towards cyclization precursor **236**.

At this stage we did not optimize the ester coupling step, but instead continued to explore the macroetherification approach with the more abundant diastereomer **8,9-cis-239**. This was converted into cyclization precursor **8,9-cis-236** by reaction with TBAF under buffered conditions (**Scheme 74**). With phenol **8,9-cis-236** in hand, we investigated the [2.6]paracyclophane formation. For this purpose, we applied the previously developed conditions for intermolecular fragment coupling (Cs<sub>2</sub>CO<sub>3</sub>, dioxane, 90 °C). Although the possible paracyclophanes **209** and **232** could not be isolated, they were clearly found by mass spectroscopy. The presence of *p*-toluenesulfonic acid, as the predominant component of the crude reaction mixture suggested that an S<sub>N</sub>2 displacement had indeed taken place. It was concluded that the desired macrocyclization reaction did proceed (to an unknown extent), but was accompanied by extensive substrate degradation due to the base sensitive nature of the  $\beta$ -hydroxy ketone.



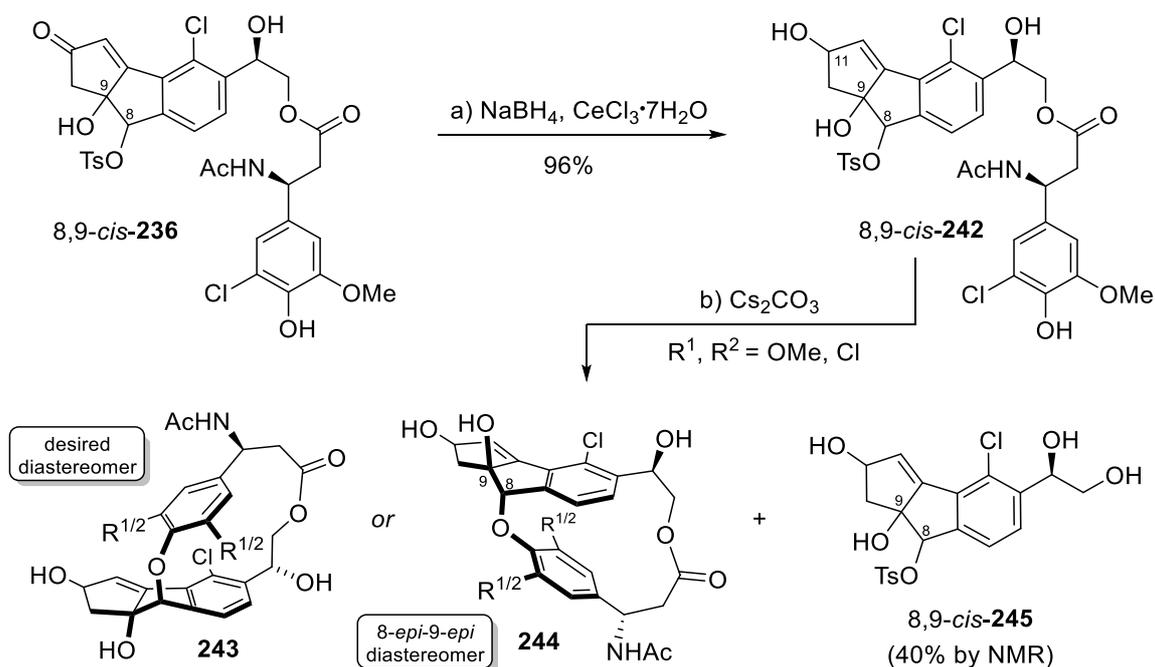
Reagents and conditions: a) TBAF (1.5 eq), AcOH (26 eq), THF, 0 °C, 3 h, 82%; b) Cs<sub>2</sub>CO<sub>3</sub> (4.0 eq), dioxane, 23 °C, 1 h, then 90 °C, 18 h.

**Scheme 74:** Attempted paracyclophane formation *via* keto ester 8,9-*cis*-**236**.

In order to address this shortcoming, cyclization precursor 8,9-*cis*-**236** was reduced under Luche conditions (**Scheme 75**). Remarkably, 1,2-reduction proceeded with complete diastereoselectivity, providing cyclization precursor 8,9-*cis*-**242** of unknown absolute configuration at C-8, C-9 and C-11.<sup>159</sup> At this stage, we did not assign the relative configuration between C-9 and C-11 as it was assumed to be irrelevant for testing its ability to undergo paracyclophane formation. In a further macrocyclization attempt, submission of 8,9-*cis*-**242** to Cs<sub>2</sub>CO<sub>3</sub>/dioxane in the presence of 4Å molecular sieves resulted in formation of deacetylated vicinal diol **245** (40%), along with an unknown product in 38% yield. <sup>1</sup>H NMR analysis of the isolated compound revealed a loss of the tosylate, while maintaining all other functional groups present in the targeted [2.6]paracyclophanes **243** and **244**.<sup>160</sup> Unfortunately, the unidentified product degraded completely before a full structure elucidation could be achieved.

<sup>159</sup> A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454-5459.

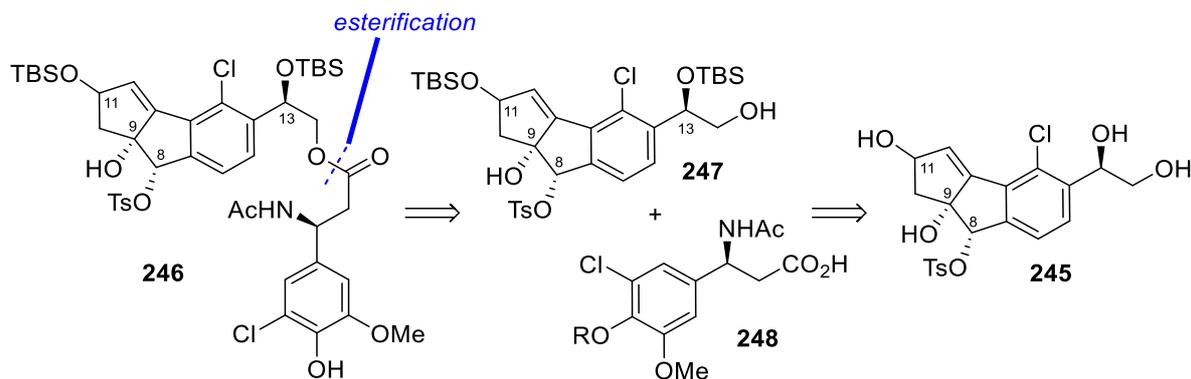
<sup>160</sup> A high resolution mass for **243**/atrop-**243** corresponding to [M+H]<sup>+</sup> or [M+Na]<sup>+</sup> was not detected, but a mass corresponding to [M+H-H<sub>2</sub>O]<sup>+</sup> was.



*Reagents and conditions:* a) NaBH<sub>4</sub> (3.0 eq), CeCl<sub>3</sub>·7H<sub>2</sub>O (3.0 eq), THF/MeOH (v/v = 1/1), -78 °C to -50 °C, 3 h, 96%; b) Cs<sub>2</sub>CO<sub>3</sub> (12 eq), 4Å-MS, dioxane, 90 °C, 5 h.

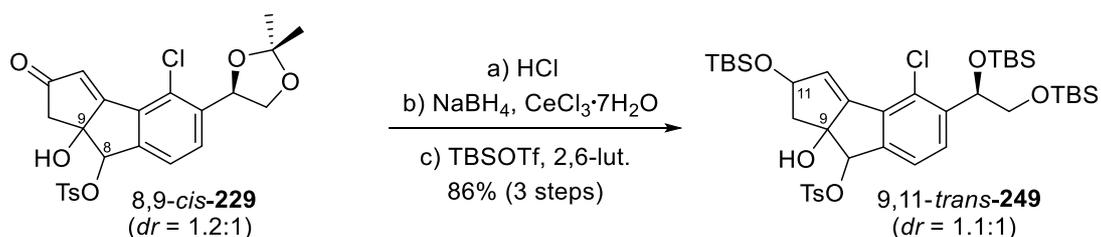
**Scheme 75:** Attempted paracyclophane formation *via* hydroxy ester 8,9-*cis*-**242**.

Despite not obtaining spectroscopic proof for a macrocyclic aryl ether, the aforementioned results appeared promising, and prompted us to further explore the macroetherification approach. We aimed to prepare a more sophisticated substrate for macrocyclization, and precursor **246** was designed as the next target to be investigated (**Scheme 76**). **246** features a protected secondary benzylic hydroxyl group at C-13, and was planned to be synthesized from likewise protected primary alcohol **247**. Thus, formation of undesired diester products during fragment coupling could be avoided. From the outset, the C-11 position would be reduced to the alcohol oxidation state and appropriately protected. We assumed that TBS protection of both the C-13 and C-11 hydroxyl group would be suitable, hence a preparation of **247** by trisilylation of tetraol **245**, followed by selective cleavage of the presumably most labile primary silyl ether was envisioned.



**Scheme 76:** Retrosynthetic analysis for doubly protected cyclization precursor **246**.

In order to accomplish the outlined synthetic strategy towards cyclization precursor **246**, acetonide **8,9-cis-229** was converted into *tris*-silyl ether **9,11-trans-249** by sequential acetonide cleavage, Luche reduction of the enone moiety, and threefold TBS protection of the intermediate tetraol (**Scheme 77**).



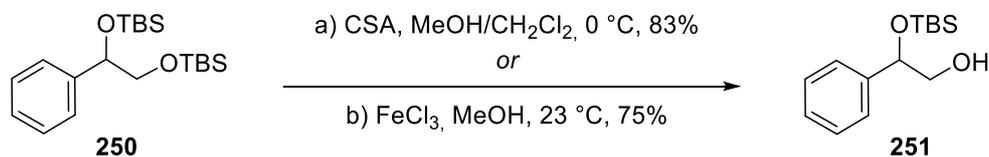
*Reagents and conditions:* a) 2 M HCl (26 eq), MeCN, 23 °C, 1 h; b) NaBH<sub>4</sub> (1.5 eq), CeCl<sub>3</sub>·7H<sub>2</sub>O (1.5 eq), THF/MeOH (1/1), -50 °C, 40 min; c) TBSOTf (5.0 eq), 2,6-lutidine (17 eq), CH<sub>2</sub>Cl<sub>2</sub>/THF (10/1), 0 °C, 1 h, 86% (3 steps).

**Scheme 77:** Synthesis of *tris*-silyl ether **9,11-trans-249**.

As observed earlier, enone reduction proceeded with complete diastereoselectivity. Based on NOE NMR experiments of a closely related model substrate, the relative configuration between C-9 and C-11 was tentatively assigned to be *trans*. We concluded that the tertiary alcohol at C-9 directs hydride delivery to the same face of the indenylcyclopentenone, giving rise to the *trans*-relationship between C-9/C-11. Synthesis of **247** required a selective desilylation of the primary alcohol in preference to both secondary alcohols. As the *tert*-butyldimethylsilyl group is the most commonly used protecting group for this type of transformation, two literature conditions for the selective TBS cleavage of model substrate **250** were examined first.<sup>161</sup>

<sup>161</sup> R. D. Crouch, *Tetrahedron* **2013**, *69*, 2383-2417.

As shown in **Scheme 78**, both CSA in MeOH/CH<sub>2</sub>Cl<sub>2</sub> and FeCl<sub>3</sub> in pure MeOH provided known *mono*-silyl alcohol **251** in good yields.<sup>162,163</sup>



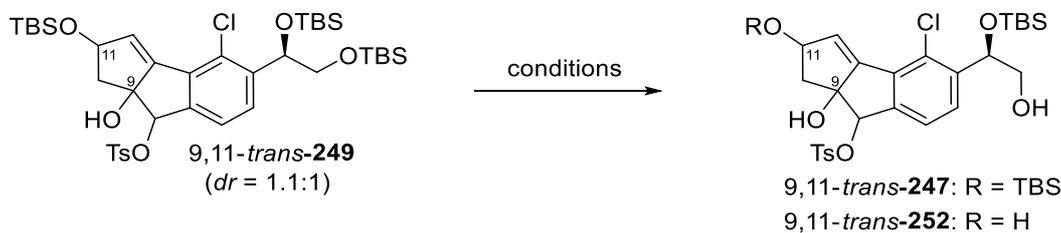
Reagents and conditions: a) CSA (20 mol%), MeOH/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1.5 h, 83%;  
b) FeCl<sub>3</sub> (100 mol%), MeOH, 23 °C, 3.5 h, 75%.

**Scheme 78:** Reaction conditions for selective TBS cleavage on model substrate **250**.

However, employing the higher yielding conditions to 9,11-*trans*-**249** mainly resulted in double silyl ether cleavage (**Table 18**). Thus, allylic alcohol 9,11-*trans*-**252** was the predominant reaction product, and only 14% of desired 9,11-*trans*-**247** was obtained (entry 1). Numerous conditions for selective primary silyl ether cleavage were screened. PPTS, ammonium fluoride and buffered TBAF, all provided significant quantities of *mono*-silyl ether 9,11-*trans*-**252** (entries 2-5). Using 1% AcOH in THF did not cleave any silyl ether bond at 30 °C (entry 6), and NBS in aqueous DMSO led to oxidative side reactions (entry 7). Reflecting on these results, we inferred that the intrinsic lability of the allylic C-11 silyl ether was too high to implement a chemoselective *mono*-desilylation.

<sup>162</sup> J. A. Gladding, J. P. Bacci, S. A. Shaw, A. B. Smith III, *Tetrahedron* **2011**, 67, 6697-6706.

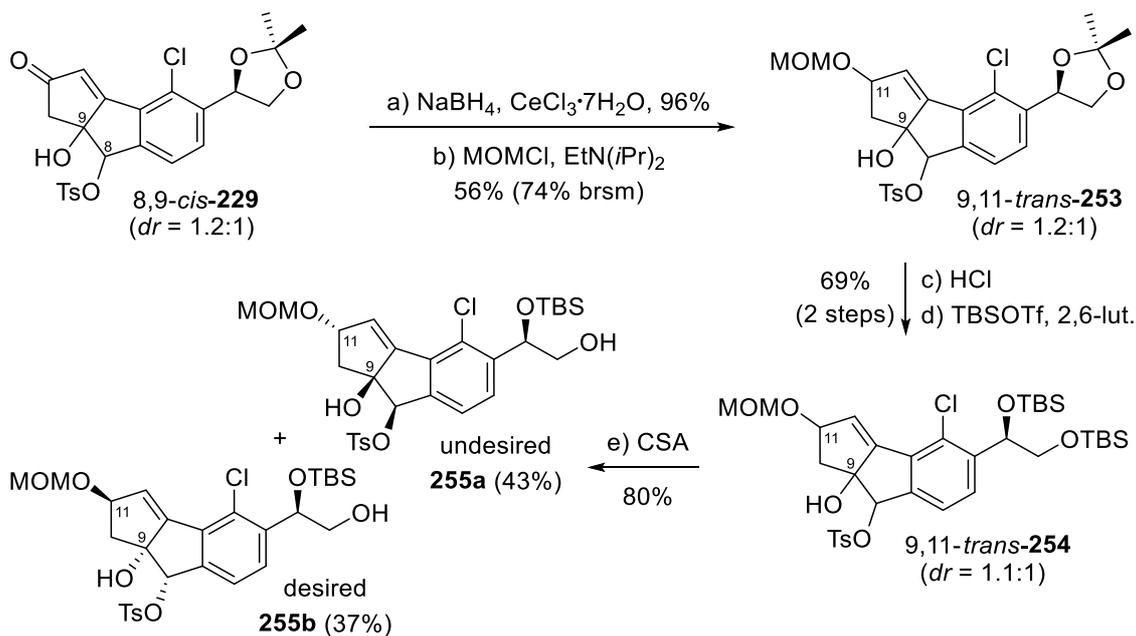
<sup>163</sup> P. Saravanan, V. K. Singh, *J. Indian Chem. Soc.* **1998**, 75, 565-567.

**Table 18:** Attempted selective primary TBS ether cleavage of *tris*-silyl ether 9,11-*trans*-**249**.

Entry	Reagents (eq) and conditions	Result
1	CSA (0.2), MeOH, 0 °C, 5 h	14% <b>247</b> + 74% <b>252</b>
2	PPTS (0.3), MeOH, 0 °C to 23 °C, 48 h.	low conversion to <b>252</b>
3	NH <sub>4</sub> F (20), MeOH, 23 °C, 14 h	mainly formation of <b>252</b>
4	NH <sub>4</sub> F (1.0), MeOH, 60 °C, 24 h	low conversion to <b>252</b>
5	TBAF (1.0), AcOH (1.1) THF, 0 °C to 23 °C, 14 h	low conversion to <b>252</b>
6	1% AcOH, THF, 30 °C, 92 h	no conversion
7	NBS (1.0), aq. DMSO, 30 °C, 13 h	(oxidative) side reactions

The *bis*-silyl ether protecting group strategy was abandoned and a more orthogonal approach involving MOM protection of the C-11 hydroxyl group was pursued. Once again starting from acetonide 8,9-*cis*-**229**, Luche reduction of the enone afforded the corresponding allylic alcohol in a diastereoselective manner (**Scheme 79**). Reaction with freshly prepared MOMCl<sup>164</sup> furnished C-11-methoxymethyl ether 8,9-*cis*-**253** in acceptable yield. Treatment with 2 M aqueous HCl cleanly hydrolyzed the acetonide, leaving the previously installed MOM ether untouched. Subsequent protection of the vicinal diol delivered *bis*-TBS ether 8,9-*cis*-**254** in 69% yield. Chemoselective deprotection with CSA in MeOH/CH<sub>2</sub>Cl<sub>2</sub> proceeded smoothly to selectively provide the primary alcohol. The two diastereoisomers **255a** and **255b** could now be separated by flash chromatography, and were obtained in 43% and 37% yield, respectively.

<sup>164</sup> M. Berliner, K. Belecki, *Org. Synth.* **2007**, *84*, 102.

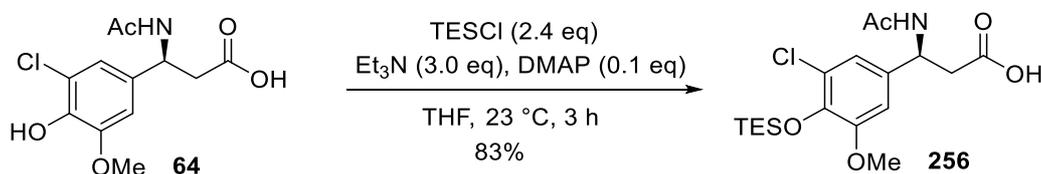


*Reagents and conditions:* a)  $\text{NaBH}_4$  (1.5 eq),  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (1.5 eq),  $\text{THF}/\text{MeOH}$  (1/1),  $-50^\circ\text{C}$ , 45 min, 96%; b)  $\text{MOMCl}$  (3.0 eq),  $\text{EtN}(\text{iPr})_2$  (3.0 eq),  $\text{CH}_2\text{Cl}_2$ ,  $23^\circ\text{C}$ , 16 h, 56% (74% brsm); c) 2 M  $\text{HCl}$  (13 eq),  $\text{MeCN}$ ,  $23^\circ\text{C}$ , 3 h; d)  $\text{TBSOTf}$  (3.0 eq), 2,6-lutidine (6.0 eq),  $\text{CH}_2\text{Cl}_2$ ,  $0^\circ\text{C}$ , 1 h, 69% (2 steps); e)  $\text{CSA}$  (0.2 eq),  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (1/1),  $0^\circ\text{C}$ , 6 h, 43% **255a** (undesired), 37% **255b** (desired).

**Scheme 79:** Synthesis of MOM protected primary alcohols **255a** and **255b**.

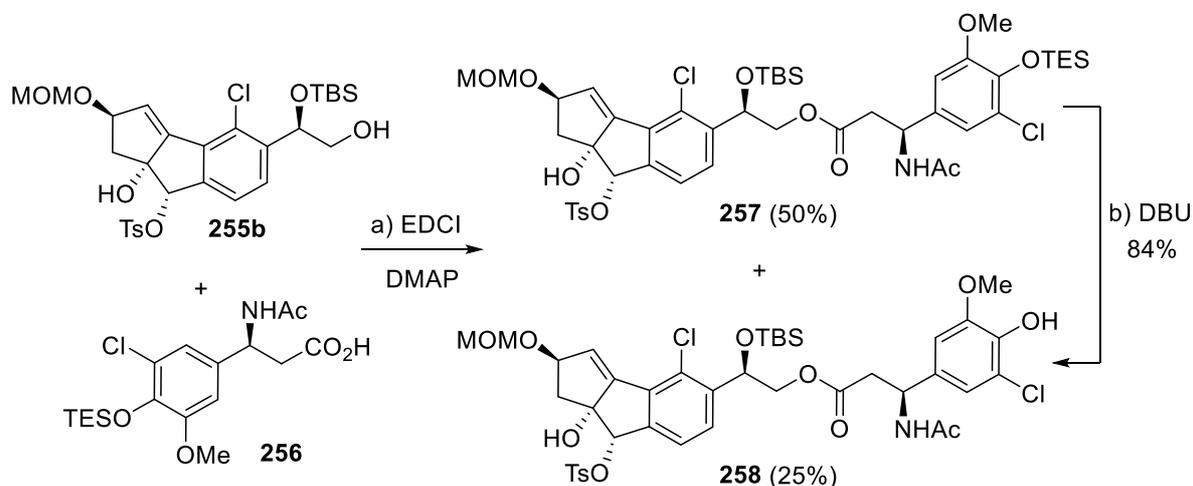
With **255a** and **255b** in hand, we focused on the conversion into the desired macrocyclization precursor. At this point, we were still not aware of the absolute configuration at C-8/C-9 for both diastereomers, and elected to use **255b**.

In contrast to the preparation of cyclization precursor **236**, fragment **255b** was not subjected to esterification with TBS protected  $\beta$ -amino acid **237**, but with its TES derived congener **256** (**Scheme 80**).



**Scheme 80:** Synthesis of  $\beta$ -amino acid **256** from **64**.

We undertook this modification for two reasons: first, synthesis of **256** from **64** proceed in much higher yield compared to TBS protection due to the more facile hydrolytic cleavage of the unavoidably formed trialkylsilyl ester.<sup>165</sup> Secondly, a higher chemoselectivity for cleavage of a TES aryl ether in the presence of an alkyl TBS ether was assumed. EDCI mediated coupling of **255b** and **256** gave TES protected ester **257** in 50% yield, along with 25% of the deprotected and targeted phenol **258** (Scheme 81). According to TLC analysis, TES cleavage occurred during workup with saturated aqueous sodium bicarbonate, suggesting a hydrolytically labile silyl ether bond. The remaining quantities of **257** were submitted to mild aryl silyl ether cleavage using DBU in aqueous MeCN.<sup>166</sup>



Reagents and conditions: a) **255b** (1.0 eq), **256** (1.4 eq), EDCI (1.3 eq), DMAP (25 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 4 h, 50% **257**, 25% **258**; b) DBU (1.0 eq), MeCN/H<sub>2</sub>O (95/5), 23 °C, 30 min, 84%.

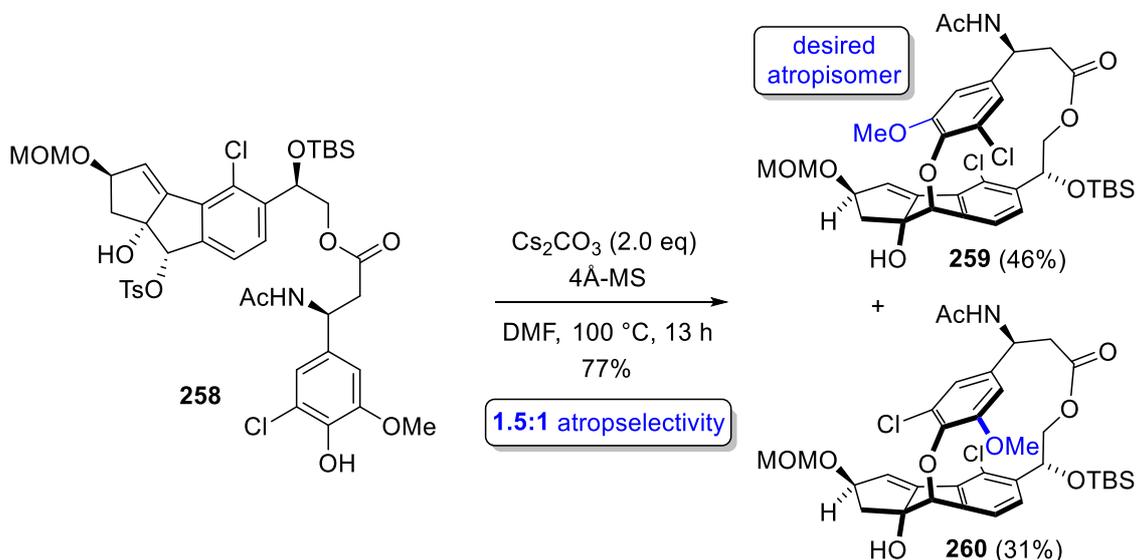
Scheme 81: Synthesis of MOM protected cyclization precursor **258**.

The macroetherification of **258**, constructing the desired [2.6]paracyclophane ring, and introducing axial chirality into the molecule, was now the focus of our studies. Heating of **258** in the presence of two equivalents of cesium carbonate in DMF cleanly provided two products of distinctly different polarity on TLC. After isolation, both products were extensively analyzed by 1D and 2D NMR, revealing the [2.6]paracyclophane motif in both compounds. Much to our delight, and largely by means of <sup>1</sup>H-<sup>1</sup>H-ROESY NMR data, the major product, isolated in 46% yield, could be assigned as the desired atropisomer **259** (Scheme 82). Accordingly, the minor and more polar isomer (31% yield) was identified as atropisomer **260**, exhibiting an opposite orientation of the β-

<sup>165</sup> T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons, Inc., 1999.

<sup>166</sup> C.-E. Yeom, H. W. Kim, S. Y. Lee, B. M. Kim, *Synlett* 2007, 2007, 146-150.

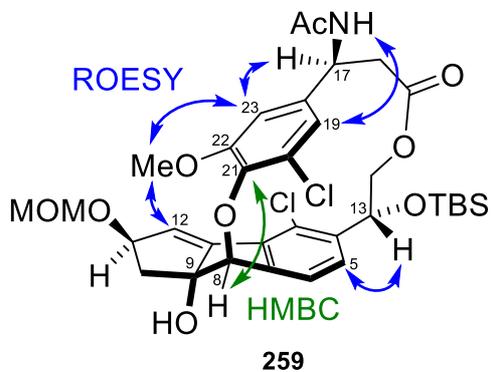
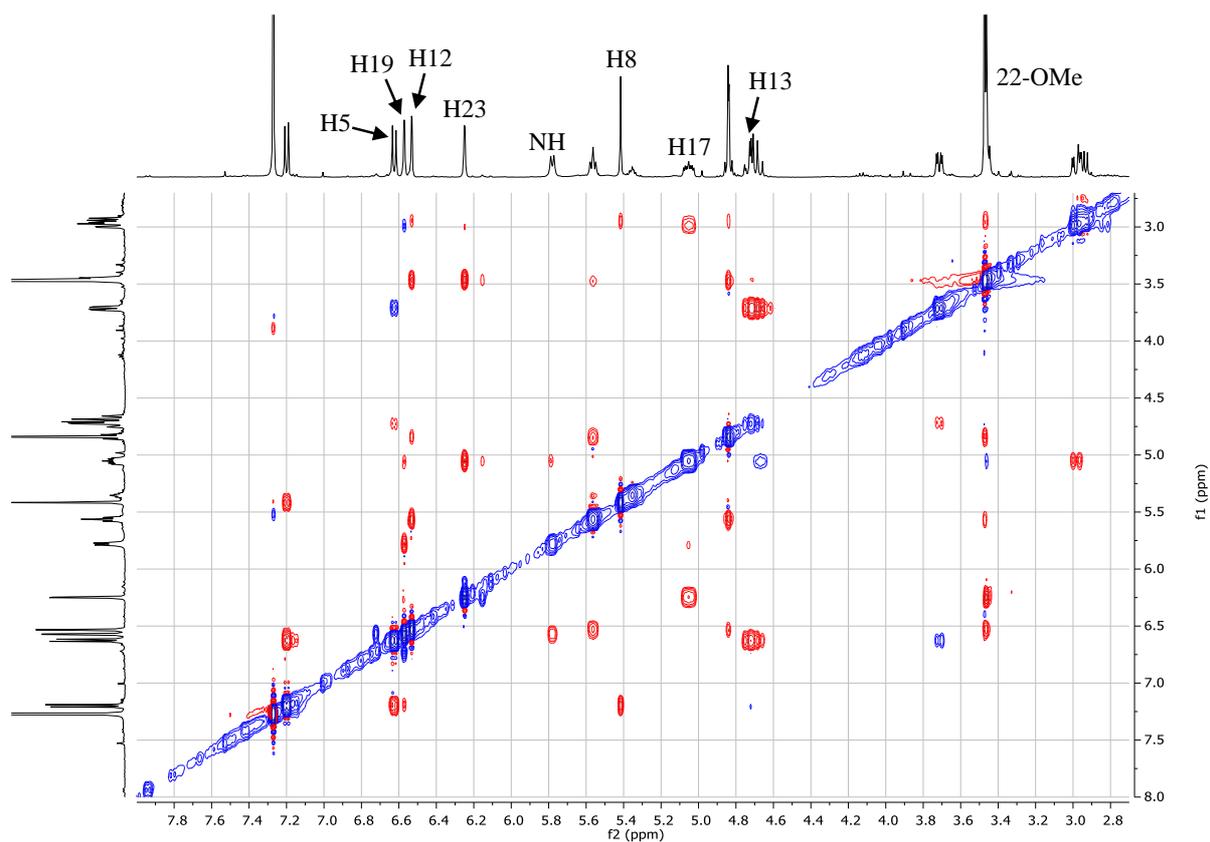
tyrosine arene core. Thus, the realized [2.6]paracyclophane forming macrocyclization featured an atropselectivity of 1.5:1 (**259:260**),<sup>167</sup> and proceeded in high overall yield of 77% (**Scheme 82**).



**Scheme 82:** First realized atropselective [2.6]paracyclophane formation.

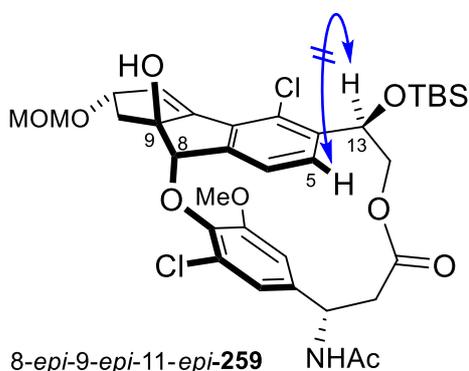
The key  $^1\text{H}$ - $^1\text{H}$ -ROESY correlations, used for structure elucidation of species **259**, and an excerpt of the corresponding 2D NMR spectrum are provided in **Figure 6**. Distinct dipolar coupling between H-23/H-17, and H-12/22-OMe, as well as between H-19/17-NH strongly suggest an orientation of the  $\beta$ -tyrosine aromatic core in the depicted manner. In addition, a heteronuclear scalar coupling between H-8/C-21 was observed by HMBC NMR spectroscopy providing evidence for macrocyclic ring closure by the intended nucleophilic substitution at C-8. As for structure assignment of fijiolide A and B (*cf.* chapter 1.2), the absolute configuration of **259** at C-8/C-9 could now be assigned by means of ROESY NMR experiments.

<sup>167</sup> Determined by  $^1\text{H}$  NMR spectroscopy of the crude reaction product.

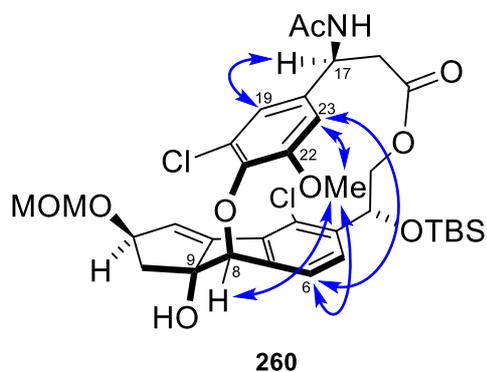
a) Key ROESY correlations for [2.6]paracyclophane **259**.b) Excerpt of the ROESY spectrum of [2.6]paracyclophane **259** (400 MHz, CDCl<sub>3</sub>).Figure 6: Results of the 2D NMR analysis of [2.6]paracyclophane **259**.

Dipolar coupling between H-5/H-13 strongly supports a C-8/C-9 configuration as shown in **Figure 6** and allows for assignment of **259** as the targeted [2.6]paracyclophane diastereomer. By way of illustration, no ROESY correlation between H-5/H-13 would be anticipated for diastereomer 8-*epi*-9-*epi*-11-*epi*-**259** (**Figure 7a**). For the sake of completeness, the observed key ROESY correlation allowing structural assignment of atropisomer **260** are indicated in **Figure 7b**.

a) Anticipated nonexistent ROESY correlation for 8-*epi*-9-*epi*-11-*epi*-**259** (↔).



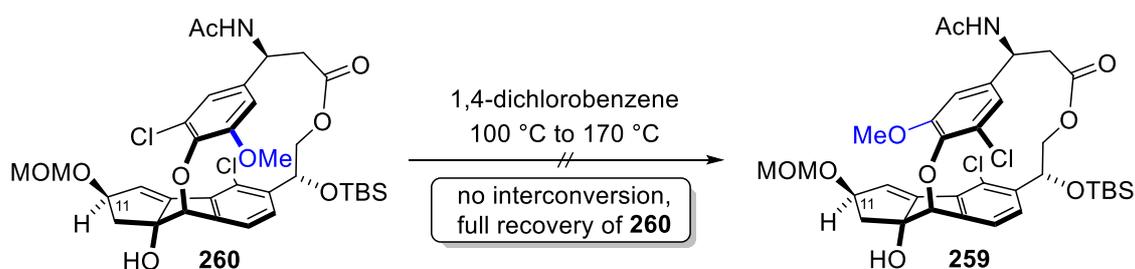
b) Observed key ROESY correlations for **260** (↔).



**Figure 7:** Structures and ROESY correlation for hypothetical 8-*epi*-9-*epi*-11-*epi*-**259** and **260**.

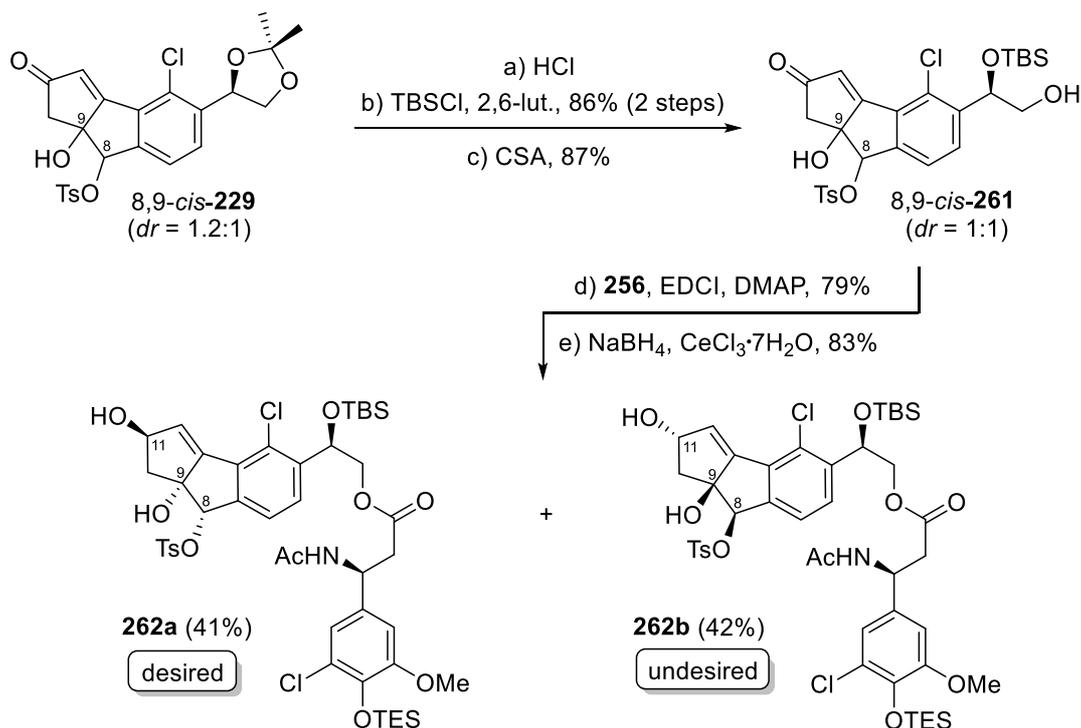
In contrast to **259**, the ROESY spectrum of **260** does not exhibit a correlation according to dipolar coupling between 17-NH and the proximate arene proton (H-23). However, ROESY correlations between H-19/H-17 and 22-OMe/H-8 as well 22-OMe/H-6 clearly indicate the presence of the depicted atropisomer. In addition, a direct dipolar coupling between protons H23 and H6, being located on the two different benzene rings, is indicative for the shown atropisomer. Moreover, this illustrates the close proximity of the aromatic cores, resulting in restricted rotation of the  $\beta$ -tyrosine benzene, and giving rise to its planar chirality.

We attempted to interconvert **260** into the desired atropisomer **259** (Scheme 83). Heating **260** up to 170 °C for 5 h, did not result in any conversion. Instead, full recovery of the starting material was achieved, evidencing the configurational stability of cyclophane **260** and its excellent thermal stability.



Scheme 83: Attempted interconversion of [2.6]paracyclophane **260** into **259**.

As thermal atropisomer interconversion had proven infeasible, we were interested in tuning the macrocyclization process to enhance the atropselectivity. The influence of the C-11 hydroxyl substituent on the orientation of the phenolic moiety during nucleophilic ring closure was investigated first. In terms of both synthesis of the cyclization precursor, and the installation of the cyclopentadiene motif after macrocyclization, an unprotected C-11 hydroxyl group appeared to be the most step-economic option. To this end, hydroxy esters **262a** and its 8-*epi*-9-*epi*-11-*epi* diastereomer **262b** were successfully synthesized from 8,9-*cis*-**229**, according to Scheme 84. A three-step sequence beginning with acetonide cleavage, followed by a double TBS protection, and selective *mono*-desilylation delivered a 1:1 diastereomeric mixture of primary alcohols **261**. Esterification with previously described  $\beta$ -amino acid **256**, followed by Luche reduction, provided a separable mixture of **262a** and its 8-*epi*-9-*epi*-11-*epi* diastereomer **262b**. The stereochemistry of both diastereomers was tentatively assigned by comparison with the  $^1\text{H}$  NMR spectra of **257** and **258**. The chemical shift of the acetamide methyl group was the most characteristic signal appearing at a lower chemical shift for the desired diastereomer.



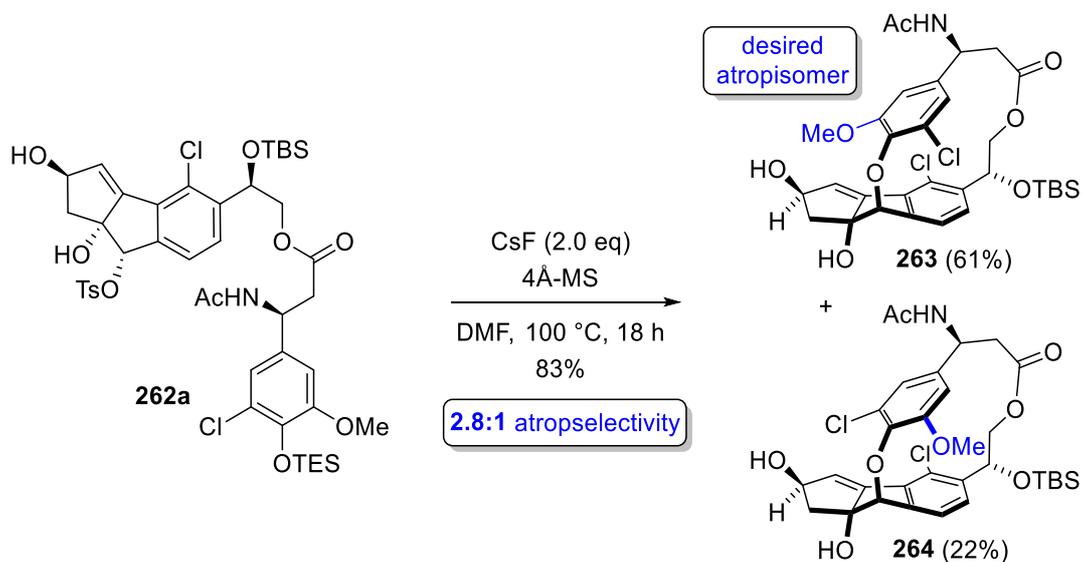
*Reagents and conditions:* a) 2 M HCl (26 eq), MeCN, 23 °C, 1.5 h; b) TBSOTf (2.3 eq), 2,6-lutidine (4.5 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 75 min, 86% (2 steps); c) CSA (25 mol%), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1/1), 0 °C, 6.5 h, 87%; d)  $\beta$ -amino acid **45** (1.4 eq), EDCI, (1.3 eq), DMAP (23 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 19 h, 79%; e) NaBH<sub>4</sub> (1.5 eq), CeCl<sub>3</sub>·7H<sub>2</sub>O (1.5 eq), THF/MeOH (1/1), -55 °C, 40 min, 41% **262a**, 42% **262b**.

**Scheme 84:** Synthesis of 11-hydroxy cyclization precursors **262a** and **262b**.

Inspired by the work of Sorensen *et al.* reporting a CsF mediated *O*-alkylation of a triethylsilyl phenol ether for the total synthesis of viridin,<sup>168,169</sup> we hypothesized that a treatment of **262a** with CsF would accordingly result in direct [2.6]paracyclophane formation. In this way, the additional TES deprotection step could be cut. Remarkably, reacting **262a** with 2.0 equivalents of CsF at 100 °C in DMF smoothly induced macrocyclization, affording desired product **263** in 61% isolated yield, along with 22% of atropisomer **264** (**Scheme 85**). This corresponds to an improved atropselectivity of 2.8:1.<sup>167</sup> Notably, the secondary benzylic TBS ether is fully retained under these conditions.

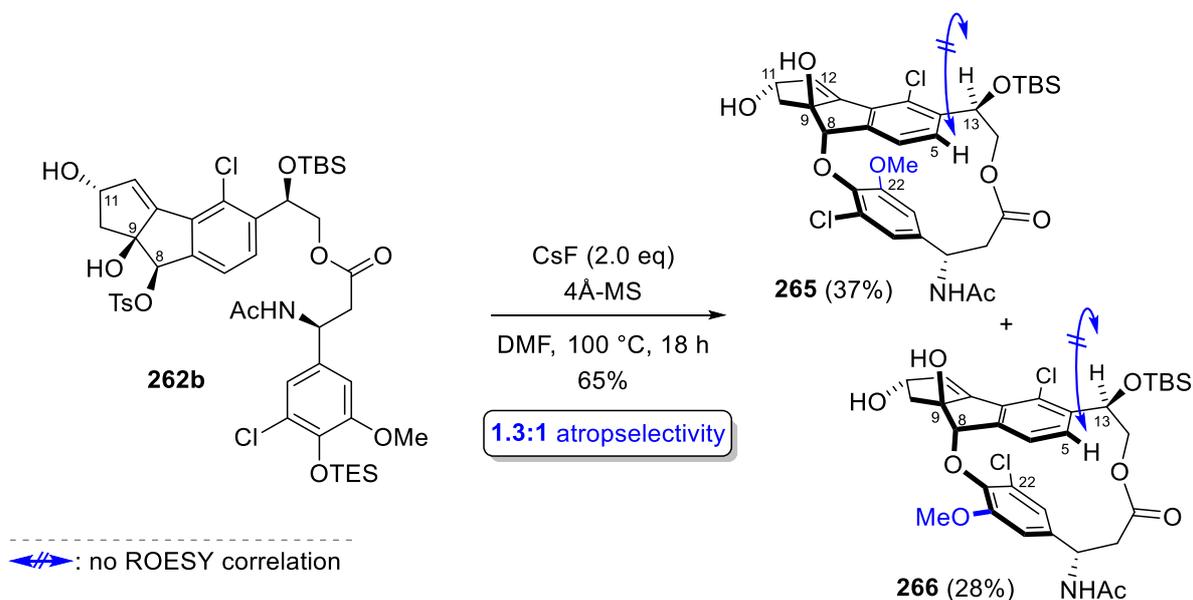
<sup>168</sup> E. A. Anderson, E. J. Alexanian, E. J. Sorensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1998-2001.

<sup>169</sup> T. Oriyama, K. Noda, K. Yatabe, *Synlett* **1997**, 1997, 701-703.



**Scheme 85:** Improved [2.6]paracyclophane formation employing 11-hydroxy silyl ether **262a** and CsF.

After developing a shorter, higher yielding and more atropselective synthesis of the fijiolide A [2.6]paracyclophane ring, we were interested if macrocyclization also occurs when the 8-*epi*-9-*epi*-11-*epi* diastereomer **262b** is subjected to the reaction conditions. Indeed, the corresponding macrocyclic aryl ethers **265** and **266** were formed upon treatment with CsF in hot DMF (**Scheme 86**). However, the isolated yields of 37% (**265**) and 28% (**266**), as well as the atropselectivity of 1.3:1 are considerably lower than those for the cyclization of **262a**.<sup>167</sup> In agreement with the atropselectivities of paracyclophane formations discussed earlier, the major atropisomer **265** displays an aromatic ring orientation that brings the 22-OMe group in close proximity to the C-12 and the C-11 hydroxyl group. Further indication for a correctly assigned absolute configuration at C-8/C-9 in **259/260**, and hence also in **263/264**, was provided by the anticipated absence of a <sup>1</sup>H-ROESY correlation between H-5 and H-13 for **265** and **266** (*cf.* **Scheme 86** and **Figure 7a**).

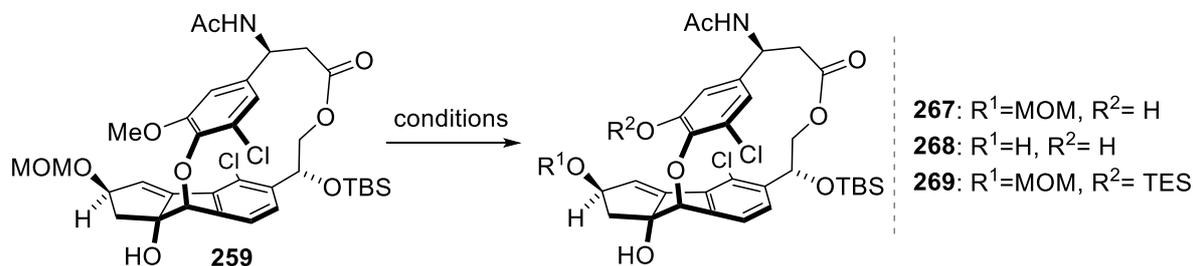


**Scheme 86:** [2.6]paracyclophane formation employing **262b**.

As fijiolide A features a free phenolic hydroxyl group, tests to hydrolyze the methyl ether at 22-OMe of **259** were conducted at this stage (**Table 19**). Lewis acidic conditions, for instance boron tribromide, were first examined as they could potentially cleave both the methyl ether and the MOM protecting group, directly providing **268**.<sup>170</sup> Exposure of **259** to  $\text{BBr}_3$  resulted in complex product mixtures, without observable demethylation (entries 1-2). Moreover, a  $\text{B}(\text{C}_6\text{F}_5)_3$  mediated one-pot arylether cleavage/silylether formation, as reported by Yamamoto *et al.*, failed to provide **269** (entry 4).<sup>171</sup> Nucleophilic deprotection of **259** using  $n\text{PentylSLi}/\text{DMF}$  led to complete substrate degradation within 30 minutes (entry 4).

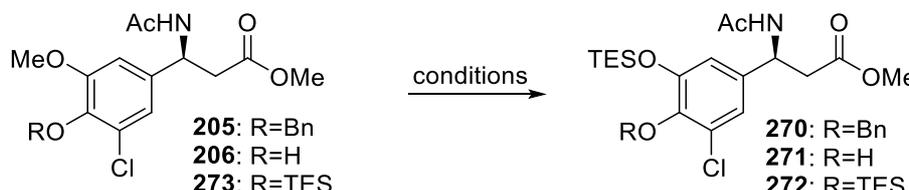
<sup>170</sup> Y. Wu, O. R. Seguil, J. K. De Brabander, *Org. Lett.* **2000**, *2*, 4241-4244.

<sup>171</sup> V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu, Y. Yamamoto, *J. Org. Chem.* **2000**, *65*, 6179-6186.

**Table 19:** Attempted demethylation of [2.6]paracyclophane **259**.

Entry	Conditions	Expected product	Result
1	BBr <sub>3</sub> (4.0 eq), CH <sub>2</sub> Cl <sub>2</sub> , -78 °C to 0 °C, 3 h	<b>267/268</b>	Complex mixture
2	BBr <sub>3</sub> (5.0 eq), CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 45 min	<b>267/268</b>	Complex mixture
3	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> (2.0 eq), Et <sub>3</sub> SiH (10 eq), CH <sub>2</sub> Cl <sub>2</sub> , 0 °C to 23 °C, 30 min	<b>269</b>	Complex mixture
4	<i>n</i> PentylSLi (2.5 eq), DMF, 120 °C, 30 min	<b>267</b>	Degradation

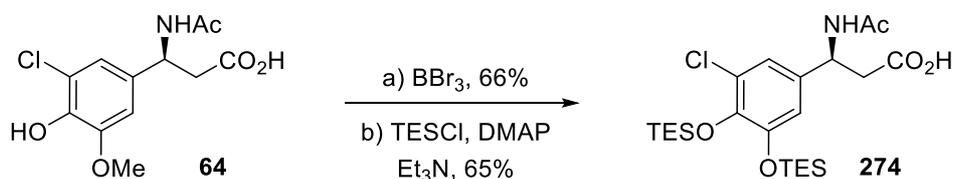
Due to its potential synthetic merits, the Yamamoto protocol was further evaluated on simpler model substrates, containing fewer Lewis basic sites than the advanced [2.6]paracyclophane (**Table 20**). Catalytic B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (10 mol%) in the presence of triethylsilane, resulted in no conversion of **205** into silylether **270** (entry 1). In contrast, stoichiometric quantities of Lewis acid quantitatively converted phenol **206** into TES aryl ether **273**, without demethylation being detected. Re-subjection of **273** to even higher B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> loadings gave rise to methyl ester cleavage, but did not affect methyl ether bond scission to deliver **272**.

**Table 20:** Attempted demethylation of  $\beta$ -amino methyl esters utilizing the Yamamoto protocol.


Entry	Starting material	Conditions	Result
1	<b>205</b>	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> (0.1 eq), Et <sub>3</sub> SiH (2.2 eq), CH <sub>2</sub> Cl <sub>2</sub> , -55 °C to 23 °C, 24 h	No conversion
2	<b>206</b>	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> (1.0 eq), Et <sub>3</sub> SiH (2.3 eq), CH <sub>2</sub> Cl <sub>2</sub> , 0 °C to 23 °C, 6.5 h	98% <b>273</b>
3	<b>273</b>	B(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> (3.0 eq), Et <sub>3</sub> SiH (5.0 eq), CH <sub>2</sub> Cl <sub>2</sub> , 23 °C, 7 h	Ester cleavage

In summary, demethylation at the 22-OMe position to reveal the free phenol could not be accomplished. In addition, direct conversion of model methyl ethers into TES protected phenols were met with failure. These findings prompted us to revise the structure of the macrocyclization precursor. Having regard to our previous observation that an unprotected C-11 hydroxyl group increased the atropselectivity of [2.6]paracyclophane formation, we wondered if this process would allow - or even benefit - from employment of an unprotected or an *in situ* generated 22-OH group.

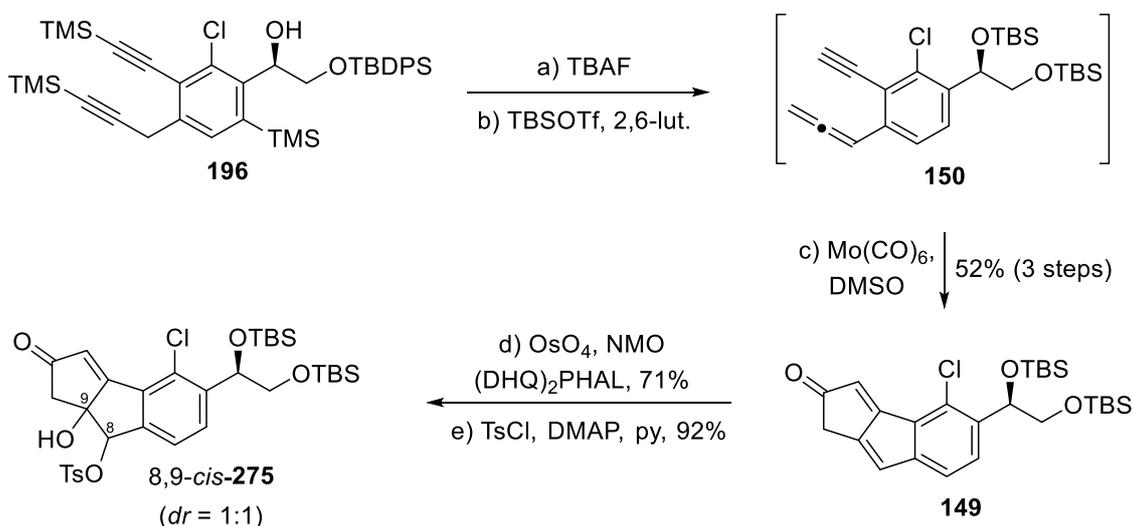
In order to investigate this proposal,  $\beta$ -amino-acid **64** was successfully demethylated with BBr<sub>3</sub>. The resulting catechol moiety was silylated to afford double TES protected  $\beta$ -amino-acid **274** (Scheme 87).



Reagents and conditions: a) BBr<sub>3</sub> (5.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 28 h, 66%; b) TESCl (3.6 eq), DMAP (15 mol%), Et<sub>3</sub>N (4.5 eq), THF, 23 °C, 2h, 65%

**Scheme 87:** Syntheses of *bis*-TES protected  $\beta$ -amino acid **274** from **64**.

Synthesis of previous cyclization precursors *via bis*-TBS ether 8,9-*cis*-**275** had proven expedient. Therefore, a more concise synthetic approach towards this intermediate was developed, omitting the intermediate acetone protection of the vicinal diol (**Scheme 88**). In this respect, aryl chloride **196** was first globally desilylated and isomerized with TBAF, followed by a double TBS protection of the diol moiety, furnishing the previously proposed allene-yne **150** (*cf.* **Scheme 36**). In turn, **150** was immediately subjected to a Pauson-Khand reaction, affording indenylcyclopentenone **149** in 52% overall yield. Although being extensively studied, Sharpless asymmetric dihydroxylation of **149** at the indenyl double bond proceeded at best in 71% yield, and with low facial selectivity (*dr* = 1.1:1, *vide infra*),<sup>172</sup> affording 8,9-*cis*-**275** as a 1:1 mixture of diastereomers after tosylation of the secondary benzylic hydroxyl group.

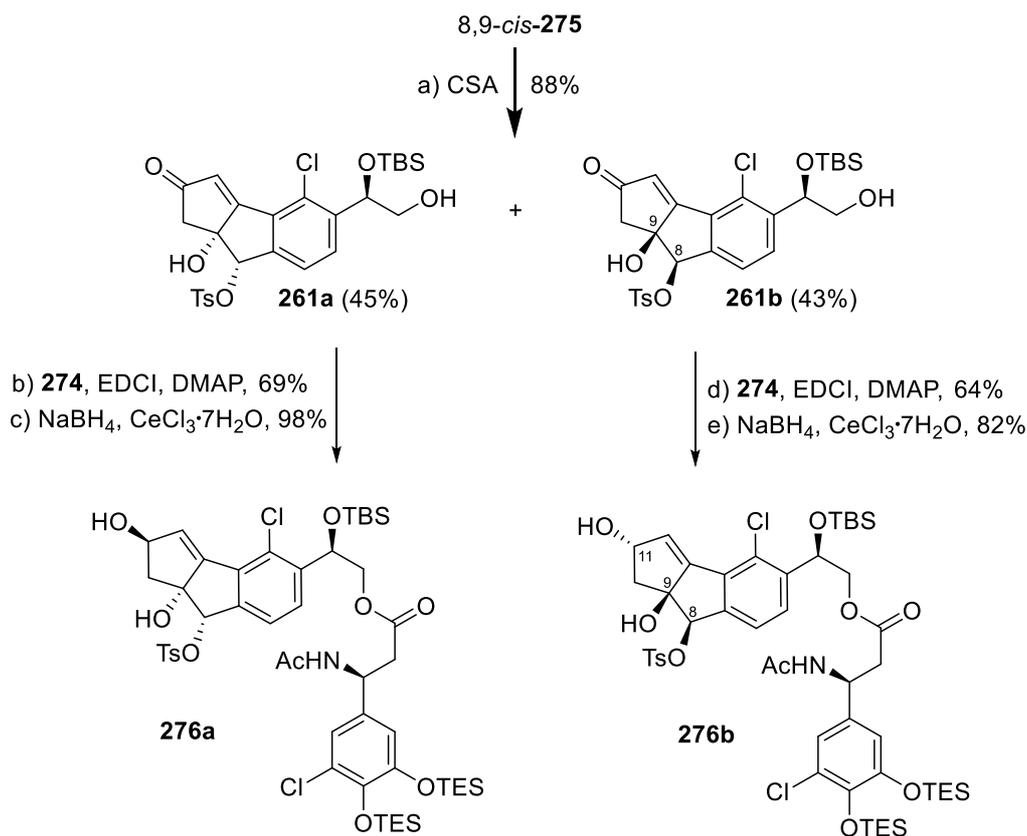


*Reagents and conditions:* a) TBAF (5.0 eq), THF, 23 °C, 45 min; b) TBSOTf (2.5 eq), 2,6-lutidine (5.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h; c) Mo(CO)<sub>6</sub> (1.5 eq), DMSO (10 eq), PhMe, 90 °C, 20 min, 52% (3 steps); d) OsO<sub>4</sub> (4.0 mol%), (DHQ)<sub>2</sub>PHAL (10 mol%), NMO (2.0 eq), THF/H<sub>2</sub>O (v/v = 10/1), 0 °C, 4 h, 71% (*dr* = 1.1:1); e) TsCl (4.0 eq), DMAP (15 mol%), pyridine, 23 °C, 15 h, 92%.

**Scheme 88:** Shortened synthesis of *bis*-TBS ether 8,9-*cis*-**275**.

<sup>172</sup> a) E. N. Jacobsen, I. Marko, W. S. Mungall, G. Schroeder, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 1968-1970; b) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, *J. Org. Chem.* **1992**, *57*, 2768-2771; c) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483-2547.

In analogy to previous routes, the diastereomeric mixture of *bis*-TBS ether 8,9-*cis*-**275** was selectively *mono*-desilylated with CSA, and the diastereomers were separated by flash chromatography. In parallel, **261a** and **261b** were subjected to esterification with  $\beta$ -amino acid **274**, followed by Luche reduction to provide desired cyclization precursor **276a** and its 8-*epi*-9-*epi*-11-*epi* counterpart **276b**.

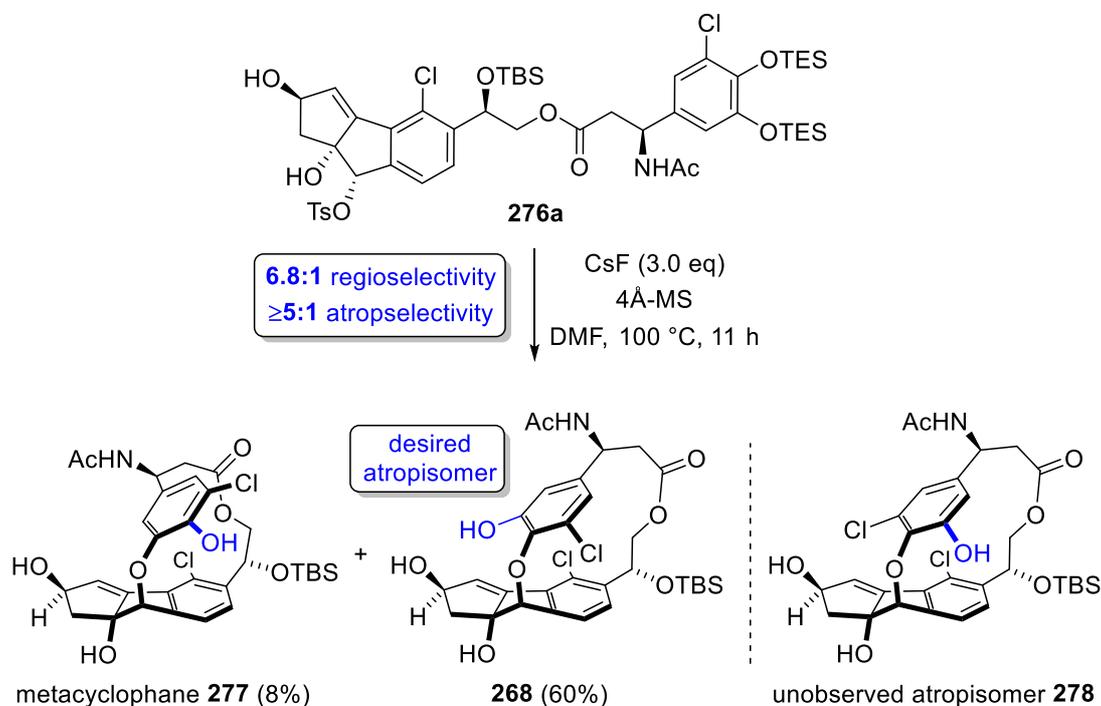


*Reagents and conditions:* a) CSA (25 mol%), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1/1), 0 °C, 7 h, 45% **261a**, 43% **261b**; b) **274** (1.5 eq), EDCI, (2.0 eq), DMAP (20 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 5 h, 69%; c) NaBH<sub>4</sub> (1.5 eq), CeCl<sub>3</sub>·7H<sub>2</sub>O (1.5 eq), THF/MeOH (1/1), -55 °C, 45 min, 98%; d) **274** (1.4 eq), EDCI, (1.4 eq), DMAP (25 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 18 h, 64%; e) NaBH<sub>4</sub> (1.5 eq), CeCl<sub>3</sub>·7H<sub>2</sub>O (1.5 eq), THF/MeOH (1/1), -55 °C, 1 h, 82%.

**Scheme 89:** Synthesis of cyclization precursor **276a** and its 8-*epi*-9-*epi*-11-*epi* diastereomer **276b**.

**276a** was subjected to macroetherification, bearing in mind that a double silyl protection of the catechol moiety could lead to unintended [2.6]metacyclophane formation. CsF mediated double TES cleavage led to formation of the desired [2.6]paracyclophane **268** in 60% isolated yield (**Scheme 90**). Notably, the macrocyclization occurs in a highly atrop- and regioselective manner. While regioisomeric [2.6]metacyclophane **277** was isolated as a byproduct in 8% yield, the corresponding [2.6]paracyclophane atropisomer **278** was not observed.

Thus, the regioselectivity of the realized paracyclophane formation was determined to be 6.8:1,<sup>167</sup> whereas the atropselectivity was benchmarked to  $\geq 5:1$ .<sup>173</sup>

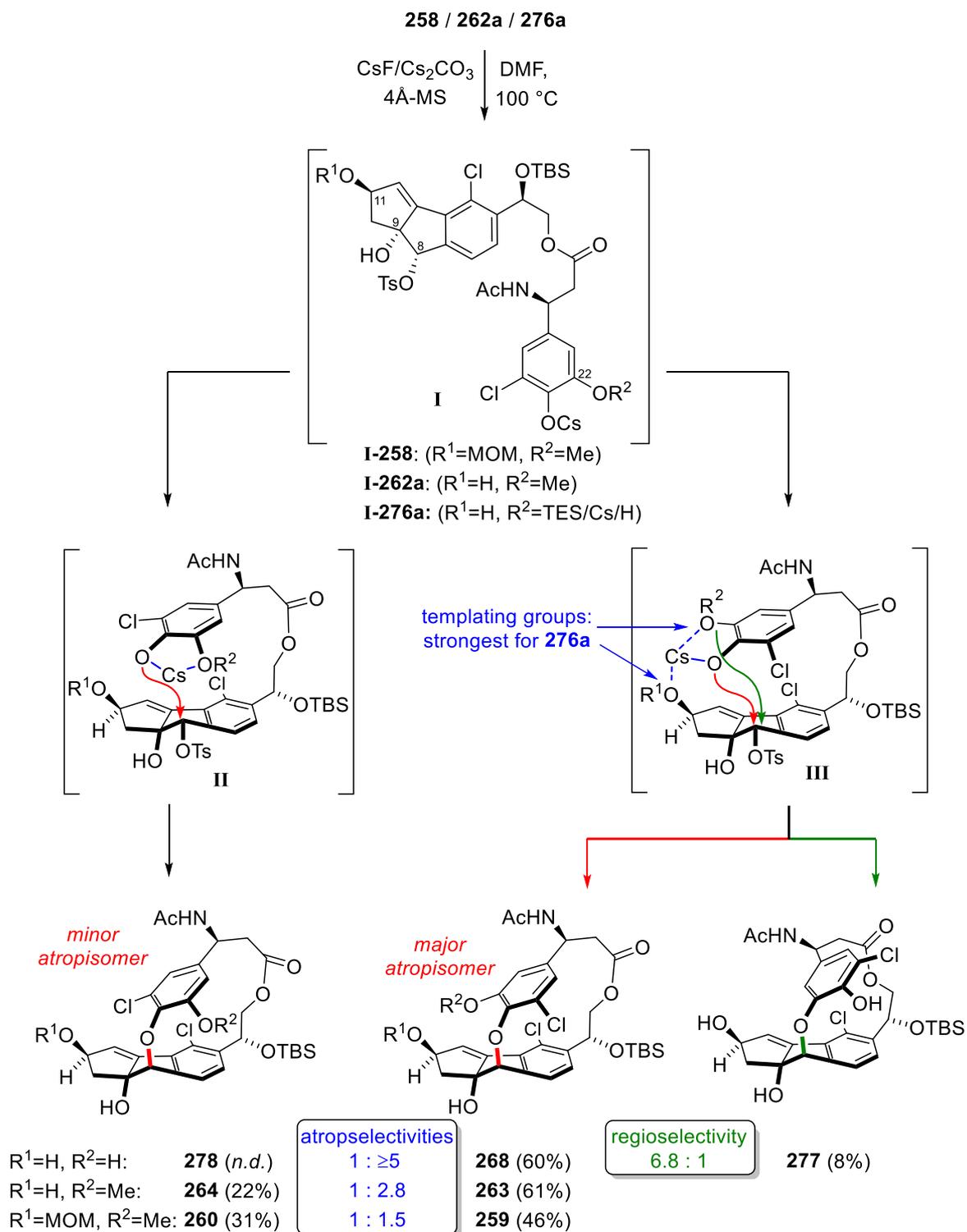


**Scheme 90:** [2.6]paracyclophane formation of cyclization precursor **276a**.

A rationale for the observed regio- and atropselectivity of [2.6]paracyclophane formation is presented in **Scheme 91**.<sup>174</sup> Each of the investigated substrates with desired C-8/C-9 configuration forms an intermediate cesium phenolate of the general structure **I** upon treatment with CsF or Cs<sub>2</sub>CO<sub>3</sub>. The coordination abilities of the C-22, and in particular the C-11 substituents, are thought to induce a substrate preorganization, preferentially leading to intermediate **III** vs. **II**. The favorable templating interactions in **III** are believed to facilitate nucleophilic substitution of the tosylate by the proximate phenolate, resulting in formation of the desired atropisomer. Moreover, this rationalized templating effect, which should be strongest for cyclization precursor **276a**, also controls catechol orientation of [2.6]metacyclophane **277** by ring closure *via* the same preorganized intermediate **III**. Furthermore, the observed relationship between decreasing atropselectivity with increasing substitution at C-11 and C-22 is in agreement with the outlined rationale.

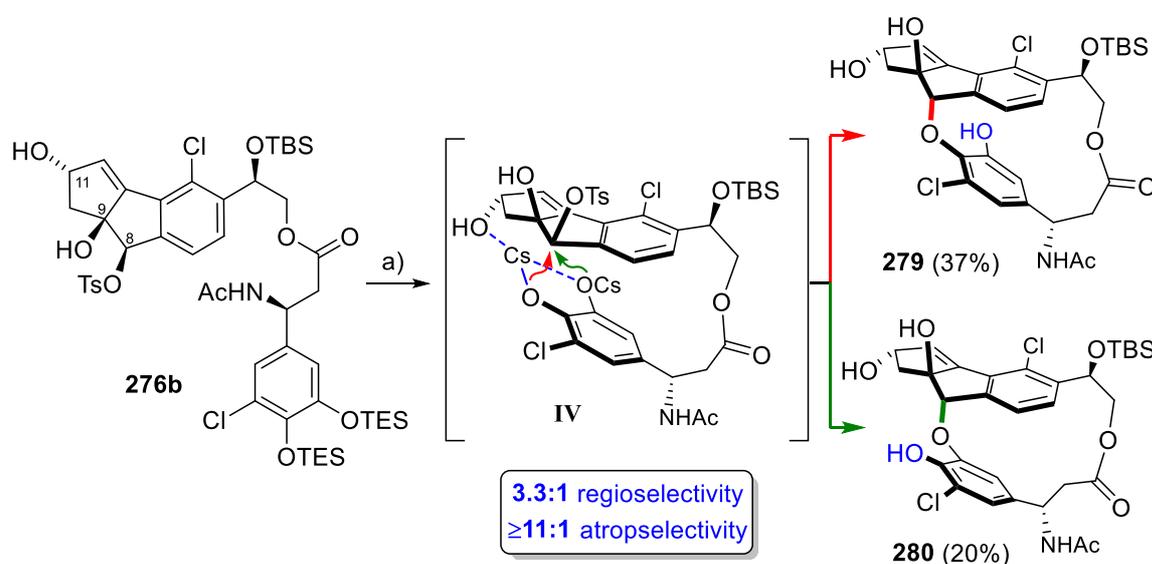
<sup>173</sup> The major unidentified product by <sup>1</sup>H NMR spectroscopy was assumed to be the undesired atropisomer **278**, although its structure could not be ascribed reliably.

<sup>174</sup> C. Heinz, N. Cramer, *J. Am. Chem. Soc.* **2015**, *137*, 11278-11281.



**Scheme 91:** Rationale for the encountered atrop- and regioselectivity in [2.6]paracyclophane formation.

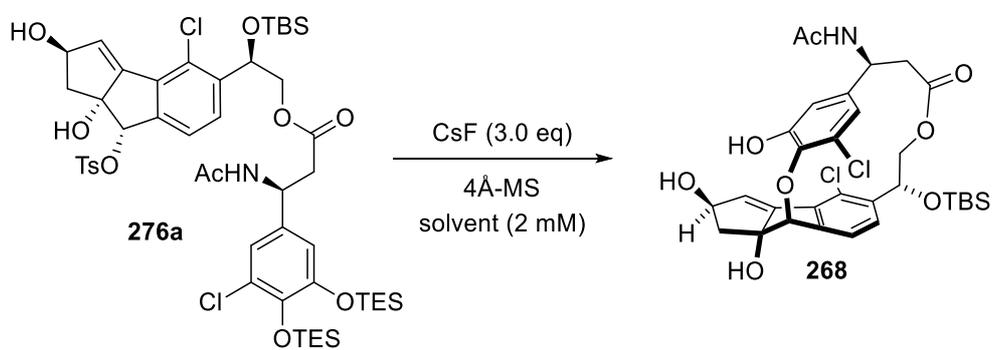
An additional piece of evidence for this template effect was obtained by macrocyclization of 8-*epi*-9-*epi*-11-*epi*-diastereomer **276b** (Scheme 92). [2.6]Paracyclophane **279** was isolated as the expected predominant regio- and atropisomer, presumably formed *via* preorganized intermediate **IV**. Similar to the cyclization of substrate **276a**, the corresponding atropisomer was not detected. However, [2.6]metacyclophane **280** was isolated as the main reaction byproduct, again with a catechol orientation arising from templated intermediate **IV**. Thus, macrocyclization of **276b** proceeded with a regioselectivity of 3.3:1,<sup>167</sup> and an atropselectivity of  $\geq 11:1$ .<sup>173</sup>



Reagents and conditions: a) CsF (3.0 eq), 4Å-MS, DMF, 100 °C, 11 h, 37% **279**, 20% **280**.

Scheme 92: [2.6]paracyclophane formation of cyclization precursor **276b**.

Additional optimization of the macroetherification process was then investigated (Table 21).<sup>167</sup> Starting from an isolated yield of 56% and 7.0:1 regioselectivity under standard conditions (entry 1), an increased regioselectivity of 12:1 was obtained by lowering the temperature to 80 °C. However, a considerably longer reaction time was required to provide **268** in slightly diminished yield (entry 2). Executing the reaction in *N*-methyl-2-pyrrolidone (NMP) led to increased side product formation, resulting in only 38% yield, however the regioselectivity appeared to be slightly enhanced. Thus, CsF in DMF at 100 °C persisted as the conditions of choice for [2.6]paracyclophane formation.

**Table 21:** Investigation of temperature and solvent influence on [2.6]paracyclophane formation.

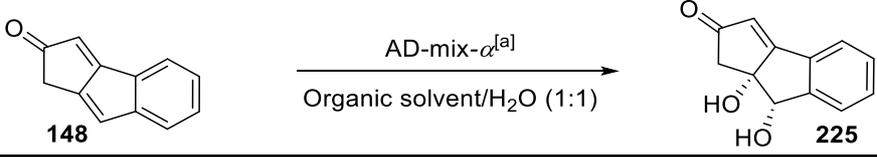
Entry	Conditions <sup>[a]</sup>	Yield [%]	Regioselectivity 268:277
1	DMF, 100 °C, 8.5 h	56	7.0:1
2	DMF, 80 °C, 36 h	53	12:1
3	NMP, 100 °C, 8.5 h	38 <sup>[b]</sup>	8.9:1

<sup>[a]</sup> Reactions were conducted in 30.0 mg (28.5 μmol) scale; <sup>[b]</sup> 83% conversion of **276a**.

### 6.2.2 Dihydroxylation Studies

Nowadays, the asymmetric dihydroxylation (AD) of olefins could be considered as a largely overcome synthetic obstacle. However, we found the OsO<sub>4</sub> catalyzed facial selective dihydroxylation of indenyl-cyclopentenones to be an extremely challenging task. Our studies towards this end will be presented in this section. We commenced our studies by application of the “classical” Sharpless AD procedure to model system **148** (Table 22). Employment of (DHQ)<sub>2</sub>PHAL containing AD-mix- $\alpha$  under biphasic conditions (*t*BuOH/H<sub>2</sub>O) resulted in poor solubility of the dihydroxylation substrate and sluggish conversion (entry 1). Thus, moderately enantioenriched diol **225** (45% *ee*) was obtained in poor yield of 35%. While the use of MTBE as the organic solvent was observed to dramatically slow down the process (entry 2), employment of THF accelerated the conversion of **148**. However, the low yields of **225** as the only identifiable reaction product suggested an incompatibility of the indenylcyclopentenone substrate with basic reaction conditions. In fact, K<sub>2</sub>CO<sub>3</sub> mediated degradation of **148** was also observed in the absence of the AD-mix (entry 4).

Table 22: Studied “classical” SAD of model system **148**.



Reaction scheme: Model system **148** (indenyl-cyclopentenone) reacts with AD-mix- $\alpha$  in an organic solvent/H<sub>2</sub>O (1:1) mixture to yield diol **225** (facial dihydroxylation product).

Entry	Additives	Solvent	T [°C]	t [h]	Conv. / Yield <sup>[b]</sup> / <i>ee</i>
1	MeSO <sub>2</sub> NH <sub>2</sub> (1.0 eq)	<i>t</i> BuOH	0	72	72 / 35 / 45
2	MeSO <sub>2</sub> NH <sub>2</sub> (1.0 eq)	MTBE	23	14 d	<i>n.d.</i> / trace / <i>n.d.</i>
3	MeSO <sub>2</sub> NH <sub>2</sub> (1.0 eq)	THF	23	12	86 / 18 / 37
4	No AD mix, K <sub>2</sub> CO <sub>3</sub> (3.0 eq)	<i>t</i> BuOH	23	26	74 / 0 / -

<sup>[a]</sup> Classical SAD conditions were applied (1.4 g AD-mix- $\alpha$ /mmol olefin  $\cong$  0.2 mol% K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub>, 1.0 mol% (DHQ)<sub>2</sub>PHAL, 3.0 eq K<sub>2</sub>CO<sub>3</sub>, 3.0 eq K<sub>3</sub>Fe(CN)<sub>6</sub>) <sup>[b]</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-TMB as internal standard.

Consequently, we aimed to improve the dihydroxylation outcome by the employment of increased catalyst and ligand loadings in combination with buffered conditions (**Table 23**). As a reference reaction, **148** was first dihydroxylated using  $K_2CO_3$  as the sole base, providing **225** in 31% yield and 43% *ee* after 21 h (entry 1). Addition of  $NaHCO_3$  resulted in slightly improved yields of equally enantioenriched diol **225** (entry 2). A 5% increase in *ee* was gained by executing the reaction at 0 °C, although base induced decomposition of **148** persisted to be a severely competitive process (entry 3). With respect to this result, the common employment of *t*BuOH/THF was found to be beneficial in terms of product yield (45%, entry 4). The replacement of  $K_2CO_3$  by  $Na_2CO_3$  resulted in an unfavorable 35% yield, however, the facial selectivity was slightly improved to afford **225** in 51% *ee*.

**Table 23:** Studied asymmetric dihydroxylation of **148** under modified Sharpless conditions.

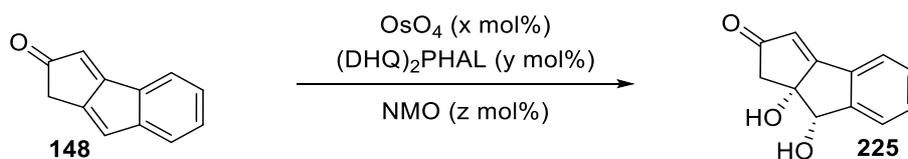
Entry	Additives (3.0 eq)	Solvent	T [°C]	t [h]	Conv. / Yield <sup>[a]</sup> / <i>ee</i>
1	$K_2CO_3$	<i>t</i> BuOH	23	21	91 / 31 / 43
2	$K_2CO_3/NaHCO_3$	<i>t</i> BuOH	23	22	80 / 43 / 44
3	$K_2CO_3/NaHCO_3$	<i>t</i> BuOH	0	36	77 / 28 / 49
4	$K_2CO_3/NaHCO_3$	<i>t</i> BuOH/THF (1:1)	0	36	87 / 45 / 46
5	$Na_2CO_3/NaHCO_3$	<i>t</i> BuOH	0	36	83 / 35 / 51

<sup>[a]</sup> Determined by  $^1H$  NMR spectroscopy using 1,3,5-TMB as internal standard.

As both yield and enantiomeric excess of the dihydroxylation reaction still lagged behind preparatively useful levels, we refrained from employment of basic reaction conditions and  $K_3Fe(CN)_6$  as the terminal oxidant. Instead, attention was shifted to NMO as the oxidant in virtually neutral reaction media (**Table 24**). Still using Sharpless' (DHQ)<sub>2</sub>PHAL ligand, asymmetric dihydroxylation of **148** in *t*BuOH/H<sub>2</sub>O at ambient temperature proceeded sluggishly to afford poorly enantioenriched diol **225** (10% *ee*) in 17% yield (entry 1). Attempted process acceleration by addition of methanesulfonamide – generally resulting in accelerated hydrolysis of the intermediate osmium(VI) glycolate – had no impact on the reaction outcome (entry 2).<sup>172b</sup>

Application of these conditions to **148** in CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O led to an increased yield of 45% for **225**, although almost no facial selectivity was observed (entry 3). While the use THF/acetone/H<sub>2</sub>O as the reaction media was even inferior in terms of yield and *ee* (entry 4), a significant increase in yield to 86% was observed by executing the reaction in THF/H<sub>2</sub>O (entry 5). As the enantioselectivity of this transformation was poor (14% *ee*), another chinchona alkaloid derived, but anthraquinone-based ligand class was evaluated.<sup>175</sup> Employment of (DHQD)<sub>2</sub>AQN resulted in an optimized yield of 92%, concomitant with a slight increase in enantioselectivity to 22% *ee* (entry 6). Unexpectedly, utilization of this dihydroquinidine (DHQD) derived ligand led to preferential dihydroxylation of the same face of **148** as observed for (DHQ)<sub>2</sub>PHAL, derived from “pseudoenantiomeric” dihydroquinine (DHQ). Further variation of the AD conditions by decreasing the reaction temperature to 0 °C (entry 7), or additional employment of methanesulfonamide (entry 8), did not lead to higher enantioselectivities.

**Table 24:** Studied dihydroxylation of **148** employing NMO as the terminal oxidant.



Entry	x / y / z [mol%]	Solvent	T [°C]	t [h]	Conv. / Yield <sup>[a]</sup> / <i>ee</i>
1	5 / 10 / 130	<i>t</i> BuOH/H <sub>2</sub> O (1:1)	23	45	51 / 17 / 10
2	5 / 10 / 130 <sup>[b]</sup>	<i>t</i> BuOH/H <sub>2</sub> O (1:1)	23	45	50 / 18 / 10
3	5 / 10 / 130 <sup>[b]</sup>	CH <sub>2</sub> Cl <sub>2</sub> /H <sub>2</sub> O (4:1)	23	45	62 / 45 / 3
4	3 / 10 / 200	THF/Acetone/H <sub>2</sub> O <sup>[c]</sup>	0	70	48 / 21 / 0
5	5 / 10 / 200	THF/H <sub>2</sub> O (10:1)	23	1.5	100 / 86 / 14
6	5 / 10 <sup>[d]</sup> / 200	THF/H <sub>2</sub> O (10:1)	23	1	100 / 92 / 22
7	4 / 10 <sup>[d]</sup> / 200	THF/H <sub>2</sub> O (10:1)	0	4	100 / 87 / 20
8	4 / 10 <sup>[d]</sup> / 200 <sup>[b]</sup>	THF/H <sub>2</sub> O (10:1)	0	4	100 / 80 / 18

<sup>[a]</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-TMB as internal standard; <sup>[b]</sup> 1.0 eq MeSO<sub>2</sub>NH<sub>2</sub> were added; <sup>[c]</sup> Solvent ratio 1:1:1; <sup>[d]</sup> (DHQD)<sub>2</sub>AQN was employed instead of (DHQ)<sub>2</sub>PHAL.

<sup>175</sup> H. Becker, K. B. Sharpless, *Angew. Chem. Int. Ed.* **1996**, *35*, 448-451.

Subsequently, we changed the dihydroxylation substrate, and hoped to achieve higher facial selectivity for *bis*-silyl ether **149** by the potential synergy of its inherent stereochemical bias and ligand control (Table 25). Application of the previously highest yielding conditions ((DHQD)<sub>2</sub>AQN/THF/H<sub>2</sub>O) to **149** resulted in 79% yield of a 1:2.3 diastereomeric mixture of **281** in favor of the undesired (8*R*,9*S*) diastereomer (entry 1). Employment of “pseudoenantiomeric” ligand (DHQ)<sub>2</sub>AQN led to a comparable yield, but to an equimolar mixture of the desired (8*S*,9*R*)-**281** with its 8-*epi*-9-*epi* counterpart (entry 2). As observed previously, AD using mixtures of *t*BuOH proceeded dramatically slower (entry 3), and even favored formation of the undesired diastereomer when THF was omitted (entry 4).

Table 25: Studied asymmetric dihydroxylation of **149**.

Entry	Ligand	Solvent	T [°C]	t [h]	Conv. / Yield <sup>[a]</sup> / <i>dr</i> <sup>[b]</sup>
1	(DHQD) <sub>2</sub> AQN	THF/H <sub>2</sub> O (10:1)	23	1	100 / 79 / 1:2.3
2	(DHQ) <sub>2</sub> AQN	THF/H <sub>2</sub> O (10:1)	23	1.5	100 / 77 / 1:1
3	(DHQ) <sub>2</sub> AQN <sup>[c]</sup>	<i>t</i> BuOH/THF/H <sub>2</sub> O/(4:4:1)	23	22	81 / 64 / 1:1
4	(DHQ) <sub>2</sub> AQN	<i>t</i> BuOH/H <sub>2</sub> O (1:1)	23	43	73 / 47 / 1:1.4
5	(DHQ) <sub>2</sub> PHAL	<i>t</i> BuOH/THF/H <sub>2</sub> O <sup>[d]</sup> (1:1:2)	0	24	96 / 43 / 1.8:1
6	(DHQ) <sub>2</sub> PHAL	<i>t</i> BuOH/H <sub>2</sub> O (1:1)	23	72	93 / 76 / 1:1.3
7	(DHQ) <sub>2</sub> PHAL	THF/H <sub>2</sub> O (10:1)	23	1	100 / 71 / 1:1.2
8	(DHQ) <sub>2</sub> PHAL	THF/H <sub>2</sub> O (10:1)	0	2	100 / 91 / 1:1.1
9	(DHQ) <sub>2</sub> PHAL	THF/H <sub>2</sub> O (10:1)	0	4	100 / 71 / 1:1.1 <sup>[e]</sup>
10	(DHQ) <sub>2</sub> Pyr	THF/H <sub>2</sub> O (10:1)	0	3	96 / 66 / 1:1.2
11	(DHQ) <sub>2</sub> Pyr	<i>t</i> BuOH/H <sub>2</sub> O (1:1)	23	68	100 / 42 / 1:1.5

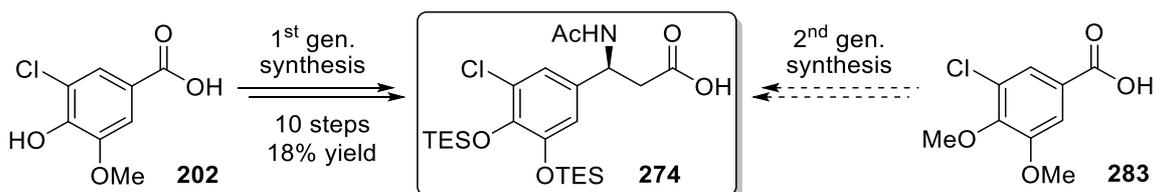
<sup>[a]</sup> Determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-TMB as internal standard; <sup>[b]</sup> ratio of desired/undesired diastereomer; <sup>[c]</sup> Addition of **149** over 11 h; <sup>[d]</sup> biphasic conditions using K<sub>3</sub>Fe(CN)<sub>6</sub>, K<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, MeSO<sub>2</sub>NH<sub>2</sub>;

<sup>[e]</sup> Reaction was conducted on 1.0 mmol scale: isolated yield is reported.



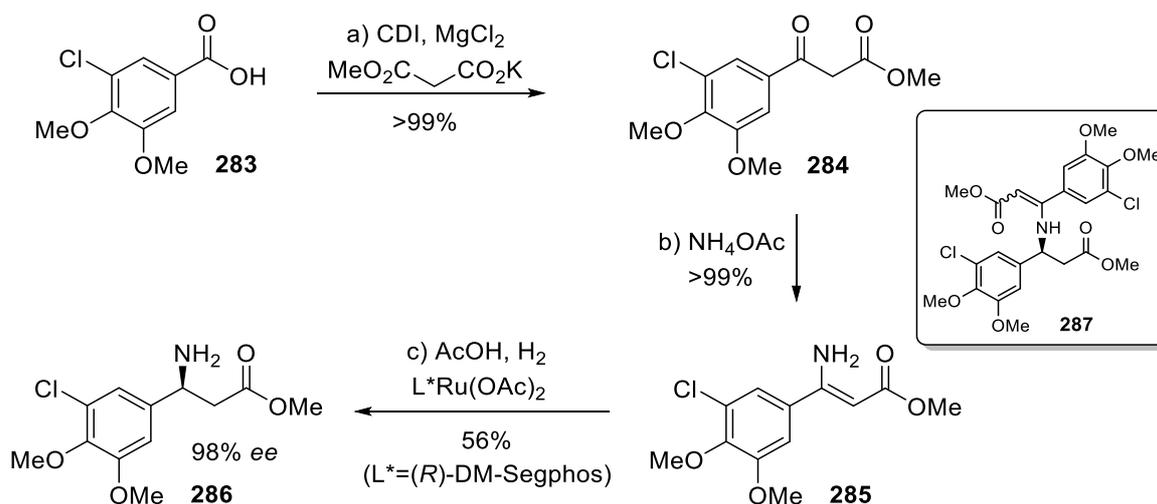
### 6.3 2<sup>nd</sup> Generation Synthesis of the $\beta$ -Amino Acid from 5-Chloroveratric Acid

As discussed in section 6.2.1, double TES protection of the catechol moiety of the  $\beta$ -amino acid proved beneficial to the atropselectivity of the macrocyclization process. As preparation of double TES protected  $\beta$ -amino acid **274** is not requiring a chemical differentiation between both phenolic hydroxyl groups, a shorter synthesis of this building block was envisaged. Thus, commercially available 5-chloroveratric acid (**283**) was identified as a viable starting material (**Scheme 94**).



**Scheme 94:** 1<sup>st</sup> generation and planned 2<sup>nd</sup> generation synthesis of  $\beta$ -amino acid **274**.

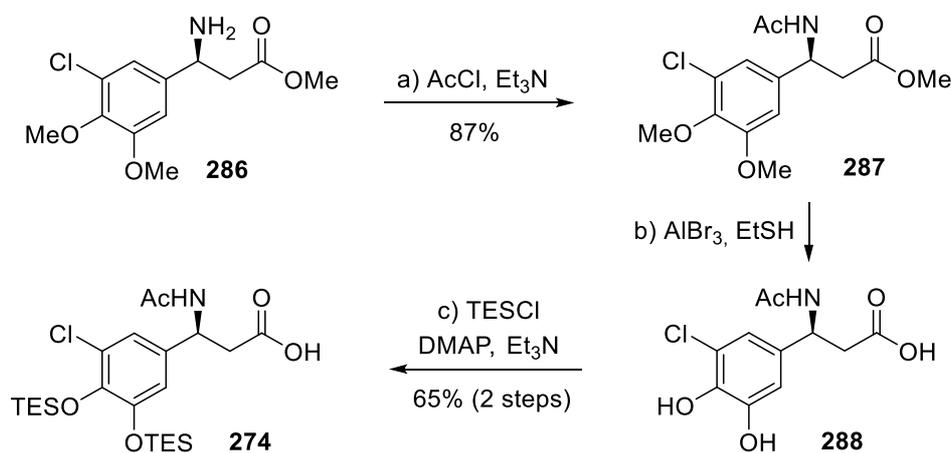
In analogy, benzoic acid **283** was converted into  $\beta$ -keto ester **284** in quantitative yield (**Scheme 95**). Similarly, transformation of **284** into enamine **285** proceeded without loss of material. Enantioselective enamine reduction provided  $\beta$ -amino ester **286** in excellent optical purity (98% *ee*) and 56% yield after the first chromatographic purification step of the synthesis. We ascribed the moderate yield **286** to the formation of a dimer-like side product, which was tentatively assigned as **287**.



**Reagents and conditions:** a) CDI (1.2 eq), MgCl<sub>2</sub> (1.1 eq), MeO<sub>2</sub>CCH<sub>2</sub>CO<sub>2</sub>K (1.5 eq), THF, 23 °C, 18 h, >99%; b) NH<sub>4</sub>OAc (5.0 eq), MeOH, 70 °C, 12 h, >99%; c) ((*R*)-DM-Segphos)Ru(OAc)<sub>2</sub> (1.0 mol%), AcOH (2.0 eq), H<sub>2</sub> (30 atm.), MeOH, 80 °C, 6.5 h, 56%, 98% *ee*.

**Scheme 95:** Synthesis of  $\beta$ -amino ester **286**.

Ensuing *N*-acetylation proceeded smoothly affording acetamide **287** (Scheme 96). Global demethylation of **287** was accomplished using Fujita's method, employing AlBr<sub>3</sub>/EtSH in CH<sub>2</sub>Cl<sub>2</sub>.<sup>177</sup> The obtained crude catechol **288** was subjected to TES protection, furnishing bis-triethylsilyl  $\beta$ -amino acid **274** in good yield over two steps.



Reagents and conditions: a) AcCl (1.2 eq), Et<sub>3</sub>N (1.3 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 1 h, 87%; b) AlBr<sub>3</sub> (8.0 eq), EtSH (70 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 21 h, c) TESCl (6.6 eq), DMAP (15 mol%), Et<sub>3</sub>N (8.0 eq), DMF, 23 °C, 8 h, 65% (2 steps).

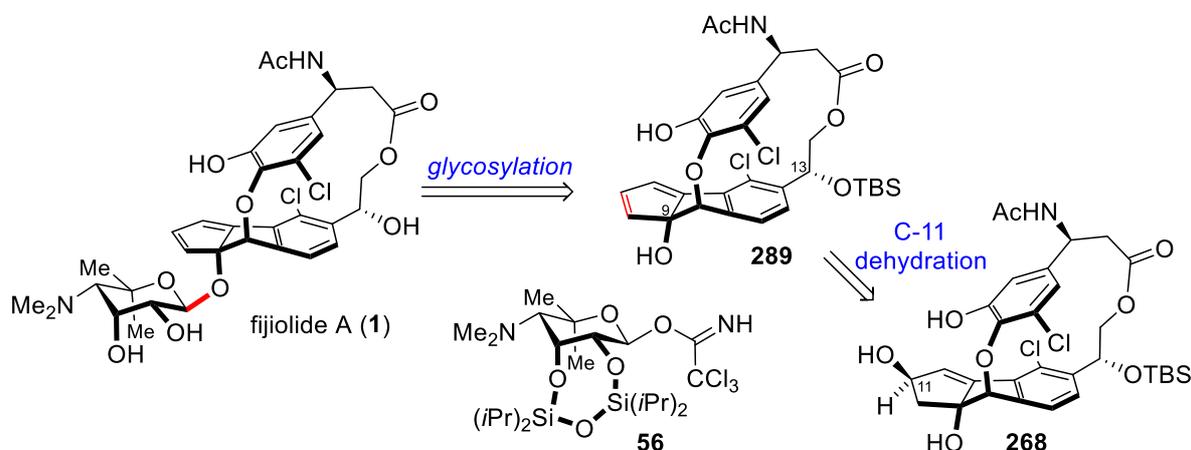
Scheme 96: Synthesis of  $\beta$ -amino acid **274**.

Thus, the 2<sup>nd</sup> generation synthesis of **274** provided the  $\beta$ -amino acid fragment of fijiolide A in 6 steps and good overall yield of 32% from commercially available 5-chloroveratric acid. As only three chromatographic purification steps were required, this approach allows rapid access to multi-gram quantities of the highly enantioenriched **274**.

<sup>177</sup> M. Node, K. Nishide, K. Fuji, E. Fujita, *J. Org. Chem.* **1980**, *45*, 4275-4277.

### 6.4 Studies Targeting Dehydration of the C-11 Allylic Alcohol

With a reliable synthetic route toward [2.6]paracyclophane **268** in hand, our focus shifted towards elimination of the C-11 hydroxyl group to install the cyclopentadiene moiety. According to our recent retrosynthetic analysis (**Scheme 97**), **1** was to be obtained from postulated fijiolide A precursor **289** via glycosylation of the tertiary C-9 hydroxyl group. **289** was envisaged to be directly accessed from **268** via C-11 dehydration, and would allow synthesis of the fijiolide A aglycone by cleavage of the C-13 silyl ether.



**Scheme 97:** Envisioned completion of the synthesis of **1** via protected fijiolide A aglycone **289**.

In order to investigate the dehydration reaction, 22-OMe [2.6]paracyclophane **263** was selected as an advanced model system. Its protected phenol reduces the number of nucleophilic sites that could potentially interfere with dehydration strategies. Still, the desired transformation would require high chemoselectivity, ensuring dehydration of the secondary allylic alcohol in favor of the tertiary allylic hydroxyl group. We began our studies employing freshly prepared Burgess reagent (**Table 26**, entries 1-2).<sup>178,179</sup> While no conversion to **290** was achieved in toluene, execution of the reaction in THF resulted in formation of an unidentified product, which did not contain a cyclopentadiene moiety. Next, Martin's sulfurane (**Figure 8a**) was screened.<sup>180</sup> Employment of 1.2 equivalents of reagent on less than 2 mg scale of **263**, cleanly led to formation of a new product (entry 3). The structure of this species was tentatively assigned as benzyl ether **291**, with an inverted configuration

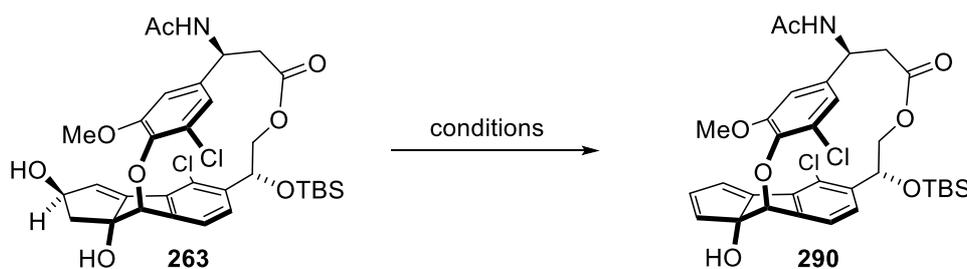
<sup>178</sup> E. M. Burgess, H. R. Penton, E. A. Taylor, *J. Am. Chem. Soc.* **1970**, *92*, 5224-5226.

<sup>179</sup> S. Carret, A. Blanc, Y. Coquerel, M. Berthod, A. E. Greene, J.-P. Deprés, *Angew. Chem. Int. Ed.* **2005**, *44*, 5130-5133.

<sup>180</sup> a) J. C. Martin, R. J. Arhart, *J. Am. Chem. Soc.* **1971**, *93*, 4327-4329; b) R. J. Arhart, J. C. Martin, *J. Am. Chem. Soc.* **1972**, *94*, 5003-5010.

at C-11 (**Figure 8b**). This result is unexpected as secondary *bis*(trifluoromethyl)benzyl ethers usually undergo elimination to the corresponding olefin, and only a few secondary *bis*(trifluoromethyl)benzyl ethers have even been isolated.<sup>181</sup> Addition of base to the reaction mixture did not facilitate elimination, perhaps as result of poor orbital overlap for an E<sub>2</sub> elimination to occur (entry 4). Dehydration *via* activation of the C-11 hydroxyl group with MsCl, followed by Et<sub>3</sub>N or DBU mediated elimination did not deliver the desired **290**, but instead resulted in substrate decomposition (entries 5-6). Altering the electrophilic activation reagent to Tf<sub>2</sub>O gave rise to a new product, whose structure could not be assigned due to rapid decomposition of the sample after isolation. An attempt to dehydrate **263** under acidic conditions with *p*TSA showed no conversion after 24 h (entry 8).

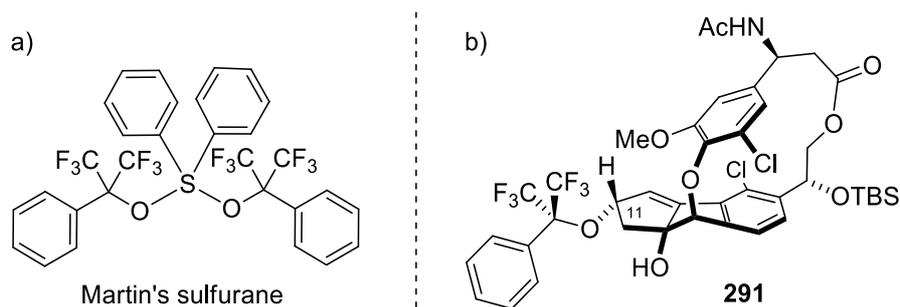
**Table 26:** Investigated dehydration of [2.6]paracyclophane **263**.



Entry	Conditions	T [°C]	t [h]	Result
1	Burgess reagent (1.1 eq), PhMe	23	8	No conversion
2	Burgess reagent (2.6 eq), THF	23	16	Undesired product
3	Martin's sulfurane <sup>[a]</sup> (1.2 eq), CH <sub>2</sub> Cl <sub>2</sub>	0	1	42% <b>291</b>
4	Martin's sulfurane <sup>[a]</sup> (1.2 eq), Et <sub>3</sub> N (5.0 eq), CH <sub>2</sub> Cl <sub>2</sub>	23	1	<b>291</b> (yield <i>n.d.</i> )
5	MsCl (1.2 eq), Et <sub>3</sub> N (5.0 eq), CH <sub>2</sub> Cl <sub>2</sub>	0	3	Decomposition
6	MsCl (2.4 eq), DBU (5.0 eq), CH <sub>2</sub> Cl <sub>2</sub>	23	24	Decomposition
7	Tf <sub>2</sub> O (2.4 eq), 2,6-lut. (10 eq), CH <sub>2</sub> Cl <sub>2</sub>	-78	1.5	Unidentified product <sup>[b]</sup>
8	<i>p</i> TSA (1.0 eq), PhMe	23	24	No conversion

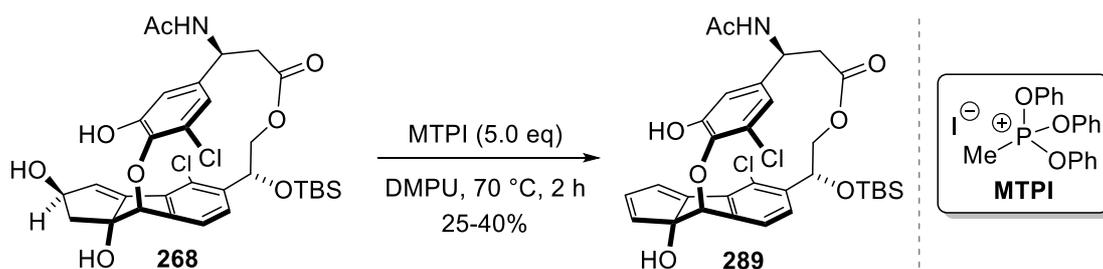
<sup>[a]</sup> Martin's sulfurane was purchased from TCI Chemicals and used as received; <sup>[b]</sup> An unidentified pure product by <sup>1</sup>H NMR was isolated but rapidly decomposed in CDCl<sub>3</sub>.

<sup>181</sup> a) H.-S. Cho, J. Yu, J. R. Falck, *J. Am. Chem. Soc.* **1994**, *116*, 8354-8355; b) J. R. Falck, J. Yu, H.-S. Cho, *Tetrahedron Lett.* **1994**, *35*, 5997-6000; c) T. Sato, T. Yamazaki, Y. Nakanishi, J.-i. Uenishi, M. Ikeda, *J. Chem. Soc., Perkin Trans. 1* **2002**, 1438-1443; d) K. Iwasaki, R. Kanno, T. Morimoto, T. Yamashita, S. Yokoshima, T. Fukuyama, *Angew. Chem. Int. Ed.* **2012**, *51*, 9160-9163.



**Figure 8:** a) Structure of Martin's sulfurane; b) Isolated product after reacting **263** with Martin's sulfurane.

Although efforts to install the cyclopentadiene motif on model substrate **263** were not successful, direct dehydration of the more advanced paracyclophane **268** was also attempted. Utilization of Martin's Sulfurane, Burgess Reagent, or dehydration conditions such as  $I_2/PPH_3/1H$ -imidazole and  $POCl_3$ /pyridine likewise failed to provide desired **289**, and substrate decomposition was observed in most cases. As a consequence, we investigated methyltriphenoxyphosphonium iodide (MTPI) for direct dehydration of **268**. MTPI is reported to selectively dehydrate secondary alcohols in polar aprotic solvents, such as HMPA or DMPU, while tertiary alcohols and phenols are unaffected.<sup>182</sup> Pleasingly, conversion of **268** with MTPI in DMPU was found to provide desired cyclopentadiene **289** in 25-40% yield after isolation by preparative HPLC (Scheme 98).<sup>183</sup> Detrimentally, **289** turned out to be quite unstable, especially toward acidic media. We attribute this finding to the cyclopentadieneol motif. In fact, we are only aware of a single report by Itô *et al.* describing an isolated 1,2-disubstituted cyclopentadienol and its facile elimination to fulvene derivatives.<sup>184</sup>



**Scheme 98:** Successful dehydration of **268** with MTPI.

<sup>182</sup> J.-R. Dormoy, B. Castro, in *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, **2001**.

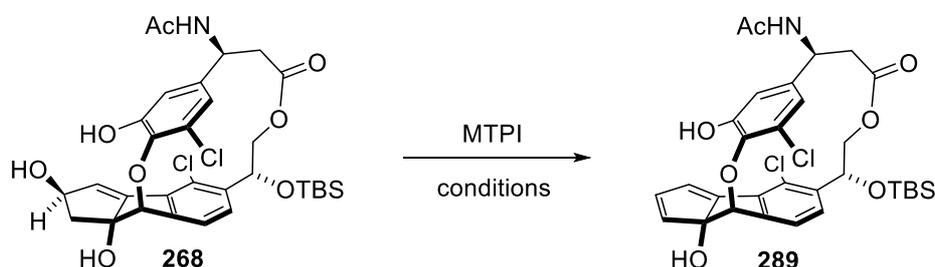
<sup>183</sup> Reaction was conducted employing 2.0 mg (3.1  $\mu$ mol) of azeotropically dried **268** and purchased MTPI (Sigma Aldrich), purified by washing with dry Et<sub>2</sub>O.

<sup>184</sup> Y. Fujise, T. Morishima, K. Namiwa, T. Shiokawa, Y. Fukazawa, S. Itô, *Tetrahedron Lett.* **1983**, *24*, 4261-4264.

In addition, reproducing the dehydration of **268** with MTPI proved difficult. Numerous modifications to the reaction conditions were evaluated to improve the reproducibility, and are presented in **Table 27**. Neither altering the reaction temperature (entries 2-4), nor the solvent to HMPA or DMI (5-7), or addition of a basic additive aiming to prevent acid mediated substrate decomposition (entries 8-10), improved the reproducibility and yield. Moreover, application of different purification methods for MTPI (entries 11-14), or utilization of freshly prepared MTPI<sup>185</sup> (entries 15-17) were also unsuccessful.

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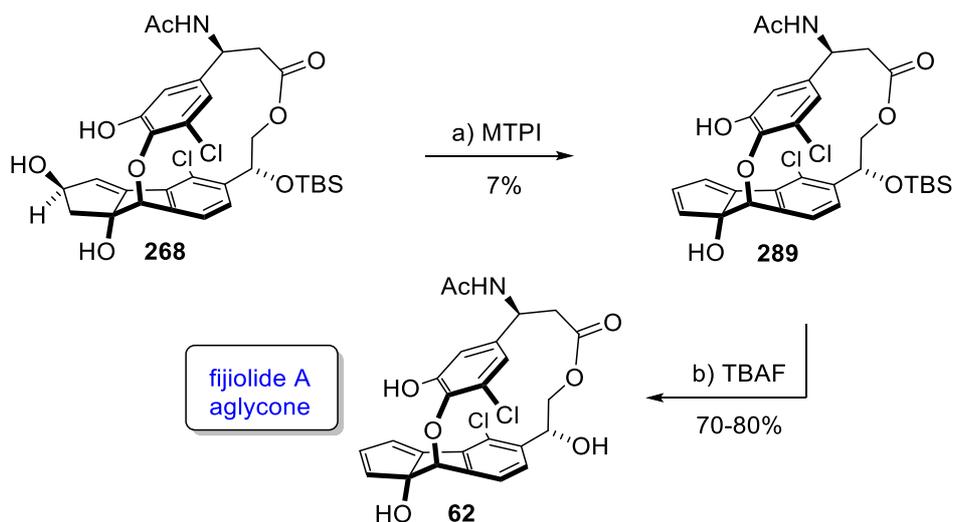
<sup>185</sup> J. P. H. Verheyden, J. G. Moffatt, *J. Org. Chem.* **1970**, *35*, 2319-2326.

**Table 27:** Attempts to reproduce the C-11 dehydration of **268** with MTPI.

Entry	MTPI [Eq]	Conditions	Additive	Result (Crude NMR)
1	5.0 <sup>[a]</sup>	DMPU, 70 °C, 2 h	-	50-60% Conversion / 25-40% <b>289</b>
2	10 <sup>[b]</sup>	DMPU, 70 °C, 1 h	-	≤5% <b>289</b> / decomposition
3	2.0 <sup>[b]</sup>	DMPU, 50 °C, 1 h	-	Complete decomposition
4	5.0 <sup>[a]</sup>	DMPU, 23 °C, 24 h	-	No conversion
5	2.0 <sup>[b]</sup>	DMI, 50 °C, 1 h	-	62% Conversion / decomposition
6	10 <sup>[b]</sup>	HMPA, 70 °C, 1 h	-	≤17% <b>289</b> / decomposition
7	5.0 <sup>[a]</sup>	HMPA, 70 °C, 2 h	-	Traces of <b>289</b> / decomposition
8	5.0 <sup>[a]</sup>	DMPU, 70 °C, 2 h	K <sub>2</sub> CO <sub>3</sub> (1.5 eq)	Traces of <b>289</b> / decomposition
9	3.0 <sup>[b]</sup>	DMPU, 70 °C, 2 h	K <sub>2</sub> CO <sub>3</sub> (6.0 eq)	Complete decomposition
10	2.0 <sup>[d]</sup>	DMPU, 70 °C, 1 h	DBU (4.0 eq)	65% Conversion / traces of <b>289</b>
11	5.0 <sup>[c]</sup>	DMPU, 70 °C, 2 h	-	≤7% <b>289</b> / decomposition
12	3.2 <sup>[c]</sup>	DMPU, 70 °C, 2 h	-	43% Conversion / decomposition
13	5.7 <sup>[e]</sup>	DMPU, 70 °C, 2 h	-	Complete decomposition
14	14 <sup>[e]</sup>	DMPU, 70 °C, 2 h	-	Complete decomposition
15	2.0 <sup>[f]</sup>	DMPU, 70 °C, 1 h	-	45% Conversion / decomposition
16	3.0 <sup>[f]</sup>	DMPU, 70 °C, 75 min	-	20% of a more polar product
17	3.0 <sup>[f]</sup>	DMPU, 70 °C, 45 min	-	26% of an unidentified product
18	7.7 <sup>[b]</sup>	DMPU, 70 °C, 4 h	-	7% Isolated yield / decomposition

<sup>[a]</sup> Purchased MTPI (Sigma Aldrich) was washed with dry Et<sub>2</sub>O (6 x) to afford a pale brown solid; <sup>[b]</sup> Purchased MTPI (Sigma Aldrich) was precipitated from dry CH<sub>2</sub>Cl<sub>2</sub> (5 x) to afford an off-white solid; <sup>[c]</sup> Purchased MTPI (Sigma Aldrich) was washed with dry Et<sub>2</sub>O (3 x) to afford a brown solid; <sup>[d]</sup> Purchased MTPI (Sigma Aldrich) was washed with dry Et<sub>2</sub>O (4 x) followed by dry EtOAc (3 x) to afford a yellow/orange solid; <sup>[e]</sup> Purchased MTPI (Acros Organics) was used as received (dark brown moist solid); <sup>[f]</sup> Freshly prepared MTPI (yellow solid) of highest purity by NMR, compared to all other MTPI batches.

Still, a single further dehydration experiment of slightly increased reaction scale provided **289** in 7% isolated yield (**Scheme 99**). Treatment with TBAF on sub-milligram scale cleanly afforded the fijiolide A aglycone **62** in 70-80% yield.<sup>186</sup> Similar to **289**, the fijiolide A aglycone did not prove stable and decomposed when stored at  $-30\text{ }^{\circ}\text{C}$  in a DMSO matrix.



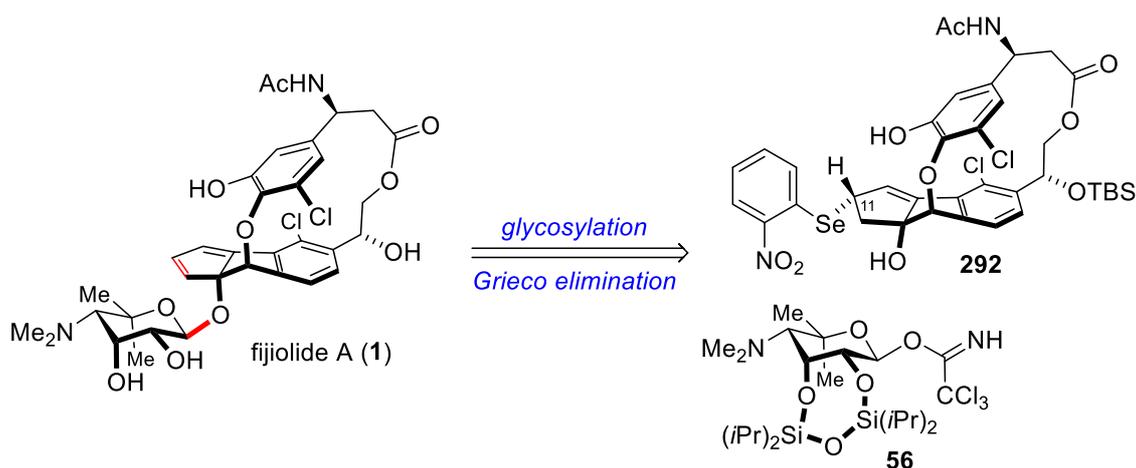
Reagents and conditions: a) MTPI (6.6 eq), DMPU, 70 °C, 4 h, 7%, b) TBAF (3.0 eq), 0 °C, 1 h, 70-80%.

**Scheme 99:** Synthesis of the fijiolide A aglycone **62**.

The instability of cyclopentadienols **289** and **62** prompted us to revise our synthetic strategy for installation of the amino sugar moiety (*cf.* **Scheme 97**). In particular, Brønsted or Lewis acid

<sup>186</sup> The structure of **62** was tentatively assigned by <sup>1</sup>H, COSY and ROESY NMR spectroscopy and in comparison with the reported NMR data for fijiolide A.

assisted activation of glycosyl donor **56** in presence of protected fijiolide A aglycone **289** was deemed critical. This would require a stable coupling partner. Our new strategy towards **1** involved a Grieco elimination step after successful coupling of selenide **292** to the amino sugar (Scheme 100).<sup>187</sup>



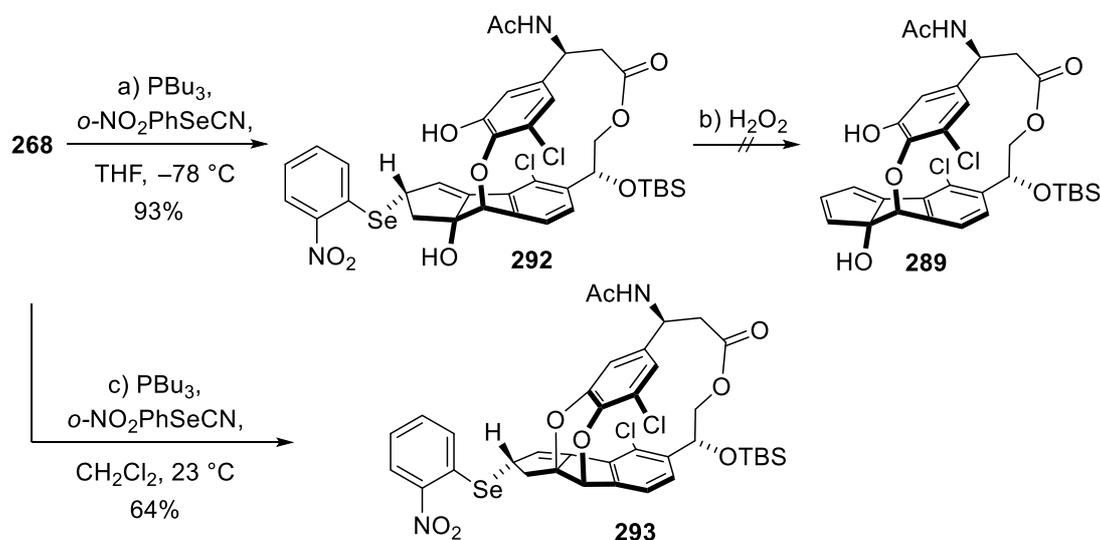
**Scheme 100:** Revised strategy for completion of the synthesis of **1** via selenide **292**.

To realize this goal, Mitsunobu-type installation of an *o*-nitrophenylselenide substituent at C-11 was necessary.<sup>188</sup> Employment of PBU<sub>3</sub>/*o*-NO<sub>2</sub>PhCN proved suitable for this purpose, however, low and erratic yields of 24-53% were initially attained for selenide **292**.<sup>189</sup> In an effort to address this shortcoming, lowering the reaction temperature from ambient temperature to -78 °C turned out to be crucial for clean conversion. Thus, reproducible and scale-independent yields of up to 93% were obtained (Scheme 101).

<sup>187</sup> a) K. B. Sharpless, M. W. Young, R. F. Lauer, *Tetrahedron Lett.* **1973**, *14*, 1979-1982; b) P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485-1486; c) H. J. Reich, S. Wollowitz, J. E. Trend, F. Chow, D. F. Wendelborn, *J. Org. Chem.* **1978**, *43*, 1697-1705.

<sup>188</sup> P. A. Grieco, S. Gilman, M. Nishizawa, *J. Org. Chem.* **1976**, *41*, 1485-1486.

<sup>189</sup> The C-11 stereochemistry in **293** was determined by ROESY NMR studies.



*Reagents and conditions:* a) *o*-NO<sub>2</sub>PhSeCN (3.0 eq), PBu<sub>3</sub> (3.1 eq), THF, -78 °C, 1.5 h, 93%; b) H<sub>2</sub>O<sub>2</sub> (32 eq), THF, 23 °C, 23 h, decomposition; c) *o*-NO<sub>2</sub>PhSeCN (4.0 eq), PBu<sub>3</sub> (4.2 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 75 min, 64%.

**Scheme 101:** Selenylation of [2.6]paracyclophane **268** and attempted direct Grieco elimination.

Interestingly, formation of a different reaction product was observed when the solvent was changed to CH<sub>2</sub>Cl<sub>2</sub>, or DMPU contaminated starting material was employed. Although we do not yet have unequivocal evidence for the structure of this compound, NMR studies, HRMS, IR, and the experimentally demonstrated absence of a free hydroxyl group,<sup>190</sup> suggests the formation of doubly bridged *bis*-aryl ether **293**. We rationalize this outcome by additional activation of the tertiary allylic alcohol, and subsequent nucleophilic substitution by the spatially close free phenol. Although uncommon, Mitsunobu reactions of tertiary alcohols with phenols, proceeding with inversion of configuration have been reported.<sup>191</sup>

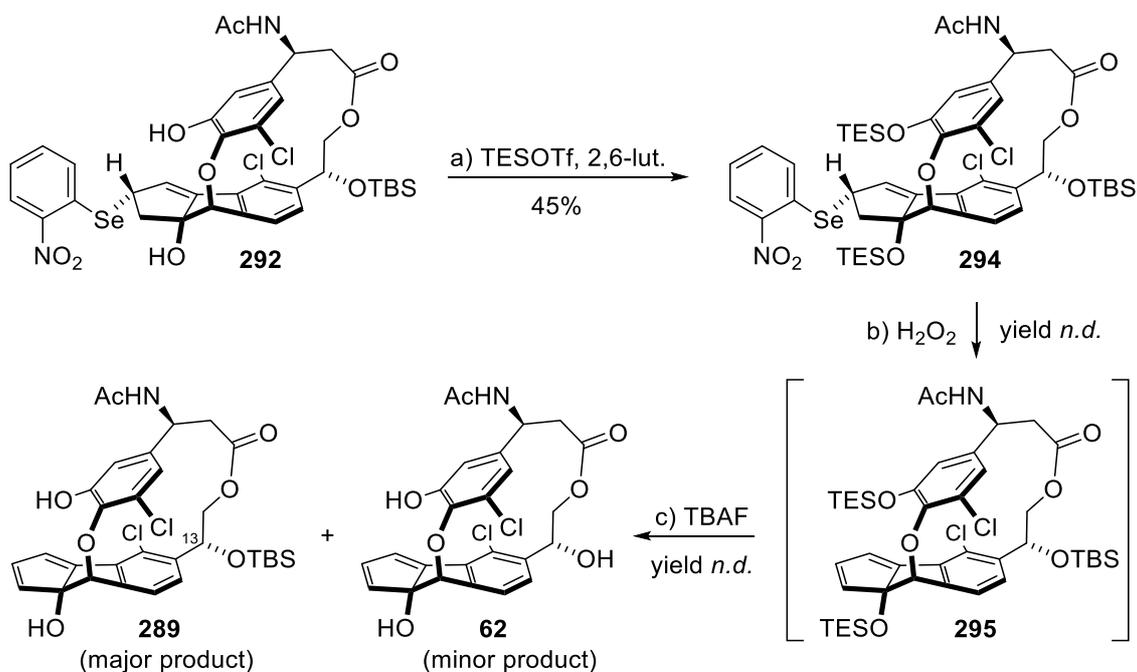
In order to probe the feasibility of installing the desired cyclopentadiene motif *via syn*-elimination of an intermediate selenoxide, **292** was treated with hydrogen peroxide, disappointingly resulting in substrate degradation. Considering the successful Grieco elimination of a related, but simpler substrate by Hirama *et al.*, it was reasoned that the free tertiary alcohol in **292** may be interfering with intended *syn*-elimination.<sup>192</sup> To probe this proposal, selenide **292** was converted into *bis*-TES ether **294**, which was then subjected to selenide oxidation with H<sub>2</sub>O<sub>2</sub> (**Scheme 102**). In this case, *syn*-elimination provided a mixture of compounds, including cyclopentadiene **295**. Subsequent

<sup>190</sup> All attempts to install a silyl group on **293** *via* reaction with TESOTf/2,6-lutidine were met with failure.

<sup>191</sup> Y.-J. Shi, D. L. Hughes, J. M. McNamara, *Tetrahedron Lett.* **2003**, *44*, 3609-3611.

<sup>192</sup> M. Inoue, S. Hatano, M. Kodama, T. Sasaki, T. Kikuchi, M. Hirama, *Org. Lett.* **2004**, *6*, 3833-3836.

addition of TBAF afforded a mixture of the previously synthesized fijiolide A aglycone **62**, and its 13-OH protected congener **289**. Thus, the feasibility of the Grieco elimination procedure for the synthesis of fijiolide A was demonstrated.



*Reagents and conditions:* a) TESOTf (30 eq), 2,6-lutidine (60 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 7 h, 45%; b) H<sub>2</sub>O<sub>2</sub> (20 eq), THF, 23 °C, 8 h, yield *n.d.*; c) TBAF (10 eq), THF, THF/CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1.5 h, **62** (minor product, yield *n.d.*), **289** (major product, yield *n.d.*).

**Scheme 102:** Synthesis of the fijiolide A aglycone **62** via Grieco elimination.

Glycosylation of selenide **292** posed the next challenge, and studies concerning this matter are discussed in chapter 8.



***7. Synthesis and Activation  
of the Amino Sugar Moiety***

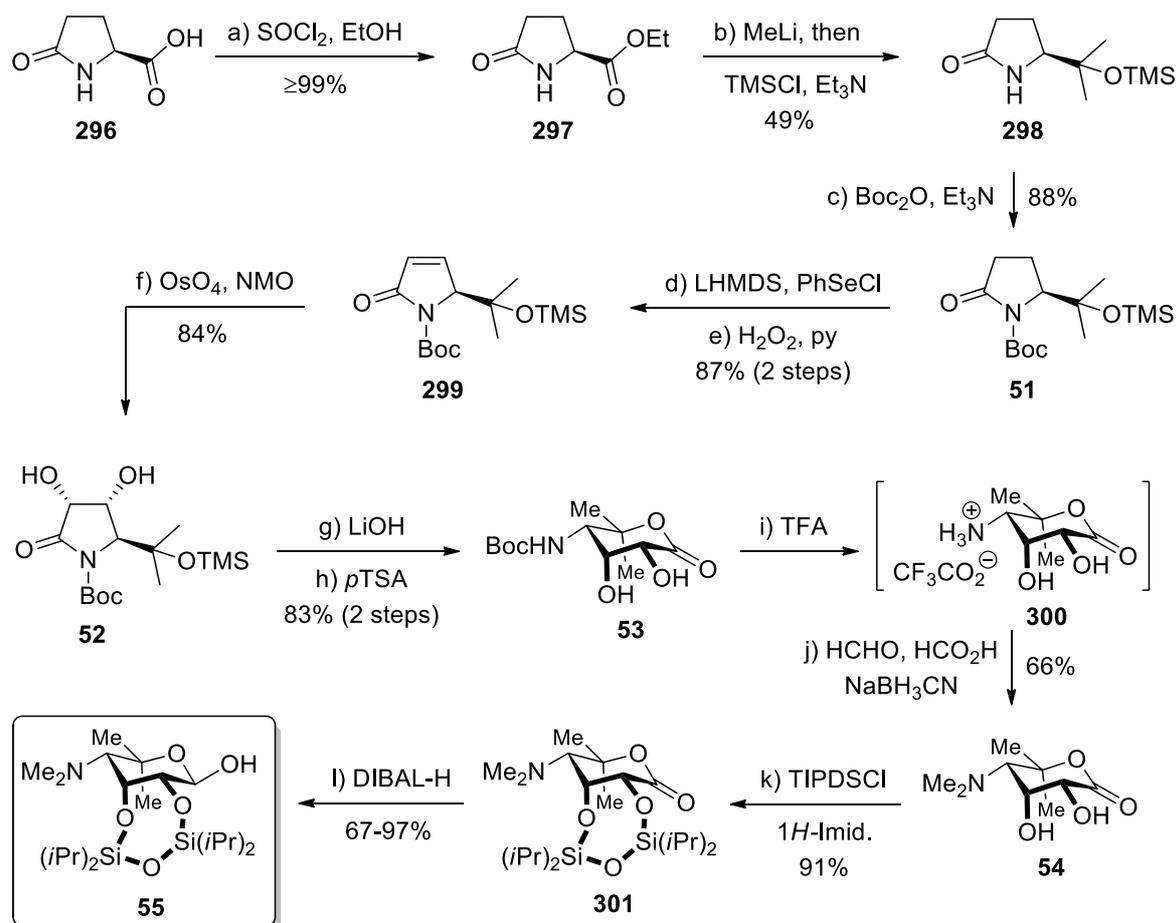
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## 7.1 Synthesis of TIPDS Protected Amino Sugar **55**

A synthesis of the amino sugar moiety, found in both the C-1027 chromophore and the fijiolides, has been previously reported by Hirama and Semmelhack (*cf.* chapter 2.2).<sup>52,53</sup> We elected to follow Hirama's second generation approach towards the amino ribopyranose for several reasons: This synthesis provides direct access to the useful tetraisopropylidisiloxane (TIPDS) protected amino sugar **55**, which was reported to undergo the required selective  $\beta$ -glycosylation of tertiary alcohols after trichloroacetimidate activation (*cf.* chapter 2.3). In addition, we presumed that glycosylation of a late-stage fijiolide A precursor would require extensive evaluation of reaction conditions, and would potentially necessitate glycosylation studies on a model substrate. As a high excess of glycosyl donor was expected to be essential to achieve acceptable levels of conversion, a synthesis of the amino sugar must ensure ample supply of this building block in a reliable and reproducible manner. In being explicitly described to provide large scale quantities of **55** (10.6 g, 23.7 mmol), Hirama's synthesis meets this criterion well. Our synthesis of **55** is summarized in **Scheme 103** and follows closely Hirama's route. Generally, high reproducibility was encountered allowing straightforward access to **55**. However, minor modification to the original procedure was undertaken, and a brief discussion is disclosed. In deviation from Hirama's report, ethyl L-pyroglutamate **297** was accessed in quantitative yield *via* esterification of readily available L-pyroglutamic acid **296**.<sup>193</sup> Transformation to tertiary TMS ether **298**, Boc protection of the  $\gamma$ -lactam, and selenoxide elimination proceeded smoothly to provide **299**. The reported catalyst loading of OsO<sub>4</sub> was decreased from 10 mol% to 2.0 mol% in the subsequent dihydroxylation step, resulting in only a marginally lower yield for diol **52** compared to Hirama's result (84% *vs.* 91%). Whereas the subsequent 2-step procedure for transformation of  $\gamma$ -lactam **52** into  $\delta$ -lactone **53** proceeded smoothly, practical challenges were encountered during synthesis of dimethylamino diol **54**. Due to the extremely high water solubility of **54**, low yields were obtained following Hirama's protocol. A modified workup procedure provided remedy. Further alkalization of the NaCl saturated aqueous phase (NaHCO<sub>3</sub>) from pH 8-9 to pH 10 with 2 M NaOH, followed by extraction with chloroform instead of EtOAc, turned out to be key for isolation of **54** in greater than 60% yield. Despite our yield (66%) lagging behind Hirama's reported yield of 79% yield, we attained dramatically higher yields for the subsequent TIPDS protection to furnish lactone **301** (91% *vs.*

<sup>193</sup> L. S. Nazarova, Y. B. Rozonov, A. M. Likhoshestov, T. V. Morozova, A. P. Skoldinov, N. V. Kaverina, V. A. Markin, *Pharm. Chem. J.* **1984**, *18*, 811-815; J. Zamirer, C. Brockmann, P. Huy, R. Opitz, C. Reuter, M. Beyermann, C. Freund, M. Müller, H. Oschkinat, R. Kühne, H.-G. Schmalz, *Angew. Chem. Int. Ed.* **2010**, *49*, 7111-7115.

56%), thus compensating for the aforementioned shortcoming. Lactone reduction provided desired **55** as an inconsequential mixture of its cyclic hemiacetal and open-chain aldehyde form. However, erratic yields for this step were encountered, with an observed tendency for lower yields upon scale-up.<sup>194</sup>



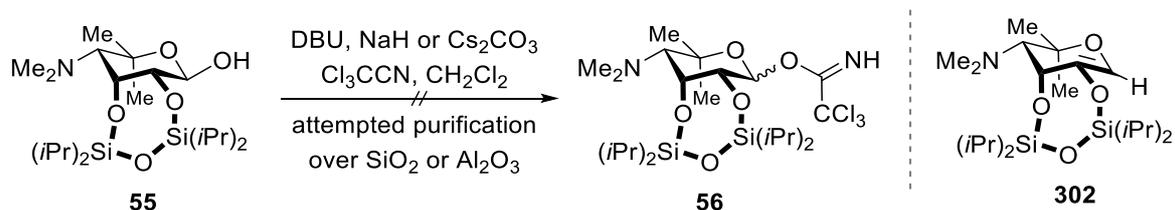
**Reagents and conditions:** a)  $\text{SOCl}_2$ , (1.2 eq), EtOH, 23 °C, 17 h,  $\geq 99\%$ ; b) MeLi (2.5 eq), THF,  $-78$  °C to 23 °C, 3 h, then TMSCl (6.0 eq), Et<sub>3</sub>N, (6.1 eq), 4.5 h, 49%; c) Boc<sub>2</sub>O (1.9 eq), Et<sub>3</sub>N (2.0 eq), DMAP (0.2 eq), MeCN, 23 °C, 14 h; d) LHMDS (1.5 eq), PhSeCl (1.3 eq), THF,  $-78$  °C, 1.5 h; e) H<sub>2</sub>O<sub>2</sub> (3.4 eq), pyridine (3.0 eq), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 75 min, 87% (2 steps); f) OsO<sub>4</sub> (2.0 mol%), NMO (2.0 eq), acetone/*t*BuOH/H<sub>2</sub>O (v/v = 1/3.3/1.5), 23 °C, 18 h, 84%; g) LiOH (3.0 eq), THF/H<sub>2</sub>O, 0 °C, 2 h; h) *p*TSA (5.0 mol%), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 6 h, 83% (2 steps); i) TFA (26 eq), CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 100 min; j) HCHO (36 eq), HCO<sub>2</sub>H (2.0 eq), NaBH<sub>3</sub>CN (2.1 eq), MeCN, 23 °C, 3.5 h, 66% (2 steps); k) TIPDSCI (2.0 eq), 1*H*-imidazole (4.0 eq), DMF, 23 °C, 14 h, 91%; l) DIBAL-H (2.0 eq), CH<sub>2</sub>Cl<sub>2</sub>,  $-78$  °C, 80 min, 67-97%.

**Scheme 103:** Synthesis of the protected fijiolide amino sugar moiety, according to the procedure of Hirama *et al.*

<sup>194</sup> Loss of material appears to arise from prolonged exposure to SiO<sub>2</sub> during chromatographic purification.

## 7.2 Trichloroacetimidate Activation of Amino Sugar 55

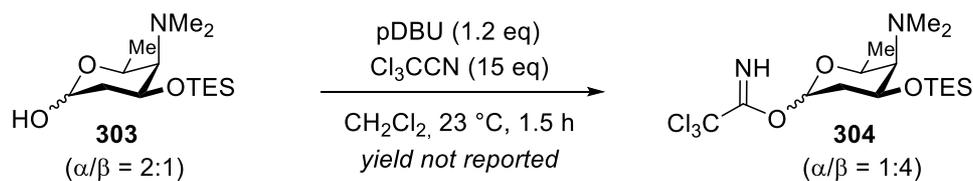
A glycosylation of tertiary alcohols with amino sugar **55** has already been reported by Hirama *et al.* and was initially discussed in chapter 2.3. Conversion of hemiacetal **55** into its corresponding trichloroacetimidate **56** was found to be the method of choice to attain both high reactivity, and suitable  $\beta$ -selectivity.<sup>65</sup> Although utilized in glycosylation studies, neither a procedure for the DBU mediated trichloroacetimidate activation of hemiacetal **55**, nor spectroscopic data for glycosyl donor **56** were provided. Additionally, no information about the stability of **56** can be gathered from Hirama's report. Concerning isolation of **56**, we hypothesized that a purification step would be required to remove DBU as it was expected to interfere with any subsequent Lewis or Brønsted acid glycosylation promoter.<sup>195</sup> However, classical acid-base extraction was deemed unsuitable for removal due to the amino group of **56**, and potential for hydrolysis of the formed trichloroacetimidate. Direct chromatographic purification of the reaction mixture was therefore anticipated to be the isolation technique of choice. However, several trials to synthesize glycosyl donor **56** by reaction with trichloroacetonitrile (10 – 40 eq) and DBU (0.2 – 2.0 eq) in dichloromethane led to complex mixtures and incomplete conversion even after prolonged reaction times, judged by TLC. Similar results were obtained using NaH or Cs<sub>2</sub>CO<sub>3</sub> as the base (**Scheme 104**). Moreover, attempted isolation of **56** by flash chromatography did not provide the desired glycosyl donor. Instead, glycal **302**, arising from trichloroacetimidate elimination or direct dehydration of the free anomeric hydroxyl group of **55**, was isolated in up to 69% yield after purification over SiO<sub>2</sub>. In contrast, use of basic Al<sub>2</sub>O<sub>3</sub> as the stationary phase, did not allow for isolation of any amino sugar species, presumably due to complete substrate degradation.



**Scheme 104:** Failed attempts for synthesis of Schmidt donor **56**.

<sup>195</sup> a) R. R. Schmidt, *Angew. Chem. Int. Ed.* **1986**, 25, 212-235; b) S. Hanessian, *Preparative carbohydrate chemistry*, Marcel Dekker, New York, **1997**.

The DBU mediated activation of **55** with trichloroacetonitrile (25 eq) was subsequently monitored by  $^1\text{H}$  NMR spectroscopy. Only trace conversion was observed in the presence of 0.2 eq DBU after 2 h in  $\text{CD}_2\text{Cl}_2$ . However, further addition of DBU (0.5 eq) led to exceedingly clean formation of a new product, which became almost the only detectable species upon addition of further 0.2 eq DBU after 4.5 h. This was assigned to be the desired trichloroacetimidate by comparison with  $^1\text{H}$  NMR chemical shifts of related glycosyl donors.<sup>196</sup> However, increasing formation of the elimination product was observed upon prolonged reaction times, resulting in 16% glycal **302** after 21 h. We concluded, that the DBU mediated formation of **56** is indeed a very clean process.<sup>197</sup> However, the reaction time has to be carefully chosen to avoid unfavorable elimination of the newly formed trichloroacetimidate. Moreover, it became apparent that specific reagents and isolation conditions had to be carefully developed in order to allow separation of **56** from DBU. Guided by studies on the synthesis of highly unstable L-kedarsamine Schmidt donor **304** (Scheme 105),<sup>198</sup> we contemplated the utilization of polymer-bound DBU (pDBU), which would allow isolation of **56** by simple filtration of the reaction mixture.



**Scheme 105:** pDBU mediated activation of unstable L-kedarsamine amino sugar **27**.

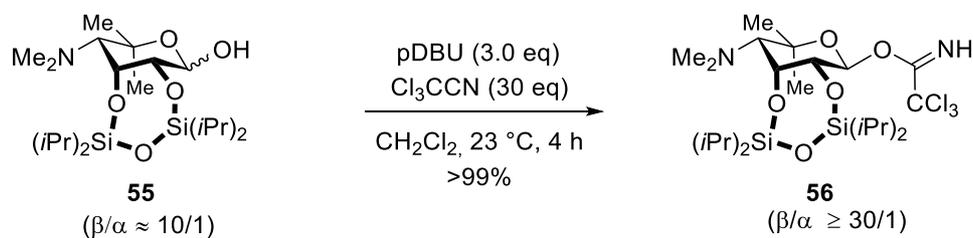
Pleasingly, a brief optimization of reaction conditions resulted in isolation of desired the Schmidt donor in quantitative yield after reacting **55** with trichloroacetonitrile and pDBU for 4 h, followed by filtration and removal of all volatiles under inert atmosphere (Scheme 106). Similar to our previous observation, increasing formation of glycal **302** was observed if pDBU was not filtered off in a timely manner. Interestingly, further elimination of **56** was ascertained even after filtration and storage of **56** as a solution in  $\text{CD}_2\text{Cl}_2$  at ambient temperature. Complete conversion into glycal **302** was observed within 24 h hours. By contrast, **56** was discovered to be exceedingly more stable in aromatic solvents. Thus, a NMR sample in  $\text{C}_6\text{D}_6$  did not show formation of **302**, or any other degradation product after storage for 4 days at ambient temperature. In addition, the stability of **56**

<sup>196</sup> A. G. Myers, R. Glatthar, M. Hammond, P. M. Harrington, E. Y. Kuo, J. Liang, S. E. Schaus, Y. Wu, J.-N. Xiang, *J. Am. Chem. Soc.* **2002**, *124*, 5380-5401.

<sup>197</sup> In retrospect, previously observed unclear and incomplete conversion is likely to be the result of product decomposition on analytical  $\text{SiO}_2$  or  $\text{Al}_2\text{O}_3$  coated TLC plates.

<sup>198</sup> I. Ohashi, M. J. Lear, F. Yoshimura, M. Hirama, *Org. Lett.* **2004**, *6*, 719-722.

in benzene- $d_6$  was not affected by contamination with residual water. Conveniently from a preparative point view, the Schmidt donor could even be stored for 2 – 3 weeks at  $-30\text{ }^\circ\text{C}$  in a benzene matrix (glovebox) without detectable evidence for degradation.



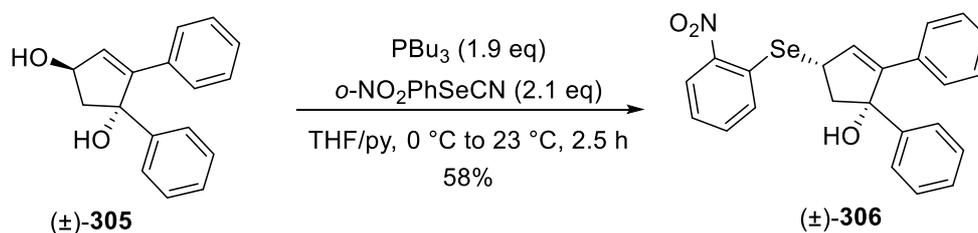
**Scheme 106:** Successful trichloroacetimidate activation of **55** using pDBU.

With a reliable and scalable synthesis of Schmidt donor **56** in hand, we were now able to start subsequent glycosylation studies on selenide **292**. We began by first modelling this reaction, and these studies are described in chapter 8.

## 8. *Completion of the Synthesis*

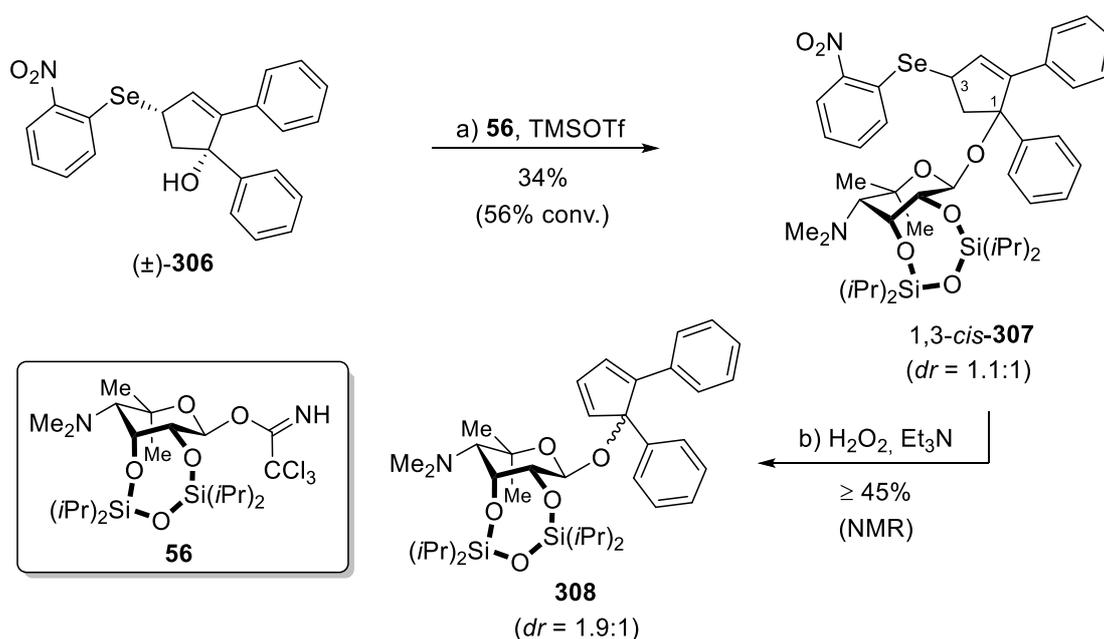
## 8.1 Glycosylation Studies

From the outset, late-stage coupling of the amino sugar moiety to any fijiolide A precursor was considered a key challenge of the synthesis. Glycosylation of the sterically encumbered tertiary C-9 hydroxyl group would require a highly activated glycosyl donor. At the same time, harsh reaction conditions to promote glycosylation had to be circumvented due to the sensitivity of the glycosyl acceptor. As initially outlined in chapter 2.3, Schmidt donors featuring an anomeric trichloroacetimidate group have emerged as powerful building blocks for glycosylation under fairly mild conditions. For that reason, Schmidt donor **56** has been employed by Hiramama *et al.* for successful glycosylation of synthetic intermediates in the context of their synthetic studies towards the C-1027 chromophore.<sup>65</sup> According to our envisioned late-stage Grieco elimination strategy (*cf.* **Scheme 100**, chapter 6.4), glycosylation of the intended acceptor **292** was thought to be particularly challenging due to the close proximity of the C-11 arylselenide substituent. Hence, glycosylation studies were initially conducted on model substrate **306**, which was accessible by Mitsunobu-type arylselenylation of known diol **305**.<sup>199</sup>



With (±)-**306** in hand, glycosylation was first attempted in dichloromethane using TMSOTf for activation of **56**.<sup>64,65</sup> The desired  $\beta$ -glycosylated species 1,3-*cis*-**307** was obtained in 34% yield, and as a 1.1:1 mixture of diastereoisomers (**Scheme 108**). Following this, Grieco elimination was attempted with H<sub>2</sub>O<sub>2</sub>. Et<sub>3</sub>N was additionally added as a sacrificial amine to prevent *N*-oxide formation of the amino sugar moiety. Thus, glycosylated cyclopentadienol **308** was obtained in  $\geq 45\%$  NMR yield, as a 1.9:1 mixture of diastereomers. This positive result prompted us to apply our glycosylation/elimination procedure to the synthesis of fijiolide A.

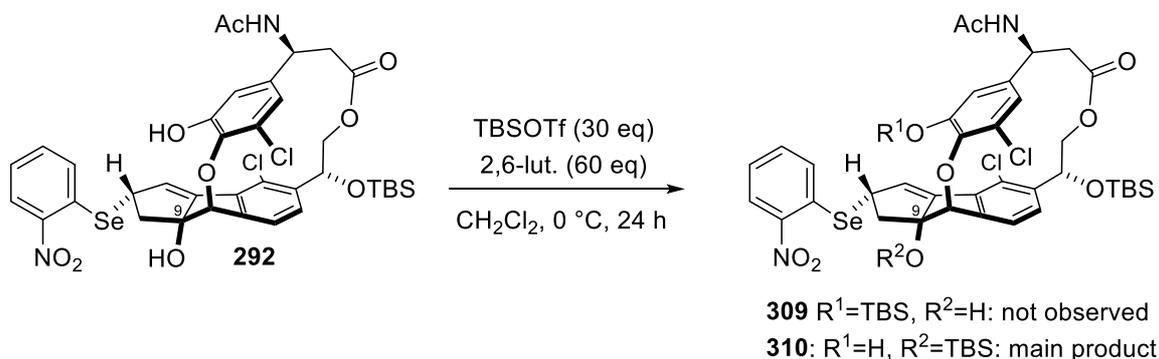
<sup>199</sup> P. Bladon, S. McVey, P. L. Pauson, G. D. Broadhead, W. M. Horspool, *J. Chem. Soc. C* **1966**, 306-312.



*Reagents and conditions:* a) Schmidt donor **56** (2.5 eq), TMSOTf (2.0 eq), 4Å-MS, CH<sub>2</sub>Cl<sub>2</sub>, -40 °C to 0 °C, 6 h, 34% (56% conversion); b) H<sub>2</sub>O<sub>2</sub> (40 eq), Et<sub>3</sub>N (10 eq), THF, 23 °C, 22 h, ≥45% (<sup>1</sup>H NMR).

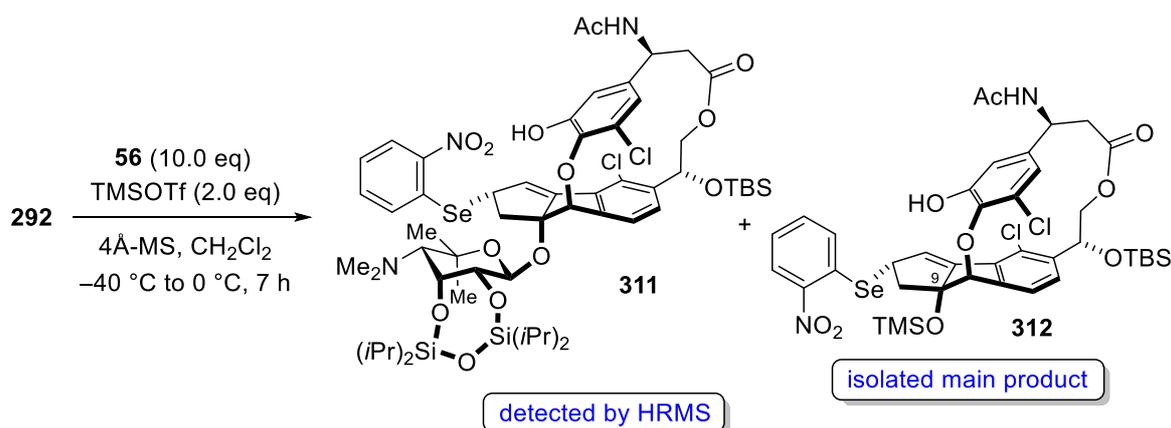
**Scheme 108:** Glycosylation and subsequent Grieco elimination of model substrate (±)-**306**.

Protection of the presumably more nucleophilic free phenol in **292** prior to glycosylation was considered necessary for progression of the synthesis. Consequently, **292** was reacted with TBSOTf/2,6-lutidine. Unexpectedly, this reaction provided the C-9 TBS ether **310** instead of **309** (**Scheme 109**). Even upon addition of 30 equivalents TBSOTf, we observed chemoselectivity for the protection of the tertiary alcohol and a reluctance of the phenol to engage in the silylation reaction. This prompted us to use **292** directly as the glycosylation substrate (**Scheme 110**).



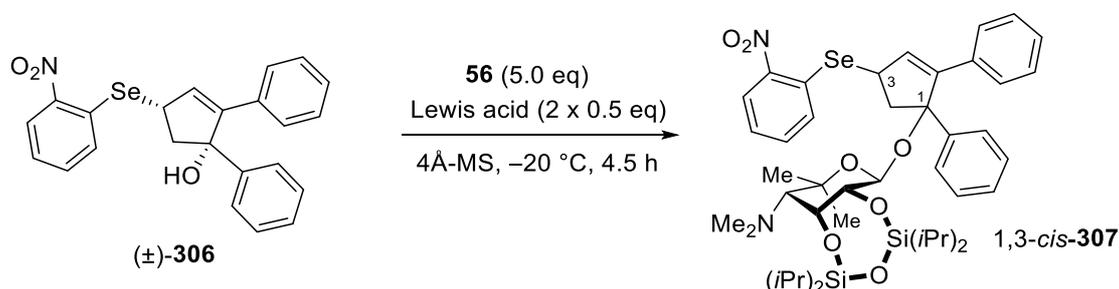
**Scheme 109:** Unexpected selectivity in silylation of selenide **292**.

The glycosylation of **292** with 10 equivalents of Schmidt donor **56** yielded only trace amounts of the targeted species **311**. Instead the C-9 TMS ether **312** was isolated as the main product. We attribute the formation of **312** to a direct silylation of the tertiary alcohol with TMSOTf, enabled by amino sugar **56** carrying a built-in base.



**Scheme 110:** Attempted glycosylation of **292** utilizing TMSOTf as the activating Lewis acid.

As a result, we were forced to re-examine glycosylation conditions to prevent parasitic 9-OH silylation. Model substrate ( $\pm$ )-**306** was re-consulted for this purpose and our results are summarized in **Table 28**. In an attempt to shut down alcohol silylation by using  $\text{BF}_3\cdot\text{OEt}_2$  as the activating Lewis acid, substrate degradation was observed as the predominant process (entries 1 and 2). As dichloromethane is the most common solvent for silylation employing trialkylsilyl triflates, it appeared to be an inappropriate choice for the desired glycosylation reaction. Hence, we aimed to limit silylether formation by utilization of solvents that would hamper this process. Glycosylation using TMSOTf in  $\text{Et}_2\text{O}$  and PhMe provided higher yields of 1,3-*cis*-**307** (entries 3-4). It was observed that 20% and 35% of Schmidt donor **56**, respectively, had not been consumed during these reactions. We interpreted this observation as a potential for further improvement in yield by prolonged reaction times, or increased Lewis acid loading. Activation of **56** with the less reactive TESOTf afforded 57% of the glycosylation product in PhMe (entries 5-6). Even sterically encumbered TBSOTf in  $\text{Et}_2\text{O}$  or PhMe performed well, furnishing 1,3-*cis*-**307** in 38% and 32%, respectively. Notably, conversion of both ( $\pm$ )-**306** and **56** was lower in these cases, especially when PhMe was used (entries 7-8). Finally, a significant increase in yield to 70% was observed by running the glycosylation in PhMe, employing 3.0 equivalents of the activating TBSOTf. As previously, no TBS protection of ( $\pm$ )-**306** occurred at  $-20\text{ }^\circ\text{C}$ .

**Table 28:** Glycosylation optimization studies.

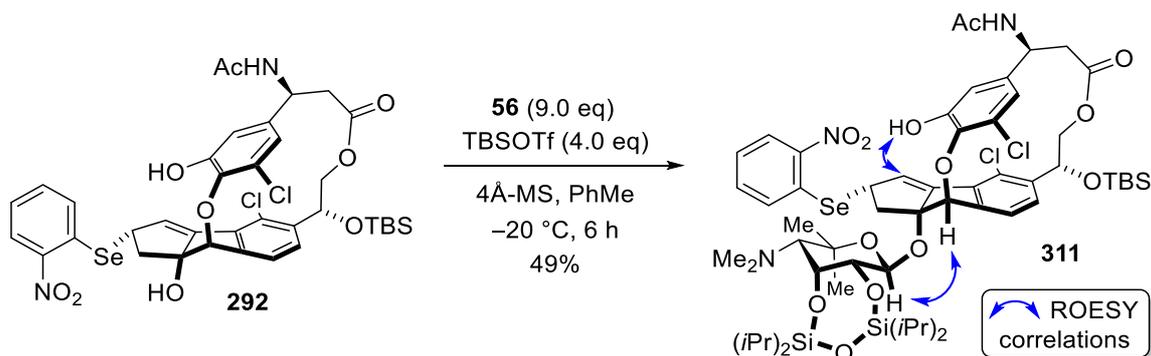
Entry	Lewis Acid	Solvent	Conversion / Yield <sup>[a]</sup> [%]	Unreacted 56 [%]
1	BF <sub>3</sub> •OEt <sub>2</sub> <sup>[b,c]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	75 / 17	0
2	BF <sub>3</sub> •OEt <sub>2</sub> <sup>[c]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	71 / 17	0
3	TMSOTf	Et <sub>2</sub> O	77 / 48	20
4	TMSOTf	PhMe	89 / 46	35
5	TESOTf	Et <sub>2</sub> O	58 / 39	18
6	TESOTf	PhMe	75 / 57	31
7	TBSOTf	Et <sub>2</sub> O	54 / 38	26
8	TBSOTf	PhMe	57 / 32	43
9	TBSOTf <sup>[d]</sup>	PhMe	85 / 70	36

<sup>[a]</sup> Determined by <sup>1</sup>H NMR using dimethyl terephthalate as internal standard;

<sup>[b]</sup> Excess of Lewis acid resulted in predominant decomposition of (±)-306, 56 and 1,3-cis-307;

<sup>[c]</sup> Reaction was conducted at 0 °C; <sup>[d]</sup> 3.0 eq TBSOTf were used.

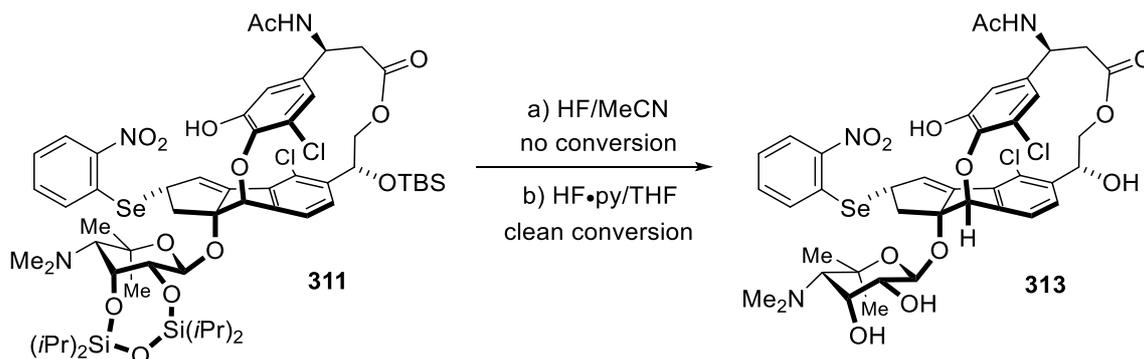
Since TBSOTf was assumed to be too sterically hindered for 9-OH silylation, while still efficiently activating Schmidt donor **56**, it became the Lewis acid of choice for the follow-up glycosylation studies of **292** (Scheme 111). Remarkably, the desired β-anomer **311** could be isolated in 49% yield after activation of 9.0 equivalents of **56** with TBSOTf. Formation of the corresponding α-anomer was not observed at all. The glycosylation of **292** at the tertiary alcohol in favor of the free phenol was confirmed by ROESY NMR spectroscopy (Scheme 111).



**Scheme 111:** Glycosylation of selenide **292** and key ROESY correlations verifying the structure of **311**.

## 8.2 Installation of the Cyclopentadiene and Isolation of Synthetic Fijiolide A

Having achieved the key glycosylation step, synthesis of fijiolide A was to be completed by *syn*-elimination of the aryl selenide, and finally a global deprotection. Based on the previously observed instability of cyclopentadiene featuring fijiolide A precursors, global desilylation of **311** was envisaged first. A screen of few deprotection conditions rapidly provided satisfactory results (**Scheme 112**). HF•pyridine was found to first cleave the disiloxane protecting group, followed by the benzylic TBS ether in very clean manner.

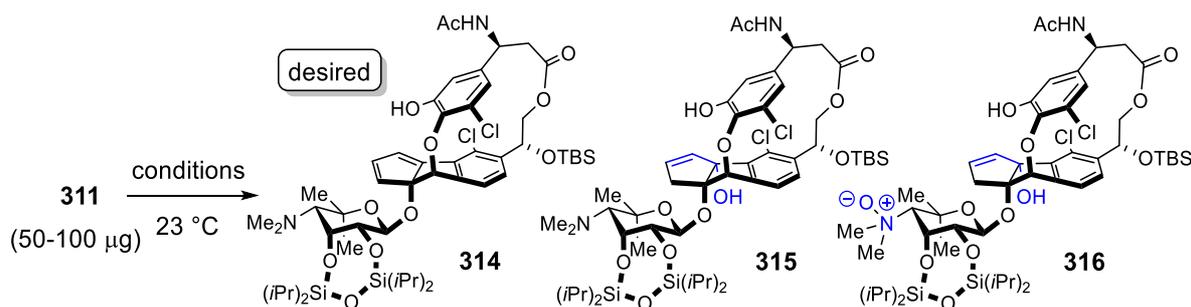


*Reagents and conditions:* a) 40% HF (233 eq), MeCN, 23 °C, 4.5 h; b) HF•py (300 eq), THF/py (10/1), 23 °C, 17 h.

**Scheme 112:**  $\mu$ g-Scale global desilylation of selenide **311**.

Subsequent tests to perform a *syn*-elimination of **313** to afford fijiolide A were not fruitful. Product mixtures, containing trace amounts of the target molecule were obtained, as detected by HRMS. Use of H<sub>2</sub>O<sub>2</sub>/THF, H<sub>2</sub>O<sub>2</sub>/Et<sub>3</sub>N/THF, *m*CPBA/CH<sub>2</sub>Cl<sub>2</sub> or *m*CPBA/TFA/CH<sub>2</sub>Cl<sub>2</sub> for Grieco elimination led to preferential formation of a “hydrated” form of **1**, along with an additionally oxidized species, which is attributed to *N*-oxide formation (*vide infra*). As a result, Grieco elimination prior to desilylation was investigated (**Table 29**). Submission of **311** to H<sub>2</sub>O<sub>2</sub>/Et<sub>3</sub>N in THF resulted in slow formation of a mixture of compounds (entry 1). By HRMS analysis the mixture was tentatively assigned to consist of the desired elimination product **314**, allylic alcohol **315**, allylic alcohol *N*-oxide **316**, and an oxidized starting material (not shown).<sup>200</sup> We attribute the formation of allylic alcohols **315** and **316** to a seleno-Mislow-Evans [2,3] sigmatropic rearrangement, typically observed upon oxidation of allylic selenides.<sup>201</sup>

**Table 29:** Studies on the selective *syn*-elimination of selenide **311**.



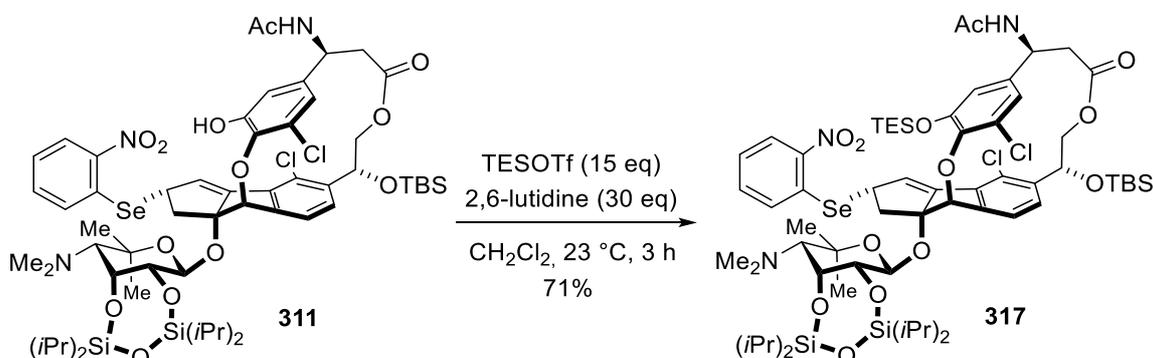
Entry	Reagent	Solvent	t [h]	Result <sup>[a]</sup>
1	H <sub>2</sub> O <sub>2</sub> /Et <sub>3</sub> N <sup>[b]</sup>	THF	24	<b>314</b> + <b>315</b> + <b>316</b> + oxidized <b>311</b>
2	H <sub>2</sub> O <sub>2</sub> <sup>[b]</sup>	THF	1	Exclusively <b>315</b>
3	H <sub>2</sub> O <sub>2</sub> <sup>[b]</sup>	MeOH	1.5	Nearly exclusively <b>316</b>
4	<i>m</i> CPBA <sup>[c]</sup>	CH <sub>2</sub> Cl <sub>2</sub>	1	<b>315</b> + oxidized <b>311</b>
5	H <sub>2</sub> O <sub>2</sub> /Et <sub>3</sub> N <sup>[b]</sup>	PhMe	17	<b>314</b> + <b>315</b> (3:1)
6	H <sub>2</sub> O <sub>2</sub> /Et <sub>3</sub> N <sup>[b,d]</sup>	PhMe	23	<b>314</b> + oxidized <b>311</b> (1.6:1)

<sup>[a]</sup> Evaluated by direct HRMS analysis of the reaction mixture or the crude product; <sup>[b]</sup> 10 eq of Et<sub>3</sub>N and 500-5000 eq of H<sub>2</sub>O<sub>2</sub> were used; <sup>[c]</sup> 1.0 eq *m*CPBA was used; <sup>[d]</sup> Reaction was conducted with 500 μg **311**.

<sup>200</sup> Due to identical molecular formula, differentiation between presence of a selenoxide or *N*-oxide species could not be effected by means of HRMS.

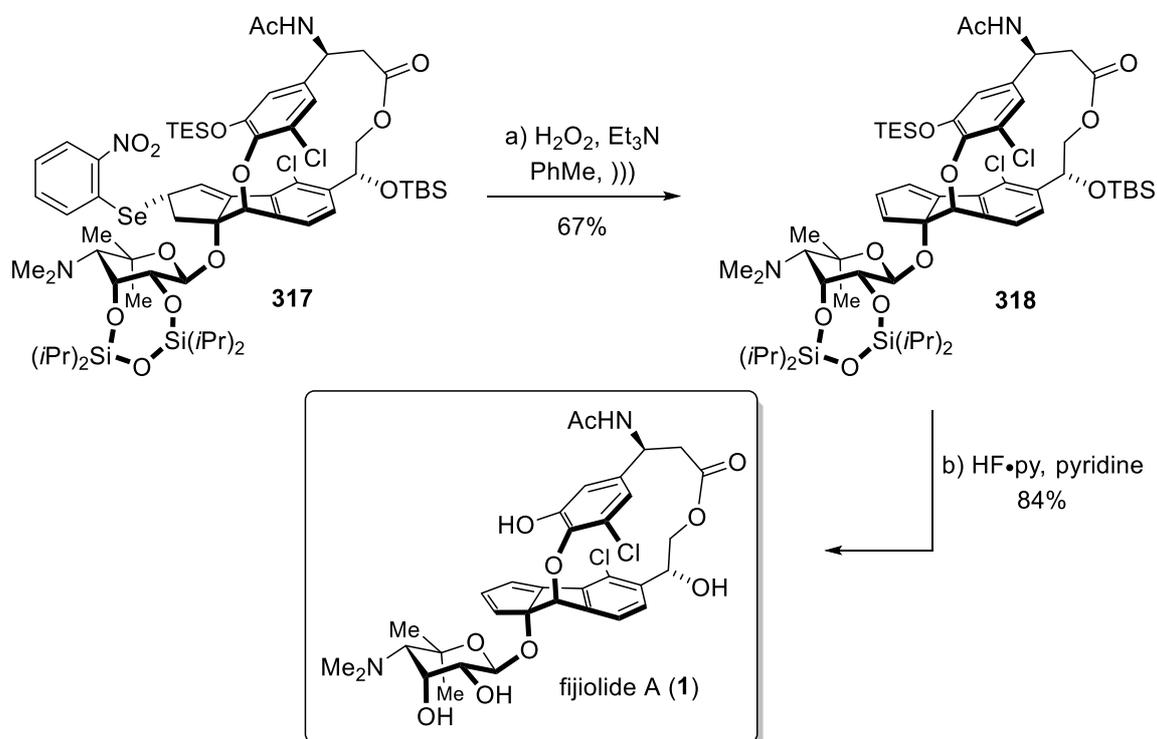
<sup>201</sup> a) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4869-4876; b) K. B. Sharpless, R. F. Lauer, *J. Am. Chem. Soc.* **1972**, *94*, 7154-7155; c) D. A. Evans, G. C. Andrews, *Acc. Chem. Res.* **1974**, *7*, 147-155; d) H. J. Reich, *J. Org. Chem.* **1975**, *40*, 2570-2572.

In order to suppress the rearrangement pathway, further reaction conditions were screened. Omission of Et<sub>3</sub>N led to rapid oxidation of the selenide and subsequent [2,3] sigmatropic rearrangement to give undesired **315** exclusively (entry 2). This was an unexpected result as Et<sub>3</sub>N - initially added as a sacrificial amine to prevent *N*-Oxide formation - appears to slow the rate of selenium oxidation as well as impact the fate of the intermediate selenoxide. A tremendous solvent effect on *N*-oxide formation was observed when H<sub>2</sub>O<sub>2</sub> in MeOH was used, resulting in predominant formation of **316** after 1.5 h (entry 3). Employment of *m*CPBA as the oxidant in dichloromethane yielded a 1:1 mixture of the undesired **315** and oxidized starting material after 1 h. No further conversion was observed (entry 4). A biphasic reaction mixture using toluene and aqueous H<sub>2</sub>O<sub>2</sub> as solvents turned out to promote the desired *syn*-elimination. Initially rapid and clean conversion to **314** (30% after 35 min) was observed. An additional 16.5 h were required to afford a 3:1 mixture of **314** with rearranged alcohol **315** (entry 5). A similar behavior was observed on larger scale (500 μg **311**). A formed equimolar mixture of **314** and oxidized **311** after 5 h required an additional 18 h for conversion into a 1.6:1 mixture of the same species (entry 6). We speculated that if **311** gives rise to a mixture of diastereomeric selenoxides upon oxidation, then one selenoxide diastereomer may undergo facile *syn*-elimination, whereas this process may be considerably slower for the other diastereomer. An alternative explanation to this is that the reaction is inhibited by *o*-nitrophenol selenenic acid, which is inevitably formed by *syn*-elimination of **311** (product inhibition). Neither reaction deceleration nor a [2,3] sigmatropic rearrangement had been observed in previously executed Grieco elimination of selenides **294** and 1,3-*cis*-**307** (cf. **Scheme 102** and **Scheme 108**). This suggests that the free phenol in **311** could detrimentally interact with the selenoxide, for instance, by hydrogen bonding to the Se→O bond or, more likely, to the more proximal *o*-nitrophenyl substituent. In order to probe this hypothesis, **311** was subjected to phenol protection, affording TES ether **317** in 71% yield (**Scheme 113**).



**Scheme 113:** TES protection of **311**.

A 30  $\mu\text{g}$  sample of **317** was subsequently reacted with  $\text{Et}_3\text{N}$  (10 eq) in toluene/aq.  $\text{H}_2\text{O}_2$  (~8:1, 1500 eq  $\text{H}_2\text{O}_2$ ). Remarkably, exclusive formation of the desired cyclopentadiene **318** within 3.5 h was observed (**Scheme 114**). Thus, the phenol was demonstrated to wield an enormous influence on the reaction outcome, and selective *syn*-elimination occurs when protected as the corresponding TES ether. Grieco elimination of **317** was successively scaled up. Whereas clean and rapid conversion to **318** was observed for 0.5 mg of substrate, a noticeably longer reaction time, and increased byproduct formation was encountered on 3.9 mg scale. We ascribed this finding to a less efficient phase exchange between aqueous  $\text{H}_2\text{O}_2$  and the organic layer upon scale-up. Constant sonication of the reaction mixture was found to address this problem, leading to reduced reaction times and reproducible results. To complete the synthesis of **1**, multi-milligram quantities of **317** were apportioned into 2.0 mg reaction batches and treated with  $\text{H}_2\text{O}_2/\text{Et}_3\text{N}$  under constant sonication, in parallel. Thus, a preparatively useful 67% yield of **318** was achieved for the crucial elimination step (**Scheme 114**). Subsequent global desilylation proceeded smoothly under previously established conditions ( $\text{HF}\cdot\text{py}$ , pyridine), and provided the putative target molecule fijiolide A in 84% isolated yield.



Reagents and conditions: a)  $\text{H}_2\text{O}_2$  (1500 eq),  $\text{Et}_3\text{N}$  (10 eq),  $\text{PhMe}$ , 25  $^\circ\text{C}$ , sonication, 5 h, 67%:

b)  $\text{HF}\cdot\text{py}$  (356 eq), pyridine (566 eq), THF, 23  $^\circ\text{C}$ , 7.5 h, 84%.

**Scheme 114:** Completion of the synthesis of fijiolide A by Grieco elimination and global deprotection.

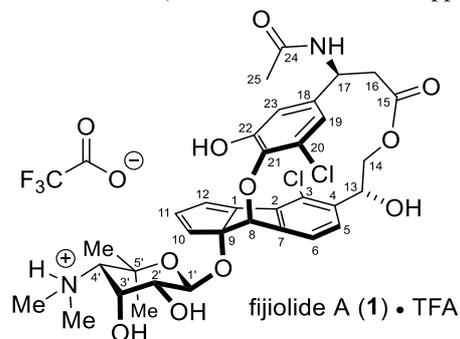
In order to compare **1** with the isolated natural fijiolide A, the synthetic sample was converted into its trifluoroacetic acid salt by addition of 2.0 equivalents TFA in DMSO- $d_6$ . NMR spectroscopic analysis (600 MHz, DMSO- $d_6$ ) revealed a match with the spectra of natural **1**.<sup>202</sup> The presence of fijiolide A as the corresponding TFA salt was not reported by Fenical and coworkers. However, the demonstrated match of NMR spectra only upon addition of TFA to the free base strongly indicates isolation of **1** as the TFA salt. Utilization of TFA as a HPLC eluent additive explains this fact. The purest sample of synthetic material was obtained by preparative reverse-phase HPLC, and was used for final comparison with natural fijiolide A. An excellent accordance of NMR chemical shifts was observed, with only very minor deviations for the exchangeable protons and the amino sugar moiety (chapter 8.3). This observation was traced back to *non*-identical NMR sample preparation. Our sample of synthetic fijiolide A • TFA in DMSO- $d_6$  appeared to be considerably less concentrated, while the water content was higher, compared to Fenical's NMR sample. A temperature-dependent deviation in NMR chemical shifts of the exchangeable protons was excluded as both spectra were acquired at 27 °C. Interestingly, the  $^1\text{H}$  chemical shifts of fijiolide A proved largely unaffected by the TFA concentration.

In summary, an atropselective synthesis of fijiolide A was realized in 18 steps in the longest linear sequence and 37 total steps including the 12 steps for the preparation of the known Schmidt donor. The match of NMR spectroscopic data and optical rotations for synthetic and natural fijiolide A verifies a correct structure assignment by Fenical *et al*, including the atropisomerism.

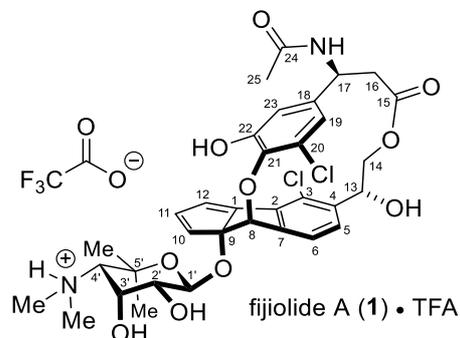
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<sup>202</sup> Kindly provided by Fenical *et al*.

## 8.3 NMR Spectroscopic Comparison of Natural and Synthetic Fijiolide A

**Table 30:** Comparison of  $^1\text{H}$  NMR (600 MHz,  $\text{DMSO-d}_6$ ) spectroscopic data of natural and synthetic fijiolide A  $\cdot$  TFA (referenced to H8 = 5.870 ppm).

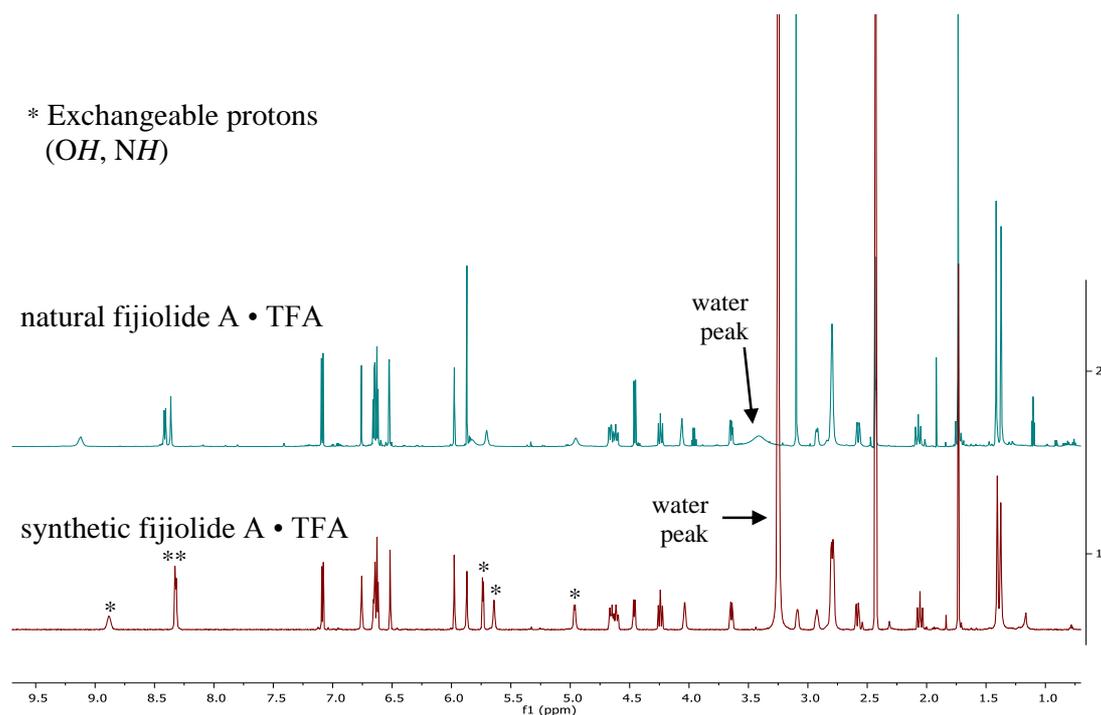
No	Natural 1 $\cdot$ TFA		Synthetic 1 $\cdot$ TFA		Deviation $\Delta\delta$ [ppm]
	$\delta_{\text{H}}$ [ppm]	mult. ( $J$ [Hz])	$\delta_{\text{H}}$ [ppm]	mult. ( $J$ [Hz])	
5	6.64	d (8.0)	6.64	d (8.1)	0.00
6	7.09	d (7.7)	7.08	d (8.0)	-0.01
8	5.87	s	5.87	s	0.00
10	6.62	d (5.5)	6.62	d (5.5)	0.00
11	6.65	dd (5.5, 2.2)	6.65	dd (5.5, 1.9)	0.00
12	6.76	d (2.0)	6.76	s	0.00
13	4.66	dd (11.1, 4.1)	4.66	dt (11.2, 4.3)	0.00
14	4.24; 3.65	t (10.5); dd (9.8, 3.9)	4.24; 3.64	t (10.5); dd (9.8, 3.7)	0.00; -0.01
16	2.58; 2.07	dd (13.5, 3.6); t (13.2)	2.58; 2.06	dd (13.3, 3.9); t (13.0)	0.00; -0.01
17	4.62	ddd (12.1, 8.3, 3.6)	4.61	ddd (11.9, 8.2, 3.4)	-0.01
19	6.53	d (2.0)	6.52	d (1.9)	-0.01
23	5.98	d (2.1)	5.98	d (1.9)	0.00
25	1.74	s	1.74	s	0.00
1'	4.46	d (8.0)	4.46	d (7.9)	0.00
2'	2.92	dd (8.5, 3.7)	2.95-2.89	m	0.00
3'	4.08-4.03	m	4.06-4.01	m	-0.02
4'	3.12-3.06	m	3.12-3.06	m	0.00
4'-Me <sub>2</sub>	2.80	br. s	2.80	d (3.3)	0.00
4'-Me <sub>2</sub>	2.80	br. s	2.79	d (3.3)	-0.01
6'-Me $\alpha$	1.37	s	1.37	s	0.00
6'-Me $\beta$	1.42	s	1.42	s	0.00
13-OH	5.84	br. s	5.74	d (4.4)	-0.10
17-NH	8.41	d (8.2)	8.32	d (7.7)	-0.09
22-OH	8.36	s	8.32	s	-0.04
2'-OH	4.95	br. s	4.96	d (5.5)	0.01
3'-OH	5.70	br. s	5.64	br. s	-0.06
4'-NH <sup>+</sup>	9.12	br. s	8.88	br. s	-0.24

**Table 31:** Comparison of  $^{13}\text{C}\{^1\text{H}\}$  NMR (600 MHz,  $\text{DMSO-d}_6$ ) spectroscopic data of natural and synthetic fijiolide A • TFA (referenced to  $\text{H}_9 = 99.80$  ppm).

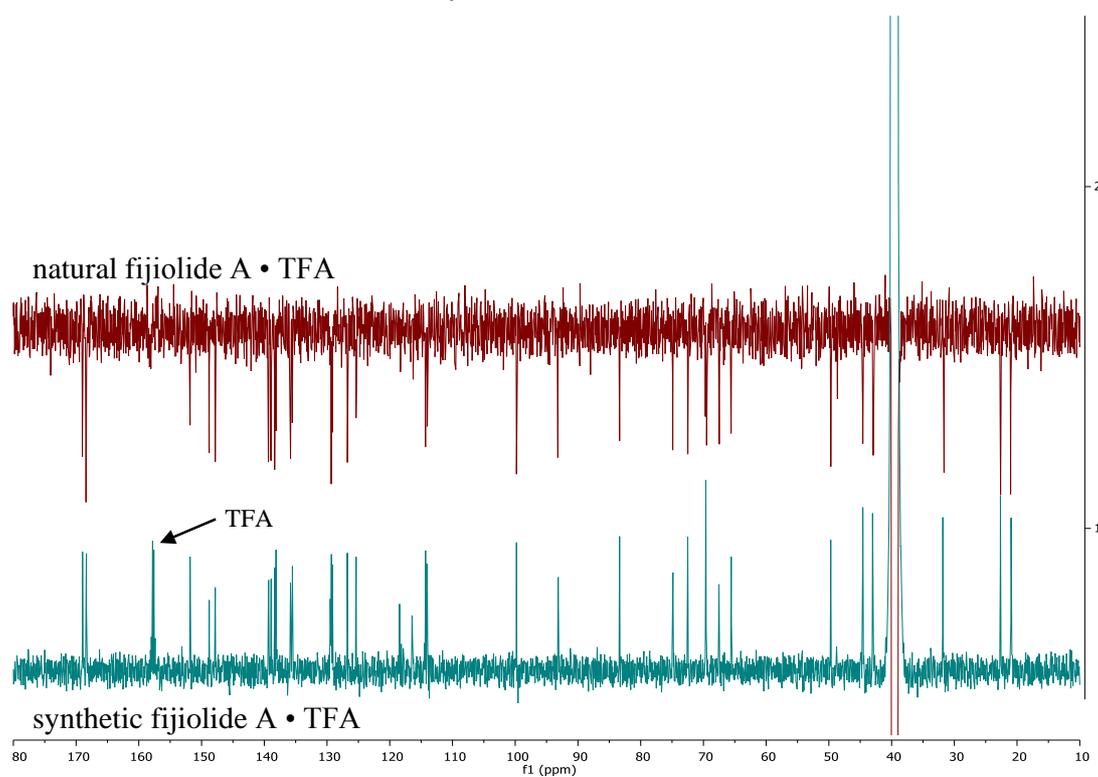
No	Natural 1 • TFA	Synthetic 1 • TFA	Deviation $\Delta\delta_c$ [ppm]
	$\delta_c$ [ppm]	$\delta_c$ [ppm]	
1	148.79	148.78	0.01
2	135.82	135.82	0.00
3	126.75	126.76	-0.01
4	139.35	139.31	0.04
5	129.15	129.14	0.01
6	125.37	125.36	0.01
7	147.82	147.81	0.01
8	83.36	83.37	-0.01
9	99.80	99.80	0.00
10	135.54	135.52	0.02
11	138.11	138.13	-0.02
12	129.46	129.48	-0.02
13	72.48	72.50	-0.02
14	65.58	65.57	0.01
15	169.01	168.97	0.04
16	42.89	43.03	-0.14
17	49.69	49.70	-0.01
18	138.94	138.91	0.03
19	114.3	114.30	0.00
20	129.33	129.30	0.03
21	138.35	138.36	-0.01
22	151.83	151.83	0.00
23	114.01	114.05	-0.04
24	168.42	168.36	0.06
25	22.63	22.65	-0.02

Continued **Table 31**

1'	93.21	93.15	0.06
2'	69.49	69.6	-0.11
3'	67.47	67.53	-0.06
4'	69.68	69.61	0.07
5'	74.89	74.86	0.03
4'-Me <sub>2</sub>	42.89	43.03	-0.14
4'-Me <sub>2</sub>	44.59	44.58	0.01
6'-Me <sub>α</sub>	31.64	31.83	-0.19
6'-Me <sub>β</sub>	21.02	20.95	0.07



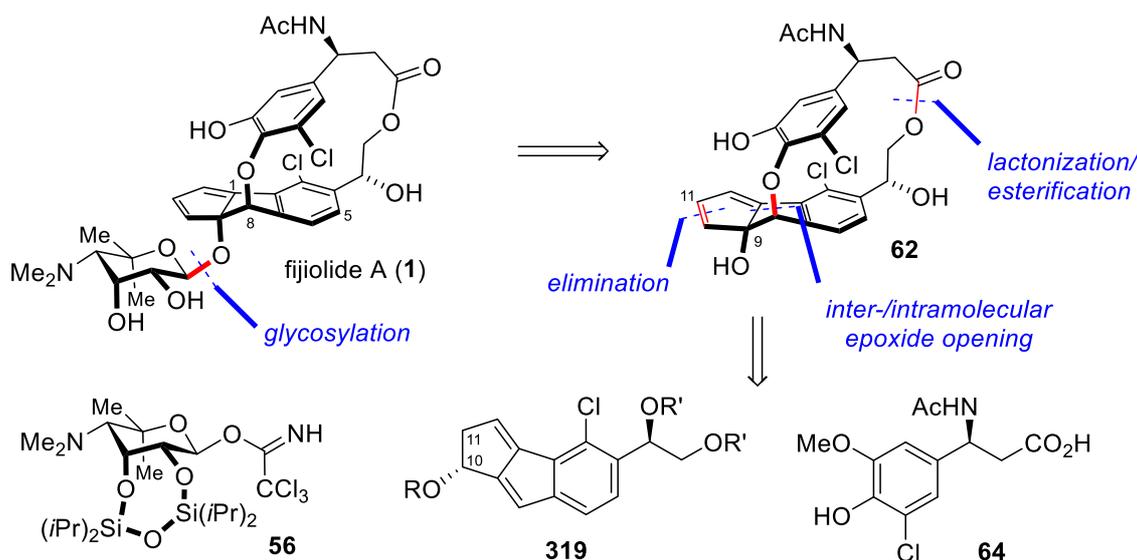
**Figure 9:** Comparison of  $^1\text{H}$  NMR spectra (600 MHz,  $\text{DMSO-d}_6$ ) of natural fijiolide A • TFA (top) and synthetic material (bottom).



**Figure 10:** Comparison of  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra (600 MHz,  $\text{DMSO-d}_6$ ) of natural fijiolide A • TFA (top) and synthetic material (bottom).

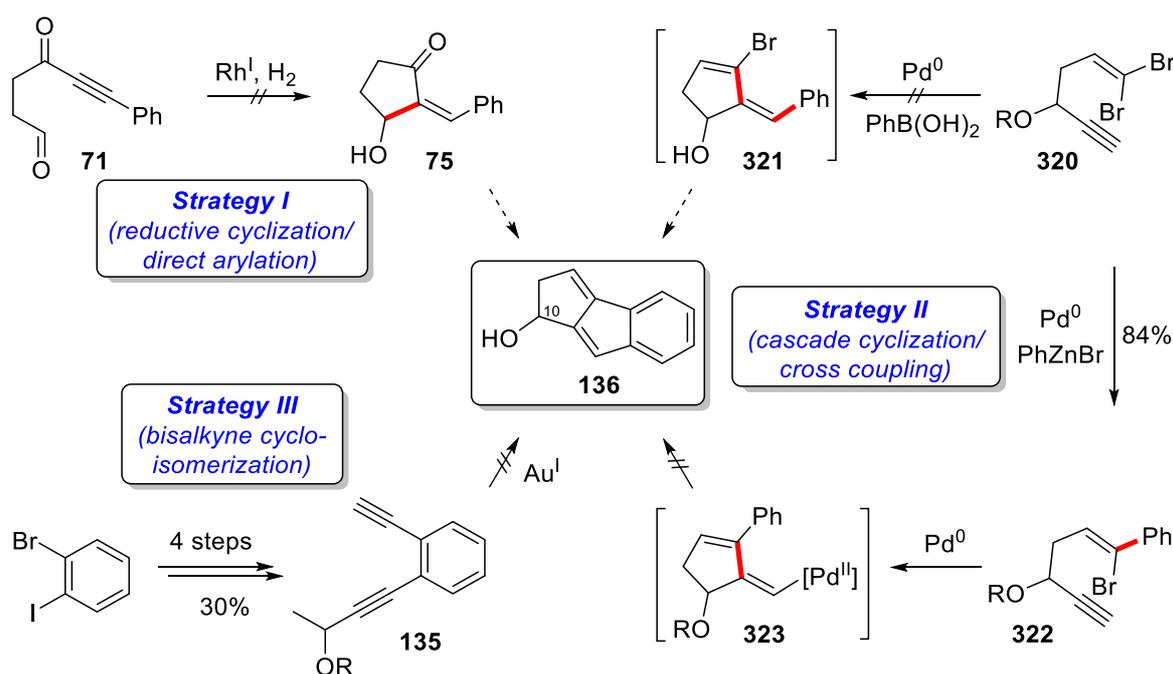
## ***9. Summary and Conclusion***

This thesis discusses our conducted synthetic studies towards fijiolide A and presents the first total synthesis of this highly bioactive natural product. Fijiolide A (**1**) is a secondary metabolite of a marine-derived actinomycete strain of the genus *Nocardioopsis*. Its isolation and structure elucidation was reported by Fenical *et al.* in 2010. Concomitantly, **1** was described to reduce the TNF- $\alpha$ -induced NF $\kappa$ B activation by 70% with an IC<sub>50</sub> value of 0.57  $\mu$ M. As an inducible, rapid-acting transcription factor, NF $\kappa$ B is involved in cellular responses to harmful stimuli, and has been linked to numerous inflammatory and autoimmune diseases, as well as to cancer. The constitutive NF $\kappa$ B activation in tumor cells, results in anti-apoptosis, cell survival, tumor promotion, metastasis and proliferation, rendering the selective NF $\kappa$ B inhibition a promising therapeutic tool for cancer therapy and chemoprevention. Apart from its biological profile, fijiolide A impresses by its intriguing structural assembly featuring a rotationally restricted chlorinated  $\beta$ -tyrosine moiety within a [2.6]paracyclophane structure. Moreover, **1** possesses a C-3 chlorinated cyclopenta[*a*]indene skeleton, which is embedded into the macrocyclic aglycone of an amino ribopyranose unit. Thus, fijiolide A represents an equally attractive as well as challenging target for total synthesis. Retrosynthetically, **1** was disassembled into aglycone **62** and the known Schmidt donor **56**<sup>49</sup> by glycosidic bond scission (Scheme 115). Paracyclophane **62** was further dissected into cyclopenta[*a*]indene **319** and  $\beta$ -amino acid **64** by strategic cleavage of the aryl ether and ester functionality.



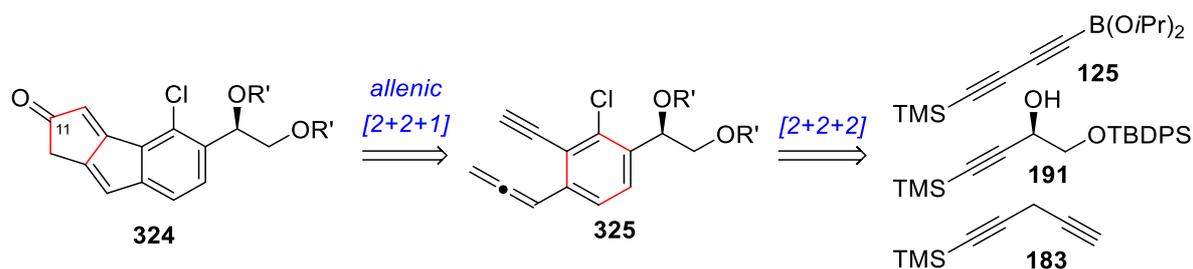
Scheme 115: Disconnection strategy for fijiolide A.

Our studies initially focused on the C-10 functionalized key fragment **319**, which we aimed to further functionalize by a directed epoxidation of the indenyl double bond. However, already the simplified model system **136** remained synthetically inaccessible (**Scheme 116**). Rhodium catalyzed reductive cyclization of ynal **71** and related substrates failed to provide hydroxy cyclopentanone **75** due to predominant reduction of the ynone moiety (strategy I).<sup>68</sup> An investigated cascade cyclization/cross coupling approach, employing dibromoenyne **320** also did not prove expedient (strategy II). The unanticipated selective oxidative addition of Pd<sup>0</sup> into the (*E*)-vinyl bromide bond prevented the envisaged cyclization/cross coupling to produce **321**,<sup>74</sup> but instead enabled synthesis of (*Z*)-vinyl bromide **322**. However, the envisioned cyclization cascade to form tricycle **136** via palladium(II) species **323** could also not be realized. In the context of strategy III, a gold(I) catalyzed cycloisomerization of *bis*-alkynes **135** was investigated. However, hetero and silyl substitution at the propargylic position was demonstrated to be incompatible with the cyclization procedure reported by Zhang *et al.*<sup>87</sup>



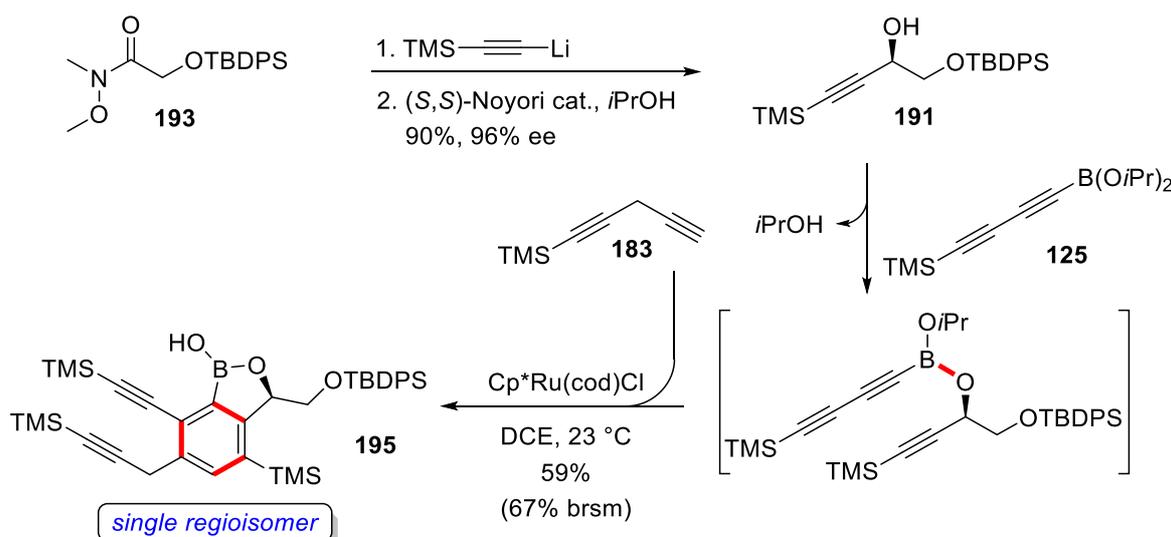
**Scheme 116:** Unsuccessful approaches towards C-10 functionalized model system **136**.

Consequently, an allenic Pauson-Khand strategy targeting the C-11 functionalized indenylcyclopentenone **319** was envisaged (**Scheme 117**). For the synthesis of the required highly substituted allene-yne precursor **325**, an intermolecular [2+2+2] cycloaddition approach was pursued that inverted the regioselectivity reported by Yamamoto *et al.*<sup>88</sup>



**Scheme 117:** Revised strategy for the fijiolide A key fragment **324**.

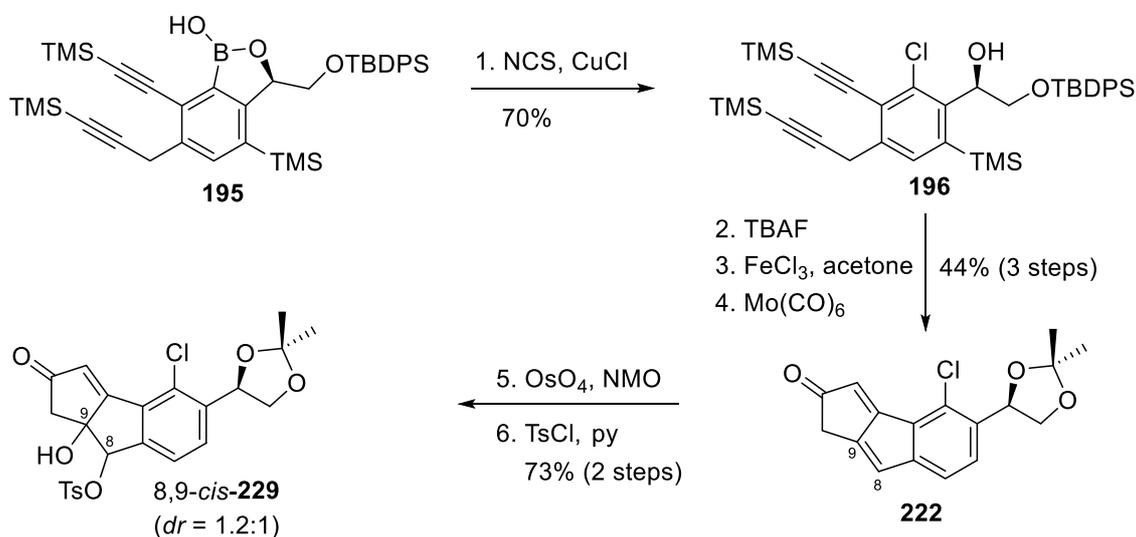
For this purpose, Weinreb amide **193** was converted into propargyl alcohol **191** via enantioselective transfer hydrogenation of the corresponding ynone (Scheme 118). The strategically installed, removable TMS group of **191** allowed a regioselective [2+2+2] cycloaddition with diynylboronate **125** and terminal alkyne **183** via a boron-tethered 1,6-diyne species. This enabled the isolation of boraphthalide **195** in 59% yield as a single regioisomer.



**Scheme 118:** Regioselective intermolecular [2+2+2] cycloaddition for the fijiolide arene core.

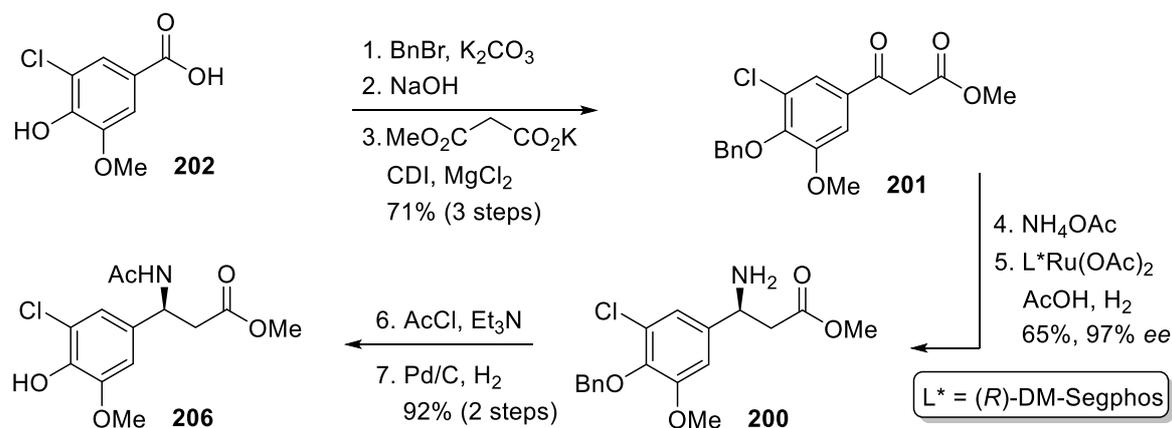
Exploitation of the boronic acid handle allowed oxidative conversion of **195** into aryl chloride **196** (Scheme 119). Indenylcyclopentenone **222** could be rapidly accessed in three steps by desilylation with excess TBAF, which concomitantly triggered an isomerization of the propargyl group. Subsequent glycol protection, and the key allenic Pauson-Khand reaction provided tricycle **222**. Although chemoselective epoxidation of **222** at the indenyl double bond was feasible, the inherent base sensitivity of the corresponding keto-epoxide prevented aryl ether linkage at C-8 via nucleophilic epoxide opening. The C-8 position was therefore activated via chemoselective Upjohn

dihydroxylation, followed by tosylation of the secondary benzylic hydroxyl group to obtain 8,9-*cis*-**229**.



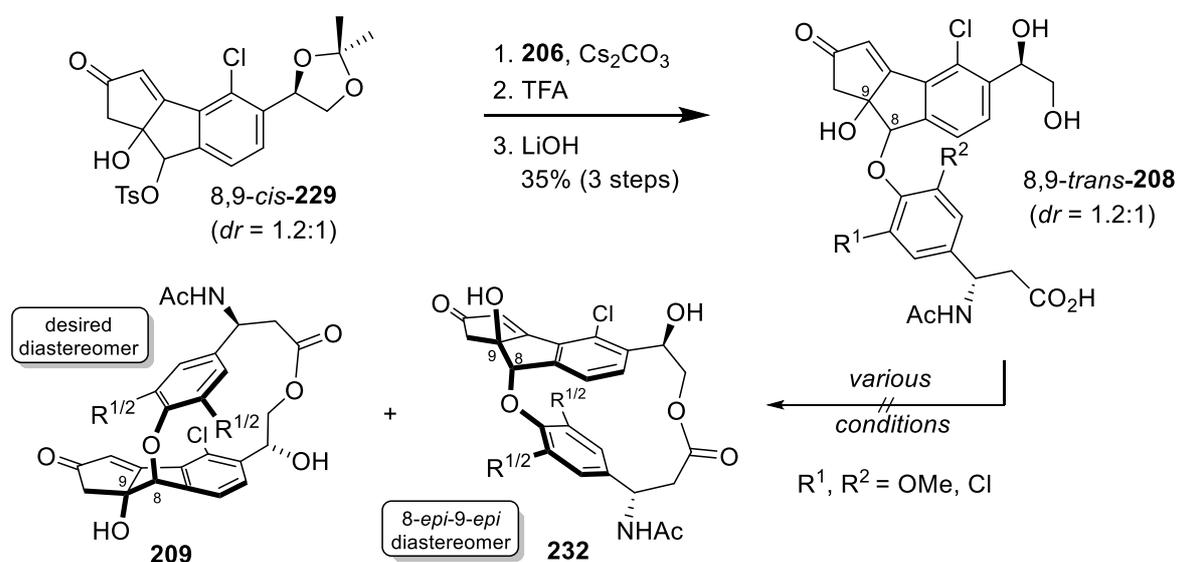
**Scheme 119:** Synthesis of key fragment 8,9-*cis*-**229** via chlorodeboronation/allenic Pauson-Khand reaction.

An elaborated concise synthesis of the  $\beta$ -amino acid fragment of fijiolide A is presented in **Scheme 120**. Conversion of 5-chlorovanillic acid (**202**) into the corresponding benzyl ether was followed by a decarboxylative Claisen condensation to furnish  $\beta$ -keto ester **201**. Ensuing enantioselective reduction of the corresponding enamine provided access to highly enantioenriched  $\beta$ -amino ester **200**. Acetylation of the primary amine, and hydrogenolysis completed the synthesis of the  $\beta$ -amino acid fragment **206** in only 7 steps and 42% overall yield.



**Scheme 120:** 1<sup>st</sup> generation synthesis of the fijiolide  $\beta$ -amino acid fragment **206**.

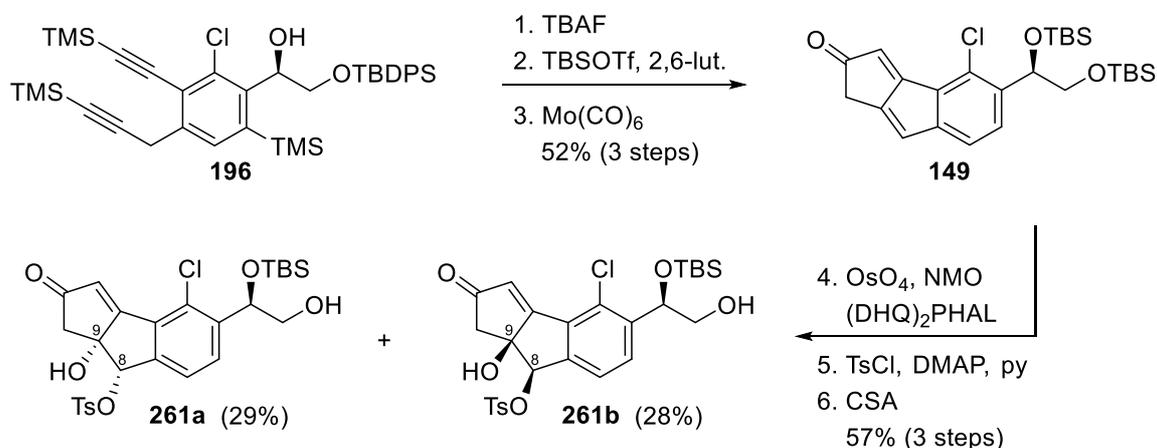
With building blocks **8,9-cis-229** and **206** in hand, a macrolactonization strategy towards the fijiolide paracyclophane was evaluated (**Scheme 121**). Fragment coupling *via* nucleophilic displacement at C-8 performed best in the presence of Cs<sub>2</sub>CO<sub>3</sub>. Subsequent acetone hydrolysis, and ester saponification provided *seco*-acid **8,9-trans-208** as a mixture of two C-8 and C-9 epimeric diastereomers. Despite an extensive screen of macrolactonization conditions, including the procedures of Corey and Nicolaou, Yamaguchi, Mukaiyama, Shiina, Mitsunobu, and Masamune, both possible [2.6]paracyclophanes **209** and **232** remained inaccessible.



**Scheme 121:** Synthesis of *seco*-acid **8,9-trans-208** and attempted macrolactonization.

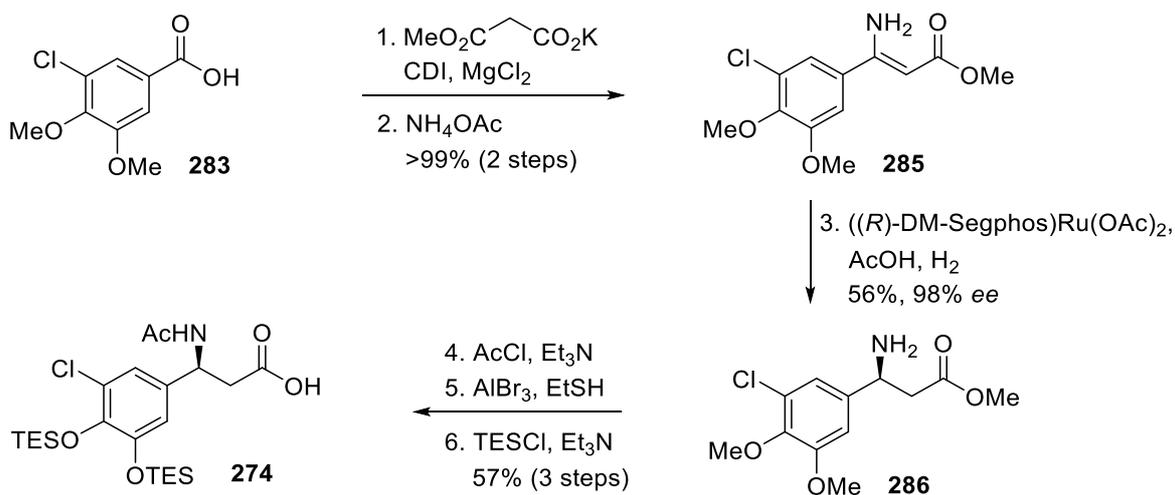
Consequently, an alternative strategy towards macrocyclic ring closure *via* aryl ether linkage at C-8 was pursued. For this purpose, various cyclization precursors were investigated. For the realization of a step-economic route to the most elaborated congener, the syntheses of both building blocks were modified. Desilylation/isomerization of aryl chloride **196** was followed by double TBS protection of the resulting glycol, and a subsequent allenic Pauson-Khand reaction to afford indenylcyclopentenone **149** (**Scheme 122**). Although being subjected to extensive optimization studies, asymmetric dihydroxylation of the indenyl double bond proceeded with low facial selectivity (*dr* = 1.1:1) in favor of the undesired diastereomer. Classical SAD conditions (AD-mix- $\alpha$ ) were not applicable due to the high base sensitivity of **149**, resulting in substrate decomposition. nevertheless, employment of (DHQ)<sub>2</sub>PHAL allowed reproducible yields of the corresponding C-8/C-9 diol, which was subsequently tosylated at 8-OH. Selective acidic cleavage of the primary

silyl ether enabled facile separation of the desired alcohol **261a** from its 8-*epi*-9-*epi* diastereomer **261b**.



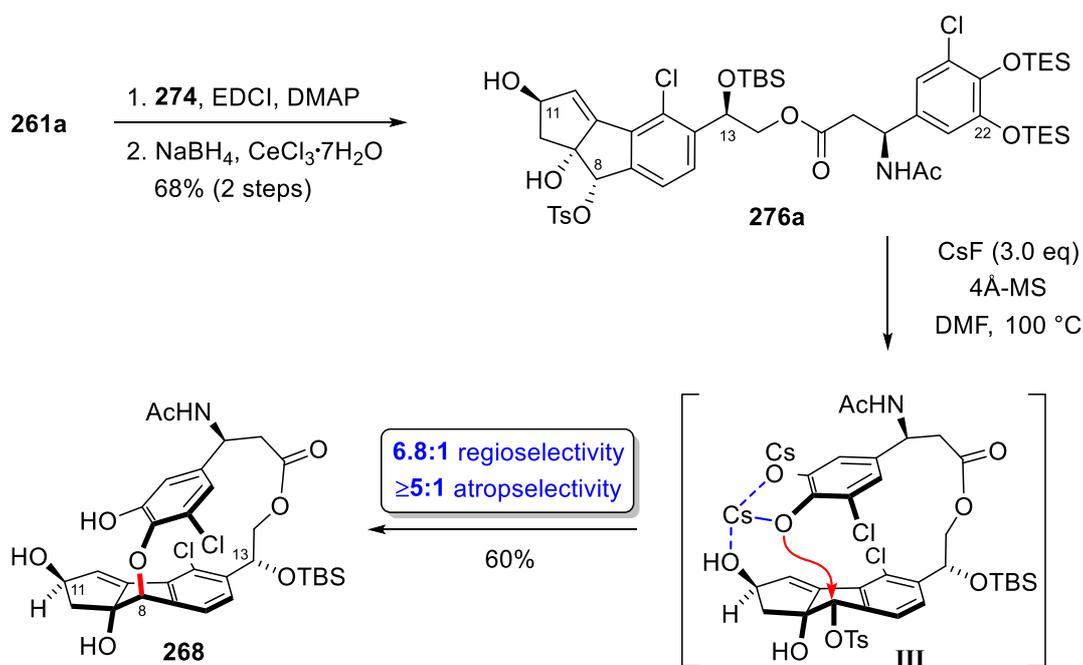
**Scheme 122:** 6-Step synthesis of primary alcohol **261a** from aryl chloride **196**.

The synthesis of double TES protected  $\beta$ -amino acid fragment **274** could be realized in only 6 steps from 5-chloroveratric acid (**283**). In analogy to the 1<sup>st</sup> generation synthesis, **283** was first converted into  $\beta$ -amino ester **286** in an enantioselective manner. An ensuing three-step procedure comprising acetylation, followed by global demethylation, and TES protection of the catechol moiety gave rise to  $\beta$ -amino acid **274** in 32% overall yield.



**Scheme 123:** 2<sup>nd</sup> generation synthesis of the fijiolide  $\beta$ -amino acid fragment.

EDCI mediated ester coupling of **261a** with **274**, and subsequent diastereoselective 1,2-reduction provided access to cyclization precursor **276a** (**Scheme 124**). Treatment with CsF in hot DMF cleaved at first both phenolic TES groups and induced then an intramolecular cyclization to give the desired cyclophane **268** in 60% isolated yield. The remarkably high regio- and atropselectivity of this [2.6]paracyclophane formation was rationalized by a template effect, leading to preorganized intermediate **III**. Facile nucleophilic substitution of the tosylate by the proximate phenolate closes the macrocycle in atropselective manner. The observed relationship between decreasing atropselectivity with increasing substitution at C-11 and C-22 is in full agreement with this template-effect rational. While we could not isolate the atropisomer of **268**, the regioisomeric [2.6]*metacyclophane* was formed in 8% yield by nucleophilic substitution at C-8 by the distal C-22 phenolate in **III**.



**Scheme 124:** Regio- and atropselective synthesis of the fijiolide [2.6]paracyclophane core.





## ***10. Experimental Section***

## 10.1 General Methods

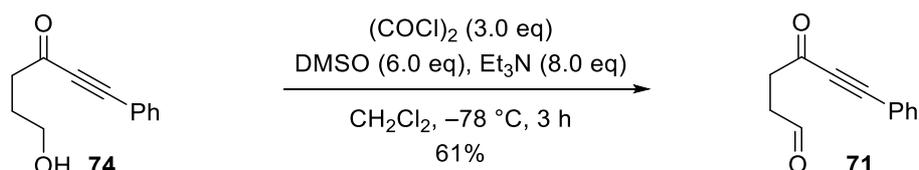
All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring, unless otherwise indicated. Toluene, THF, Et<sub>2</sub>O, acetonitrile and dichloromethane were purified by an Innovative Technology Solvent Delivery System. Chemicals were used as obtained from the suppliers, unless otherwise indicated. If needed, reagents and solvents were distilled from CaH<sub>2</sub> except for DMF (CaSO<sub>4</sub>). Reaction progress was generally monitored by analytical thinlayer chromatography (TLC) on commercial glass plates coated with 0.25 mm silica gel (E. Merck, Kieselgel 60 F254). Compounds were either visualized under UV-light at 254 nm or by dipping the plates in either an ethanolic vanillin solution or an aqueous potassium permanganate solution followed by heating. Flash chromatography was performed with Silicycle silica gel 60 (0.040-0.063 μm grade) using the indicated eluent mixtures. Selenium containing compounds were chromatographically purified using N<sub>2</sub> overpressure instead of compressed air. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) data were generally acquired at 400 MHz on a Bruker AV400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to incompletely deuterated CDCl<sub>3</sub> (s, 7.27 ppm), C<sub>6</sub>D<sub>6</sub> (s, 7.16 ppm), CD<sub>2</sub>Cl<sub>2</sub> (t, 5.32 ppm), acetone-d<sub>6</sub> (quin, 2.05 ppm) or DMSO-d<sub>6</sub> (quin, 2.50 ppm). Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet; br., broad. Proton decoupled Carbon-13 nuclear magnetic resonance (<sup>13</sup>C{<sup>1</sup>H} NMR) data were generally acquired at 101 MHz on a Bruker AV400 spectrometer. Chemical shifts are reported in ppm relative to CDCl<sub>3</sub> (77.00 ppm), C<sub>6</sub>D<sub>6</sub> (128.39 ppm), CD<sub>2</sub>Cl<sub>2</sub> (54.00 ppm), acetone-d<sub>6</sub> (29.92 ppm) or DMSO (39.51 ppm). All NMR data were recorded at 298 K. Infrared (IR) data were recorded on an Alpha-P Bruker FT-IR Spectrometer. Absorbance frequencies are reported in reciprocal centimeters (cm<sup>-1</sup>). HRMS measurements were performed by an Agilent LC-MS TOF. High resolution mass are given in *m/z*. Optical rotations were measured on a Polartronic M polarimeter using a 0.5 cm cell with a Na 589 nm filter.

## 10.2 Studies towards the Chlorocyclopenta[*a*]indene Fragment

### 10.2.1 Studies Involving Rh<sup>I</sup> Catalyzed Reductive Cyclization / Pd<sup>0</sup> Catalyzed Direct Arylation

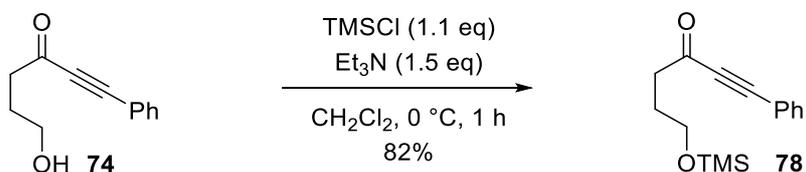
#### Arylation

#### 1,5-Ynal **71**



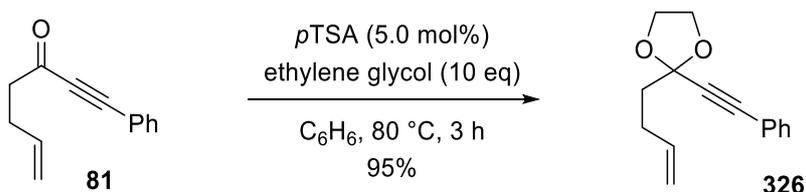
To a solution of (COCl)<sub>2</sub> (1.80 mL, 20.9 mmol, 3.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added DMSO (2.97 mL, 41.8 mmol, 6.0 eq) dropwise at -78 °C. The resulting mixture was stirred for 20 min before a solution of keto alcohol **74**<sup>70</sup> (1.31 g, 6.96 mmol, 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added at -78 °C. After stirring at -78 °C for 2 h, Et<sub>3</sub>N (7.76 mL, 55.7 mmol, 8.0 eq) was added dropwise and the resulting mixture was stirred for an additional hour at -78 °C. The reaction was then quenched by addition of sat. aqueous sodium bicarbonate (50 mL) and allowed to warm to 23 °C. The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL), the combined organic layers were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 10/1) to afford 1,5-ynal **71** (791 mg, 4.25 mmol, 61%) as a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.85 (t, *J* = 0.6 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.50 – 7.44 (m, 1H), 7.42 – 7.37 (m, 2H), 3.05 (t, *J* = 6.3 Hz, 2H), 2.88 (t, *J* = 6.4 Hz, 2H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 199.6, 185.1, 133.0 (2C), 130.8, 128.6 (2C), 119.7, 91.5, 87.3, 37.6, 37.3 ppm; *R*<sub>f</sub> = 0.22 (*n*-pentane/EtOAc 10/1).

**TMS ether 78**

To an ice-cooled solution of keto alcohol **74** (200 mg, 1.06 mmol, 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) was added Et<sub>3</sub>N (221 μL, 1.59 mmol, 1.5 eq) and TMSCl (148 μL, 1.17 mmol, 1.1 eq). The resulting mixture was stirred at 0 °C for 1 h before being quenched by addition of additional Et<sub>3</sub>N (1 mL) and water (4 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL), the combined organic layers were washed with brine (8 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 60/1 to 30/1) to afford TMS ether **78** (228 mg, 0.876 mmol, 82%) as a yellow oil.

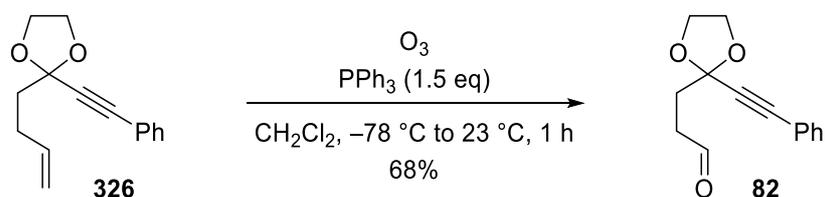
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.61 – 7.55 (m, 2H), 7.49 – 7.43 (m, 1H), 7.42 – 7.36 (m, 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.76 (t, *J* = 7.3 Hz, 2H), 1.97 (p, *J* = 7.1, 6.7 Hz, 2H), 0.13 (s, 9H) ppm; *R*<sub>f</sub> = 0.81 (*n*-pentane/Et<sub>2</sub>O 3/1).

**Ketal 326**

To a solution of ynone **81**<sup>73</sup> (235 mg, 1.28 mmol, 1.0 eq) in dry benzene (15 mL) was added ethylene glycol (0.711 mL, 12.8 mmol, 10.0 eq) and *p*TSA (12.1 mg, 63.8 μmol, 5.0 mol%). The reaction mixture was refluxed using a Dean-Stark water separator. After 3 h, the reaction mixture was allowed to cool to 23 °C and quenched by addition of sat. aqueous sodium bicarbonate (8 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 50/1) to afford ketal **326** (277 mg, 1.21 mmol, 95%) as a yellow oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.49 – 7.44 (m, 2H), 7.37 – 7.29 (m, 3H), 5.91 (ddt,  $J = 16.8, 10.2, 6.5$  Hz, 1H), 5.09 (dq,  $J = 17.1, 1.6$  Hz, 1H), 5.00 (dq,  $J = 10.2, 1.4$  Hz, 1H), 4.22 – 4.13 (m, 2H), 4.10 – 4.00 (m, 2H), 2.44 – 2.36 (m, 2H), 2.13 – 2.07 (m, 2H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  137.8, 131.8 (2C), 128.6, 128.2 (2C), 121.9, 114.6, 103.4, 86.6, 83.9, 64.8 (2C), 38.6, 28.3 ppm;  $R_f = 0.34$  (*n*-pentane/EtOAc 50/1).

### 1,5-Ynal **82**

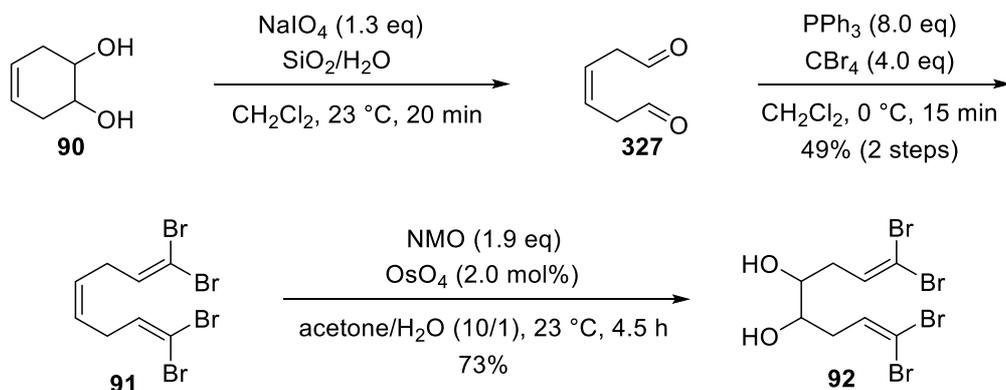


A solution of ketal **326** (31.4 mg, 138  $\mu\text{mol}$ , 1.0 eq) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was cooled to  $-78$  °C and purged with  $\text{O}_2$  for 1 min. The solution was then saturated with ozone until a blue color persisted (2 min). Excess ozone was then removed with a stream of  $\text{N}_2$  and  $\text{PPh}_3$  (54.1 mg, 206  $\mu\text{mol}$ , 1.5 eq) was added at  $-78$  °C. The reaction mixture was stirred at  $-78$  °C for 30 min and then allowed to warm to  $23$  °C within additional 30 min. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography (*n*-pentane/EtOAc 6/1) to afford unstable 1,5-yenal **82** (21.6 mg, 93.8  $\mu\text{mol}$ , 68%) as a yellow liquid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.80 (t,  $J = 1.5$  Hz, 1H), 7.47 – 7.42 (m, 2H), 7.37 – 7.29 (m, 3H), 4.19 – 4.13 (m, 2H), 4.07 – 3.99 (m, 2H), 2.70 (td,  $J = 7.2, 1.6$  Hz, 2H), 2.42 (t,  $J = 7.2$  Hz, 2H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  201.5, 131.8 (2C), 128.9, 128.3 (2C), 121.6, 102.6, 86.1, 84.2, 64.9 (2C), 38.4, 32.1 ppm;  $R_f = 0.23$  (*n*-pentane/EtOAc 4/1).

### 10.2.2 Studies Involving Pd<sup>0</sup> Catalyzed Cascade Cyclization via Carbopalladation / Suzuki Coupling / Direct Arylation

#### Tetrabromodiols 92



**Step 1:** To a suspension of silica gel immobilized NaIO<sub>4</sub><sup>76</sup> (19.1 g, 15 wt.%, 13.0 mmol, 1.3 eq) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added a solution of diol **90**<sup>75</sup> (1.14 g, 10.0 mmol, 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the resulting suspension was stirred at 23 °C for 20 min. The suspension was then filtered, the filtrate was dried over MgSO<sub>4</sub>, filtered again, and the solvent was removed under reduced pressure. Crude *bis*-aldehyde **327** was obtained as a pale yellow oil and was used in the next step without further purification.

$R_f = 0.62$  (EtOAc).

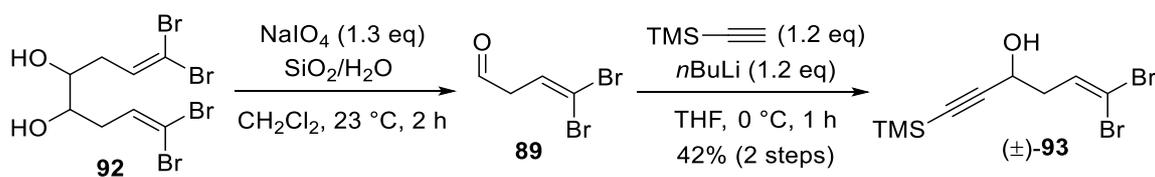
**Step 2:** To an ice-cooled solution of PPh<sub>3</sub> (15.7 g, 60.0 mmol, 6.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (85 mL) was added CBr<sub>4</sub> (9.95 g, 30.0 mmol, 3.0 eq) in four portions over a period of 5 min. The resulting mixture was stirred at 0 °C for additional 5 min before a solution of crude *bis*-aldehyde **327** in dry CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise at 0 °C. The resulting solution was stirred at 0 °C for 20 min before it was quenched by addition of sat. aqueous sodium bicarbonate (100 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure to afford a black oil. Pentane was then added, the resulting precipitate (triphenylphosphine oxide) was filtered off, and the solvent was removed under reduced pressure. The crude product was flashed through a short pad of silica (pentane) to afford tetrabromotriene **91** (2.06 g, 4.86 mmol, 49%) as a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.37 (t, *J* = 7.2 Hz, 1H), 5.46 (t, *J* = 4.7 Hz, 1H), 2.94 – 2.84 (m, 4H) ppm;  $R_f = 0.56$  (*n*-pentane).

**Step 3:** To a solution of tetrabromotriene **91** (1.91 g, 4.52 mmol, 1.0 eq) in acetone/H<sub>2</sub>O (44 mL, v/v = 10/1) was subsequently added a solution of NMO (50 wt.% in H<sub>2</sub>O, 1.39 mL, 6.77 mmol, 1.5 eq) and a solution of OsO<sub>4</sub> (2.5 wt.% in *t*BuOH, 1.13 mL, 0.090 mmol, 2.0 mol%). The resulting solution was stirred at 23 °C for 3.5 h before additional NMO (50 wt.% in H<sub>2</sub>O, 0.37 mL, 1.81 mmol, 0.4 eq) was added. Stirring was continued at 23 °C for 1 h and the reaction was then quenched by addition of sat. aqueous sodium thiosulfate (30 mL). The aqueous phase was extracted with EtOAc (3 x 40 mL), the combined organic layers were washed with sat. aqueous CuSO<sub>4</sub> (2 x 10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 4/1 to 2/1) to afford tetrabromodiol **92** (1.51 g, 3.30 mmol, 73%) as a pale brown solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.56 (t, *J* = 7.2 Hz, 2H), 3.81 – 3.72 (m, 2H), 2.40 – 2.35 (m, 4H), 1.98 (d, *J* = 4.2 Hz, 2H) ppm; *R*<sub>T</sub> = 0.14 (*n*-pentane/EtOAc 4/1).

### Propargylic alcohol (±)-**93**



**Step 1:** To a suspension of silica gel immobilized NaIO<sub>4</sub><sup>76</sup> (6.08 g, 14.6 w%, 4.15 mmol, 1.3 eq) in CH<sub>2</sub>Cl<sub>2</sub> (16 mL) was added a solution of tetrabromodiol **92** (1.46 g, 3.19 mmol, 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (21 mL) and the resulting suspension was stirred at 23 °C for 2 h. The suspension was then filtered, the filtrate was dried over MgSO<sub>4</sub>, filtered again, and the solvent was removed under reduced pressure. Crude dibromoaldehyde **89** was obtained as a yellow oil and was used in the next step without further purification.

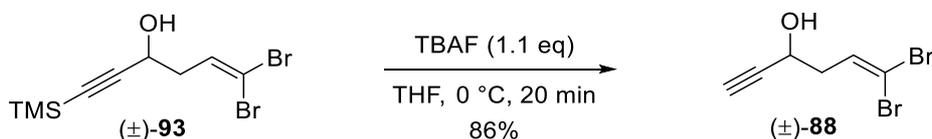
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.69 (t, *J* = 0.9 Hz, 1H), 6.72 (t, *J* = 6.8 Hz, 1H), 3.31 (dd, *J* = 6.8, 1.0 Hz, 2H).

**Step 2:** To an ice-cooled solution of trimethylsilylacetylene (1.06 mL, 7.66 mmol, 1.2 eq) in dry THF (30 mL) was added a solution of *n*BuLi (2.5 M in *n*-hexane, 3.06 mL, 7.66 mmol, 1.2 eq) dropwise. The reaction mixture was stirred at 0 °C for 10 min before a solution of crude dibromoaldehyde **89** (1.46 g, 6.38 mmol, 1.0 eq) in dry THF (5.0 mL) was added. The resulting yellow reaction mixture was stirred at 0 °C for 1 h before it was quenched by addition of sat.

aqueous ammonium chloride (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 25/1 to 15/1) to afford propargylic alcohol (±)-**93** (874 mg, 2.68 mmol, 42% over 2 steps) as a yellow oil.

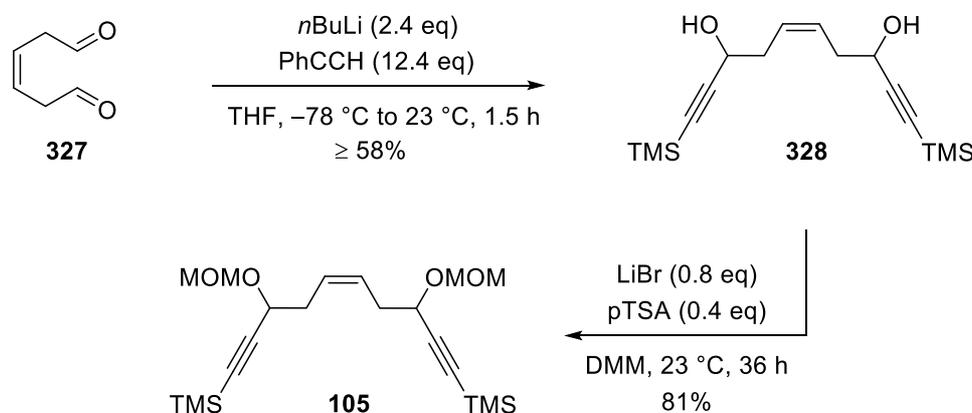
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.55 (t, *J* = 7.2 Hz, 1H), 4.48 (q, *J* = 5.9 Hz, 1H), 2.53 (t, *J* = 6.9 Hz, 3H), 1.96 (d, *J* = 4.9 Hz, 1H), 0.19 (s, 9H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 133.5, 104.9, 91.5, 90.9, 60.8, 41.0, -0.2 (3C) ppm; *R*<sub>f</sub> = 0.70 (*n*-pentane/EtOAc 4/1).

### Propargylic alcohol (±)-**88**



To an ice-cooled solution of propargylic alcohol (±)-**93** (853 mg, 2.62 mmol, 1.0 eq) in dry THF (5.0 mL) was added a solution of TBAF (1.0 M in THF, 2.88 mL, 2.88 mmol, 1.1 eq) and the resulting solution mixture was stirred at 0 °C for 20 min. The reaction mixture was then diluted with EtOAc (20 mL), washed with water (2 x 5 mL) and brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 6/1) to afford propargylic alcohol (±)-**88** (570 mg, 2.24 mmol, 86%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.58 (t, *J* = 7.1 Hz, 1H), 4.51 (qd, *J* = 6.1, 2.1 Hz, 1H), 2.59 – 2.53 (m, 3H), 1.91 (d, *J* = 5.5 Hz, 1H) ppm; *R*<sub>f</sub> = 0.41 (*n*-pentane/EtOAc 4/1).

**Bis-MOM ether 105**

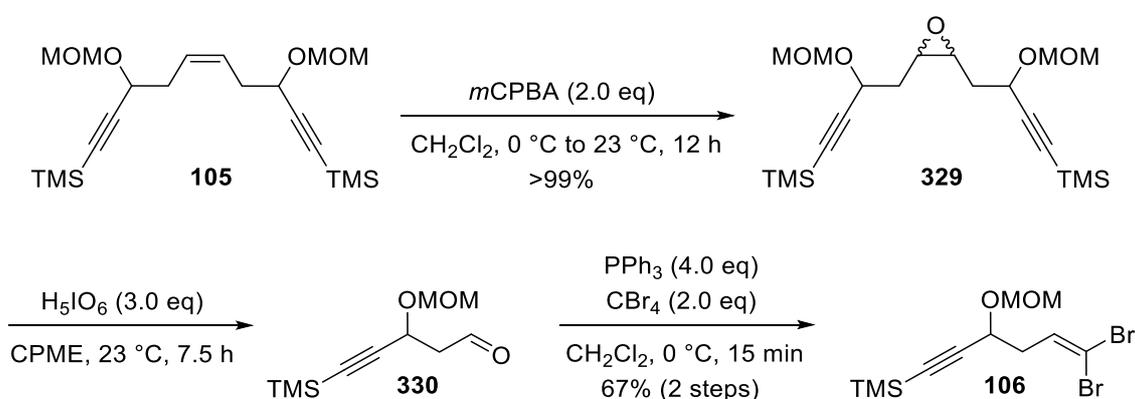
**Step 1:** To a solution of trimethylsilylacetylene (2.54 mL, 18.4 mmol, 2.4 eq) in dry THF (40 mL) was added a solution of *n*BuLi (1.6 M in *n*-hexane, 11.5 mL, 18.4 mmol, 2.4 eq) dropwise at  $-78\text{ }^\circ\text{C}$ . The reaction mixture was stirred at  $-78\text{ }^\circ\text{C}$  for 15 min before a solution of crude *bis*-aldehyde **327** (858 mg, 7.65 mmol, 1.0 eq) in dry THF (10 mL) was added dropwise (*vide supra*). The mixture was allowed to warm to  $0\text{ }^\circ\text{C}$  over a period of 1.5 h before it was quenched by addition of sat. aqueous ammonium chloride (30 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine (30 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 6/1) to afford *bis*-propargylic alcohol **328** (1.38 g, 4.46 mmol, 58% from diol **90**) as a yellow oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.81 – 5.68 (m, 2H), 4.44 (q,  $J = 5.9\text{ Hz}$ , 2H), 2.61 – 2.46 (m, 4H), 1.82 (br. s, 2H), 0.18 (s, 18H) ppm;  $R_f = 0.45$  (*n*-pentane/EtOAc 3/1).

**Step 2:** To a solution of *bis*-propargylic alcohol **328** (1.31 g, 4.23 mmol, 1.0 eq) in dimethoxymethane (10 mL) was subsequently added LiBr (147 mg, 1.70 mmol, 0.4 eq) and *p*TSA (161 mg, 0.85 mmol, 0.2 eq). The resulting mixture was stirred at  $23\text{ }^\circ\text{C}$  for 12 h before additional portions of LiBr (147 mg, 1.70 mmol, 0.4 eq) and *p*TSA (161 mg, 0.85 mmol, 0.2 eq) were added. The reaction mixture was stirred at  $23\text{ }^\circ\text{C}$  for a further 24 h, quenched by addition of brine (6 mL) and stirred for additional 10 min at  $23\text{ }^\circ\text{C}$ . The aqueous phase was extracted with EtOAc (3 x 8 mL), the combined organic layers were washed with brine (10 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 40/1 to 15/1) to afford *bis*-MOM ether **105** (1.36 g, 3.44 mmol, 81%) as a pale yellow oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.67 (m, 2H), 4.94 (d,  $J = 6.8$  Hz, 2H), 4.60 (d,  $J = 6.7$  Hz, 2H), 4.33 (t,  $J = 6.5$  Hz, 2H), 3.38 (s, 6H), 2.54 (m, 4H), 0.17 (s, 18H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  127.2 (2C), 103.8 (2C), 94.1 (2C), 90.5 (2C), 65.7 (2C), 55.6 (2C), 33.9 (2C), -0.1 (6C) ppm; **IR (ATR)**:  $\tilde{\nu} = 2957, 2895, 2171, 1342, 1250, 1151, 1098, 1028, 843, 761$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{20}\text{H}_{36}\text{NaO}_4\text{Si}_2]^+$ : 419.2044, found: 419.2044;  $R_f = 0.45$  (*n*-pentane/EtOAc 20/1).

### Dibromoenyne ( $\pm$ )-106



**Step 1:** To an ice-cooled solution of *bis*-MOM ether **105** (1.02 g, 2.57 mmol, 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (26 mL) was added *m*CPBA (70 wt.%, 1.27 g, 5.14 mmol, 2.0 eq). The reaction mixture was stirred at 0 °C for 1 h and then at 23 °C for 11 h before it was quenched by addition of sat. aqueous sodium thiosulfate (20 mL) and stirred for an additional 10 min. The organic phase was washed with sat. aqueous sodium bicarbonate (2 x 15 mL) and the combined aqueous layers were extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 30 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure to afford crude epoxide **329**, which was used in the next step without further purification.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.98 (t,  $J = 6.4$  Hz, 2H), 4.67 – 4.60 (m, 2H), 4.57 – 4.50 (m, 2H), 3.40 (s, 3H), 3.40 (s, 3H), 3.28 – 3.18 (m, 2H), 2.13 – 1.87 (m, 4H), 0.18 (s, 18H) ppm.

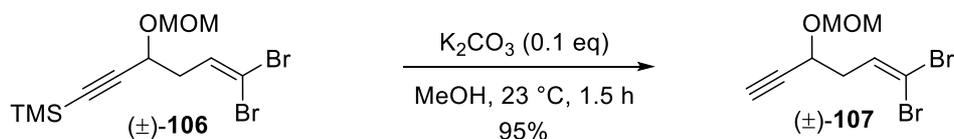
**Step 2:** To an ice-cooled solution of crude epoxide **329** (1.37 g, 3.32 mmol, 1.0 eq) in dry CPME (20 mL) was added periodic acid (1.13 g, 4.98 mmol, 1.5 eq) and the reaction mixture was stirred at 0 °C for 2.5 h before being allowed to warm to 23 °C. After 4 h, additional periodic acid (0.38 g, 1.66 mmol, 0.5 eq) was added followed by addition of a third portion of periodic acid (0.76 g, 3.32 mmol, 1.0 eq) after 5 h. After a total reaction time of 7.5 h, the reaction was

quenched by addition of sat. aqueous sodium thiosulfate (20 mL). The organic phase was washed with sat. aqueous sodium bicarbonate (2 x 10 mL) and the combined aqueous layers were extracted with Et<sub>2</sub>O (3 x 30 mL). The combined organic layers were washed with sat. aqueous sodium bicarbonate (20 mL) and brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure to afford crude aldehyde **330**, which was used in the next step without further purification.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 9.84 (t, *J* = 1.9 Hz, 1H), 4.98 (d, *J* = 6.9 Hz, 1H), 4.85 (dd, *J* = 7.5, 4.7 Hz, 1H), 4.63 (d, *J* = 6.9 Hz, 1H), 3.40 (s, 3H), 2.88 (dd, *J* = 16.8, 7.4 Hz, 1H), 2.77 (dd, *J* = 16.8, 4.0 Hz, 1H), 0.20 (s, 9H) ppm.

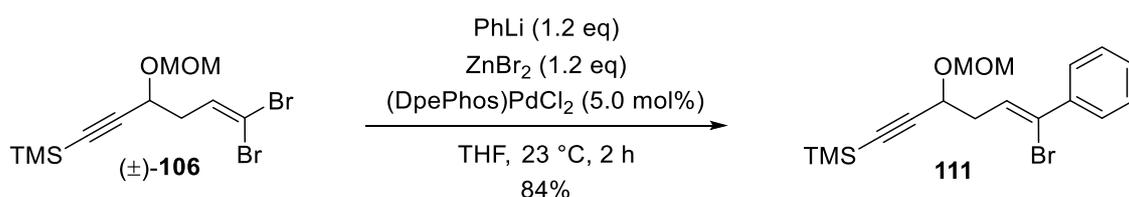
**Step 3:** To an ice-cooled solution of PPh<sub>3</sub> (6.97 g, 26.6 mmol, 4.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (45 mL) was added CBr<sub>4</sub> (4.56 g, 13.3 mmol, 2.0 eq) in 4 portions over a period of 5 min. The resulting orange solution was stirred at 0 °C for additional 5 min before a solution of crude aldehyde **330** in dry CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL) was added. The reaction mixture was stirred at 0 °C for 15 min and was then quenched by addition of sat. aqueous sodium bicarbonate (50 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 50 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 50/1) to afford dibromoenyne (±)-**106** (1.65 g, 4.47 mmol, 67% over 2 steps) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.55 (t, *J* = 7.0 Hz, 1H), 4.93 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 6.8 Hz, 1H), 4.41 (t, *J* = 6.2 Hz, 1H), 3.39 (s, 3H), 2.55 (t, *J* = 6.6 Hz, 2H), 0.19 (s, 9H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 133.8, 102.6, 94.1, 91.6, 91.1, 63.9, 55.8, 39.1, -0.2 (3C) ppm; **IR (ATR):**  $\tilde{\nu}$  = 2958, 2897, 2171, 1744, 1250, 1151, 1098, 1020, 891, 841, 761 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>11</sub>H<sub>19</sub><sup>79</sup>Br<sub>2</sub>O<sub>2</sub>Si]<sup>+</sup>: 370.9496, found: 370.9494; **R<sub>f</sub>** = 0.50 (*n*-pentane/EtOAc 20/1).

**Dibromoenyne ( $\pm$ )-107**

To a solution of dibromoenyne ( $\pm$ )-**106** (500 mg, 1.35 mmol, 1.0 eq) in MeOH (14 mL) was added  $K_2CO_3$  (18.7 mg, 0.135 mmol, 0.1 eq) and the resulting mixture was stirred at 23 °C for 1.5 h. The reaction mixture was then diluted with Et<sub>2</sub>O (20 mL) and quenched by addition of sat. aqueous ammonium chloride (20 mL). The aqueous phase extracted with Et<sub>2</sub>O (3 x 10 mL), the combined organic layers were washed with brine (20 mL), dried over  $MgSO_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 20/1) to afford dibromoenyne ( $\pm$ )-**107** (382 mg, 1.28 mmol, 95%) as a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.58 (t,  $J$  = 6.9 Hz, 1H), 4.93 (d,  $J$  = 6.9 Hz, 1H), 4.62 (d,  $J$  = 6.9 Hz, 1H), 4.44 (td,  $J$  = 6.2, 1.6 Hz, 1H), 3.40 (s, 3H), 2.57 (t,  $J$  = 6.6 Hz, 2H), 2.48 (d,  $J$  = 2.0 Hz, 1H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  133.5, 94.1, 91.4, 81.1, 74.5, 63.2, 55.8, 39.0 ppm; IR (ATR):  $\tilde{\nu}$  = 3297, 2949, 2844, 1627, 1217, 1150, 1095, 1020, 919, 846, 809, 780, 668, 640 cm<sup>-1</sup>; HRMS (ESI) calc'd. for  $[M+H]^+ = [C_8H_{11}^{79}Br_2O_2]^+$ : 298.9100, found: 298.9094;  $R_f$  = 0.42 (*n*-pentane/EtOAc 20/1).

**(Z)-Vinyl bromide 111**

To an ice-cooled solution of  $ZnBr_2$ <sup>203</sup> (270 mg, 1.2 mmol, 1.2 eq) in dry THF (5.0 mL) was added a solution of phenyl lithium (2.0 M in *n*Bu<sub>2</sub>O, 0.60 mL, 1.20 mmol, 1.2 eq) and the resulting mixture was stirred at 23 °C for 30 min. Concurrently, a second flask was charged with dibromoenyne ( $\pm$ )-**106** (370 mg, 1.00 mmol, 1.0 eq) and (DpePhos) $PdCl_2$ <sup>204</sup> (34.0 mg,

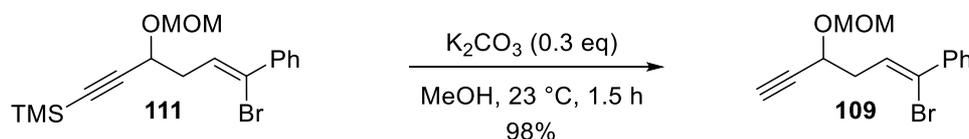
<sup>203</sup> Previously dried by heating to 150 °C under high vacuum overnight.

<sup>204</sup> Prepared according to a literature procedure: M. Kranenburg, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Eur. J. Inorg. Chem.* **1998**, 1998, 155-157.

0.047 mmol, 5.0 mol%) before the prepared solution of phenylzinc bromide was added. The resulting mixture was stirred at 23 °C for 2 h before it was quenched by addition of sat. aqueous ammonium chloride (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 80/1) to afford (*Z*)-vinyl bromide **111** (308 mg, 0.838 mmol, 84%) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.58 – 7.51 (m, 2H), 7.38 – 7.29 (m, 3H), 6.37 (t, *J* = 6.7 Hz, 1H), 4.97 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 6.8 Hz, 1H), 4.52 (t, *J* = 6.4 Hz, 1H), 3.40 (s, 3H), 2.83 (td, *J* = 6.6, 1.5 Hz, 2H), 0.19 (s, 9H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 139.8, 128.5, 128.2 (2C), 127.5 (2C), 127.5, 126.5, 103.3, 94.1, 91.2, 64.6, 55.7, 38.7, -0.2 (3C) ppm; **IR (ATR)**:  $\tilde{\nu}$  = 2956, 2892, 2172, 1444, 1250, 1151, 1097, 1026, 843, 758, 694 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>17</sub>H<sub>24</sub><sup>79</sup>BrO<sub>2</sub>Si]<sup>+</sup>: 367.0723, found: 367.0717; **R<sub>f</sub>** = 0.52 (*n*-pentane/Et<sub>2</sub>O 10/1).

### (*Z*)-Vinyl bromide **109**

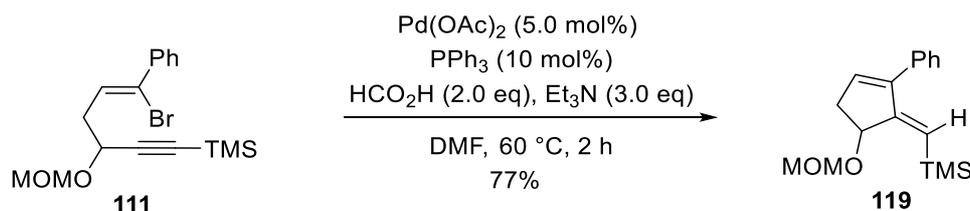


To a solution of (*Z*)-vinyl bromide **111** (200 mg, 0.544 mmol, 1.0 eq) in MeOH (5.4 mL) was added K<sub>2</sub>CO<sub>3</sub> (22.6 mg, 0.163 mmol, 0.3 eq) and the resulting mixture was stirred at 23 °C for 1.5 h. The reaction mixture was then diluted with Et<sub>2</sub>O (20 mL) and quenched by addition of sat. aqueous ammonium chloride (20 mL). The aqueous phase extracted with Et<sub>2</sub>O (3 x 10 mL), the combined organic layers were washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 30/1) to afford (*Z*)-vinyl bromide **109** (157 mg, 0.532 mmol, 98%) as a pale yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.58 – 7.53 (m, 2H), 7.38 – 7.28 (m, 3H), 6.39 (t, *J* = 6.6 Hz, 1H), 4.97 (d, *J* = 6.8 Hz, 1H), 4.66 (d, *J* = 6.8 Hz, 1H), 4.55 (td, *J* = 6.4, 1.5 Hz, 1H), 3.41 (s, 3H), 2.85 (t, *J* = 6.3 Hz, 2H), 2.49 (d, *J* = 2.0 Hz, 1H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 139.7, 128.6, 128.2 (2C), 127.8, 127.6 (2C), 126.2, 94.1, 81.7, 74.2, 64.0, 55.8, 38.6 ppm; **IR**

(ATR):  $\tilde{\nu}$  = 3293, 2928, 2890, 1444, 1150, 1096, 1021, 919, 875, 757, 693, 647, 635  $\text{cm}^{-1}$ ;  
**HRMS (ESI)** calc'd. for  $[\text{M}-\text{Br}]^+ = [\text{C}_{14}\text{H}_{15}\text{O}_2]^+$ : 215.1067, found: 215.1063;  $R_f$  = 0.39 (*n*-pentane/Et<sub>2</sub>O 10/1).

### Monocycle 119

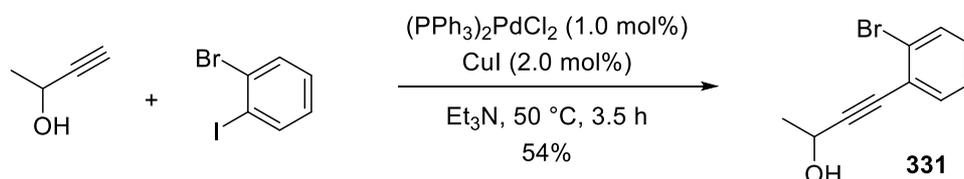


A vial was charged with (*Z*)-vinyl bromide **111** (11.0 mg, 30.0  $\mu\text{mol}$ , 1.0 eq),  $\text{Pd}(\text{OAc})_2$  (0.34 mg, 1.5  $\mu\text{mol}$ , 5.0 mol%) and  $\text{PPh}_3$  (0.79 mg, 3.0  $\mu\text{mol}$ , 10 mol%). The vial was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). Dry DMF (300  $\mu\text{L}$ ),  $\text{Et}_3\text{N}$  (12.7  $\mu\text{L}$ , 90.0  $\mu\text{mol}$ , 3.0 eq) and formic acid (2.26  $\mu\text{L}$ , 60.0  $\mu\text{mol}$ , 2.0 eq) were then added. The yellow solution was degassed by freeze-pump-thaw cycles (3 x) before it was stirred at 60 °C for 2 h. The red/brown reaction mixture was then allowed to cool to ambient temperature, filtered through a short pad of silica gel (*n*-pentane/EOAc 10/1), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 60/1) to afford monocycle **119** (6.70 mg, 23.2  $\mu\text{mol}$ , 77%) as a colorless oil.

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 – 7.30 (m, 5H), 6.14 (t,  $J$  = 2.8 Hz, 1H), 5.73 (dd,  $J$  = 1.8, 0.8 Hz, 1H), 4.86 – 4.81 (m, 3H), 3.45 (s, 3H), 2.87 (ddd,  $J$  = 18.3, 6.6, 2.7 Hz, 1H), 2.70 (dt,  $J$  = 18.3, 2.6 Hz, 1H), 0.15 (s, 9H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  159.7, 146.3, 135.9, 134.0, 128.5 (2C), 128.2 (2C), 127.4, 122.7, 96.7, 79.7, 56.3, 38.7, 0.1 (3C) ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{17}\text{H}_{25}\text{O}_2\text{Si}]^+$ : 289.1618, found: 289.1616;  $R_f$  = 0.52 (*n*-pentane/Et<sub>2</sub>O 10/1).

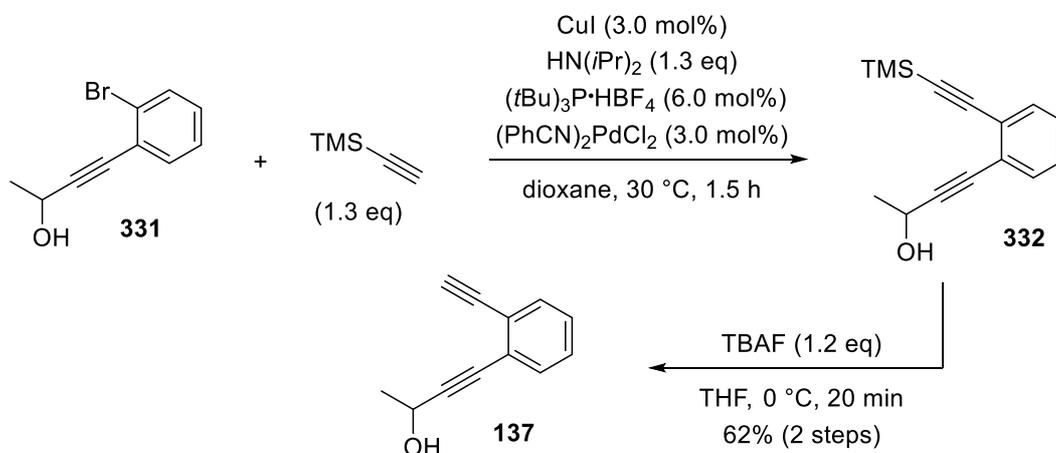
### 10.2.3 Studies Involving Ru<sup>II</sup> Catalyzed [2+2+2] Cycloaddition / Au<sup>I</sup> Catalyzed *Bis*-Alkyne Isomerization

#### Bromopropargylic alcohol **331**



A round-bottom flask was charged with (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (82.0 mg, 0.117 mmol, 1.0 mol%) and CuI (44.0 mg, 0.234 mol, 2.0 mol%). The flask was sealed, placed under vacuum and backfilled with N<sub>2</sub> (3 x). Freshly distilled Et<sub>3</sub>N (33 mL) was added followed by 2-bromoiodobenzene (1.50 mL, 11.7 mmol, 1.0 eq) and but-3-yn-2-ol (1.12 mL, 14.0 mmol, 1.2 eq). The dark reaction mixture was degassed by passing gaseous N<sub>2</sub> through the solution before it was stirred at 50 °C. Since the reaction progress had stopped after 3.5 h (TLC in *n*-pentane), the reaction mixture was then allowed to cool to ambient temperature, filtered through a short pad of Celite (Et<sub>2</sub>O), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 4/1) to afford bromopropargylic alcohol **331** (1.42 g, 6.33 mmol, 54%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.58 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.26 (td, *J* = 7.6, 1.2 Hz, 1H), 7.17 (td, *J* = 7.8, 1.7 Hz, 1H), 4.81 (q, *J* = 6.6 Hz, 1H), 1.94 (br. s, 1H), 1.60 (d, *J* = 6.6 Hz, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 133.4, 132.4, 129.5, 127.0, 125.5, 124.7, 95.6, 82.6, 58.9, 24.2 ppm; IR (ATR):  $\tilde{\nu}$  = 3322, 2981, 2930, 1469, 1434, 1103, 1026, 935, 854, 751, 654 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M-OH]<sup>+</sup> = [C<sub>10</sub>H<sub>8</sub><sup>79</sup>Br]<sup>+</sup>: 206.9804, found: 206.9800; *R*<sub>f</sub> = 0.36 (*n*-pentane/EtOAc 4/1).

**Propargylic alcohol 137**

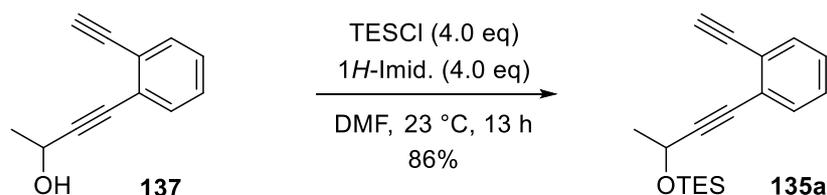
**Step 1:** A round-bottom flask was charged with (PhCN)<sub>2</sub>PdCl<sub>2</sub> (68.5 mg, 0.179 mmol, 3.0 mol%), CuI (34.1 mg, 0.179 mmol, 3.0 mol%), (*t*Bu)<sub>3</sub>P•HBF<sub>4</sub> (104 mg, 0.357 mmol, 6.0 mol%) and bromopropargylic alcohol **331** (1.34 g, 5.95 mmol, 1.0 eq). The flask was sealed, placed under vacuum and backfilled with N<sub>2</sub> (3 x). Dry dioxane (12 mL) was added followed by HN(*i*Pr)<sub>2</sub> (1.09 mL, 7.74 mmol, 1.3 eq) and trimethylsilylacetylene (1.07 mL, 7.74 mmol, 1.3 eq). The resulting brown suspension was degassed by passing gaseous N<sub>2</sub> through the solution before it was stirred at 30 °C for 1.5 h. The reaction mixture was then filtered through a short pad of Celite (Et<sub>2</sub>O), and the solvent was removed under reduced pressure. Crude *bis*-alkyne **332** was obtained as a black residue and used in the next step without further purification. *R*<sub>f</sub> = 0.52 (*n*-pentane/EtOAc 3/1).

**Step 2:** To an ice-cooled solution of crude *bis*-alkyne **332** (1.44 g, 5.95 mmol, 1.0 eq) in dry THF (60 mL) was added a solution of TBAF (1.0 M in THF, 7.14 mL, 7.14 mmol, 1.2 eq) dropwise and the resulting black solution was stirred at 0 °C for 20 min. The reaction was then quenched by addition of sat. aqueous ammonium chloride (30 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 30 mL), the combined organic layers were washed brine (30 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 4/1) to afford propargylic alcohol **137** (626 mg, 3.68 mmol, 62% over 2 steps) as a brown oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.52 – 7.46 (m, 1H), 7.45 – 7.40 (m, 1H), 7.31 – 7.23 (m, 2H), 4.80 (q, *J* = 6.6 Hz, 1H), 3.32 (s, 1H), 2.29 (br. s, 1H), 1.57 (d, *J* = 6.6 Hz, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 132.5, 131.9, 128.5, 128.0, 125.5, 124.6, 95.2, 82.3, 82.0, 81.1, 58.8,

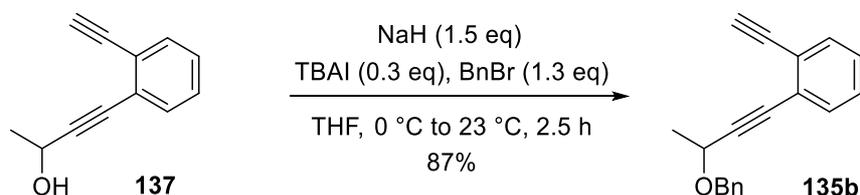
24.3 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3282, 2981, 1477, 1440, 1327, 1107, 1092, 1075, 1028, 934, 857, 755, 621  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M-OH}]^+ = [\text{C}_{12}\text{H}_9]^+$ : 153.0699, found: 153.0686; **R<sub>f</sub>** = 0.41 (*n*-pentane/EtOAc 3/1).

### TES protected *bis*-alkyne **135a**



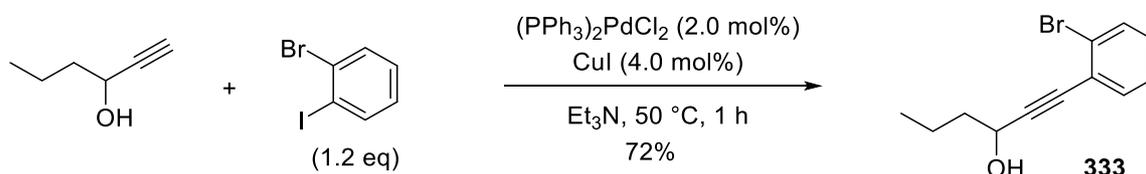
To a solution of propargylic alcohol **137** (50.0 mg, 0.294 mmol, 1.0 eq) in dry DMF (2.9 mL) were added 1*H*-imidazole (80.0 mg, 1.18 mmol, 4.0 eq) and chlorotriethylsilane (197  $\mu\text{L}$ , 1.18 mmol, 4.0 eq). The resulting mixture was stirred at 23 °C for 13 h and was then quenched by addition of half-sat. aqueous sodium bicarbonate (4 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 5 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 60/1) to afford *bis*-alkyne **135a** (72.2 mg, 0.254 mmol, 86%) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.51 – 7.47 (m, 1H), 7.45 – 7.41 (m, 1H), 7.32 – 7.22 (m, 2H), 4.81 (q, *J* = 6.5 Hz, 1H), 3.27 (s, 1H), 1.56 (d, *J* = 6.5 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.71 (qd, *J* = 8.4, 7.9, 2.3 Hz, 6H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  132.5, 132.0, 128.4, 127.8, 126.1, 124.5, 95.9, 82.1, 81.5, 80.8, 59.1, 25.5, 6.8 (3C), 4.8 (3C) ppm; **IR (ATR):**  $\tilde{\nu}$  = 2954, 2876, 1478, 1337, 1239, 1097, 1054, 1005, 978, 892, 756, 743, 645  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M-OSiEt}_3]^+ = [\text{C}_{12}\text{H}_9]^+$ : 153.0699, found: 153.0696; **R<sub>f</sub>** = 0.30 (*n*-pentane/Et<sub>2</sub>O 60/1).

**Benzyl protected bis-alkyne 135b**

To an ice-cooled solution of propargylic alcohol **137** (50.0 mg, 0.294 mmol, 1.0 eq) in dry THF (2.9 mL) was added sodium hydride (10.6 mg, 0.441 mmol, 1.5 eq) in one portion. The resulting suspension was stirred at 0 °C for 30 min before tetrabutylammonium iodide (32.6 mg, 88.3  $\mu$ mol, 0.3 eq) and benzyl bromide (45.4  $\mu$ L, 0.382 mmol, 1.3 eq) was added subsequently. The resulting reaction mixture was allowed to warm to 23 °C and stirred for 2.5 h before it was quenched by addition of sat. ammonium chloride (4 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 50/1) to afford *bis*-alkyne **135b** (66.8 mg, 0.257 mmol, 87%) as a yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 – 7.42 (m, 4H), 7.40 – 7.26 (m, 5H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.51 (q, *J* = 6.6 Hz, 1H), 3.29 (s, 1H), 1.60 (d, *J* = 6.6 Hz, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  138.0, 132.5, 131.9, 128.5, 128.4 (2C), 128.2 (2C), 128.0, 127.7, 125.8, 124.7, 93.3, 83.6, 82.2, 81.0, 70.5, 64.8, 22.1 ppm; IR (ATR):  $\tilde{\nu}$  = 3285, 2985, 2862, 1478, 1441, 1328, 1095, 1059, 758, 698, 619 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M+H]<sup>+</sup> = [C<sub>19</sub>H<sub>17</sub>O]<sup>+</sup>: 261.1274, found: 261.1267; *R*<sub>f</sub> = 0.21 (*n*-pentane/Et<sub>2</sub>O 50/1).

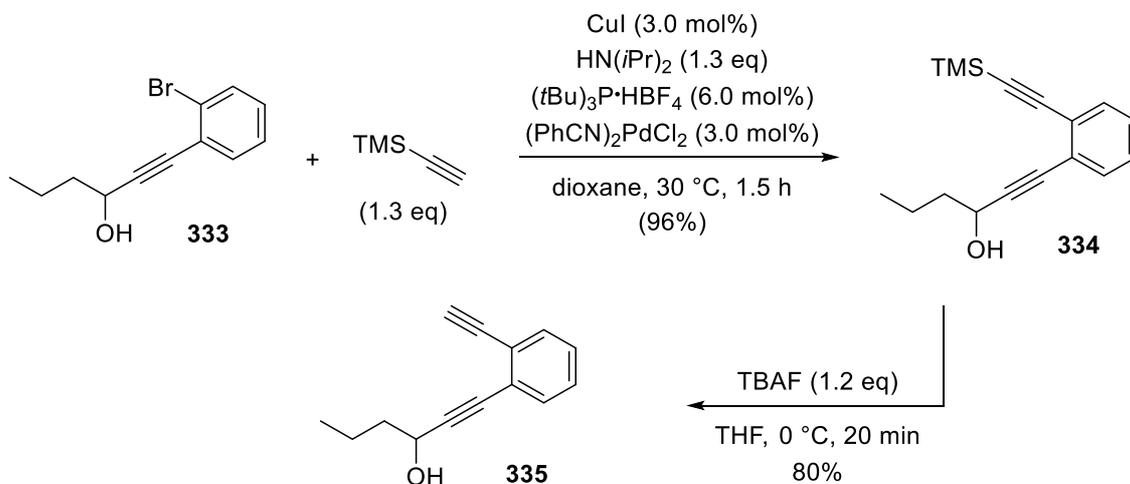
**Bromopropargylic alcohol 333**

A round-bottom flask was charged with (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (45.6 mg, 65.0  $\mu$ mol, 2.0 mol%) and CuI (24.8 mg, 130  $\mu$ mol, 4.0 mol%). The flask was sealed, placed under vacuum and backfilled with N<sub>2</sub> (3 x). Freshly distilled Et<sub>3</sub>N (9.2 mL) was added followed by 2-bromoiodobenzene (0.501 mL, 3.90 mmol, 1.2 eq) and hex-1-yn-3-ol<sup>89</sup> (319 mg, 3.25 mmol, 1.0 eq). The dark

reaction mixture was degassed by passing gaseous N<sub>2</sub> through the solution before it was stirred at 50 °C for 1 h. The reaction mixture was then allowed to cool to ambient temperature, filtered through a short pad of Celite (Et<sub>2</sub>O), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 12/1 to 5/1) to afford bromopropargylic alcohol **333** (589 mg, 2.33 mmol, 72%) as a brown oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.25 (tt, *J* = 7.7, 1.2 Hz, 1H), 7.19 – 7.13 (m, 1H), 4.66 (t, *J* = 6.6 Hz, 1H), 2.18 (br. d, *J* = 22.0 Hz, 1H), 1.86 – 1.79 (m, 2H), 1.60 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 133.4, 132.3, 129.5, 126.9, 125.5, 124.8, 94.9, 83.3, 62.8, 39.8, 18.4, 13.8 ppm; IR (ATR):  $\tilde{\nu}$  = 3327, 2958, 2932, 2872, 1468, 1433, 1120, 1025, 927, 750, 655 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M-OH]<sup>+</sup> = [C<sub>12</sub>H<sub>12</sub>Br]<sup>+</sup>: 235.0117, found: 235.0102; R<sub>f</sub> = 0.40 (*n*-pentane/Et<sub>2</sub>O 2/1).

### Propargylic alcohol **335**



**Step 1:** A round-bottom flask was charged with (PhCN)<sub>2</sub>PdCl<sub>2</sub> (26.8 mg, 69.9 μmol, 3.0 mol%), CuI (13.3 mg, 69.9 μmol, 3.0 mol%), (*t*Bu)<sub>3</sub>P·HBF<sub>4</sub> (40.5 mg, 0.140 mmol, 6.0 mol%) and bromopropargylic alcohol **333** (589 mg, 2.33 mmol, 1.0 eq). The flask was sealed, placed under vacuum and backfilled with N<sub>2</sub> (3 x). Dry dioxane (5.0 mL) was added followed by HN(*i*Pr)<sub>2</sub> (0.426 mL, 3.02 mmol, 1.3 eq) and trimethylsilylacetylene (0.419 mL, 3.02 mmol, 1.3 eq). The resulting brown suspension was degassed by passing gaseous N<sub>2</sub> through the solution before it was stirred at 30 °C for 1.5 h. The reaction mixture was then filtered through a short pad of Celite

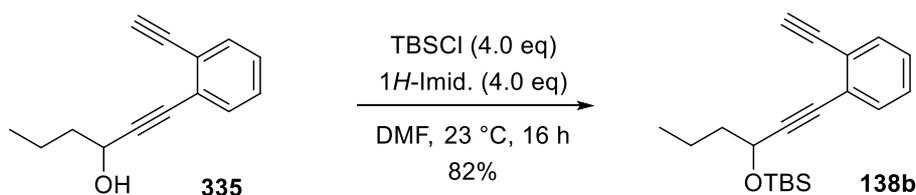
(Et<sub>2</sub>O), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 20/1) to afford *bis*-alkyne **334** (607 mg, 2.24 mmol, 96%) as a brown oil, which was directly used for the subsequent TMS cleavage step.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.51 – 7.46 (m, 1H), 7.45 – 7.40 (m, 1H), 7.29 – 7.23 (m, 2H), 4.66 (q, *J* = 6.4 Hz, 1H), 1.87 – 1.79 (m, 3H), 1.65 – 1.56 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.28 (s, 9H) ppm; *R*<sub>f</sub> = 0.49 (*n*-pentane/Et<sub>2</sub>O 1/1).

**Step 2:** To an ice-cooled solution of *bis*-alkyne **334** (607 mg, 2.24 mmol, 1.0 eq) in dry THF (22 mL) was added a solution of TBAF (1.0 M in THF, 2.69 mL, 2.69 mmol, 1.2 eq) dropwise and the resulting black solution was stirred at 0 °C for 20 min. The reaction was then quenched by addition of sat. aqueous ammonium chloride (20 mL). The aqueous phase was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 20/1 to 10/1 to 5/1) to afford propargylic alcohol **335** (356 mg, 1.80 mmol, 80%) as a brown oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.50 – 7.45 (m, 1H), 7.45 – 7.39 (m, 1H), 7.29 – 7.23 (m, 2H), 4.66 (q, *J* = 6.4 Hz, 1H), 1.87 – 1.78 (m, 2H), 1.66 – 1.53 (m, 2H), 1.49 (d, *J* = 13.1 Hz, 1H), 1.02 (s, 3H), 0.28 (s, 9H) ppm; *R*<sub>f</sub> = 0.35 (*n*-pentane/EtOAc 5/1).

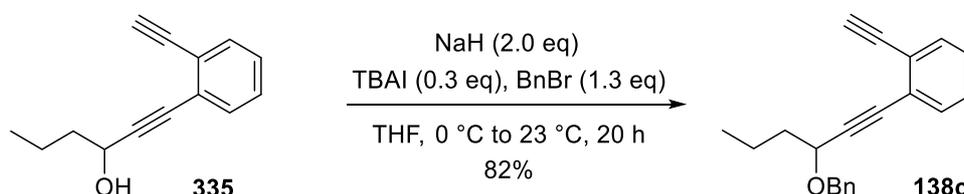
### TBS Protected *bis*-alkyne **138b**



To a solution of propargylic alcohol **335** (50.0 mg, 0.252 mmol, 1.0 eq) in dry DMF (3.0 mL) were added 1*H*-imidazole (68.7 mg, 1.01 mmol, 4.0 eq) and TBSCl (152 mg, 1.01 mmol, 4.0 eq). The resulting mixture was stirred at 23 °C for 16 h and was then quenched by addition of half-sat. aqueous sodium bicarbonate (4 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 5 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 60/1) to afford *bis*-alkyne **138b** (64.9 mg, 0.208 mmol, 82%) as a yellow oil.

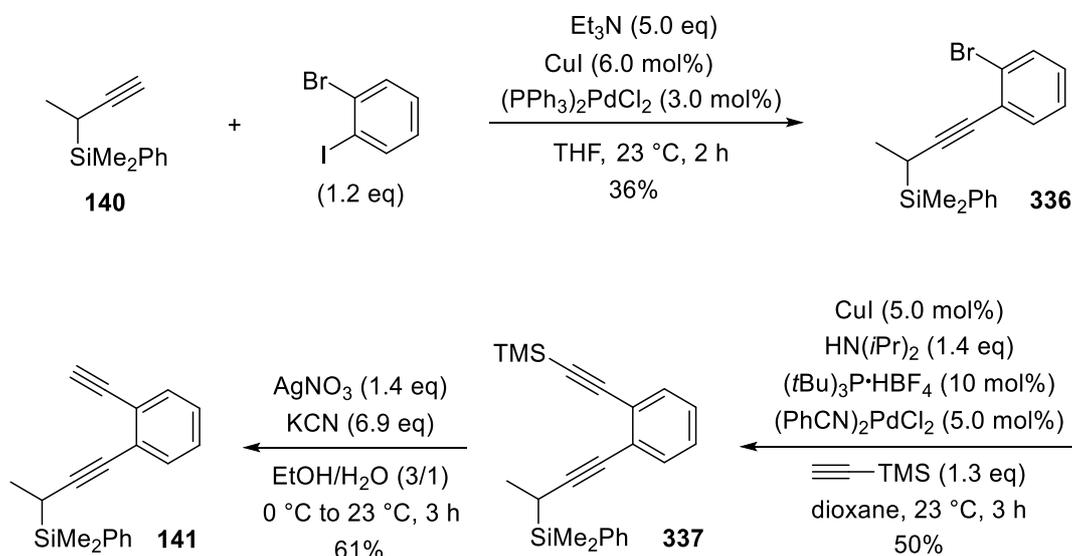
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.51 – 7.47 (m, 1H), 7.45 – 7.41 (m, 1H), 7.32 – 7.23 (m, 2H), 4.64 (t,  $J = 6.6$  Hz, 1H), 3.25 (s, 1H), 1.84 – 1.74 (m, 2H), 1.55 (ddd,  $J = 12.3, 8.4, 5.7$  Hz, 2H), 0.97 (t,  $J = 7.4$  Hz, 3H), 0.94 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  132.5, 132.0, 128.4, 127.7, 126.2, 124.4, 95.4, 82.2, 82.2, 80.8, 63.3, 40.8, 25.9 (3C), 18.6, 18.3, 13.8, -4.3, -4.9 ppm; **IR (ATR)**:  $\tilde{\nu} = 2957, 2929, 2857, 1477, 1251, 1112, 1076, 1038, 835, 776, 756, 645, 614$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{20}\text{H}_{29}\text{OSi}]^+$ : 313.1982, found: 313.1976;  $R_f = 0.58$  (*n*-pentane/Et<sub>2</sub>O 30/1).

### Benzyl protected bis-alkyne **138c**



To an ice-cooled solution of propargylic alcohol **335** (58.3 mg, 0.294 mmol, 1.0 eq) in dry THF (2.9 mL) was added sodium hydride (14.1 mg, 0.588 mmol, 2.0 eq) in one portion. The resulting suspension was stirred at 0 °C for 30 min before tetrabutylammonium iodide (32.6 mg, 88.3  $\mu\text{mol}$ , 0.3 eq) and benzyl bromide (45.4  $\mu\text{L}$ , 0.382 mmol, 1.3 eq) was added subsequently. The resulting reaction mixture was allowed to warm to 23 °C and stirred for 20 h before it was quenched by addition of sat. ammonium chloride (4 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 120/1) to afford benzyl protected bis-alkyne **138c** (69.4 mg, 0.241 mmol, 82%) as a yellow oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.54 – 7.40 (m, 4H), 7.39 – 7.24 (m, 5H), 4.94 (d,  $J = 11.7$  Hz, 1H), 4.65 (d,  $J = 11.7$  Hz, 1H), 4.38 (t,  $J = 6.6$  Hz, 1H), 3.27 (s, 1H), 1.94 – 1.77 (m,  $J = 6.5$  Hz, 2H), 1.65–1.56 (m, 2H), 0.96 (t,  $J = 7.4$  Hz, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  138.2, 132.5, 132.0, 128.4, 128.3 (2C), 128.1 (2C), 127.9, 127.6, 126.0, 124.7, 92.7, 84.3, 82.3, 80.9, 70.5, 69.0, 37.8, 18.7, 13.8 ppm; **IR (ATR)**:  $\tilde{\nu} = 2958, 2931, 2870, 1477, 1454, 1333, 1112, 1070, 756, 735, 697, 648, 618$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{21}\text{H}_{21}\text{O}]^+$ : 289.1587, found: 289.1582;  $R_f = 0.44$  (*n*-pentane/Et<sub>2</sub>O 30/1).

Silylated bis-alkyne **141**

**Step 1:** A round-bottom flask was charged with  $(\text{PPh}_3)_2\text{PdCl}_2$  (20.1 mg, 28.6  $\mu\text{mol}$ , 3.0 mol%) and CuI (10.9 mg, 57.2  $\mu\text{mol}$ , 6.0 mol%). The flask was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). Dry THF (1.9 mL) was added followed by freshly distilled  $\text{Et}_3\text{N}$  (672  $\mu\text{L}$ , 4.78 mmol, 5.0 eq), 2-bromoiodobenzene (147  $\mu\text{L}$ , 1.15 mmol, 1.2 eq) and alkyne **140**<sup>92</sup> (180 mg, 0.956 mmol, 1.0 eq). The dark reaction mixture was degassed by passing gaseous  $\text{N}_2$  through the solution before it was stirred at 23  $^\circ\text{C}$  for 2 h. The reaction mixture was then filtered through a short pad of Celite ( $\text{Et}_2\text{O}$ ), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane) to afford bromoalkyne **336** (117 mg, 0.341 mmol, 36%) as a brown oil, which was directly used in the subsequent Sonogashira cross-coupling step.

**<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.66 – 7.61 (m, 2H), 7.58 – 7.53 (m, 1H), 7.41 – 7.35 (m, 4H), 7.21 (td,  $J = 7.6, 1.2$  Hz, 1H), 7.09 (td,  $J = 7.8, 1.7$  Hz, 1H), 2.20 (q,  $J = 7.2$  Hz, 1H), 1.27 (d,  $J = 7.2$  Hz, 3H), 0.48 (s, 3H), 0.47 (s, 3H) ppm.

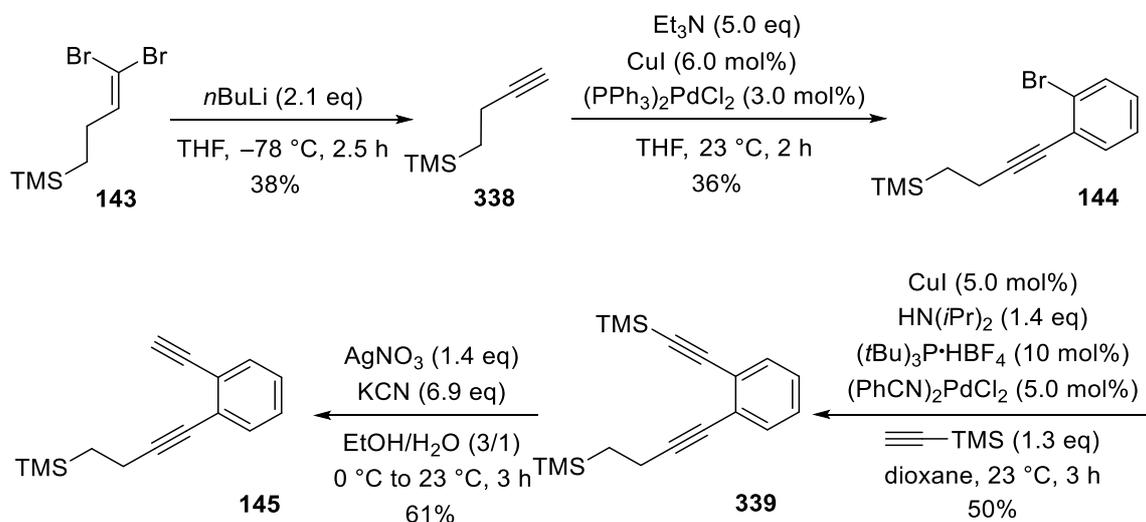
**Steps 2:** A vial was charged with  $(\text{PhCN})_2\text{PdCl}_2$  (6.54 mg, 17.1  $\mu\text{mol}$ , 5.0 mol%), CuI (3.25 mg, 17.1  $\mu\text{mol}$ , 5.0 mol%) and  $(t\text{Bu})_3\text{P}\cdot\text{HBF}_4$  (9.89 mg, 34.2 mmol, 10 mol%). The vial was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). A solution of bromoalkyne **336** (117 mg, 341  $\mu\text{mol}$ , 1.0 eq) in dry dioxane (680  $\mu\text{L}$ ) was added followed by  $\text{HN}(i\text{Pr})_2$  (67.2  $\mu\text{L}$ , 477  $\mu\text{mol}$ , 1.4 eq) and trimethylsilylacetylene (61.4  $\mu\text{L}$ , 443  $\mu\text{mol}$ , 1.3 eq). The resulting brown suspension was degassed by freeze-pump-thaw cycles (3 x) before it was stirred at 23  $^\circ\text{C}$  for 3 h. The

reaction mixture was then filtered through a short pad of Celite (Et<sub>2</sub>O), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane) to afford *bis*-alkyne **337** (61.3 mg, 170 μmol, 50%) as a pale brown oil, which was directly used for the subsequent TMS cleavage step.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.65 – 7.60 (m, 2H), 7.45 (dd, *J* = 7.1, 1.6 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.33 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.21 (td, *J* = 7.6, 1.8 Hz, 1H), 7.17 (td, *J* = 7.5, 1.7 Hz, 1H), 2.19 (q, *J* = 7.2 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 3H), 0.47 (s, 6H), 0.25 (s, 9H) ppm.

**Step 3:** To an ice-cooled solution of *bis*-alkyne **337** (54.0 mg, 150 μmol, 1.0 eq) in EtOH (2.4 mL) was added a solution of AgNO<sub>3</sub> (35.0 mg, 206 μmol, 1.4 eq) in EtOH/H<sub>2</sub>O (2.8 mL, v/v = 3/1) in four equal portions over a period of 1 h, resulting in formation of a brown suspension. Stirring was continued at 0 °C for 30 min before a solution of KCN (67.0 mg, 1.03 mmol, 6.9 eq) in H<sub>2</sub>O (1.0 mL) was added, resulting in precipitation of a white solid. The reaction mixture was then stirred at 23 °C for 2 h before it was diluted with H<sub>2</sub>O (5 mL) and pentane (5 mL). The aqueous phase was extracted with pentane (3 x 5 mL), the combined organic layers were washed with water (3 x 5 mL) and brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane) to afford silylated *bis*-alkyne **141** (26.4 mg, 91.4 μmol, 61%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.66 – 7.61 (m, 2H), 7.47 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.41 – 7.34 (m, 4H), 7.26 (td, *J* = 7.6, 1.5 Hz, 1H), 7.20 (td, *J* = 7.6, 1.4 Hz, 1H), 3.21 (s, 1H), 2.20 (q, *J* = 7.2 Hz, 1H), 1.26 (d, *J* = 7.2 Hz, 3H), 0.47 (s, 3H), 0.47 (s, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 136.7, 134.1 (2C), 132.9, 132.4, 131.9, 129.3 (2C), 128.3, 127.7 (2C), 126.7, 98.4, 82.7, 80.3, 79.2, 15.0, 13.9, -4.4, -5.4 ppm.

Silylated bis-alkyne **145**

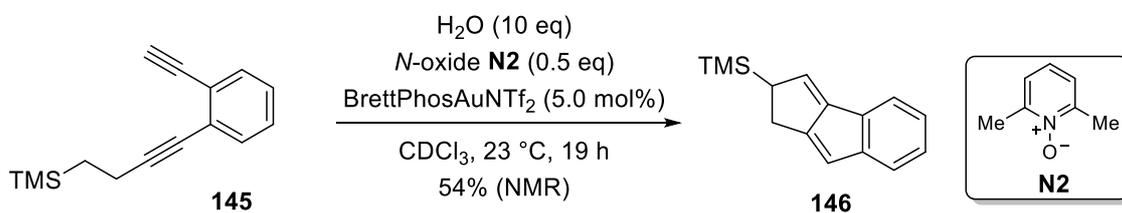
**Step 1:** To a solution of dibromoalkene **143**<sup>95</sup> (901 mg, 3.15 mmol, 1.0 eq) in dry THF (40 mL) was added a solution of *n*BuLi (1.6 M in Et<sub>2</sub>O, 4.54 mL, 7.27 mmol, 2.1 eq) dropwise at  $-78$  °C. The resulting mixture was stirred at  $-78$  °C for 1 h and then allowed to warm to 23 °C. Stirring was continued at 23 °C for an additional 1.5 h before the reaction was quenched by addition of sat. aqueous ammonium chloride (20 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure (25 °C). The crude product was purified by flash chromatography (*n*-pentane) to afford highly volatile alkyne **338** (150 mg, 1.19 mmol, 38%) as a pale yellow oil. The product was immediately subjected to the subsequent Sonogashira cross coupling.

**Step 2:** A round-bottom flask was charged with (PPh<sub>3</sub>)<sub>2</sub>PdCl<sub>2</sub> (25.0 mg, 35.6 μmol, 3.0 mol%) and CuI (13.6 mg, 71.3 μmol, 6.0 mol%). The flask was sealed, placed under vacuum and backfilled with N<sub>2</sub> (3 x). Dry THF (2.4 mL) was added followed by freshly distilled Et<sub>3</sub>N (835 μL, 5.94 mmol, 5.0 eq), 2-bromoiodobenzene (168 μL, 1.31 mmol, 1.1 eq) and alkyne **338** (150 mg, 1.19 mmol, 1.0 eq). The dark reaction mixture was degassed by passing gaseous N<sub>2</sub> through the solution before it was stirred at 23 °C for 2 h. The reaction mixture was then filtered through a short pad of Celite (Et<sub>2</sub>O), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane) to afford bromoalkyne **144** (28.5 mg, 101 μmol, 9%) as a brown oil, which was directly used in the subsequent Sonogashira cross-coupling step.

**Steps 3:** A vial was charged with  $(\text{PhCN})_2\text{PdCl}_2$  (2.3 mg, 6.08  $\mu\text{mol}$ , 6.0 mol%), CuI (1.2 mg, 6.08  $\mu\text{mol}$ , 6.0 mol%) and  $(t\text{Bu})_3\text{P}\cdot\text{HBF}_4$  (3.5 mg, 12.2  $\mu\text{mol}$ , 12 mol%). The vial was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). A solution of bromoalkyne **144** (28.5 mg, 301  $\mu\text{mol}$ , 1.0 eq) in dry dioxane (200  $\mu\text{L}$ ) was added followed by  $\text{HN}(i\text{Pr})_2$  (20.0  $\mu\text{L}$ , 142  $\mu\text{mol}$ , 1.4 eq) and trimethylsilylacetylene (21.1  $\mu\text{L}$ , 152  $\mu\text{mol}$ , 1.5 eq). The resulting brown suspension was degassed by freeze-pump-thaw cycles (3 x) before it was stirred at 30 °C for 3 h. The reaction mixture was then filtered through a short pad of Celite ( $\text{Et}_2\text{O}$ ), and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane) to afford *bis*-alkyne **339** (23.8 mg, 79.7  $\mu\text{mol}$ , 79%) as a yellow oil, which was directly used for the subsequent TMS cleavage step.

**Step 4:** To an ice-cooled solution of *bis*-alkyne **339** (23.8 mg, 79.7  $\mu\text{mol}$ , 1.0 eq) in EtOH (1.3 mL) was added a solution of  $\text{AgNO}_3$  (18.6 mg, 110  $\mu\text{mol}$ , 1.4 eq) in EtOH/ $\text{H}_2\text{O}$  (1.5 mL, v/v = 3/1) in four equal portions over a period of 1 h. Stirring was continued at 0 °C for 30 min before a solution of KCN (35.7 mg, 548  $\mu\text{mol}$ , 6.9 eq) in  $\text{H}_2\text{O}$  (0.5 mL) was added, resulting in precipitation of a white solid. The reaction mixture was then stirred at 23 °C for 2 h before it was diluted with  $\text{H}_2\text{O}$  (5 mL) and pentane (5 mL). The aqueous phase was extracted with pentane (3 x 5 mL), the combined organic layers were washed with water (3 x 5 mL) and brine (5 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane) to afford silylated *bis*-alkyne **145** (16.7 mg, 73.8  $\mu\text{mol}$ , 93%) as a colorless oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.48 (dd,  $J = 7.6, 1.3$  Hz, 1H), 7.40 (dd,  $J = 7.7, 1.1$  Hz, 1H), 7.30 – 7.24 (m, 1H), 7.22 (td,  $J = 7.5, 1.5$  Hz, 1H), 3.28 (s, 1H), 2.52 (t,  $J = 8.0$  Hz, 2H), 0.93 (t,  $J = 8.0$  Hz, 2H), 0.07 (s, 9H) ppm.

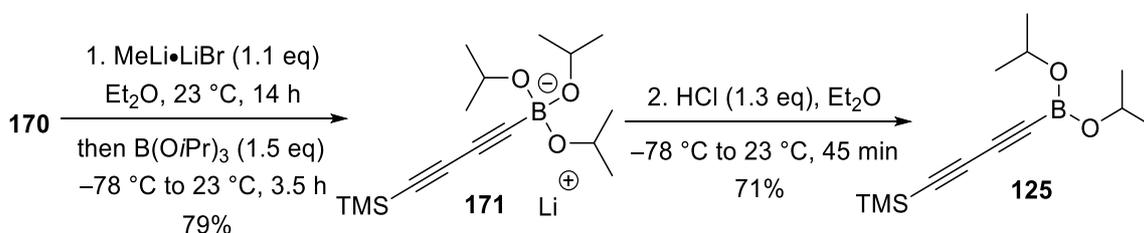
**Cyclopenta[*a*]indene 146**

To a solution of *bis*-alkyne **145** (3.5 mg, 15.5  $\mu$ mol, 1.0 eq) in CDCl<sub>3</sub> (300  $\mu$ l) was added *N*-oxide **N2** (1.0 mg, 7.73  $\mu$ mol, 0.5 eq), BrettPhosAuNTf<sub>2</sub> (0.8 mg, 0.773  $\mu$ mol, 5.0 mol%) and water (2.79  $\mu$ L, 155  $\mu$ mol, 10 eq). The resulting yellow reaction mixture was stirred at 23 °C for 19 h before a solution of 1,3,5-TMB (0.01 M, 400  $\mu$ L, 4.00  $\mu$ mol) was added as internal standard. After determination of the crude <sup>1</sup>H NMR yield (54%), the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 100/1) to afford a yellow oily product that was tentatively assigned to be cyclopenta[*a*]indene **146** (yield *n.d.*).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.61 (d, *J* = 7.4 Hz, 1H), 7.23 (dd, *J* = 15.1, 7.8 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.89 (s, 1H), 6.29 (s, 1H), 2.92 – 2.83 (m, 2H), 2.73 – 2.64 (m, 1H), 0.04 (s, 9H) ppm.

10.2.4 Studies involving Ru<sup>II</sup> Catalyzed [2+2+2] Cycloaddition / Allenic Pauson-Khand

## Reaction

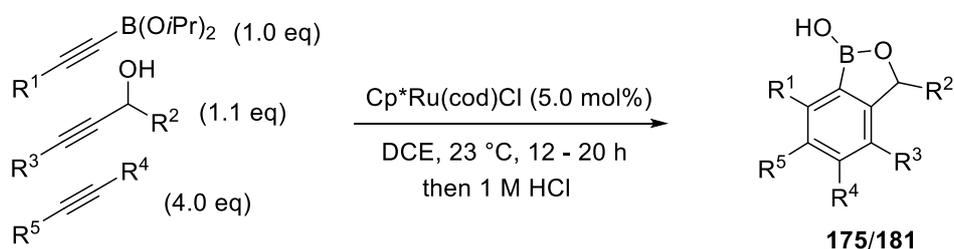
Diynylboronate **125**

**Step 1:** To an ice-cooled solution of TMS acetylene dimer **170**<sup>205</sup> (18.3 g, 93.9 mmol) in dry Et<sub>2</sub>O (105 mL) was slowly added a solution of MeLi•LiBr complex (2.2 M in Et<sub>2</sub>O, 46.9 mL, 103 mmol) over a period of 20 min. The mixture was allowed to warm to 23 °C and stirred for 14 h under a N<sub>2</sub> atmosphere. The dark green solution was then cooled to -78 °C and slowly added to a -78 °C cold solution of triisopropyl borate (32.4 mL, 141 mmol) in dry Et<sub>2</sub>O (90 mL) over a period of 50 min *via* cannula. The first flask was rinsed with additional Et<sub>2</sub>O (10 mL), and the resulting yellow suspension was stirred at -78 °C for 2 h before being allowed to warm to 23 °C over 1.5 h. After stirring for one additional hour at 23 °C the suspension was filtered, and the filter cake was thoroughly washed with dry Et<sub>2</sub>O (400 mL) under air and dried under high vacuum to afford lithium borate **171** (23.4 g, 74.0 mmol, 79%).

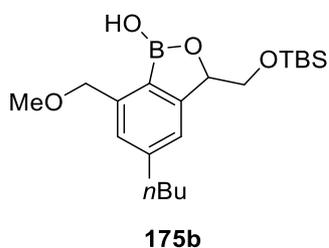
**Step 2:** To a suspension of lithium borate **171** (6.00 g, 19.0 mmol) in dry Et<sub>2</sub>O (60 mL) at -78 °C was slowly added an anhydrous solution of HCl (2.0 M in Et<sub>2</sub>O, 12.5 mL, 25 mmol) under a N<sub>2</sub> atmosphere, and the resulting yellow solution was stirred at -78 °C for 15 min before being allowed to warm to 23 °C over 30 min. Stirring was then stopped and the resulting white precipitate (LiCl) was allowed to settle. The supernatant liquid was filtered through a POR4 frit under N<sub>2</sub>, and the solvent was removed under high vacuum. The obtained neat liquid was filtered through KIMTECH paper in a glovebox to afford diynylboronate **125** (3.36 g, 13.4 mmol, 71%) as an amber colored liquid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 4.56 (sept, *J* = 6.3 Hz, 2H), 1.20 (d, *J* = 6.3 Hz, 12H), 0.21 (s, 9H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ = 99.2, 88.2, 87.6, 85.2, 68.2 (2C), 24.4 (4C), -0.6 (3C) ppm; IR (ATR):  $\tilde{\nu}$  = 3228, 2093, 1371, 1341, 846 cm<sup>-1</sup>.

<sup>205</sup> Prepared according to a literature procedure: A. B. Smith III, S. Dong, R. J. Fox, J. B. Brennehan, J. A. Vanecko, T. Maegawa, *Tetrahedron* **2011**, *67*, 9809-9828.

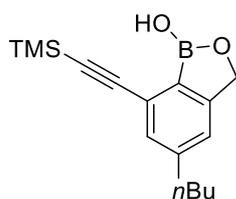
**General Procedure for the [2+2+2] Cycloaddition of Three Different Alkynes:**

To a degassed solution of the alkynylboronate (0.100 mmol, 1.0 eq), the third alkyne component (0.400 mmol, 4.0 eq) and Cp<sup>\*</sup>Ru(cod)Cl (1.9 mg, 5.00 μmol, 5.0 mol%) in dry DCE (0.3 mL) was added a degassed solution of the propargyl alcohol<sup>206</sup> (0.110 mmol, 1.1 eq) in dry DCE (0.7 mL) over a period of 20 min. The dark brown reaction mixture was stirred at 23 °C for 12 - 20 h under a N<sub>2</sub> atmosphere. The solvent was then removed under reduced pressure, the residue was taken up in Et<sub>2</sub>O (10 mL) and washed with aqueous 1 M HCl (4 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc) and the obtained boraphthalides (brown oils) were analyzed by <sup>1</sup>H NMR spectroscopy.



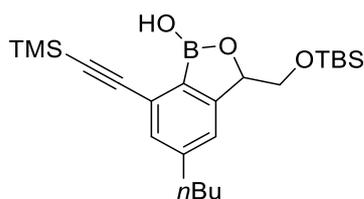
Isolated in 62%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.36 (s, 1H), 7.19 (s, 1H), 6.96 (s, 1H), 5.21 (t, *J* = 5.6 Hz, 1H), 4.73 (s, 2H), 3.94 (dd, *J* = 10.3, 5.4 Hz, 1H), 3.75 (dd, *J* = 10.3, 5.8 Hz, 1H), 3.48 (s, 3H), 2.67 – 2.61 (m, 2H), 1.65 – 1.57 (m, 2H), 1.36 (dt, *J* = 14.6, 7.4 Hz, 2H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.05 (s, 3H) ppm.

<sup>206</sup> In case of TMS (or bromine) substituted propargyl alcohols, an increased catalyst loading of Cp<sup>\*</sup>Ru(cod)Cl (3.8 mg, 10.00 μmol, 10 mol%) was employed.



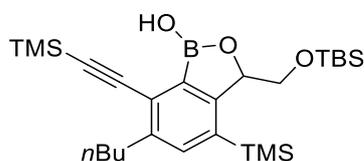
175c

Isolated in 72% yield;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (s, 1H), 7.14 (s, 1H), 5.22 (s, 1H), 5.04 (s, 2H), 2.68 – 2.62 (m, 2H), 1.65 – 1.56 (m, 2H), 1.35 (dq,  $J = 14.6, 7.3$  Hz, 2H), 0.93 (t,  $J = 7.3$  Hz, 3H), 0.30 (s, 9H) ppm.



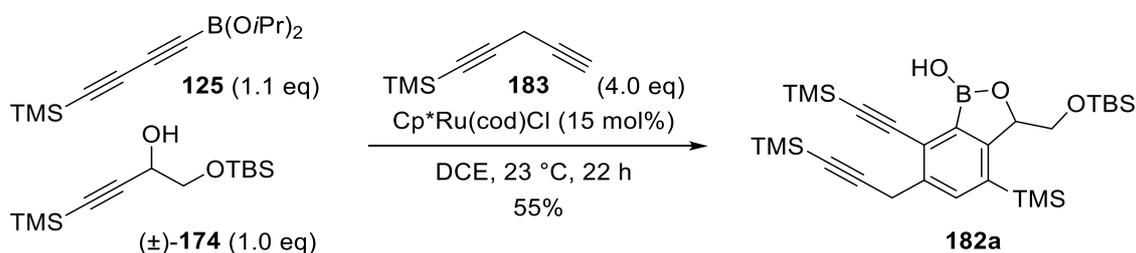
175d

Isolated in 70% yield;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.27 (s, 1H), 7.25 (s, 1H), 5.20 (s, 1H), 5.16 (t,  $J = 5.8$  Hz, 1H), 3.93 (dd,  $J = 10.3, 5.5$  Hz, 1H), 3.70 (dd,  $J = 10.3, 6.0$  Hz, 1H), 2.64 (t,  $J = 7.7$  Hz, 2H), 1.61 (p,  $J = 7.6$  Hz, 2H), 1.36 (dt,  $J = 14.9, 7.4$  Hz, 2H), 0.93 (t,  $J = 7.3$  Hz, 3H), 0.88 (s, 9H), 0.30 (s, 9H), 0.05 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.2, 146.5, 146.1, 130.8, 123.8, 122.9, 104.5, 96.8, 81.0, 66.4, 35.8, 33.4, 25.8 (3C), 22.3, 18.3, 13.9, -0.1 (3C), -5.4 (2C) ppm;  $R_f = 0.66$  (*n*-pentane/EtOAc 6/1).



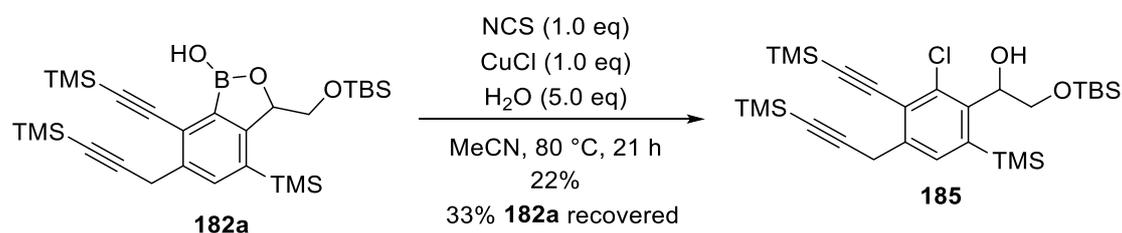
181

Isolated in 23% yield;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (s, 1H), 5.48 (s, 1H), 5.33 (dd,  $J = 5.8, 1.8$  Hz, 1H), 4.13 (dd,  $J = 11.2, 1.9$  Hz, 1H), 3.56 (dd,  $J = 11.2, 5.8$  Hz, 1H), 2.81 – 2.75 (m, 2H), 1.65 – 1.58 (m, 2H), 1.39 (dq,  $J = 14.6, 7.3$  Hz, 2H), 0.96 (t,  $J = 7.3$  Hz, 3H), 0.80 (s, 9H), 0.34 (s, 9H), 0.30 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H) ppm.

**Boraphthalide 182a**

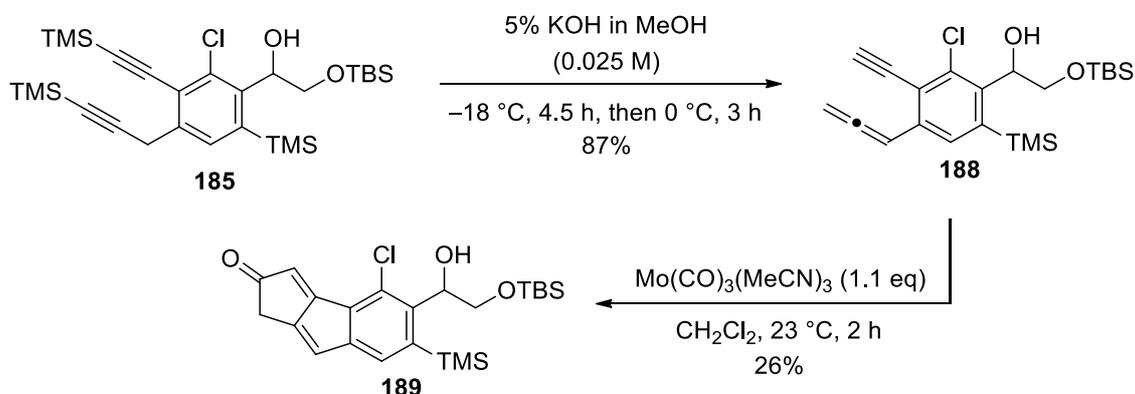
In a glovebox, diynylboronate **125** (50.4 mg, 201  $\mu\text{mol}$ , 1.1 eq) and propargylic alcohol **(±)-174** (53.1 mg, 181  $\mu\text{mol}$ , 1.0 eq) were loaded into a vial. Dry  $\text{Et}_2\text{O}$  (1.0 mL) was added and the solution was stirred at 23 °C under a  $\text{N}_2$  atmosphere. After 4 h, the solvent was removed under high vacuum to afford a pale brown oil, which was stirred under reduced pressure (1 mbar) for an additional 4 h. To this oil was added  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (5.1 mg, 13.6  $\mu\text{mol}$ , 7.5 mol%) (glovebox) and a degassed solution of diyne **183** (62.5  $\mu\text{L}$ , 362  $\mu\text{mol}$ , 2.0 eq) in dry DCE (1.8 mL). The mixture was stirred for 13 h at 23 °C under a  $\text{N}_2$  atmosphere before an additional portion of  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (5.1 mg, 13.6  $\mu\text{mol}$ , 7.5 mol%) in dry DCE (200  $\mu\text{L}$ ) and diyne **183** (62.5  $\mu\text{L}$ , 362  $\mu\text{mol}$ , 2.0 eq) was added. After stirring at 23 °C for additional 9 h, the solvent was removed under reduced pressure (25 °C), the black residue was taken up in  $\text{Et}_2\text{O}$  (10 mL) and washed with 1 N aq. HCl (6 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified using a Biotage Isolera™ Four chromatographic isolation system under gradient elution (2% EtOAc to 10% EtOAc/*n*-pentane) to afford boraphthalide **182a** (55.3 mg, 99.3  $\mu\text{mol}$ , 55%) as a brown oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 (s, 1H), 5.39 (br. s, 1H), 5.35 (dd,  $J = 5.6, 1.7$  Hz, 1H), 4.14 (dd,  $J = 11.3, 1.9$  Hz, 1H), 3.87 (d,  $J = 19.8$  Hz, 1H), 3.79 (d,  $J = 19.8$  Hz, 1H), 3.59 (dd,  $J = 11.2, 5.7$  Hz, 1H), 0.81 (s, 9H), 0.37 (s, 9H), 0.30 (s, 9H), 0.22 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  157.2, 137.2 (2C), 136.1, 134.8, 123.3, 103.6, 102.9, 102.1, 87.8, 83.0, 67.1, 25.8 (3C), 24.2, 18.2, 0.2 (3C), 0.1 (3C), -0.1 (3C), -5.3, -5.4 ppm; **IR (ATR)**:  $\tilde{\nu} = 3596, 2956, 2929, 2898, 2857, 2178, 2144, 1437, 1343, 1250, 1126, 835, 759$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{28}\text{H}_{50}\text{BO}_3\text{Si}_4]^+$ : 557.2925, found: 557.2911;  $R_f = 0.56$  (*n*-pentane/EtOAc 6/1).

**Chlorobenzene 185**

To a solution of boraphthalide **182a** (98.7 mg, 177  $\mu\text{mol}$ , 1.0 eq) in MeCN (3.5 mL) was added copper(I) chloride (17.5 mg, 177  $\mu\text{mol}$ , 1.0 eq), NCS (23.7 mg, 177  $\mu\text{mol}$ , 1.0 eq) and H<sub>2</sub>O (16.0  $\mu\text{L}$ , 886  $\mu\text{mol}$ , 5.0 eq). The resulting yellow solution was stirred at 80 °C for 21 h and was then allowed to cool to 23 °C. The brown reaction mixture was diluted with Et<sub>2</sub>O (20 mL) and washed with 1 M HCl (6 mL), 1 M NaOH (6 mL) and brine (4 mL). The organic layer was then dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 20/1 to 3/1 to 1/1) to afford chloroarene **185** (22.5 mg, 39.8  $\mu\text{mol}$ , 22%) as a yellow oil, along with unreacted starting material **182a** (32.2 mg, 57.8  $\mu\text{mol}$ , 33%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.91 (s, 1H), 5.28 (d,  $J$  = 9.7 Hz, 1H), 3.89 (dd,  $J$  = 10.1, 3.6 Hz, 1H), 3.87 – 3.74 (m, 2H), 3.61 (t,  $J$  = 10.0 Hz, 1H), 3.11 (s, 1H), 0.94 (s, 9H), 0.37 (s, 9H), 0.28 (s, 9H), 0.22 (s, 9H), 0.11 (s, 6H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  148.4, 141.3, 140.6, 138.0, 133.4, 123.4, 106.7, 102.9, 99.3, 88.3, 74.2, 65.3, 25.9 (3C), 25.5, 18.3, 2.5 (3C), 0.1 (3C), -0.1 (3C), -5.2, -5.3 ppm;  $R_f$  = 0.64 (*n*-pentane/Et<sub>2</sub>O 5/1).

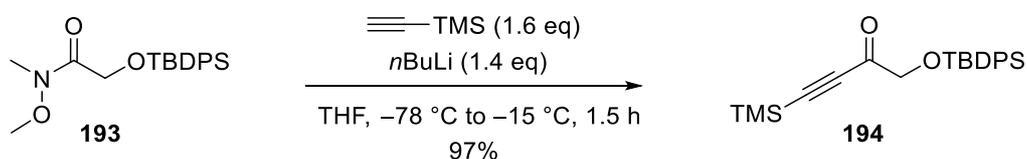
**Indenylcyclopentenone 189**

**Step 1:** To cooled chloroarene **185** (25.4 mg, 44.9  $\mu\text{mol}$ , 1.0 eq) was added a cooled solution of KOH (5 wt.% in MeOH, 1.8 mL) and the resulting solution was stirred at  $-18 ^\circ\text{C}$  for 4.5 h. The reaction mixture was then warmed to  $0 ^\circ\text{C}$  and stirred for an additional 3 h before it was quenched by addition of sat. aqueous ammonium chloride (4 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/ $\text{EtOAc}$  20/1) to afford allene-yne **188** (16.4 mg, 38.9  $\mu\text{mol}$ , 87%) as an orange oil. Due to the observed instability, allene-yne **188** was directly subjected to the subsequent Pauson-Khand reaction.

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (s, 1H), 6.71 (t,  $J = 6.8$  Hz, 1H), 5.27 (dd,  $J = 9.6, 3.8$  Hz, 1H), 5.22 (d,  $J = 6.8$  Hz, 2H), 3.90 (dd,  $J = 10.1, 3.9$  Hz, 1H), 3.68 – 3.59 (m, 2H), 3.12 (s, 1H), 0.94 (s, 9H), 0.35 (s, 9H), 0.11 (s, 6H) ppm.

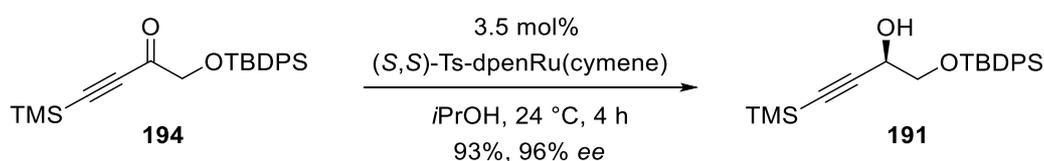
**Step 2:** To  $\text{Mo(CO)}_3\text{(MeCN)}_3^{115}$  (4.0 mg, 13.1  $\mu\text{mol}$ , 1.1 eq) was added a solution of allene-yne **188** (5.0 mg, 11.9  $\mu\text{mol}$ , 1.0 eq) in dry and degassed  $\text{CH}_2\text{Cl}_2$  (240  $\mu\text{l}$ ) and the dark orange solution was stirred at  $23 ^\circ\text{C}$  under a  $\text{N}_2$  atmosphere. After 2 h, the reaction mixture was filtered through a short pad of silica gel (*n*-pentane/ $\text{Et}_2\text{O}$  1/1) and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/ $\text{Et}_2\text{O}$  10/1) to afford indenylcyclopentenone **189** (1.4 mg, 3.12  $\mu\text{mol}$ , 26%) as a yellow oil.

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (s, 1H), 6.86 (s, 1H), 6.45 (s, 1H), 5.32 – 5.26 (m, 1H), 3.89 (dd,  $J = 10.2, 4.3$  Hz, 1H), 3.82 (t,  $J = 10.2$  Hz, 1H), 3.22 (s, 2H), 0.94 (s, 9H), 0.39 (s, 9H), 0.12 (s, 6H) ppm (the proton of the alcohol was not detected in  $\text{CDCl}_3$ );  $R_f = 0.28$  (*n*-pentane/ $\text{Et}_2\text{O}$  10/1).

**Ynone 194**

To a solution of trimethylsilylacetylene (7.08 mL, 51.1 mmol, 1.6 eq) in dry THF (80 mL) was added a solution of  $n\text{BuLi}$  (1.6 M in  $n$ -hexane, 28.9 mL, 46.2 mmol, 1.4 eq) at  $-78\text{ }^{\circ}\text{C}$  over 15 minutes, and the reaction was then stirred for a further 30 min at  $-78\text{ }^{\circ}\text{C}$ . In a second flask, Weinreb amide **193**<sup>124,125</sup> (11.8 g, 33.0 mmol, 1.0 eq) was dissolved in dry THF (120 mL) and cooled to  $-78\text{ }^{\circ}\text{C}$ . The solution of lithium trimethylsilylacetylide was slowly added over 30 min *via* cannula. The reaction mixture was allowed to warm to  $-15\text{ }^{\circ}\text{C}$  over 1.5 h, cooled to  $-78\text{ }^{\circ}\text{C}$ , and quenched by addition of glacial acetic acid (2.80 mL). The cooling bath was removed and the mixture was allowed to warm to  $-10\text{ }^{\circ}\text{C}$  before being poured onto a mixture of brine (100 mL) and  $\text{Et}_2\text{O}$  (100 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 70 mL), the combined organic layers were washed with brine (100 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure to afford ynone **194** (12.6 g, 31.9 mmol, 97%) as a pale yellow oil. The crude product was used in the next step without further purification.

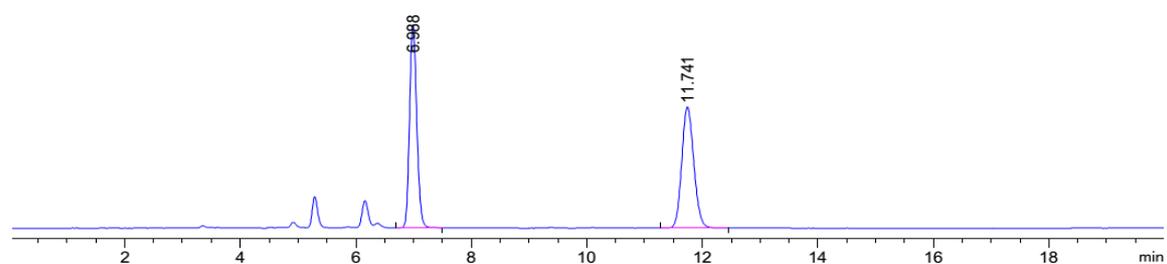
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.71 - 7.69 (m, 4H), 7.46 - 7.41 (m, 6H), 4.30 (s, 2H), 1.12 (s, 9H), 0.24 (s, 9H) ppm;  **$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 186.0, 135.5 (4C), 132.6 (2C), 129.9 (2C), 127.8 (4C), 101.3, 100.2, 70.3, 26.7 (3C), 19.3, -0.8 (3C) ppm; **IR (ATR)**:  $\tilde{\nu}$  = 3072, 3050, 2959, 2931, 2858, 2152, 1679, 1428, 1253, 1112, 1085, 845, 701, 504  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}-\text{C}_6\text{H}_5]^+ = [\text{C}_{17}\text{H}_{25}\text{O}_2\text{Si}_2]^+$ : 317.1388, found: 317.1393;  $R_f$  = 0.50 ( $n$ -pentane/ $\text{EtOAc}$  4/1).

**Propargylic alcohol 191**

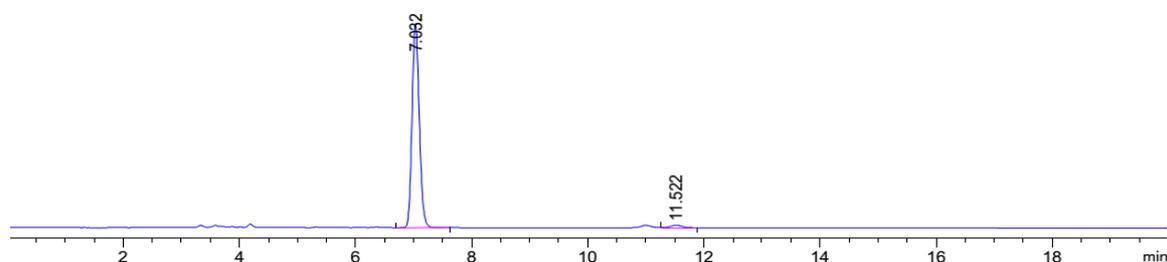
To a degassed solution of ynone **194** (6.71 g, 17.0 mmol, 1.0 eq) in dry  $i\text{PrOH}$  (113 mL) was added ( $S,S$ )-Ts-DpenRu(cymene) (0.366 g, 0.595 mmol, 3.5 mol%) (glovebox), and the

resulting brown reaction mixture was stirred at 24 °C under a N<sub>2</sub> atmosphere. After 4 h, the solvent was removed under reduced pressure (24 °C). The crude product was directly purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 20/1 to 10/1) to afford enantioenriched propargylic alcohol **191** (6.30 g, 15.9 mmol, 93%, 96% *ee*) as a pale yellow oil.

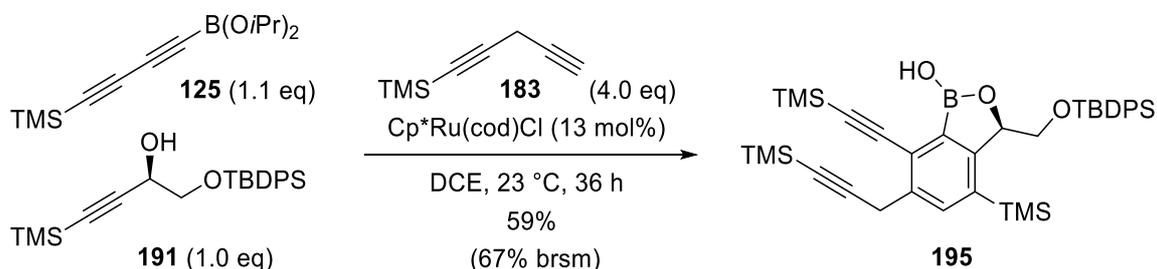
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.76 - 7.68 (m, 4H), 7.50 - 7.39 (m, 6H), 4.54 - 4.45 (m, 1H), 3.83 (dd, *J* = 10.0, 4.0 Hz, 1H), 3.76 (dd, *J* = 10.0, 6.5 Hz, 1H), 2.69 (br. s, 1H), 1.10 (s, 9H), 0.19 (s, 9H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ = 135.6 (2C), 135.5 (2C), 132.9, 132.7, 129.9 (2C), 127.8 (2C), 127.8 (2C), 103.5, 90.2, 67.3, 63.6, 26.7 (3C), 19.3, -0.2 (3C) ppm; IR (ATR):  $\tilde{\nu}$  = 3437, 3072, 3051, 2958, 2931, 2858, 1429, 1113, 843, 702, 613, 505 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M+Na]<sup>+</sup> = [C<sub>23</sub>H<sub>32</sub>NaO<sub>2</sub>Si<sub>2</sub>]<sup>+</sup>: 419.1833, found: 419.1833; [α]<sub>D</sub><sup>20</sup> = +15.0 (*c* = 1.0, CHCl<sub>3</sub>); *R*<sub>f</sub> = 0.45 (*n*-pentane/EtOAc 12/1); HPLC separation (Chiralpak IB, 4.6 x 250 mm; 1% *i*PrOH/*n*-hexane, 1.0 mL/min, 222 nm; t<sub>R</sub>(major) = 7.0 min, t<sub>R</sub>(minor) = 11.5 min), 96% *ee*.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.988	BB	0.1331	1942.31348	224.12758	50.0959
2	11.741	BB	0.2249	1934.87354	133.65933	49.9041



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.032	BB	0.1346	3689.16064	427.76920	98.1110
2	11.522	VB	0.2173	71.02924	5.01321	1.8890

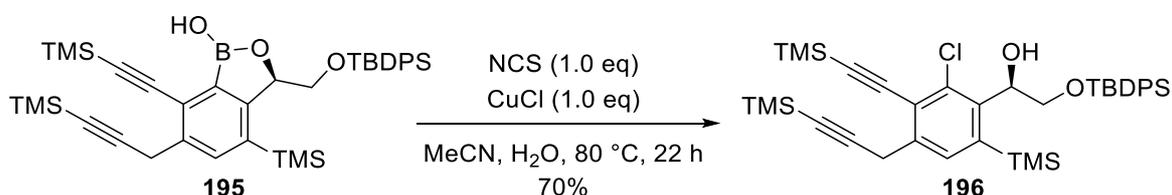
**Boraphthalide 195**

In a glovebox, diynylboronate **125** (1.54 g, 6.17 mmol, 1.1 eq) and propargylic alcohol **191** (2.33 g, 5.87 mmol, 1.0 eq) were loaded into a two-neck round-bottom flask. Dry Et<sub>2</sub>O (20 mL) was added and the solution was stirred at 23 °C under a N<sub>2</sub> atmosphere. After 4.5 h the solvent was removed under high vacuum to afford a pale brown oil, which was stirred under reduced pressure (1 mbar) for an additional 4.5 h. To this oil was added added  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (100 mg, 0.263 mmol, 4.5 mol%) (glovebox) and a degassed solution of diyne **183** (1.40 mL, 8.11 mmol, 1.3 eq) in dry DCE (59 mL). The mixture was stirred for 12 h at 23 °C under a N<sub>2</sub> atmosphere before an additional portion of  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (100 mg, 0.263 mmol, 4.5 mol%) and diyne **183** (1.40 mL, 8.11 mmol, 1.3 eq) in degassed DCE (2.0 mL each) were added. After 12 h of stirring at 23 °C, further  $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$  (95 mg, 0.250 mmol, 4.3 mol%) and diyne **183** (1.40 mL, 8.11 mmol, 1.3 eq) in degassed DCE (2.0 mL each) was added, and stirring was continued at 23 °C. After a total reaction time of 36 h, the solvent was removed under reduced pressure (25 °C), the black residue was taken up in Et<sub>2</sub>O (50 mL) and washed with 1 N aq. HCl (50 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 50 mL), the combined organic layers were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 60/1 to 10/1) in order to remove major impurities (predominately the trimerization product of **183** and ruthenium residues). Unreacted starting material was then separated from the target using a Biotage Isolera™ Four chromatographic isolation system under gradient elution (1% EtOAc to 10% EtOAc/*n*-pentane) to afford pure boraphthalide **195** (2.35 g, 3.46 mmol, 59%, 67% brsm) as a yellow foam along with unreacted propargylic alcohol **191** (283 mg, 0.71 mmol, 12%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.90 (s, 1H), 7.65 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.53 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.44 - 7.32 (m, 6H), 5.46 (dd, *J* = 5.0, 2.0 Hz, 1H), 5.39 (s, 1H), 4.16 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.91 - 3.79 (m, 2H), 3.63 (dd, *J* = 11.0, 5.0 Hz, 1H), 0.98 (s, 9H), 0.32 (s, 9H), 0.22

(s, 18H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 157.2, 137.2 (2C), 136.1, 135.7 (2C), 135.7 (2C), 134.8, 133.4, 133.1, 129.6, 129.5, 127.6 (2C), 127.6 (2C), 123.2, 103.6, 102.9, 102.2, 87.8, 82.6, 67.3, 26.6 (3C), 24.3, 19.2, 0.1 (3C), 0.1 (3C), -0.1 (3C) ppm; IR (ATR):  $\tilde{\nu}$  = 3595, 2957, 2931, 2857, 2179, 2145, 1546, 1435, 1343, 1250, 1113, 836, 760, 701  $\text{cm}^{-1}$ ; HRMS (ESI) calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{38}\text{H}_{54}\text{BO}_3\text{Si}_4]^+$ : 681.3238, found: 681.3240;  $[\alpha]_{\text{D}}^{20} = +6.0$  ( $c = 1.0$ ,  $\text{CHCl}_3$ );  $R_f = 0.55$  ( $n$ -pentane/EtOAc 12/1).

### Chlorobenzene 196

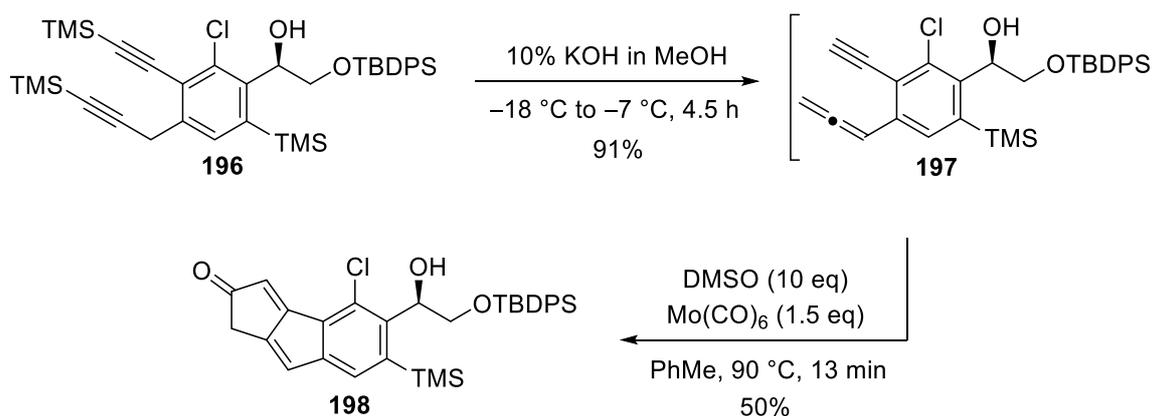


A two-neck round-bottom flask was charged with boraphthalide **195** (5.33 g, 7.83 mmol, 1.0 eq), NCS (1.05 g, 7.83 mmol, 1.0 eq) and copper(I) chloride (0.775 g, 7.83 mmol, 1.0 eq). The flask was placed under vacuum and backfilled with  $\text{N}_2$  (3 x). A degassed mixture of water (0.71 mL, 39.1 mmol, 5.0 eq) and acetonitrile (150 mL) was added and the resulting solution was stirred at 80 °C for 22 h. The reaction was cooled to ambient temperature, diluted with  $\text{Et}_2\text{O}$  (150 mL) and washed with 1 N aq. HCl (60 mL), 1 N aq. NaOH (60 mL) and brine (60 mL). The organic phase was dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/EtOAc 100/1 to 60/1) to afford chlorobenzene **196** (1.59 g, 2.31 mmol, 30%) as a yellow foam, along with unreacted boraphthalide **195** (3.30 g, 4.85 mmol, 62%). The re-isolated starting material was again subjected to the reaction conditions to afford chlorobenzene **196** (3.77 g, 5.47 mmol, 70% overall yield) after 5 consecutive chlorodeboronation steps.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.86 (s, 1H), 7.68 (dd,  $J = 7.8, 1.5$  Hz, 4H), 7.47 - 7.35 (m, 6H), 5.38 (dt,  $J = 9.7, 3.0$  Hz, 1H), 3.90 (dd,  $J = 10.3, 3.8$  Hz, 1H), 3.76 (s, 2H), 3.72 (t,  $J = 10.0$  Hz, 1H), 3.17 (d,  $J = 2.5$  Hz, 1H), 1.10 (s, 9H), 0.36 (s, 9H), 0.25 (s, 9H), 0.21 (s, 9H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 141.3, 140.4, 138.1, 135.5 (2C), 135.5 (2C), 133.9, 133.3, 132.9, 132.9, 129.9, 129.9, 127.8 (2C), 127.8 (2C), 123.4, 106.6, 102.9, 99.2, 88.3, 74.2,

66.0, 26.9 (3C), 25.4, 19.3, 2.4 (3C), 0.1 (3C), -0.1 (3C) ppm; **IR (ATR):**  $\tilde{\nu}$  = 3564, 2957, 2897, 2858, 2179, 1249, 1113, 842, 760, 701, 505  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{38}\text{H}_{53}^{35}\text{ClNaO}_2\text{Si}_4]^+$ : 711.2703, found: 711.2704;  $[\alpha]_{\text{D}}^{20} = +9.0$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_{\text{f}} = 0.30$  ( $n$ -pentane/EtOAc 60/1).

### Indenylcyclopentenone **198**



**Step 1:** To a solution of chlorobenzene **196** (425 mg, 0.616 mmol, 1.0 eq) in MeOH (6.2 mL) was added a solution of KOH (20 wt.% in MeOH, 6.2 mL, 17.5 mmol, 28 eq) at  $-18\text{ }^{\circ}\text{C}$  and the resulting mixture was stirred for 1.5 h and at  $-18\text{ }^{\circ}\text{C}$  and was then allowed to warm to  $-7\text{ }^{\circ}\text{C}$  over 3 h before the reaction was quenched by addition of sat. aqueous ammonium chloride (50 mL). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (3 x 30 mL), the combined organic layers were washed with brine (20 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/EtOAc 120/1 to 80/1) to afford allene-yne **197** (306 mg, 0.561 mmol, 91%) as an orange oil, which was directly subjected to the subsequent reaction conditions.

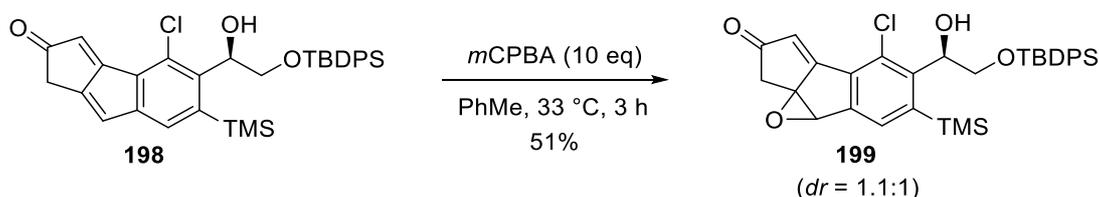
**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 – 7.58 (m, 5H), 7.38 – 7.27 (m, 6H), 6.59 (t,  $J = 6.8$  Hz, 1H), 5.29 (dd,  $J = 9.6, 3.4$  Hz, 1H), 5.11 (d,  $J = 6.8$  Hz, 2H), 3.82 (dd,  $J = 10.4, 3.8$  Hz, 1H), 3.63 (t,  $J = 10.3$  Hz, 1H), 3.53 (s, 1H), 3.09 (s, 1H), 1.03 (s, 9H), 0.25 (s, 9H) ppm;  $R_{\text{f}} = 0.45$  ( $n$ -pentane/ $\text{Et}_2\text{O}$  5/1).

**Step 2:** A two-neck round-bottom flask equipped with a reflux condenser was charged with  $\text{Mo}(\text{CO})_6$  (222 mg, 0.839 mmol, 1.5 eq). A degassed solution of allene-yne **197** and DMSO (397  $\mu\text{l}$ , 4.59 mmol, 10 eq) in dry toluene (10 mL) was added. The resulting yellow suspension was

placed in a pre-heated oil bath and stirred at 90 °C under a N<sub>2</sub> atmosphere. After 13 min the reaction mixture was cooled to 0 °C in an ice bath and was then directly purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 1/0 to 8/1 to 5/1) to afford indenylcyclopentenone **198** (161 mg, 0.281 mmol, 50% over 2 steps) as an orange foam.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.70 (ddd, *J* = 8.0, 3.9, 1.5 Hz, 4H), 7.48 – 7.37 (m, 6H), 7.34 (s, 1H), 6.79 (d, *J* = 1.7 Hz, 1H), 6.41 (d, *J* = 1.5 Hz, 1H), 5.39 (dd, *J* = 9.0, 4.8 Hz, 1H), 3.99 – 3.82 (m, 2H), 3.19 (d, *J* = 1.2 Hz, 2H), 3.15 (br. s, 1H), 1.11 (s, 9H), 0.37 (s, 9H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 207.0, 169.1, 147.5, 147.0, 143.1, 139.2, 135.6 (2C), 135.5 (2C), 132.8 (2C), 132.0, 129.9, 129.9, 129.6, 129.1, 127.8 (2C), 127.8 (2C), 126.7, 122.2, 74.0, 66.1, 35.4, 26.9 (3C), 19.3, 2.2 (3C) ppm; **IR (ATR):**  $\tilde{\nu}$  = 3517, 2952, 2893, 2857, 1712, 1605, 1428, 1248, 1112, 841, 738, 701, 505 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>33</sub>H<sub>38</sub><sup>35</sup>ClO<sub>3</sub>Si<sub>2</sub>]<sup>+</sup>: 573.2043, found: 573.2044; **[α]<sub>D</sub><sup>20</sup>** = – 50.9 (*c* = 0.9, CHCl<sub>3</sub>); **R<sub>f</sub>** = 0.57 (*n*-pentane/EtOAc 5/1).

### Indene epoxide **199**



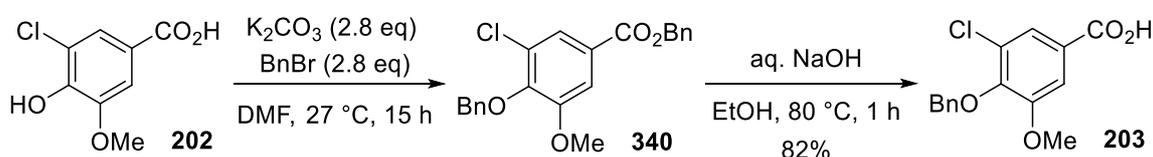
To a solution of indenylcyclopentenone **198** (20.0 mg, 34.9 μmol, 1.0 eq) in dry toluene (350 μL) was added *m*CPBA (95 wt.%, 63.4 mg, 349 μmol, 10 eq) and the resulting bright orange suspension was stirred at 33 °C. After 3 h, the almost colorless reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and washed sat. aqueous sodium thiosulfate/sodium bicarbonate (8 mL, 1/1). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 10/1) to afford a 1.1:1 diastereomeric mixture of indene epoxide **199** (10.4 mg, 17.5 μmol, 51%) as a white solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.73 (s, 1H), 7.71 – 7.66 (m, 4H), 7.47 – 7.37 (m, 6H), 6.75 (s, 1H), 5.41 (ddd, *J* = 9.5, 4.1, 1.9 Hz, 1H), 4.72 (s, 1H), 3.88 – 3.78 (m, 2H), 3.20 (d, *J* = 2.1 Hz, 1H), 3.02 (d, *J* = 19.0 Hz, 1H), 2.86 (d, *J* = 19.0 Hz, 1H), 1.11 (s, 9H), 0.38 (s, 9H) ppm;

**HRMS (ESI)** calc'd. for  $[M+H]^+ = [C_{33}H_{38}^{35}ClO_4Si_2]^+$ : 589.1992, found: 589.1995;  $R_f = 0.39$  (*n*-pentane/Et<sub>2</sub>O 3/1).

### 10.3 Synthesis of the $\beta$ -Amino Acid Fragment

#### Benzoic acid **203**



**Step 1:** To a solution of benzoic acid **202** (4.58 g, 22.6 mmol, 1.0 eq) and benzyl bromide (7.52 mL, 63.3 mmol, 2.8 eq) in dry DMF (68 mL) was added potassium carbonate (8.74 g, 63.3 mmol, 2.8 eq) and the resulting brown suspension was stirred at 27 °C for 15 h. The reaction mixture was then diluted with EtOAc (120 mL), washed with H<sub>2</sub>O (1 x 120 mL, 2 x 60 mL) and brine (60 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. Crude benzyl ester **340** was obtained as a brown solid and used in the next step without further purification.

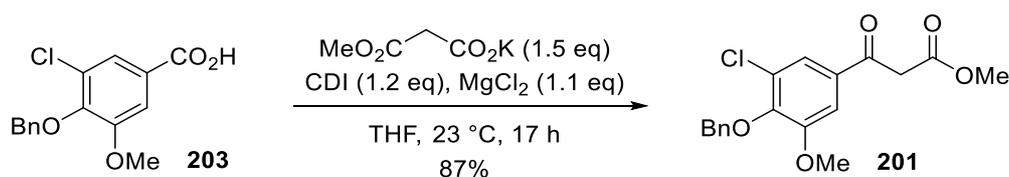
$R_f = 0.36$  (*n*-pentane/Et<sub>2</sub>O 5/1).

**Step 2:** To a solution of crude benzyl ester **340** (synthesized from 22.6 mmol benzoic acid **202**) in EtOH (35 mL) was added aqueous sodium hydroxide (2 M, 35 mL, 70.0 mmol, 3.1 eq) and the resulting brown suspension was stirred at 80 °C. After 1 h, the homogenous reaction mixture was cooled to 0 °C, followed by addition of conc. HCl (37%, 4 mL) and H<sub>2</sub>O (40 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL), the combined organic layers were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product (yellow solid) was thoroughly washed with pentane to afford known benzoic acid **203** (5.44 g, 18.6 mmol, 82% over 2 steps) as an off-white solid.<sup>207</sup>

<sup>207</sup> L. C. Raiford, W. S. Port, R. P. Perry, *J. Am. Chem. Soc.* **1949**, *71*, 3851-3851.

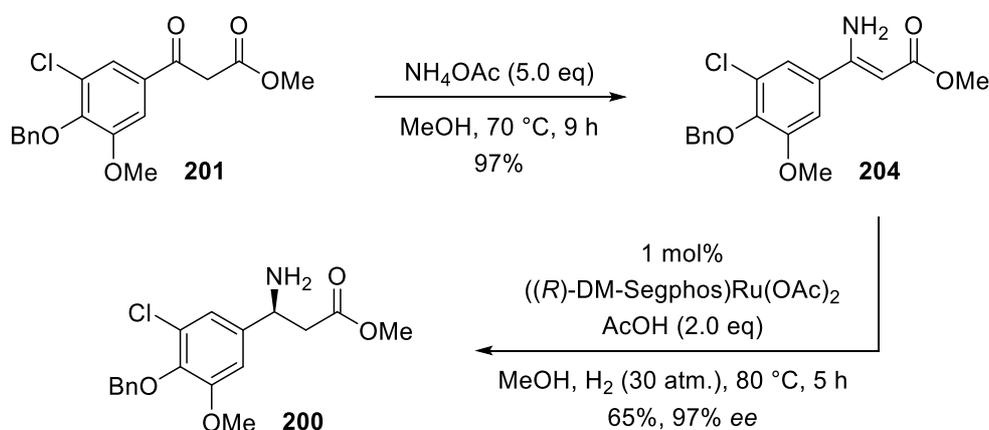
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.97 (s, 1H), 7.80 (d,  $J = 1.9$  Hz, 1H), 7.56 (d,  $J = 1.9$  Hz, 1H), 7.55 – 7.49 (m, 2H), 7.42 – 7.32 (m, 3H), 5.17 (s, 2H), 3.95 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.3, 153.7, 148.9, 136.6, 128.8, 128.5 (2C), 128.4 (2C), 128.3, 125.0, 124.6, 112.3, 75.0, 56.3 ppm;  $R_f = 0.33$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  20/1).

### $\beta$ -Keto ester **201**



Freshly dried  $\text{MgCl}_2$  (1.65 g, 17.4 mmol, 1.1 eq) and potassium 3-methoxy-3-oxopropanoate (3.87 g, 24.8 mmol, 1.5 eq) were suspended in dry THF (25 mL) and stirred at  $50\text{ }^\circ\text{C}$  for 4 h. In a separate flask, a solution of benzoic acid **203** (4.84 g, 16.5 mmol, 1.0 eq) in dry THF (40 mL) was cooled to  $0\text{ }^\circ\text{C}$  and CDI (3.22 g, 19.8 mmol, 1.2 eq) was added portionwise over 15 min. The suspension was allowed to warm to ambient temperature and stirred at  $23\text{ }^\circ\text{C}$  for 1.5 h before the resulting solution of the activated benzoic acid **203** was slowly added to the first suspension at  $23\text{ }^\circ\text{C}$  and stirring was continued for 17 h. The reaction was quenched by slow addition of aqueous HCl (1 M, 40 mL). The aqueous phase was extracted with EtOAc (3 x 30 mL), the combined organic layers were washed with brine (30 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 10/1 to 6/1) to afford  $\beta$ -keto ester **201** (5.02 g, 14.4 mmol, 87%) as a colorless oil and as a mixture of tautomers (5:1 in favor of the keto tautomer).

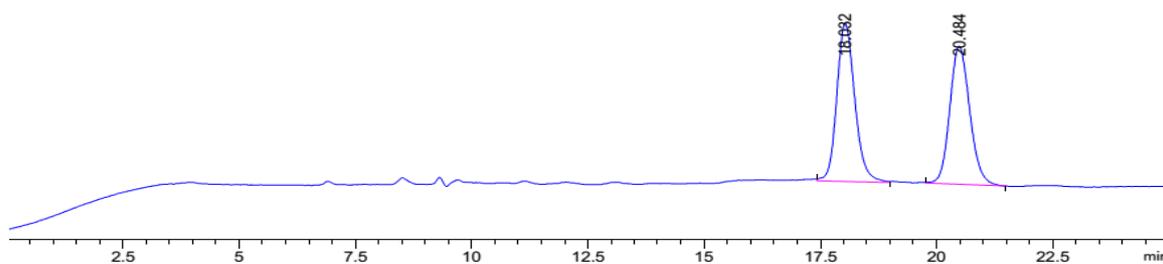
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  (keto tautomer) = 7.58 – 7.45 (m, 4H), 7.44 – 7.31 (m, 3H), 5.16 (s, 2H), 3.96 (s, 2H), 3.93 (s, 3H), 3.77 (s, 3H) ppm;  $\delta$  (enol tautomer) = 12.53 (s, 1H), 7.58 – 7.45 (m, 4H), 7.43 – 7.31 (m, 3H), 5.62 (s, 1H), 5.11 (s, 2H), 3.92 (s, 3H), 3.82 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  (keto tautomer) 190.4, 167.6, 154.0, 149.0, 136.5, 131.9, 128.4 (2C), 128.4 (2C), 128.3 (2C), 123.4, 110.3, 75.1, 56.3, 52.6, 45.4 ppm;  $\delta$  (enol tautomer) = 173.4, 169.8, 153.9, 146.6, 136.7, 129.6, 128.9, 128.5 (2C), 128.3 (2C), 128.2, 120.1, 108.6, 87.2, 75.0, 56.2, 51.6 ppm;  $R_f = 0.44$  (*n*-pentane/EtOAc 3/1).

**$\beta$ -Amino ester **200****

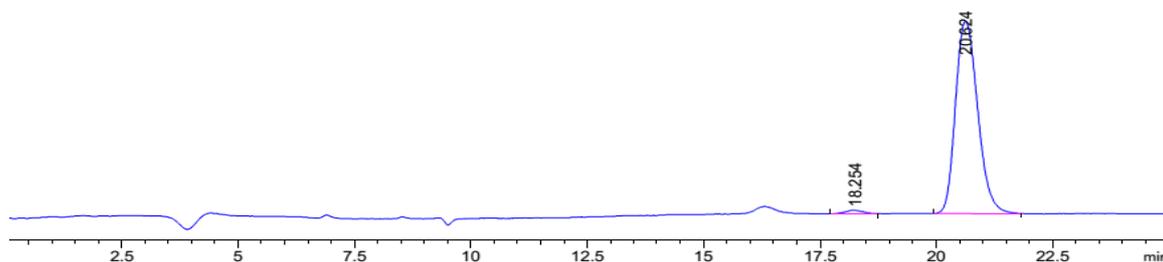
**Step 1:** A 100 mL round-bottom flask was charged with  $\beta$ -keto ester **201** 5.44 g, 15.6 mmol, 1.0 eq) and ammonium acetate (6.01 g, 78.0 mmol, 5.0 eq). Dry  $\text{MeOH}$  (31 mL) was added and the resulting solution was stirred at reflux. After 9 h, heating was stopped and the mixture was stirred at  $23\text{ }^\circ\text{C}$  for 20 h. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (50 mL) and washed with saturated aqueous sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure to afford enamine **204** (5.28 mg, 15.2 mmol, 97%) as a colorless oil, which was used in next step without further purification.

**Step 2:** A 20 mL microwave vial was charged with crude enamine **204** (1.12 g, 3.22 mmol, 1.0 eq) and  $((R)\text{-DM-Segphos})\text{Ru}(\text{OAc})_2$  (30.0 mg,  $32.2\text{ }\mu\text{mol}$ , 1.0 mol%). The vial was sealed with a rubber septum, placed under vacuum and backfilled with argon (3 x). Dry  $\text{MeOH}$  (3.2 mL) and acetic acid (368  $\mu\text{L}$ , 6.43 mmol, 2.0 eq) were added resulting in a deep green/black solution. The vial was placed in an autoclave and the rubber septum was pierced by two short cannula. The autoclave was closed and purged with  $\text{H}_2$  (3 x 10 atm.). Finally,  $\text{H}_2$  (30 atm.) was applied and the autoclave was heated to  $80\text{ }^\circ\text{C}$  under vigorous stirring. After 5 h, the autoclave was placed in an ice-bath and remaining  $\text{H}_2$  was released. The reaction mixture was diluted with  $\text{EtOAc}$  and washed with saturated aqueous sodium bicarbonate (30 mL). The aqueous phase was extracted with  $\text{EtOAc}$  (3 x 30 mL), the combined organic layers were washed with brine (30 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $\text{EtOAc}/\text{aq. NH}_3$  (25%) 100/1) to afford  $\beta$ -amino ester **200** (736 mg, 2.10 mmol, 65%, 97% ee) as a pale brown oil.

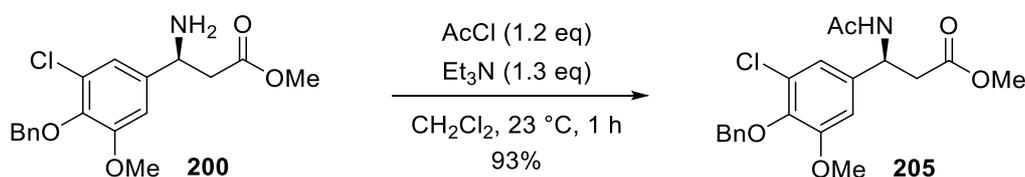
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.50 (m, 2H), 7.41 – 7.32 (m, 3H), 7.00 (d,  $J = 1.9$  Hz, 1H), 6.90 (d,  $J = 1.9$  Hz, 1H), 5.03 (s, 2H), 4.39 (t,  $J = 6.8$  Hz, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 2.68 (d,  $J = 6.6$  Hz, 2H), 1.83 (br. s, 2H) ppm;  $R_f = 0.15$  (EtOAc); **HPLC separation** (Chiralpak IC, 4.6 x 250 mm; 60% (*i*PrOH + 0.25% HNBu<sub>2</sub>)/*n*-hexane, 0.5 mL/min, 210 nm;  $t_R(\text{minor}) = 18.3$  min,  $t_R(\text{major}) = 20.6$  min), 97% *ee*.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.032	VV	0.4122	1.08618e4	403.29086	50.6623
2	20.484	VB	0.4577	1.05778e4	352.92209	49.3377

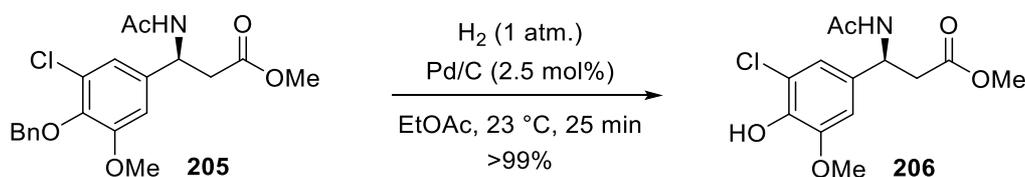


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.254	BV	0.3520	212.58754	7.33733	1.4863
2	20.624	BV	0.5260	1.40907e4	423.66135	98.5137

**$\beta$ -Acetamido ester 205**

To an ice-cooled solution of  $\beta$ -amino ester **200** (836 mg, 2.39 mmol, 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (19 mL) was added freshly distilled  $\text{Et}_3\text{N}$  (433  $\mu\text{L}$ , 3.11 mmol, 1.3 mL) and acetyl chloride (195  $\mu\text{L}$ , 2.75 mmol, 1.2 eq). The reaction mixture was stirred at 0  $^\circ\text{C}$  for 10 min before the cooling bath was removed and the mixture was allowed to warm to 23  $^\circ\text{C}$ . After 1 h, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (20 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 15 mL), the combined organic layers were washed with brine (15 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (EtOAc) to afford  $\beta$ -acetamido ester **205** (873 mg, 2.23 mmol, 93%) as a colorless oil.

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.50 (m, 2H), 7.41 – 7.31 (m, 3H), 6.90 (d,  $J = 2.0$  Hz, 1H), 6.78 (d,  $J = 2.0$  Hz, 1H), 6.58 (d,  $J = 8.4$  Hz, 1H), 5.35 (dt,  $J = 8.3, 5.8$  Hz, 1H), 5.01 (s, 2H), 3.86 (s, 3H), 3.66 (s, 3H), 2.89 (dd,  $J = 15.8, 5.8$  Hz, 1H), 2.82 (dd,  $J = 15.9, 5.8$  Hz, 1H), 2.06 (s, 3H) ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{20}\text{H}_{23}^{35}\text{ClNO}_5]^+$ : 392.1259, found: 392.1253;  $R_f = 0.33$  (EtOAc).

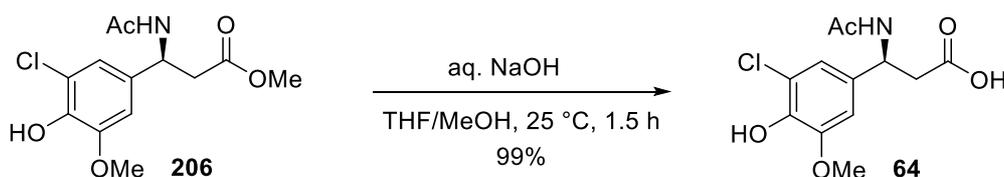
 **$\beta$ -tyrosine methyl ester 206**

A flask was charged with  $\beta$ -acetamido ester **205** (3.61 g, 9.21 mmol, 1.0 eq) and 10% Pd/C (245 mg, 230  $\mu\text{mol}$ , 2.5 mol%). The flask was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). EtOAc (60 mL) was added and the resulting black reaction mixture was stirred at 23  $^\circ\text{C}$  while getting saturated with dihydrogen by passing gaseous  $\text{H}_2$  (from a balloon) through the suspension for 10 min. The reaction mixture was stirred at 23  $^\circ\text{C}$  for an additional 15 min under a  $\text{H}_2$  atmosphere before the  $\text{H}_2$  balloon was removed and the reaction mixture was purged with

N<sub>2</sub> for 5 min in order to remove remaining H<sub>2</sub>. The suspension was then filtered through a short pad of Celite and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1.5/1 to 0/1) to afford  $\beta$ -tyrosine methyl ester **206** (2.78 g, 9.21 mmol, >99%) as a white solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.87 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 1.8 Hz, 1H), 6.62 (d, *J* = 7.2 Hz, 1H), 5.86 (s, 1H), 5.32 (dt, *J* = 8.0, 5.9 Hz, 1H), 3.89 (s, 3H), 3.65 (s, 3H), 2.89 (dd, *J* = 15.8, 5.8 Hz, 1H), 2.81 (dd, *J* = 15.8, 6.0 Hz, 1H), 2.04 (s, 3H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  171.6, 169.4, 147.5, 141.5, 132.8, 119.5, 119.2, 108.2, 56.4, 51.9, 49.2, 39.6, 23.4 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3274, 3069, 2953, 2845, 1730, 1650, 1504, 1428, 1285, 1174, 1050, 852, 730 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>13</sub>H<sub>17</sub><sup>35</sup>ClNO<sub>5</sub>]<sup>+</sup>: 302.0790, found: 302.0794; **[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = -70.3 (*c* = 1.0, CHCl<sub>3</sub>); **m.p.:** 97 - 99 °C; **R<sub>f</sub>** = 0.43 (EtOAc).

#### $\beta$ -Amino acid **64**



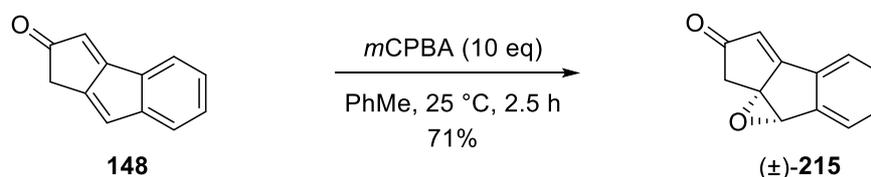
To a solution of  $\beta$ -tyrosine methyl ester **206** (500 mg, 1.66 mmol, 1.0 eq) in THF/MeOH (7.5 mL, v/v = 2/1) was added aqueous sodium hydroxide (2 M, 3.31 mL, 6.63 mmol, 4.0 eq) and the resulting mixture was stirred 25 °C for 90 min. The reaction mixture was then acidified with aqueous HCl (2 M, 5 mL) and stirred at 23 °C for an additional 20 min. The aqueous phase was then extracted with EtOAc (3 x 15 mL), the combined organic layers were washed with brine (15 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 12/1 + 1% AcOH) to afford  $\beta$ -amino acid **64** (473 mg, 1.64 mmol, 99%) as a white solid.

**<sup>1</sup>H NMR** (400 MHz, Methanol-*d*<sub>4</sub>) δ 6.89 (d, *J* = 1.9 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 5.23 (t, *J* = 7.4 Hz, 1H), 3.88 (s, 3H), 2.78 (dd, *J* = 15.6, 8.1 Hz, 1H), 2.72 (dd, *J* = 15.6, 6.8 Hz, 1H), 1.95 (s, 3H) ppm (the exchangeable phenol, amide and carboxylic acid protons were not detected in MeOH-*d*<sub>4</sub>); **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, Methanol-*d*<sub>4</sub>) δ 174.2, 172.5, 150.1, 143.6, 134.6, 121.3, 120.8, 110.0, 56.9, 51.3, 41.8, 22.8 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3335, 3083, 2940, 1713, 1610, 1546, 1505, 1427, 1286, 1188, 1050, 852 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>12</sub>H<sub>15</sub><sup>35</sup>ClNO<sub>5</sub>]<sup>+</sup>: 288.0623, found: 288.0629; **[α]<sub>D</sub><sup>20</sup>** = -80.3 (*c* = 1.0, MeOH); **m.p.:** 198 – 200 °C; **R<sub>f</sub>** = 0.30 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH 10/1/0.1).

## 10.4 Studies towards the Fijiolide A Aglycone

### 10.4.1 Intermolecular Etherification/ Macrolactonization Approach

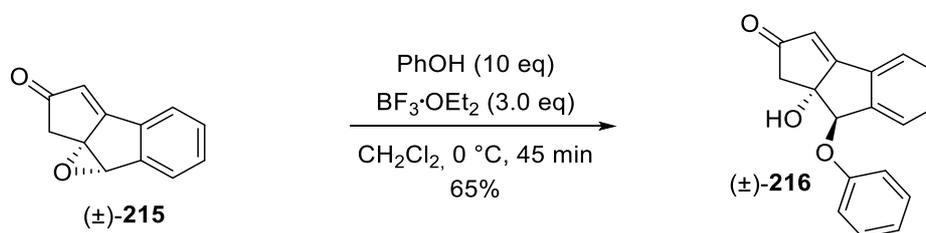
#### Model epoxide (±)-215



To a solution of indenylcyclopentenone **148**<sup>97</sup> (30.3 mg, 180 μmol, 1.0 eq) in dry toluene (1.8 mL) was added *m*CPBA (95%, 327 mg, 1.80 mmol, 10 eq) and the resulting suspension was stirred at 25 °C for 2.5 h. The reaction mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and poured into a mixture of saturated aqueous sodium thiosulfate/sodium bicarbonate (4 mL, 1/1). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 2/1) to afford model epoxide (±)-**215** (23.6 mg, 128 μmol, 71%) as an off-white solid.

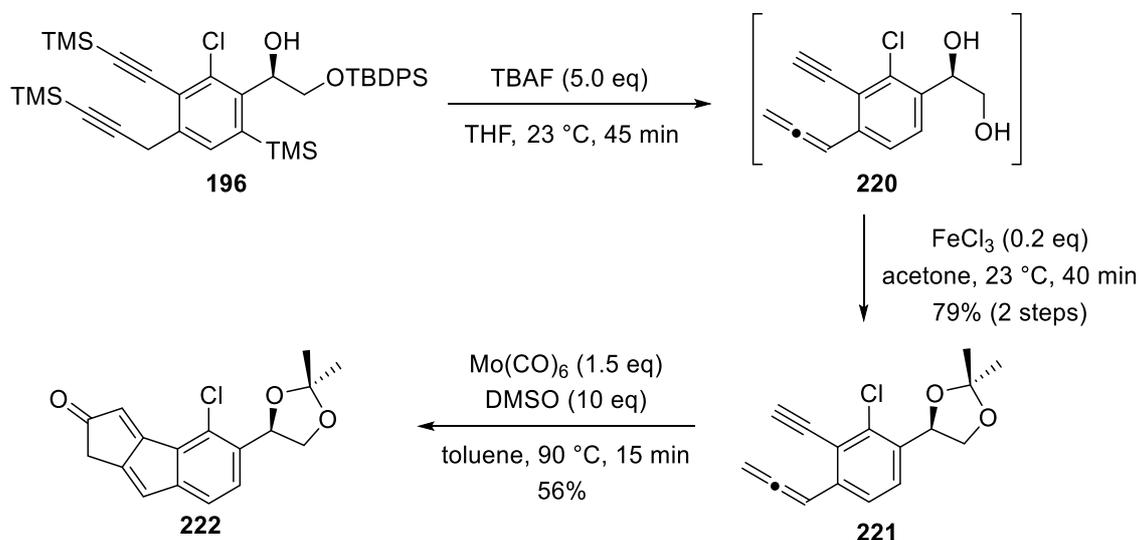
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.75 – 7.71 (m, 1H), 7.64 – 7.60 (m, 1H), 7.51 – 7.43 (m, 2H), 6.51 (s, 1H), 4.77 (s, 1H), 3.08 (d, *J* = 18.9 Hz, 1H), 2.91 (d, *J* = 18.9 Hz, 1H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 205.9, 170.9, 145.8, 133.2, 131.9, 129.6, 127.1, 126.1, 125.8, 69.3, 60.2, 36.5 ppm, **IR (ATR)**:  $\tilde{\nu}$  = 2924, 2852, 1709, 1632, 1457, 1389, 1331, 1194, 1116, 964, 856, 768, 732 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>12</sub>H<sub>9</sub>O<sub>2</sub>]<sup>+</sup>: 185.0597, found: 185.0592; **m.p.**: 103 - 106 °C; **R<sub>f</sub>** = 0.30 (*n*-pentane/Et<sub>2</sub>O 2/1).

### Phenol ether (±)-**216**



To an ice-cooled solution of epoxide (±)-**215** (1.8 mg, 10.0 μmol, 1.0 eq) and phenol (9.4 mg, 100 μmol, 10 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (200 μL) was added BF<sub>3</sub>•OEt<sub>2</sub> (7.92 μL, 30.0 μL, 3.0 eq) and the resulting solution was stirred at 0 °C for 45 min before being quenched by addition of saturated aqueous sodium bicarbonate (2 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 1.5/1 to 1/1) to afford phenol ether (±)-**216** (1.8 mg, 6.47 μmol, 65%) as a pale yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.79 (dd, *J* = 5.9, 2.8 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.34 (dd, *J* = 8.7, 7.4 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.01 – 6.97 (m, 2H), 6.31 (s, 1H), 5.55 (s, 1H), 2.84 (d, *J* = 17.3 Hz, 1H), 2.59 (d, *J* = 17.3 Hz, 1H) ppm (the tertiary alcohol was not detected in CDCl<sub>3</sub>); **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>18</sub>H<sub>15</sub>O<sub>3</sub>]<sup>+</sup>: 279.1016, found: 279.1026; **R<sub>f</sub>** = 0.34 (*n*-pentane/Et<sub>2</sub>O 1/1).

**Indenylcyclopentenone 222**

**Step 1:** To a stirred solution of chlorobenzene **196** (1.80 g, 2.61 mmol, 1.0 eq) in dry THF (26 mL) was slowly added a solution of TBAF (1 M in THF, 13.1 mL, 13.1 mmol, 5.0 eq). The reaction mixture instantaneously turned black and was stirred at 23 °C for 45 min before it was quenched by addition of sat. aqueous ammonium chloride (10 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure (25 °C). Crude allene-yne **220** was obtained as a brown oil and was used in the next step without further purification.

$R_f = 0.40$  (*n*-pentane/EtOAc 1/1).

**Step 2:** To a solution of crude allene-yne **220** (synthesized from 2.61 mmol **196**) in dry acetone (25 mL) was subsequently added FeCl<sub>3</sub> (85.0 mg, 0.522 mmol, 0.2 eq) and 4Å-MS. The resulting orange suspension was stirred at 23 °C for 40 min before the solvent was removed under reduced pressure (25 °C). The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 100/1 to 50/1 to 30/1) to afford allene-yne **221** (568 mg, 2.07 mmol, 79%) as a pale yellow oil, which was directly subjected to the subsequent reaction conditions.

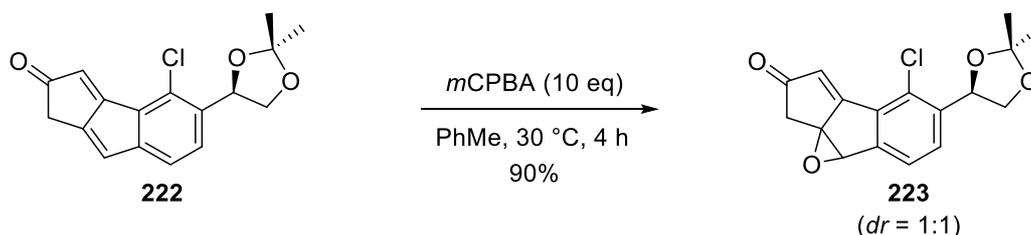
$R_f = 0.72$  (*n*-pentane/EtOAc 1/1).

**Step 3:** A two-neck round-bottom flask equipped with a reflux condenser was charged with Mo(CO)<sub>6</sub> (807 mg, 3.06 mmol, 1.5 eq). A degassed and over 4Å-MS dried solution of allene-yne **221** (560 mg, 2.04 mmol, 1.0 eq) and DMSO (1.45 mL, 20.4 mmol, 10 eq) in dry toluene

(14 mL) was added. The resulting yellow suspension was placed in a pre-heated oil bath and stirred at 90 °C under a N<sub>2</sub> atmosphere. After 15 min, the reaction mixture was cooled to 0 °C in an ice bath and was directly purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 8/1 to 4/1) to afford indenylcyclopentenone **222** (347 mg, 1.15 mmol, 56%) as an orange oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.63 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.45 (t, *J* = 6.9 Hz, 1H), 4.55 (dd, *J* = 8.3, 6.5 Hz, 1H), 3.67 (dd, *J* = 8.2, 7.3 Hz, 1H), 3.22 (d, *J* = 1.3 Hz, 2H), 1.59 (s, 3H), 1.53 (s, 3H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 206.8, 168.5, 148.9, 143.2, 135.4, 130.7, 130.3, 128.8, 128.4, 121.9, 120.2, 109.8, 74.4, 70.5, 35.3, 26.4, 25.6 ppm; **IR (ATR)**:  $\tilde{\nu}$  = 2986, 2935, 2877, 1711, 1608, 1381, 1372, 1226, 1157, 1104, 1066, 937, 851 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>17</sub>H<sub>16</sub><sup>35</sup>ClO<sub>3</sub>]<sup>+</sup>: 303.0782, found: 303.0784; [α]<sub>D</sub><sup>20</sup> = -190.5 (*c* = 1.0, CHCl<sub>3</sub>); **m.p.**: 78 - 81 °C; **R<sub>f</sub>** = 0.52 (*n*-pentane/EtOAc 5/1).

### Keto epoxide **223**

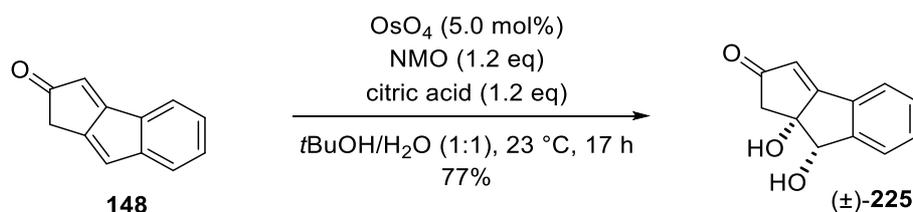


To a solution of indenylcyclopentenone **222** (31.8 mg, 105 μmol, 1.0 eq) in dry toluene (1.5 mL) was added *m*CPBA (95%, 191 mg, 1.05 mmol, 10 eq) and the resulting suspension was stirred at 30 °C for 4 h. The reaction mixture was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and poured into a mixture of saturated aqueous sodium thiosulfate/sodium bicarbonate (4 mL, 1/1). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. Crude keto epoxide **223** (90% by NMR, *dr* = 1:1) was obtained as a pale yellow oil and was used in the next step without further purification.

Characterization data for inseparable 1:1 mixture of diastereomers: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 3.3 Hz, 1H), 5.45 (q, *J* = 6.8 Hz, 1H), 4.79 (d, *J* = 2.6 Hz, 1H), 4.58 (ddd, *J* = 8.2, 6.7, 1.5 Hz, 1H), 3.65 (ddd, *J* = 14.4, 8.3, 7.1 Hz, 1H), 3.07 (dd, *J* = 18.9, 2.1 Hz, 1H), 2.90 (dd, *J* = 18.9, 1.5 Hz, 1H), 1.58 (s, 3H), 1.53

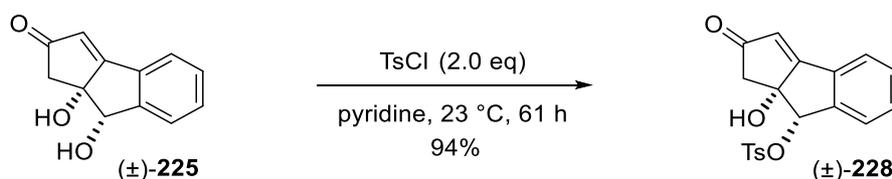
(s, 3H) ppm; **HRMS (ESI)** calc'd. for  $[M+H]^+ = [C_{17}H_{16}^{35}ClO_4]^+$ : 319.0732, found: 319.0727;  $R_f = 0.64$  (*n*-pentane/EtOAc 3/1).

### Diol ( $\pm$ )-225



To a solution of indenylcyclopentenone **148** (200 mg, 1.19 mmol, 1.0 eq) and citric acid (274 mg, 1.43 mmol, 1.2 eq) in *t*BuOH/H<sub>2</sub>O (12 mL, v/v = 1:1) was added a solution of OsO<sub>4</sub> (2.5 wt% in *t*BuOH, 0.746 mL, 59.4  $\mu$ mol, 5.0 mol%) and NMO (167 mg, 1.43 mmol, 1.2 eq). The resulting brown solution was stirred at 23 °C for 17 h before being quenched by addition of sat. aqueous sodium thiosulfate (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/1 to 1/2) to afford diol ( $\pm$ )-**225** as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 (d,  $J = 7.6$  Hz, 1H), 7.63 (d,  $J = 7.4$  Hz, 1H), 7.58 (t,  $J = 7.4$  Hz, 1H), 7.47 (t,  $J = 7.4$  Hz, 1H), 6.26 (s, 1H), 5.11 (d,  $J = 9.3$  Hz, 1H), 2.94 (d,  $J = 9.3$  Hz, 1H), 2.80 (d,  $J = 17.5$  Hz, 1H), 2.73 (d,  $J = 17.5$  Hz, 1H), 2.61 (s, 1H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  207.3, 175.2, 148.3, 132.9, 132.4, 129.5, 125.8, 125.4, 122.3, 86.3, 77.5, 47.4 ppm; **HRMS (ESI)** calc'd. for  $[M+H]^+ = [C_{12}H_{11}O_3]^+$ : 203.0703, found: 203.0700;  $R_f = 0.31$  (*n*-pentane/EtOAc 1/2).

### Tosylate ( $\pm$ )-228

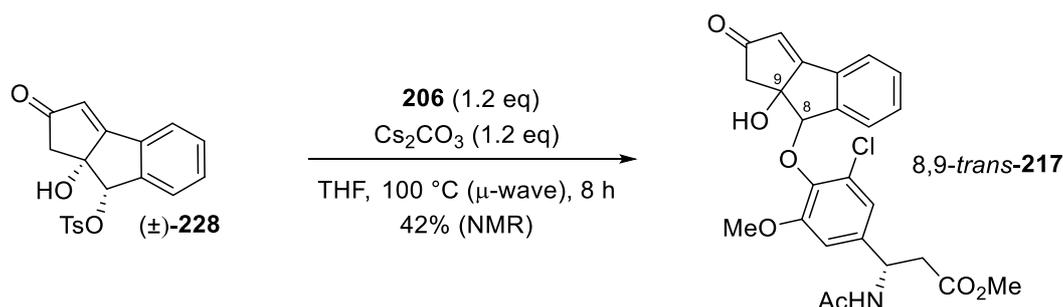


To a solution of diol ( $\pm$ )-**225** (90.0 mg, 0.445 mmol, 1.0 eq) in freshly distilled pyridine (5.5 mL) was added TsCl (170 mg, 0.890 mmol, 2.0 eq) and the resulting mixture was stirred at

23 °C. After 61 h, the reaction was quenched by addition of aqueous HCl (2 M, 20 mL) and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were washed with sat. aqueous CuSO<sub>4</sub> (15 mL) and sat. aqueous sodium bicarbonate (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 2/1 to 1/1) to afford model tosylate (±)-**228** (149 mg, 0.418 mmol, 94%) as a white solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.97 – 7.92 (m, 2H), 7.67 (d, *J* = 6.9 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.46 – 7.42 (m, 3H), 6.25 (s, 1H), 5.72 (s, 1H), 2.95 (s, 1H), 2.59 – 2.46 (m, 5H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 206.2, 173.0, 146.0, 142.1, 132.8, 132.7, 132.5, 130.4, 130.3 (2C), 128.2 (2C), 126.0, 125.5, 123.1, 86.2, 83.3, 48.0, 21.8 ppm; HRMS (ESI) calc'd. for [M+H]<sup>+</sup> = [C<sub>19</sub>H<sub>17</sub>O<sub>5</sub>S]<sup>+</sup>: 357.0791, found: 357.0801.

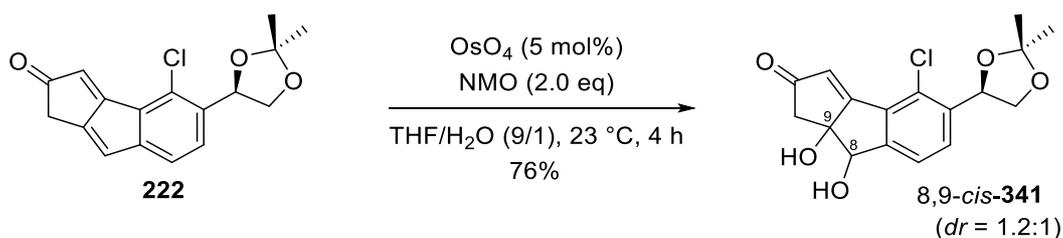
#### Aryl ether 8,9-*trans*-**217**



A microwave vial, equipped with a stir bar, was charged with tosylate (±)-**228** (5.0 mg, 14.0 μmol, 1.0 eq), β-tyrosine **206** (5.1 mg, 16.8 μmol, 1.2 eq) and Cs<sub>2</sub>CO<sub>3</sub> (11.0 mg, 32.6 μmol, 2.4 eq). The vial was sealed, placed under vacuum and backfilled with N<sub>2</sub> (3 x). Dry THF (250 μL) was added and the suspension was heated to 100 °C for 8 h under microwave irradiation. The resulting deep purple suspension was taken up in EtOAc (5 mL) and a solution of 1,3,5-TMB (0.01 M in EtOAc, 200 μL, 2.00 μmol) was added as internal standard. Aqueous pH 7 phosphate buffer (3 mL) was then added and the aqueous phase extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. After determination of the crude <sup>1</sup>H NMR yield (42%) the product was commonly purified with other batches of crude 8,9-*trans*-**217** by flash chromatography (*n*-pentane/EtOAc 1/2 to 1/4 to 0/1) to afford a 1:1 diastereomeric mixture of 8,9-*trans*-**217** as a colorless foam.

Characterization data for inseparable 1:1 mixture of diastereomers:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (d,  $J = 7.6$  Hz, 1H), 7.70 (d,  $J = 7.5$  Hz, 1H), 7.60 (t,  $J = 7.5$  Hz, 1H), 7.50 (t,  $J = 7.5$  Hz, 1H), 7.04 – 7.01 (m, 1H), 6.90 – 6.87 (m, 1H), 6.74 (d,  $J = 8.2$  Hz, 1H), 6.26 (s, 1H), 5.43 – 5.36 (m, 1H), 5.33 (s, 1H), 4.89 (s, 1H), 3.95 (s, 3H), 3.70 – 3.66 (m, 3H), 2.92 – 2.84 (m, 2H), 2.55 – 2.38 (m, 2H), 2.08 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  207.4, 207.4, 174.6, 174.5, 171.5, 171.5, 169.4 (2C), 152.9 (2C), 145.3 (2C), 142.9, 142.8, 139.0, 138.9, 133.1 (2C), 132.4 (2C), 129.6 (2C), 128.5 (2C), 126.5 (2C), 125.2 (2C), 122.7 (2C), 120.3, 120.2, 109 (2C), 88.1 (2C), 86.0 (2C), 56.3, 56.3, 52.1 (2C), 49.0, 48.9, 47.8 (2C), 39.4, 39.4, 23.4 (2C) ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{25}\text{H}_{25}^{35}\text{ClNO}_7]^+$ : 486.1314, found: 486.1316;  $R_f = 0.45$  (EtOAc).

### Diol 8,9-*cis*-341

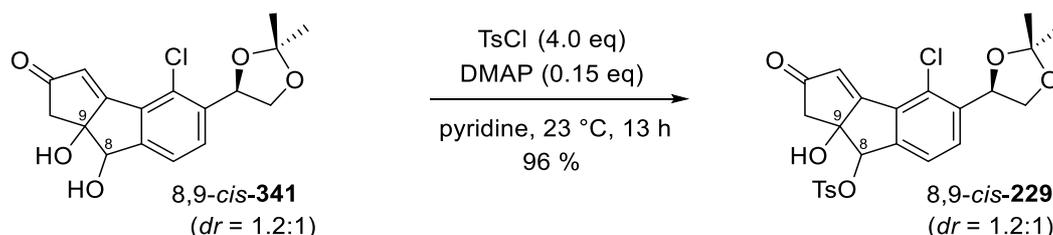


To a solution of indenylcyclopentenone **222** (300 mg, 0.991 mmol, 1.0 eq) in THF/ $\text{H}_2\text{O}$  (10 mL, v/v = 9/1) was added a solution of  $\text{OsO}_4$  (4 wt.% in  $\text{H}_2\text{O}$ , 315  $\mu\text{L}$ , 49.6  $\mu\text{mol}$ , 5.0 mol%) and NMO (232 mg, 1.98 mmol, 2.0 eq). The resulting brown solution was stirred at 23 °C for 4 h, and then directly subjected to flash chromatography (*n*-pentane/EtOAc 1/1 to 1/1.5). Mixed fraction were re-subjected to flash chromatography (*n*-pentane/EtOAc 1/1 to 1/1.5) to afford an inseparable 1.2:1 diastereomeric mixture of 8,9-*cis*-**341** (255 mg, 0.757 mmol, 76%) as an off-white amorphous solid.

Characterization data for inseparable 1.2:1 mixture diastereomers:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (d,  $J = 7.9$  Hz, 1H), 7.83 (d,  $J = 7.8$  Hz, 1H), 7.57 – 7.52 (m, 2H), 6.56 (s, 1H), 6.55 (s, 1H), 5.49 – 5.43 (m, 2H), 5.10 (s, 1H), 5.08 (s, 1H), 4.62 – 4.54 (m, 2H), 3.67 (ddd,  $J = 8.4, 7.2, 2.0$  Hz, 2H), 3.01 (br. s, 2H), 2.86 – 2.67 (m, 6H), 1.59 (s, 6H), 1.53 (s, 3H), 1.52 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  208.6, 208.6, 173.1, 173.0, 149.9, 149.9, 139.4, 139.4, 131.3, 131.3, 131.0, 131.0, 130.1, 130.0, 124.2, 124.1, 124.1, 124.1, 110.1, 110.0, 86.4, 86.2, 77.2, 77.1, 74.3 (2C), 70.1, 70.0, 47.1, 47.1, 26.2, 26.2, 25.4, 25.4 ppm; **IR (ATR):**  $\tilde{\nu} = 3395$ ,

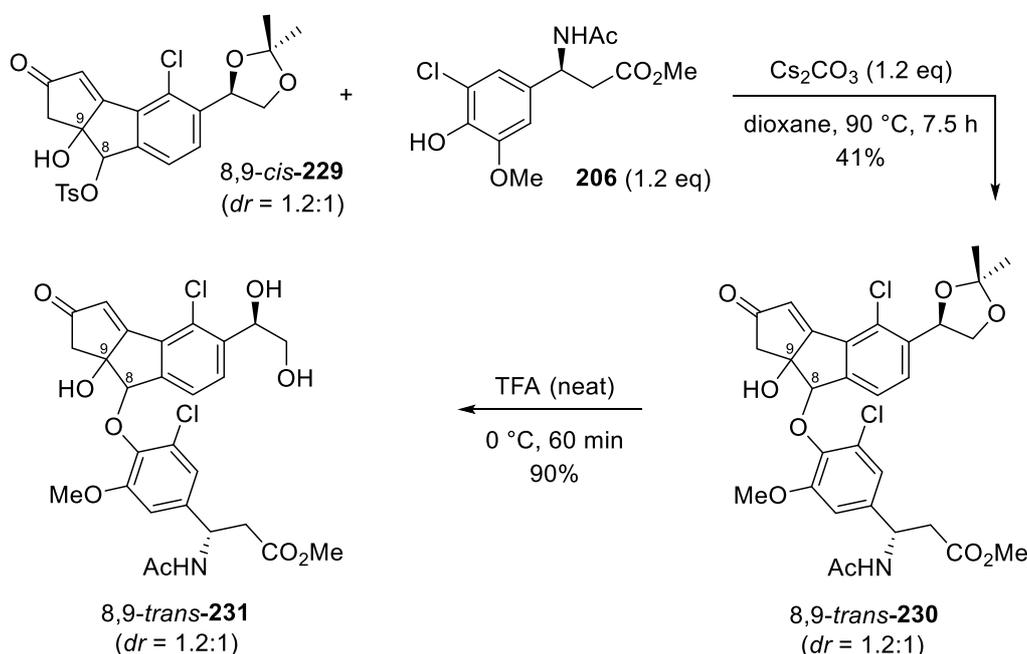
2986, 2935, 2880, 1707, 1626, 1376, 1241, 1202, 1156, 1062, 856, 692  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{17}\text{H}_{18}^{35}\text{ClO}_5]^+$ : 337.0837, found: 337.0840;  $R_f = 0.25$  (*n*-pentane/EtOAc 1/2).

### Tosylate 8,9-*cis*-229



To an ice-cooled solution of 8,9-*cis*-**341** (212 mg, 0.630 mmol, *dr* = 1.2:1, 1.0 eq) and DMAP (8.5 mg, 69.6  $\mu\text{mol}$ , 0.15 eq) in freshly distilled pyridine (5.0 mL) was added TsCl (480 mg, 2.52 mmol, 4.0 eq). The resulting yellow solution was allowed to warm to 23 °C and stirred for 13 h. The brown reaction mixture was cooled to 0 °C and quenched by addition of water (10 mL) and EtOAc (10 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with 2 M aq. HCl (2 x 10 mL) and brine (10 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 2/1) to afford an inseparable 1.2:1 diastereomeric mixture of tosylate 8,9-*cis*-**229** (297 mg, 0.605 mmol, 96 %) as an off-white solid.

Characterization data for inseparable 1.2:1 mixture diastereomers:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.3$  Hz, 4H), 7.79 (d,  $J = 8.0$  Hz, 2H), 7.44 (d,  $J = 8.1$  Hz, 4H), 7.34 (t,  $J = 8.1$  Hz, 2H), 6.56 (s, 1H), 6.56 (s, 1H), 5.71 (s, 1H), 5.68 (s, 1H), 5.43 (td,  $J = 6.8, 2.2$  Hz, 2H), 4.57 (td,  $J = 8.6, 6.8$  Hz, 2H), 3.67 – 3.58 (m, 2H), 2.93 (br. s, 2H), 2.60 – 2.43 (m, 10H), 1.57 (s, 3H), 1.56 (s, 3H), 1.51 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.0, 206.0, 169.7, 169.6, 146.2, 146.2, 143.3, 143.2, 141.3, 141.0, 132.3, 132.3, 131.6, 131.0, 130.9, 130.4, 130.3 (2C), 130.3 (4C), 128.2 (4C), 125.7, 125.5, 124.3, 124.2, 110.2 (2C), 86.4, 86.1, 82.9, 82.8, 74.4, 74.4, 70.1, 70.0, 47.8, 47.6, 26.3, 26.2, 25.5, 25.4, 21.8 (2C) ppm;  $R_f = 0.34$  (*n*-pentane/EtOAc 2/1).

**Triol 8,9-*trans*-231**

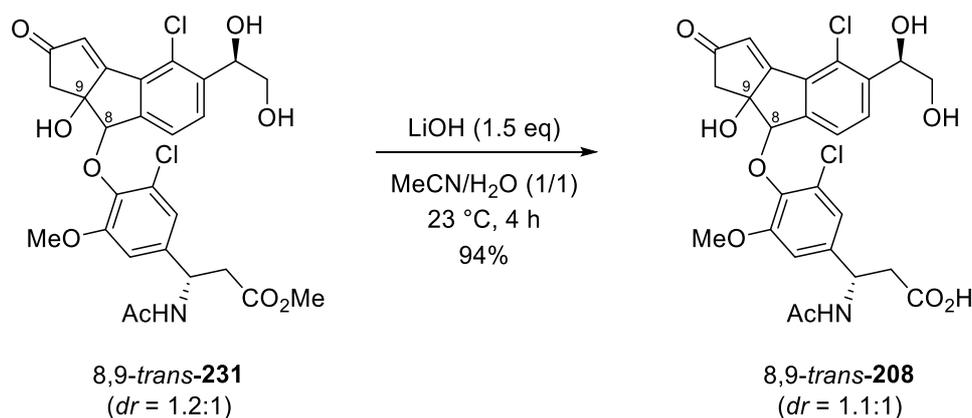
**Step 1:** A 20 mL microwave vial was charged with tosylate **8,9-*cis*-229** (315 mg, 0.642 mmol,  $dr = 1.2:1$ , 1.0 eq),  $\beta$ -tyrosine **206** (232 mg, 0.770 mmol, 1.2 eq) and  $\text{Cs}_2\text{CO}_3$  (251 mg, 0.770 mmol, 1.2 eq). The vial was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). Dry dioxane (6.4 mL) was added, the vial placed in a pre-heated oil bath and the heterogeneous reaction mixture was stirred at  $90^\circ\text{C}$  for 7.5 h. The resulting mixture was then allowed to cool to ambient temperature, taken up in EtOAc (20 mL) and quenched by addition of aqueous pH 7 phosphate buffer (15 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL), the combined organic layers were washed with brine (15 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 2/1 to 1/1 to EtOAc/MeOH 40/1 to 30/1) to afford an inseparable 1.2:1 diastereomeric mixture of arylether **8,9-*trans*-230** (348 mg, 46.6 wt.%, 0.261 mmol, 41%) as a gray solid, contaminated with inseparable unreacted  $\beta$ -tyrosine **206**.

**Steps 2:** To ice-cooled aryl ether **8,9-*trans*-230** (348 mg, 46.6 wt.%, 0.261 mmol,  $dr = 1.2:1$ , 1.0 eq) was added TFA (3.00 mL, 38.9 mmol, 149 eq) and the resulting brown reaction mixture was stirred at  $0^\circ\text{C}$  for 60 min before being diluted with  $\text{CH}_2\text{Cl}_2$  (20 mL) and quenched by addition of sat. aqueous sodium bicarbonate (30 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL) and the combined organic layers were washed with sodium bicarbonate

(15 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (EtOAc/MeOH 1/0 to 20/1) to afford an inseparable 1.2:1 diastereomeric mixture of triol 8,9-*trans*-**231** (137 mg, 0.236 mmol, 90%) as a pale yellow foam.

Characterization data for inseparable 1.2:1 mixture of diastereomers: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.93 (dd, *J* = 8.0, 2.7 Hz, 2H), 7.84 (dd, *J* = 7.9, 2.9 Hz, 2H), 7.02 (dd, *J* = 4.8, 1.7 Hz, 2H), 6.91 – 6.85 (m, 2H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.57 (s, 1H), 6.56 (s, 1H), 5.42 – 5.35 (m, 2H), 5.35 – 5.30 (m, 2H), 5.30 (s, 1H), 5.27 (s, 1H), 4.85 (br. s, 1H), 4.83 (br. s, 1H), 3.94 (s, 9H), 3.69 (s, 6H), 3.66 – 3.37 (m, 3H), 2.91 – 2.82 (m, 5H), 2.50 (dd, *J* = 17.3, 5.1 Hz, 2H), 2.43 – 2.34 (m, 3H), 2.08 (s, 6H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 207.5, 207.4, 171.4, 171.4 (2C), 171.3, 169.8, 169.8, 152.7, 152.7, 146.5 (2C), 142.6, 142.5, 140.4, 140.2, 139.2, 139.1, 131.8, 131.8, 131.8, 131.7, 130.3, 130.2, 128.3, 128.3, 125.1, 125.0, 124.8, 124.8, 120.3, 120.2, 109.5, 109.5, 87.7, 87.7, 86.2, 86.0, 70.8, 70.8, 66.0, 66.0, 56.3, 56.3, 52.1 (2C), 49.2, 49.1, 47.4, 47.4, 39.5, 39.5, 23.3 (2C) ppm; **IR (ATR):**  $\tilde{\nu}$  = 3313, 2952, 2874, 1712, 1630, 1487, 1422, 1267, 1229, 1176, 1049, 860, 731 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>27</sub>H<sub>28</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>9</sub>]<sup>+</sup>: 580.1136, found: 580.1139; **R<sub>f</sub>** = 0.46 (EtOAc/MeOH 10/1).

### Seco-acid 8,9-*trans*-**208**

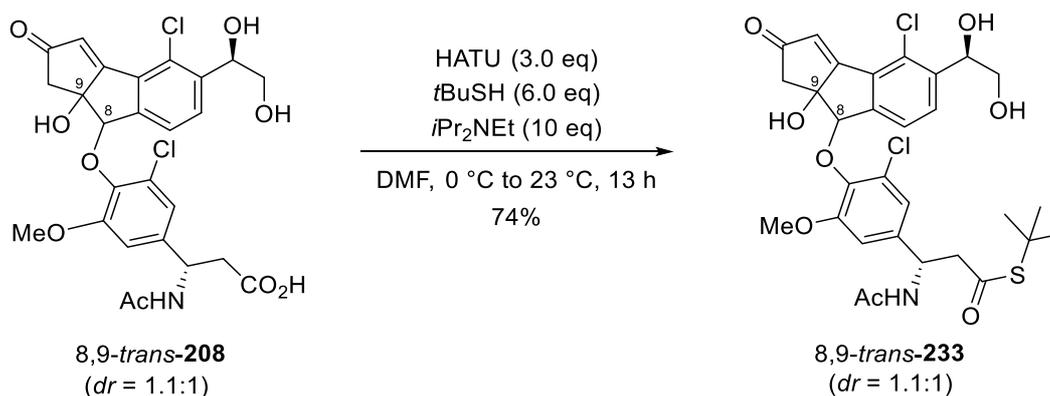


To a solution of triol 8,9-*trans*-**231** (137 mg, 0.236 mmol, *dr* = 1.2:1, 1.0 eq) in MeCN (2 mL) was added a solution of LiOH (8.5 mg, 0.354 mmol, 1.5 eq) in H<sub>2</sub>O (2 mL) and the resulting mixture was stirred at 23 °C. After 4 h, the reaction was quenched by addition of 2 M HCl (6 mL). The aqueous phase was extracted with EtOAc (8 x 10 mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The

crude product was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH 10/1/0 to 50/5/1) to afford an inseparable 1.1:1 diastereomeric mixture of *seco*-acid 8,9-*trans*-**208** (125 mg, 0.221 mmol, 94 %) as an off-white solid.

Characterization data for inseparable 1.1:1 mixture of diastereomers: <sup>1</sup>H NMR (400 MHz, Methanol-*d*<sub>4</sub>) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.86 (dd, *J* = 8.0, 2.4 Hz, 2H), 7.11 (s, 4H), 6.50 (s, 1H), 6.49 (s, 1H), 5.51 (s, 1H), 5.48 (s, 1H), 5.29 (t, *J* = 6.8 Hz, 2H), 5.26 – 5.21 (m, 2H), 3.97 (s, 6H), 3.79 – 3.76 (m, 1H), 3.76 – 3.73 (m, 1H), 3.60 – 3.57 (m, 1H), 3.55 (dd, *J* = 7.3, 1.1 Hz, 1H), 2.71 (d, *J* = 7.2 Hz, 4H), 2.63 (dd, *J* = 17.3, 4.9 Hz, 2H), 2.46 (d, *J* = 17.3 Hz, 2H), 1.98 (s, 3H), 1.98 (s, 3H) ppm (the exchangeable protons (OH, NH) were not detected in Methanol-*d*<sub>4</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, Methanol-*d*<sub>4</sub>) δ 210.4 (2C), 174.3, 174.2, 172.6 (2C), 154.3 (2C), 149.1, 149.0, 144.1, 144.1, 142.7, 142.7, 142.2, 142.1, 133.4 (2C), 133.3 (2C), 133.0, 133.0, 131.5 (2C), 129.0 (2C), 126.2, 126.1, 125.3, 125.2, 121.5, 121.4, 111.4 (2C), 88.9, 88.9, 88.2, 88.0, 72.1 (2C), 67.2 (2C), 56.9 (2C), 52.0 (2C), 50.0 (2C), 43.6 (2C), 22.8, 22.8 ppm; IR (ATR):  $\tilde{\nu}$  = 3300, 2926, 1707, 1627, 1487, 1418, 1269, 1219, 1045, 1017, 757, 731, 694 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M+H]<sup>+</sup> = [C<sub>26</sub>H<sub>26</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>9</sub>]<sup>+</sup>: 566.0979, found: 566.0974; *R*<sub>f</sub> = 0.43 (EtOAc/MeOH 1/1).

### Thioester 8,9-*trans*-**233**



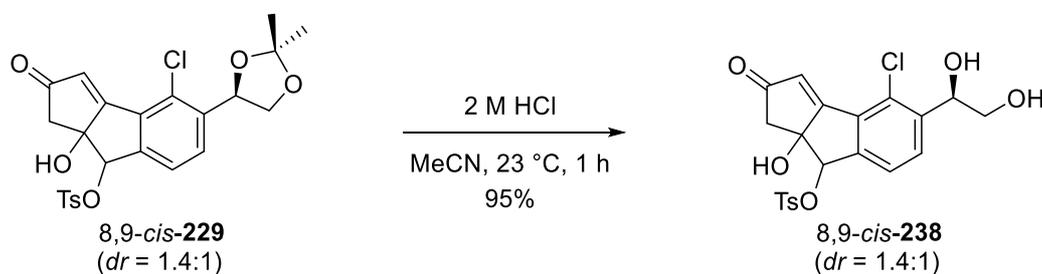
To an ice-cooled solution of *seco*-acid 8,9-*trans*-**208** (3.0 mg, 5.30 μmol, *dr* = 1.1:1, 1.0 eq) and HATU (6.0 mg, 15.9 μmol, 3.0 eq) in dry DMF (100 μL) was added a solution of *tert*-butyl mercaptan (3.58 μL, 31.8 μmol, 6.0 eq) in dry DMF (50 μL), followed by freshly distilled Hünig's base (9.25 μL, 53.0 μmol, 10 eq). The resulting reaction mixture was stirred and allowed to slowly warm to 23 °C. After 13 h, the reaction mixture was diluted with EtOAc

(5 mL) and quenched by addition of 0.5 M HCl (3 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organics layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 30/1 to 15/1) to afford an inseparable 1.1:1 diastereomeric mixture of thioester 8,9-*trans*-**233** (2.5 mg, 3.92 μmol, 74%) as a pale yellow oil.

Characterization data for inseparable 1.1:1 mixture of diastereomers: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.44 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 7.6 Hz, 2H), 7.85 (dd, J = 7.9, 3.5 Hz, 2H), 7.46 – 7.40 (m, 1H), 7.01 – 6.98 (m, 2H), 6.92 – 6.83 (m, 4H), 6.57 (s, 1H), 6.56 (s, 1H), 5.35 – 5.32 (m, 2H), 5.29 (s, 1H), 5.28 (s, 1H), 3.95 (s, 8H), 3.69 – 3.55 (m, 4H), 3.45 (s, 1H), 3.16 – 3.04 (m, 2H), 3.00 – 2.85 (m, 5H), 2.50 (dd, J = 17.3, 6.5 Hz, 2H), 2.37 (dd, J = 17.3, 2.1 Hz, 2H), 2.09 (s, 3H), 2.08 (s, 3H), 1.43 (s, 9H), 1.42 (s, 9H) ppm; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>30</sub>H<sub>34</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>8</sub>]<sup>+</sup>: 638.1377, found: 638.1382; **R<sub>f</sub>** = 0.37 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH 15/1).

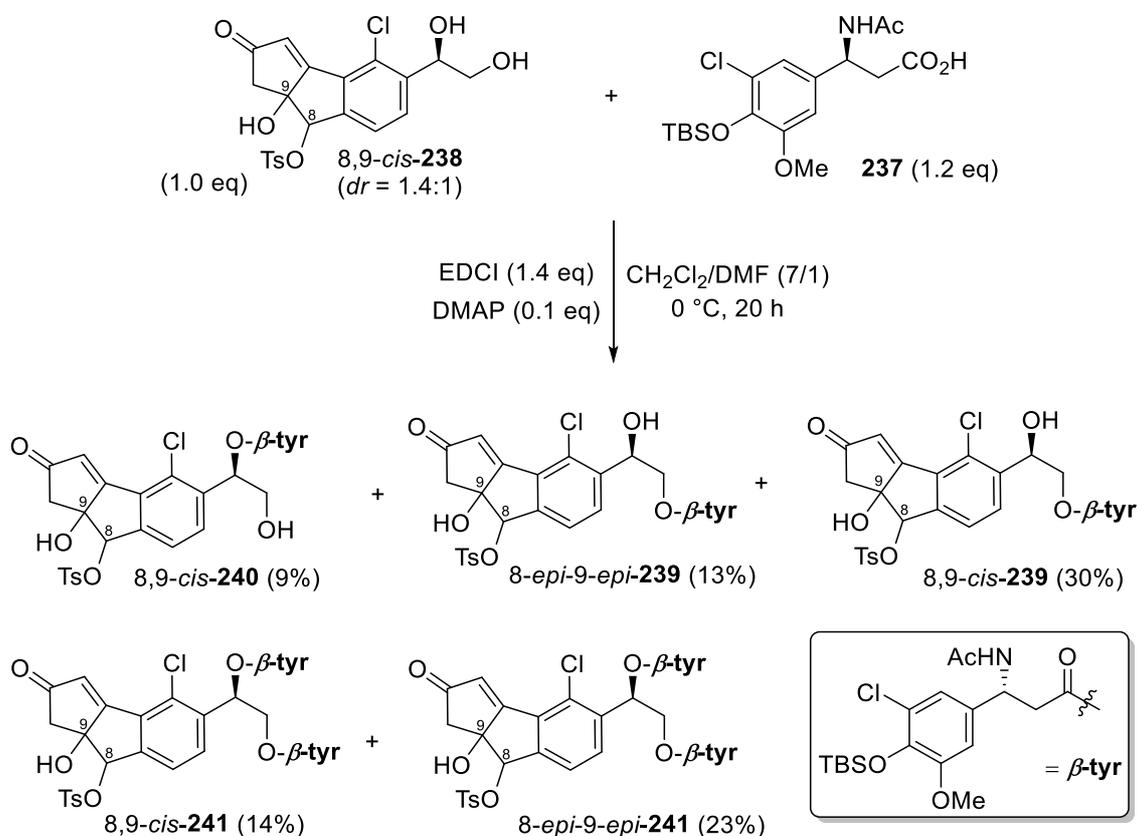
### 10.4.2 Intermolecular Esterification / Macroetherification Approach

#### Triol 8,9-*cis*-238



To a solution of acetone 8,9-*cis*-**229** (50.0 mg, 102  $\mu\text{mol}$ , *dr* = 1.4:1 1.0 eq) in MeCN (3.0 mL) was added aqueous HCl (2 M, 1.5 mL, 3.00 mmol, 30 eq) and the resulting colorless solution was stirred at 23 °C for 1 h. The reaction mixture was then diluted with EtOAc (10 mL) and quenched by addition of sat. aqueous sodium bicarbonate (8 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 3/1 to 2/1) to afford an inseparable 1.4:1 diastereomeric mixture of triol 8,9-*cis*-**238** (45.8 mg, 95 wt.%, 96.5  $\mu\text{mol}$ , 95%) as a white foam.

Characterization data for an inseparable 1:1 mixture of diastereomers:  **$^1\text{H}$  NMR** (400 MHz, Methanol- $d_4$ )  $\delta$  7.98 (d,  $J$  = 8.3 Hz, 4H), 7.80 (d,  $J$  = 8.0 Hz, 1H), 7.79 (d,  $J$  = 8.0 Hz, 1H), 7.51 (d,  $J$  = 8.2 Hz, 4H), 7.30 (d,  $J$  = 8.0 Hz, 1H), 7.29 (d,  $J$  = 8.0 Hz, 1H), 6.46 (s, 1H), 6.45 (s, 1H), 5.85 (s, 1H), 5.83 (s, 1H), 5.22 – 5.15 (m, 2H), 3.72 (dt,  $J$  = 11.4, 3.3 Hz, 2H), 3.52 (ddd,  $J$  = 11.5, 7.2, 2.0 Hz, 2H), 2.56 – 2.43 (m, 8H), 2.17 (dd,  $J$  = 17.5, 4.9 Hz, 2H) ppm (exchangeable alcohol protons were not detected in MeOH- $d_4$ );  **$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz, MeOD)  $\delta$  209.7 (2C), 173.9, 173.8, 147.4 (2C), 146.3, 146.3, 143.4, 143.3, 134.6 (2C), 133.6, 133.6, 132.9, 132.9, 131.8 (2C), 131.4 (4C), 129.7 (2C), 129.7 (2C), 125.1, 125.1, 125.0, 125.0, 87.7, 87.5, 84.2 (2C), 72.0, 72.0, 67.1, 67.1, 48.5 (2C), 21.8 (2C) ppm; **HRMS (ESI)** calc'd. for  $[\text{M-OH}]^+ = [\text{C}_{21}\text{H}_{18}^{35}\text{ClO}_6\text{S}]^+$ : 433.0507, found: 433.0514;  **$R_f$**  = 0.35 (*n*-pentane/EtOAc 1/4).

**Ester 8,9-cis-239**

A vial was charged with triol 8,9-cis-238 (35.0 mg, 77.6  $\mu$ mol, *dr* = 1.4:1, 1.0 eq),  $\beta$ -amino acid 237 (43.7 mg, 109  $\mu$ mol, 1.4 eq) and DMAP (0.9 mg, 7.76  $\mu$ mol, 0.1 eq). The vial was sealed, placed under vacuum, and backfilled with N<sub>2</sub> (3 x). Dry CH<sub>2</sub>Cl<sub>2</sub>/DMF (800  $\mu$ l, v/v = 7/1) was added and the resulting colorless solution was cooled with an ice bath. EDCI (20.8 mg, 109  $\mu$ mol, 1.4 eq) was then added and the homogenous solution was stirred at 0 °C for 20 h before being quenched by addition of sat. aqueous sodium bicarbonate (6 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/5 to 0/1) followed by preparative HPLC (Chromolith column, *n*-hexane/EtOAc 1/3 to 0/1, 25 mL/min, 254 nm) to afford ester 8,9-cis-239 (19.3 mg, 23.1  $\mu$ mol, 30%) as a white foam, along with ester 8-epi-9-epi-239 (8.5 mg, 10.2  $\mu$ mol, 13%) as a colorless foam, ester 8,9-cis-240 (6.1 mg, 7.31  $\mu$ mol, 9%) as a colorless oil, diester 8,9-cis-241 (13.4 mg, 11.0  $\mu$ mol, 14%) as a colorless foam, and diester 8-epi-9-epi-241 (21.7 mg, 17.8  $\mu$ mol, 23%) as a pale yellow foam.

**Ester 8,9-cis-239:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.3$  Hz, 2H), 7.84 (d,  $J = 8.0$  Hz, 1H), 7.43 (d,  $J = 8.0$  Hz, 2H), 7.36 (d,  $J = 7.9$  Hz, 1H), 6.85 (d,  $J = 2.0$  Hz, 1H), 6.67 (d,  $J = 2.0$  Hz, 1H), 6.54 (s, 1H), 6.14 (d,  $J = 8.4$  Hz, 1H), 5.69 (s, 1H), 5.40 (td,  $J = 8.9, 4.7$  Hz, 1H), 5.34 (dd,  $J = 7.2, 3.5$  Hz, 1H), 4.54 – 4.43 (m, 1H), 4.06 (br. s, 1H), 4.01 (dd,  $J = 11.3, 7.4$  Hz, 1H), 3.80 (s, 3H), 3.75 (br. s, 1H), 2.87 – 2.72 (m, 2H), 2.57 – 2.43 (m, 5H), 1.98 (s, 3H), 1.02 (s, 9H), 0.18 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.4, 170.3, 170.3, 170.2, 151.6, 146.1, 143.8, 141.5, 140.4, 133.1, 132.4, 132.2, 131.7, 130.7, 130.3 (2C), 128.2 (2C), 126.0, 125.4, 124.3, 119.1, 108.8, 86.3, 82.9, 67.9, 67.8, 55.5, 49.7, 47.8, 41.2, 25.8 (3C), 23.3, 21.8, 18.8, -4.1 (2C) ppm; **IR (ATR):**  $\tilde{\nu} = 3375, 2953, 2930, 2857, 1715, 1630, 1497, 1252, 1176, 1054, 1006, 909, 837, 734, 669$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{39}\text{H}_{46}^{35}\text{Cl}_2\text{NO}_{11}\text{SSi}]^+$ : 834.1932, found: 834.19.1939;  $[\alpha]_{\text{D}}^{20} = -85.3$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_f = 0.62$  (EtOAc).

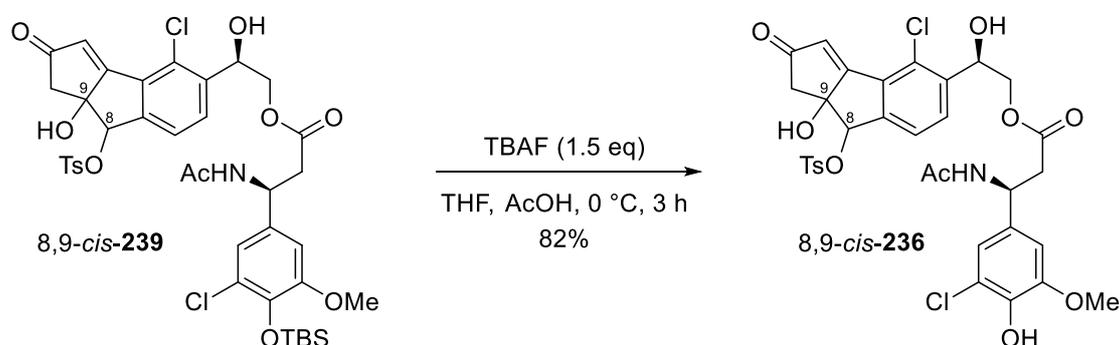
**Ester 8-epi-9-epi-239:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.3$  Hz, 2H), 7.83 (d,  $J = 8.0$  Hz, 1H), 7.44 (d,  $J = 8.0$  Hz, 2H), 7.36 (d,  $J = 7.9$  Hz, 1H), 6.87 (d,  $J = 2.0$  Hz, 1H), 6.70 (d,  $J = 2.0$  Hz, 1H), 6.56 (s, 1H), 6.21 (d,  $J = 8.8$  Hz, 1H), 5.68 (s, 1H), 5.52 – 5.43 (m, 1H), 5.27 (dd,  $J = 8.0, 2.4$  Hz, 1H), 4.50 (dd,  $J = 11.4, 2.7$  Hz, 1H), 4.16 (br. s, 1H), 3.93 (dd,  $J = 11.4, 8.1$  Hz, 1H), 3.81 (s, 3H), 3.31 (br. s, 1H), 2.88 – 2.79 (m, 2H), 2.50 (s, 3H), 2.49 (s, 2H), 2.05 (s, 3H), 1.03 (s, 9H), 0.19 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.2, 170.4, 170.2, 170.0, 151.7, 146.2, 143.7, 141.5, 140.2, 133.1, 132.3, 132.3, 131.6, 130.6, 130.3 (2C), 128.2 (2C), 126.0, 125.5, 124.3, 119.1, 108.9, 86.1, 82.9, 68.1, 67.8, 55.5, 49.6, 47.6, 41.1, 25.8 (3C), 23.4, 21.8, 18.8, -4.1 (2C) ppm; **IR (ATR):**  $\tilde{\nu} = 3352, 2929, 2857, 1716, 1630, 1497, 1252, 1177, 1054, 1006, 901, 839, 570$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{39}\text{H}_{46}^{35}\text{Cl}_2\text{NO}_{11}\text{SSi}]^+$ : 834.1932, found: 834.1935;  $R_f = 0.51$  (EtOAc).

**Ester 8,9-cis-240:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (d,  $J = 8.3$  Hz, 2H), 7.46 (d,  $J = 8.0$  Hz, 1H), 7.43 (d,  $J = 8.1$  Hz, 2H), 7.32 (d,  $J = 7.9$  Hz, 1H), 6.89 (d,  $J = 2.0$  Hz, 1H), 6.71 (d,  $J = 2.0$  Hz, 1H), 6.56 (s, 1H), 6.35 (d,  $J = 8.3$  Hz, 1H), 6.25 (dd,  $J = 6.5, 3.2$  Hz, 1H), 5.64 (s, 1H), 5.38 – 5.30 (m, 1H), 3.90 (dd,  $J = 12.4, 3.2$  Hz, 1H), 3.80 (s, 4H), 3.24 (br. s, 1H), 2.98 (dd,  $J = 15.5, 7.3$  Hz, 1H), 2.85 (dd,  $J = 15.5, 5.2$  Hz, 1H), 2.50 (s, 3H), 2.48 (s, 2H), 1.97 (s, 3H), 1.64 (br. s, 1H), 1.03 (s, 9H), 0.19 (s, 3H), 0.19 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.1, 169.9, 169.9, 169.7, 151.6, 146.2, 144.0, 141.4, 137.2, 133.5, 132.3, 132.0, 131.9, 131.2, 130.3 (2C), 128.2 (2C), 126.0, 125.7, 124.3, 119.1, 108.8, 86.1, 82.9, 73.5, 63.7, 55.5, 49.5, 47.6, 40.4, 25.8 (3C), 23.4, 21.8, 18.8, -4.1, -4.1 ppm; **IR (ATR):**  $\tilde{\nu} = 3342, 2930, 2857, 1715, 1632,$

1497, 1252, 1176, 1054, 839, 734, 668, 569  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{39}\text{H}_{46}^{35}\text{Cl}_2\text{NO}_{11}\text{SSi}]^+$ : 834.1932, found: 834.1930;  $R_f = 0.37$  (EtOAc).

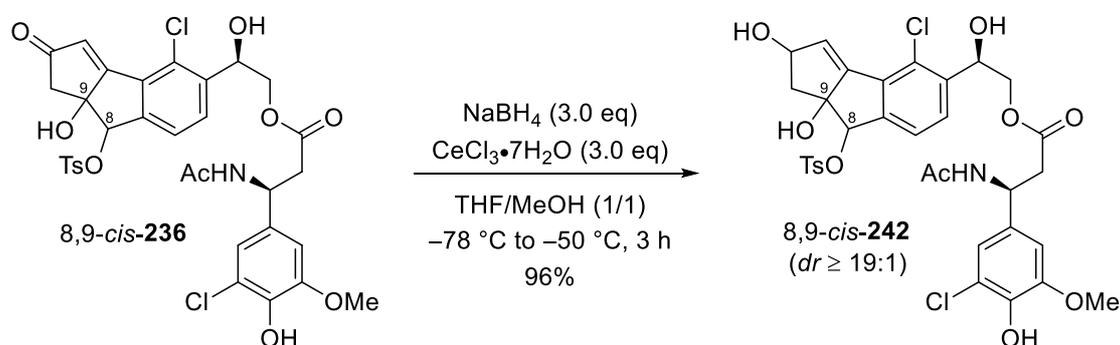
**Diester 8,9-cis-241:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.3$  Hz, 2H), 7.47 – 7.37 (m, 4H), 6.86 (d,  $J = 1.9$  Hz, 1H), 6.80 (d,  $J = 1.9$  Hz, 1H), 6.71 (d,  $J = 1.9$  Hz, 1H), 6.65 (d,  $J = 1.9$  Hz, 1H), 6.55 (s, 1H), 6.45 (d,  $J = 8.2$  Hz, 1H), 6.32 (t,  $J = 6.0$  Hz, 1H), 6.11 (d,  $J = 8.3$  Hz, 1H), 5.65 (s, 1H), 5.30 (q,  $J = 7.2$  Hz, 1H), 5.16 (q,  $J = 7.7$  Hz, 1H), 4.55 (br. s, 1H), 4.37 (dd,  $J = 11.5, 5.4$  Hz, 1H), 4.27 (dd,  $J = 11.5, 6.7$  Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.98 (dd,  $J = 15.8, 7.2$  Hz, 1H), 2.82 (dd,  $J = 16.0, 5.9$  Hz, 1H), 2.77 – 2.67 (m, 2H), 2.49 (s, 3H), 2.39 (s, 2H), 1.95 (s, 3H), 1.90 (s, 3H), 1.02 (s, 9H), 1.02 (s, 9H), 0.20 – 0.16 (m, 12H) ppm; **IR (ATR):**  $\tilde{\nu} = 3283, 2954, 2929, 2857, 1717, 1651, 1496, 1251, 1176, 1053, 908, 840, 733$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{57}\text{H}_{72}\text{Cl}_3\text{N}_2\text{O}_{15}\text{SSi}_2]^+$ : 1217.3252, found: 1217.3251;  $R_f = 0.38$  (EtOAc).

**Diester 8-epi-9-epi-241:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.92 (d,  $J = 8.2$  Hz, 2H), 7.48 – 7.40 (m, 3H), 7.35 (d,  $J = 7.9$  Hz, 1H), 6.88 (d,  $J = 1.5$  Hz, 1H), 6.83 (d,  $J = 1.6$  Hz, 1H), 6.73 – 6.71 (m, 1H), 6.70 – 6.68 (m, 1H), 6.64 (d,  $J = 7.4$  Hz, 1H), 6.54 (s, 1H), 6.43 (d,  $J = 8.2$  Hz, 1H), 6.32 (dd,  $J = 7.5, 3.2$  Hz, 1H), 5.66 (s, 1H), 5.34 – 5.21 (m, 2H), 4.37 (dd,  $J = 11.9, 3.2$  Hz, 1H), 4.19 (dd,  $J = 12.0, 7.7$  Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.55 (br. s, 1H), 2.97 (dd,  $J = 15.9, 7.6$  Hz, 1H), 2.86 – 2.71 (m, 3H), 2.49 (s, 3H), 2.46 (s, 2H), 2.01 (s, 3H), 1.94 (s, 3H), 1.02 (s, 9H), 1.02 (s, 9H), 0.18 (s, 6H), 0.17 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  **NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.1, 170.3, 169.7, 169.6, 169.6, 169.5, 151.5, 151.5, 146.2, 144.6, 141.2, 141.2, 136.1, 133.7, 133.5, 132.3, 132.2, 131.9 (2C), 131.3, 130.3 (2C), 128.2 (2C), 125.8, 125.8 (2C), 124.5, 119.1, 119.1, 108.9 (2C), 86.2, 82.8, 70.0, 64.1, 55.4 (2C), 49.2, 49.1, 47.6, 39.8, 39.7, 25.8 (6C), 23.3, 23.3, 21.8, 18.8, -4.0 (2C), -4.1 (2C) ppm; **IR (ATR):**  $\tilde{\nu} = 3293, 2930, 2857, 1651, 1492, 1251, 1176, 1148, 1053, 908, 840, 733$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{57}\text{H}_{72}\text{Cl}_3\text{N}_2\text{O}_{15}\text{SSi}_2]^+$ : 1217.3252, found: 1217.3250;  $R_f = 0.33$  (EtOAc).

**Cyclization precursor 8,9-*cis*-236**

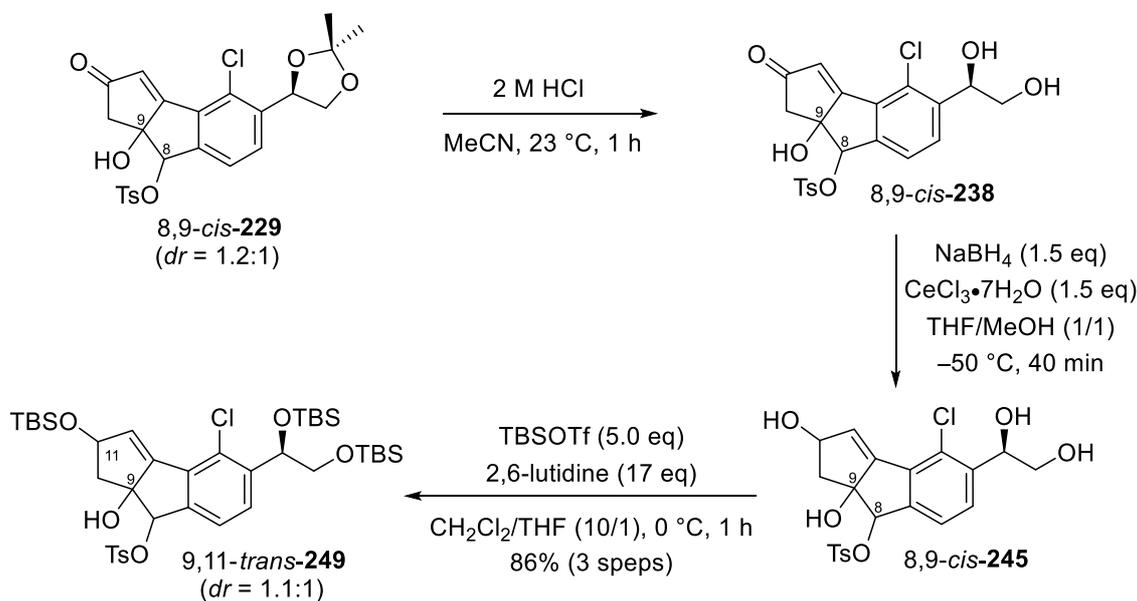
To an ice-cooled solution of ester 8,9-*cis*-**239** (19.3 mg, 23.1  $\mu\text{mol}$ , 1.0 eq) and glacial acetic acid (35.0  $\mu\text{l}$ , 0.612 mmol, 26 eq) in dry THF (1.0 mL) was added a solution of TBAF (1.0 M in THF, 34.7  $\mu\text{l}$ , 34.7  $\mu\text{mol}$ , 1.5 eq) and the resulting colorless reaction mixture was stirred at 0  $^\circ\text{C}$  for 3 h before being quenched by addition of aqueous pH 7 phosphate buffer (3 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/3 to 0/1) to afford cyclization precursor 8,9-*cis*-**236** (13.7 mg, 19.0  $\mu\text{mol}$ , 82%) as a pale yellow oil.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J$  = 8.3 Hz, 2H), 7.80 (d,  $J$  = 8.0 Hz, 1H), 7.44 (d,  $J$  = 8.0 Hz, 2H), 7.35 (d,  $J$  = 8.4 Hz, 1H), 6.84 (d,  $J$  = 1.8 Hz, 1H), 6.69 (d,  $J$  = 1.9 Hz, 1H), 6.54 (s, 1H), 6.15 (d,  $J$  = 8.7 Hz, 1H), 5.93 (s, 1H), 5.68 (s, 1H), 5.41 – 5.31 (m, 2H), 4.47 (dd,  $J$  = 11.4, 3.7 Hz, 1H), 4.05 (dd,  $J$  = 11.4, 7.0 Hz, 1H), 3.89 (s, 3H), 3.87 – 3.81 (m, 1H), 3.73 (s, 1H), 2.87 – 2.73 (m, 2H), 2.54 – 2.43 (m, 5H), 1.99 (s, 3H) ppm;  **$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.3, 170.3, 170.2, 170.1, 147.6, 146.2, 143.8, 141.8, 140.3, 132.3, 132.3, 132.1, 131.7, 130.8, 130.3, 128.2, 125.5, 124.3, 119.7, 119.1, 108.2, 86.3, 82.9, 67.8 (2C), 56.5, 49.6, 47.8, 41.0, 23.3, 21.8 ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{33}\text{H}_{31}^{35}\text{Cl}_2\text{NNaO}_{11}\text{S}]^+$ : 742.0887, found: 742.0868;  **$[\alpha]_D^{20}$**  =  $-90.0$  ( $c$  = 0.3,  $\text{CHCl}_3$ );  **$R_f$**  = 0.29 (EtOAc).

**Cyclization precursor 8,9-*cis*-242**

To a suspension of keto ester 8,9-*cis*-**236** (5.5 mg, 7.63  $\mu\text{mol}$ , 1.0 eq) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (4.3 mg, 11.5  $\mu\text{mol}$ , 1.5 eq) in dry THF/MeOH (0.4 mL, v/v = 1/1) was added  $\text{NaBH}_4$  (0.4 mg, 11.5  $\mu\text{mol}$ , 1.5 eq) at  $-78\text{ }^\circ\text{C}$  and the resulting mixture was stirred for 2 h, maintaining a cooling-bath temperature of  $-78\text{ }^\circ\text{C}$  to  $-65\text{ }^\circ\text{C}$ . An additional portion of  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (4.3 mg, 11.5  $\mu\text{mol}$ , 1.5 eq) and  $\text{NaBH}_4$  (0.4 mg, 11.5  $\mu\text{mol}$ , 1.5 eq) was then added and stirring was continued for 1 h while the cooling-bath was allowed to warm to  $-50\text{ }^\circ\text{C}$ . The reaction was then quenched by addition of acetone (0.2 mL), followed by addition of aqueous pH 7 phosphate buffer (3.0 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  15/1) to afford diastereomerically pure cyclization precursor 8,9-*cis*-**242** (5.3 mg, 7.33  $\mu\text{mol}$ , 96%) as a colorless oil.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.4$  Hz, 2H), 7.55 (d,  $J = 8.0$  Hz, 1H), 7.44 (d,  $J = 8.0$  Hz, 2H), 7.16 (d,  $J = 8.4$  Hz, 1H), 6.85 (d,  $J = 1.8$  Hz, 1H), 6.69 (d,  $J = 1.9$  Hz, 1H), 6.38 (d,  $J = 1.5$  Hz, 1H), 6.18 (d,  $J = 8.7$  Hz, 1H), 5.92 (s, 1H), 5.59 (s, 1H), 5.58 (br. s, 1H), 5.41 (td,  $J = 8.1, 5.4$  Hz, 1H), 5.30 – 5.24 (m, 1H), 4.45 (dd,  $J = 11.4, 3.2$  Hz, 1H), 3.99 (dd,  $J = 11.5, 7.3$  Hz, 1H), 3.90 (s, 3H), 3.79 – 3.71 (m, 1H), 3.50 (s, 1H), 2.92 (s, 1H), 2.88 – 2.77 (m, 2H), 2.50 (s, 4H), 2.03 (s, 3H), 1.73 (dd,  $J = 13.2, 6.6$  Hz, 1H) ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{33}\text{H}_{33}^{35}\text{Cl}_2\text{NNaO}_{11}\text{S}]^+$ : 744.1044, found: 744.1039;  $R_f = 0.15$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  15/1).

**Tris-silyl ether 9,11-trans-249**

**Steps 1:** To a solution of acetonide **8,9-cis-229** (75.0 mg, 153  $\mu\text{mol}$ ,  $dr = 1.2:1$ , 1.0 eq) in MeCN (4.0 mL) was added aqueous HCl (2 M, 2.0 mL, 4.00 mmol, 26 eq) and the resulting colorless solution was stirred at 23  $^\circ\text{C}$  for 1 h. The reaction mixture was then diluted with EtOAc (10 mL) and quenched by addition of sat. aqueous sodium bicarbonate (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. Crude keto triol **8,9-cis-238** was obtained as an off-white solid and was used in the next step without further purification.

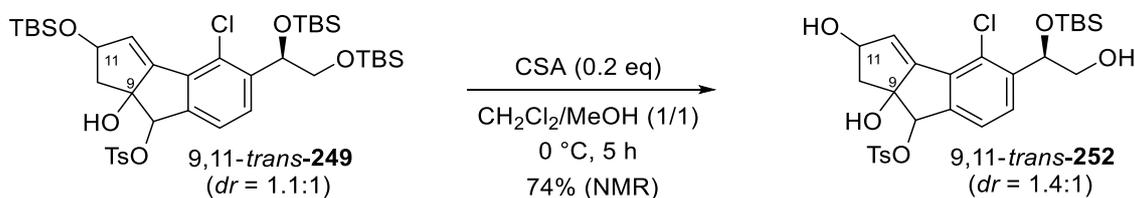
$R_f = 0.35$  ( $n$ -pentane/EtOAc 1/4).

**Steps 2:** To a solution of crude keto triol **8,9-cis-238** (synthesized from 153  $\mu\text{mol}$  **8,9-cis-229**) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (85.5 mg, 230  $\mu\text{mol}$ , 1.5 eq) in dry THF/MeOH (5.0 mL, v/v = 1/1) was added  $\text{NaBH}_4$  (8.7 mg, 230  $\mu\text{mol}$ , 1.5 eq) at  $-50 \text{ } ^\circ\text{C}$  and the resulting mixture was stirred for 40 min before being quenched by addition of acetone (0.2 mL). The reaction mixture was allowed to warm to ambient temperature over 15 min before aqueous pH 7 phosphate buffer (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. Crude tetrol **8,9-cis-245** was obtained as an off-white solid and used in the next step without further purification.

$R_f = 0.36$  (EtOAc).

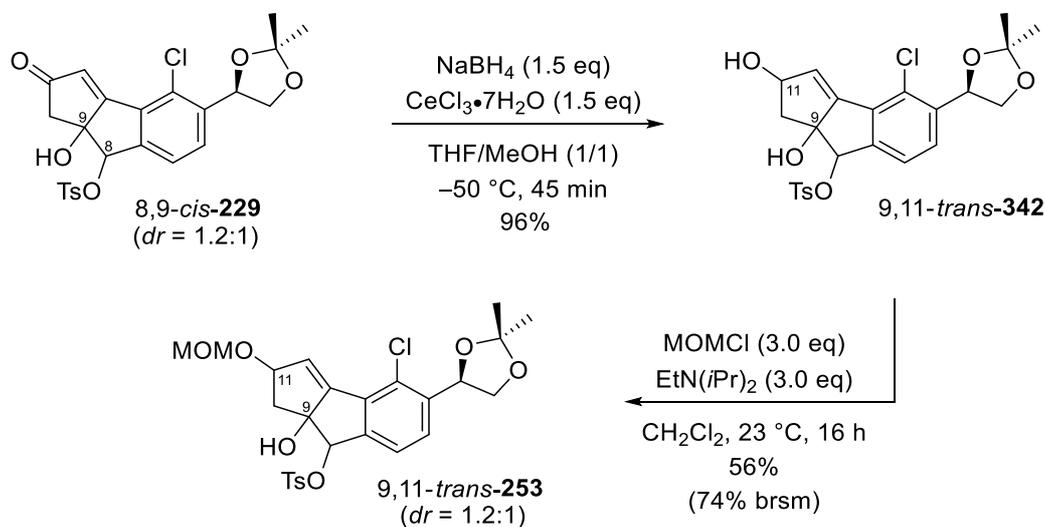
**Step 3:** To an ice-cooled solution of crude tetrol 8,9-*cis*-**245** (synthesized from 153  $\mu\text{mol}$  8,9-*cis*-**229**) in dry  $\text{CH}_2\text{Cl}_2/\text{THF}$  (5.5 mL, v/v = 10/1) was subsequently added freshly distilled 2,6-lutidine (300  $\mu\text{L}$ , 2.58 mmol, 17 eq) and TBSOTf (176  $\mu\text{L}$ , 0.765 mmol, 5.0 eq). The resulting solution was stirred at 0 °C for 1 h before being quenched by addition of sat. aqueous sodium bicarbonate (10 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 5/1) to afford an inseparable 1.1:1 diastereomeric mixture of *tris*-silyl ether 9,11-*trans*-**249** (105 mg, 132  $\mu\text{mol}$ , 86%) as a white foam.

Characterization data for inseparable 1.1:1 diastereomeric mixture of *tris*-silyl ether 9,11-*trans*-**249**:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d, 2H), 7.90 (d,  $J = 8.0$  Hz, 2H), 7.52 (d,  $J = 7.9$  Hz, 1H), 7.51 (d,  $J = 7.9$  Hz, 1H), 7.43 (d,  $J = 8.0$  Hz, 4H), 7.18 (d,  $J = 7.9$  Hz, 1H), 7.15 (d,  $J = 7.9$  Hz, 1H), 6.30 (d,  $J = 1.5$  Hz, 1H), 6.28 (d,  $J = 1.5$  Hz, 1H), 5.65 (s, 1H), 5.63 (s, 1H), 5.53 (t,  $J = 5.9$  Hz, 2H), 5.17 (dt,  $J = 8.0, 3.3$  Hz, 2H), 3.62 (ddd,  $J = 9.9, 6.4, 3.3$  Hz, 2H), 3.48 (dt,  $J = 10.5, 7.8$  Hz, 2H), 2.55 (d,  $J = 10.0$  Hz, 2H), 2.49 (s, 6H), 2.35 – 2.24 (m, 2H), 1.69 (ddd,  $J = 13.1, 8.5, 6.6$  Hz, 2H), 0.92 (s, 18H), 0.87 (s, 18H), 0.87 (s, 18H), 0.13 (s, 6H), 0.11 (s, 6H), 0.08 (s, 6H), 0.02 (s, 9H), 0.01 (s, 3H), -0.05 (s, 3H), -0.05 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  145.7 (2C), 144.3, 144.2, 142.9, 142.8, 141.8 (2C), 132.7, 132.7, 132.1, 132.0, 132.0 (2C), 130.1 (4C), 129.5, 129.3, 128.4, 128.3, 128.3 (4C), 123.5, 123.5, 91.3, 90.9, 84.6, 84.5, 81.3, 81.2, 72.5, 72.4, 68.3, 68.3, 48.3, 48.3, 26.0 (6C), 25.8 (6C), 25.8 (6C), 21.7 (2C), 18.4 (2C), 18.3, 18.2, 18.1 (2C), -4.7 (3C), -4.7, -4.8, -4.8, -5.0, -5.0, -5.3, -5.3, -5.4, -5.4 ppm; HRMS (ESI) calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{39}\text{H}_{63}^{35}\text{ClNaO}_7\text{SSi}_3]^+$ : 817.3183, found: 817.3184;  $R_f = 0.27$  (*n*-pentane/Et<sub>2</sub>O 5/1).

**Mono-silyl ether 9,11-trans-252**

To an ice-cooled solution of *tris*-silyl ether 9,11-*trans*-**249** (16.5 mg, 20.7  $\mu\text{mol}$ ,  $dr = 1.1:1$ , 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (0.5 mL,  $v/v = 1/1$ ) was added CSA (1.0 mg, 4.15  $\mu\text{mol}$ , 0.2 eq), and the resulting colorless solution was stirred at 0 °C for 5 h. The reaction was then quenched by addition of sat. aqueous sodium bicarbonate (4 mL) followed by a solution of 1,3,5-TMB (1 M in EtOAc, 0.40 mL, 40.0  $\mu\text{mol}$ ) as internal standard. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. After determination of the crude  $^1\text{H}$  NMR yield (74%) the crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/1 to 1/2) to afford a 1.4:1 diastereomeric mixture of *mono*-silyl ether 9,11-*trans*-**252** (7.6 mg, 13.6  $\mu\text{mol}$ , 65%) as a colorless oil.

**Characterization data for a 1.4:1 mixture of diastereomers:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 – 7.91 (m, 4H), 7.61 (d,  $J = 2.6$  Hz, 1H), 7.48 (d,  $J = 3.6$  Hz, 1H), 7.43 (d,  $J = 8.2$  Hz, 4H), 7.23 (d,  $J = 8.0$  Hz, 1H), 7.18 (d,  $J = 7.8$  Hz, 1H), 6.40 (d,  $J = 1.2$  Hz, 1H), 6.39 (d,  $J = 1.2$  Hz, 1H), 5.60 – 5.50 (m, 4H), 5.23 (dt,  $J = 6.3, 3.3$  Hz, 2H), 3.75 – 3.64 (m, 2H), 3.51 – 3.43 (m, 2H), 2.50 (s, 9H), 1.80 (s, 4H), 1.71 (dd,  $J = 13.1, 6.6$  Hz, 3H), 0.92 (s, 18H), 0.10 (s, 3H), 0.09 (s, 3H), -0.07 (s, 6H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  145.8, 145.8, 145.1, 145.0, 143.5, 143.4, 140.8, 138.6, 132.6, 132.5, 132.1, 132.1, 131.3, 131.3, 130.2 (2C), 130.2 (2C), 130.1, 129.4, 129.2, 128.6, 128.2 (2C), 128.2 (2C), 123.8, 123.7, 91.5, 91.1, 84.4, 84.3, 81.2, 81.1, 71.8, 71.7, 66.9, 66.9, 48.1, 48.0, 25.8 (6C), 21.8 (2C), 18.2, 18.1, -4.7 (2C), -5.0, -5.0 ppm;  $R_f$  (diastereomer 1) = 0.53 (*n*-pentane/EtOAc 1/2);  $R_f$  (diastereomer 2) = 0.45 (*n*-pentane/EtOAc 1/2).

**MOM ether 9,11-*trans*-253**

**Step 1:** To a solution of acetonide 8,9-*cis*-**229** (75.0 mg, 153  $\mu\text{mol}$ ,  $dr = 1.2:1$ , 1.0 eq) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (85.0 mg, 229  $\mu\text{mol}$ , 1.5 eq) in dry THF/MeOH (3.1 mL,  $v/v = 1/1$ ) was added  $\text{NaBH}_4$  (8.7 mg, 229  $\mu\text{mol}$ , 1.5 eq) at  $-50\text{ }^\circ\text{C}$  and the resulting mixture was stirred for 45 min before being quenched by addition of acetone (0.5 mL). The reaction mixture was allowed to warm to ambient temperature over 15 min before aqueous pH 7 phosphate buffer (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 2/3) to afford a 1.2:1 diastereomeric mixture of diol 9,11-*trans*-**342** (72.0 mg, 146  $\mu\text{mol}$ , 96%) as an off-white solid, which was directly subjected to the subsequent reaction conditions.

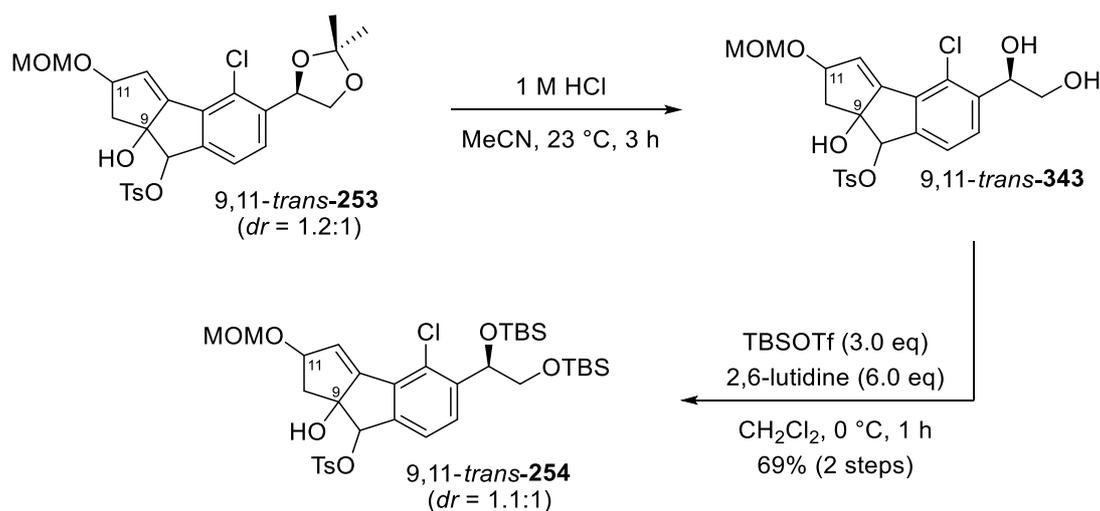
**HRMS (ESI)** calc'd. for  $[\text{M-OH}]^+ = [\text{C}_{324}\text{H}_{24}^{35}\text{ClO}_6\text{S}]^+$ : 475.0977, found: 475.0971;  $R_f = 0.36$  (*n*-pentane/EtOAc 2/3)

**Step 2:** To an ice-cooled solution of diol 9,11-*trans*-**342** (70 mg, 142  $\mu\text{mol}$ ,  $dr = 1.2:1$ , 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (1.4 mL) was added  $\text{EtN}(\text{iPr})_2$  (37.2  $\mu\text{l}$ , 213  $\mu\text{mol}$ , 1.5 eq) and a solution of  $\text{MOMCl}^{164}$  (~3.6 M in  $\text{CH}_2\text{Cl}_2$ , 59.2  $\mu\text{l}$ , 213  $\mu\text{mol}$ , 1.5 eq). The resulting mixture was stirred at  $0\text{ }^\circ\text{C}$  for 5 min and was then allowed to warm to  $23\text{ }^\circ\text{C}$ . After 3 h, additional  $\text{EtN}(\text{iPr})_2$  (37.2  $\mu\text{l}$ , 213  $\mu\text{mol}$ , 1.5 eq) and a solution of  $\text{MOMCl}$  (~3.6 M in  $\text{CH}_2\text{Cl}_2$ , 59.2  $\mu\text{l}$ , 213  $\mu\text{mol}$ , 1.5 eq) was added and stirring was continued at  $23\text{ }^\circ\text{C}$  for 13 h. The reaction was then quenched by addition of sat. aqueous bicarbonate (5 mL) and stirred at  $23\text{ }^\circ\text{C}$  for 15 min in order to decompose residual  $\text{MOMCl}$ . The aqueous phase was then extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL), the combined organic

layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 3/1 to 2/1 to 1/1) to afford an inseparable 1.2:1 diastereomeric mixture of MOM ether 9,11-*trans*-**253** (42.6 mg, 79.3  $\mu\text{mol}$ , 56%) as a colorless oil, along with unreacted diol 9,11-*trans*-**342** (16.9 mg, 34.3  $\mu\text{mol}$ , 24%) as an off-white solid.

Characterization data for inseparable 1.2:1 diastereomeric mixture of MOM ether 9,11-*trans*-**253**:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.3$  Hz, 4H), 7.56 (d,  $J = 7.9$  Hz, 2H), 7.43 (d,  $J = 8.0$  Hz, 4H), 7.18 (t,  $J = 8.3$  Hz, 2H), 6.45 – 6.41 (m, 2H), 5.65 (s, 1H), 5.62 (s, 1H), 5.45 – 5.35 (m, 4H), 4.73 (s, 2H), 4.73 (s, 2H), 4.54 (ddd,  $J = 14.4, 8.3, 6.6$  Hz, 2H), 3.63 – 3.53 (m, 2H), 3.40 (s, 3H), 3.40 (s, 3H), 2.61 (br. s, 1H), 2.57 (br. s, 1H), 2.53 – 2.41 (m, 8H), 1.84 (ddd,  $J = 16.2, 13.1, 6.7$  Hz, 2H), 1.55 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H), 1.50 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  145.8, 145.7, 145.0, 145.0, 143.6, 143.5, 140.2, 140.0, 132.6, 132.6, 132.3 (2C), 130.2 (4C), 129.9, 129.7, 128.3, 128.2 (5C), 127.6, 127.5, 123.9, 123.9, 109.9 (2C), 96.4 (2C), 91.0, 90.7, 86.8 (2C), 84.4, 84.3, 74.6 (2C), 70.2, 70.1, 55.5, 55.5, 45.7, 45.6, 26.3, 26.2, 25.6, 25.5, 21.7 (2C) ppm; HRMS (ESI) calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{26}\text{H}_{29}^{35}\text{ClNaO}_8\text{S}]^+$ : 559.1164, found: 559.1169;  $R_f = 0.36$  (*n*-pentane/EtOAc 2/1).

#### Bis-silyl ether 9,11-*trans*-**254**



**Step 1:** To a solution of acetone diol 9,11-*trans*-**253** (75.4 mg, 140  $\mu\text{mol}$ ,  $dr = 1.2:1$ , 1.0 eq) in MeCN (3.7 mL) was added aqueous HCl (1 M, 1.82 mL, 1.82 mmol, 13 eq) and the resulting colorless solution was stirred at 23  $^\circ\text{C}$  for 3 h. The reaction mixture was then diluted with EtOAc

(10 mL) and quenched by addition of sat. aqueous sodium bicarbonate (8 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. Crude triol 9,11-*trans*-**343** was obtained as an off-white solid and was used in the next step without further purification.

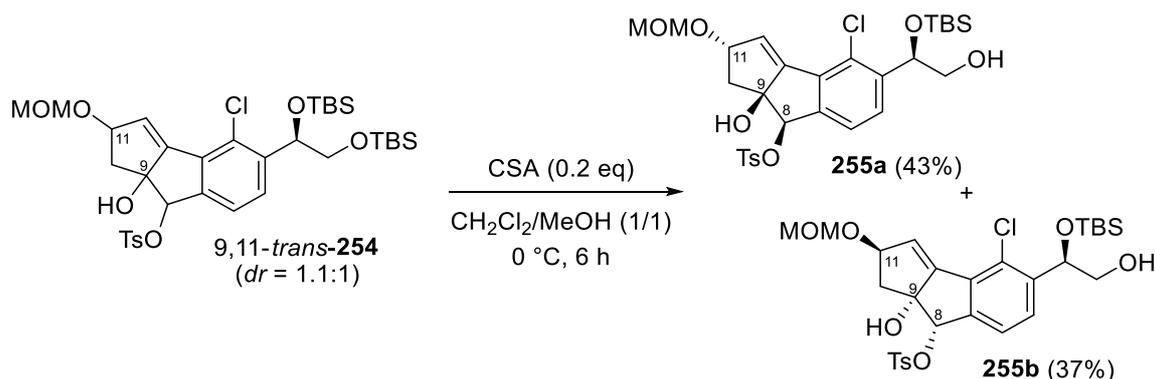
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.93 (d, *J* = 8.3 Hz, 4H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 4H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 1.4 Hz, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 5.64 (s, 1H), 5.61 (s, 1H), 5.43 – 5.34 (m, 2H), 5.25 (dd, *J* = 7.7, 2.9 Hz, 2H), 4.77 – 4.71 (m, 4H), 3.88 (ddd, *J* = 9.7, 6.5, 3.0 Hz, 2H), 3.57 – 3.45 (m, 2H), 3.43 – 3.39 (m, 6H), 2.49 (s, 8H), 1.84 (ddd, *J* = 17.4, 13.2, 6.7 Hz, 4H), 1.65 (br. s, 4H) ppm; *R*<sub>f</sub> = 0.28 (*n*-pentane/EtOAc 1/2).

**Step 2:** To an ice-cooled solution of crude triol 9,11-*trans*-**343** (synthesized from 140 μmol 9,11-*trans*-**253**) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was subsequently added freshly distilled 2,6-lutidine (107 μL, 0.918 mmol, 6.0 eq) and TBSOTf (105 μL, 0.459 mmol, 3.0 eq). The resulting solution was stirred at 0 °C for 1 h before being quenched by addition of sat. aqueous sodium bicarbonate (8 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 2/1 to 1.5/1) to afford an inseparable 1.1:1 diastereomeric mixture of *bis*-silyl ether 9,11-*trans*-**254** (70.0 mg, 96.5 μmol, 69% over 2 steps) as a yellow oil.

Characterization data for inseparable 1.1:1 diastereomeric mixture of *bis*-silyl ether 9,11-*trans*-**254**: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 8.2 Hz, 4H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 6.42 (d, *J* = 1.5 Hz, 1H), 5.65 (s, 1H), 5.63 (s, 1H), 5.40 – 5.35 (m, 2H), 5.20 – 5.15 (m, 2H), 4.76 – 4.70 (m, 4H), 3.62 (ddd, *J* = 10.5, 4.7, 3.4 Hz, 2H), 3.54 – 3.41 (m, 2H), 3.40 (s, 6H), 2.61 (br. s, 1H), 2.58 (br. s, 1H), 2.49 (s, 6H), 2.47 – 2.41 (m, 2H), 1.86 – 1.77 (m, 2H), 0.87 (s, 27H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), 0.01 (s, 3H), -0.00 (s, 3H), -0.04 (s, 3H), -0.05 (s, 3H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 145.7 (2C), 145.4, 145.4, 143.2, 143.0, 142.0, 141.8, 132.6, 132.6, 131.9, 131.8, 130.1 (2C), 130.1 (2C), 129.6, 129.5, 129.4, 129.3, 128.4, 128.4, 128.2 (4C), 123.6, 123.5, 96.4, 96.3, 90.9, 90.6, 86.8, 86.7, 84.5, 84.4, 72.5, 72.3, 68.4 (2C), 55.5 (2C), 45.7 (2C), 25.9

(3C), 25.9 (3C), 25.8 (6C), 21.7 (2C), 18.4, 18.4, 18.3, 18.2, -4.7, -4.7, -5.0, -5.0, -5.3, -5.3, -5.4 (2C) ppm; **HRMS (ESI)** calc'd. for  $[M+Na]^+ = [C_{35}H_{53}^{35}ClNaO_8SSi_2]^+$ : 747.2580, found: 747.2581;  $R_f = 0.24$  (*n*-pentane/Et<sub>2</sub>O 2/1).

### Primary alcohols **255a** and **255b**



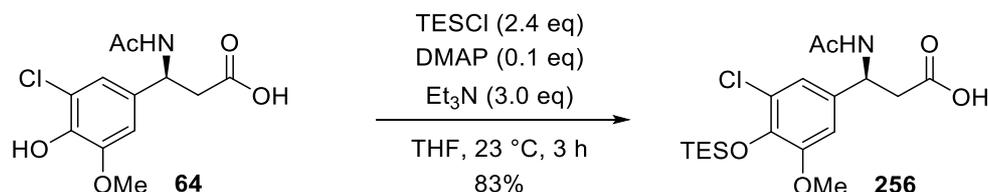
To an ice-cooled solution of *bis*-silyl ether **9,11-trans-254** (70.0 mg, 96.5  $\mu\text{mol}$ , *dr* = 1.1:1, 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (2.3 mL, *v/v* = 1/1) was added CSA (4.5 mg, 19.3  $\mu\text{mol}$ , 0.2 eq), and the resulting colorless solution was stirred at 0  $^\circ\text{C}$ . After 6 h, the reaction was quenched by addition of sat. aqueous sodium bicarbonate (6 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 1/1 to 1/2) to afford diastereomerically pure alcohol **255a** (25.5 mg, 41.7  $\mu\text{mol}$ , 43%) as white solid, along with its *8-epi-9-epi-11-epi* diastereomer **255b** (22.0 mg, 36.0  $\mu\text{mol}$ , 37%) as a colorless oil.

**Undesired diastereomer 255a:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.3$  Hz, 2H), 7.47 (d,  $J = 7.9$  Hz, 1H), 7.42 (d,  $J = 8.0$  Hz, 2H), 7.17 (d,  $J = 8.0$  Hz, 1H), 6.45 (d,  $J = 1.5$  Hz, 1H), 5.58 (s, 1H), 5.41 – 5.35 (m, 1H), 5.22 (dd,  $J = 6.6, 3.2$  Hz, 1H), 4.73 (s, 2H), 3.71 (dd,  $J = 11.3, 3.3$  Hz, 1H), 3.47 (dd,  $J = 11.3, 6.7$  Hz, 1H), 3.40 (s, 3H), 2.64 (br. s, 1H), 2.51 – 2.44 (m, 4H), 2.04 (br. s, 1H), 1.82 (dd,  $J = 13.1, 6.8$  Hz, 1H), 0.91 (s, 9H), 0.09 (s, 3H), -0.07 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  145.7, 145.2, 143.4, 140.7, 132.5, 132.2, 130.2 (2C), 129.7, 129.1, 128.2 (2C), 128.1, 123.6, 96.3, 90.5, 86.6, 84.4, 71.7, 66.8, 55.5, 45.7, 25.8 (3C), 21.7, 18.1, -4.7, -5.0 ppm; **IR (ATR):**  $\tilde{\nu} = 3426, 2952, 2929, 286, 1634, 1253, 1177, 1100, 1045, 1031,$

836, 669  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{29}\text{H}_{39}^{35}\text{ClNaO}_8\text{SSi}]^+$ : 633.1716, found: 633.1719;  $[\alpha]_{\text{D}}^{20} = -40.7$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_f = 0.48$  ( $n$ -pentane/ $\text{Et}_2\text{O}$  1/2).

**Desired diastereomer 255b:**  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.3$  Hz, 2H), 7.49 (d,  $J = 7.9$  Hz, 1H), 7.42 (d,  $J = 8.0$  Hz, 2H), 7.22 (d,  $J = 7.9$  Hz, 1H), 6.43 (d,  $J = 1.5$  Hz, 1H), 5.66 (s, 1H), 5.37 (t,  $J = 6.7$  Hz, 1H), 5.22 (dd,  $J = 7.3, 3.1$  Hz, 1H), 4.75 – 4.70 (m, 2H), 3.66 (dd,  $J = 11.3, 3.1$  Hz, 1H), 3.45 – 3.41 (m, 1H), 3.39 (s, 3H), 2.65 (br. s, 1H), 2.49 (s, 3H), 2.43 (dd,  $J = 13.1, 5.6$  Hz, 1H), 2.05 (br. s, 1H), 1.80 (dd,  $J = 13.1, 6.7$  Hz, 1H), 0.91 (s, 9H), 0.09 (s, 3H), -0.08 (s, 3H) ppm;  **$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  145.7, 145.3, 143.6, 140.7, 132.6, 132.2, 130.1 (2C), 129.7, 129.3, 128.2 (2C), 128.1, 123.8, 96.4, 90.9, 86.8, 84.3, 71.8, 66.9, 55.5, 45.6, 25.8 (3C), 21.7, 18.2, -4.7, -5.0 ppm; **IR (ATR):**  $\tilde{\nu} = 3431, 2952, 2929, 2856, 1363, 1254, 1177, 1101, 1046, 1030, 836, 669$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{29}\text{H}_{39}^{35}\text{ClNaO}_8\text{SSi}]^+$ : 633.1716, found: 633.1713;  $[\alpha]_{\text{D}}^{20} = -21.0$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_f = 0.26$  ( $n$ -pentane/ $\text{Et}_2\text{O}$  1/2).

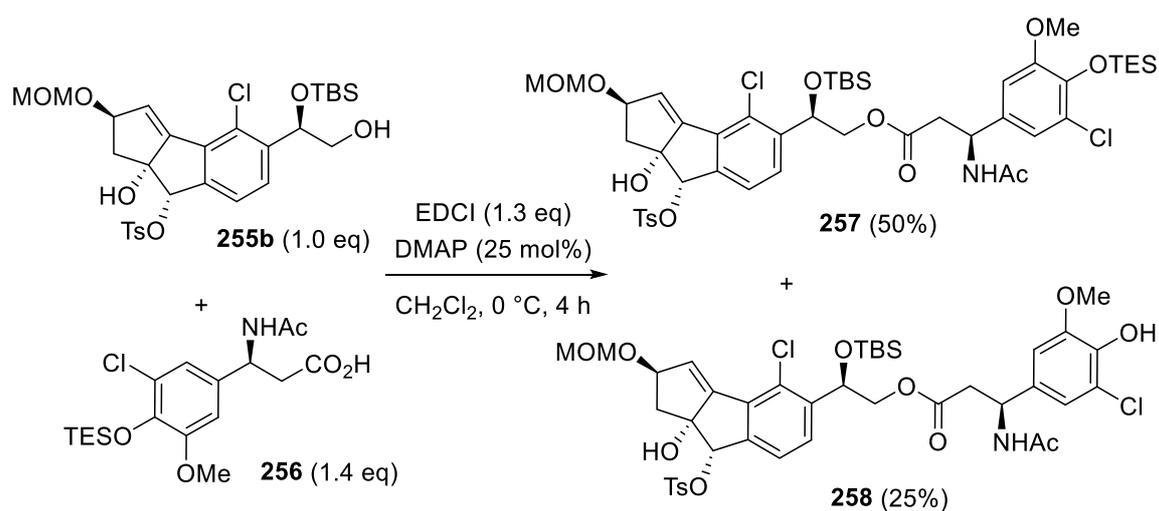
### TES Protected $\beta$ -amino acid 256



To a suspension of  $\beta$ -amino acid **64** (250 mg, 0.869 mmol, 1.0 eq) and DMAP (10.6 mg, 86.9  $\mu\text{mol}$ ) in dry THF (5.0 mL) was added triethylamine (363  $\mu\text{L}$ , 2.61 mmol, 2.4 eq). The suspension was stirred at 23 °C for 10 min resulting in a partial dissolution of the starting material. The suspension was then cooled to 0 °C and a solution of TESCl (350  $\mu\text{L}$ , 2.09 mmol, 2.4 eq) in dry THF (3.0 mL) was added dropwise. The resulting suspension was then allowed to warm to 23 °C and stirred for 2 h before the reaction was quenched by addition of sat. aqueous ammonium chloride (10 mL). The aqueous phase was extracted with  $\text{EtOAc}$  (3 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{AcOH}$  30/1/0 to 30/1/0.3) to afford TES protected  $\beta$ -amino acid **256** (314 mg, 0.717 mmol, 83 %) as a pale yellow foam.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 6.89 – 6.87 (m, 1H), 6.71 (s, 1H), 6.44 (d, *J* = 7.9 Hz, 1H), 5.40 – 5.32 (m, 1H), 3.80 (s, 3H), 2.99 – 2.80 (m, 2H), 2.04 (s, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.75 (q, *J* = 8.6, 8.0 Hz, 6H) ppm (the exchangeable carboxylic acid proton was not detected in CDCl<sub>3</sub>); **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, Acetone-d<sub>6</sub>) δ (mixture of rotamers) 172.3 (2C), 170.0, 170.0, 152.4, 149.2, 143.0, 141.5, 136.9, 134.8, 125.7 (2C), 120.5, 120.2, 110.2, 110.0, 56.7, 56.1, 50.5, 50.5, 41.4 (2C), 23.0 (2C), 7.1 (3C), 7.1 (3C), 6.6 (3C), 6.2 (3C) ppm; **IR (ATR):**  $\tilde{\nu}$  = 3283, 2955, 2915, 2877, 1720, 1617, 1573, 1498, 1285, 1237, 1053, 1006, 897, 739 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>18</sub>H<sub>29</sub><sup>35</sup>ClNO<sub>5</sub>Si]<sup>+</sup>: 402.1498, found: 402.1490; [α]<sub>D</sub><sup>20</sup> = -127.7 (*c* = 1.0, CHCl<sub>3</sub>); **R<sub>f</sub>** = 0.40 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH 10/1/0.1).

### TES Protected ester **258**

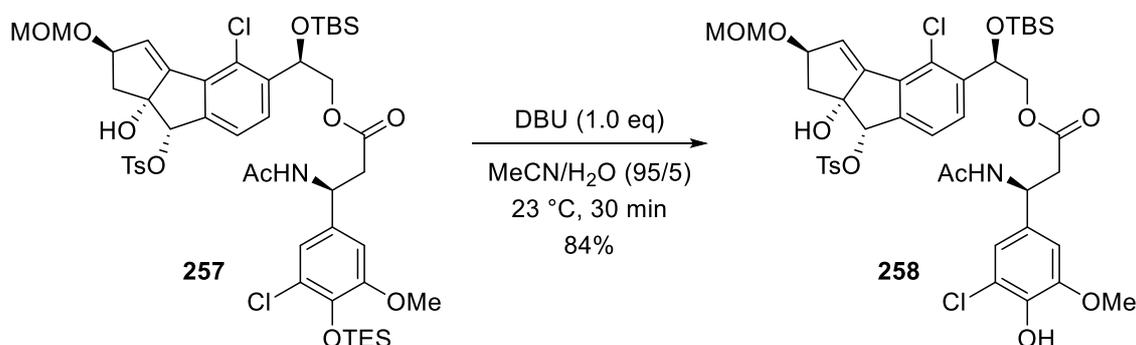


A vial was charged with alcohol **255b** (22.0 mg, 36.0 μmol, 1.0 eq), β-amino acid **256** (20.3 mg, 50.4 μmol, 1.4 eq) and DMAP (1.1 mg, 9.00 μmol, 25 mol%). The vial was sealed, placed under vacuum, and backfilled with N<sub>2</sub> (3 x). Dry CH<sub>2</sub>Cl<sub>2</sub> (360 μl) was added and the resulting colorless solution was cooled with an ice bath. EDCI (9.0 mg, 46.8 μmol, 1.3 eq) was then added and the homogenous solution was stirred at 0 °C for 4 h before being quenched by addition of sat. aqueous sodium bicarbonate (6 mL). The aqueous phase was extracted with EtOAc (4 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/1 to 0/1) to afford TES protected ester **257** (17.9 mg,

18.0  $\mu\text{mol}$ , 50%) as a colorless oil, along with free phenol **258** (7.9 mg, 9.01  $\mu\text{mol}$ , 25%) as a colorless oil.

**TES protected ester 257:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.3$  Hz, 2H), 7.51 (d,  $J = 8.0$  Hz, 1H), 7.41 (d,  $J = 8.0$  Hz, 2H), 7.27 (d,  $J = 7.4$  Hz, 1H), 6.80 (d,  $J = 2.0$  Hz, 1H), 6.65 (d,  $J = 2.0$  Hz, 1H), 6.42 (d,  $J = 1.5$  Hz, 1H), 6.22 (d,  $J = 8.3$  Hz, 1H), 5.66 (s, 1H), 5.41 – 5.31 (m, 2H), 5.22 – 5.14 (m, 1H), 4.75 – 4.70 (m, 2H), 4.12 (dd,  $J = 10.9, 5.5$  Hz, 1H), 4.04 (dd,  $J = 10.9, 6.7$  Hz, 1H), 3.78 (s, 3H), 3.40 (s, 3H), 2.82 – 2.71 (m, 2H), 2.49 (s, 3H), 2.37 (dd,  $J = 13.0, 5.5$  Hz, 1H), 1.91 (s, 3H), 1.75 (dd,  $J = 13.0, 6.7$  Hz, 1H), 0.98 (t,  $J = 7.9$  Hz, 9H), 0.86 (s, 9H), 0.74 (q,  $J = 7.9$  Hz, 6H), 0.05 (s, 3H), -0.07 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.4, 169.4, 151.5, 145.8, 145.5, 144.1, 141.3, 140.6, 133.7, 132.9, 132.4, 130.0 (2C), 129.4, 129.2, 128.5, 128.2 (2C), 125.8, 124.0, 119.0, 108.8, 96.4, 90.7, 86.9, 84.3, 68.3, 68.2, 55.5, 55.5, 49.1, 45.7, 39.9, 25.6 (3C), 23.1, 21.7, 18.1, 6.7 (3C), 5.5 (3C), -5.0, -5.1 ppm; **IR** (ATR):  $\tilde{\nu} = 3302, 2953, 2932, 2879, 1741, 1656, 1497, 1253, 1177, 1051, 836, 669$   $\text{cm}^{-1}$ ; **HRMS** (ESI) calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{47}\text{H}_{65}^{35}\text{Cl}_2\text{NNaO}_{12}\text{SSi}_2]^+$ : 1016.3035, found: 1016.3032;  $[\alpha]_{\text{D}}^{20} = -37.0$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_f = 0.16$  ( $n$ -pentane/EtOAc 1/1).

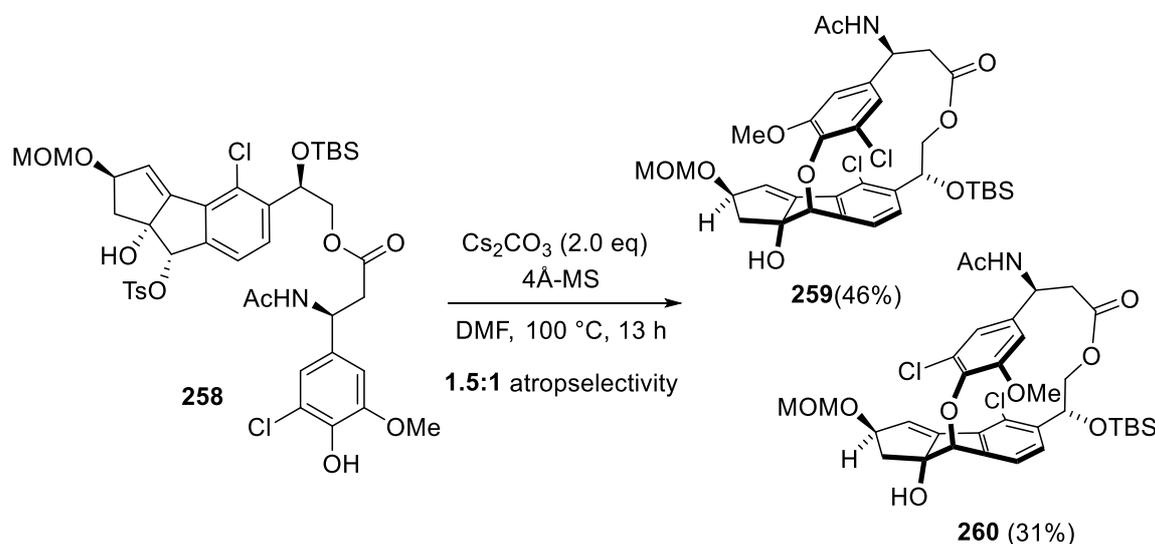
### Cyclization precursor 258



To a solution of TES aryl ether **257** (15 mg, 15.1  $\mu\text{mol}$ , 1.0 eq) in MeCN/H<sub>2</sub>O (1.5 mL, v/v = 95/5) was added DBU (2.25  $\mu\text{L}$ , 15.1  $\mu\text{mol}$ , 1.0 eq) and the reaction mixture was stirred at 23 °C for 30 min before being quenched by addition of sat. aqueous ammonium chloride (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/EtOAc 1/3) to afford cyclization precursor **258** (11.2 mg, 12.7  $\mu\text{mol}$ , 84%) as a colorless oil.

**Cyclization precursor 258:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.3$  Hz, 2H), 7.49 (d,  $J = 8.0$  Hz, 1H), 7.42 (d,  $J = 8.3$  Hz, 2H), 7.26 (d,  $J = 8.0$  Hz, 1H), 6.80 (d,  $J = 1.8$  Hz, 1H), 6.67 (d,  $J = 2.0$  Hz, 1H), 6.42 (d,  $J = 1.5$  Hz, 1H), 6.36 (br. d,  $J = 8.3$  Hz, 1H), 5.90 (s, 1H), 5.64 (s, 1H), 5.40 - 5.31 (m, 2H), 5.20 - 5.12 (m, 1H), 4.75 - 4.70 (m, 2H), 4.12 (dd,  $J = 10.8, 5.3$  Hz, 1H), 4.05 (dd,  $J = 11.0, 6.3$  Hz, 1H), 3.86 (s, 3H), 3.52 (br. s, 1H), 3.40 (s, 3H), 2.76 (dd,  $J = 6.0, 3.8$  Hz, 2H), 2.49 (s, 3H), 2.37 (dd,  $J = 13.1, 5.5$  Hz, 1H), 1.93 (s, 3H), 1.75 (dd,  $J = 13.1, 6.8$  Hz, 1H), 0.85 (s, 9H), 0.03 (s, 3H), -0.08 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.6, 169.5, 147.4, 145.7, 145.6, 144.0, 141.4, 140.5, 132.8, 132.7, 132.4, 130.1 (2C), 129.5, 129.3, 128.4, 128.2 (2C), 123.9, 119.5, 119.0, 108.1, 96.4, 90.7, 86.9, 84.3, 68.3, 68.1, 56.3, 55.5, 49.2, 45.7, 40.0, 25.6 (3C), 23.1, 21.7, 18.1, -5.0, -5.1 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3307, 2952, 2930, 1738, 1657, 1504, 1364, 1287, 1176, 1099, 1049, 836, 669  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{41}\text{H}_{51}^{35}\text{Cl}_2\text{NNaO}_{12}\text{SSi}]^+$ : 902.2170, found: 902.2171;  $[\alpha]_{\text{D}}^{20} = -30.0$  ( $c = 0.5$ ,  $\text{CHCl}_3$ ); **R<sub>f</sub>** = 0.28 ( $n$ -pentane/EtOAc 1/3).

### [2.6]Paracyclophanes 259 and 260



Cyclization precursor **258** (15.2 mg, 17.3  $\mu\text{mol}$ , 1.0 eq) was loaded into a 20 mL microwave vial and azeotroped with toluene (3 x 3 mL). Activated powdered 4Å-MS (40 mg) were then added, followed by cesium carbonate (11.2 mg, 34.62  $\mu\text{mol}$ , 2.0 eq). The vial was sealed, freshly distilled DMF (8.6 mL) was added, and the resulting mixture was stirred at 23 °C for 10 min under a  $\text{N}_2$  atmosphere before being heated to 100 °C. After 13 h the pale brown reaction mixture

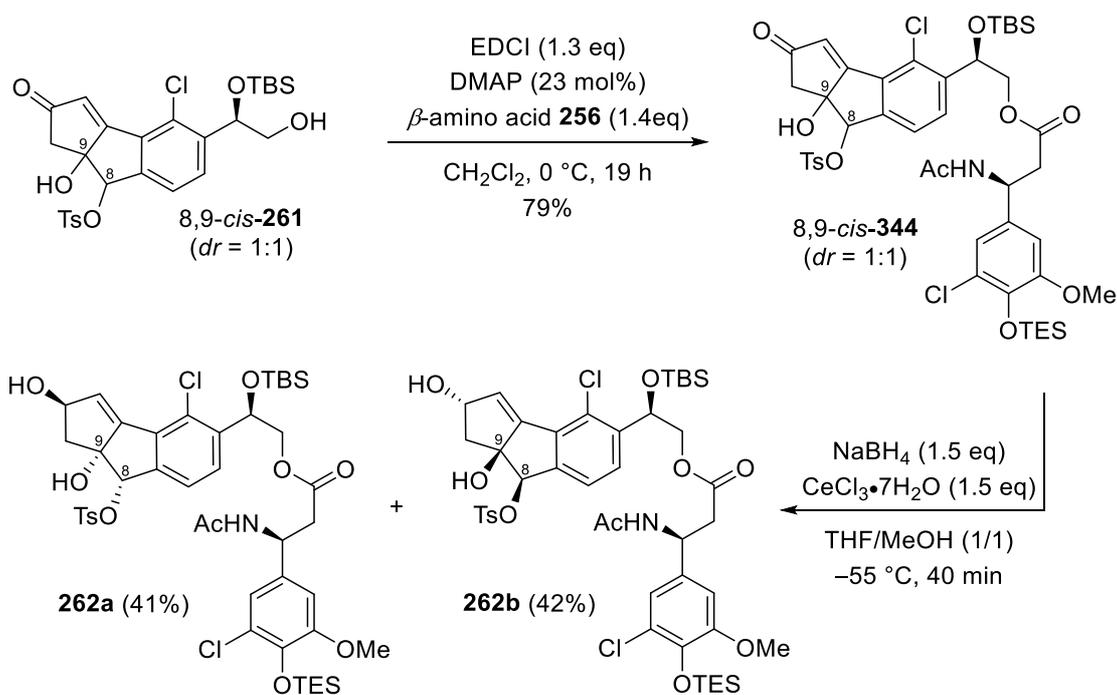
was allowed to cool to 23 °C, filtered through a short pad of Celite, and the solvent was removed under reduced pressure (45 °C). Remaining amounts of DMF were removed by azeotropic evaporation with toluene (3 x 5 mL). The obtained brown solid was entirely dissolved in MeOH-d<sub>4</sub> and subjected to <sup>1</sup>H NMR analysis for determination of product ratios (**259**:**260** = 1.5:1). The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/3 to EtOAc/MeOH 20/1) to afford [2.6]paracyclophane **259** (5.6 mg, 7.9 μmol, 46%) as a colorless foam along with its atropisomer **260** (3.8 mg, 5.4 μmol, 31%) as a white solid.

**[2.6]paracyclophane 259:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.20 (d, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.57 (d, *J* = 2.0 Hz, 1H), 6.53 (d, *J* = 1.2 Hz, 1H), 6.25 (d, *J* = 1.9 Hz, 1H), 5.79 (d, *J* = 6.7 Hz, 1H), 5.60 – 5.52 (m, 1H), 5.42 (s, 1H), 5.05 (ddd, *J* = 10.6, 6.8, 3.4 Hz, 1H), 4.86 – 4.82 (m, 2H), 4.76 – 4.65 (m, 2H), 3.71 (dd, *J* = 9.1, 3.1 Hz, 1H), 3.47 (s, 3H), 3.46 (s, 3H), 2.98 (dd, *J* = 10.7, 3.2 Hz, 1H), 2.96 – 2.92 (m, 1H), 2.55 (dd, *J* = 12.6, 5.5 Hz, 1H), 2.23 – 2.16 (m, 1H), 2.02 (s, 3H), 1.88 (br. s, 1H), 0.87 (s, 9H), 0.04 (s, 3H), -0.08 (s, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ = 169.3, 168.8, 154.3, 150.0, 145.1, 141.6, 139.2, 137.7, 135.7, 131.1, 130.5, 129.8, 128.7, 126.3, 115.0, 110.1, 96.3, 92.6, 87.5, 84.6, 74.3, 65.8, 55.5, 54.5, 51.1, 42.9, 39.9, 25.6 (3C), 23.4, 18.1, -5.0, -5.3 ppm; IR (ATR):  $\tilde{\nu}$  = 3302, 2952, 2929, 1738, 1656, 1563, 1148, 1109, 1050, 856, 839, 779 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M+H]<sup>+</sup> = [C<sub>34</sub>H<sub>44</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>9</sub>Si]<sup>+</sup>: 708.2157, found: 708.2155; [α]<sub>D</sub><sup>20</sup> = -225.8 (*c* = 0.2, CHCl<sub>3</sub>); *R*<sub>f</sub> = 0.29 (*n*-pentane/EtOAc 1/3).

**Atropisomer 260:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.95 (d, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.56 (d, *J* = 1.9 Hz, 1H), 6.55 – 6.52 (m, 1H), 6.40 (d, *J* = 1.9 Hz, 1H), 5.81 (d, *J* = 6.1 Hz, 1H), 5.53 (t, *J* = 6.3 Hz, 1H), 5.38 (s, 1H), 4.95 (ddd, *J* = 10.9, 6.2, 3.5 Hz, 1H), 4.85 - 4.79 (m, 2H), 4.73 (dd, *J* = 10.8, 4.1 Hz, 1H), 4.47 (t, *J* = 10.5 Hz, 1H), 3.94 (s, 3H), 3.74 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.45 (s, 3H), 3.06 (dd, *J* = 12.9, 7.1 Hz, 1H), 3.00 (dd, *J* = 13.7, 3.6 Hz, 1H), 2.54 (dd, *J* = 12.9, 5.7 Hz, 1H), 2.29 (dd, *J* = 13.6, 11.5 Hz, 1H), 2.02 (s, 3H), 1.89 (br. s, 1H), 0.88 (s, 9H), 0.04 (s, 3H), -0.06 (s, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ = 169.5, 168.6, 154.8, 149.0, 145.8, 141.9, 139.3, 136.3, 135.8, 131.3, 130.5, 130.4, 130.2, 125.9, 122.5, 105.9, 96.5, 92.8, 88.1, 84.5, 74.4, 66.4, 56.1, 55.4, 51.5, 42.4, 39.3, 25.6 (3C), 23.5, 18.1, -5.0, -5.2 ppm; IR (ATR):  $\tilde{\nu}$  = 3299, 2073, 2953, 2893, 1737, 1656, 1146, 1110, 1051, 857, 839, 880 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M+H]<sup>+</sup> = [C<sub>34</sub>H<sub>44</sub><sup>35</sup>Cl<sub>2</sub>NO<sub>9</sub>Si]<sup>+</sup>: 708.2157, found:

708.2156;  $[\alpha]_D^{20} = -376.7$  ( $c = 0.1$ ,  $\text{CHCl}_3$ ); **m.p.:** 177-182 °C (decomp.); **R<sub>f</sub>** = 0.31 (EtOAc/MeOH 10/1).

### Cyclization precursors **262a** and **262b**



**Steps 1:** A vial was charged with keto alcohol **8,9-cis-261** (66.0 mg, 114  $\mu\text{mol}$ ,  $dr = 1:1$ , 1.0 eq),  $\beta$ -amino acid **256** (61.8 mg, 154  $\mu\text{mol}$ , 1.4 eq) and DMAP (3.2 mg, 26.2  $\mu\text{mol}$ , 23 mol%). The vial was sealed, placed under vacuum, and backfilled with  $\text{N}_2$  (3 x). Dry  $\text{CH}_2\text{Cl}_2$  (1.1 mL) was added and the resulting colorless solution was cooled with an ice bath. EDCI (27.3 mg, 142  $\mu\text{mol}$ , 1.3 eq) was then added and the homogenous solution was stirred at 0 °C for 19 h before being quenched by addition of sat. aqueous ammonium chloride (8 mL). The aqueous phase was extracted with EtOAc (4 x 10 mL), the combined organic layers were washed with brine (10 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/EtOAc 1/1 to 1/2) to afford a 1:1 diastereomeric mixture of keto ester **8,9-cis-344** (85.7 mg, 90.2  $\mu\text{mol}$ , 79%) as a colorless oil, which was directly subjected to the subsequent reaction conditions.

**R<sub>f</sub>** (diastereomer 1) = 0.36 ( $n$ -pentane/EtOAc 1/1); **R<sub>f</sub>** (diastereomer 2) = 0.20 ( $n$ -pentane/EtOAc 1/1).

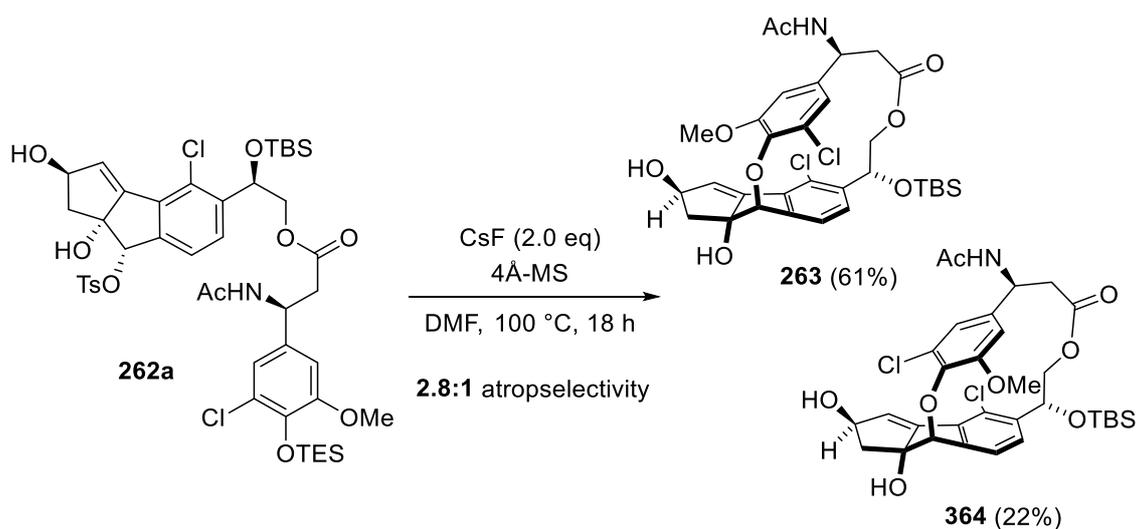
**Step 2:** To a solution of keto ester 8,9-*cis*-**344** (85.0 mg, 89.6  $\mu\text{mol}$ , *dr* = 1:1, 1.0 eq) (synthesized from 114  $\mu\text{mol}$  keto alcohol 8,9-*cis*-**261**) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (50.1 mg, 134  $\mu\text{mol}$ , 1.5 eq) in dry THF/MeOH (5.0 mL, *v/v* = 1/1) was added  $\text{NaBH}_4$  (5.1 mg, 134  $\mu\text{mol}$ , 1.5 eq) at  $-55\text{ }^\circ\text{C}$  and the resulting mixture was stirred for 40 min before being quenched by addition of acetone (0.3 mL). The reaction mixture was allowed to warm to ambient temperature over 15 min before aqueous pH 7 phosphate buffer (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/2 to 1/3 to 0/1) followed by preparative HPLC (Chromolith column, *n*-hexane/EtOAc 1/1.3, 25 mL/min, 254 nm,  $t_{\text{R}}$ (**262a**) = 11.8 min,  $t_{\text{R}}$ (**262b**) = 16.6 min), to afford the desired cyclization precursor **262a** (34.7 mg, 36.5  $\mu\text{mol}$ , 41%) as a colorless oil, along with the diastereomeric cyclization precursor **262b** (35.4 mg, 37.2  $\mu\text{mol}$ , 42%) as a white foam.

Desired cyclization precursor **262a**:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J$  = 8.3 Hz, 2H), 7.52 (d,  $J$  = 7.8 Hz, 1H), 7.41 (d,  $J$  = 8.3 Hz, 2H), 7.28 (d,  $J$  = 7.8 Hz, 1H), 6.80 (d,  $J$  = 2.0 Hz, 1H), 6.65 (d,  $J$  = 2.0 Hz, 1H), 6.37 (d,  $J$  = 1.5 Hz, 1H), 6.26 (br. d,  $J$  = 8.3 Hz, 1H), 5.65 (s, 1H), 5.54 (t,  $J$  = 5.6 Hz, 1H), 5.35 (t,  $J$  = 6.0 Hz, 1H), 5.21 - 5.13 (m, 1H), 4.12 (dd,  $J$  = 10.8, 5.5 Hz, 1H), 4.04 (dd,  $J$  = 10.9, 6.7 Hz, 1H), 3.77 (s, 3H), 2.82 - 2.70 (m, 2H), 2.48 (s, 3H), 2.40 (dd,  $J$  = 13.1, 5.5 Hz, 1H), 1.91 (s, 3H), 1.63 (dd,  $J$  = 13.1, 6.8 Hz, 1H), 0.97 (t,  $J$  = 7.9 Hz, 9H), 0.86 (s, 9H), 0.77 - 0.70 (m, 6H), 0.05 (s, 3H), -0.07 (s, 3H) ppm (both allylic alcohols were not detected in  $\text{CDCl}_3$ );  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.4, 169.5, 151.5, 145.6, 145.6, 144.0, 141.3, 140.6, 133.7, 132.8, 132.4, 131.1, 130.1 (2C), 129.2, 128.5, 128.2 (2C), 125.8, 124.0, 119.0, 108.8, 91.3, 84.4, 81.3, 68.3, 68.2, 55.5, 49.1, 48.0, 39.9, 25.6 (3C), 23.1, 21.7, 18.1, 6.7 (3C), 5.5 (3C), -5.0, -5.1 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3315, 2954, 2932, 2878, 1740, 1652, 1497, 1254, 1177, 837, 669  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{45}\text{H}_{61}^{35}\text{Cl}_2\text{NNaO}_{11}\text{SSi}_2]^+$ : 972.2773, found: 972.2776;  $[\alpha]_{\text{D}}^{20} = -44.0$  ( $c$  = 0.5,  $\text{CHCl}_3$ );  $R_{\text{f}} = 0.15$  (*n*-hexane/EtOAc 1/2).

Diastereomeric cyclization precursor **262b**:  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J$  = 8.3 Hz, 2H), 7.50 (d,  $J$  = 7.9 Hz, 1H), 7.42 (d,  $J$  = 8.1 Hz, 2H), 7.20 (d,  $J$  = 8.0 Hz, 1H), 6.81 (d,  $J$  = 1.9 Hz, 1H), 6.67 (d,  $J$  = 2.0 Hz, 1H), 6.48 (d,  $J$  = 8.4 Hz, 1H), 6.38 (d,  $J$  = 1.4 Hz, 1H), 5.62 (s, 1H), 5.54 (t,  $J$  = 5.6 Hz, 1H), 5.33 - 5.23 (m, 2H), 4.12 (dd,  $J$  = 11.1, 4.1 Hz, 1H), 3.99 (dd,

$J = 11.1, 7.2$  Hz, 1H), 3.78 (s, 3H), 2.89 – 2.75 (m, 2H), 2.69 (s, 1H), 2.49 (s, 4H), 2.09 (br. s, 1H), 2.01 (s, 3H), 1.72 (dd,  $J = 13.2, 6.6$  Hz, 1H), 0.98 (t,  $J = 7.9$  Hz, 9H), 0.86 (s, 9H), 0.74 (q,  $J = 8.6, 7.9$  Hz, 6H), 0.04 (s, 3H), -0.07 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 169.2, 151.6, 145.8, 144.9, 143.7, 141.3, 140.4, 133.6, 132.5, 132.1, 131.5, 130.2 (3C), 129.2, 128.3, 128.2 (2C), 125.8, 123.9, 119.0, 108.8, 91.1, 84.3, 81.1, 68.8, 68.2, 55.5, 48.9, 48.1, 39.6, 25.6 (3C), 23.4, 21.8, 18.1, 6.7 (3C), 5.5 (3C), -4.9, -5.0 ppm; IR (ATR):  $\tilde{\nu} = 3304, 2954, 2931, 2878, 1739, 1655, 1496, 1252, 1176, 1097, 836, 731, 669$   $\text{cm}^{-1}$ ; HRMS (ESI) calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{45}\text{H}_{61}^{35}\text{Cl}_2\text{NNaO}_{11}\text{SSi}_2]^+$ : 972.2773, found: 972.2774;  $[\alpha]_{\text{D}}^{20} = -55.3$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_f = 0.15$  ( $n$ -hexane/EtOAc 1/2).

### [2.6]Paracyclophanes **263** and **264**

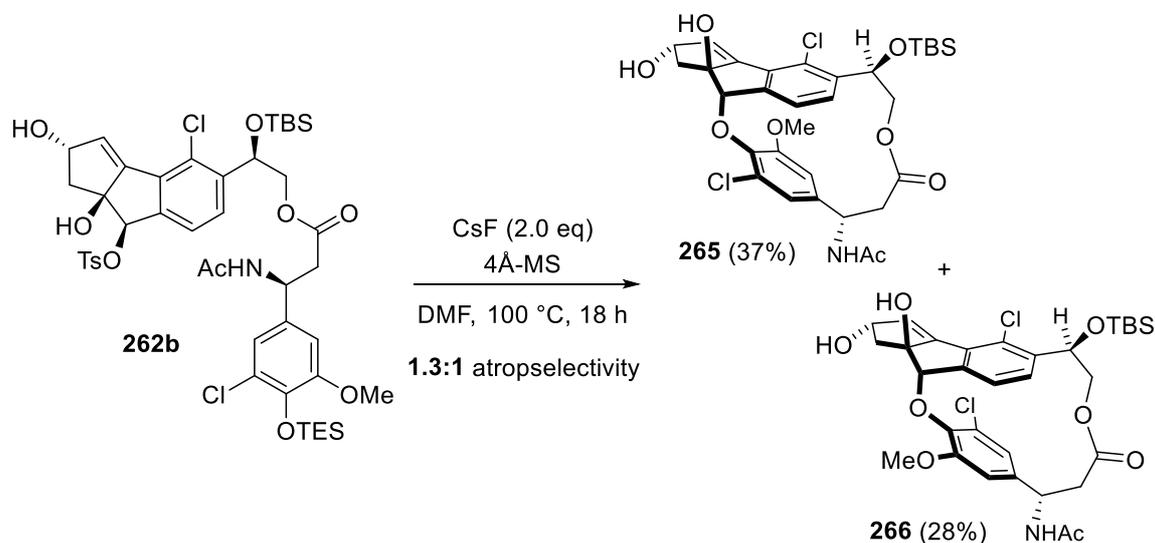


Cyclization precursor **262a** (30.0 mg, 31.5  $\mu\text{mol}$ ) was loaded into a 20 mL microwave vial and azeotroped with toluene (3 x 3 mL). Activated powdered 4Å-MS (85 mg) was then added, followed by freshly ground cesium fluoride (9.6 mg, 63.2  $\mu\text{mol}$ ) (glovebox). The vial was sealed, freshly distilled DMF (16 mL) was added, and the resulting mixture was stirred at 23 °C for 1 h under a  $\text{N}_2$  atmosphere before being heated to 100 °C. After 18 h, the slightly brownish reaction mixture was allowed to cool to ambient temperature, filtered through a short pad of Celite, and the solvent was removed under reduced pressure (45 °C). Remaining amounts of DMF were removed by azeotropic evaporation with toluene (3 x 5 mL). The obtained brown solid was entirely dissolved in  $\text{MeOH-d}_4$  and subjected to  $^1\text{H}$  NMR analysis for determination of product ratios (**263**:**264** = 2.8:1). The crude product was purified by flash chromatography

(EtOAc/MeOH 1/0 to 20/1) to afford [2.6]paracyclophane **263** (12.8 mg, 19.3  $\mu\text{mol}$ , 61%) as a white foam along with its atropisomer **264** (4.7 mg, 7.1  $\mu\text{mol}$ , 22%) as a white solid.

**[2.6]paracyclophane 263:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.17 (d,  $J$  = 7.5 Hz, 1H), 6.62 (d,  $J$  = 7.8 Hz, 1H), 6.59 (d,  $J$  = 2.0 Hz, 1H), 6.52 (d,  $J$  = 1.3 Hz, 1H), 6.27 (d,  $J$  = 1.8 Hz, 1H), 5.78 (d,  $J$  = 6.5 Hz, 1H), 5.70 (br. s, 1H), 5.41 (s, 1H), 5.06 (ddd,  $J$  = 11.2, 7.1, 3.5 Hz, 1H), 4.74 (dd,  $J$  = 10.8, 4.2 Hz, 1H), 4.63 (t,  $J$  = 10.6 Hz, 1H), 3.72 (dd,  $J$  = 10.0, 4.0 Hz, 1H), 3.47 (s, 3H), 2.97 (dd,  $J$  = 13.8, 3.3 Hz, 1H), 2.76 (dd,  $J$  = 13.2, 6.4 Hz, 1H), 2.62 (dd,  $J$  = 13.2, 5.8 Hz, 1H), 2.20 (dd,  $J$  = 13.7, 11.7 Hz, 1H), 2.03 (s, 3H), 1.90 (br. s, 2H), 0.88 (s, 9H), 0.04 (s, 3H), -0.07 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 169.3, 168.8, 154.1, 149.8, 145.2, 141.6, 139.3, 137.7, 135.7, 131.1, 130.6, 130.3, 129.9, 126.2, 115.3, 110.2, 93.5, 84.1, 82.4, 74.3, 66.0, 54.8, 51.0, 42.9, 42.2, 25.6 (3C), 23.4, 18.1, -5.0, -5.3 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3299, 2956, 2929, 1736, 1656, 1486, 1296, 1193, 1145, 1106, 853, 838, 753, 666  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{32}\text{H}_{40}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 664.1895, found: 664.1896;  $[\alpha]_{\text{D}}^{20} = -274.2$  ( $c$  = 0.2,  $\text{CHCl}_3$ );  $R_f$  = 0.36 (EtOAc).

**Atropisomer 264:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.94 (d,  $J$  = 7.8 Hz, 1H), 6.60 (d,  $J$  = 7.8 Hz, 1H), 6.57 (d,  $J$  = 2.0 Hz, 1H), 6.47 (d,  $J$  = 1.3 Hz, 1H), 6.42 (d,  $J$  = 2.0 Hz, 1H), 5.79 (br. d,  $J$  = 6.3 Hz, 1H), 5.71 - 5.66 (m, 1H), 5.38 (s, 1H), 4.95 (ddd,  $J$  = 10.8, 6.7, 3.5 Hz, 1H), 4.74 (dd,  $J$  = 10.7, 4.1 Hz, 1H), 4.44 (t,  $J$  = 10.5 Hz, 1H), 3.95 (s, 3H), 3.75 (dd,  $J$  = 10.3, 4.0 Hz, 1H), 3.00 (dd,  $J$  = 13.7, 3.4 Hz, 1H), 2.87 - 2.80 (m, 1H), 2.64 (dd,  $J$  = 13.3, 5.8 Hz, 1H), 2.29 (dd,  $J$  = 13.6, 11.5 Hz, 1H), 2.06 - 2.01 (m, 4H), 1.88 (br. s, 1H), 0.88 (s, 9H), 0.04 (s, 3H), -0.05 (s, 3H);  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 169.5, 168.6, 154.8, 149.1, 145.8, 141.8, 139.4, 136.5, 135.7, 132.5, 130.6, 130.3, 129.9, 125.9, 122.4, 106.1, 93.6, 84.3, 82.7, 74.4, 66.5, 56.2, 51.4, 42.4, 42.1, 25.6 (3C), 23.5, 18.1, -5.0, -5.2 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3304, 2953, 2930, 2857, 1733, 1654, 1301, 1144, 1109, 1052, 855, 836, 732, 667  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{32}\text{H}_{40}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 664.1895, found: 664.1896;  $[\alpha]_{\text{D}}^{20} = -249.2$  ( $c$  = 0.2,  $\text{CHCl}_3$ ); **m.p.:** 200 - 202  $^{\circ}\text{C}$ ;  $R_f$  = 0.23 (EtOAc/MeOH 20/1).

**[2.6]Paracyclophanes 265 and 266**

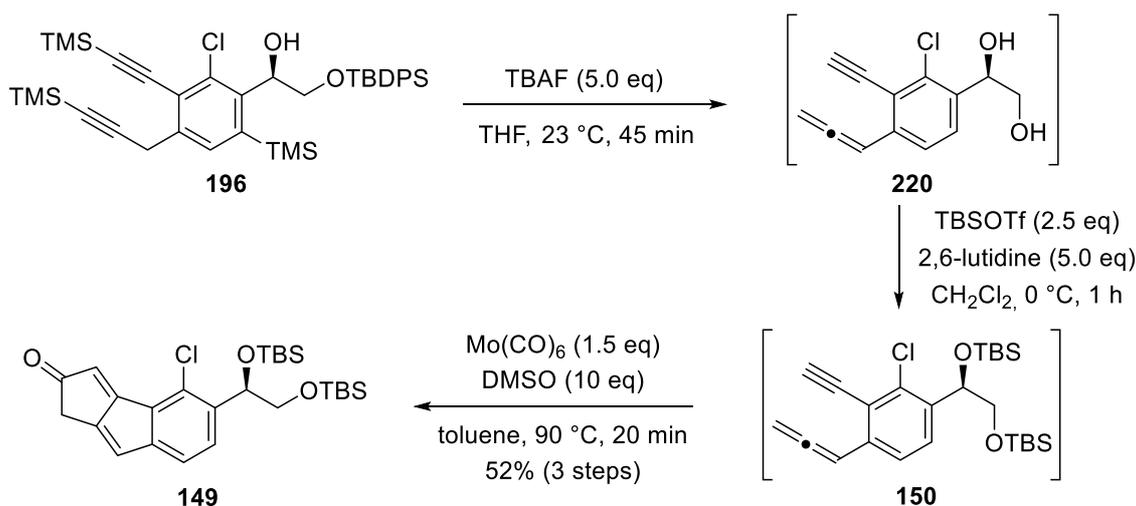
Cyclization precursor **262b** (35.0 mg, 37.8  $\mu\text{mol}$ ) was loaded into a 20 mL microwave vial and azeotroped with toluene (3 x 5 mL). Activated powdered 4Å-MS (100 mg) were then added, followed by freshly ground cesium fluoride (11.4 mg, 75.6  $\mu\text{mol}$ ) (glovebox). The vial was sealed, freshly distilled DMF (18 mL) was added, and the resulting mixture was stirred at 23  $^\circ\text{C}$  for 1 h under a  $\text{N}_2$  atmosphere before being heated to 100  $^\circ\text{C}$ . After 18 h, the slightly brownish reaction mixture was allowed to cool to ambient temperature, filtered through a short pad of Celite, and the solvent was removed under reduced pressure (45  $^\circ\text{C}$ ). Remaining amounts of DMF were removed by azeotropic evaporation with toluene (3 x 5 mL). The obtained brown solid was entirely dissolved in  $\text{MeOH-d}_4$  and subjected to  $^1\text{H}$  NMR analysis for determination of product ratios (**265:266** = 1.3:1). The crude product was purified by flash chromatography (pure EtOAc), followed by preparative HPLC (Chromolith column, *n*-hexane/EtOAc 1/2.5, 25 mL/min, 254 nm,  $t_{\text{R}}(\text{minor})$  = 8.7 min,  $t_{\text{R}}(\text{major})$  = 10.4 min) to afford [2.6]paracyclophane **265** (9.1 mg, 13.7  $\mu\text{mol}$ , 37%) as a white foam along with its atropisomer **266** (6.8 mg, 10.4  $\mu\text{mol}$ , 28%) as a white foam.

**[2.6]paracyclophane 265:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.47 (d,  $J$  = 8.2 Hz, 1H), 7.19 (d,  $J$  = 7.9 Hz, 1H), 7.12 (d,  $J$  = 7.9 Hz, 1H), 6.73 (d,  $J$  = 1.9 Hz, 1H), 6.45 (d,  $J$  = 1.3 Hz, 1H), 6.06 (d,  $J$  = 1.9 Hz, 1H), 5.71 - 5.64 (m, 1H), 5.40 (s, 1H), 5.38 (s, 1H), 5.11 (dt,  $J$  = 8.0, 4.0 Hz, 1H), 4.30 (dd,  $J$  = 11.5, 1.4 Hz, 1H), 3.88 (dd,  $J$  = 11.5, 2.2 Hz, 1H), 3.34 (s, 3H), 2.78 - 2.58 (m, 3H), 2.48 (dd,  $J$  = 14.8, 3.6 Hz, 1H), 2.01 (s, 5H), 0.87 (s, 9H), 0.04 (s, 3H), -0.05 (s, 3H) ppm;

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 169.2, 154.3, 149.8, 144.8, 141.8, 139.5, 138.0, 133.6, 130.6, 129.4, 129.1, 126.7, 126.5, 119.0, 105.7, 93.5, 83.7, 82.3, 68.2, 67.7, 54.6, 49.4, 42.5, 41.1, 25.7 (3C), 23.4, 18.1, -4.9, -5.2 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3408, 2953, 2930, 2857, 1720, 1664, 1486, 1382, 1259, 1053, 834, 779  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{32}\text{H}_{40}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 664.1895, found: 664.1891;  $[\alpha]_{\text{D}}^{20} = +204.2$  ( $c = 0.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.33$  (EtOAc).

**Atropisomer 266:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 (d,  $J = 8.3$  Hz, 1H), 7.15 (d,  $J = 7.9$  Hz, 1H), 6.88 (d,  $J = 7.9$  Hz, 1H), 6.51 (d,  $J = 2.0$  Hz, 1H), 6.41 (d,  $J = 1.2$  Hz, 1H), 6.35 (d,  $J = 2.0$  Hz, 1H), 5.69 (s, 1H), 5.40 (s, 1H), 5.38 (s, 1H), 5.14 (dt,  $J = 8.1, 3.9$  Hz, 1H), 4.10 (dd,  $J = 11.4, 1.3$  Hz, 1H), 3.98 (s, 3H), 3.90 (dd,  $J = 11.4, 2.3$  Hz, 1H), 2.78 - 2.69 (m, 2H), 2.64 (dd,  $J = 13.3, 5.8$  Hz, 1H), 2.51 (dd,  $J = 14.5, 3.7$  Hz, 1H), 2.05 - 1.99 (m, 4H), 1.79 (br. s, 1H), 0.87 (s, 9H), 0.05 (s, 3H), -0.05 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.8, 169.3, 154.4, 149.4, 145.6, 141.4, 139.6, 137.2, 133.4, 131.4, 130.1, 129.1, 127.4, 126.0, 117.8, 108.6, 93.3, 83.7, 82.6, 68.0, 67.9, 56.0, 49.3, 42.3, 41.1, 25.7 (3C), 23.4, 18.1, -4.9, -5.2 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3402, 2953, 2930, 2930, 2857, 1719, 1665, 1382, 1261, 1053, 946, 834, 755  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{32}\text{H}_{40}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 664.1895, found: 664.1894;  $[\alpha]_{\text{D}}^{20} = +207.3$  ( $c = 0.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.42$  (EtOAc).

### Indenylcyclopentenone 149



**Step 1:** To a stirred solution of chlorobenzene **196** (309 mg, 0.448 mmol, 1.0 eq) in dry THF (4.5 mL) was slowly added a solution of TBAF (1 M in THF, 2.24 mL, 2.24 mmol, 5.0 eq). The

reaction mixture instantaneously turned black and was stirred at 23 °C for 45 min before it was quenched by addition of sat. aqueous ammonium chloride (10 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 15 mL), the combined organic layers were washed with brine (15 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure (25 °C). Crude allene-yne **220** was obtained as a brown oil and was used in the next step without further purification.

$R_f = 0.40$  (*n*-pentane/EtOAc 1/1).

**Step 2:** To an ice-cooled solution of crude allene-yne **220** (synthesized from 0.448 mmol **196**) in dry CH<sub>2</sub>Cl<sub>2</sub> (4.5 mL) was subsequently added freshly distilled 2,6-lutidine (0.261 mL, 2.24 mmol, 5.0 eq) and TBSOTf (0.257 mL, 1.12 mmol, 2.5 eq). The resulting solution was stirred at 0 °C for 1 h before being quenched by addition of saturated aqueous sodium bicarbonate (8 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure (25 °C). Crude allene-yne **150** was obtained as an orange oil and was used in the next step without further purification.

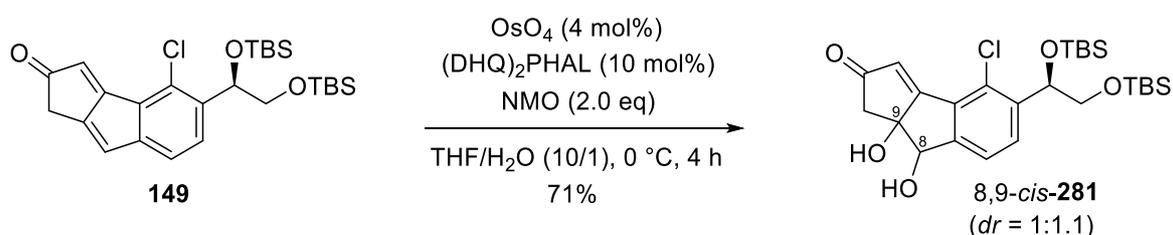
$R_f = 0.43$  (*n*-pentane/Et<sub>2</sub>O 50/1).

**Step 3:** A two-neck round-bottom flask equipped with a reflux condenser was charged with Mo(CO)<sub>6</sub> (177 mg, 0.672 mmol, 1.5 eq). A degassed and over 4Å-MS dried solution of allene-yne **150** (synthesized from 0.448 mmol **196**) and DMSO (318 μl, 4.48 mmol, 10 eq) in dry toluene (3.0 mL) was added. The resulting yellow suspension was placed in a pre-heated oil bath and stirred at 90 °C under a N<sub>2</sub> atmosphere. After 20 min the reaction mixture was cooled to 0 °C in an ice bath and was directly purified by flash chromatography (*n*-pentane/Et<sub>2</sub>O 1/0 to 150/1 to 66/1 to 15/1) to afford indenylcyclopentenone **149** (120 mg, 0.234 mmol, 52% over 3 steps) as an orange oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 7.58 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 5.20 (dd, *J* = 7.0, 3.8 Hz, 1H), 3.68 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.58 (dd, *J* = 10.4, 7.2 Hz, 1H), 3.22 (d, *J* = 1.0 Hz, 2H), 0.89 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.02 (s, 6H), -0.01 (s, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ = 207.0, 169.1, 148.6, 143.0, 137.7, 132.3, 131.0, 128.7, 128.0, 122.0, 120.0, 72.1, 68.6, 35.4, 25.9 (3C), 25.8 (3C), 18.4, 18.3, -4.7, -4.9, -5.3, -5.4 ppm; IR (ATR):  $\tilde{\nu}$  = 2954, 2929, 2857, 1717, 1608, 1471,

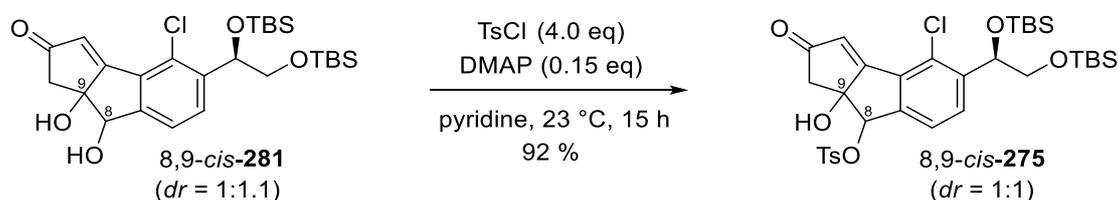
1255, 1131, 1099, 835, 728  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{26}\text{H}_{40}\text{ClO}_3\text{Si}_2]^+$ : 491.2199, found: 491.2201;  $[\alpha]_{\text{D}}^{26} = -131.7$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_f = 0.27$  ( $n$ -pentane/Et<sub>2</sub>O 15/1).

### Diol 8,9-*cis*-281



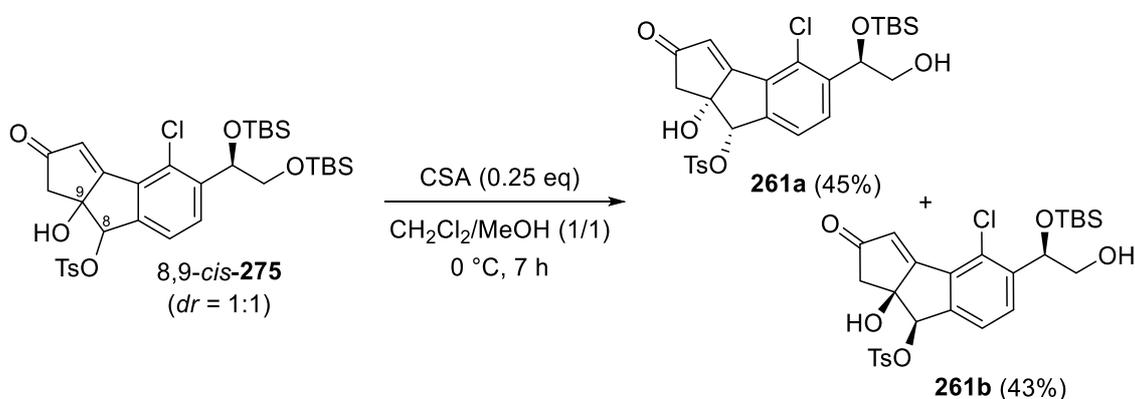
To an ice-cooled solution of indenylcyclopentenone **149** (523 mg, 1.07 mmol, 1.0 eq) in THF/ $\text{H}_2\text{O}$  (11 mL, v/v = 10/1) was added  $(\text{DHQ})_2\text{PHAL}$  (87.0 mg, 0.106 mmol, 10 mol%),  $\text{OsO}_4$  (5% in  $\text{H}_2\text{O}$ , 0.217 mL, 42.6  $\mu\text{mol}$ , 4.0 mol%) and NMO (249 mg, 2.13 mmol, 2.0 eq). The resulting brown solution was stirred at 0 °C for 4 h, and was then quenched by addition of saturated aqueous sodium thiosulfate (20 mL). Stirring was continued for 10 min at 0 °C, and then for 15 min at 23 °C. The aqueous phase was extracted with EtOAc (3 x 20 mL), the combined organic layers were washed with brine, dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/EtOAc 3/1 to 2/1) to afford an inseparable 1:1.1 diastereomeric mixture of diol 8,9-*cis*-**281** (396 mg, 0.754 mmol, 71%) as a brown oil.

Characterization data for inseparable 1:1.1 mixture of diastereomers:  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta = 7.81$  (d,  $J = 7.8$  Hz, 1H), 7.80 (d,  $J = 7.9$  Hz, 1H), 7.51 (br. d,  $J = 7.9$  Hz, 2H), 6.55 (s, 1H), 6.54 (s, 1H), 5.27 - 5.20 (m, 2H), 5.09 (br. s, 1H), 5.06 (br. s, 1H), 3.70 - 3.64 (m, 2H), 6.63 - 6.53 (m, 2H), 3.32 (br. s, 2H), 3.20 (br. s, 2H), 2.81 - 2.6 (m, 4H), 0.90 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.86 (s, 9H), 0.11 (s, 6H), 0.02 (s, 6H), 0.00 (s, 6H), -0.01 (s, 6H) ppm;  **$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta = 207.8$  (2C), 173.0, 172.9, 149.5, 149.3, 141.8, 141.7, 133.2, 133.1, 130.9, 130.8, 130.4 (2C), 124.4, 124.2, 123.8, 123.7, 86.4, 86.2, 77.4 (2C), 72.2, 72.1, 68.3 (2C), 47.2 (2C), 25.9 (3C), 25.9 (3C), 25.8 (6C), 18.4, 18.4, 18.3, 18.2, -4.7 (2C), -4.9, -4.9, -5.3, -5.3, -5.4, -5.5 ppm; **IR (ATR):**  $\tilde{\nu} = 3374, 2953, 2929, 2886, 1701, 1624, 1252, 1131, 1099, 831, 776, 733$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{26}\text{H}_{42}^{35}\text{ClO}_5\text{Si}_2]^+$ : 525.2254, found: 525.2253;  $R_f = 0.33$  ( $n$ -pentane/EtOAc 2/1).

**Tosylate 8,9-*cis*-275**

To an ice-cooled solution of diol 8,9-*cis*-**281** (390 mg, 0.743 mmol, *dr* = 1:1, 1.0 eq) and DMAP (13.6 mg, 0.111 mmol, 0.15 eq) in freshly distilled pyridine (6.0 mL) was added TsCl (566 mg, 2.97 mmol, 4.0 eq). The resulting yellow solution was allowed to warm to 23 °C and stirred for 15 h. The brown reaction mixture was cooled to 0 °C and quenched by addition of water (15 mL) and EtOAc (15 mL). The biphasic mixture was stirred for additional 10 min at 23 °C before the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with 1 M aq. HCl (2 x 40 mL), saturated aqueous sodium bicarbonate (15 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 5/1) to afford an inseparable 1:1 diastereomeric mixture of tosylate 8,9-*cis*-**275** (464 mg, 0.683 mmol, 92 %) as a white solid.

Characterization data for inseparable 1:1 mixture of diastereomers: **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.95 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.44 (br. d, *J* = 8.5 Hz, 4H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 6.57 (s, 1H), 6.57 (s, 1H), 5.71 (s, 1H), 5.70 (s, 1H), 5.24 - 5.18 (m, 2H), 3.67 - 3.63 (m, 2H), 3.60 - 3.50 (m, 2H), 2.90 (br. s, 1H), 2.87 (br. s, 1H), 2.59 - 2.46 (m, 10H), 0.88 (s, 9H), 0.88 (s, 9H), 0.86 (s, 9H), 0.85 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H), 0.01 (s, 6H), -0.01 (s, 6H), -0.03 (s, 3H), -0.03 (s, 3H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 206.1, 206.1, 170.2, 170.2, 146.2, 146.2, 143.1, 143.0, 142.9, 142.8, 133.0, 133.0, 132.4, 132.3, 131.2, 131.2, 130.6, 130.5, 130.3 (2C), 130.3 (2C), 128.2 (4C), 125.5, 125.2, 123.9, 123.8, 86.3, 86.1, 83.0, 82.9, 72.2, 72.0, 68.2, 68.2, 47.7 (2C), 25.9 (3C), 25.9 (3C), 25.8 (6C), 21.8 (2C), 18.4, 18.4, 18.2, 18.2, -4.7, -4.7, -5.0, -5.0, -5.3, -5.4, -5.5, -5.5 ppm; **IR (ATR):**  $\tilde{\nu}$  = 2954, 2929, 2857, 1718, 1630, 1372, 1255, 1177, 834, 779, 668, 567 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>33</sub>H<sub>48</sub><sup>35</sup>ClO<sub>7</sub>SSi<sub>2</sub>]<sup>+</sup>: 679.2342, found: 679.2335; **R<sub>f</sub>** = 0.30 (*n*-pentane/EtOAc 5/1).

**Primary alcohols 261a and 261b**

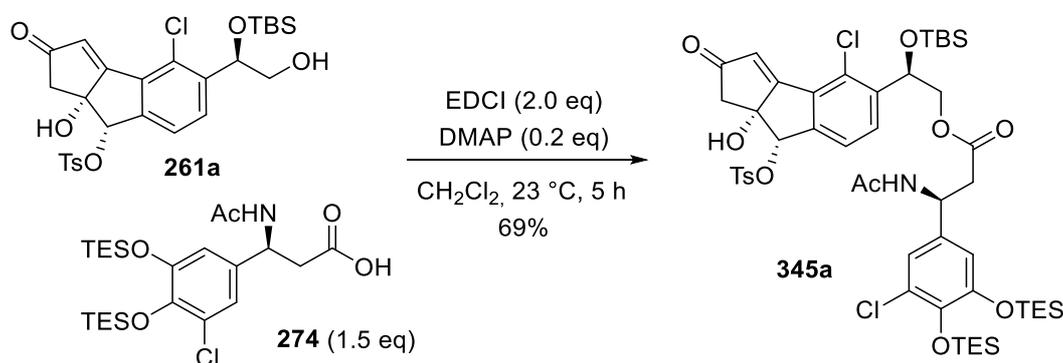
To an ice-cooled solution of tosylate **8,9-cis-275** (464 mg, 0.683 mmol, *dr* = 1:1, 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (13.0 mL, *v/v* = 1/1) was added CSA (39.7 mg, 0.171 mmol, 0.25 eq), and the resulting colorless solution was stirred at 0 °C. After 7 h, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (15 mL). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (4 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$  10/1 to 4/1) to afford primary alcohol **261a** (175 mg, 0.309 mmol, 45%) as a colorless foam along with its diastereomer **261b** (166 mg, 0.294 mmol, 43%) as a pale yellow foam.

**Primary alcohol 261a:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.92 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 1H), 6.51 (s, 1H), 5.67 (s, 1H), 5.25 (dd, *J* = 6.1, 3.1 Hz, 1H), 3.70 (ddd, *J* = 11.2, 8.0, 3.2 Hz, 1H), 3.55 - 3.44 (m, 1H), 3.00 (s, 1H), 2.54 - 2.35 (m, 5H), 2.06 (dd, *J* = 7.4, 6.0 Hz, 1H), 0.91 (s, 9H), 0.11 (s, 3H), -0.06 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CD}_2\text{Cl}_2$ )  $\delta$  = 206.4, 170.6, 147.0, 144.1, 142.4, 133.4, 132.8, 132.1, 130.9 (2C), 130.7, 128.7 (2C), 125.9, 124.5, 86.9, 83.6, 72.3, 67.2, 48.2, 26.1 (3C), 22.1, 18.6, -4.5, -4.7 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3402, 2953, 2929, 2857, 1710, 1629, 1365, 1191, 1177, 834, 811, 567  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+$  =  $[\text{C}_{27}\text{H}_{34}^{35}\text{ClO}_7\text{SSi}]^+$ : 565.1478, found: 565.1484;  $[\alpha]_{\text{D}}^{20}$  = -48.3 (*c* = 0.5,  $\text{CH}_2\text{Cl}_2$ ); **R<sub>f</sub>** = 0.31 (*n*-pentane/EtOAc 3/2).

**Diastereomer 261b:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.82 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.46 (s, 1H), 5.54 (s, 1H), 5.14 (dd, *J* = 6.1, 3.3 Hz, 1H), 3.64 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.41 (dd, *J* = 11.4, 6.2 Hz, 1H), 2.46 - 2.36 (m 2H), 2.39 (s, 3H), 2.23 (br. s, 2H), 0.81 (s, 9H), 0.00 (s, 3H), -0.16 (s, 3H) ppm;

$^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 206.2, 169.9, 146.2, 143.3, 141.7, 132.5, 132.2, 131.5, 130.3, 130.1, 128.2, 125.4, 123.9, 86.0, 82.9, 71.5, 66.7, 47.7, 25.8, 21.8, 18.1, -4.8, -5.0 ppm;  
**IR (ATR):**  $\tilde{\nu}$  = 3400, 2953, 2928, 2857, 1710, 1630, 1368, 1191, 1177, 1006, 869, 835, 668  $\text{cm}^{-1}$ ;  
**HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{27}\text{H}_{34}^{35}\text{ClO}_7\text{SSi}]^+$ : 565.1478, found: 565.1476;  
 $\alpha_{\text{D}}^{23} = -23.0$  ( $c = 0.5$ ,  $\text{CHCl}_3$ );  $R_{\text{f}} = 0.39$  ( $n$ -pentane/EtOAc 3/2).

### Keto ester 345a

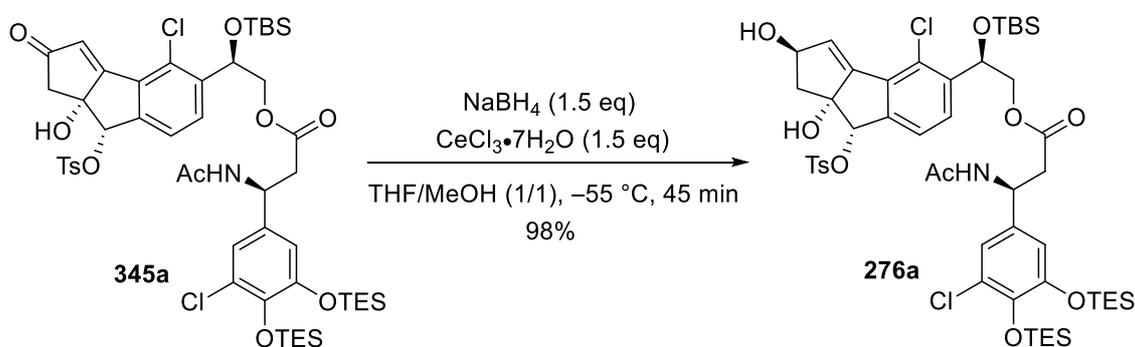


To an ice-cooled solution of  $\beta$ -amino acid **274** (242 mg, 0.481 mmol, 1.5 eq) and DMAP (7.84 mg, 0.064 mmol, 0.2 eq) in dry  $\text{CH}_2\text{Cl}_2$  (1.5 mL) was added EDCI (123 mg, 0.642 mmol, 2.0 eq). The resulting solution was allowed to warm to 23 °C and stirred for 30 min before being added to an ice-cooled suspension of alcohol **261a** (200 mg, 0.321 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (2.0 mL). The mixture was allowed to warm to 23 °C and was stirred for 5 h before it was quenched by addition of aqueous pH 7 phosphate buffer (15 mL) at 0 °C. The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (4 x 10 mL) and EtOAc (2 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/acetone 6/1 to 4/1) to afford keto ester **345a** (293 mg, 0.221 mmol, 69%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.94 (d,  $J = 8.3$  Hz, 2H), 7.72 (d,  $J = 8.0$  Hz, 1H), 7.48 (d,  $J = 8.0$  Hz, 1H), 7.40 (d,  $J = 8.3$  Hz, 2H), 6.73 (d,  $J = 2.3$  Hz, 1H), 6.62 (d,  $J = 2.3$  Hz, 1H), 6.53 (s, 1H), 6.02 (d,  $J = 8.3$  Hz, 1H), 5.70 (s, 1H), 5.46 (t,  $J = 6.8$  Hz, 1H), 5.38 (br. s, 1H), 5.03 (td,  $J = 8.4, 5.3$  Hz, 1H), 4.22 - 4.08 (m, 2H), 2.75 (dd,  $J = 15.6, 5.3$  Hz, 1H), 2.64 (dd,  $J = 15.6, 8.8$  Hz, 1H), 2.48 (s, 3H), 2.36 - 2.24 (m, 2H), 1.76 (s, 3H), 0.95 (td,  $J = 7.9, 4.0$  Hz, 18H), 0.87 (s, 9H), 0.79 - 0.71 (m, 12H), 0.08 (s, 3H), -0.07 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )

$\delta$  = 206.9, 171.1, 169.9, 169.7, 148.1, 145.7, 144.2, 143.3, 141.7, 133.5, 132.8, 132.2 (2C), 130.8, 130.0 (2C), 128.2 (2C), 126.6, 125.0, 124.4, 119.3, 116.7, 86.0, 83.0, 68.6, 67.4, 49.0, 47.9, 40.2, 25.6 (3C), 22.6, 21.8, 18.0, 6.7 (3C), 6.6 (3C), 5.4 (3C), 5.0 (3C), -4.9, -5.1 ppm; **IR** (**ATR**):  $\tilde{\nu}$  = 3289, 2955, 2936, 2878, 1719, 1490, 1490, 1177, 1004, 836, 746, 568  $\text{cm}^{-1}$ ; **HRMS** (**ESI**) calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{50}\text{H}_{72}^{35}\text{Cl}_2\text{NO}_{11}\text{SSi}_3]^+$ : 1048.3505, found: 1048.3506;  $[\alpha]_{\text{D}}^{20} = -40.8$  ( $c = 0.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.27$  ( $n$ -pentane/EtOAc 2/1).

### Cyclization precursor **276a**

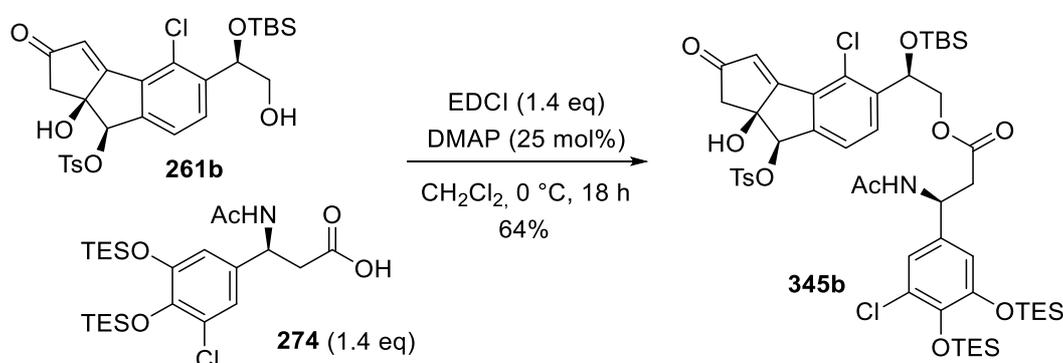


To a solution of keto ester **345a** (205 mg, 0.195 mmol, 1.0 eq) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (109 mg, 0.293 mmol, 1.5 eq) in dry THF/MeOH (6.5 mL, v/v = 1/1) at  $-55$  °C was added  $\text{NaBH}_4$  (11.1 mg, 0.293 mmol, 1.5 eq). The reaction mixture was stirred for 45 min maintaining a temperature between  $-60$  °C and  $-55$  °C before it was quenched by addition of acetone (1.0 mL). The mixture was allowed to warm to  $0$  °C and aqueous pH 7 phosphate buffer (10 mL) was added. The aqueous phase was extracted with EtOAc (3 x 15 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/acetone 4/1 to 2/1) to afford diastereomerically pure cyclization precursor **276a** (201 mg, 0.192 mmol, 98%) as a colorless oil.

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.92 (d,  $J = 8.3$  Hz, 2H), 7.50 (d,  $J = 8.0$  Hz, 1H), 7.40 (d,  $J = 8.3$  Hz, 2H), 7.27 (d,  $J = 8.0$  Hz, 1H), 6.79 (d,  $J = 2.3$  Hz, 1H), 6.64 (d,  $J = 2.3$  Hz, 1H), 6.36 (d,  $J = 1.5$  Hz, 1H), 6.34 (br. d,  $J = 8.3$  Hz, 1H), 5.63 (s, 1H), 5.58 - 5.47 (m, 1H), 5.36 (t,  $J = 6.3$  Hz, 1H), 5.20 - 5.07 (m, 1H), 4.14 (dd,  $J = 10.8, 5.5$  Hz, 1H), 3.99 (dd,  $J = 10.8, 6.8$  Hz, 1H), 3.86 (s, 1H), 2.80 - 2.67 (m, 2H), 2.47 (s, 3H), 2.37 (dd,  $J = 12.9, 5.6$  Hz, 1H), 2.21 (br. s, 1H), 1.88 (s, 3H), 1.61 (dd,  $J = 13.1, 6.8$  Hz, 1H), 0.99 - 0.92 (m, 18H), 0.86 (s, 9H), 0.81 - 0.70

(m, 12H), 0.05 (s, 3H), -0.08 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.4, 169.5, 148.0, 145.5, 145.5, 144.0, 143.1, 140.5, 133.6, 132.8, 132.5, 131.2, 130.0 (2C), 129.1, 128.5, 128.2 (2C), 126.5, 124.0, 119.7, 116.4, 91.2, 84.4, 81.2, 68.3, 68.1, 48.7, 48.0, 39.8, 25.6 (3C), 22.9, 21.7, 18.1, 6.7 (3C), 6.6 (3C), 5.3 (3C), 5.0 (3C), -5.0, -5.1 ppm; IR (ATR):  $\tilde{\nu}$  = 3308, 2955, 2934, 2878, 1741, 1657, 1490, 1254, 1176, 837, 748, 669, 565  $\text{cm}^{-1}$ ; HRMS (ESI) calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{50}\text{H}_{73}^{35}\text{Cl}_2\text{NNaO}_{11}\text{SSi}_3]^+$ : 1072.3481, found: 1072.3483;  $[\alpha]_{\text{D}}^{20} = -43.8$  ( $c = 0.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.36$  ( $n$ -pentane/EtOAc 2/3).

### Keto Ester **345b**

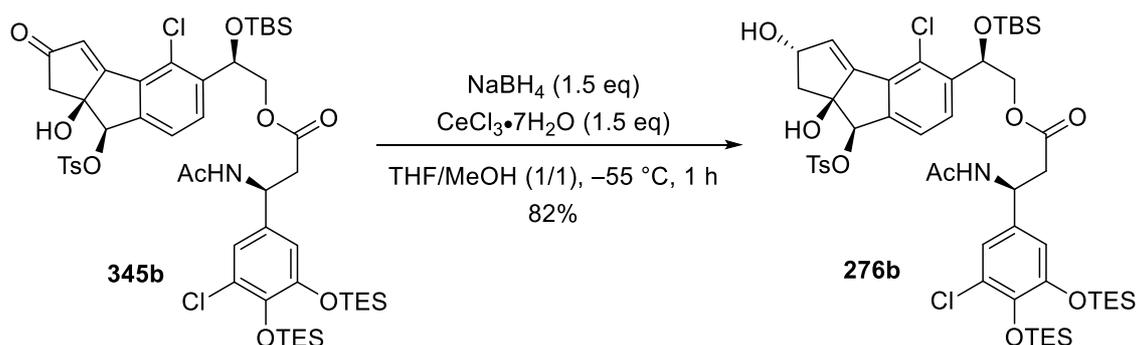


A 5 mL microwave vial was charged with alcohol **261b** (97.5 mg, 168  $\mu\text{mol}$ , 1.0 eq),  $\beta$ -amino acid **274** (115 mg, 229  $\mu\text{mol}$ , 1.4 eq, 1.4 eq) and DMAP (5.1 mg, 42.0  $\mu\text{mol}$ , 25 mol%), and the content was azeotroped with toluene (2 x 2 mL). The vial was sealed, placed under vacuum, and backfilled with  $\text{N}_2$  (3 x). Dry  $\text{CH}_2\text{Cl}_2$  (1.7 mL) was added and the resulting colorless solution was cooled with an ice bath. EDCI (45.0 mg, 236  $\mu\text{mol}$ , 1.4 eq) was then added and the homogenous solution was stirred at 0 °C for 18 h before being quenched by addition of sat. aqueous ammonium chloride (15 mL). The aqueous phase was extracted with EtOAc (4 x 15 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/EtOAc 3/1 to 3/2) to afford hydroxy ester **345b** (113.0 mg, 108  $\mu\text{mol}$ , 64%) as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 8.3$  Hz, 2H), 7.73 (d,  $J = 8.0$  Hz, 1H), 7.44 (d,  $J = 8.4$  Hz, 2H), 7.36 (d,  $J = 8.0$  Hz, 1H), 6.81 (d,  $J = 2.2$  Hz, 1H), 6.66 (d,  $J = 2.2$  Hz, 1H), 6.57 (s, 1H), 6.45 (d,  $J = 8.5$  Hz, 1H), 5.69 (s, 1H), 5.32 (dd,  $J = 7.2, 3.6$  Hz, 1H), 5.29 – 5.22 (m,

1H), 4.18 (dd,  $J = 11.2, 3.7$  Hz, 1H), 3.92 (dd,  $J = 11.2, 7.4$  Hz, 1H), 3.20 (br. s, 1H), 2.85 (dd,  $J = 16.1, 5.6$  Hz, 1H), 2.78 (dd,  $J = 16.2, 5.9$  Hz, 1H), 2.53 – 2.49 (m, 5H), 2.01 (s, 3H), 0.96 (q,  $J = 7.6$  Hz, 18H), 0.88 (s, 9H), 0.76 (q,  $J = 7.9$  Hz, 12H), 0.07 (s, 3H), -0.04 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  206.1, 170.7, 169.8, 169.2, 148.1, 146.2, 143.7, 143.3, 141.2, 133.4, 132.5, 132.2, 131.6, 130.3 (2C), 129.0, 128.2 (2C), 126.6, 125.5, 124.2, 119.8, 116.4, 86.1, 82.9, 68.9, 67.9, 48.4, 47.8, 39.4, 25.6 (3C), 23.3, 21.8, 18.1, 6.7 (3C), 6.6 (3C), 5.4 (3C), 5.0 (3C), -5.0, -5.0 ppm; **IR (ATR):**  $\tilde{\nu} = 3350, 2955, 2933, 2878, 1719, 1657, 1633, 1461, 1310, 1177, 1005, 837$   $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{50}\text{H}_{72}^{35}\text{Cl}_2\text{NO}_{11}\text{SSi}_3]^+$ : 1048.3505, found: 1048.3506;  $[\alpha]_{\text{D}}^{25} = -42.5$  ( $c = 0.2, \text{CHCl}_3$ ); **m.p.:** 88-90 °C; **R<sub>f</sub>** = 0.20 (*n*-pentane/EtOAc 2/1).

### Cyclization precursor **276b**

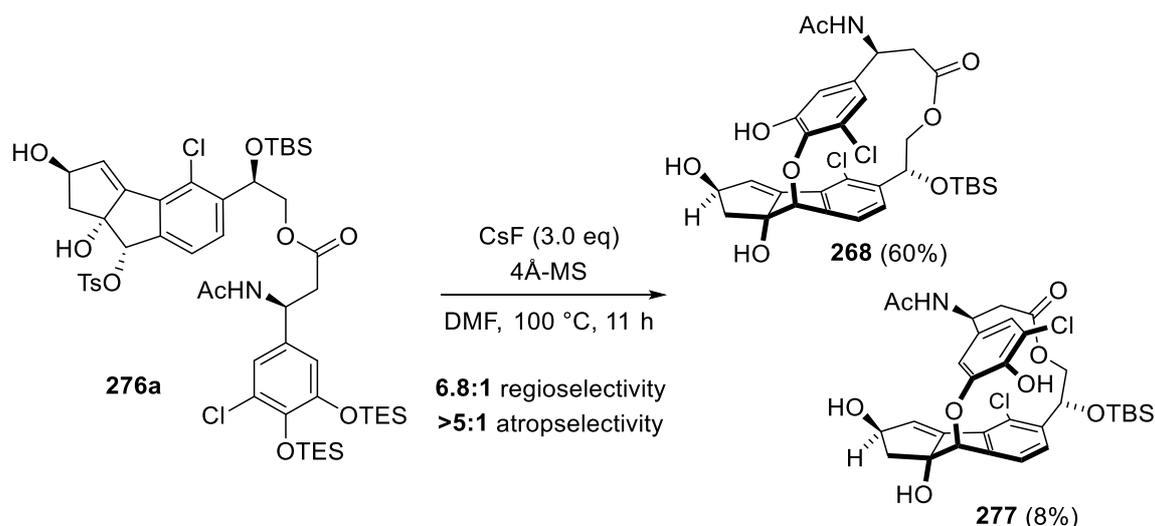


To a solution of keto ester **345b** (56.5 mg, 53.8  $\mu\text{mol}$ , 1.0 eq) and  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  (30.1 mg, 80.8  $\mu\text{mol}$ , 1.5 eq) in dry  $\text{THF}/\text{MeOH}$  (1.8 mL, v/v = 1/1) at  $-55$  °C was added  $\text{NaBH}_4$  (3.1 mg, 80.8  $\mu\text{mol}$ , 1.5 eq). The reaction mixture was stirred for 1 h maintaining a temperature between  $-60$  °C and  $-55$  °C before it was quenched by addition of acetone (0.5 mL). The mixture was allowed to warm to 0 °C and aqueous pH 7 phosphate buffer (15 mL) was added. The aqueous phase was extracted with EtOAc (3 x 15 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/acetone 4/1 to 2/1) to afford diastereomerically pure cyclization precursor **276b** (4.2 mg, 43.9  $\mu\text{mol}$ , 82%) as a colorless oil.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (d,  $J = 8.3$  Hz, 2H), 7.51 (d,  $J = 8.0$  Hz, 1H), 7.43 (d,  $J = 8.1$  Hz, 2H), 7.21 (d,  $J = 7.9$  Hz, 1H), 6.81 (d,  $J = 2.1$  Hz, 1H), 6.66 (d,  $J = 2.2$  Hz, 1H), 6.47 (d,  $J = 8.5$  Hz, 1H), 6.40 (d,  $J = 1.4$  Hz, 1H), 5.62 (s, 1H), 5.60 – 5.52 (m, 1H), 5.30 (dd,  $J = 7.3,$

3.9 Hz, 1H), 5.24 (dt,  $J = 8.4, 5.6$  Hz, 1H), 4.15 (dd,  $J = 11.1, 4.0$  Hz, 1H), 3.92 (dd,  $J = 11.1, 7.4$  Hz, 1H), 2.87 – 2.74 (m, 2H), 2.66 (s, 1H), 2.54 – 2.46 (m, 4H), 2.01 (s, 3H), 1.98 (d,  $J = 6.2$  Hz, 1H), 1.72 (dd,  $J = 13.2, 6.6$  Hz, 1H), 0.97 (q,  $J = 7.8$  Hz, 18H), 0.87 (s, 9H), 0.77 (q,  $J = 7.9$  Hz, 12H), 0.05 (s, 3H), -0.06 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8, 169.1, 148.1, 145.8, 144.9, 143.7, 143.2, 140.4, 133.5, 132.5, 132.2, 131.5, 130.2 (2C), 129.2, 128.3, 128.2 (2C), 126.6, 123.9, 119.9, 116.4, 91.1, 84.3, 81.1, 68.8, 68.2, 48.4, 48.1, 39.3, 25.6 (3C), 23.4, 21.8, 18.1, 6.7 (3C), 6.6 (3C), 5.4 (3C), 5.0 (3C), -4.9, -5.0 ppm; IR (ATR):  $\tilde{\nu} = 2956, 2932, 2878, 1741, 1656, 1490, 1371, 1310, 1252, 1177, 1004, 838, 745$   $\text{cm}^{-1}$ ; HRMS (ESI) calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{50}\text{H}_{73}^{35}\text{Cl}_2\text{NNaO}_{11}\text{SSi}_3]^+$ : 1072.3481, found: 1072.3482;  $[\alpha]_{\text{D}}^{20} = -45.8$  ( $c = 0.2, \text{CHCl}_3$ );  $R_f = 0.29$  ( $n$ -pentane/EtOAc 2/3).

### [2.6]Paracyclophane 268

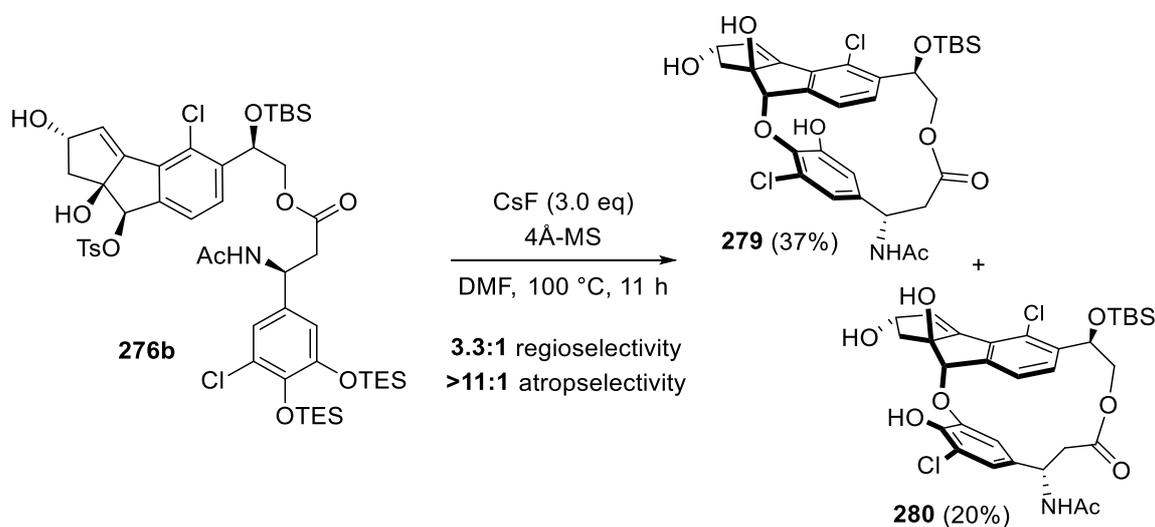


Cyclization precursor **276a** (232 mg, 0.221 mmol, 1.0 eq) was loaded into a 250 mL two-neck round- bottom flask and azeotroped with toluene (3 x 20 mL). Activated powdered 4Å-MS (720 mg) were then added, followed by freshly ground cesium fluoride (101 mg, 0.663 mmol, 3.0 eq) (glovebox). Freshly distilled DMF (120 mL) was added and the resulting mixture was stirred at 23 °C for 1 h under a  $\text{N}_2$  atmosphere before being heated to 100 °C. After 11 h the pale brown reaction mixture was allowed to cool to 23 °C, filtered through a short pad of Celite, and the solvent was removed under reduced pressure (45 °C). Remaining amounts of DMF were removed by azeotropic evaporation with toluene (3 x 10 mL). The obtained brown solid was

dissolved in MeOH- $d_4$  and subjected to  $^1\text{H}$  NMR analysis for determination of product ratios (**268:277** = 6.8:1). The crude product was purified by flash chromatography (toluene/acetone 2/1 to 1.5/1), followed by preparative HPLC (Chromolith column, *n*-hexane/EtOAc 2/3, 25 mL/min, 254 nm,  $t_{\text{r}}$ (major) = 12.3 min,  $t_{\text{r}}$ (minor) = 15.8 min), to afford [2.6]paracyclophane **268** (87.4 mg, 0.134 mmol, 60%) as a white solid along with [2.6]metacyclophane **277** (10.9 mg, 16.8  $\mu\text{mol}$ , 7.6%) as an off-white solid.

**[2.6]paracyclophane 268:**  $^1\text{H}$  NMR (400 MHz, Acetone- $d_6$ )  $\delta$  7.63 (d,  $J$  = 7.5 Hz, 1H), 7.22 (d,  $J$  = 7.5 Hz, 1H), 6.83 (d,  $J$  = 7.8 Hz, 1H), 6.76 (d,  $J$  = 2.3 Hz, 1H), 6.65 (s, 1H), 6.40 (d,  $J$  = 1.5 Hz, 1H), 6.22 (d,  $J$  = 2.3 Hz, 1H), 5.66-5.60 (m, 1H), 5.38 (s, 1H), 4.96 (ddd,  $J$  = 11.8, 7.9, 3.5 Hz, 1H), 4.89 (dd,  $J$  = 11.0, 4.0 Hz, 1H), 4.64 (s, 1H), 4.49 - 4.40 (m, 2H), 3.71 (dd,  $J$  = 10.0, 4.0 Hz, 1H), 2.80 (dd,  $J$  = 13.6, 3.5 Hz, 1H), 2.67 (dd,  $J$  = 13.6, 5.5 Hz, 1H), 2.49 (dd,  $J$  = 13.6, 6.0 Hz, 1H), 2.28 (dd,  $J$  = 13.6, 12.3 Hz, 1H), 1.87 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H), -0.02 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz, Acetone- $d_6$ )  $\delta$  = 169.7, 169.3, 152.3, 150.1, 147.5, 140.6, 140.4, 140.1, 136.9, 133.1, 131.6, 130.5, 130.5, 126.8, 116.4, 115.3, 94.4, 85.3, 82.1, 75.4, 66.7, 51.4, 44.0, 42.7, 26.2 (3C), 23.0, 18.8, -4.7, -5.0 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3289, 2950, 2855, 1735, 1656, 1259, 1144, 1111, 857, 839, 757, 667  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{31}\text{H}_{38}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 650.1738, found: 650.1738;  $[\alpha]_{\text{D}}^{20} = -244.2$  ( $c$  = 0.2,  $\text{CHCl}_3$ ), **m.p.:** 226 – 232  $^{\circ}\text{C}$  (decomp.); **R<sub>f</sub>** = 0.47 (EtOAc), 0.20 (toluene/acetone 2/1).

**[2.6]metacyclophane 277:**  $^1\text{H}$  NMR (400 MHz, Acetone- $d_6$ )  $\delta$  8.66 (s, 1H), 7.62 (br. d,  $J$  = 8.0 Hz, 1H), 7.08 (d,  $J$  = 2.3 Hz, 1H), 6.71 (d,  $J$  = 7.5 Hz, 1H), 6.47 (d,  $J$  = 1.5 Hz, 1H), 6.32 (d,  $J$  = 7.5 Hz, 1H), 5.84 (d,  $J$  = 2.0 Hz, 1H), 5.62 - 5.55 (m, 1H), 5.47 (t,  $J$  = 10.5 Hz, 1H), 5.22 (s, 1H), 4.94 (ddd,  $J$  = 11.2, 8.0, 1.9 Hz, 1H), 4.76 (dd,  $J$  = 10.7, 5.1 Hz, 1H), 4.46 (s, 1H), 4.31 (d,  $J$  = 8.0 Hz, 1H), 3.70 (dd,  $J$  = 10.4, 5.1 Hz, 1H), 2.73 (dd,  $J$  = 17.2, 1.9 Hz, 1H), 2.45 - 2.31 (m, 3H), 1.82 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), -0.07 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz, Acetone- $d_6$ )  $\delta$  = 169.8, 168.9, 149.0, 147.9, 147.2, 144.7, 139.1, 136.9, 136.1, 133.3, 132.4, 131.2, 126.2, 125.1, 122.5, 122.1, 93.0, 82.9, 82.2, 75.7, 64.3, 49.0, 43.7, 42.9, 26.1, 23.0, 18.7, -4.6, -4.9 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3375, 2954, 2857, 1746, 1641, 1426, 1253, 1110, 862, 839, 781  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{31}\text{H}_{38}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 650.1738, found 650.1738;  $[\alpha]_{\text{D}}^{20} = -183.3$  ( $c$  = 0.2,  $\text{CHCl}_3$ ), **m.p.:** 172 – 176  $^{\circ}\text{C}$  (decomp.); **R<sub>f</sub>** = 0.33 (toluene/acetone 1/1).

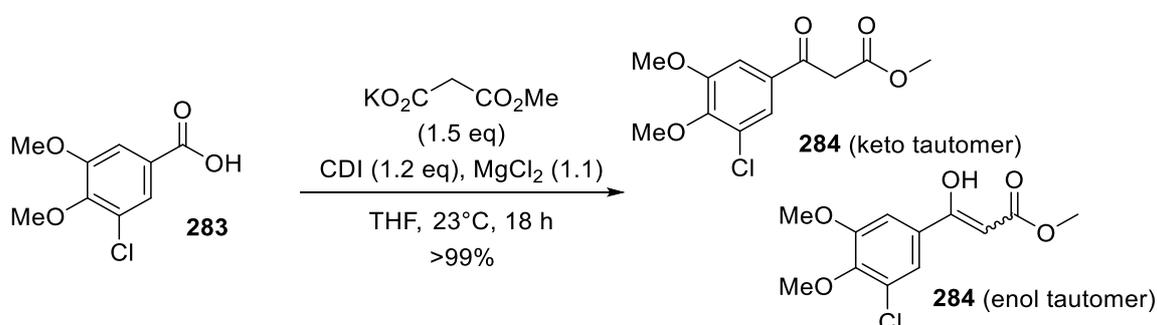
**[2.6]Paracyclophanes 279 and 280**

Cyclization precursor **276b** (45.0 mg, 42.8  $\mu\text{mol}$ , 1.0 eq) was loaded into a 25 mL two-necked flask and azeotroped with toluene (3 x 5 mL). Activated powdered 4Å-MS (140 mg) were then added, followed by freshly ground cesium fluoride (19.5 mg, 128  $\mu\text{mol}$ , 3.0 eq) (glovebox). The vial was sealed, freshly distilled DMF (21 mL) was added, and the resulting mixture was stirred at 23 °C for 1 h under a  $\text{N}_2$  atmosphere before being heated to 100 °C. After 11 h, the slightly brownish reaction mixture was allowed to cool to ambient temperature, filtered through a short pad of Celite, and the solvent was removed under reduced pressure (45 °C). Remaining amounts of DMF were removed by azeotropic evaporation with toluene (3 x 5 mL). The obtained brown solid was entirely dissolved in Acetone- $d_6$  and subjected to  $^1\text{H}$  NMR analysis for determination of product ratios (**279:280** = 3.3:1). The crude product was purified by flash chromatography (*n*-pentane/acetone 4/1 to 1/1), followed by preparative HPLC (Chromolith column, *n*-hexane/EtOAc 1/1.6, 25 mL/min, 254 nm,  $t_{\text{R}}$ (major) = 10.20 min,  $t_{\text{R}}$ (minor) = 18.1 min) to afford [2.6]paracyclophane **279** (10.3 mg, 15.8  $\mu\text{mol}$ , 37%) as a white foam, along with [2.6]metacyclophane **280** (5.6 mg, 8.61  $\mu\text{mol}$ , 20%) as a colorless film.

**[2.6]paracyclophane 279:**  $^1\text{H}$  NMR (400 MHz, Acetone- $d_6$ )  $\delta$  7.54 (d,  $J$  = 8.2 Hz, 1H), 7.25 (d,  $J$  = 7.9 Hz, 1H), 7.18 (d,  $J$  = 7.9 Hz, 1H), 6.74 (d,  $J$  = 2.1 Hz, 1H), 6.37 (d,  $J$  = 1.2 Hz, 1H), 6.30 (s, 1H), 6.27 (d,  $J$  = 2.1 Hz, 1H), 5.64 (t,  $J$  = 5.3 Hz, 1H), 5.52 - 5.47 (m, 1H), 5.42 (s, 1H), 5.03 (dt,  $J$  = 8.3, 4.7 Hz, 1H), 4.67 (s, 1H), 4.51 (s, 1H), 4.17 (dd,  $J$  = 11.6, 1.8 Hz, 1H), 4.03 (dd,  $J$  = 11.5, 2.6 Hz, 1H), 2.77 (dd,  $J$  = 14.7, 5.0 Hz, 1H), 2.61 (dd,  $J$  = 13.6, 5.8 Hz, 1H), 2.54 - 2.46 (m, 2H), 1.90 (s, 3H), 0.88 (s, 9H), 0.10 (s, 3H), -0.01 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,

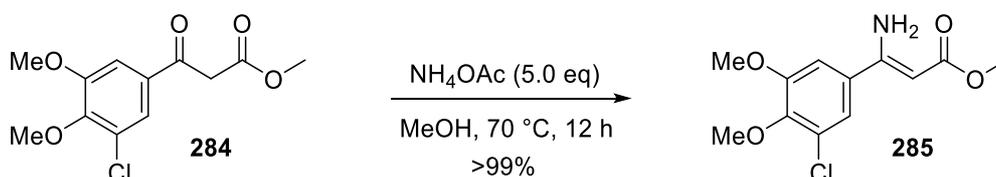
Acetone- $d_6$ )  $\delta$  172.2, 169.1, 152.7, 149.9, 146.9, 140.8, 140.5, 140.3, 134.7, 132.5, 130.0, 129.5, 127.8, 127.1, 119.5, 112.1, 94.0, 84.9, 82.0, 69.2, 68.1, 50.2, 42.7, 41.4, 26.2 (3C), 23.1, 18.8, -4.7, -4.8 ppm; **IR (ATR)**:  $\tilde{\nu}$  = 3401, 2953, 2930, 2857, 1719, 1659, 1517, 1383, 1126, 1011, 834, 778  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{31}\text{H}_{38}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 650.1738, found: 650.1734;  $[\alpha]_{\text{D}}^{20} = +187.5$  ( $c = 0.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.56$  ( $n$ -pentane/acetone 1/1).

**[2.6]metacyclophane 280**:  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.21 (d,  $J = 9.0$  Hz, 1H), 7.10 (d,  $J = 7.8$  Hz, 1H), 6.96 (d,  $J = 1.9$  Hz, 1H), 6.56 (s, 1H), 6.35 (d,  $J = 7.8$  Hz, 1H), 6.17 (br. s, 1H), 5.95 (d,  $J = 1.9$  Hz, 1H), 5.72 (t,  $J = 5.8$  Hz, 1H), 5.38 – 5.33 (m, 1H), 5.22 (s, 1H), 5.11 (dd,  $J = 11.3, 2.0$  Hz, 1H), 5.00 - 4.94 (m, 1H), 3.85 (dd,  $J = 11.3, 2.6$  Hz, 1H), 3.80 – 3.62 (m, 1H), 2.78 (dd,  $J = 18.2, 6.4$  Hz, 1H), 2.57 - 2.45 (m, 2H), 2.37 (dd,  $J = 13.2, 6.6$  Hz, 1H), 2.16 (d,  $J = 16.3$  Hz, 1H), 1.93 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), -0.03 (s, 3H) ppm;  **$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  170.9, 169.5, 148.3, 145.4, 145.3, 143.3, 139.9, 133.6, 133.2, 131.3, 128.8, 127.7, 126.4, 125.0, 122.7, 120.1, 92.8, 82.2, 82.0, 69.7, 66.3, 48.2, 42.4, 38.6, 25.7 (3C), 23.5, 18.2, -4.9, -5.1 ppm; **IR (ATR)**:  $\tilde{\nu}$  = 3313, 2954, 2929, 2857, 1742, 1653, 1493, 1430, 1255, 1174, 1102, 837, 781  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{31}\text{H}_{38}^{35}\text{Cl}_2\text{NO}_8\text{Si}]^+$ : 650.1738, found: 650.1739;  $[\alpha]_{\text{D}}^{20} = +124.2$  ( $c = 0.2$ ,  $\text{CHCl}_3$ );  $R_f = 0.45$  ( $n$ -pentane/acetone 1/1).

10.4.3 2<sup>nd</sup> Generation Synthesis of the  $\beta$ -Amino Acid from 5-Chloroveratric acid $\beta$ -Keto ester **284**

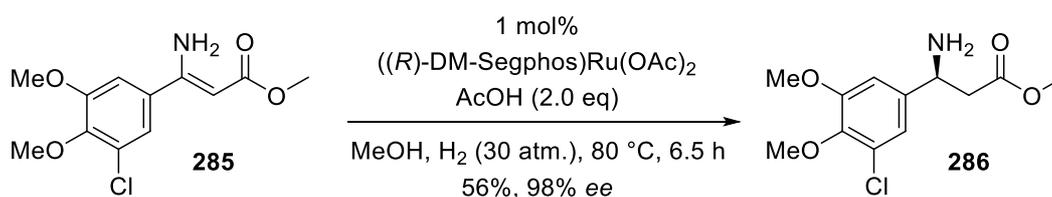
Freshly dried MgCl<sub>2</sub> (231 mg, 2.42 mmol, 1.1) and potassium 3-methoxy-3-oxopropanoate (541 mg, 3.46 mmol, 1.5 eq) were suspended in dry THF (3.6 mL) and stirred at 50 °C for 4 h. In a separate flask, a solution of benzoic acid **283** (500 mg, 2.31 mmol) in dry THF (8.5 mL) was cooled to 0 °C and CDI (449 mg, 2.77 mmol, 1.2 eq) was added portionwise over 15 min. The resulting suspension was allowed to warm to 23 °C and became homogenous after 1.5 h. The solution of activated benzoic acid **283** was then slowly added to the first suspension at 23 °C and stirring was continued for 18 h. The reaction was quenched by slow addition of 1 N aq. HCl (10 mL). The aqueous phase was extracted with EtOAc (3 x 10 mL), the combined organic layers were washed with saturated aqueous sodium bicarbonate (15 mL), brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. Crude  $\beta$ -keto ester **284** (629 mg, 2.31 mmol, >99%) was obtained as a mixture of tautomers (5:1 in favor of the keto tautomer) and the colorless oil was used in the next step without further purification.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  (keto tautomer) = 7.55 (d,  $J$  = 1.8 Hz, 1H), 7.47 (d,  $J$  = 1.8 Hz, 1H), 3.96 (s, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.77 (s, 3H) ppm;  $\delta$  (enol tautomer) = 12.52 (s, 1H), 7.41 (d,  $J$  = 1.8 Hz, 1H), 7.25 (d,  $J$  = 1.8 Hz, 1H), 5.61 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.82 (s, 3H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  (keto tautomer) = 109.3, 167.6, 153.8, 150.2, 131.8, 128.3, 123.3, 110.4, 60.8, 56.2, 52.5, 45.4;  $\delta$  (enol tautomer) = 173.3, 169.8, 153.6, 147.9, 129.5, 121.9, 120.0, 108.6, 87.2, 60.8, 56.2, 51.5; IR (ATR):  $\tilde{\nu}$  = 2948, 1745, 1686, 1569, 1406, 1327, 1289, 1144, 1040, 998, 855 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M+H]<sup>+</sup> = [C<sub>12</sub>H<sub>14</sub><sup>35</sup>ClO<sub>5</sub>]<sup>+</sup>: 273.0524, found: 273.0525; **R<sub>f</sub>** = 0.46 (*n*-pentane/EtOAc 3/1).

**Enamine 285**

A 10 mL round-bottom flask was charged with crude  $\beta$ -keto ester **284** (629 mg, 2.31 mmol, 1.0 eq) and ammonium acetate (890 mg, 11.5 mmol, 5.0 eq). Dry MeOH (4.6 mL) was added and the resulting solution was stirred at reflux. After 12 h heating was stopped and the mixture was stirred at 23 °C for 13 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and washed with saturated aqueous sodium bicarbonate (15 mL) and brine (10 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure to afford enamine **285** (626 mg, 2.30 mmol, >99%) as a colorless oil, which was used in next step without further purification.

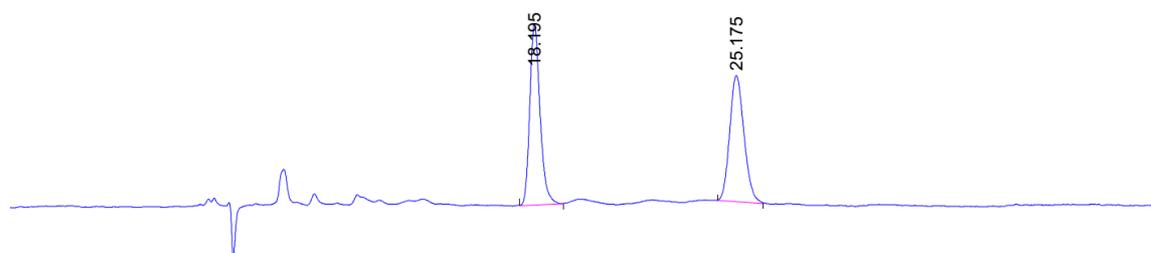
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 7.18 (d,  $J$  = 2.3 Hz, 1H), 6.97 (d,  $J$  = 2.3 Hz, 1H), 4.93 (s, 1H), 3.91 (s, 3H), 3.91 (s, 3H), 3.73 (s, 3H) ppm (the protons of the amino group were not detected in CDCl<sub>3</sub>); <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 170.4, 159.1, 153.9, 146.9, 134.0, 128.7, 119.8, 108.9, 84.5, 60.8, 56.2, 50.5 ppm; IR (ATR):  $\tilde{\nu}$  = 3444, 3328, 2945, 1666, 1672, 1556, 1489, 1263, 1163, 1050, 998, 855, 792 cm<sup>-1</sup>; HRMS (ESI) calc'd. for [M+H]<sup>+</sup> = [C<sub>12</sub>H<sub>15</sub><sup>35</sup>ClNO<sub>4</sub>]<sup>+</sup>: 272.0684, found: 272.0673;  $R_f$  = 0.44 (*n*-pentane/Et<sub>2</sub>O 1/1).

 **$\beta$ -Amino Ester 286**

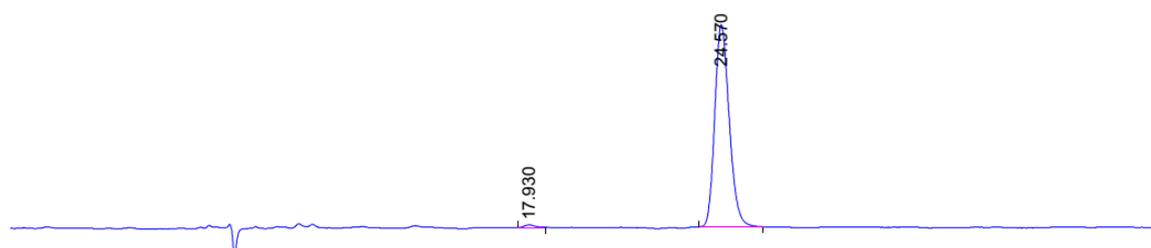
A vial was charged with enamine **285** (432 mg, 1.59 mmol, 1.0 eq) and ((*R*)-DM-Segphos)Ru(OAc)<sub>2</sub> (15.0 mg, 0.016 mmol, 1.0 mol%). The vial was sealed with a rubber septum, placed under vacuum and backfilled with argon (3 x). Dry MeOH (1.6 mL) and acetic acid (182  $\mu$ l, 3.18 mmol, 2.0 eq) were added, resulting in deep green/black solution. The vial was placed in an autoclave and the rubber septum was pierced by two short cannula. The

autoclave was closed and purged with H<sub>2</sub> (3 x 10 atm.). Finally, H<sub>2</sub> (30 atm.) was applied and the autoclave was heated to 80 °C under vigorous stirring. After 6.5 h, the autoclave was placed in an ice-bath and remaining H<sub>2</sub> was released. The reaction mixture was diluted with EtOAc and washed with saturated aqueous sodium bicarbonate (15 mL). The aqueous phase was extracted with EtOAc (3 x 15 mL), the combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (EtOAc/aq. NH<sub>3</sub> (25%) 100/0 to 100/1 to 100/2) to afford  $\beta$ -amino ester **286** (245 mg, 0.895 mmol, 56%, 98% *ee*) as a pale brown gum.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.98 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 4.37 (dd, *J* = 7.5, 6.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.70 (s, 3H), 2.70 – 2.58 (m, 2H), 1.90 (br. s, 2H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 172.1, 153.9, 144.6, 140.6, 128.2, 119.5, 108.9, 60.6, 56.1, 52.1, 51.8, 43.4 ppm; **IR (ATR)**:  $\tilde{\nu}$  = 3380, 2941, 2833, 1731, 1574, 1491, 1279, 1138, 1050, 1002, 848 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>12</sub>H<sub>17</sub><sup>35</sup>CINO<sub>4</sub>]<sup>+</sup>: 274.0841, found: 274.0843; **[ $\alpha$ ]<sub>D</sub><sup>25</sup>** = -9.5 (*c* = 1.0, CHCl<sub>3</sub>); **R<sub>f</sub>** = 0.50 (EtOAc/aq. NH<sub>3</sub> (25%) 50/1); **HPLC separation** (Chiralpak IC, 4.6 x 250 mm; 60% (*i*PrOH + 0.25% HNBu<sub>2</sub>)/*n*-hexane, 0.5 mL/min, 224 nm; *t<sub>R</sub>*(minor) = 17.9 min, *t<sub>R</sub>*(major) = 24.6 min), 98% *ee*.

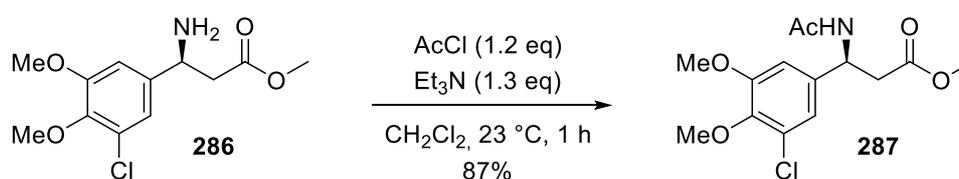


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.195	VB	0.3754	3869.62012	155.99609	50.7765
2	25.175	BV	0.4885	3751.26709	108.73959	49.2235



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.930	BB	0.2966	102.82481	4.30582	0.8653
2	24.570	BB	0.5331	1.17804e4	339.23050	99.1347

### $\beta$ -Acetamido ester **287**

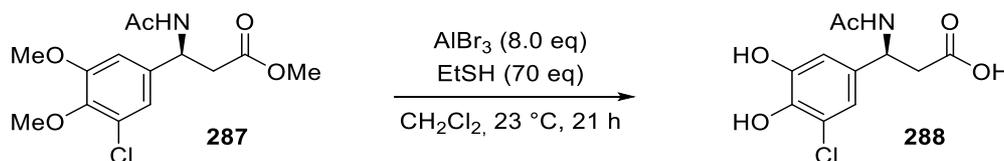


To an ice-cooled solution of  $\beta$ -amino ester **286** (195 mg, 0.705 mmol, 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (5.7 mL) was added freshly distilled Et<sub>3</sub>N (129  $\mu$ L, 0.926 mmol, 1.3 eq) and acetyl chloride (58.3  $\mu$ L, 0.819 mmol, 1.2 eq). The reaction mixture was stirred at 0 °C for 15 min before the cooling bath was removed and the mixture was allowed to warm to 23 °C. After 1 h, the reaction was quenched by addition of saturated aqueous sodium bicarbonate (10 mL). The aqueous phase

was extracted with  $\text{CH}_2\text{Cl}_2$  (4 x 10 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/acetone 2.5/1) to afford  $\beta$ -acetamido ester **287** (193 mg, 0.611 mmol, 87%) as a white solid.

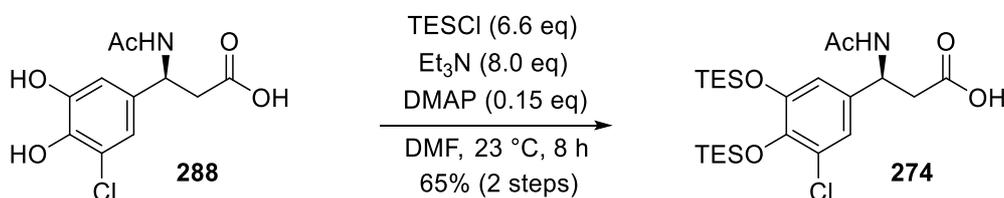
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 6.89 (dd,  $J$  = 2.0, 0.6 Hz, 1H), 6.77 (d,  $J$  = 2.0 Hz, 1H), 6.60 (br. d,  $J$  = 8.3 Hz, 1H), 5.33 (dt,  $J$  = 8.3, 5.9 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.66 (s, 3H), 2.88 (dd,  $J$  = 15.9, 5.9 Hz, 1H), 2.81 (dd,  $J$  = 15.9, 5.9 Hz, 1H), 2.05 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  = 171.5, 169.3, 153.8, 144.7, 137.3, 128.4, 119.2, 109.6, 60.6, 56.1, 51.9, 49.2, 39.6, 23.3 ppm; **IR (ATR)**:  $\tilde{\nu}$  = 3280, 3068, 2946, 2833, 1737, 1651, 1542, 1493, 1432, 1371, 1283, 1237, 1144, 1050, 1001, 851  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{14}\text{H}_{19}^{35}\text{ClNO}_5]^+$ : 316.0946, found: 316.0949;  $[\alpha]_{\text{D}}^{24} = -68.8$  ( $c$  = 1.0,  $\text{CHCl}_3$ ); **m.p.**: 125 – 126 °C; **R<sub>f</sub>** = 0.19 (*n*-pentane/acetone 2.5/1).

### Catechol carboxylic acid **288**



To an ice-cooled solution of aluminum tribromide (4.16 g, 15.6 mmol, 8.0 eq) in ethanethiol (10.1 mL, 136 mmol, 70 eq) was added a solution of  $\beta$ -acetamido ester **287** (0.615 g, 1.95 mmol, 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (9.4 mL). The mixture was allowed to warm to 23 °C and stirred for 21 h before being quenched by addition of 2 M aq. HCl (20 mL) and diluted with EtOAc. The aqueous phase was saturated with NaCl and extracted with EtOAc (8 x 20 mL) until the product could no longer be detected in the aqueous phase (TLC). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure to afford crude catechol carboxylic acid **288** (653 mg, ~82% purity) as a brown foam, which was used in the next step without further purification.

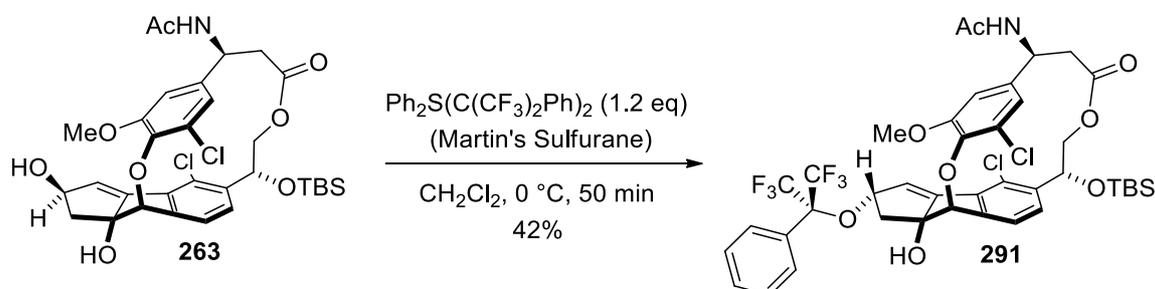
**R<sub>f</sub>** = 0.19 ( $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{AcOH}$  10/1/0.5).

**$\beta$ -Amino acid 274**

To a stirred solution of crude catechol carboxylic acid **288** (300 mg, ~82% purity, 0.899 mmol, 1.0 eq) and DMAP (16.7 mg, 0.136 mmol, 0.15 eq) in dry DMF (4.5 mL) was added triethylamine (1.02 mL, 7.28 mmol, 8.0 eq). The resulting suspension was cooled to 0 °C before TESCl (0.616 mL, 3.64 mmol, 4.0 eq) was added dropwise. The reaction mixture was then allowed to warm to 23 °C and stirred for 4 h before additional TESCl (0.40 mL, 2.36 mmol, 2.6 eq) was added. The reaction was stirred for 4 h at 23 °C, and was then quenched by addition of saturated aqueous ammonium chloride (15 mL). The aqueous phase was extracted with Et<sub>2</sub>O (3 x 15 mL), the combined organic layers were washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH 10/1/0 to 100/2/1) to afford  $\beta$ -amino acid **274** (293 mg, 0.583 mmol, 65% over 2 steps) as a colorless oil.

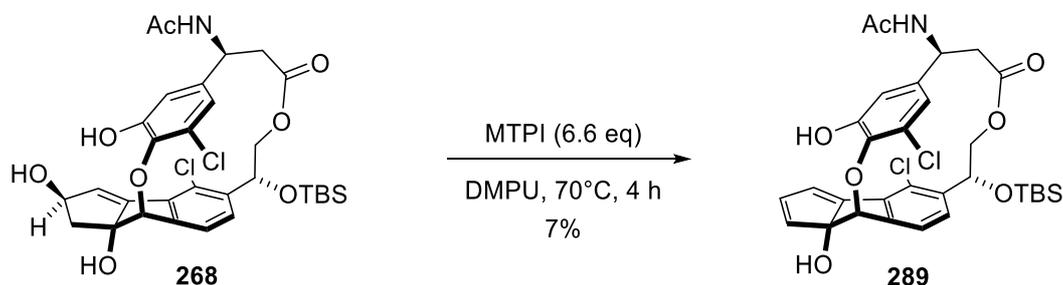
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 6.87 (d,  $J$  = 2.3 Hz, 1H), 6.68 (d,  $J$  = 2.3 Hz, 1H), 6.47 (d,  $J$  = 8.5 Hz, 1H), 5.32 (dt,  $J$  = 8.4, 5.8 Hz, 1H), 2.91 (dd,  $J$  = 16.1, 5.8 Hz, 1H), 2.82 (dd,  $J$  = 16.1, 5.8 Hz, 1H), 2.04 (s, 3H), 0.97 (td,  $J$  = 7.8, 6.0 Hz, 18H), 0.82 - 0.73 (m, 12H) ppm (the carboxylic acid proton of pure **274** was not detected in CDCl<sub>3</sub>, but in the crude product: 9.60 (br. s, 1H)); **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 175.0, 170.1, 148.2, 143.4, 133.3, 126.6, 119.8, 116.4, 48.6, 39.5, 23.2, 6.7 (3C), 6.6 (3C), 5.4 (3C), 5.0 (3C) ppm; **IR (ATR)**:  $\tilde{\nu}$  = 3271, 3075, 2956, 2878, 1716, 1653, 1566, 1490, 1425, 1310, 1005, 911, 744 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>23</sub>H<sub>41</sub><sup>35</sup>ClNO<sub>5</sub>Si<sub>2</sub>]<sup>+</sup>: 502.2206, found: 502.2210; **[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = -54.8 ( $c$  = 1.0, CHCl<sub>3</sub>); **R<sub>f</sub>** = 0.16 (CH<sub>2</sub>Cl<sub>2</sub>/MeOH/AcOH 100/2/1).

## 10.4.4 Studies Targeting Dehydration of the C-11 Allylic Alcohol

Bis(trifluoromethyl)benzyl ether **291**

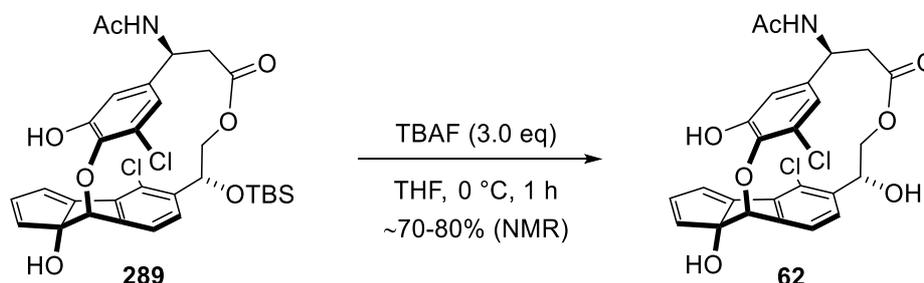
A vial was charged with [2.6]paracyclophane **263** (1.8 mg, 2.71  $\mu\text{mol}$ , 1.0 eq) and the content was azeotroped with toluene (3 x 0.2 mL). The vial was then sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). Dry  $\text{CH}_2\text{Cl}_2$  (180  $\mu\text{L}$ ) was added and the resulting colorless solution was cooled with an ice bath. A solution of Martin's sulfurane (2.2 mg, 3.25  $\mu\text{mol}$ , 1.2 eq) in dry  $\text{CH}_2\text{Cl}_2$  (20  $\mu\text{L}$ ) was added and the resulting yellow solution was stirred at  $0\text{ }^\circ\text{C}$  for 50 min before being quenched by addition of sat. aqueous sodium bicarbonate (3 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/2.5) to afford bis(trifluoromethyl)benzyl ether **291** (1.0 mg, 1.12  $\mu\text{mol}$ , 42%) as a pale yellow oil.

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.80 – 7.71 (m, 2H), 7.58 – 7.53 (m, 3H), 7.20 (d,  $J = 7.7\text{ Hz}$ , 1H), 6.66 (d,  $J = 7.8\text{ Hz}$ , 1H), 6.57 (d,  $J = 2.0\text{ Hz}$ , 1H), 6.47 (d,  $J = 2.8\text{ Hz}$ , 1H), 6.15 (d,  $J = 2.0\text{ Hz}$ , 1H), 5.74 (d,  $J = 6.9\text{ Hz}$ , 1H), 5.56 (s, 1H), 5.10 (dd,  $J = 5.9, 2.9\text{ Hz}$ , 1H), 5.03 (ddd,  $J = 11.0, 6.9, 3.5\text{ Hz}$ , 1H), 4.75 (dd,  $J = 10.8, 4.1\text{ Hz}$ , 1H), 4.59 (t,  $J = 10.6\text{ Hz}$ , 1H), 3.72 (dd,  $J = 10.3, 4.1\text{ Hz}$ , 1H), 3.19 – 3.11 (m, 4H), 2.93 (dd,  $J = 13.8, 3.5\text{ Hz}$ , 1H), 2.51 (s, 1H), 2.36 (d,  $J = 14.3\text{ Hz}$ , 1H), 2.22 – 2.14 (m, 1H), 2.01 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), -0.04 (s, 3H) ppm;  
**HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{41}\text{H}_{43}\text{Cl}_2\text{F}_6\text{NNaO}_8\text{Si}]^+$ : 912.1931, found 912.1923;  
 $R_f = 0.67$  (EtOAc).

**Cyclopentadienol 289**

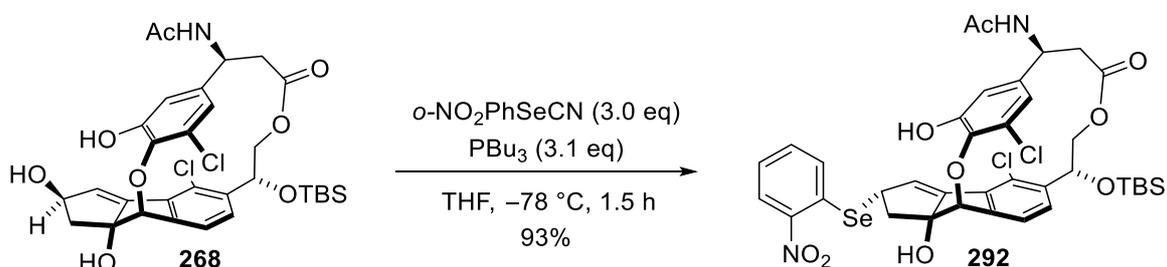
A microwave vial was charged with [2.6]paracyclophane **268** (8.4 mg, 12.9  $\mu\text{mol}$ , 1.0 eq) and the content was azeotroped with toluene (3 x 1.0 mL). The vial was then sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). A solution of MTPI (29.2 mg, 64.6  $\mu\text{mol}$ , 5.0 eq) in freshly distilled DMPU (300  $\mu\text{l}$ ) was added and the yellow reaction mixture was stirred at 70 °C. After 3.5 h, additional MTPI (9.3 mg, 20.7  $\mu\text{mol}$ , 1.6 eq) in DMPU (100  $\mu\text{l}$ ) was added and stirring was continued at 70 °C for an additional 30 min. The brown reaction mixture was then allowed to cool to 23 °C, quenched by addition of MeOH (0.5 mL) and diluted with Et<sub>2</sub>O (10 mL). The organic phase was washed with sat. aqueous sodium thiosulfate (2 x 5 mL), water (3 x 5 mL) and brine (5 mL). The organic layer was then dried over  $\text{MgSO}_4$ , filtered, and the solvent were removed under reduced pressure (25 °C). The crude product was purified by flash chromatography (toluene/acetone 1.5:1), followed by preparative HPLC (Chromolith column, *n*-hexane/EtOAc 1/1, 25 mL/min, 254 nm,  $t_{\text{R}}$  = 15.3 min) to afford unstable cyclopentadienol **289** (0.6 mg, 0.95  $\mu\text{mol}$ , 7%) as a pale yellow amorphous solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40 (d,  $J$  = 7.7 Hz, 1H), 6.92 (d,  $J$  = 1.8 Hz, 1H), 6.85 (dd,  $J$  = 5.4, 1.9 Hz, 1H), 6.81 (d,  $J$  = 5.3 Hz, 1H), 6.69 (d,  $J$  = 7.8 Hz, 1H), 6.48 (d,  $J$  = 2.1 Hz, 1H), 6.30 (d,  $J$  = 2.1 Hz, 1H), 6.03 (s, 1H), 5.69 (d,  $J$  = 6.5 Hz, 1H), 5.09 (s, 1H), 4.94 (ddd,  $J$  = 11.1, 6.6, 3.4 Hz, 1H), 4.78 (dd,  $J$  = 10.8, 4.2 Hz, 1H), 4.54 (t,  $J$  = 10.6 Hz, 1H), 3.77 (dd,  $J$  = 10.3, 4.2 Hz, 1H), 2.96 (dd,  $J$  = 13.3, 3.5 Hz, 1H), 2.63 (s, 1H), 2.17 (dd,  $J$  = 13.4, 11.7 Hz, 1H), 2.00 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), -0.05 (s, 3H) ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{31}\text{H}_{36}^{35}\text{Cl}_2\text{NO}_7\text{Si}]^+$ : 632.1633, found 632.1629;  $R_{\text{f}}$  = 0.65 (toluene/acetone 1:1).

**Fijiolide A aglycone 62**

To an ice-cooled solution of cyclopentadienol **289** (0.6 mg, 0.95  $\mu\text{mol}$ , 1.0 eq) in dry THF (300  $\mu\text{L}$ ) was added a solution of TBAF (1.0 M in THF, 2.85  $\mu\text{L}$ , 3.0 eq) and the resulting reaction mixture was stirred at 0  $^{\circ}\text{C}$ . Formation of white precipitate was observed after  $\sim 30$  min, and the reaction was quenched after 1 h by addition of aqueous pH 7 buffer (3 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (toluene/acetone 2:1 to 1:1) to afford unstable fijiolide A aglycone **62** (yield *n.d.*) as an amorphous off-white solid.

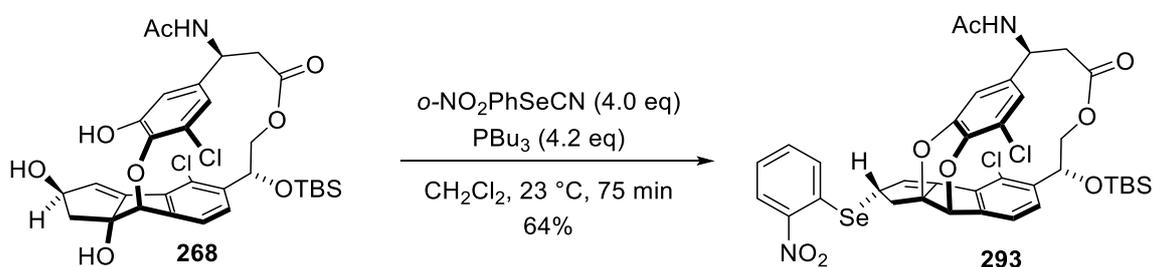
$^1\text{H NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  8.40 (d,  $J = 8.2$  Hz, 1H), 8.10 (s, 1H), 7.19 (d,  $J = 7.7$  Hz, 1H), 6.73 (d,  $J = 7.8$  Hz, 1H), 6.69 (d,  $J = 1.9$  Hz, 1H), 6.66 (dd,  $J = 5.4, 2.0$  Hz, 1H), 6.60 – 6.57 (m, 2H), 6.04 (d,  $J = 2.0$  Hz, 1H), 5.81 (d,  $J = 4.0$  Hz, 1H), 5.66 (s, 1H), 5.55 (s, 1H), 4.76 – 4.65 (m, 2H), 4.39 – 4.32 (m, 1H), 3.70 (dd,  $J = 9.8, 3.9$  Hz, 1H), 2.69 – 2.65 (m, 1H), 2.18 – 2.09 (m, 1H), 1.80 (s, 3H) ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{25}\text{H}_{22}^{35}\text{Cl}_2\text{NO}_7]^+$ : 518.0768, found 518.0752;  $R_f = 0.32$  (toluene/acetone 1:1).

**Selenide 292**

To a solution of [2.6]paracyclophane **268** (28.0 mg, 43.0  $\mu\text{mol}$ , 1.0 eq) and *o*- $\text{NO}_2\text{PhSeCN}$  (14.8 mg, 64.5  $\mu\text{mol}$ , 1.5 eq) in dry THF (1.4 mL) at  $-78$   $^{\circ}\text{C}$  was added tributylphosphine (16.7

$\mu\text{l}$ , 66.7  $\mu\text{mol}$ , 1.1 eq) dropwise. The resulting red mixture was stirred at  $-78\text{ }^{\circ}\text{C}$  for 45 min before additional *o*-NO<sub>2</sub>PhSeCN (14.8 mg, 64.5  $\mu\text{mol}$ , 1.5 eq) in dry THF (0.2 mL) and tributylphosphine (16.7  $\mu\text{l}$ , 66.7  $\mu\text{mol}$ , 1.1 eq) was added. After stirring at  $-78\text{ }^{\circ}\text{C}$  for an additional 45 min, the reaction was quenched by addition of pH 7 phosphate buffer (8 mL) and diluted with EtOAc. The mixture was allowed to warm to  $23\text{ }^{\circ}\text{C}$ , the aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure ( $30\text{ }^{\circ}\text{C}$ ). The crude product was purified by flash chromatography (toluene/acetone 6/1 to 4/1 to 2/1) to afford selenide **292** (33.6 mg, 40.3  $\mu\text{mol}$ , 93 %) as a yellow solid.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.37 (dd,  $J$  = 8.3, 1.5 Hz, 1H), 7.76 - 7.72 (m, 1H), 7.66 (td,  $J$  = 7.7, 1.5 Hz, 1H), 7.43 (ddd,  $J$  = 8.3, 7.2, 1.1 Hz, 1H), 7.20 (d,  $J$  = 7.5 Hz, 1H), 6.73 (d,  $J$  = 3.3 Hz, 1H), 6.67 (d,  $J$  = 7.8 Hz, 1H), 6.55 (d,  $J$  = 2.0 Hz, 1H), 6.30 (d,  $J$  = 2.0 Hz, 1H), 5.89 (br. d,  $J$  = 6.8 Hz, 1H), 5.59 (s, 1H), 5.22 (s, 1H), 5.05 (dd,  $J$  = 7.0, 3.3 Hz, 1H), 5.00 (ddd,  $J$  = 11.1, 7.2, 3.9 Hz, 1H), 4.77 (dd,  $J$  = 10.8, 4.0 Hz, 1H), 4.41 (t,  $J$  = 10.5 Hz, 1H), 3.79 (dd,  $J$  = 10.3, 4.0 Hz, 1H), 3.61 (dd,  $J$  = 14.6, 7.0 Hz, 1H), 2.88 (dd,  $J$  = 13.1, 3.5 Hz, 1H), 2.60 (br. s, 1H), 2.50 (d,  $J$  = 14.6 Hz, 1H), 2.19 (dd,  $J$  = 13.1, 11.8 Hz, 1H), 2.03 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), -0.04 (s, 3H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 169.3, 168.6, 152.7, 150.8, 147.5, 146.5, 139.8, 139.4, 138.4, 134.2, 134.1, 133.7, 131.2, 130.9, 129.6, 129.4, 126.7, 126.2, 126.0, 126.0, 115.1, 114.0, 93.5, 83.3, 74.3, 66.6, 50.9, 48.2, 43.0, 37.6, 25.7 (3C), 23.4, 18.1, -4.9, -5.3 ppm; **IR (ATR)**:  $\tilde{\nu}$  = 2955, 2928, 2856, 1737, 1658, 1517, 1331, 1303, 1260, 1146, 1115, 855, 839 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>37</sub>H<sub>41</sub><sup>35</sup>Cl<sub>2</sub>N<sub>2</sub>O<sub>9</sub>SeSi]<sup>+</sup>: 835.1118, found 835.1114; **[ $\alpha$ ]<sub>D</sub><sup>20</sup>** = -295.8 ( $c$  = 0.2, CHCl<sub>3</sub>); **m.p.**: 174 – 179 °C (decomp.); **R<sub>f</sub>** = 0.24 (*n*-pentane/EtOAc 1/2), 0.39 (toluene/acetone 2/1).

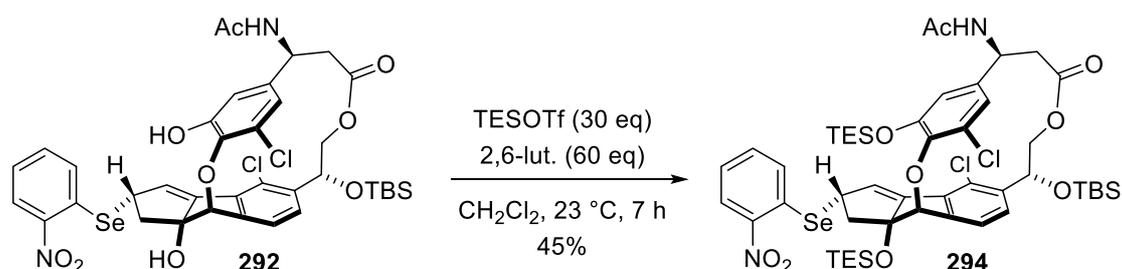
**Doubly bridged bis-aryl ether 293**

A vial was charged with [2.6]paracyclophane **268** (5.0 mg, 7.68  $\mu\text{mol}$ , 1.0 eq) and the content was azeotroped with toluene (3 x 0.3 mL). The vial was then sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). The solid was dissolved in dry  $\text{CH}_2\text{Cl}_2$  (100  $\mu\text{L}$ ) and cooled to 0  $^\circ\text{C}$ . A solution of *o*- $\text{NO}_2\text{PhSeCN}$  (3.5 mg, 15.4  $\mu\text{mol}$ , 2.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (50  $\mu\text{L}$ ) was added, followed by tributylphosphine (4.03  $\mu\text{L}$ , 16.2  $\mu\text{mol}$ , 2.1 eq). The resulting red mixture was stirred at 0  $^\circ\text{C}$  for 5 min and then allowed to warm to 23  $^\circ\text{C}$ . After 45 min, additional *o*- $\text{NO}_2\text{PhSeCN}$  (3.5 mg, 15.4  $\mu\text{mol}$ , 2.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (50  $\mu\text{L}$ ) and tributylphosphine (4.03  $\mu\text{L}$ , 16.2  $\mu\text{mol}$ , 2.1 eq) was added. After stirring at 23  $^\circ\text{C}$  for an additional 30 min, the reaction was quenched by addition of pH 7 phosphate buffer (5 mL) and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure (30  $^\circ\text{C}$ ). The crude product was purified by flash chromatography (toluene/acetone 5/1 to 3/1) to afford doubly bridged *bis*-aryl ether **293** (4.1 mg, 4.91  $\mu\text{mol}$ , 64%) as a yellow solid.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (dd,  $J = 8.3, 1.4$  Hz, 1H), 7.79 (d,  $J = 7.6$  Hz, 1H), 7.67 (td,  $J = 8.2, 7.8, 1.4$  Hz, 1H), 7.46 – 7.37 (m, 1H), 7.00 (d,  $J = 8.3$  Hz, 1H), 6.77 (d,  $J = 7.8$  Hz, 1H), 6.65 (d,  $J = 1.9$  Hz, 1H), 6.58 (d,  $J = 1.9$  Hz, 1H), 6.44 (d,  $J = 1.5$  Hz, 1H), 5.93 (s, 1H), 5.79 (d,  $J = 5.1$  Hz, 1H), 5.44 (t,  $J = 10.5$  Hz, 1H), 5.25 (t,  $J = 6.1$  Hz, 1H), 4.92 (ddd,  $J = 10.7, 6.1, 3.1$  Hz, 1H), 4.66 (dd,  $J = 10.2, 5.0$  Hz, 1H), 3.59 (dd,  $J = 10.8, 5.0$  Hz, 1H), 3.21 (dd,  $J = 14.2, 5.9$  Hz, 1H), 2.96 (dd,  $J = 15.8, 3.2$  Hz, 1H), 2.44 (dd,  $J = 14.2, 7.4$  Hz, 1H), 2.12 (dd,  $J = 15.8, 11.0$  Hz, 1H), 1.99 (s, 3H), 0.84 (s, 9H), 0.02 (s, 3H), -0.13 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  169.5, 168.4, 148.5, 146.6, 146.5, 144.5, 142.5, 142.0, 137.7, 136.8, 135.7, 134.2, 133.5, 132.2, 130.8, 129.7, 127.1, 126.7, 126.0, 125.0, 122.4, 118.7, 118.5, 104.6, 84.2, 74.2, 50.7, 47.2, 42.1, 40.5, 25.6 (3C), 23.4, 18.1, -4.9, -5.2 ppm; IR (ATR):  $\tilde{\nu} = 2953, 2924, 2853, 1737, 1656, 1515, 1461, 1377, 1303, 1260, 1147, 1100, 856, 781, 730$   $\text{cm}^{-1}$ ; HRMS (ESI)

calc'd. for  $[M+H]^+ = [C_{37}H_{39}^{35}Cl_2N_2O_8SeSi]^+$ : 817.1012, found 817.1015;  $R_f = 0.42$  (toluene/acetone 3/1).

### Bis-TES ether **294**

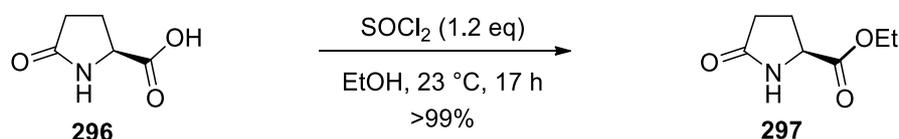


To an ice-cooled solution of selenide **292** (3.5 mg, 4.19  $\mu$ mol, 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (500  $\mu$ l) was added freshly distilled 2,6-lutidine (4.88  $\mu$ l, 41.9  $\mu$ mol, 10 eq) and TESOTf (4.74  $\mu$ l, 21.0  $\mu$ mol, 5.0 eq). The resulting dark yellow reaction mixture was stirred at 0 °C for 5 min and then allowed to warm to 23 °C. After 60 min, additional 2,6-lutidine (4.88  $\mu$ l, 41.9  $\mu$ mol, 10 eq) and TESOTf (4.74  $\mu$ l, 21.0  $\mu$ mol, 5.0 eq) was added and stirring was continued at 23 °C. After 4.5 h, additional 2,6-lutidine (19.5  $\mu$ L, 168  $\mu$ mol, 40 eq) and TESOTf (19.0  $\mu$ L, 83.8  $\mu$ mol, 20 eq) was added. After a total reaction time of 7 h, the reaction was quenched by addition of aqueous pH 7 phosphate buffer (5 mL) and diluted with EtOAc. The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were washed with brine (5 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/acetone 4/1 to 3/1) to afford *bis*-TES ether **294** (2.0 mg, 1.88  $\mu$ mol, 45%) as a pale yellow oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.33 (dd,  $J = 8.3, 1.4$  Hz, 1H), 7.75 (d,  $J = 8.0$  Hz, 1H), 7.62 – 7.58 (m, 1H), 7.36 (t,  $J = 7.4$  Hz, 1H), 7.19 (d,  $J = 7.7$  Hz, 1H), 6.63 – 6.55 (m, 3H), 6.23 (d,  $J = 2.0$  Hz, 1H), 5.78 (d,  $J = 6.6$  Hz, 1H), 5.54 (s, 1H), 5.01 (ddd,  $J = 10.9, 6.8, 3.3$  Hz, 1H), 4.92 (dd,  $J = 7.5, 3.3$  Hz, 1H), 4.78 (dd,  $J = 10.7, 4.2$  Hz, 1H), 4.50 (t,  $J = 10.5$  Hz, 1H), 3.75 (dd,  $J = 10.3, 4.2$  Hz, 1H), 3.61 (dd,  $J = 13.4, 7.5$  Hz, 1H), 2.97 (dd,  $J = 13.9, 3.5$  Hz, 1H), 2.37 – 2.30 (m, 1H), 2.22 – 2.18 (m, 1H), 2.04 (s, 3H), 0.95 (t,  $J = 7.9$  Hz, 9H), 0.88 (s, 9H), 0.81 (t,  $J = 7.9$  Hz, 9H), 0.73 – 0.67 (m, 6H), 0.43 – 0.29 (m, 6H), 0.03 (s, 3H), -0.06 (s, 3H) ppm; HRMS (ESI) calc'd. for  $[M+H]^+ = [C_{49}H_{69}^{35}Cl_2N_2O_9SeSi_3]^+$ : 1053.2848, found 1063.2850;  $R_f = 0.36$  (*n*-pentane/acetone 3/1).

## 10.5 Synthesis and Activation of the Amino Sugar Moiety

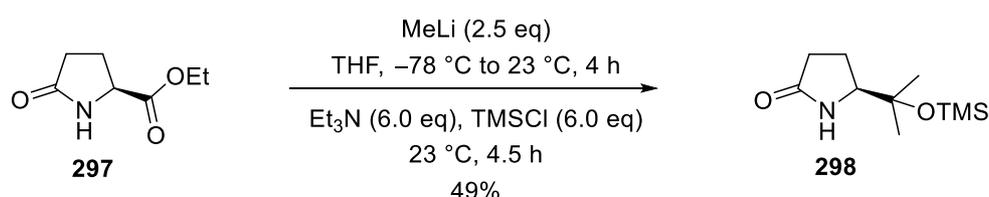
### Ethyl L-pyroglutamate **297**



To an ice-cooled suspension of L-pyroglutamic acid **296** (15.0 g, 116 mmol, 1.0 eq) in dry EtOH (50 mL) was added thionyl chloride (10.2 mL, 139 mmol, 1.2 eq) dropwise *via* a dropping funnel. The reaction mixture was allowed to slowly warm to 23 °C and stirred for 17 h before all volatiles were removed under reduced pressure. The resulting greenish oil was taken up in EtOAc (250 mL) and stirred over  $\text{K}_2\text{CO}_3$  (40.0 g, 289 mmol, 2.5 eq) for 45 min. The mixture was then filtered, the organic phase was dried over  $\text{MgSO}_4$ , filtered again, and the solvent was removed under reduced pressure to afford ethyl L-pyroglutamate **297** (18.9 g, 96 wt.%, 115 mmol, >99%) as a pale yellow solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.71 (br. s, 1H), 4.25 – 4.17 (m, 3H), 2.52 – 2.27 (m, 3H), 2.25 – 2.15 (m, 1H), 1.28 (t,  $J = 7.1$  Hz, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.0, 172.0, 61.6, 55.4, 29.2, 24.7, 14.1 ppm.

### Tertiary TMS ether **298**

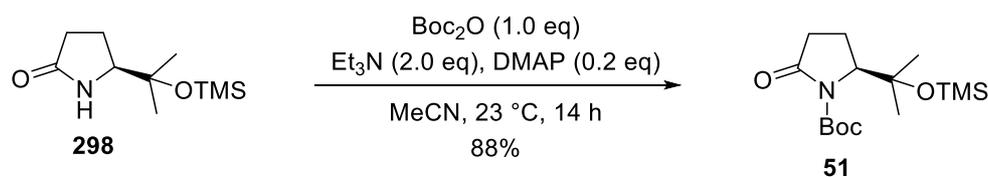


To a solution of (*S*)-ethyl 5-oxopyrrolidine-2-carboxylate (9.90 g, 63.0 mmol, 1.0 mmol) in dry THF (315 mL) was added a solution of MeLi (1.6 M in  $\text{Et}_2\text{O}$ , 98.0 mL, 157 mmol, 2.5 eq) over 40 min at  $-78$  °C. The reaction mixture was stirred for further 10 min at  $-78$  °C before the cooling bath was removed and the reaction mixture was allowed to warm to 23 °C within 1 h. After stirring at 23 °C for further 3 h,  $\text{Et}_3\text{N}$  (53.6 mL, 384 mmol, 6.1 eq) and TMSCl (48.3 mL, 378 mmol, 6.0 eq) were added to the reaction mixture. The resulting suspension was stirred at 23 °C for further 4.5 h before being quenched by addition of sat. aqueous ammonium chloride (200 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 x 100 mL), the combined

organic layers were washed with brine (100 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/1 to 0/1) to afford tertiary TMS ether **298** (6.63 g, 30.8 mmol, 49%) as a colorless oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.31 (br. s, 1H), 3.49 (dd,  $J = 8.2, 5.3$  Hz, 1H), 2.40 – 2.24 (m, 2H), 2.13 – 2.02 (m, 1H), 1.89 – 1.79 (m, 1H), 1.21 (s, 3H), 1.16 (s, 3H), 0.11 (s, 9H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  178.8, 75.2, 64.1, 30.4, 25.9, 24.9, 21.8, 2.3 (3C) ppm; **IR** (ATR):  $\tilde{\nu} = 3206, 3097, 2957, 1691, 1462, 1385, 1248, 1172, 1142, 1039, 834, 750$   $\text{cm}^{-1}$ ; **HRMS** (ESI) calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{10}\text{H}_{22}\text{NO}_2\text{Si}]^+$ : 216.1414, found 216.1417;  $R_f = 0.27$  (*n*-pentane/EtOAc 1/2).

### Boc protected $\gamma$ -lactam **51**

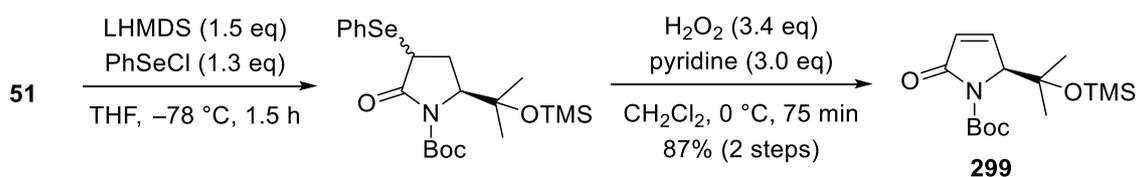


To an ice-cooled solution of TMS ether **298** (6.18 g, 28.7 mmol, 1.0 eq) and DMAP (701 mg, 5.74 mmol, 0.2 eq) in dry MeCN (137 mL) was added  $\text{Et}_3\text{N}$  (8.00 mL, 57.4 mmol, 2.0 eq) and  $\text{Boc}_2\text{O}$  (11.9 g, 54.5 mmol, 1.9 eq). The resulting slightly brown solution was allowed to slowly warm to 23 °C under stirring. After 14 h, the dark brown reaction mixture was quenched with sat. aqueous ammonium chloride (150 mL) at 0 °C. The aqueous phase was extracted with EtOAc (3 x 100 mL), the combined organic layers were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 10/1 to 5/1) to afford Boc protected  $\gamma$ -lactam **51** (8.00 g, 25.4 mmol, 88%) as a yellow oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.06 (dd,  $J = 8.7, 0.9$  Hz, 1H), 2.68 (ddd,  $J = 17.6, 11.3, 9.3$  Hz, 1H), 2.30 (ddd,  $J = 17.6, 10.1, 1.3$  Hz, 1H), 2.10 (dd,  $J = 12.8, 9.2$  Hz, 1H), 2.05 – 1.92 (m, 1H), 1.52 (s, 9H), 1.28 (s, 3H), 1.23 (s, 3H), 0.10 (s, 9H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  175.7, 150.8, 82.5, 77.1, 65.6, 32.9, 27.9 (3C), 27.9, 27.2, 20.6, 2.4 (3C) ppm; **IR** (ATR):  $\tilde{\nu} = 2979, 1786, 1750, 1713, 1366, 1301, 1249, 1151, 1137, 1036, 876, 839$   $\text{cm}^{-1}$ ; **HRMS** (ESI)

calc'd. for  $[M+Na]^+ = [C_{15}H_{29}NNaO_4Si]^+$ : 338.1758, found 338.1755;  $[\alpha]_D^{20} = -48.2$  ( $c = 1.0$ ,  $CHCl_3$ );  $R_f = 0.48$  ( $n$ -pentane/EtOAc 5/1).

### Unsaturated $\gamma$ -lactam **299**

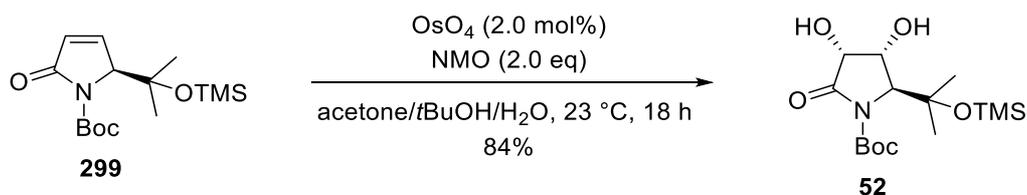


**Steps 1:** To an ice-cooled solution of hexamethyldisilazane (9.73 mL, 45.8 mmol, 1.6 eq) in dry THF (60 mL) was added a solution of  $nBuLi$  (1.6 M in  $n$ -hexane, 26.8 mL, 43.0 mmol, 1.5 eq) over a period of 5 min. The resulting solution was stirred at  $0\text{ }^\circ\text{C}$  for 30 min before being cooled to  $-78\text{ }^\circ\text{C}$ . A solution of  $\gamma$ -lactam **51** (9.04 g, 28.6 mmol, 1.0 eq) in dry THF (60 mL) was slowly added over 10 min *via* cannula. The yellow solution was stirred at  $-78\text{ }^\circ\text{C}$  for 50 min before a solution of PhSeCl (6.86 g, 35.8 mmol, 1.3 eq) in dry THF (30 mL) was added dropwise. Stirring was continued at  $-78\text{ }^\circ\text{C}$  for 1.5 h before the dark reaction mixture was quenched by addition of sat. aqueous ammonium chloride (150 mL) at  $-78\text{ }^\circ\text{C}$  and allowed to warm to  $23\text{ }^\circ\text{C}$ . The aqueous phase was extracted with EtOAc (3 x 70 mL), the combined organic layers were washed with brine (70 mL), dried over  $Na_2SO_4$ , filtered, and the solvent was removed under reduced pressure. The crude phenylselenide was obtained as a yellow oil and used in the next step without further purification.

**Steps 2:** To an ice-cooled solution of crude phenylselenide (synthesized from 28.6 mmol  $\gamma$ -lactam **51**) in  $CH_2Cl_2$  (143 mL) was subsequently added pyridine (6.94 mL, 85.8 mmol, 3.0 eq) and aqueous  $H_2O_2$  (30 wt.%, 9.93 mL, 97.3 mmol, 3.4 eq). The resulting yellow solution was stirred at  $0\text{ }^\circ\text{C}$  for 75 min before being diluted with  $CH_2Cl_2$  (100 mL). The organic phase was washed with water (70 mL), sat. aqueous sodium thiosulfate (70 mL) and brine (70 mL), dried over  $MgSO_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography ( $n$ -pentane/EtOAc 15/1 to 5/1) to afford unsaturated  $\gamma$ -lactam **299** (7.83 g, 25.0 mmol, 87%) as a pale yellow oil.

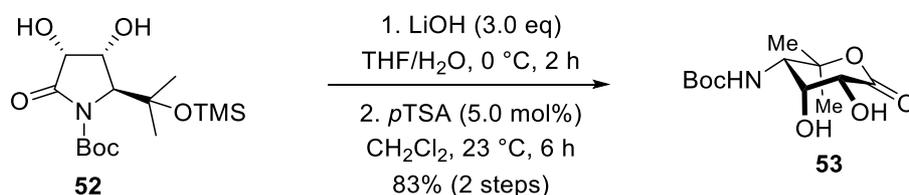
$^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.27 – 7.24 (m, 1H), 6.10 (dd,  $J = 6.1, 1.2$  Hz, 1H), 4.73 (t,  $J = 1.6$  Hz, 1H), 1.56 (s, 9H), 1.38 (s, 3H), 1.10 (s, 3H), 0.14 (s, 9H) ppm;  $^{13}C\{^1H\}$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  170.4, 151.2, 150.3, 126.5, 83.0, 76.3, 69.9, 29.7, 28.0 (3C), 25.4, 2.4 (3C)

ppm; **IR (ATR):**  $\tilde{\nu}$  = 2980, 1781, 1741, 1719, 1368, 1298, 1250, 1153, 1035, 837, 751  $\text{cm}^{-1}$ ;  
**HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{15}\text{H}_{27}\text{NNaO}_4\text{Si}]^+$ : 336.1602, found 336.1609;  
 $[\alpha]_{\text{D}}^{24} = -197.8$  ( $c = 1.0$ ,  $\text{CH}_2\text{Cl}_2$ ); **R<sub>f</sub>** = 0.44 (*n*-pentane/EtOAc 7/1).

**Diol 52**

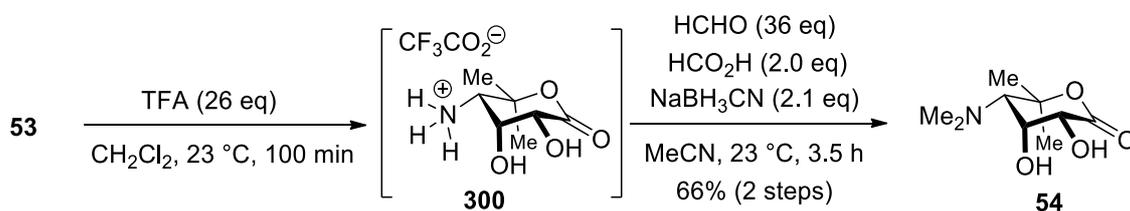
To a solution of unsaturated  $\gamma$ -lactam **299** (7.80 g, 24.9 mmol, 1.0 eq) in acetone/*t*BuOH/ $\text{H}_2\text{O}$  (42 mL,  $v/v = 1/3.3/1.2$ ) was subsequently added NMO (5.83 g, 49.8 mmol, 2.0 eq) and a solution of  $\text{OsO}_4$  (5% wt.% in  $\text{H}_2\text{O}$ , 2.53 mL, 0.498 mmol, 2.0 mol%). The brown reaction mixture was then stirred at 23 °C for 18 h before being quenched by addition of sat. aqueous sodium thiosulfate (20 mL) at 0 °C. Stirring was then continued at 0 °C for 30 min and additional sat. aqueous sodium thiosulfate (20 mL) was added. The aqueous phase was extracted with EtOAc (3 x 40 mL), the combined organic layers were washed with sat. aqueous sodium thiosulfate (30 mL) and brine (30 mL), dried over  $\text{MgSO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 2/1 to 1/1) to afford diol **52** (7.24 g, 20.8 mmol, 84%) as a pale yellow oil.

**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.60 (d,  $J = 4.8$  Hz, 1H), 4.45 (d,  $J = 4.9$  Hz, 1H), 4.01 (s, 1H), 3.59 (br. s, 1H), 3.18 (br. s, 1H), 1.52 (s, 9H), 1.42 (s, 3H), 1.23 (s, 3H), 0.09 (s, 9H) ppm;  
 **$^{13}\text{C}\{^1\text{H}\}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  175.0, 150.7, 83.6, 75.4, 71.9, 71.5, 68.6, 28.2, 27.8 (3C), 27.7, 2.3 (3C) ppm; **IR (ATR):**  $\tilde{\nu}$  = 3434, 2980, 1779, 1724, 1367, 1292, 1250, 1151, 1126, 1027, 895, 837, 730  $\text{cm}^{-1}$ ; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{Na}]^+ = [\text{C}_{15}\text{H}_{29}\text{NNaO}_6\text{Si}]^+$ : 370.1656, found 370.1654;  $[\alpha]_{\text{D}}^{24} = -21.7$  ( $c = 1.0$ ,  $\text{CHCl}_3$ ); **R<sub>f</sub>** = 0.57 (*n*-pentane/EtOAc 1/2).

**$\delta$ -Lactone 53**

To an ice-cooled solution of diol **52** (7.24 g, 20.8 mmol, 1.0 eq) in THF (70 mL) was added a solution of lithium hydroxide (1.1 M in H<sub>2</sub>O, 57.3 mL, 62.5 mmol, 3.0 eq) and the resulting slightly yellow biphasic mixture was stirred at 0 °C. After 2.5 h, the reaction mixture was diluted with water (35 mL) and acidified with 15 wt.% aqueous potassium bisulfate (80 mL). The aqueous phase was saturated with sodium chloride and extracted with EtOAc (4 x 70 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The obtained pale yellow foam was taken up in dry CH<sub>2</sub>Cl<sub>2</sub> (70 mL) and *p*TSA (198 mg, 1.04 mmol, 5.0 mol%) was added. The resulting solution was stirred at 23 °C for 6 h before being poured into ice-cooled sat. aqueous sodium bicarbonate (50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL), the combined organic layers were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc 1/1 to 1/2) to afford  $\delta$ -lactone **53** (5.42 g, 17.3 mmol, 83% over 2 steps) as a colorless oil.

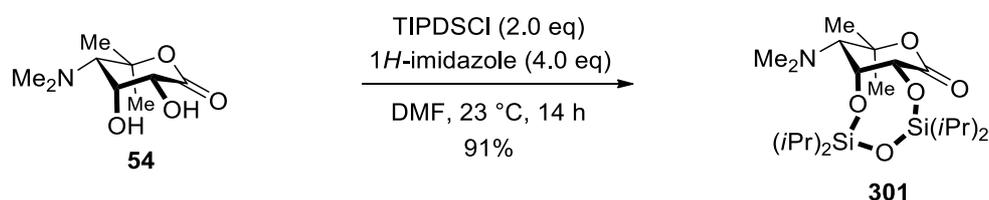
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  5.96 – 5.43 (m, 1H), 4.27 (s, 3H), 4.09 (d, *J* = 9.8 Hz, 1H), 3.93 – 3.76 (m, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 1.45 (s, 9H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  172.6, 155.4, 87.6, 80.4, 70.8, 69.8, 53.6, 30.1, 28.3 (3C), 25.5 ppm; **IR (ATR)**:  $\tilde{\nu}$  = 3435, 2980, 2936, 1703, 1501, 1368, 1248, 1162, 1116, 1004, 914, 878, 731 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+Na]<sup>+</sup> = [C<sub>12</sub>H<sub>21</sub>NNaO<sub>6</sub>]<sup>+</sup>: 298.1261, found 298.1260; **[ $\alpha$ ]<sub>D</sub><sup>24</sup>** = +9.5 (*c* = 1.0, CHCl<sub>3</sub>); **R<sub>f</sub>** = 0.45 (*n*-pentane/EtOAc 1/2).

**Dimethyl amine 54**

**Step 1:** To an ice-cooled solution of  $\delta$ -lactone **53** (2.40 g, 8.72 mmol, 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (70 mL) was added TFA (17.5 mL, 227 mmol, 26 eq) dropwise. The resulting colorless solution was stirred at 0 °C for 5 min and then allowed to warm to 23 °C. After 100 min, toluene (3 x 4 mL) was added and all volatiles were azeotropically removed under reduced pressure (30 °C).

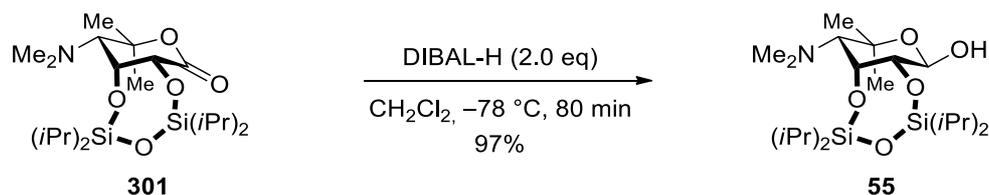
**Step 2:** The obtained yellow residue was dissolved in MeCN (43 mL) at 0 °C. Aqueous formaldehyde (30% wt.%, 28.8 mL, 314 mmol, 36 eq) was added, followed by formic acid (0.669 mL, 17.4 mmol, 2.0 eq) and  $\text{NaBH}_3\text{CN}$  (1.18 g, 17.9 mmol, 2.1 eq). After stirring for 10 min at 0 °C, the reaction mixture was allowed to warm to 23 °C and stirred for 3.5 h. The reaction was then quenched by addition of sat. aqueous sodium bicarbonate (50 mL) at 0 °C. The aqueous phase was saturated with NaCl and the pH was adjusted to pH 10 with 2 M NaOH. The aqueous phase was then extracted with  $\text{CHCl}_3$  (5 x 50 mL), the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/acetone 4/1 to 3/1) to afford dimethylamine **54** (1.17 g, 5.76 mmol, 66%) as a colorless oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.54 – 4.48 (m, 1H), 4.08 (d,  $J = 2.9$  Hz, 1H), 3.41 (br. s, 2H), 2.63 (d,  $J = 1.5$  Hz, 1H), 2.52 (s, 6H), 1.63 (s, 3H), 1.50 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  172.7, 90.4, 71.4, 67.4, 65.7, 45.2 (2C), 30.4, 25.3 ppm.

**TIPDS protected lactone 301**

To a solution of dimethylamine **54** (1.17 g, 5.76 mmol, 1.0 eq) and 1*H*-imidazol (1.57 g, 23.0 mmol, 4.0 eq) in dry DMF (29 mL) was added TIPDSCI (3.80 mL, 11.5 mmol, 2.0 eq) and the resulting colorless solution was stirred at 23 °C. After 14 h, the reaction mixture was quenched by addition of sat. aqueous sodium bicarbonate (40 mL) at 0 °C. The aqueous phase was extracted with Et<sub>2</sub>O (3 x 50 mL), the combined organic layers were washed with water (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/Acetone 30/1 to 20/1) to afford TIPDS protected lactone **301** (2.33 g, 5.22 mmol, 91%) as colorless needles.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.85 – 4.80 (m, 1H), 4.44 (d, *J* = 2.1 Hz, 1H), 2.73 – 2.69 (m, 1H), 2.54 (s, 6H), 1.62 (s, 3H), 1.46 (s, 3H), 1.17 – 0.97 (m, 28H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>) δ 169.3, 87.3, 76.7, 71.9, 68.7, 44.9 (2C), 31.3, 25.7, 17.9, 17.6, 17.6, 17.3, 17.2, 17.2, 16.9, 16.8, 14.3, 14.0, 13.3, 12.8 ppm; IR (ATR):  $\tilde{\nu}$  = 2945, 2895, 2867, 2826, 1742, 1456, 1274, 1180, 1115, 1041, 1015, 948, 885, 802, 695 cm<sup>-1</sup>; [α]<sub>D</sub><sup>24</sup> = +6.5 (*c* = 1.0, CHCl<sub>3</sub>); m.p.: 164–166 °C; *R*<sub>f</sub> = 0.23 (*n*-pentane/EtOAc 20/1).

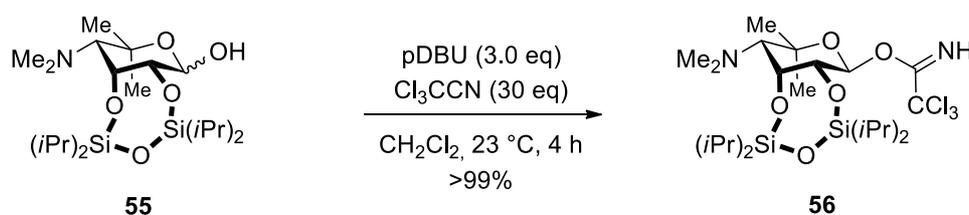
**Amino sugar 55**

To a cooled solution of lactone **301** (163 mg, 0.478 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (4.8 mL) was added a solution of DIBAL-H (1 M in *n*-hexane, 0.956 mL, 0.956 mmol, 2.0 eq) dropwise at -78 °C. The resulting colorless solution was stirred at -78 °C for 80 min before being quenched by addition of sat. aqueous potassium sodium tartrate (10 mL). The reaction mixture was allowed to warm to 23 °C and stirred for 1.5 h. The aqueous phase was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (4 x

10 mL), the combined organic layers were washed with brine (10 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/EtOAc/Et<sub>3</sub>N 10/1/0.1 to 5/1/0.05) to afford amino sugar **55** (219 mg, 95 wt.%, 0.465 mmol, 97%) as a colorless oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 5.02 (dd, *J* = 7.7, 3.3 Hz, 1H), 4.75 (t, *J* = 2.7 Hz, 1H), 3.50 (dd, *J* = 7.9, 3.1 Hz, 1H), 2.84 (br. s, 1H), 2.56 (s, 6H), 2.47 (d, *J* = 2.3 Hz, 1H), 1.61 (s, 3H), 1.31 (s, 3H), 1.16 – 1.03 (m, 28H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ 90.5, 78.3, 78.1, 74.8, 69.4, 44.5 (2C), 30.8, 23.7, 17.6, 17.5, 17.5, 17.4, 17.4, 17.4, 17.1, 17.0, 14.4, 13.6, 13.3, 13.1 ppm; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>21</sub>H<sub>46</sub>NNaO<sub>5</sub>Si<sub>2</sub>]<sup>+</sup>: 448.2909, found 448.3148.

### Schmidt donor **56**

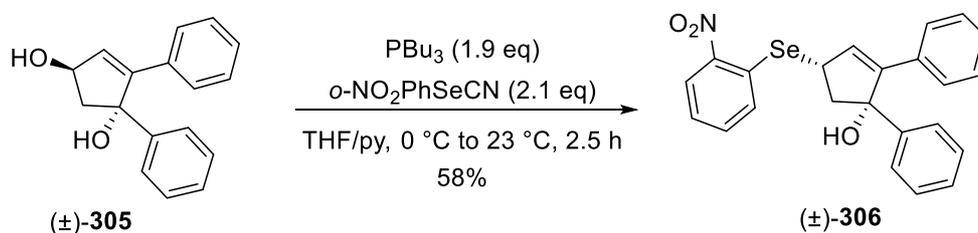


Amino sugar **55** (451 mg, 0.957 mmol) was loaded into a 25 mL round-bottom flask and azeotroped with toluene (3 x 5 mL). Freshly distilled 2,2,2-trichloroacetonitrile (2.88 mL, 28.7 mmol) was added, followed by dry CH<sub>2</sub>Cl<sub>2</sub> (9.6 mL) and polymer-bound DBU (pDBU) (1.4 - 2.2 mmol/g, 2.05 g, 2.87 mmol). The reaction mixture was gently stirred at 23 °C under a N<sub>2</sub> atmosphere for 4 h and then filtered through dry KIMTECH paper (glovebox). The filter cake was washed with CH<sub>2</sub>Cl<sub>2</sub> and the solvent was removed under high vacuum to afford Schmidt donor **56** (564 mg, 0.952 mmol, >99%) as a pale brown oil. If not immediately used for glycosylation, **56** was stored in a benzene matrix at –30 °C under a N<sub>2</sub> atmosphere. Thus, no degradation was observed, even after prolonged storage over 2-3 weeks.

**<sup>1</sup>H NMR** (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ 8.54 (s, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 4.80 (t, *J* = 2.9 Hz, 1H), 4.00 (dd, *J* = 8.3, 3.5 Hz, 1H), 2.44 - 2.40 (m, 7H), 1.87 (s, 3H), 1.35 (s, 3H), 1.25 - 1.07 (m, 28H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, C<sub>6</sub>D<sub>6</sub>) δ = 162.4, 94.7, 92.5, 79.3, 76.8, 76.0, 69.8, 44.9 (2C), 31.4, 24.3, 18.1, 18.0 (2C), 18.0 (2C), 17.9, 17.8, 17.7, 15.2, 14.1 (2C), 13.9 ppm.

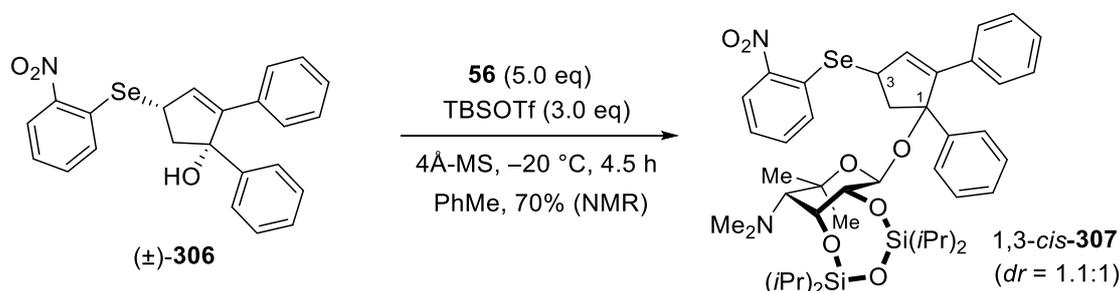
## 10.6 Completion of the Synthesis

### Selenide ( $\pm$ )-**306**



To an ice-cooled solution of *trans*-diol ( $\pm$ )-**305**<sup>199</sup> (100 mg, 0.396 mmol, 1.0 eq) and *o*-NO<sub>2</sub>PhSeCN (135 mg, 0.595 mmol, 1.5 eq) in dry THF/pyridine (2.0 mL, v/v = 1/1) was added a solution of tributylphosphine (160  $\mu$ L, 0.643 mmol, 1.6 eq) in dry THF (0.16 mL) dropwise. The resulting red mixture was stirred at 0 °C for 15 min and was then allowed to warm to 23 °C. After 75 min additional *o*-NO<sub>2</sub>PhSeCN (36.0 mg, 159  $\mu$ mol, 0.4 eq) and tributylphosphine (50.0  $\mu$ L, 201  $\mu$ mol, 0.5 eq) in dry THF (50  $\mu$ L each) was added. After stirring for an additional 60 min at 23 °C, the reaction was quenched by addition of sat. aqueous sodium bicarbonate (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL), the combined organic layers were dried over MgSO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (*n*-pentane/CH<sub>2</sub>Cl<sub>2</sub> 2/1 to 1/2 to 1/3) to afford selenide ( $\pm$ )-**306** (100 mg, 229  $\mu$ mol, 58%) as a yellow solid.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.34 (dd,  $J$  = 8.3, 1.3 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.56 (td,  $J$  = 8.2, 7.7, 1.4 Hz, 1H), 7.47 – 7.42 (m, 2H), 7.42 – 7.35 (m, 3H), 7.33 – 7.28 (m, 2H), 7.25 – 7.17 (m, 4H), 6.58 (d,  $J$  = 2.5 Hz, 1H), 4.66 (dt,  $J$  = 7.0, 2.4 Hz, 1H), 3.12 (dd,  $J$  = 14.7, 7.2 Hz, 1H), 2.72 – 2.63 (m, 2H) ppm; <sup>13</sup>C{<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  150.4, 146.7, 145.1, 133.8, 133.8, 133.2, 129.6, 128.8, 128.3 (2C), 128.2 (2C), 128.0, 127.3 (2C), 126.8, 126.6, 126.0, 125.0 (2C), 86.9, 52.5, 41.8 ppm; HRMS (ESI) calc'd. for [M-OH]<sup>+</sup> = [C<sub>23</sub>H<sub>18</sub>NO<sub>2</sub>Se]<sup>+</sup>: 420.0497, found: 420.0494; m.p.: 157-159 °C;  $R_f$  = 0.48 (*n*-pentane/CH<sub>2</sub>Cl<sub>2</sub> 1/1).

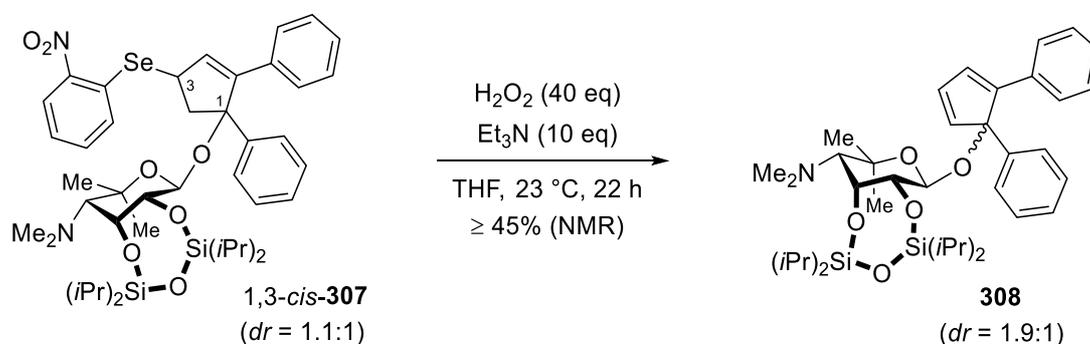
**Selenyl glycoside 1,3-cis-307**

Selenide ( $\pm$ )-**306** (3.0 mg, 6.88  $\mu\text{mol}$ , 1.0 eq) was loaded into a glass vial and azeotroped with toluene (3 x 0.5 mL). Activated powdered 4 $\text{\AA}$ -MS (14 mg) were added, the vial was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). A solution of Schmidt donor **56** (20.4 mg, 34.4  $\mu\text{mol}$ , 5.0 eq) in dry benzene (0.4 mL) was added, followed by removal of all volatiles by sublimation under high vacuum at 0  $^\circ\text{C}$ . Dry toluene (220  $\mu\text{L}$ ) was added and the yellow suspension was stirred for 1.5 h at 23  $^\circ\text{C}$ . After being cooled to  $-20\text{ }^\circ\text{C}$ , freshly distilled TBSOTf (0.8  $\mu\text{L}$ , 3.44  $\mu\text{mol}$ , 0.5 eq) was added and stirring was continued at  $-20\text{ }^\circ\text{C}$ . Additional portions of TBSOTf (0.8  $\mu\text{L}$ , 3.44  $\mu\text{mol}$ , 0.5 eq) were added after 1 h, 2 h and 3 h. After 4 h an additional portion of TBSOTf (1.6  $\mu\text{L}$ , 6.88  $\mu\text{mol}$ , 1.0 eq) was added and stirring was continued at  $-20\text{ }^\circ\text{C}$ . After a total reaction time of 4.5 h,  $\text{Et}_3\text{N}$  (19.2  $\mu\text{L}$ , 138  $\mu\text{mol}$ , 20 eq) was added at  $-20\text{ }^\circ\text{C}$ , followed by saturated aqueous sodium bicarbonate (3 mL) and a solution of 1,4-DMT (0.01 M in EtOAc, 100  $\mu\text{L}$ , 1.00  $\mu\text{mol}$ ). The aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL), the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure (30  $^\circ\text{C}$ ). After determination of the crude  $^1\text{H}$  NMR yield (70%) the product was commonly purified with other batches of crude 1,3-*cis*-**307** by flash chromatography (*n*-pentane/EtOAc 40/1 to 25/1).

**1.1:1 mixture of diastereomers:**  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 – 8.30 (m, 2H), 7.72 (d,  $J = 7.8$  Hz, 1H), 7.63 – 7.47 (m, 7H), 7.40 – 7.29 (m, 10H), 7.26 – 7.20 (m, 2H), 7.19 – 7.13 (m, 3H), 7.12 – 7.04 (m, 3H), 6.72 (d,  $J = 2.2$  Hz, 1H), 6.71 (d,  $J = 2.2$  Hz, 1H), 5.13 (d,  $J = 7.9$  Hz, 1H), 5.03 (d,  $J = 7.7$  Hz, 1H), 4.69 – 4.60 (m, 3H), 4.58 – 4.52 (m, 1H), 3.80 (td,  $J = 8.6, 8.1, 3.8$  Hz, 2H), 3.62 (dd,  $J = 14.4, 6.5$  Hz, 1H), 3.21 (dd,  $J = 15.0, 6.2$  Hz, 1H), 3.01 (dd,  $J = 15.0, 8.1$  Hz, 1H), 2.93 (dd,  $J = 14.4, 8.6$  Hz, 1H), 2.54 – 2.49 (m, 7H), 2.47 (s, 6H), 2.39 (d,  $J = 2.6$  Hz, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.17 – 0.98 (m, 44H), 0.94 (s, 3H), 0.90 (s, 3H), 0.77 (d,  $J = 7.6$  Hz, 3H), 0.66 (d,  $J = 7.4$  Hz, 3H), 0.58 (s, 3H) ppm;  $^{13}\text{C}\{^1\text{H}\}$  NMR

(101 MHz, CDCl<sub>3</sub>)  $\delta$  147.4, 146.9, 146.7, 146.3, 146.0, 145.8, 134.9, 134.7, 133.9, 133.7, 133.6, 133.5, 132.4, 130.5, 129.8, 129.8, 128.6 (2C), 128.3 (2C), 128.1 (2C), 127.9 (2C), 127.6, 127.5 (2C), 127.4, 126.9, 126.8 (2C), 126.7, 126.5, 126.5, 125.5 (2C), 124.7 (2C), 124.2 (2C), 93.7, 93.2, 92.2, 92.0, 78.0, 77.0, 76.6, 76.3, 76.2, 75.5, 69.1, 69.0, 49.4, 49.2, 44.5 (4C), 41.5, 41.0, 31.0, 29.9, 23.9, 23.3, 17.7, 17.7, 17.6, 17.6, 17.5 (3C), 17.4, 17.3, 17.3, 17.2, 17.2, 17.2, 17.0, 16.9, 16.9, 14.3 (2C), 14.1, 13.8, 13.7, 13.5, 13.4, 13.3 ppm; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>44</sub>H<sub>63</sub>N<sub>2</sub>O<sub>7</sub>SeSi<sub>2</sub>]<sup>+</sup>: 867.3334, found: 867.3337; **R<sub>f</sub>** = 0.28 (*n*-pentane/EtOAc 25/1).

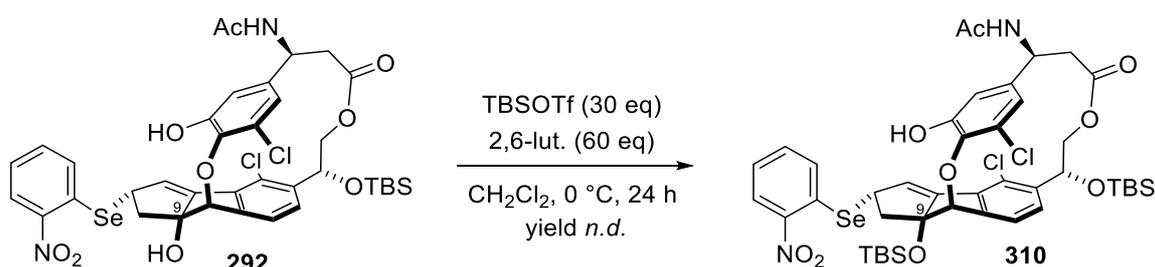
### Cyclopentadienyl glycoside **308**



To an ice-cooled solution of selenide **1,3-cis-307** (3.0 mg, 3.46  $\mu\text{mol}$ , *dr* = 1.1:1, 1.0 eq) in THF (200  $\mu\text{L}$ ) was added Et<sub>3</sub>N (4.83  $\mu\text{L}$ , 34.7  $\mu\text{mol}$ , 10 eq), followed by aqueous H<sub>2</sub>O<sub>2</sub> (30%, 3.54  $\mu\text{L}$ , 34.7  $\mu\text{mol}$ , 10 eq). The bright yellow reaction mixture was stirred at 0 °C for 5 min and then allowed to warm to 23 °C. After 4 h, additional H<sub>2</sub>O<sub>2</sub> (30%, 3.54  $\mu\text{L}$ , 34.7  $\mu\text{mol}$ , 10 eq) was added, followed by a further portion of H<sub>2</sub>O<sub>2</sub> (30%, 7.08  $\mu\text{L}$ , 69.4  $\mu\text{mol}$ , 20 eq) after 8 h. Stirring was continued at 23 °C. After a total reaction time of 22 h, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (6 mL) and poured into mixture of saturated aqueous sodium thiosulfate/pH 7 buffer (6 mL, 1/1). A solution of 1,3,5-TMB (0.01 M in EtOAc, 100  $\mu\text{L}$ , 1.00  $\mu\text{mol}$ ) was added as internal standard, and the aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 5 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under reduced pressure (30 °C). After determination of the crude <sup>1</sup>H NMR yield ( $\geq 45\%$ ), the crude product was purified by flash chromatography (*n*-pentane/EtOAc 50/1 to 30/1) to afford a 1.9:1 diastereomeric mixture of cyclopentadienyl glycoside **308** as a pale yellow oil.

**1.9: 1 mixture of diastereomers:**  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 – 7.39 (m, 4H), 7.25 – 7.05 (m, 6H), 6.93 (dt,  $J = 7.1, 1.8$  Hz, 1H), 6.50 – 6.26 (m, 1H), 6.23 – 6.15 (m, 1H), 4.77 – 4.60 (m, 2H), 3.76 – 3.71 (m, 1H), 2.54 – 2.44 (m, 7H), 1.50 – 1.45 (m, 3H), 1.35 – 1.30 (m, 3H), 1.05 – 0.98 (m, 10H), 0.94 – 0.73 (m, 18H) ppm; **HRMS (ESI)** calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{38}\text{H}_{58}\text{NO}_5\text{Si}_2]^+$ : 66.3848, found: 664.3857;  $R_f = 0.80$  (*n*-pentane/*Et*<sub>2</sub>O 5/1).

### C-9-TBS Ether **310**

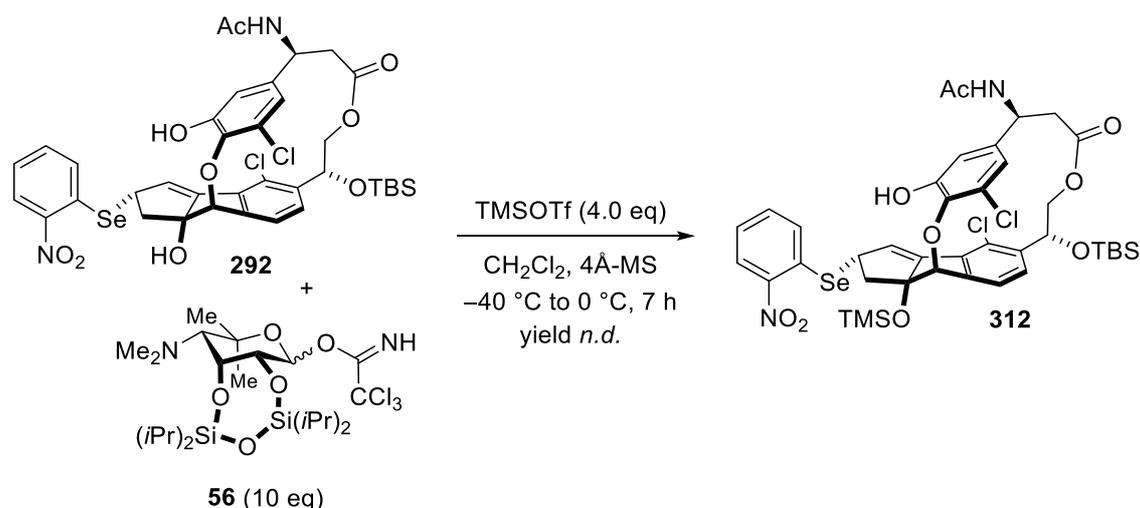


To an ice-cooled solution of selenide **292** (2.0 mg, 2.40  $\mu\text{mol}$ , 1.0 eq) in dry  $\text{CH}_2\text{Cl}_2$  (100  $\mu\text{L}$ ) was added freshly distilled 2,6-lutidine (1.40  $\mu\text{L}$ , 12.0  $\mu\text{mol}$ , 5.0 eq) and TBSOTf (1.38  $\mu\text{L}$ , 5.99  $\mu\text{mol}$ , 2.5 eq) under a  $\text{N}_2$  atmosphere. The yellow reaction mixture was stirred at 0 °C for 2 h before additional 2,6-lutidine (2.80  $\mu\text{L}$ , 24.0  $\mu\text{mol}$ , 10 eq) and TBSOTf (2.75  $\mu\text{L}$ , 12.0  $\mu\text{mol}$ , 5.0 eq) was added. Further portions of 2,6-lutidine (4.20  $\mu\text{L}$ , 36.0  $\mu\text{mol}$ , 15 eq) and TBSOTf (4.13  $\mu\text{L}$ , 18.0  $\mu\text{mol}$ , 7.5 eq) were added after 5 h and stirring was continued at 0 °C. After 22 h, additional 2,6-lutidine (8.40  $\mu\text{L}$ , 72.0  $\mu\text{mol}$ , 30 eq) and TBSOTf (8.26  $\mu\text{L}$ , 36.0  $\mu\text{mol}$ , 15 eq) was added. The reaction mixture was stirred at 0 °C for an additional 2 h, and quenched after a total reaction time of 24 h by addition of saturated aqueous sodium bicarbonate (3 mL). The aqueous phase was extracted with *Et*<sub>2</sub>O (3 x 5 mL), the combined organic layers were washed with saturated aqueous ammonium chloride (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and the solvent was removed under reduced pressure (30 °C). The crude product was purified by flash chromatography (toluene/acetone 4/1 to 2/1) to afford the main reaction product C-9 TBS ether **310** as a bright yellow oil.

$^1\text{H NMR}$  (400 MHz, Acetone-*d*<sub>6</sub>)  $\delta$  8.33 (dd,  $J = 8.3, 1.3$  Hz, 1H), 8.01 (d,  $J = 7.8$  Hz, 1H), 7.83 – 7.74 (m, 1H), 7.56 – 7.47 (m, 1H), 7.32 (d,  $J = 7.7$  Hz, 1H), 6.90 (d,  $J = 7.7$  Hz, 1H), 6.74 (d,  $J = 2.1$  Hz, 1H), 6.63 (d,  $J = 3.4$  Hz, 1H), 6.26 (d,  $J = 2.1$  Hz, 1H), 5.43 (s, 1H), 5.15 (dd,  $J = 7.8, 3.4$  Hz, 1H), 4.95 – 4.86 (m, 2H), 4.67 (t,  $J = 10.5$  Hz, 1H), 4.07 (t,  $J = 6.6$  Hz, 1H), 3.95 (dd,

$J = 14.3, 8.0$  Hz, 1H), 3.68 (dd,  $J = 9.9, 4.1$  Hz, 1H), 2.61 (t,  $J = 7.1$  Hz, 1H), 2.33 – 2.24 (m, 3H), 1.86 (s, 3H), 0.88 (s, 9H), 0.77 (s, 9H), 0.09 (s, 3H), -0.03 (s, 3H), -0.04 (s, 3H), -0.35 (s, 3H) ppm; **HRMS (ESI)** calc'd. for  $[M+H]^+ = [C_{43}H_{55}^{35}Cl_2N_2O_9SeSi_2]^+$ : 949.1983, found 949.1983;  $R_f = 0.43$  (toluene/acetone 2/1).

### C-9 TMS Ether 312

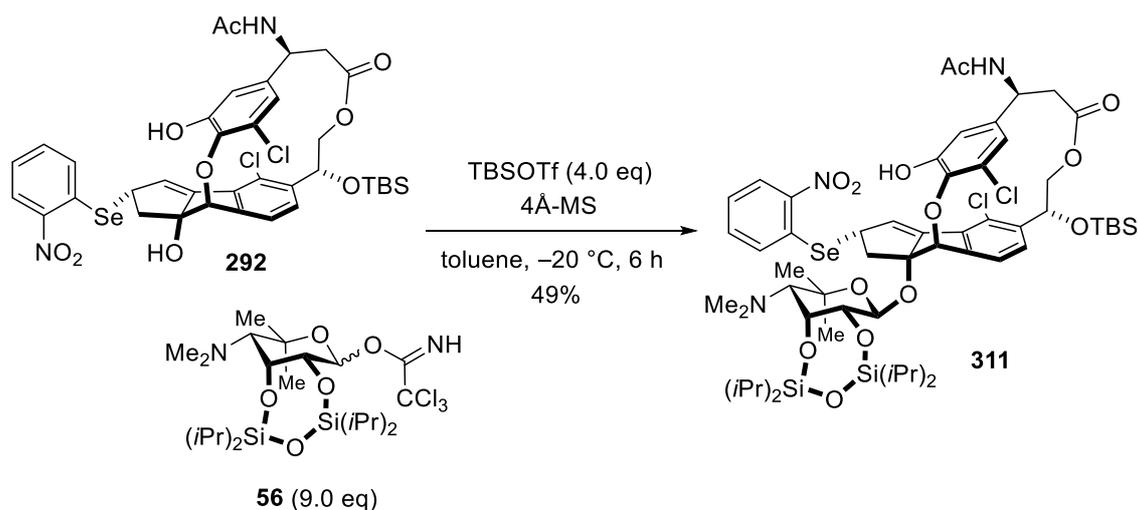


Selenide **292** (2.5 mg, 3.00  $\mu$ mol, 1.0 eq) was loaded into a glass vial and azeotroped with toluene (3 x 0.2 mL). Activated powdered 4Å-MS (6.0 mg) were added, the vial was sealed, placed under vacuum and backfilled with  $N_2$  (3 x). A solution of previously azeotroped Schmidt donor **56** (17.7 mg, 30.0  $\mu$ mol, 10 eq) in dry  $CH_2Cl_2$  (100  $\mu$ L) was added and the yellow suspension was stirred for 1.5 h at 23 °C. After being cooled to -40 °C, a solution of freshly distilled TMSOTf (1.1  $\mu$ L, 6.00  $\mu$ mol, 2.0 eq) in dry  $CH_2Cl_2$  (5.0  $\mu$ L) was added and the mixture was allowed to warm to -25 °C over a period of 1 h. After stirring for an additional hour at -25 °C, the mixture was allowed to further warm to 0 °C over a period of 2.5 h before an additional portion of TMSOTf (1.1  $\mu$ L, 6.00  $\mu$ mol, 2.0 eq) in dry  $CH_2Cl_2$  (5.0  $\mu$ L) was added. Stirring was continued at 0 °C before the reaction was quenched after a total reaction time of 7 h by addition of  $Et_3N$  (30.0  $\mu$ L, 215  $\mu$ mol, 72 eq) followed by sat. aqueous sodium bicarbonate (3 mL). The aqueous phase was extracted with  $Et_2O$  (3 x 5 mL), the combined organic layers were dried over  $Na_2SO_4$ , filtered, and the solvent was removed under reduced pressure (25 °C). The crude product was purified by flash chromatography (toluene/acetone 10/1 to 7/1 to 3/1), followed by preparative HPLC (Chromolith column, *n*-hexane/ $EtOAc$  1/1.8, 25 mL/min,

254 nm,  $t_R(\mathbf{312}) = 10.0$  min) to afford the main reaction product C-9 TMS ether **312** as a bright yellow oil.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.35 (dd,  $J = 8.3, 1.4$  Hz, 1H), 7.78 (d,  $J = 7.9$  Hz, 1H), 7.63 (td,  $J = 8.2, 7.7, 1.4$  Hz, 1H), 7.39 (ddd,  $J = 8.3, 7.3, 1.2$  Hz, 1H), 7.16 (d,  $J = 7.7$  Hz, 1H), 6.81 (d,  $J = 3.2$  Hz, 1H), 6.67 (d,  $J = 7.8$  Hz, 1H), 6.55 (d,  $J = 2.1$  Hz, 1H), 6.32 (d,  $J = 2.1$  Hz, 1H), 5.74 (d,  $J = 6.1$  Hz, 1H), 5.56 (s, 1H), 5.08 (s, 1H), 5.04 – 4.97 (m, 2H), 4.78 (dd,  $J = 10.7, 4.1$  Hz, 1H), 4.45 (t,  $J = 10.6$  Hz, 1H), 3.80 (dd,  $J = 10.3, 4.3$  Hz, 1H), 3.54 (dd,  $J = 14.5, 7.8$  Hz, 1H), 2.92 (dd,  $J = 13.2, 3.7$  Hz, 1H), 2.47 (d,  $J = 14.6$  Hz, 1H), 2.20 (dd,  $J = 13.1, 11.7$  Hz, 1H), 2.03 (s, 3H), 0.87 (s, 9H), 0.04 (s, 3H), -0.07 (s, 3H), -0.07 (s, 9H) ppm; **HRMS (ESI)** calc'd. for  $[\text{M-H}]^- = [\text{C}_{40}\text{H}_{47}^{35}\text{Cl}_2\text{N}_2\text{O}_9\text{SeSi}_2]^-$ : 905.1368, found 905.1370;  $R_f = 0.34$  (toluene/acetone 2/1).

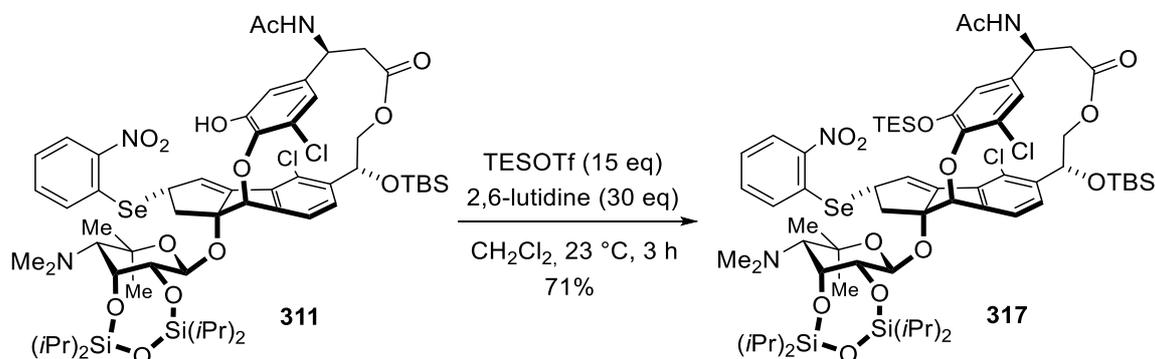
### Glycosyl selenide **311**



Selenide **292** (33.5 mg, 40.1  $\mu\text{mol}$ , 1.0 eq) was loaded into a glass vial and azeotroped with toluene (3 x 1 mL). Activated powdered 4Å-MS (140 mg) were added, the vial was sealed, placed under vacuum and backfilled with  $\text{N}_2$  (3 x). A solution of Schmidt donor **56** (214 mg, 0.361 mmol, 9.0 eq) in dry benzene (3.0 mL) was added, followed by removal of all volatiles by sublimation under high vacuum at 0 °C. Dry toluene (1.0 mL) was added and the yellow suspension was stirred at 23 °C for 1.5 h. After being cooled to -20 °C, freshly distilled TBSOTf (9.22  $\mu\text{L}$ , 40.1  $\mu\text{mol}$ , 1.0 eq) was added and stirring was continued at -20 °C. Additional portions of TBSOTf (9.22  $\mu\text{L}$ , 40.1  $\mu\text{mol}$ , 1.0 eq) were added after 1.3 h, 2.5 h and 4.5 h. After a total reaction time of 6 h,  $\text{Et}_3\text{N}$  (0.224 mL, 1.61 mmol, 40 eq) was added at -20 °C, followed by

saturated aqueous sodium bicarbonate (10 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure (30 °C). The crude product was purified by flash chromatography (toluene/acetone 3/1 to 2/1 to 1/1) to afford glycosyl selenide **311** (25.0 mg, 19.8 μmol, 49%) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ = 8.32 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.62 - 7.58 (m, 1H), 7.38 - 7.32 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 3.3 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 2.0 Hz, 1H), 6.29 (d, *J* = 2.0 Hz, 1H), 5.99 (s, 1H), 5.78 (br. d, *J* = 6.8 Hz, 1H), 5.15 (s, 1H), 5.01 (ddd, *J* = 11.0, 6.8, 4.2 Hz, 1H), 4.94 (dd, *J* = 7.9, 3.4 Hz, 1H), 4.80 (d, *J* = 7.3 Hz, 1H), 4.74 (dd, *J* = 10.8, 4.0 Hz, 1H), 4.63 - 4.59 (m, 1H), 4.28 (t, *J* = 10.5 Hz, 1H), 3.80 (dd, *J* = 10.3, 4.0 Hz, 1H), 3.64 - 3.54 (m, 2H), 2.90 (dd, *J* = 12.8, 3.5 Hz, 1H), 2.76 (d, *J* = 14.6 Hz, 1H), 2.50 (s, 6H), 2.46 (d, *J* = 2.3 Hz, 1H), 2.20 (t, *J* = 12.2 Hz, 1H), 2.04 (s, 3H), 1.44 (s, 3H), 1.23 (s, 3H), 1.12 - 1.02 (m, 14 H), 1.00 - 0.93 (m, 14H), 0.90 (s, 9H), 0.07 (s, 3H), -0.01 (s, 3H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>) δ = 169.3, 168.8, 151.1, 148.9, 147.0, 146.6, 139.3, 138.3, 136.1, 135.4, 133.7, 130.6, 130.2, 129.5, 129.4, 129.4, 129.0, 128.2, 126.3, 125.4, 125.3, 115.0, 113.8, 98.7, 94.1, 82.6, 75.7, 75.4, 74.3, 68.5, 67.0, 51.0, 49.5, 44.5 (2C), 43.2, 37.0, 31.1, 25.6 (3C), 23.7, 23.4, 22.3, 18.1, 17.5, 17.5 (2C), 17.5, 17.4, 17.3, 17.3, 14.2, 14.0, 13.4, 12.7, -5.0, -5.1 ppm; **IR (ATR):**  $\tilde{\nu}$  = 3293, 2947, 2930, 2866, 1738, 1517, 1146, 1115, 1006, 867, 780, 700 cm<sup>-1</sup>; **HRMS (ESI)** calc'd. for [M+H]<sup>+</sup> = [C<sub>58</sub>H<sub>84</sub><sup>35</sup>Cl<sub>2</sub>N<sub>3</sub>O<sub>13</sub>SeSi<sub>3</sub>]<sup>+</sup>: 1264.3849, found: 1264.3850; [α]<sub>D</sub><sup>20</sup> = -371.7 (*c* = 0.1, CH<sub>2</sub>Cl<sub>2</sub>); **R<sub>f</sub>** = 0.51 (toluene/acetone 2/1).

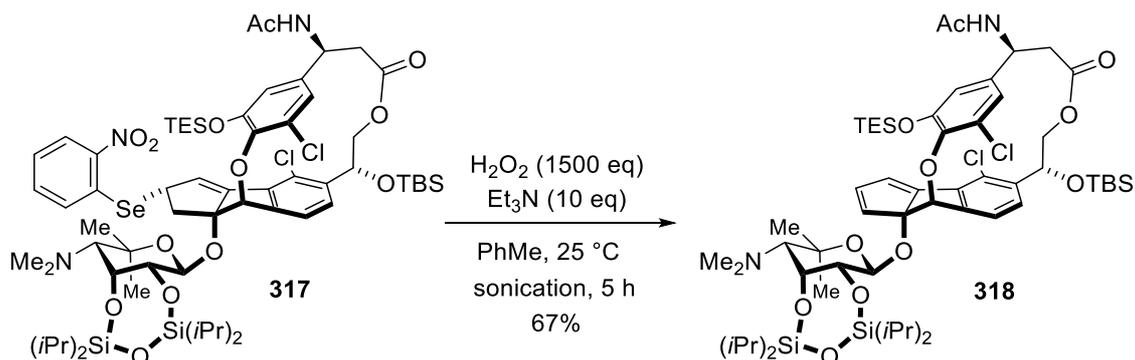
**TES Ether 317**

To an ice-cooled solution of glycosyl selenide **311** (21.9 mg, 17.3  $\mu\text{mol}$ , 1.0 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (2.0 mL) was added freshly distilled 2,6-lutidine (40.0  $\mu\text{L}$ , 347  $\mu\text{mol}$ , 20 eq) and TESOTf (39.0  $\mu\text{L}$ , 176  $\mu\text{mol}$ , 10 eq) under a N<sub>2</sub> atmosphere. The resulting solution was allowed to warm to 23 °C and was stirred for 2 h before additional 2,6-lutidine (20.0  $\mu\text{L}$ , 174  $\mu\text{mol}$ , 10 eq) and TESOTf (19.5  $\mu\text{L}$ , 86.5  $\mu\text{mol}$ , 5.0 eq) was added at 23 °C. After stirring for one additional hour, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and quenched by addition of saturated aqueous sodium bicarbonate (8 mL). The aqueous phase was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL), the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed under reduced pressure (30 °C). The crude product was purified by flash chromatography (*n*-pentane/acetone 10/1 to 5/1 to 4/1) to afford TES ether **317** (17.0 mg, 12.3  $\mu\text{mol}$ , 71%) as a yellow oil.

**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  = 8.30 (d,  $J$  = 8.3 Hz, 1H), 7.74 (d,  $J$  = 8.0 Hz, 1H), 7.56 (t,  $J$  = 8.2 Hz, 1H), 7.33 (t,  $J$  = 7.8 Hz, 1H), 7.10 (d,  $J$  = 7.8 Hz, 1H), 6.64 (d,  $J$  = 3.5 Hz, 1H), 6.61 (d,  $J$  = 2.0 Hz, 1H), 6.53 (d,  $J$  = 7.8 Hz, 1H), 6.21 (d,  $J$  = 2.0 Hz, 1H), 5.92 (s, 1H), 5.82 (br. d,  $J$  = 6.5 Hz, 1H), 5.01 (ddd,  $J$  = 11.0, 7.0, 3.4 Hz, 1H), 4.86 (dd,  $J$  = 7.5, 3.5 Hz, 1H), 4.77 (dd,  $J$  = 10.8, 4.0 Hz, 1H), 4.66 (d,  $J$  = 7.3 Hz, 1H), 4.61 - 4.55 (m, 1H), 4.34 (t,  $J$  = 10.5 Hz, 1H), 3.75 (dd,  $J$  = 10.2, 4.1 Hz, 1H), 3.68 - 3.57 (m, 2H), 2.96 (dd,  $J$  = 13.8, 3.5 Hz, 1H), 2.63 (br. d,  $J$  = 13.3 Hz, 1H), 2.48 (s, 6H), 2.44 (d,  $J$  = 2.0 Hz, 1H), 2.22 (dd,  $J$  = 13.8, 11.3 Hz, 1H), 2.04 (s, 3H), 1.29 (s, 3H), 1.19 (s, 3H), 1.12 - 1.01 (m, 19H), 0.99 0.91 (m, 18H), 0.90 (s, 9H), 0.72 - 0.63 (m, 6H), 0.06 (s, 3H), -0.01 (s, 3H) ppm; **<sup>13</sup>C{<sup>1</sup>H} NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  = 169.3, 168.7, 150.6, 148.8, 147.0, 146.9, 143.6, 138.5, 137.3, 136.7, 136.6, 133.4, 131.1, 129.8, 129.6, 129.1, 128.3, 126.2, 125.5, 125.1, 118.2, 116.1, 98.3, 93.6, 82.5, 77.1, 75.8 (2C), 74.4, 68.6, 66.8, 51.2, 50.7, 44.6 (2C), 42.7, 37.7, 31.1, 25.7 (3C), 23.6, 23.4, 18.1, 17.7, 17.6, 17.6, 17.5, 17.5 (2C), 17.4, 17.3, 14.2, 13.5, 13.4, 13.0, 6.6 (3C), 4.9 (3C), -5.0, -5.1 ppm; **IR**

(ATR):  $\tilde{\nu}$  = 2951, 2895, 2867, 1742, 1657, 1518, 1473, 1302, 1146, 1115, 1004, 856, 778, 730  $\text{cm}^{-1}$ ; HRMS (ESI) calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{64}\text{H}_{98}^{35}\text{Cl}_2\text{N}_3\text{O}_{13}\text{SeSi}_4]^+$ : 1378.4714, found: 1378.4721;  $[\alpha]_{\text{D}}^{20} = -228.3$  ( $c = 0.1$ ,  $\text{CH}_2\text{Cl}_2$ );  $R_f = 0.24$  ( $n$ -pentane/acetone 4/1).

### Protected fijiolide A **318**

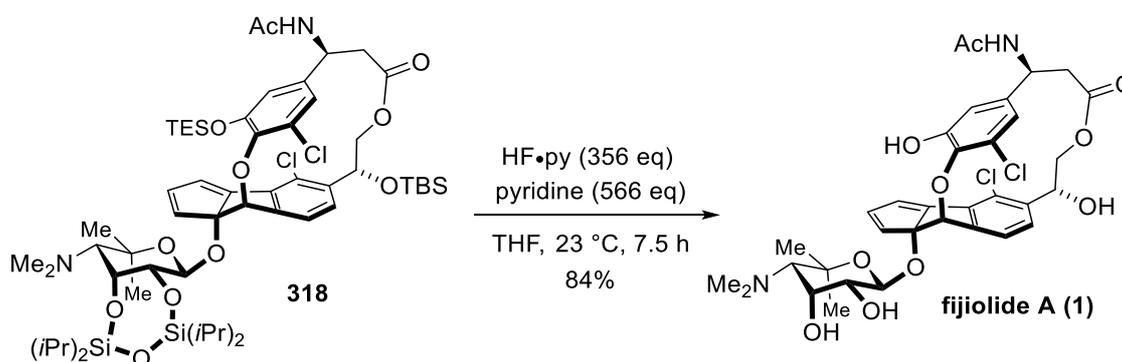


A solution of selenide **317** (9.0 mg, 6.53  $\mu\text{mol}$ , 1.0 eq) in toluene (9.0 mL) was distributed into five 15-mL Falcon® tubes (4 x 2 mL, 1 x 1 mL).  $\text{Et}_3\text{N}$  (2.02  $\mu\text{L}$ , 14.5  $\mu\text{mol}$ , 10 eq and 1.01  $\mu\text{L}$ , 0.73  $\mu\text{mol}$ , 10 eq) in toluene (100  $\mu\text{L}$  and 50  $\mu\text{L}$ , respectively) was added, followed by aqueous  $\text{H}_2\text{O}_2$  (30%, 148  $\mu\text{L}$  and 74.1  $\mu\text{L}$ , 1000 eq, respectively) with a micropipette. The reaction tubes were sealed and continuously sonicated keeping the water bath temperature at 25 °C. After 2.5 h, additional portions of aqueous  $\text{H}_2\text{O}_2$  (30%, 74.1  $\mu\text{L}$  and 37.1  $\mu\text{L}$ , 500 eq, respectively) were added and the mixtures were sonicated for additional 2.5 h at 25 °C. After a total reaction time of 5 h, the contents of all reaction tubes were combined, cooled to 0 °C and poured into an ice-cold mixture of saturated aqueous sodium thiosulfate/sodium bicarbonate (20 mL, 1/1). The aqueous phase was extracted with  $\text{Et}_2\text{O}$  (4 x 10 mL), the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and the solvent was removed under reduced pressure (30 °C). The crude product was purified by flash chromatography ( $n$ -pentane/acetone 8/1 to 6/1 to 4/1) to afford protected fijiolide A **318** (5.1 mg, 4.37  $\mu\text{mol}$ , 67%) as a yellow oil, which was used in the next step without further purification.

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.17 (d,  $J = 7.5$  Hz, 1H), 6.89 (s, 1H), 6.76 (d,  $J = 5.2$  Hz, 1H), 6.62 (d,  $J = 4.6$  Hz, 1H), 6.56 (s, 1H), 6.47 (d,  $J = 7.6$  Hz, 1H), 6.23 (s, 1H), 6.11 (d,  $J = 1.8$  Hz, 1H), 5.74 (d,  $J = 6.7$  Hz, 1H), 4.95 (ddd,  $J = 10.7, 6.7, 3.4$  Hz, 1H), 4.76 (dd,  $J = 10.7, 3.5$  Hz, 1H), 4.68 (d,  $J = 7.9$  Hz, 1H), 4.61 (s, 1H), 4.20 (t,  $J = 10.5$  Hz, 1H), 3.79 (dd,  $J = 10.2, 3.8$  Hz,

1H), 3.45 (dd,  $J = 7.5, 2.7$  Hz, 1H), 2.97 (dd,  $J = 13.3, 3.5$  Hz, 1H), 2.52 (s, 6H), 2.40 (br. s, 1H), 2.20 – 2.16 (m, 1H), 2.02 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.11 - 0.95 (m, 19H), 0.93 (s, 9H), 0.88 (t,  $J = 8.0$  Hz, 12H), 0.79 – 0.56 (m, 12H), 0.11 (s, 3H), 0.04 (s, 3H) ppm; **HRMS (ESI)** calc'd. for  $[M+H]^+ = [C_{58}H_{93}^{35}Cl_2N_2O_{11}Si_4]^+$ : 1175.5228, found: 1175.5228;  $R_f = 0.38$  (*n*-pentane/acetone 4/1).

### Fijiolide A (1)



In a 15-mL Falcon® tube, protected fijiolide A **318** (5.1 mg, 4.37  $\mu$ mol, 1.0 eq) was dissolved in dry THF (1.1 mL). Freshly distilled pyridine (200  $\mu$ L, 2.47 mmol, 566 eq) and HF·py (70% HF, 200  $\mu$ L, 1.55 mmol, 356 eq) were added and the solution was stirred at 23 °C until complete desilylation was suggested by HRMS analysis (7.5 h). The reaction mixture was then diluted with  $CH_2Cl_2$  and poured into ice-cold saturated aqueous sodium bicarbonate (12 mL). The aqueous phase (pH 8-9) was extracted with  $CH_2Cl_2$  (4 x 10 mL), the combined organic layers were dried over  $Na_2SO_4$  and the solvent was removed under reduced pressure (30 °C). The oily residue was azeotroped with toluene in order to remove residual pyridine. The crude product was purified by flash chromatography ( $CH_2Cl_2/MeOH$  20/1 to 10/1 to 5/1) to afford fijiolide A (**1**) (2.6 mg, 3.68  $\mu$ mol, 84%) as an off-white foam.

**Free base fijiolide A (1):**  **$^1H$  NMR** (600 MHz,  $CDCl_3$ )  $\delta = 7.43$  (d,  $J = 7.6$  Hz, 1H), 7.03 (d,  $J = 1.8$  Hz, 1H), 6.94 (d,  $J = 5.6$  Hz, 1H), 6.85 (dd,  $J = 5.4, 1.9$  Hz, 1H), 6.75 (d,  $J = 7.9$  Hz, 1H), 6.48 (d,  $J = 1.8$  Hz, 1H), 6.31 (d,  $J = 2.1$  Hz, 1H), 6.17 (s, 1H), 5.73 (br. d,  $J = 6.7$  Hz, 1H), 5.08 (br. s, 1H), 4.96 (ddd,  $J = 10.6, 6.5, 3.5$  Hz, 1H), 4.83 (dd,  $J = 10.9, 4.1$  Hz, 1H), 4.52 (t,  $J = 10.6$  Hz, 1H), 4.45 (d,  $J = 7.9$  Hz, 1H), 4.28 (t,  $J = 2.6$  Hz, 1H), 3.96 (dd,  $J = 10.3, 3.8$  Hz, 1H), 3.07 (dd,  $J = 7.8, 3.1$  Hz, 1H), 2.96 (dd,  $J = 13.5, 3.5$  Hz, 1H), 2.45 (s, 6H), 2.22 - 2.15 (m, 2H), 2.10 (s, 1H), 2.01 (s, 3H), 1.78 (br. s, 2H), 1.46 (s, 3H), 1.35 (s, 3H) ppm;

$^{13}\text{C}\{^1\text{H}\}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  169.3, 168.5, 150.9, 149.5, 148.7, 138.5, 138.5, 138.3, 138.1, 137.4, 134.5, 130.3, 128.9, 128.8, 127.4, 126.7, 115.1, 113.9, 100.7, 92.8, 84.1, 79.2, 74.2, 71.7, 69.8, 67.7, 65.6, 51.0, 45.1 (2C), 42.7, 30.9, 23.4, 21.8; IR (ATR):  $\tilde{\nu}$  = 3493, 3371, 2928, 1680, 1437, 1207, 1138, 801, 724  $\text{cm}^{-1}$ ; HRMS (ESI) calc'd. for  $[\text{M}+\text{H}]^+ = [\text{C}_{34}\text{H}_{39}^{35}\text{Cl}_2\text{N}_2\text{O}_{10}]^+$ : 705.1976, found: 705.1979;  $[\alpha]_{\text{D}}^{24} = -418.2$  ( $c = 0.055$ , MeOH) (Lit.  $[\alpha]_{\text{D}}^{21} = -440$  ( $c = 0.5$ , MeOH);  $R_f = 0.16$  ( $\text{CH}_2\text{Cl}_2/\text{MeOH}$  5/1).

Synthetic fijiolide A was finally purified by preparative HPLC (Agilent 1260 Infinity Series) on reversed-phase C18 column (Phenomenex Kinetex EVO, 150mm x 21.2 mm, 100 Å, 5  $\mu\text{m}$ ). Elution was performed using a linear gradient of 5% B to 40% B over 30 min at a flow rate of 25 mL/min with UV detection at 220 nm (Solvent A:  $\text{H}_2\text{O} + 0.05\%$  TFA; Solvent B: 95/5 MeCN/ $\text{H}_2\text{O} + 0.05\%$  TFA;  $t_{\text{R}}$  (fijiolide A) = 15.0 min) to afford fijiolide A • TFA as a white foam.  $^1\text{H}$  and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectroscopic data (DMSO- $d_6$ , 600 MHz) of synthetic fijiolide A • TFA, thus obtained, are provided below. By way of comparison, corresponding data of natural fijiolide A • TFA are also provided.

Synthetic Fijiolide A • TFA (referenced to H8 = 5.870 ppm)

$^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  8.88 (br. s, 1H), 8.32 (d,  $J = 7.7$  Hz, 1H), 8.32 (s, 1H), 7.08 (d,  $J = 8.0$  Hz, 1H), 6.76 (s, 1H), 6.65 (dd,  $J = 5.5, 1.9$  Hz, 1H), 6.64 (d,  $J = 8.1$  Hz, 1H), 6.62 (d,  $J = 5.5$  Hz, 1H), 6.52 (d,  $J = 1.9$  Hz, 1H), 5.98 (d,  $J = 1.9$  Hz, 1H), 5.87 (s, 1H), 5.74 (d,  $J = 4.4$  Hz, 1H), 5.64 (s, 1H), 4.96 (d,  $J = 5.5$  Hz, 1H), 4.66 (dt,  $J = 11.2, 4.3$  Hz, 1H), 4.61 (ddd,  $J = 11.9, 8.2, 3.4$  Hz, 1H), 4.46 (d,  $J = 7.9$  Hz, 1H), 4.24 (t,  $J = 10.5$  Hz, 1H), 4.06 - 4.01 (m, 1 H), 3.64 (dd,  $J = 9.8, 3.7$  Hz, 1H), 3.12 - 3.06 (m, 1H), 2.95 - 2.89 (m, 1 H), 2.80 (d,  $J = 3.3$  Hz, 3H), 2.79 (d,  $J = 3.3$  Hz, 3H), 2.58 (dd,  $J = 13.3, 3.9$  Hz, 1H), 2.06 (t,  $J = 13.0$  Hz, 1H), 1.73 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H) ppm.

Natural Fijiolide A • TFA (referenced to H8 = 5.870 ppm)

$^1\text{H}$  NMR (600 MHz, DMSO- $d_6$ )  $\delta$  9.12 (br. s, 1H), 8.41 (d,  $J = 8.2$  Hz, 1H), 8.36 (s, 1H), 7.09 (d,  $J = 7.7$  Hz, 1H), 6.76 (d,  $J = 2.0$  Hz, 1H), 6.65 (dd,  $J = 5.5, 2.2$  Hz, 1H), 6.64 (d,  $J = 8.0$  Hz, 1H), 6.62 (d,  $J = 5.5$  Hz, 1H), 6.53 (d,  $J = 2.0$  Hz, 1H), 5.98 (d,  $J = 2.1$  Hz, 1H), 5.87 (s, 1H), 5.84 (br. s, 1H), 5.70 (br. s, 1H), 4.95 (br. s, 1H), 4.66 (dd,  $J = 11.1, 4.1$  Hz, 1H), 4.62 (ddd,  $J = 12.1, 8.1, 3.6$  Hz, 1H), 4.46 (d,  $J = 8.0$  Hz, 1H), 4.24 (t,  $J = 10.5$  Hz, 1H), 4.08 - 4.03 (m,

1H), 3.65 (dd,  $J = 9.8, 3.9$  Hz, 1H), 3.12 - 3.06 (m, 1H), 2.92 (dd,  $J = 8.5, 3.7$  Hz, 1H), 2.80 (br. s, 6H), 2.58 (dd,  $J = 13.5, 3.6$  Hz, 1H), 2.07 (t,  $J = 13.2$  Hz, 1H), 1.74 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H) ppm.

Synthetic Fijiolide A • TFA (referenced to C9 = 99.80 ppm)

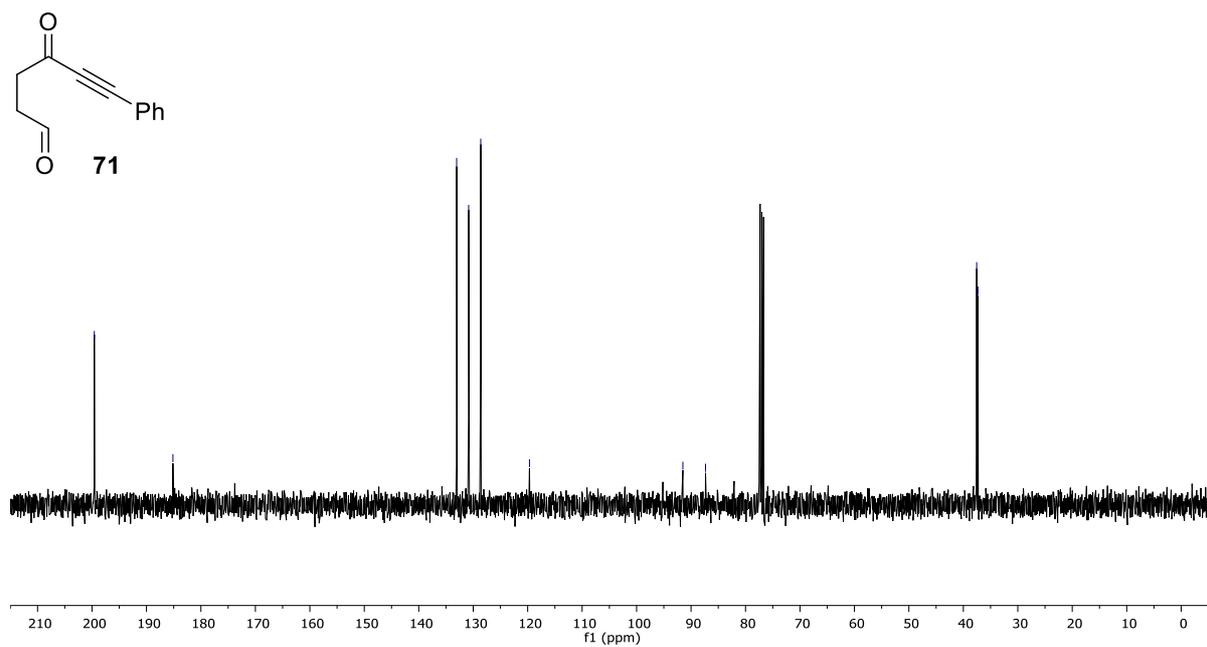
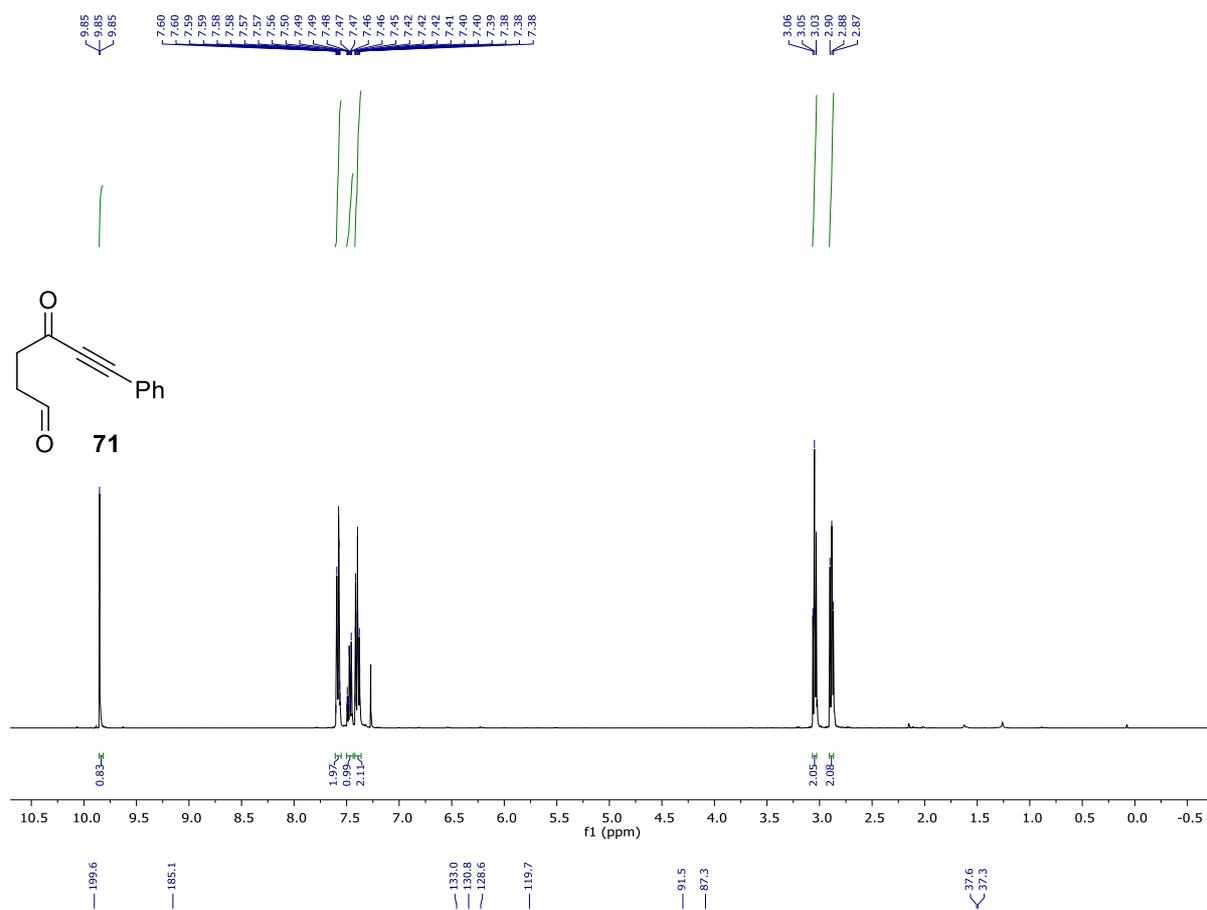
$^{13}\text{C}\{^1\text{H}\}$  NMR (150 MHz, DMSO- $d_6$ )  $\delta$  169.0, 168.4, 151.8, 148.8, 147.8, 139.3, 138.9, 138.4, 138.1, 135.8, 135.5, 129.5, 129.3, 129.1, 126.8, 125.4, 114.3, 114.0, 99.8, 93.2, 83.4, 74.9, 72.5, 69.6 (2C), 67.5, 65.6, 49.7, 44.6, 43.0, 43.0, 31.8, 22.7, 20.9 ppm.

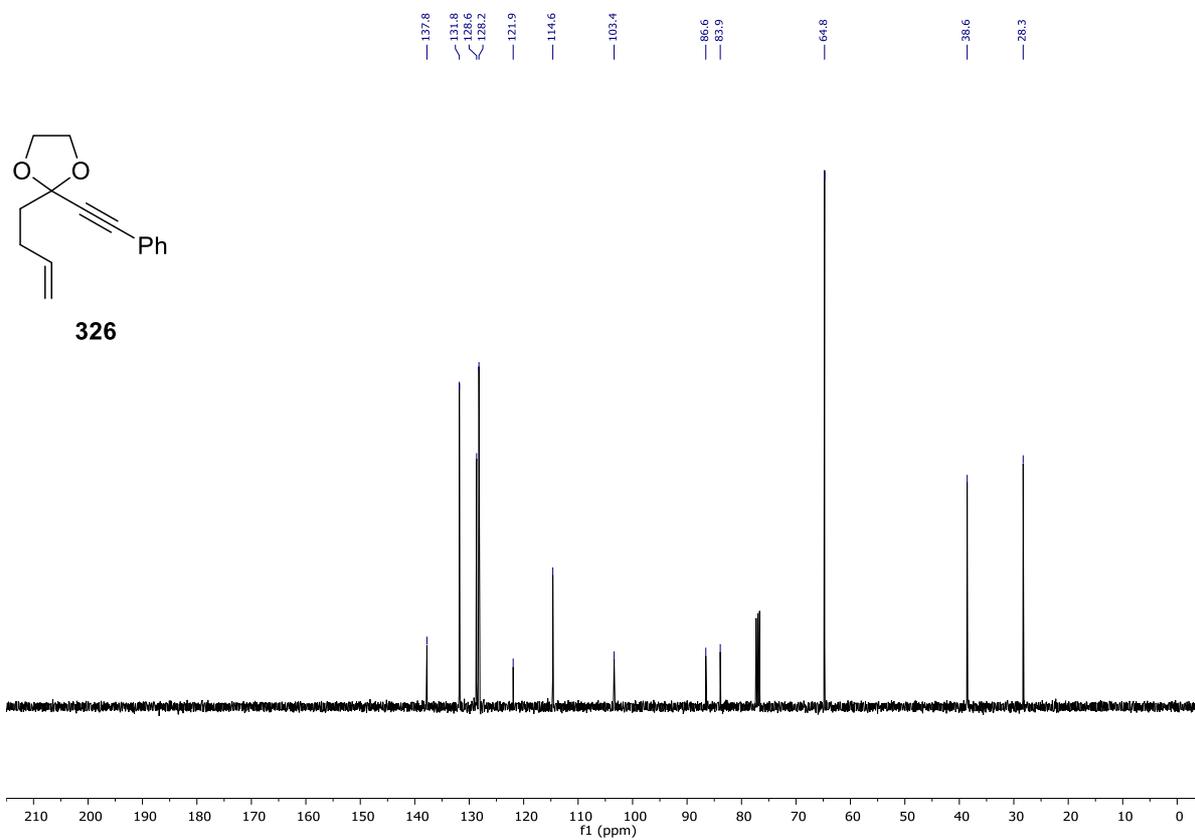
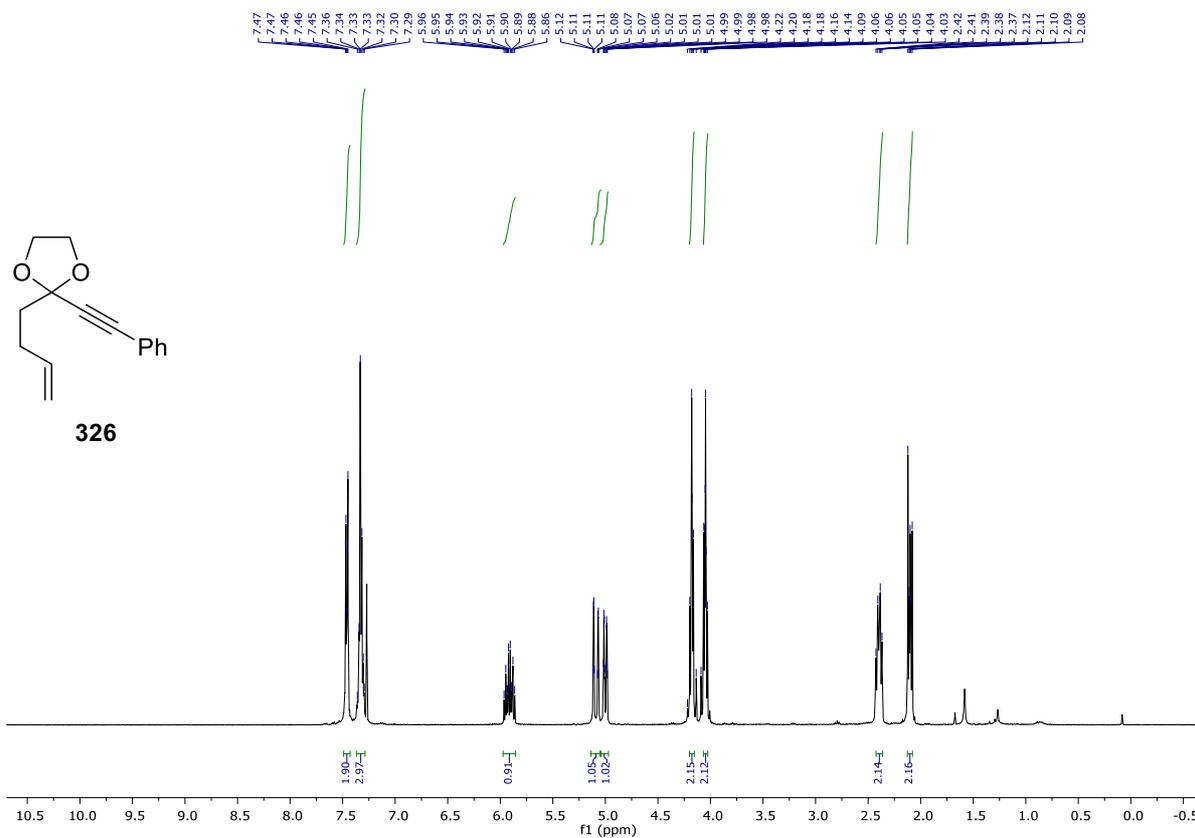
Natural Fijiolide A • TFA (referenced to C9 = 99.80 ppm)

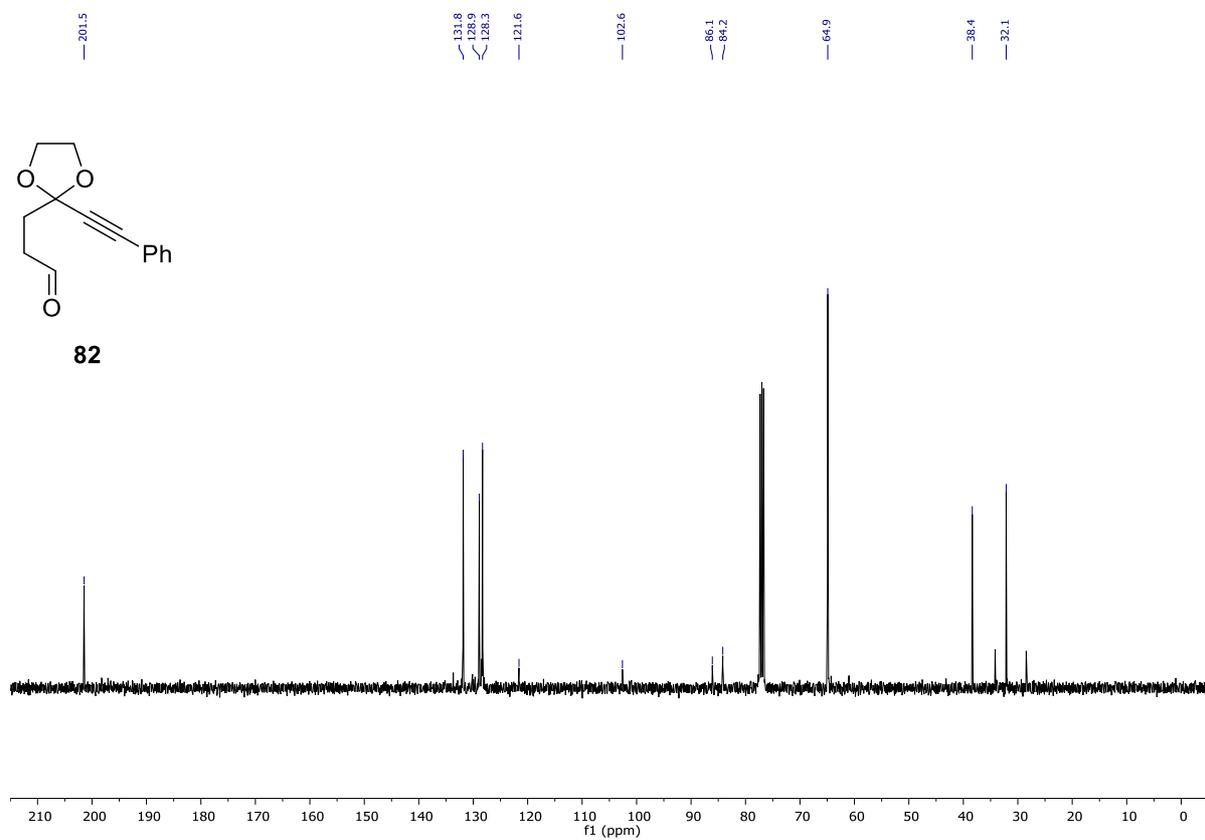
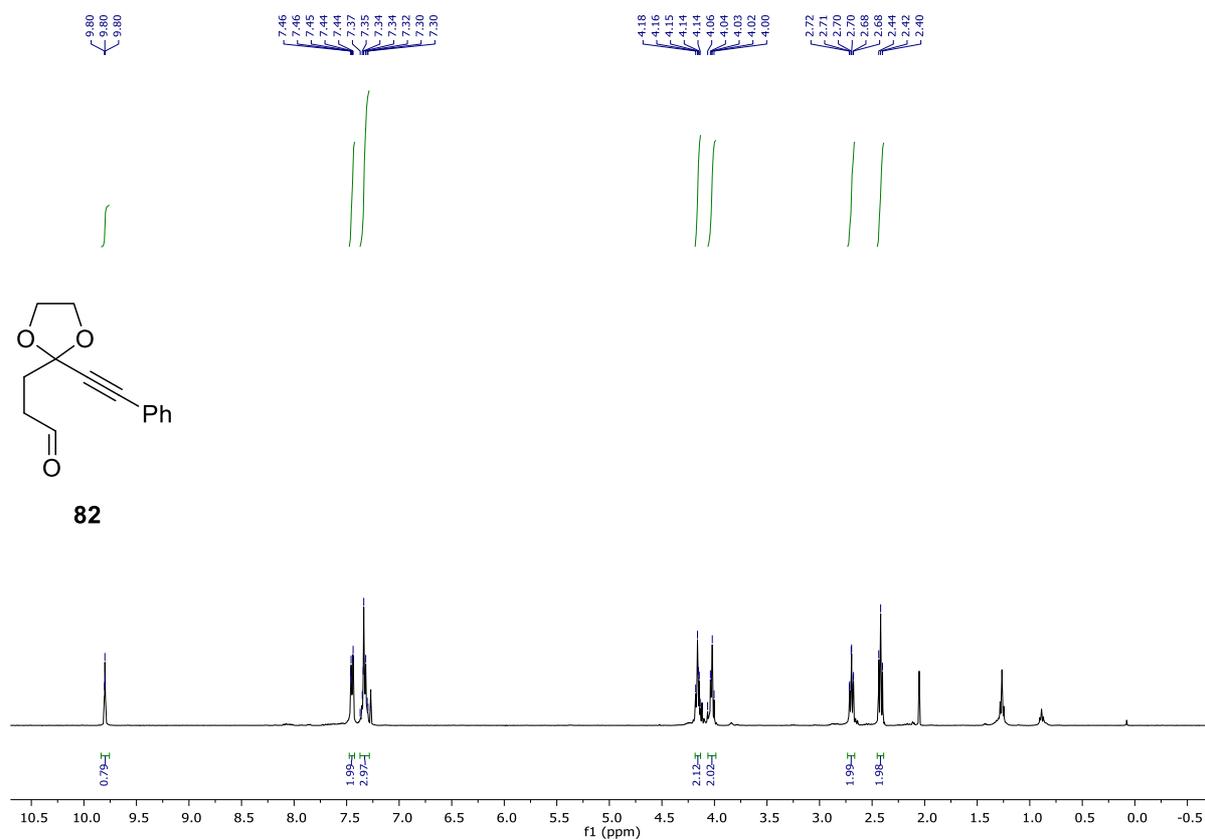
$^{13}\text{C}\{^1\text{H}\}$ MR (150 MHz, DMSO- $d_6$ )  $\delta$  169.0, 168.4, 151.8, 148.8, 147.8, 139.3, 138.9, 138.4, 138.1, 135.8, 135.5, 129.5, 129.3, 129.2, 126.8, 125.4, 114.3, 114.0, 99.8, 93.2, 83.4, 74.9, 72.5, 69.7, 69.5, 67.5, 65.6, 49.7, 44.6, 42.9, 42.8, 31.6, 22.6, 21.0 ppm.

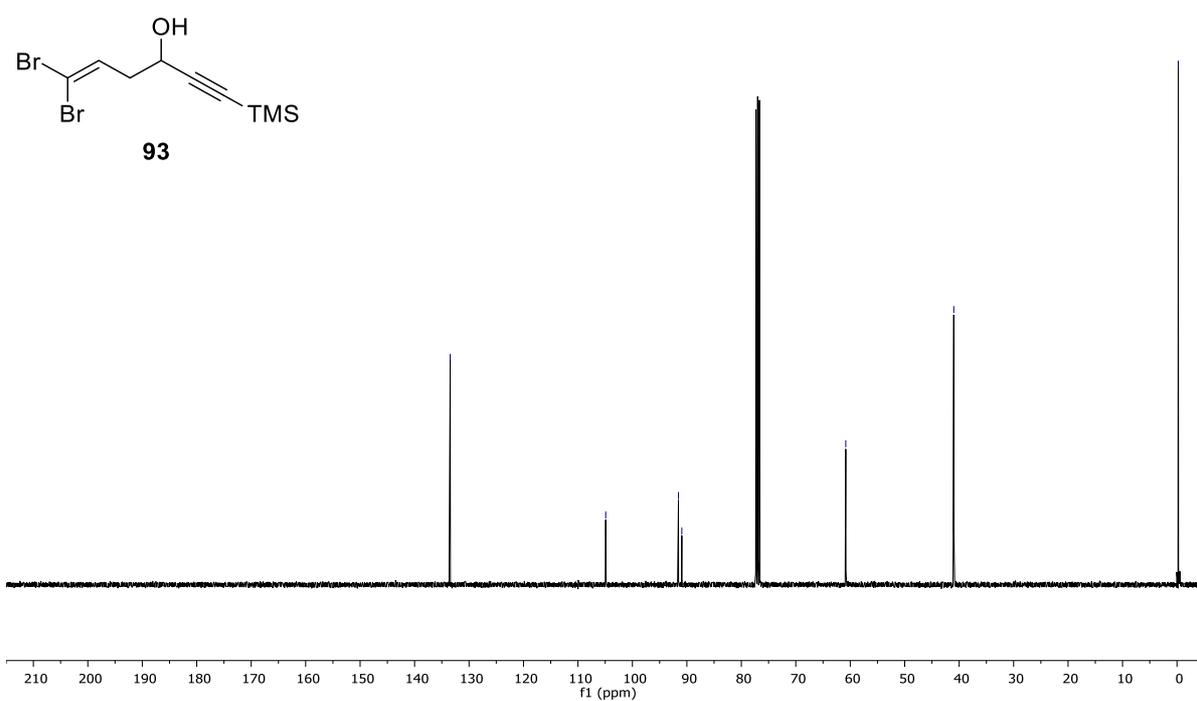
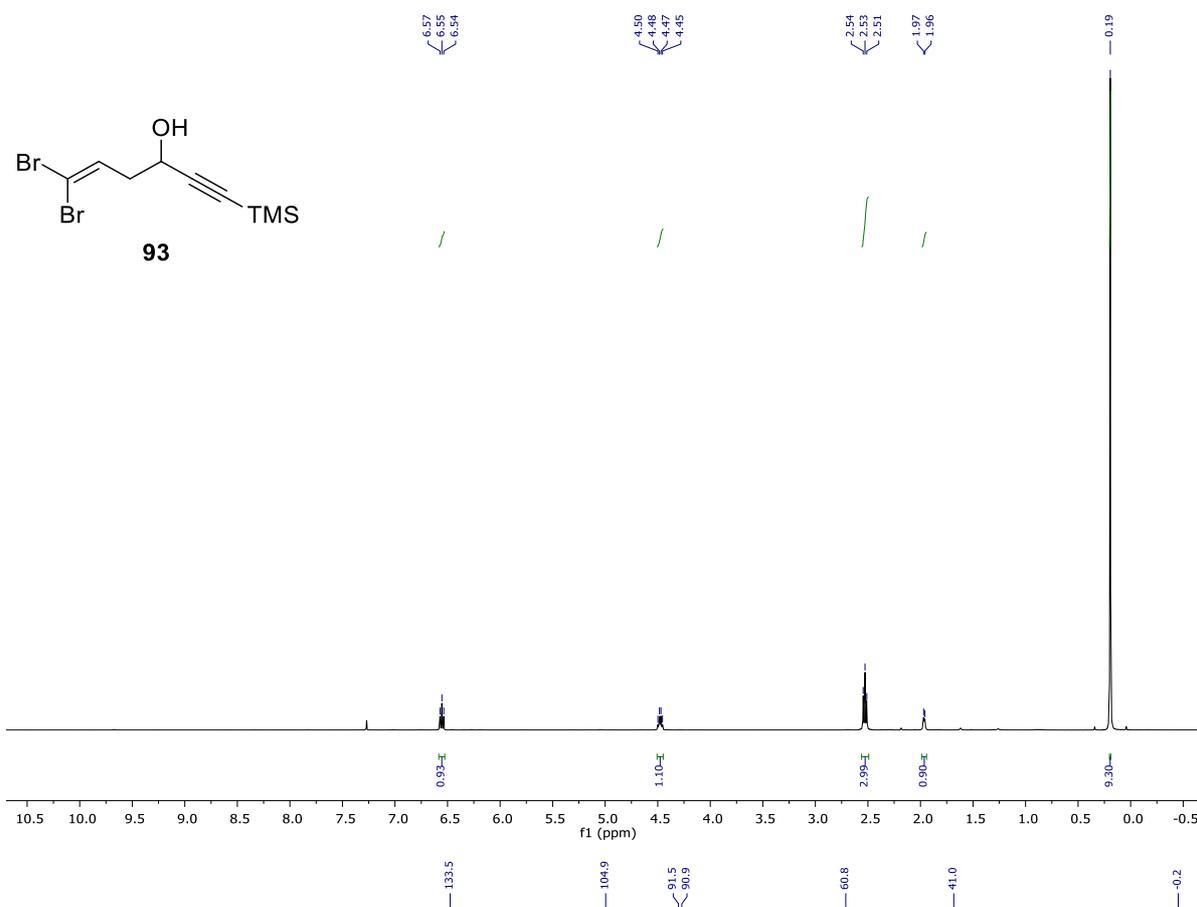
## *11. Appendices*

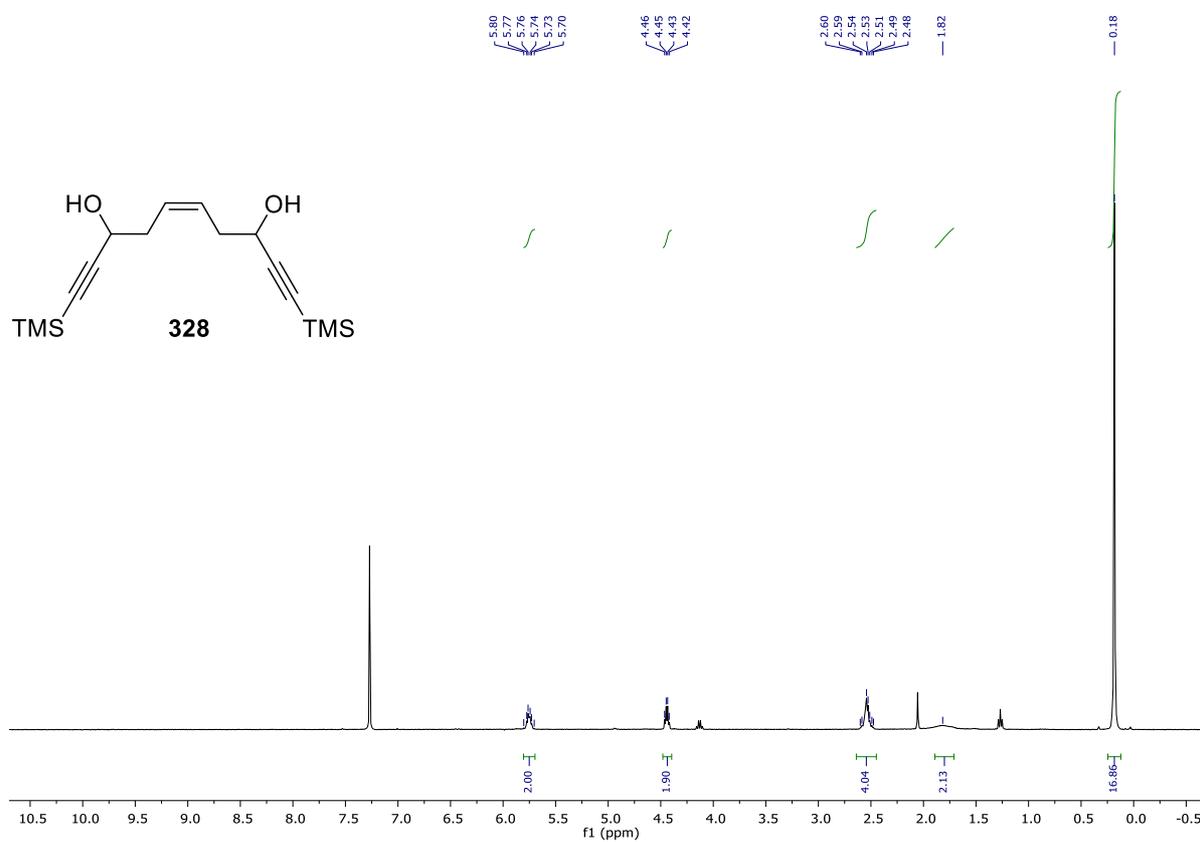
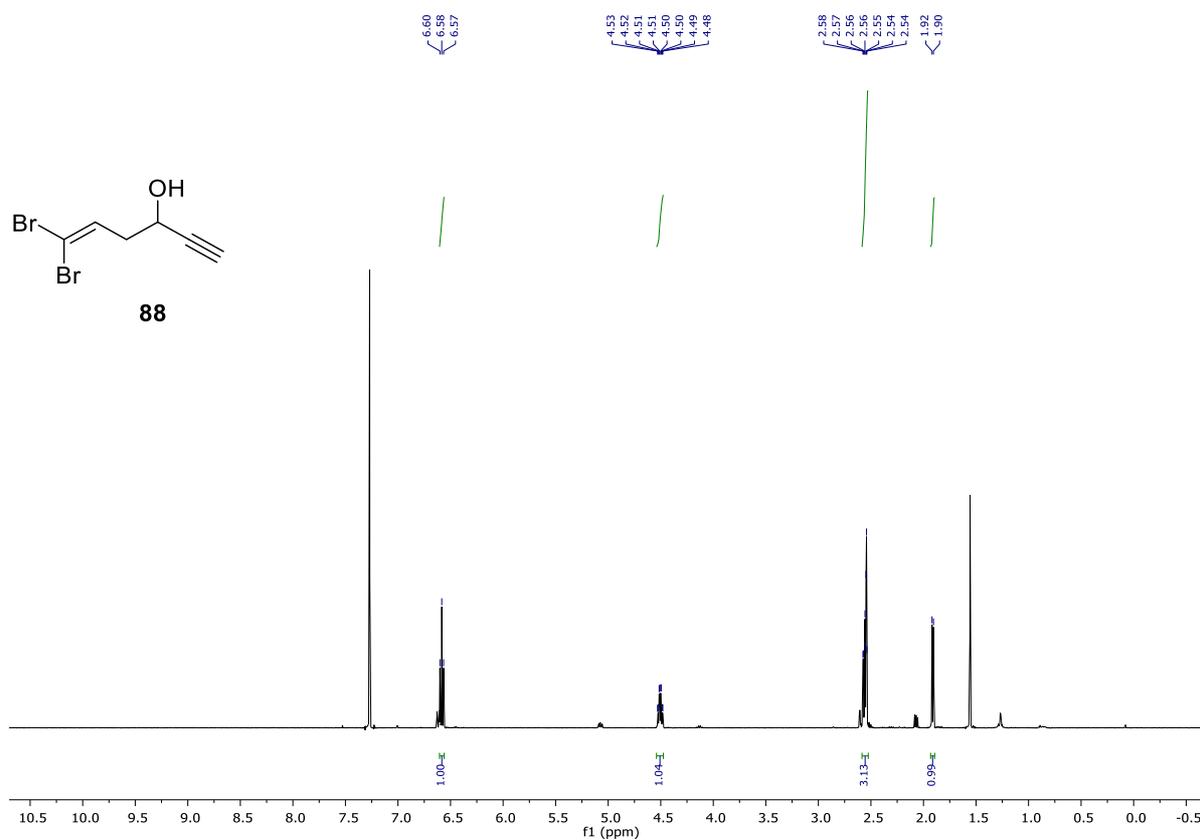


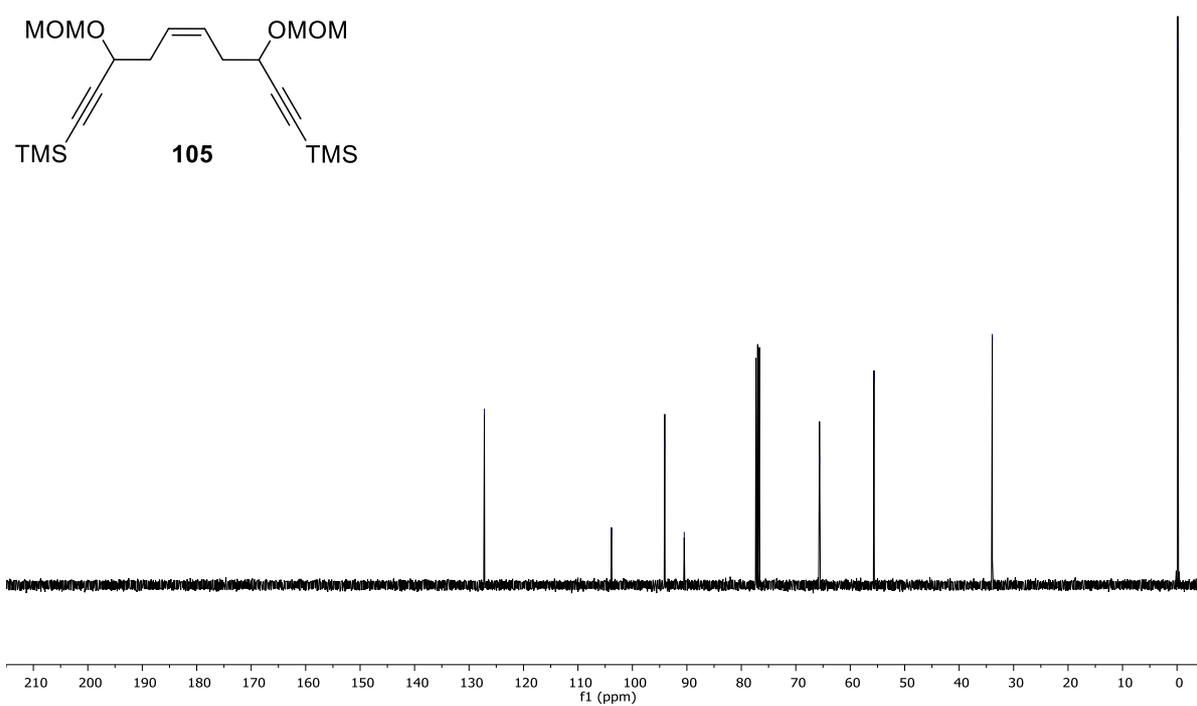
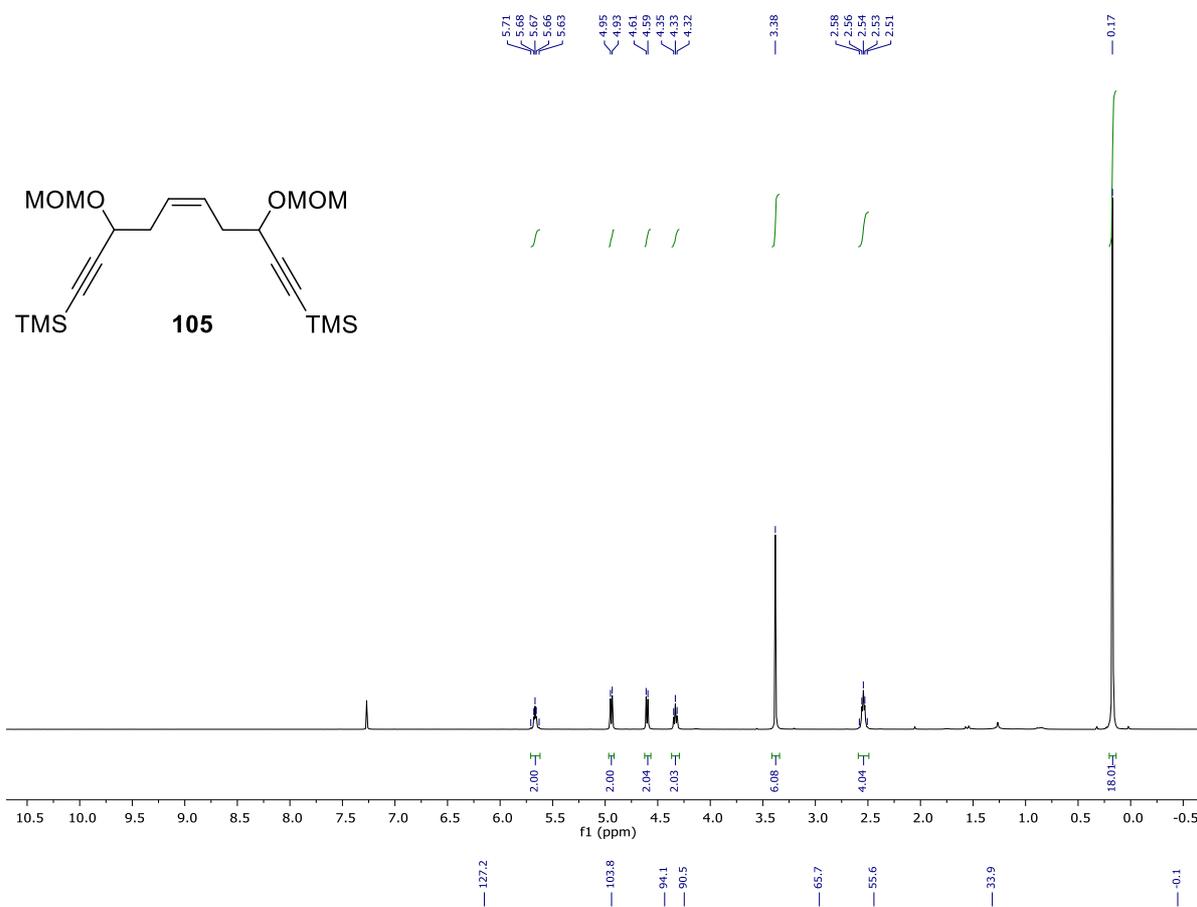


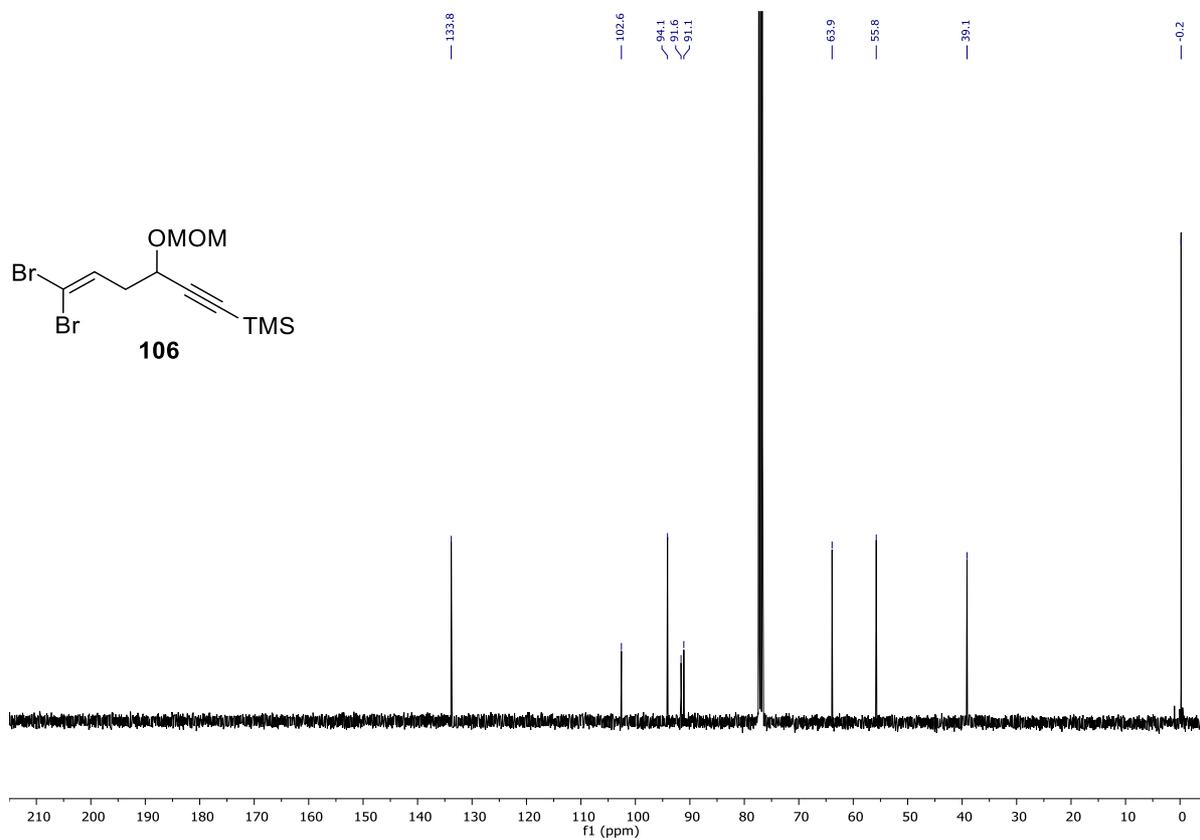
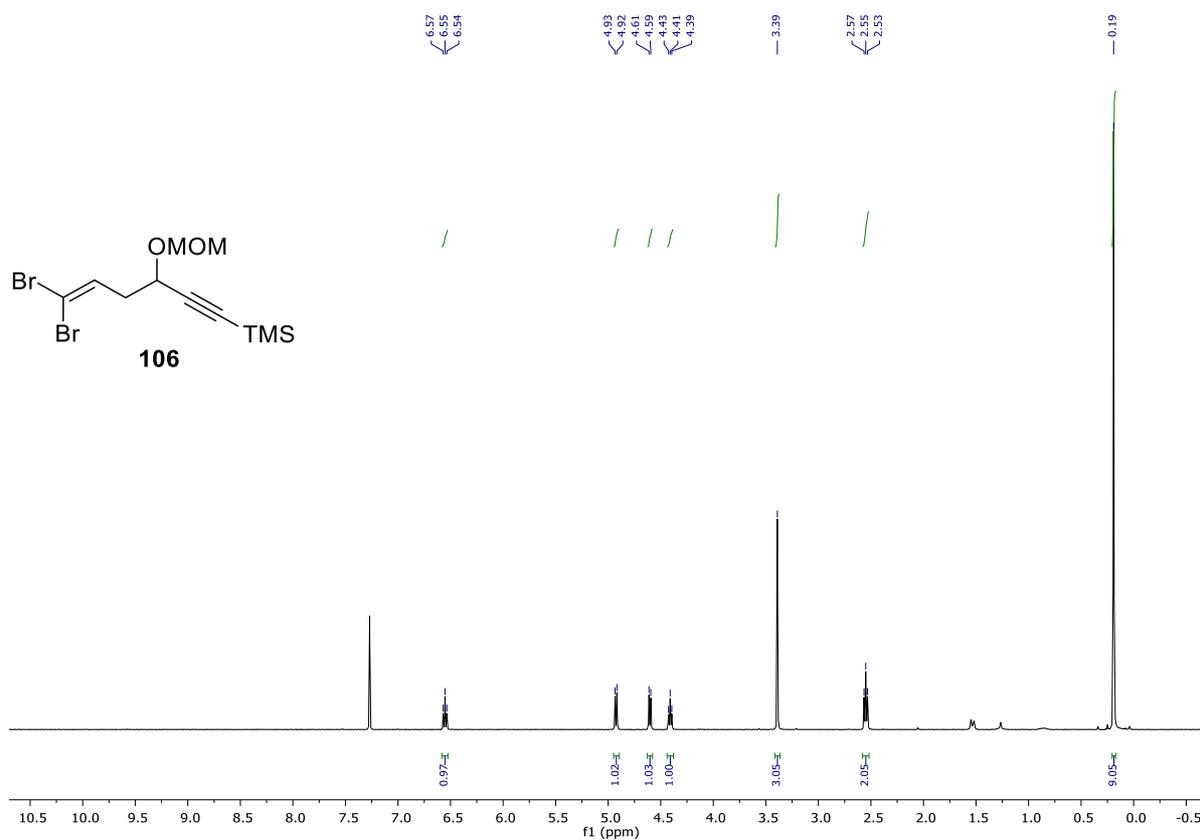


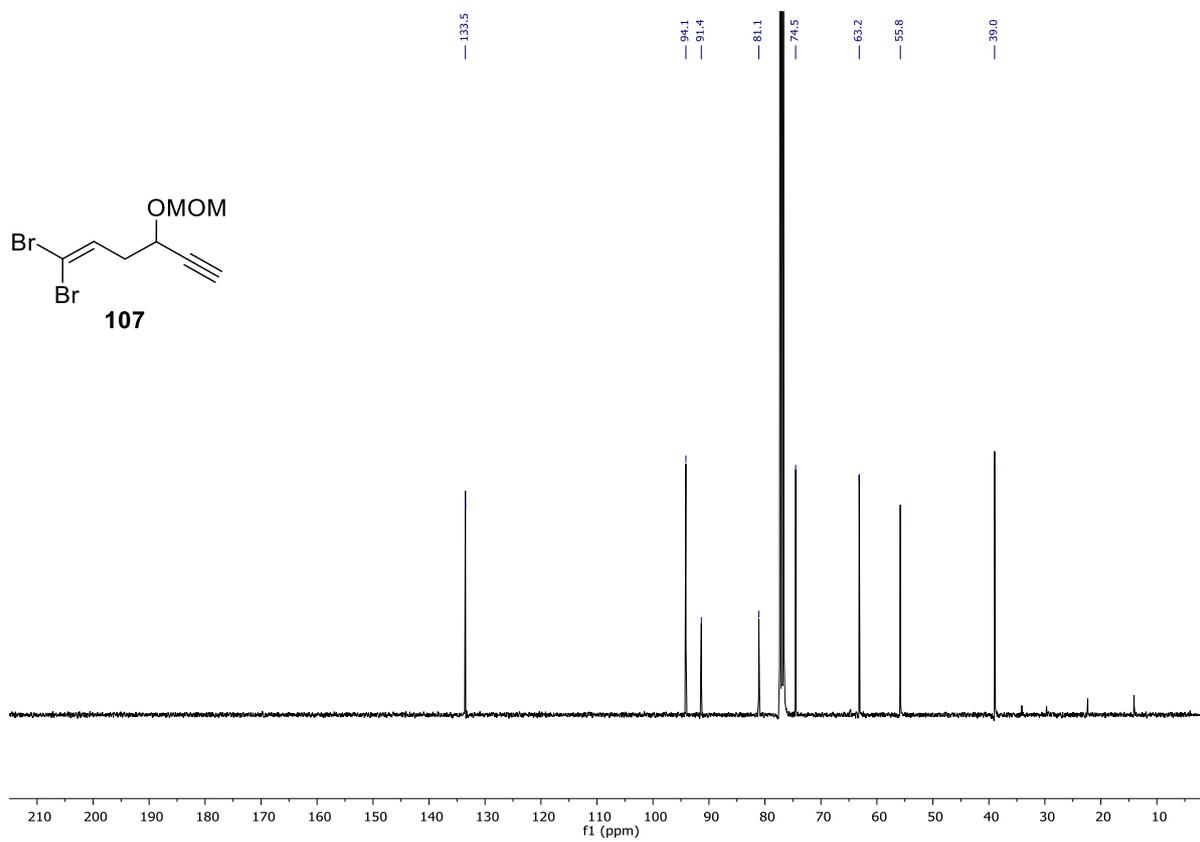
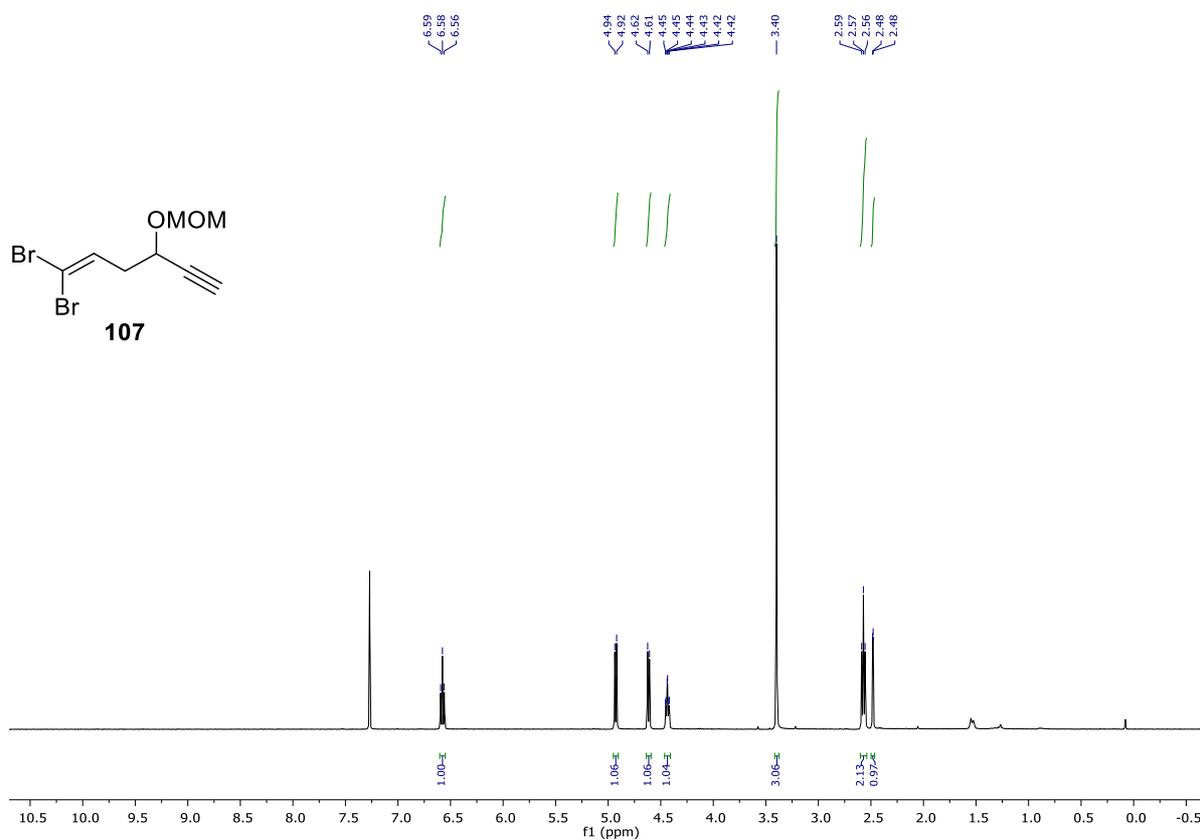


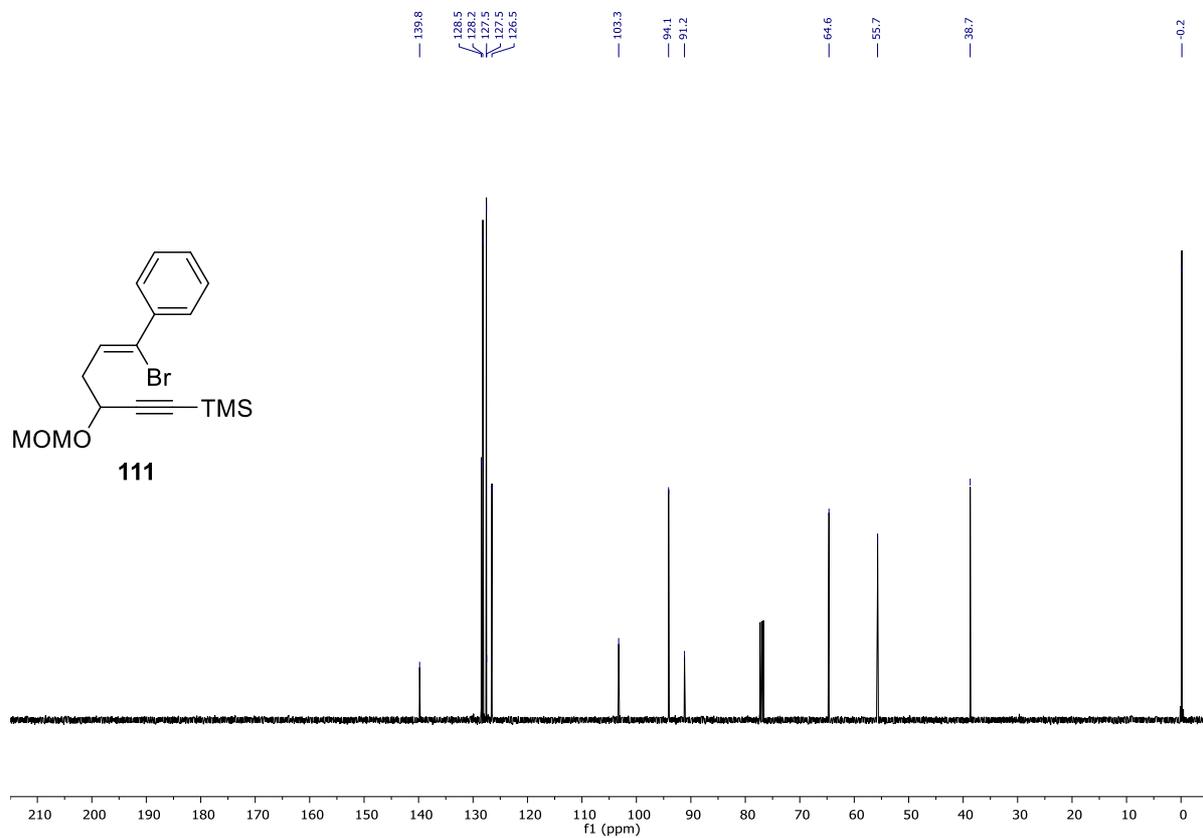
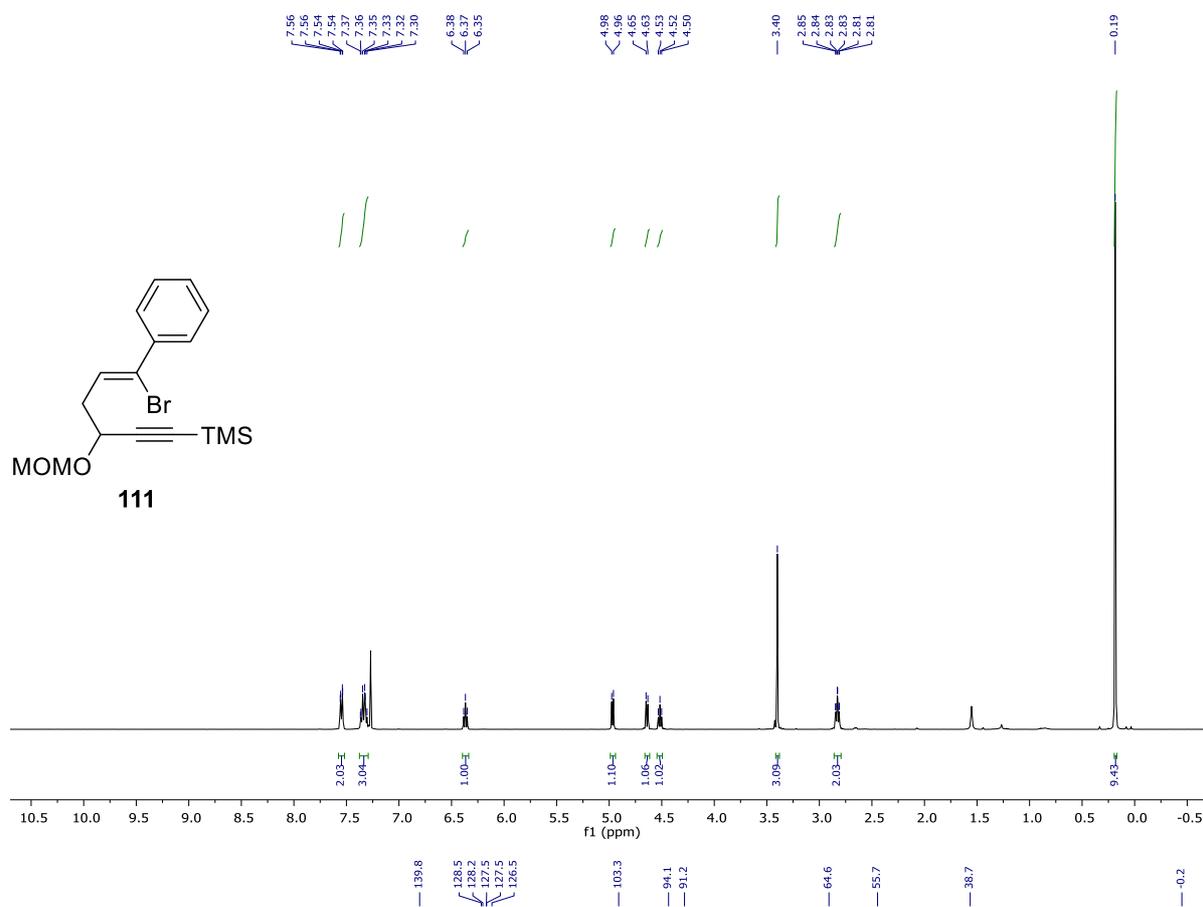


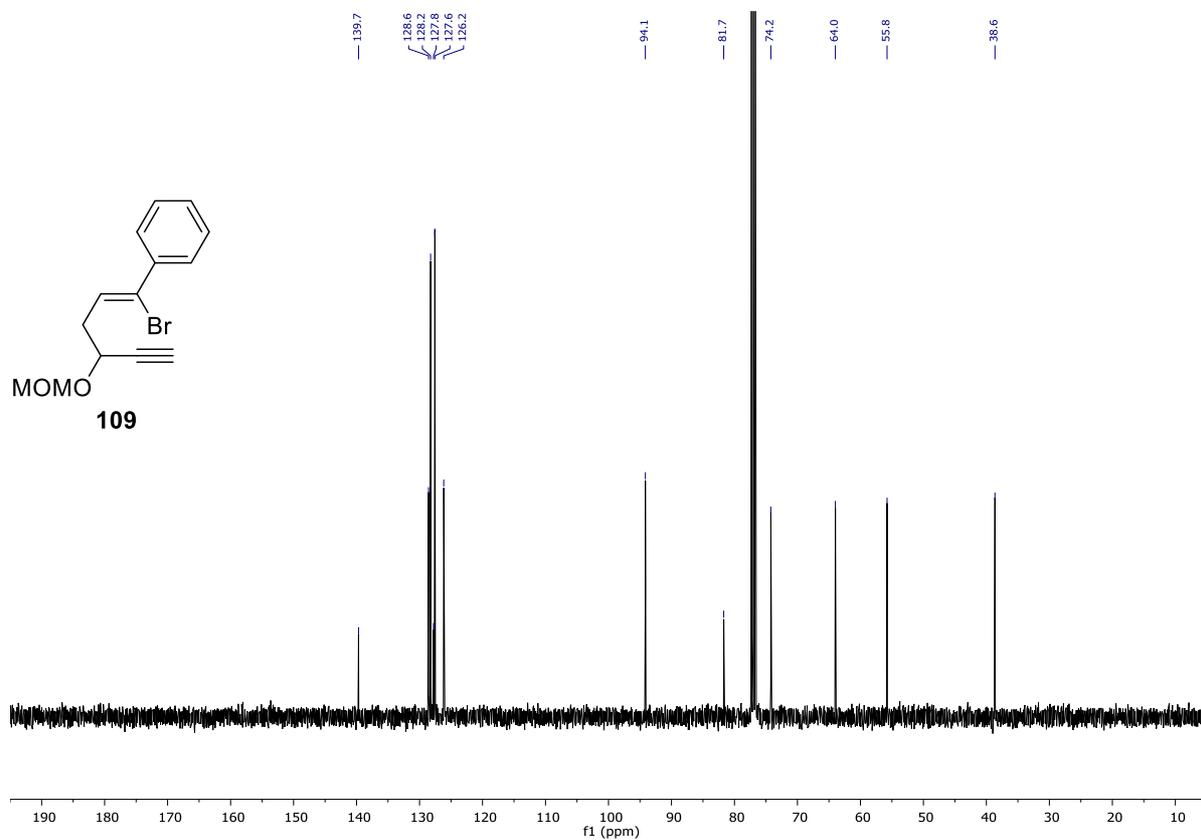
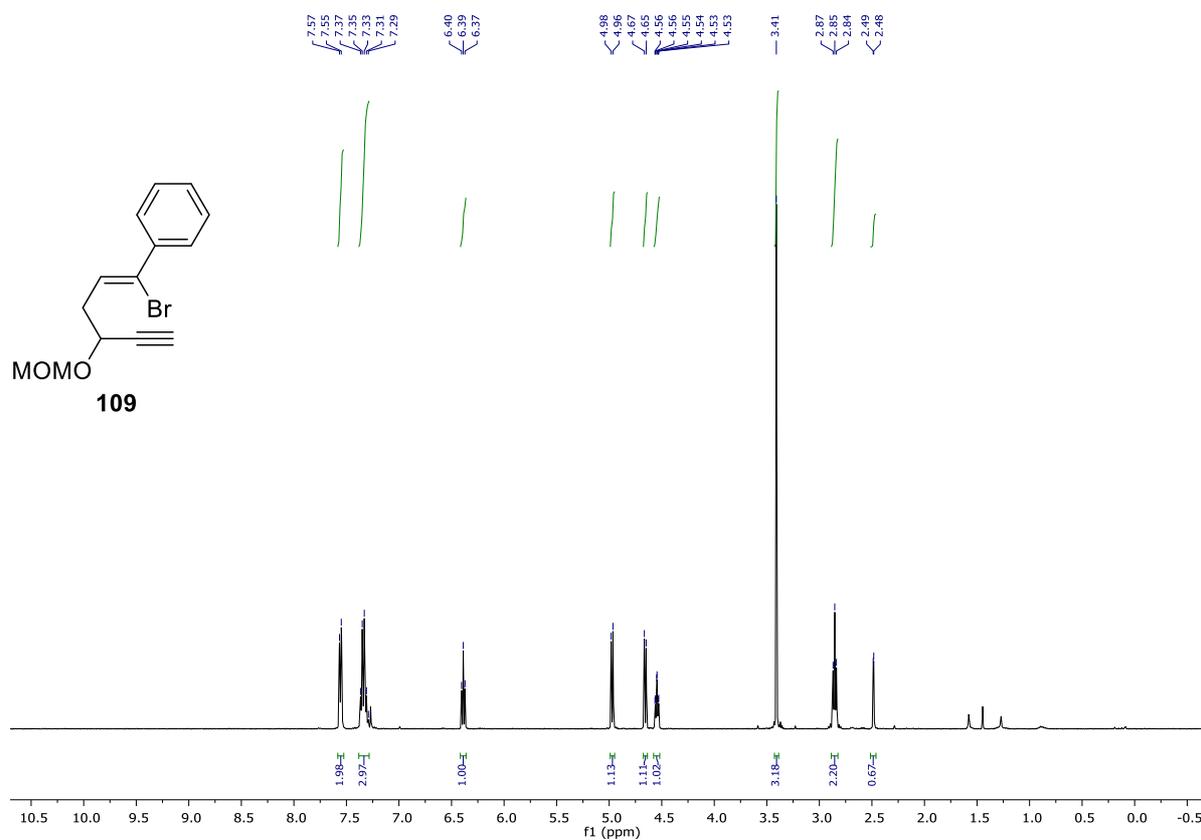


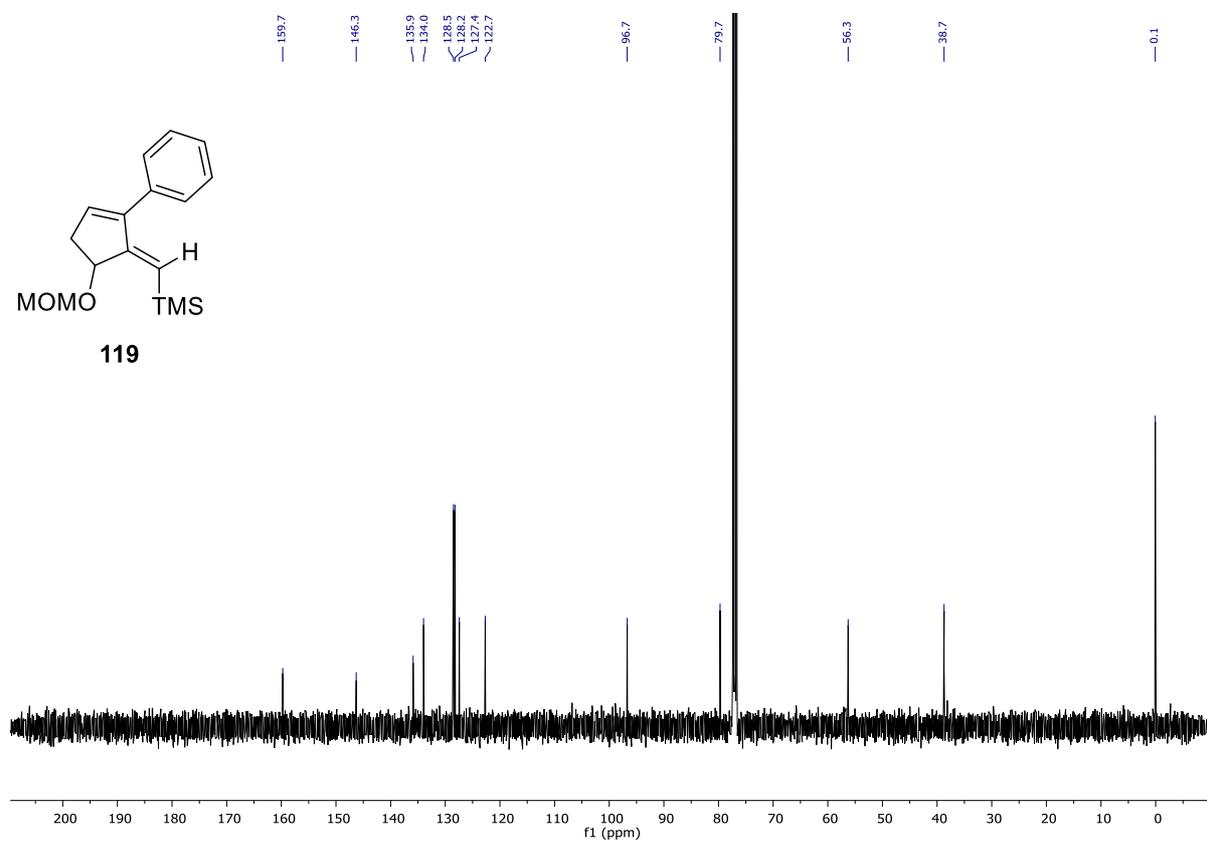
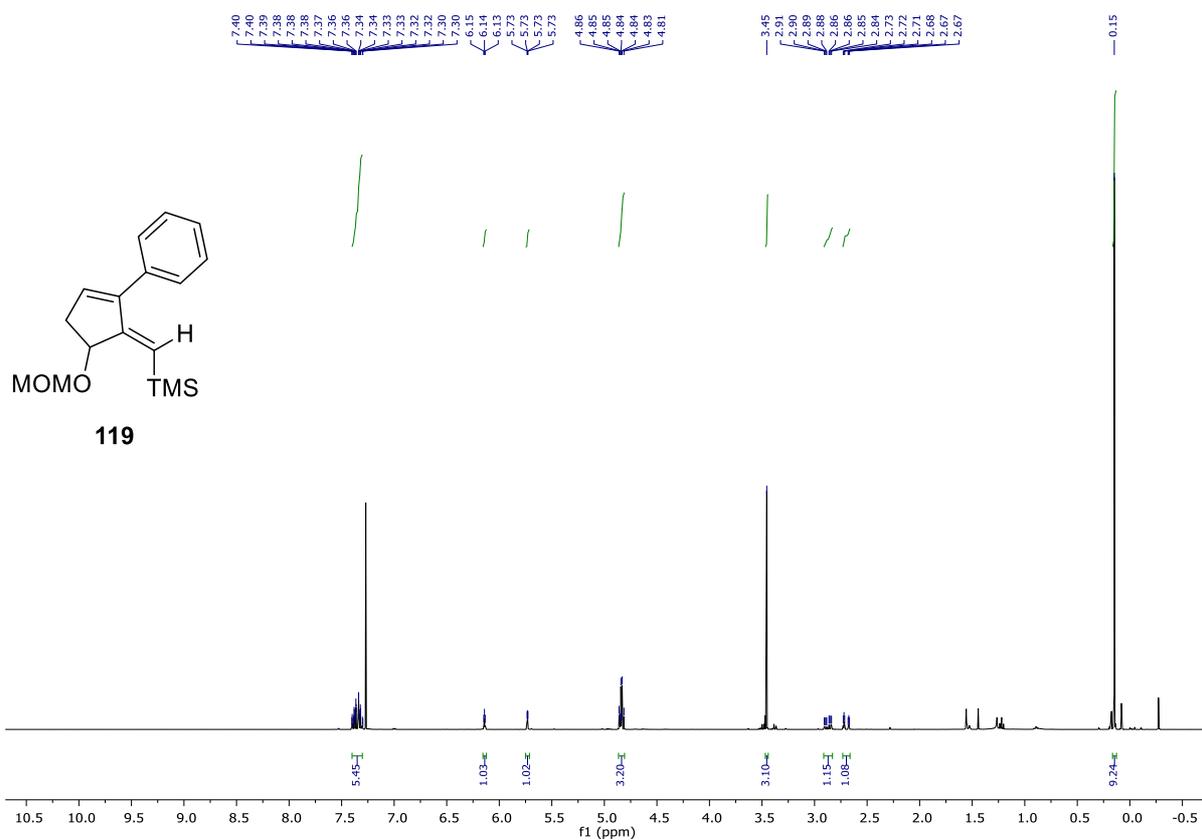


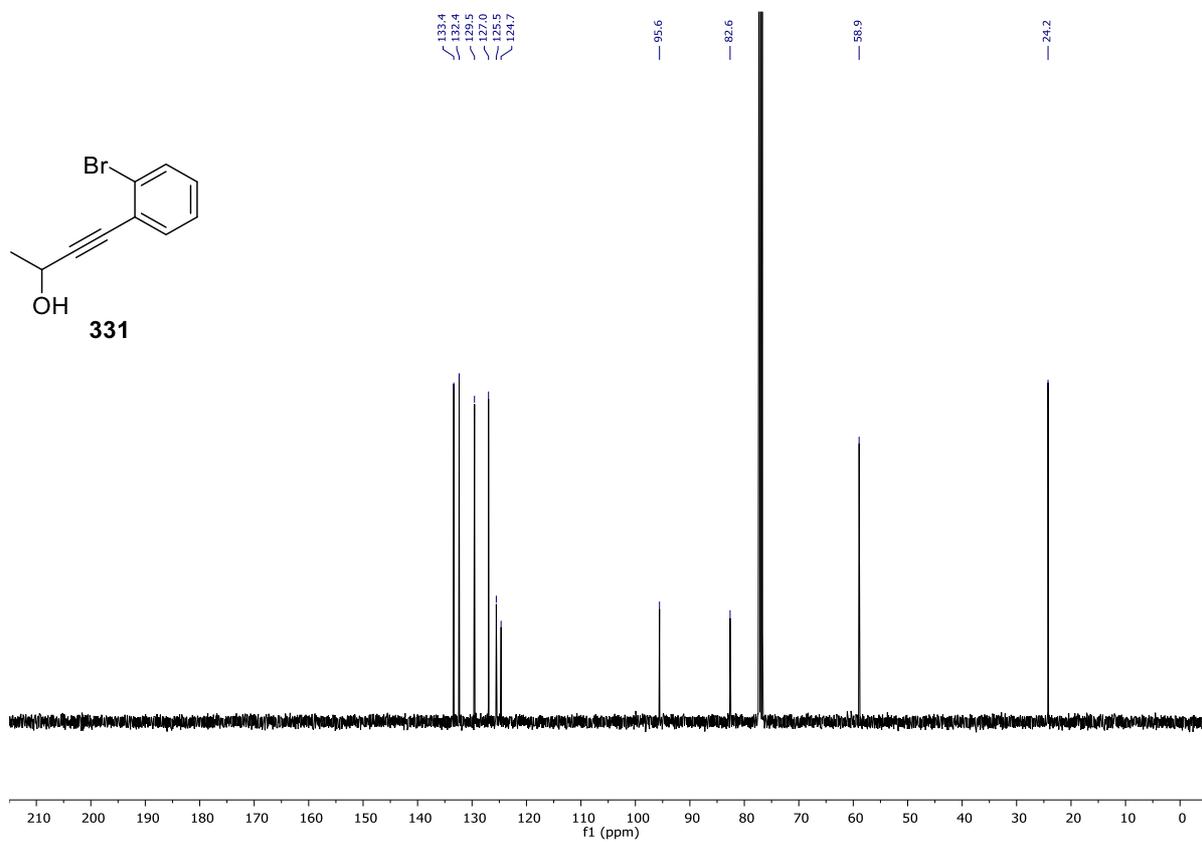
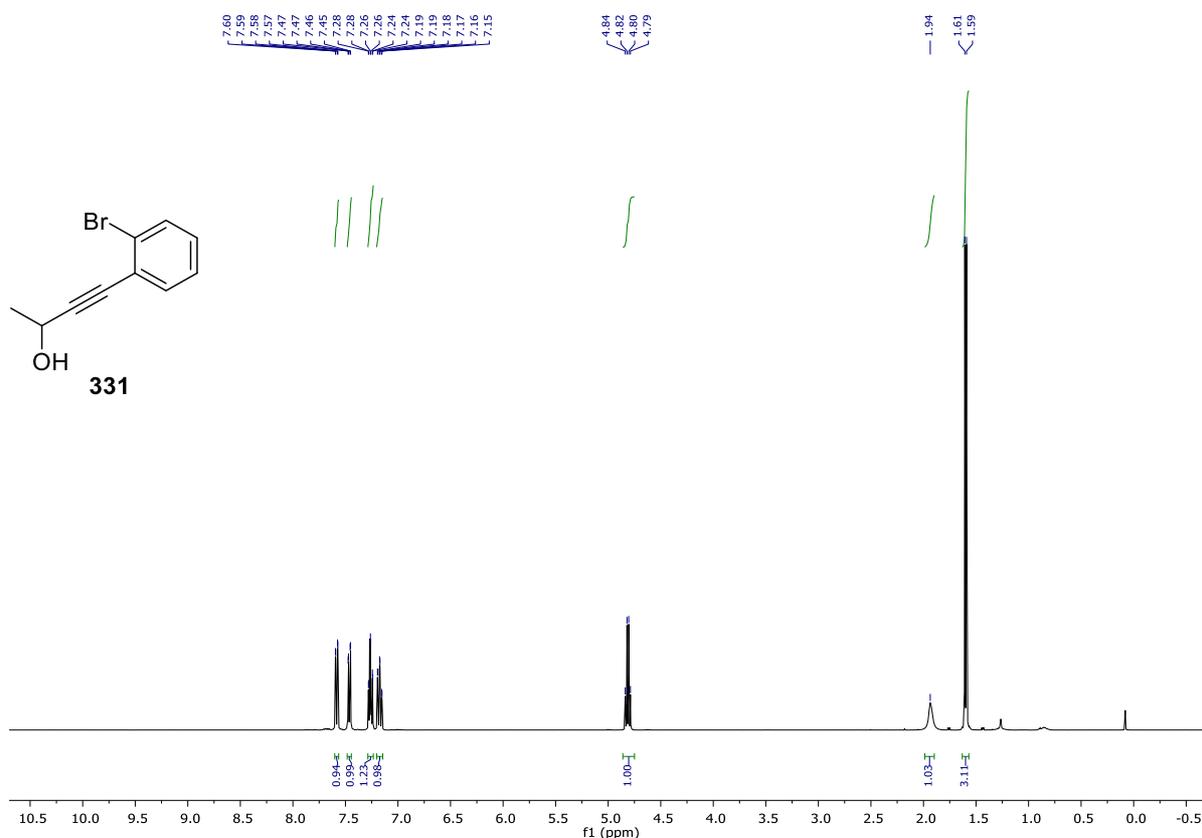


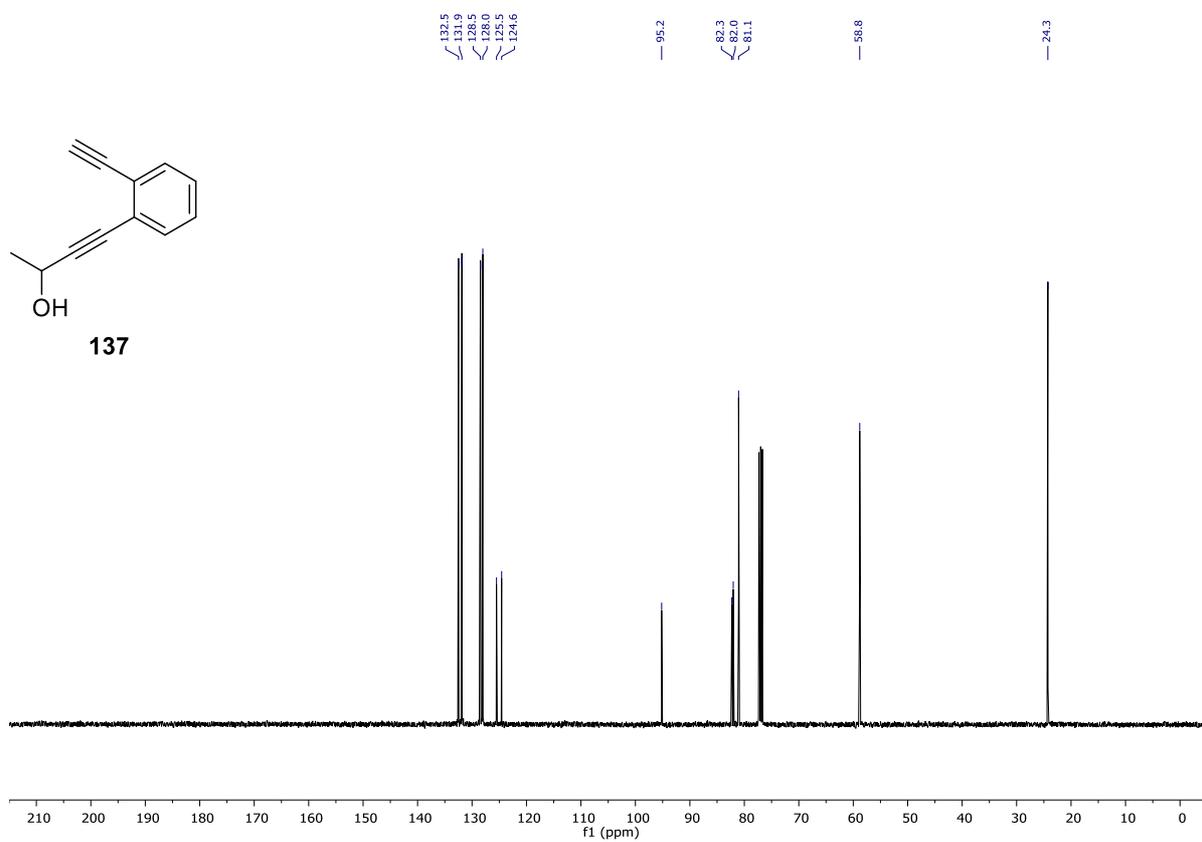
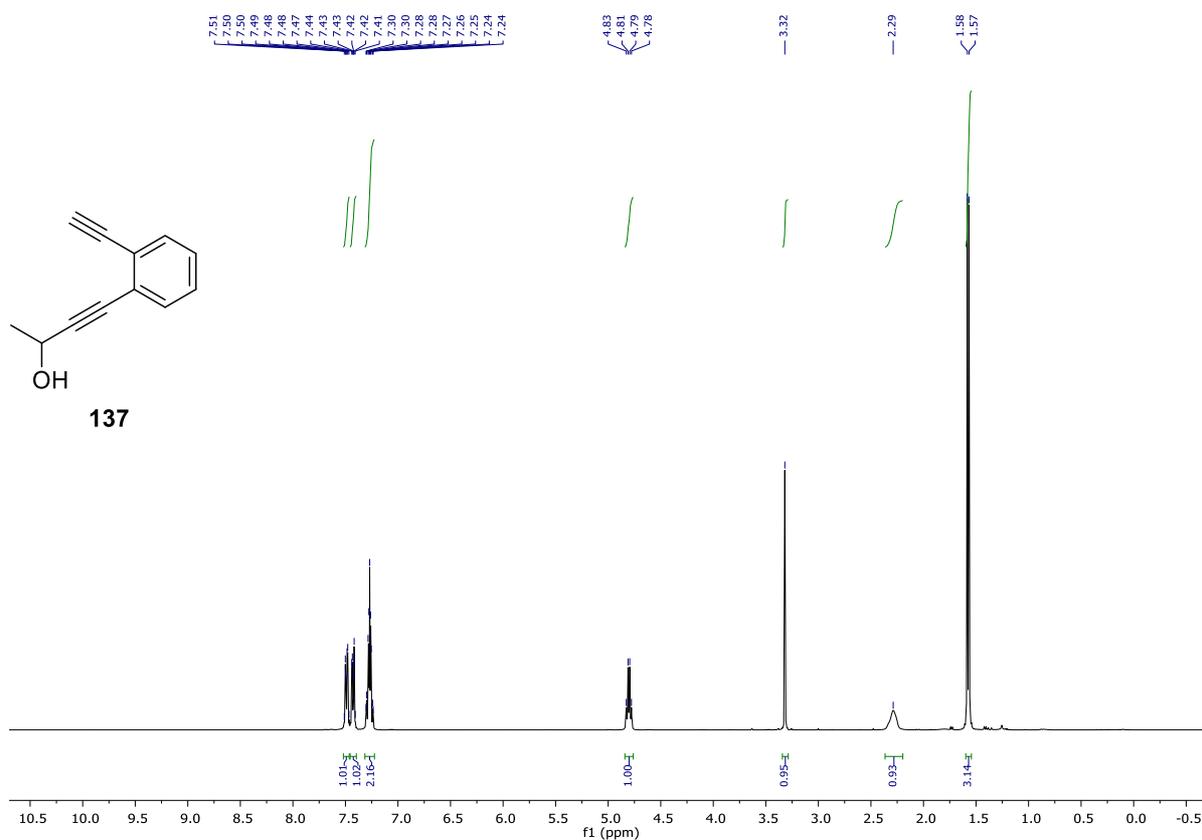


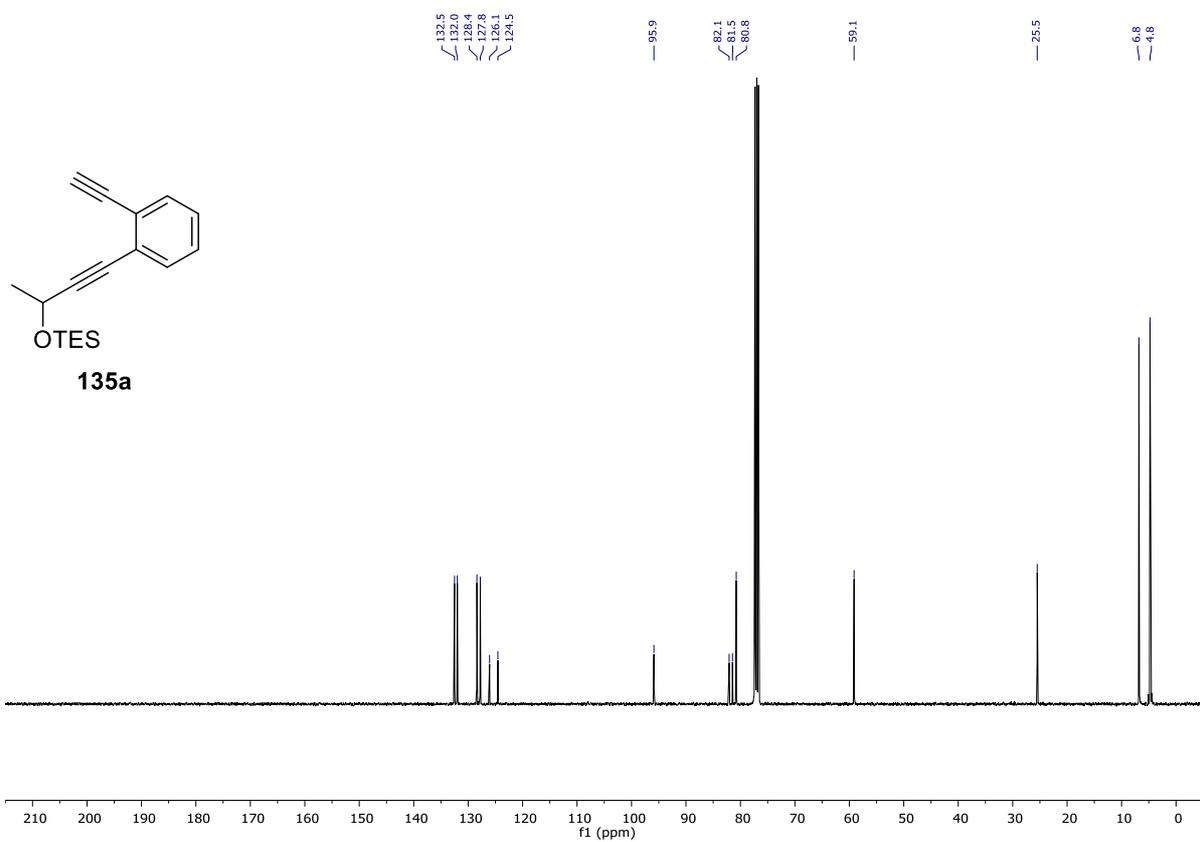
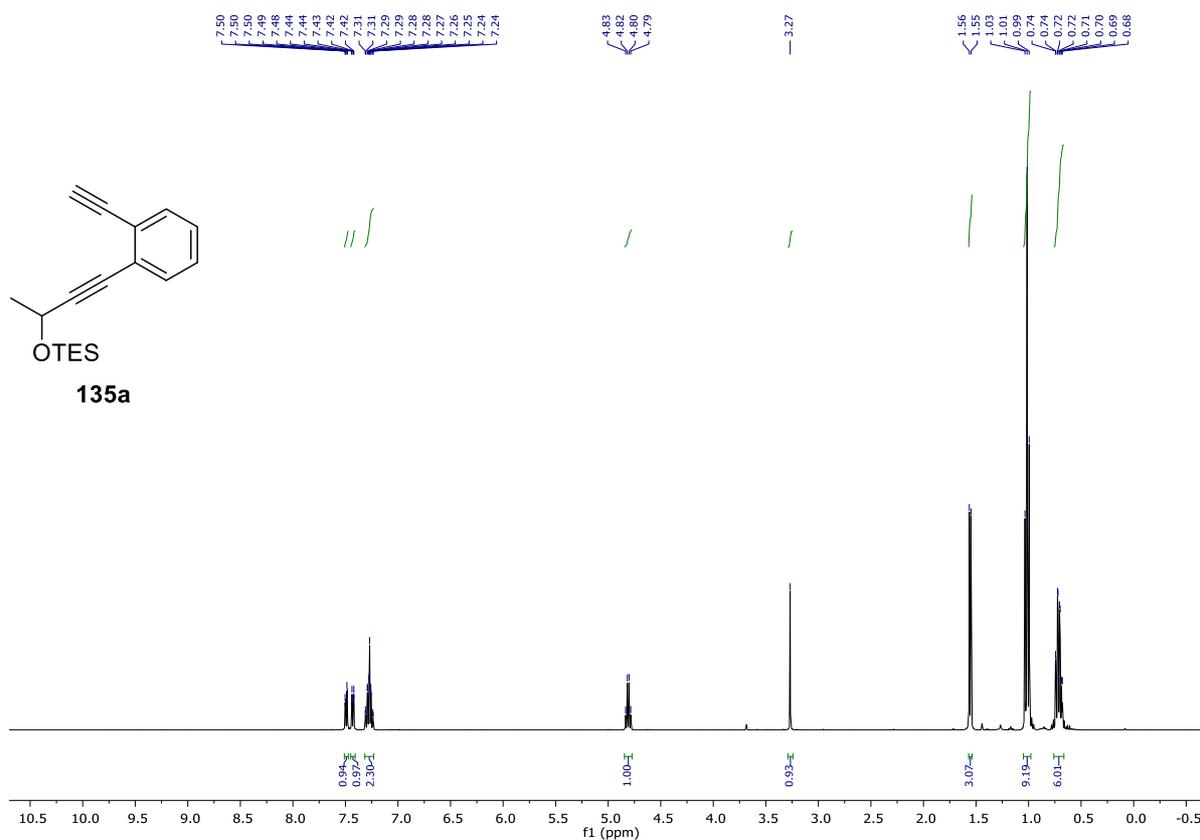


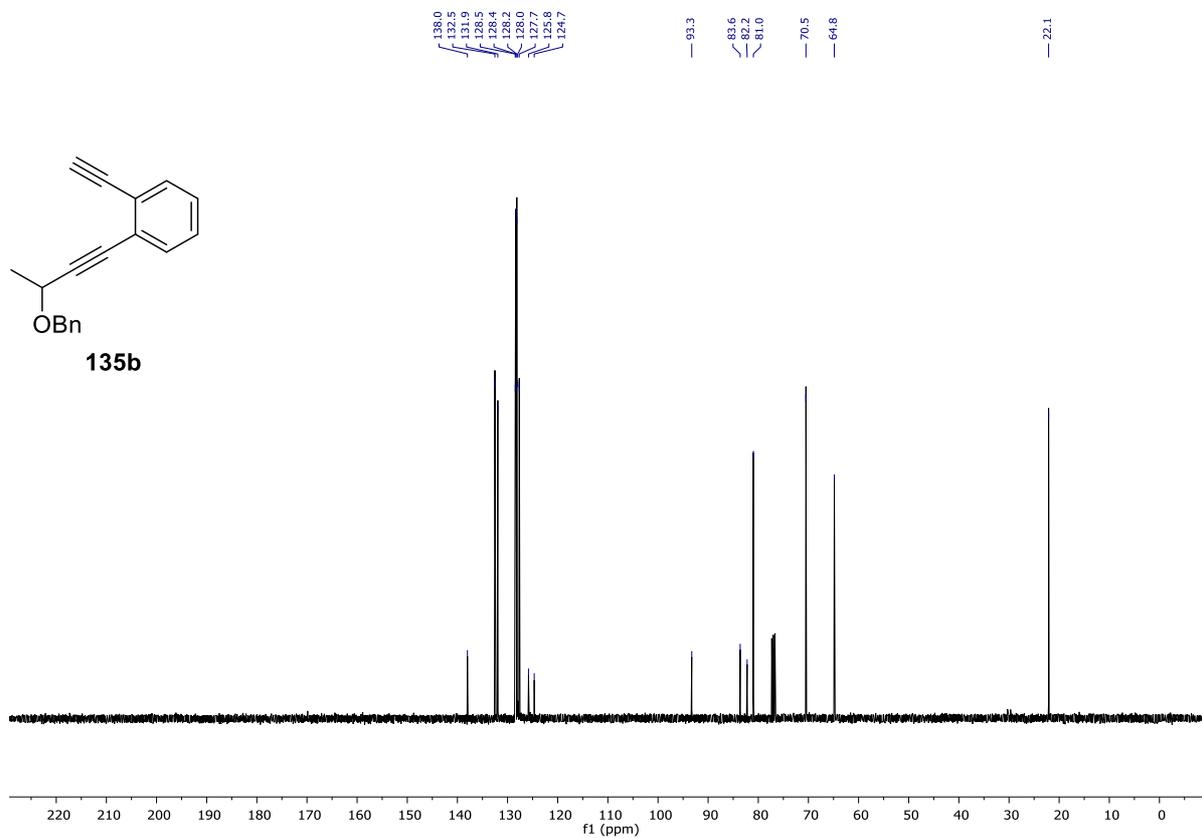
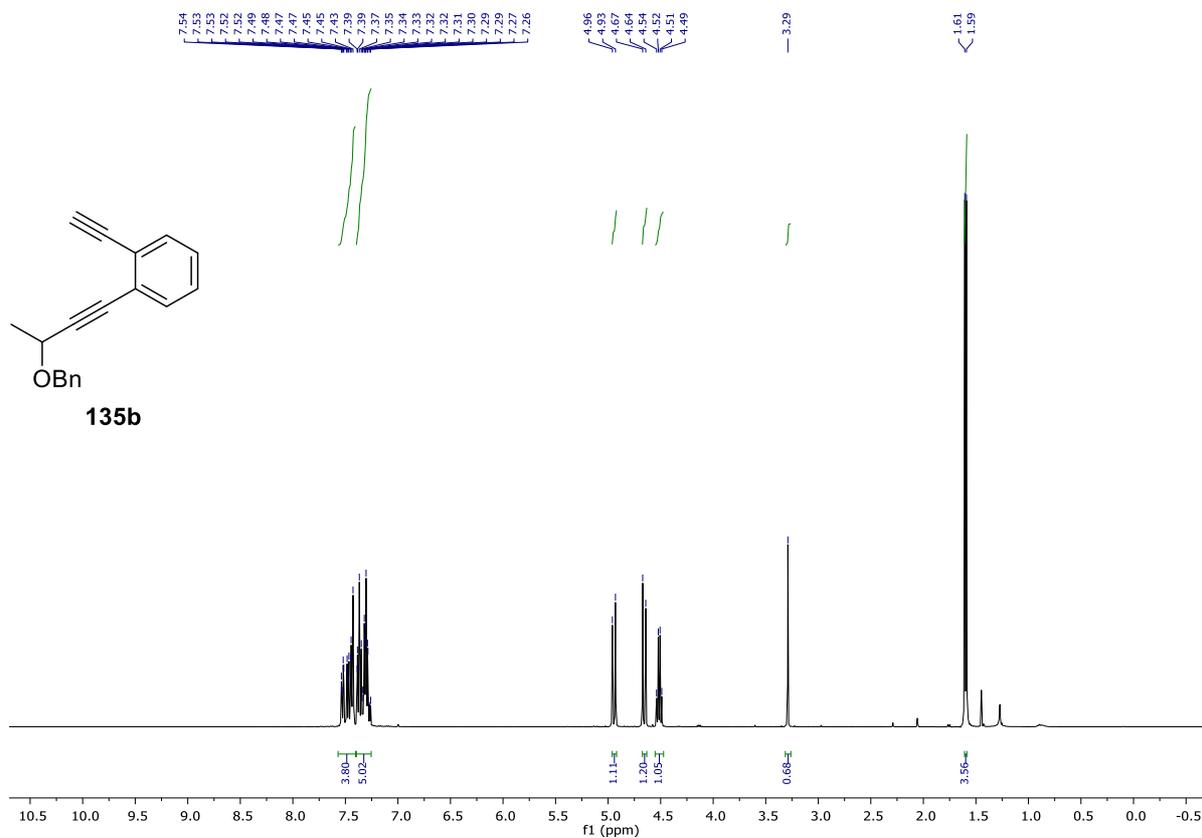


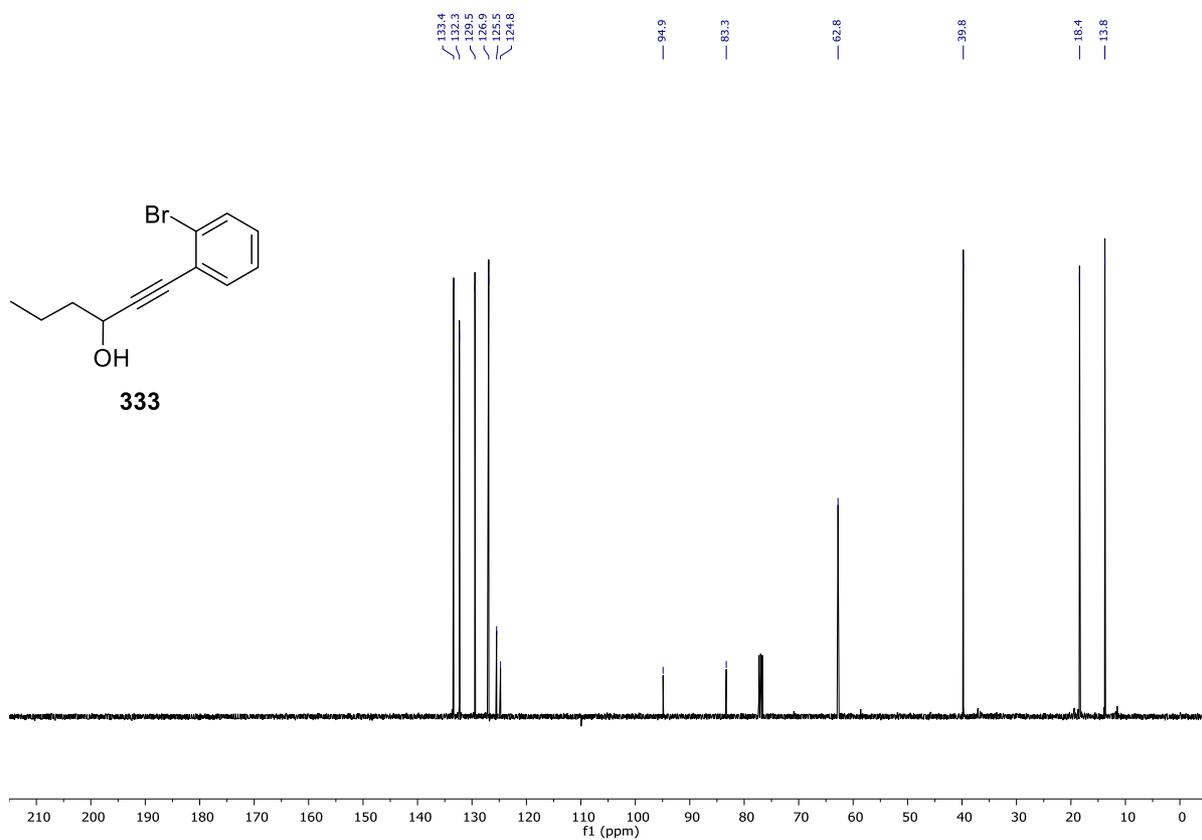
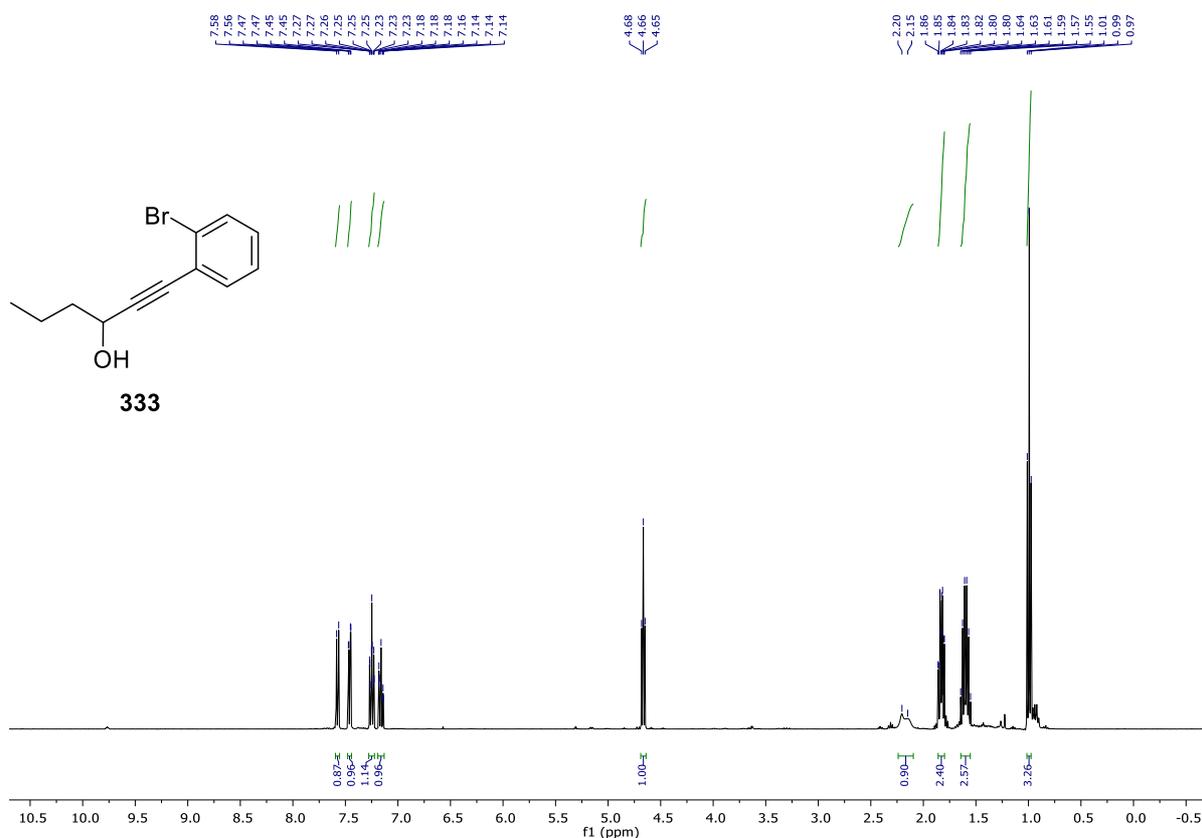


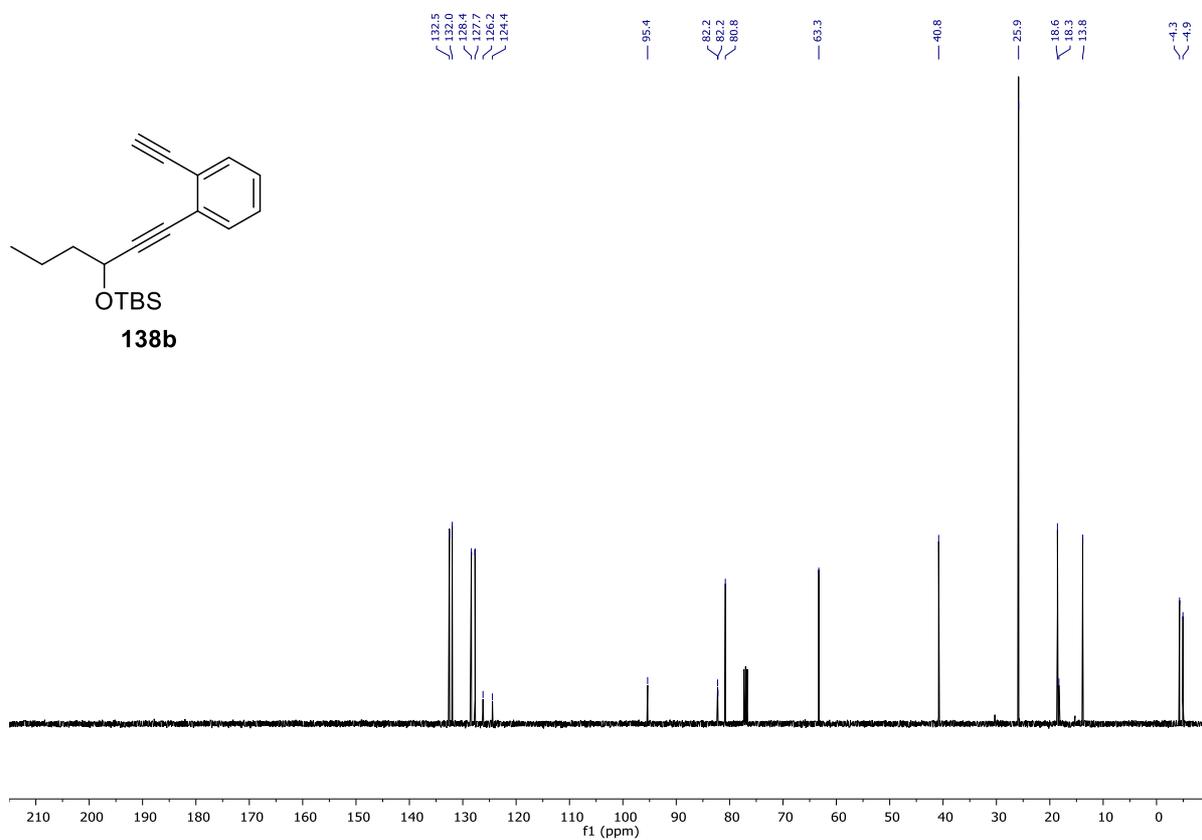
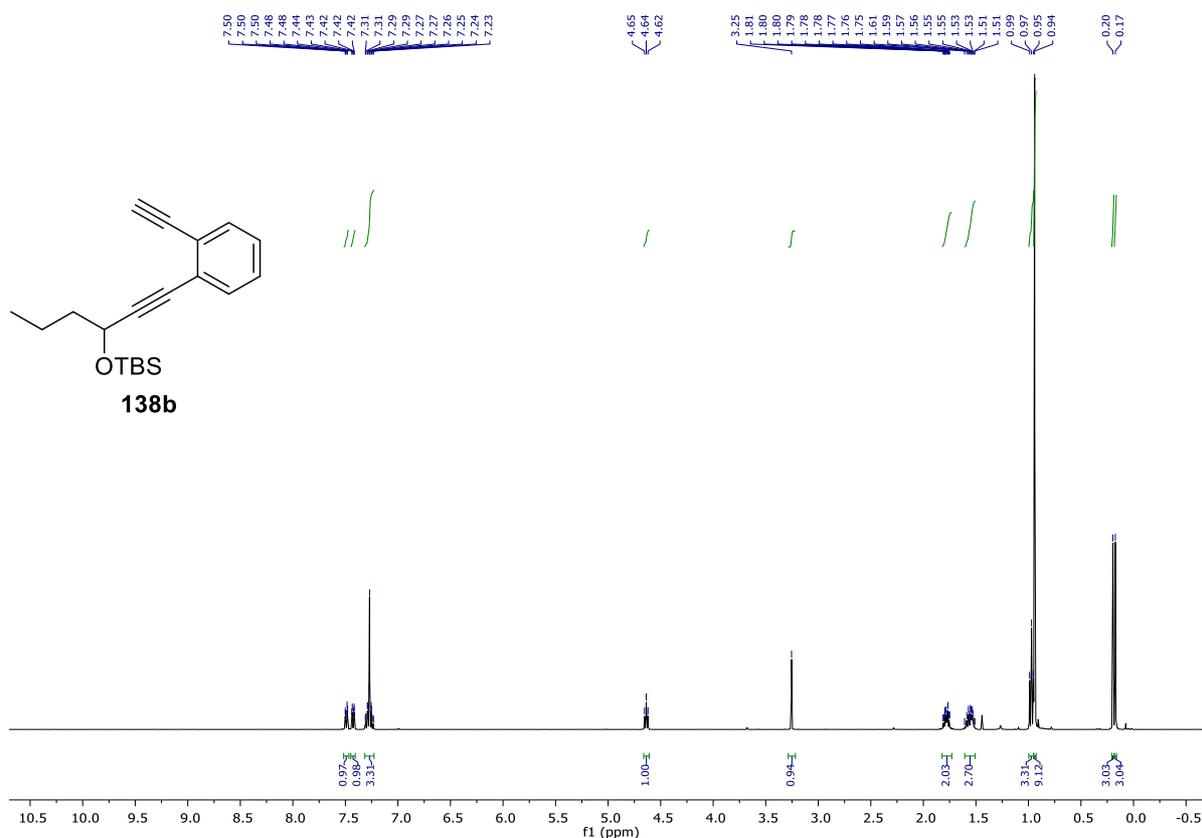


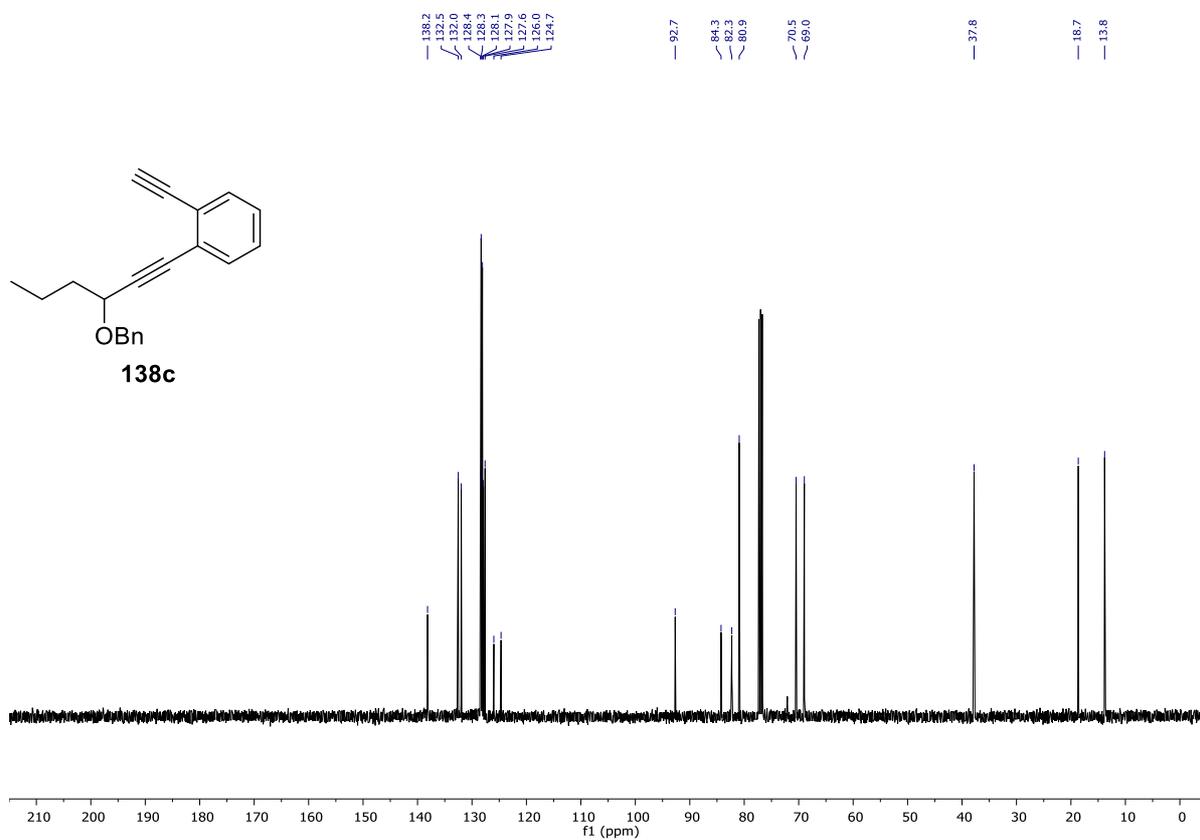
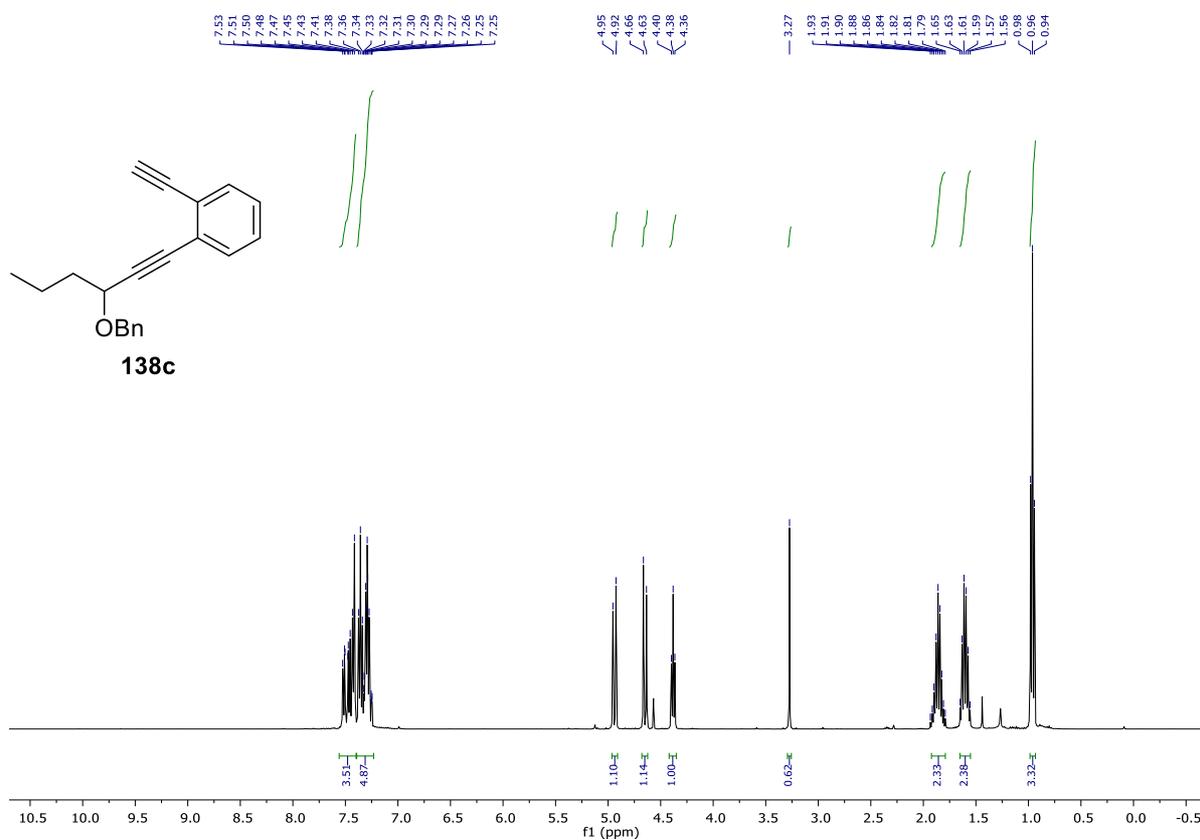


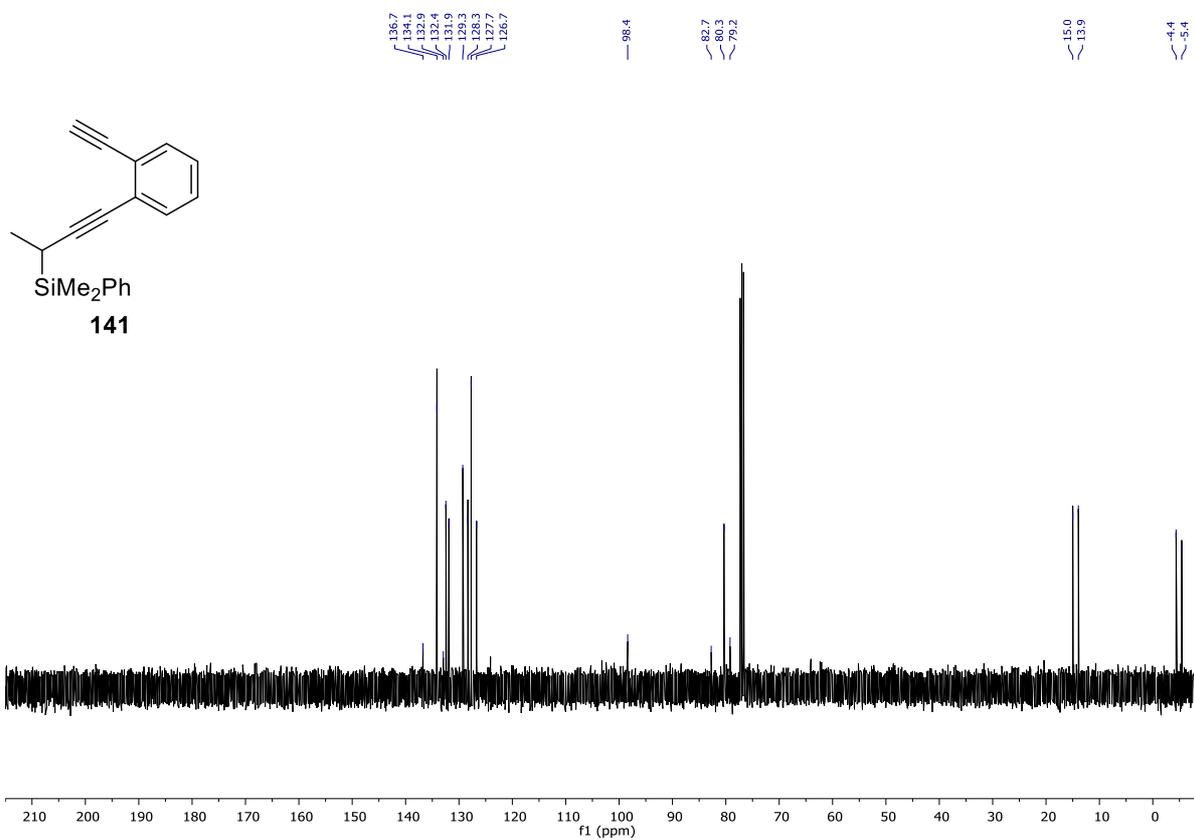
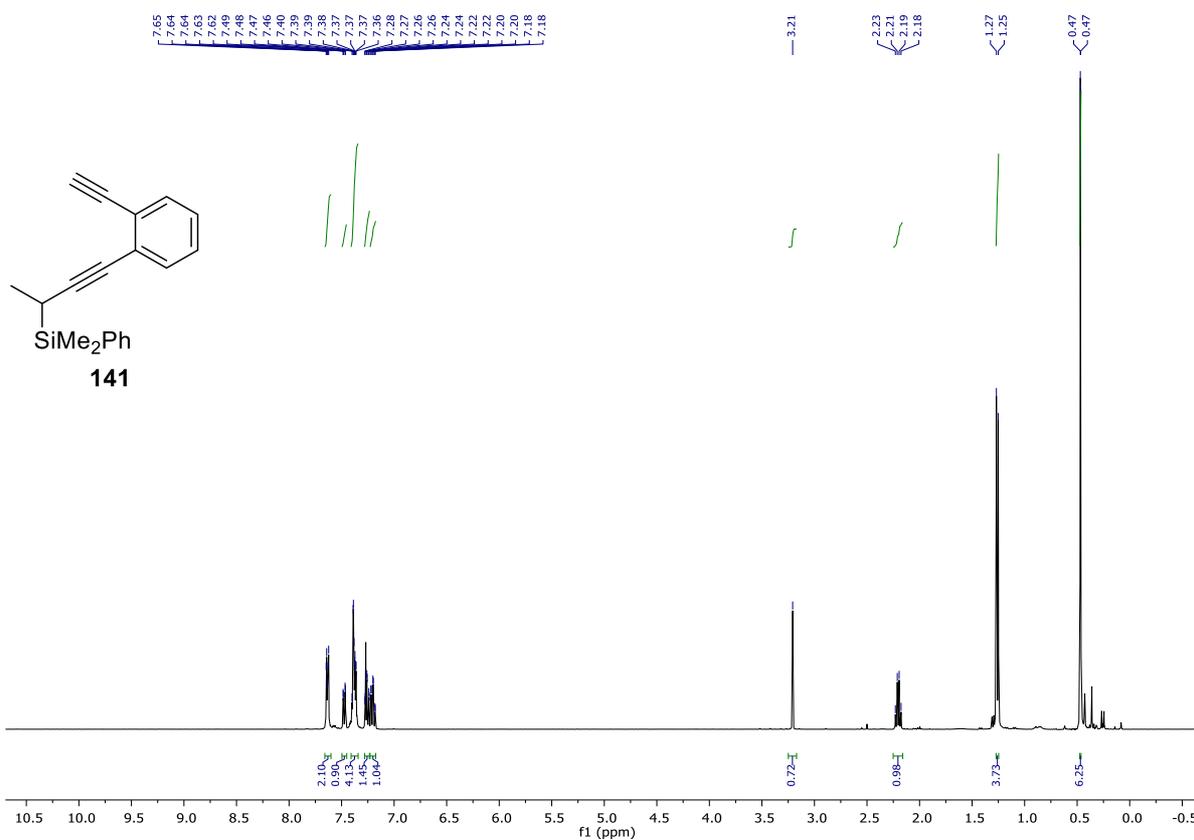


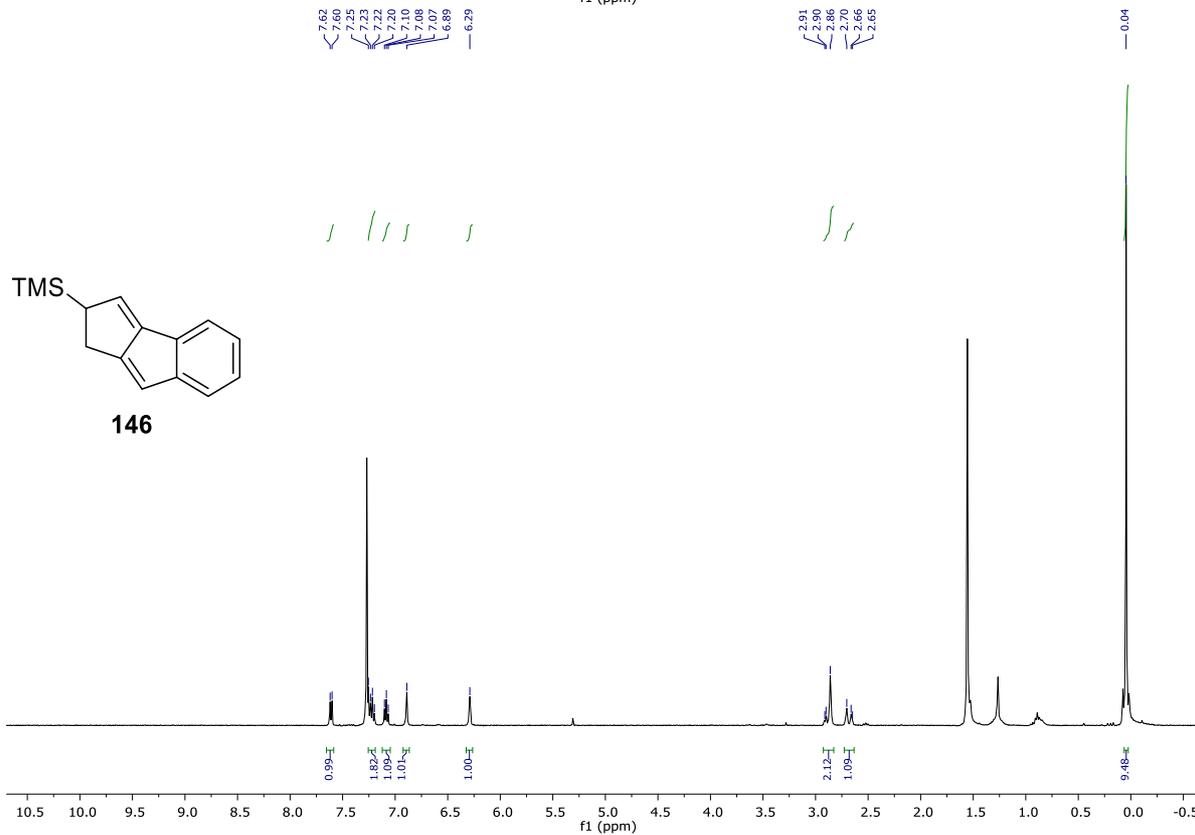
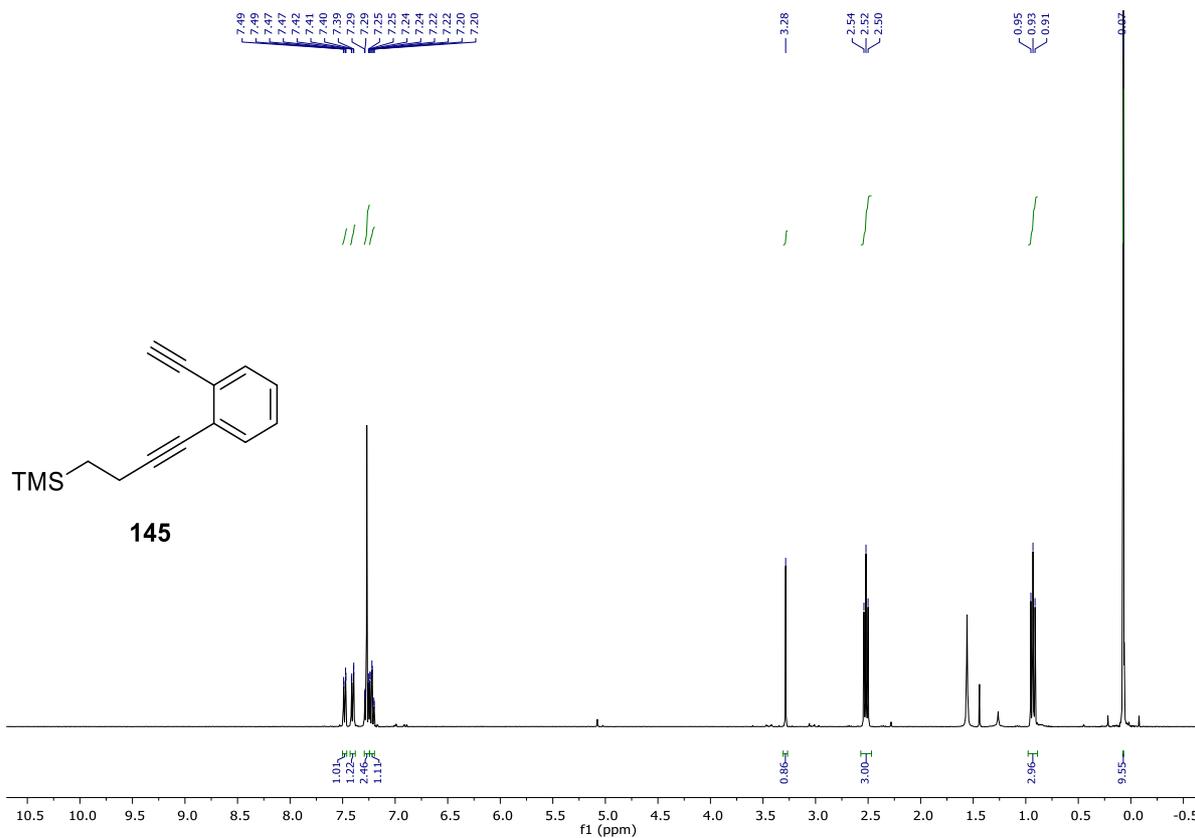


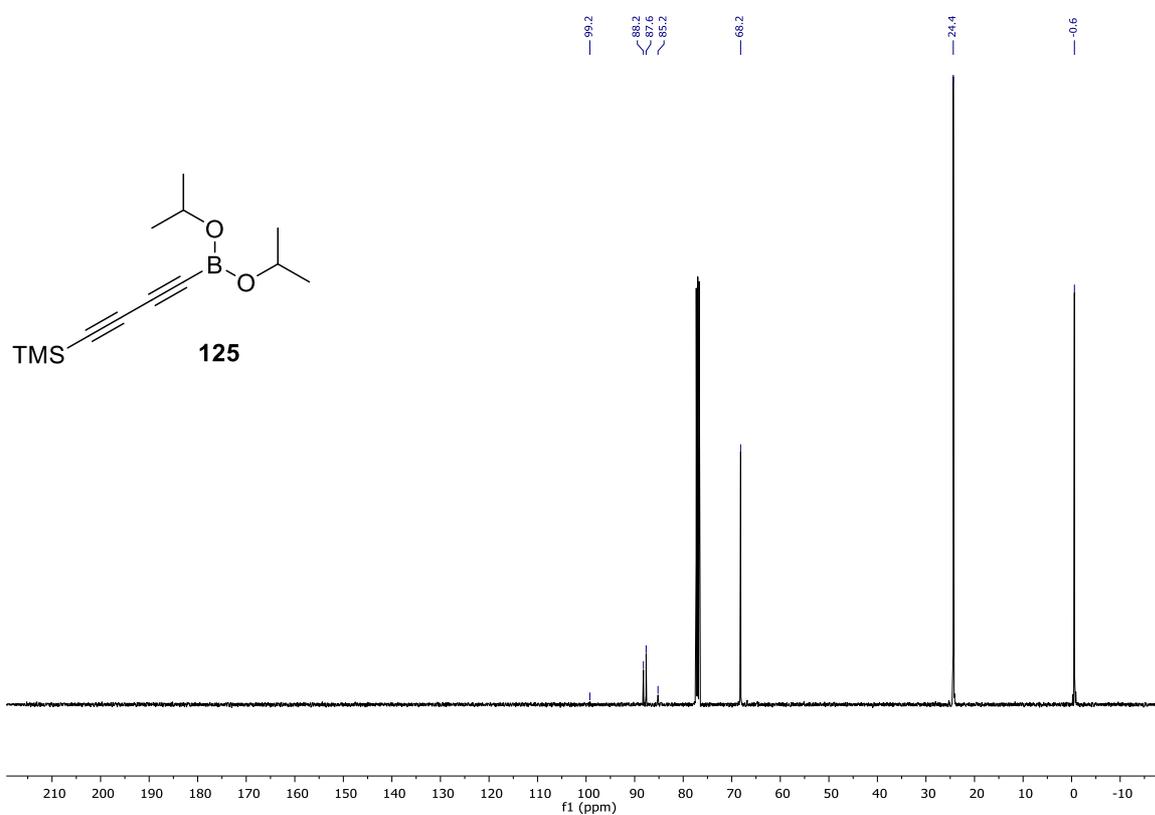
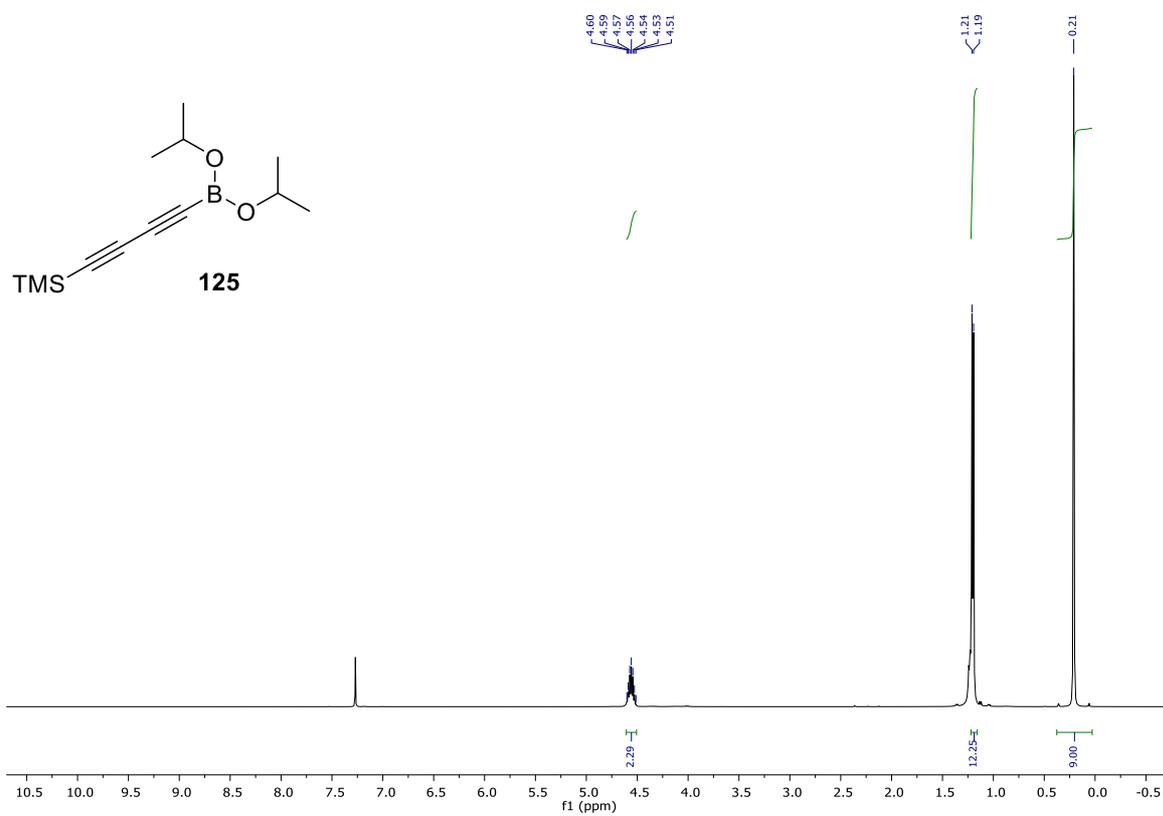


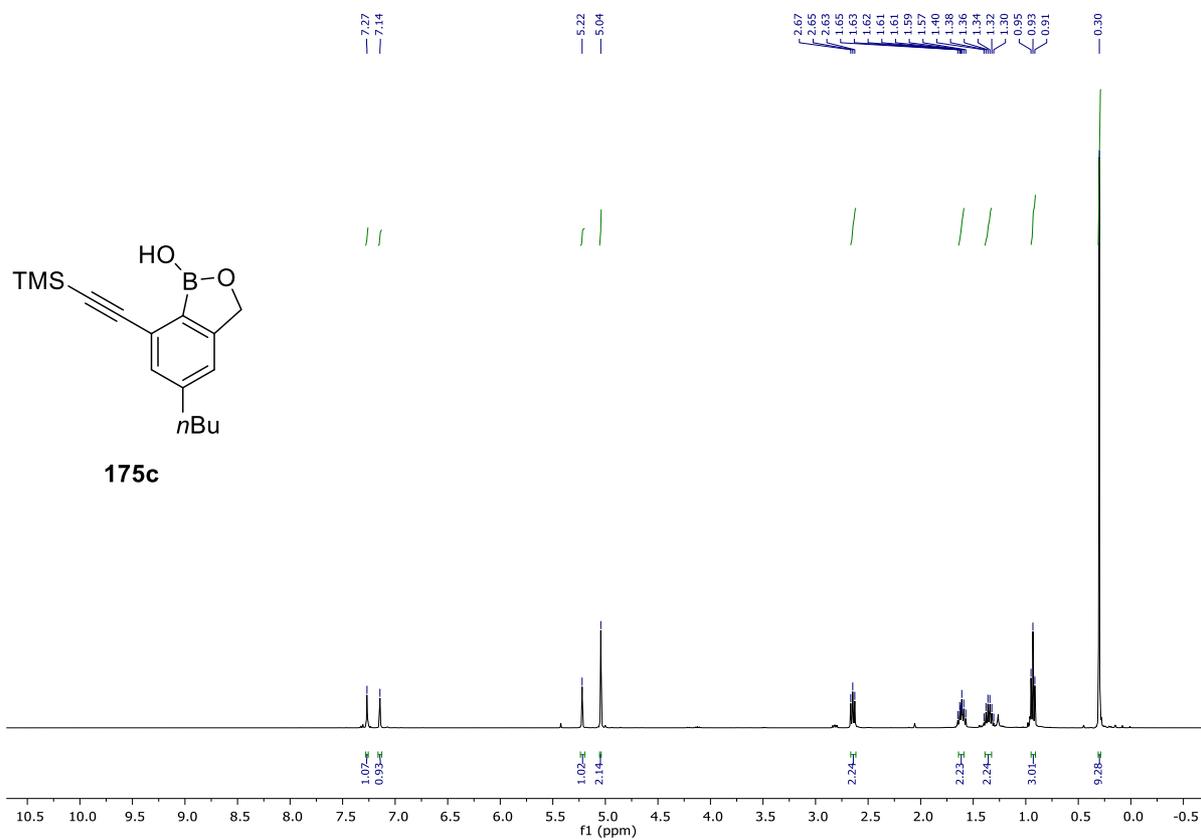
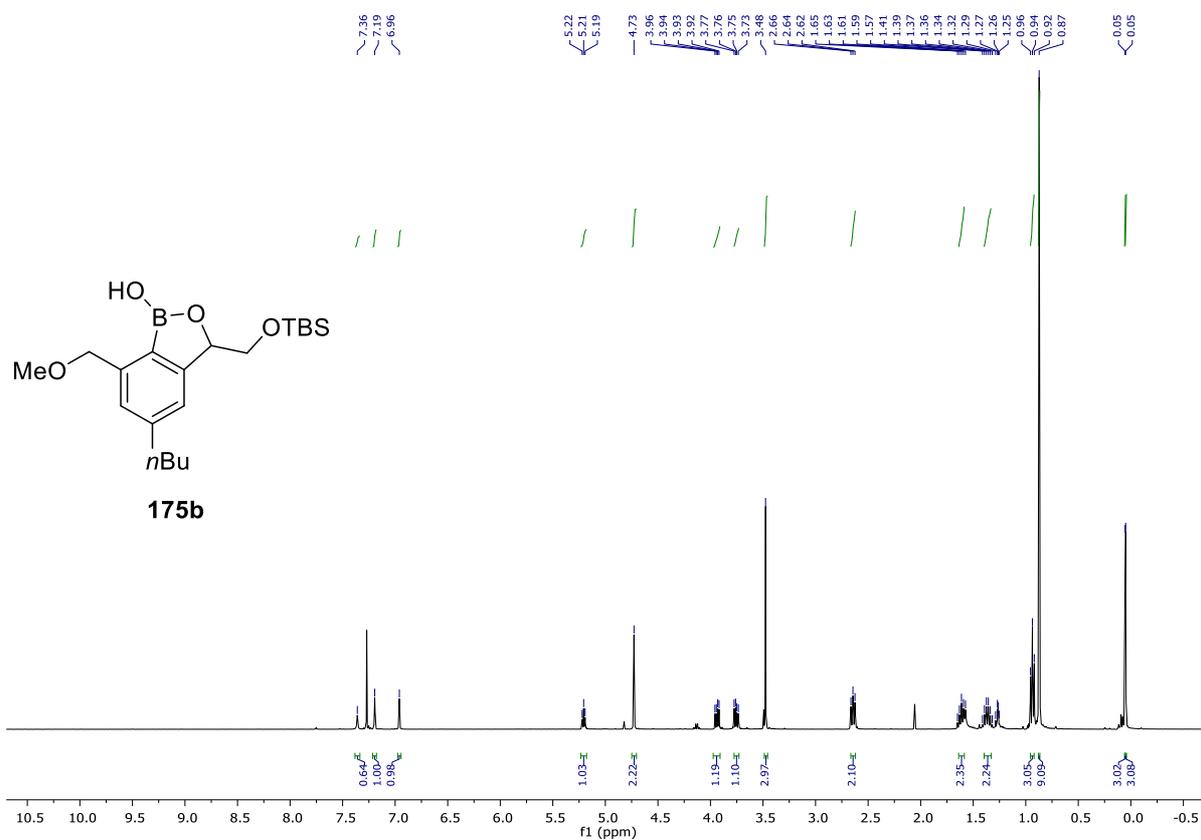


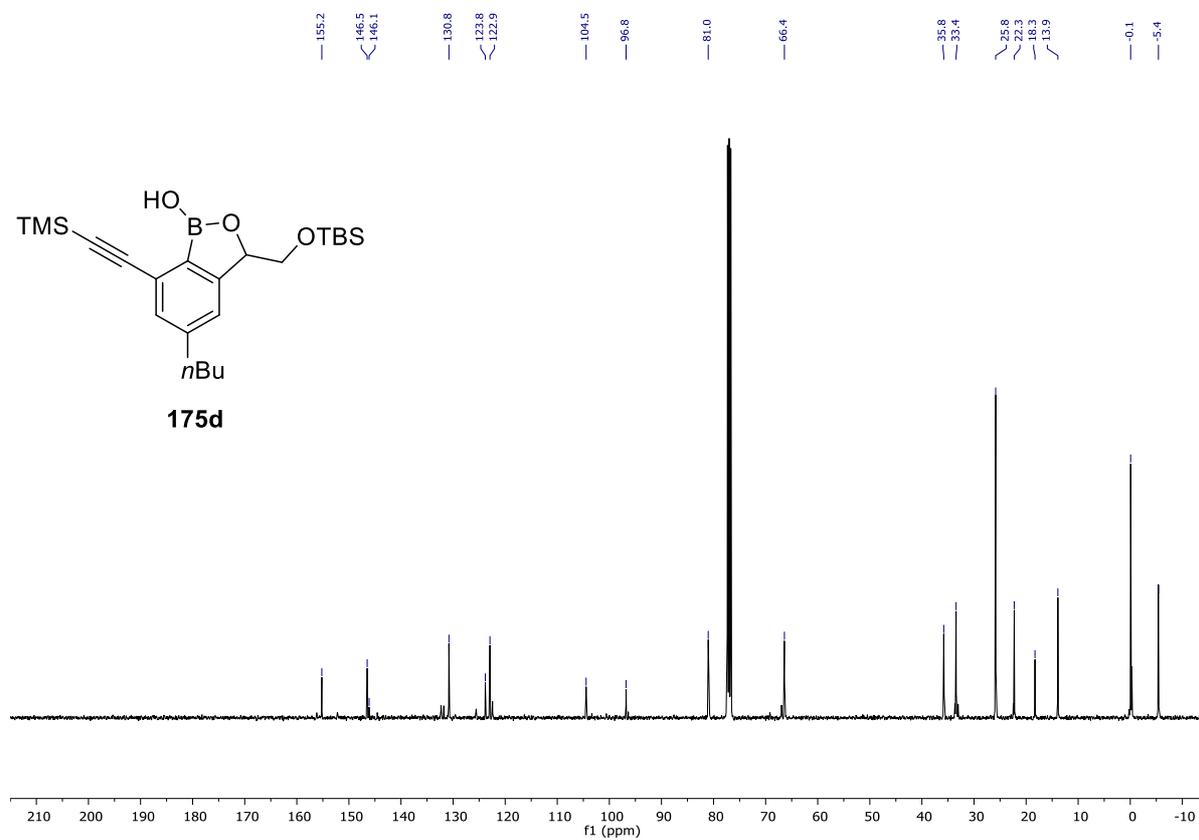
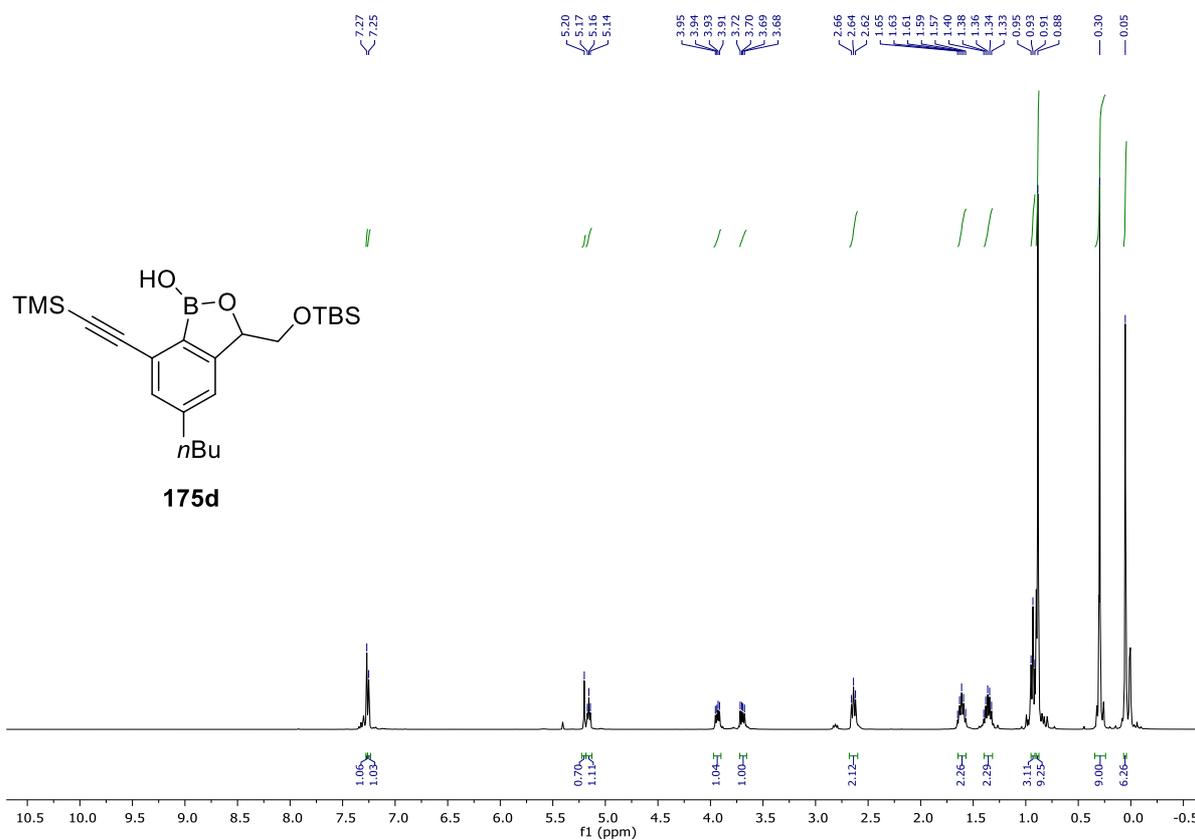




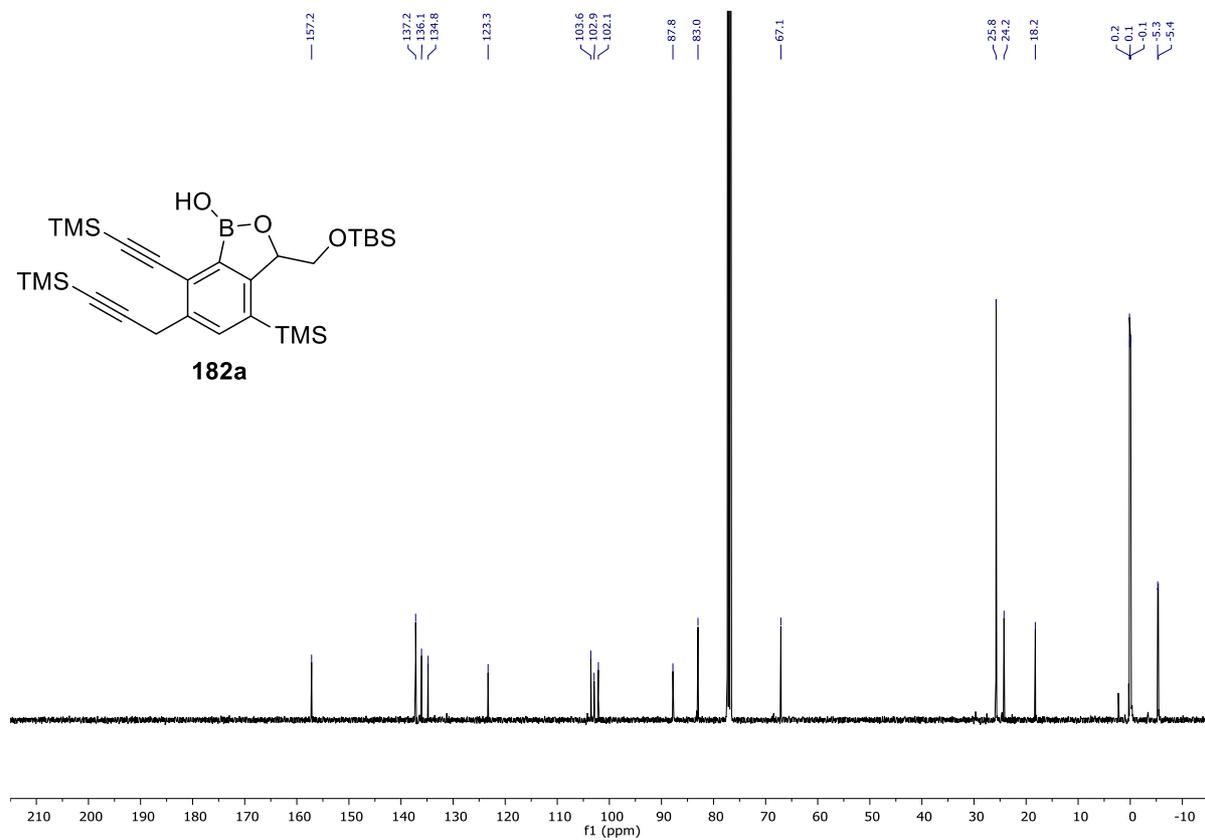
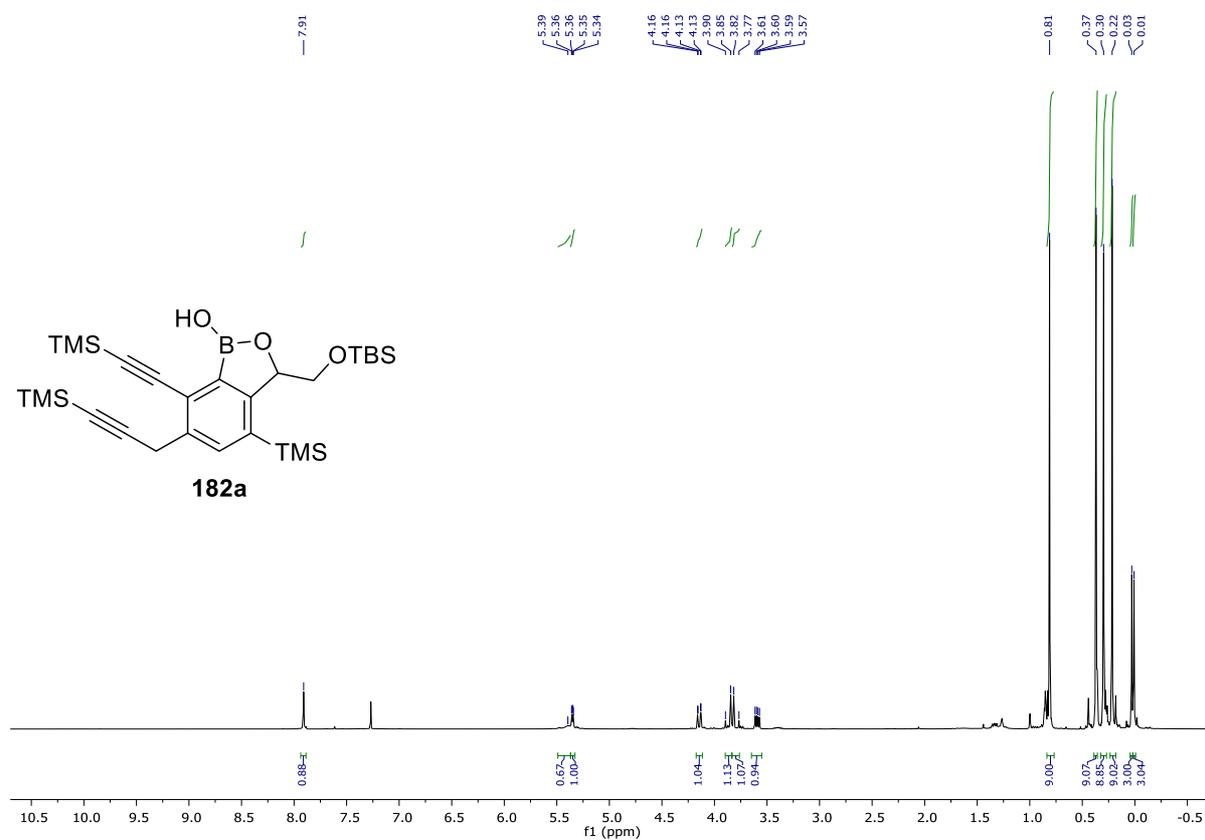


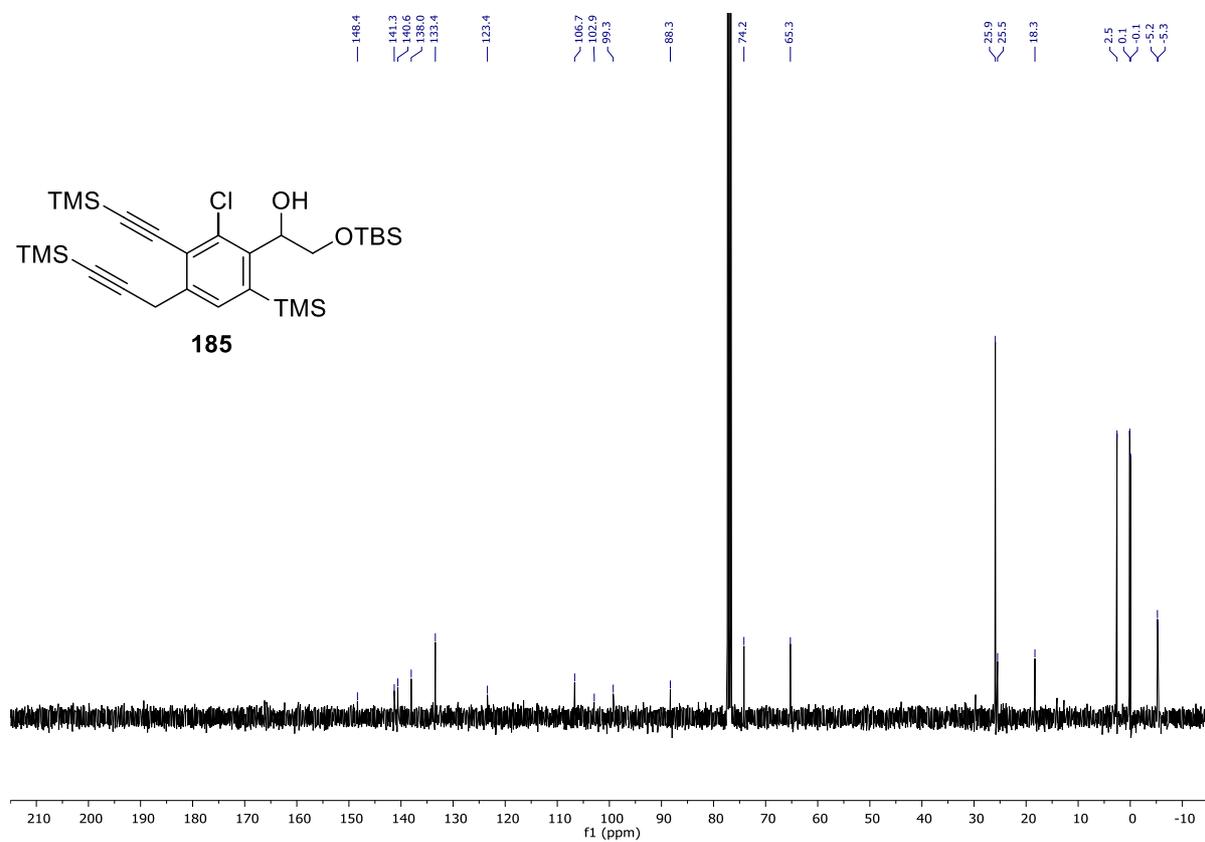
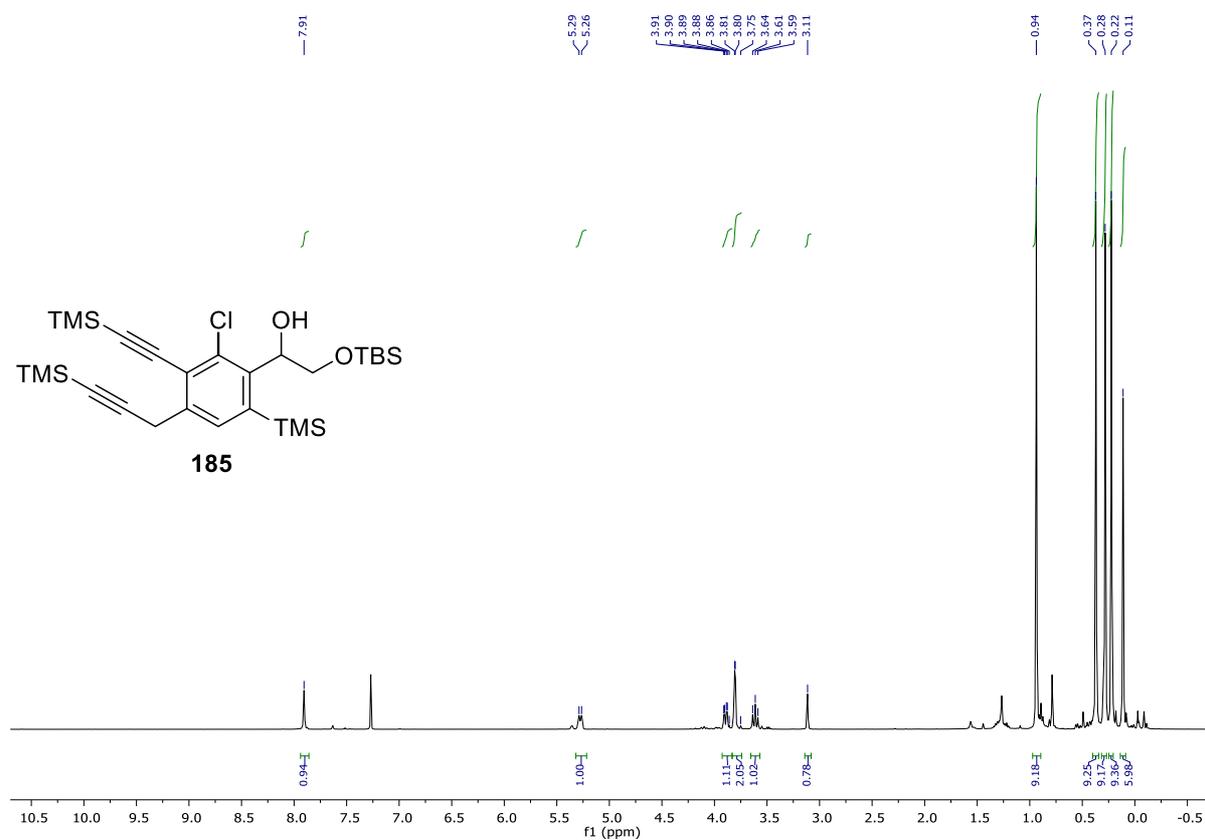


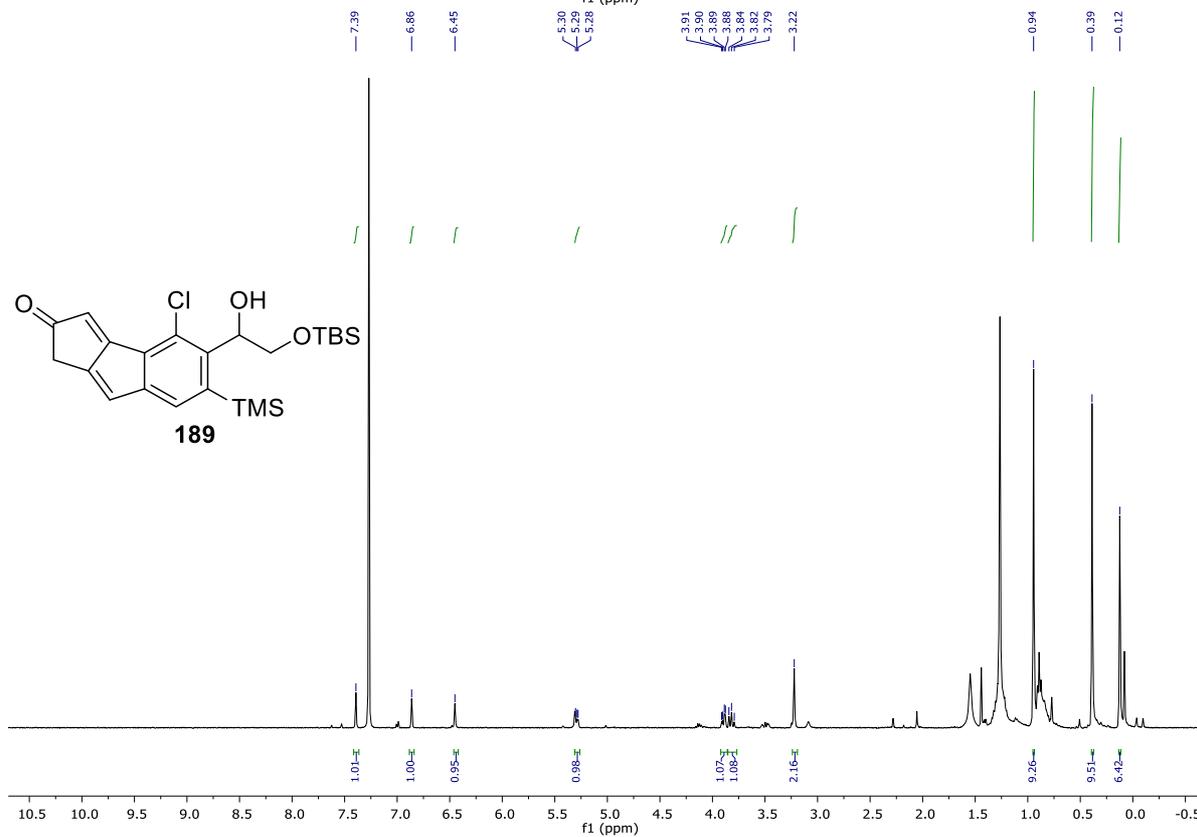
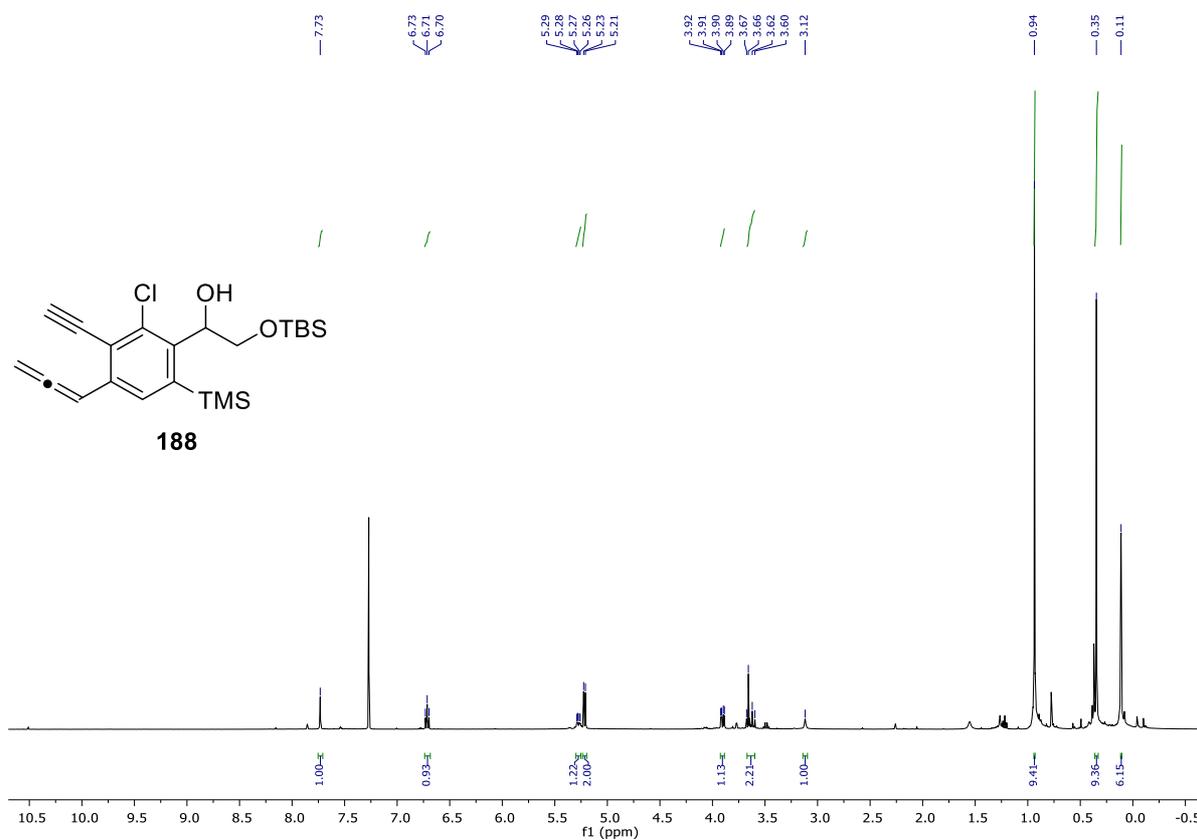


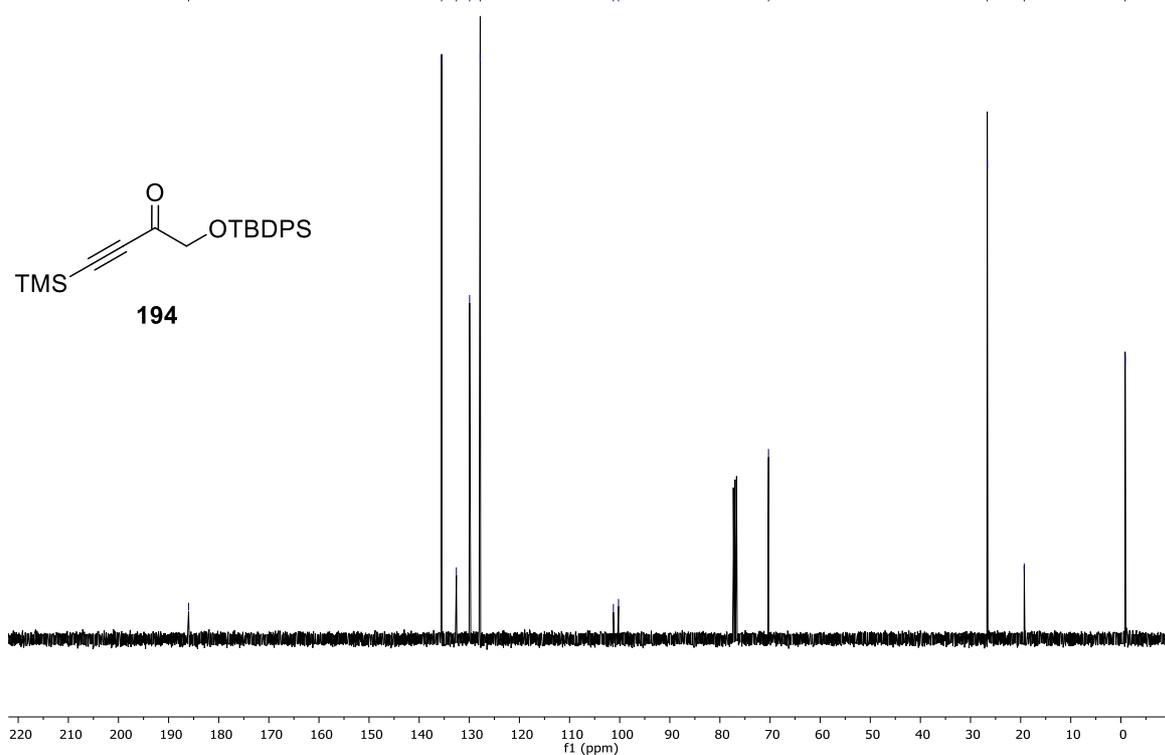
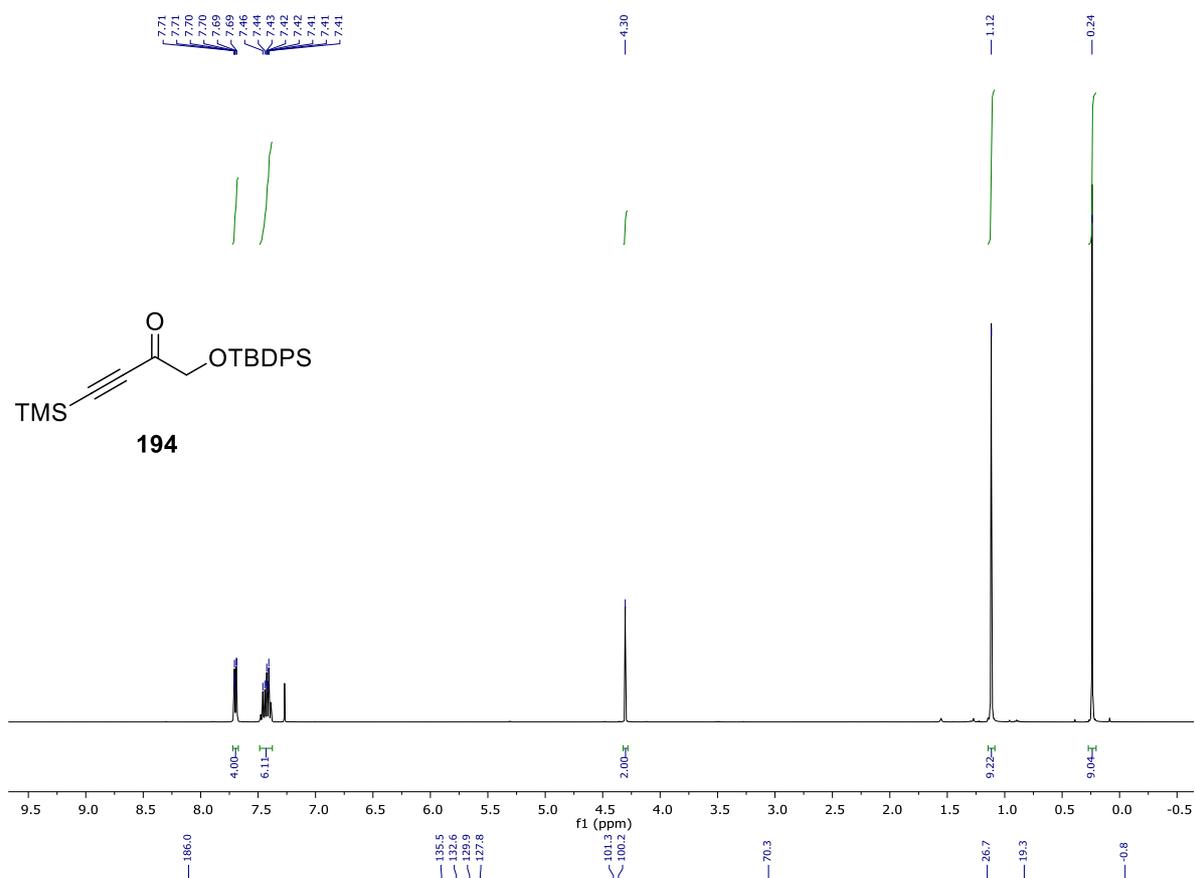


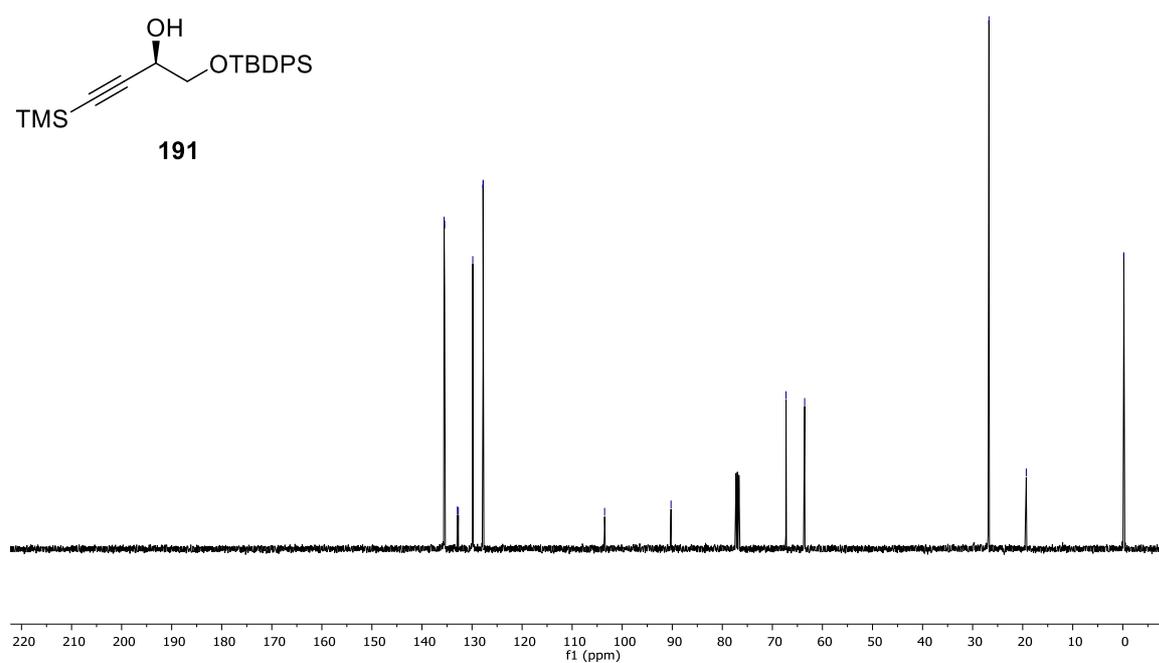
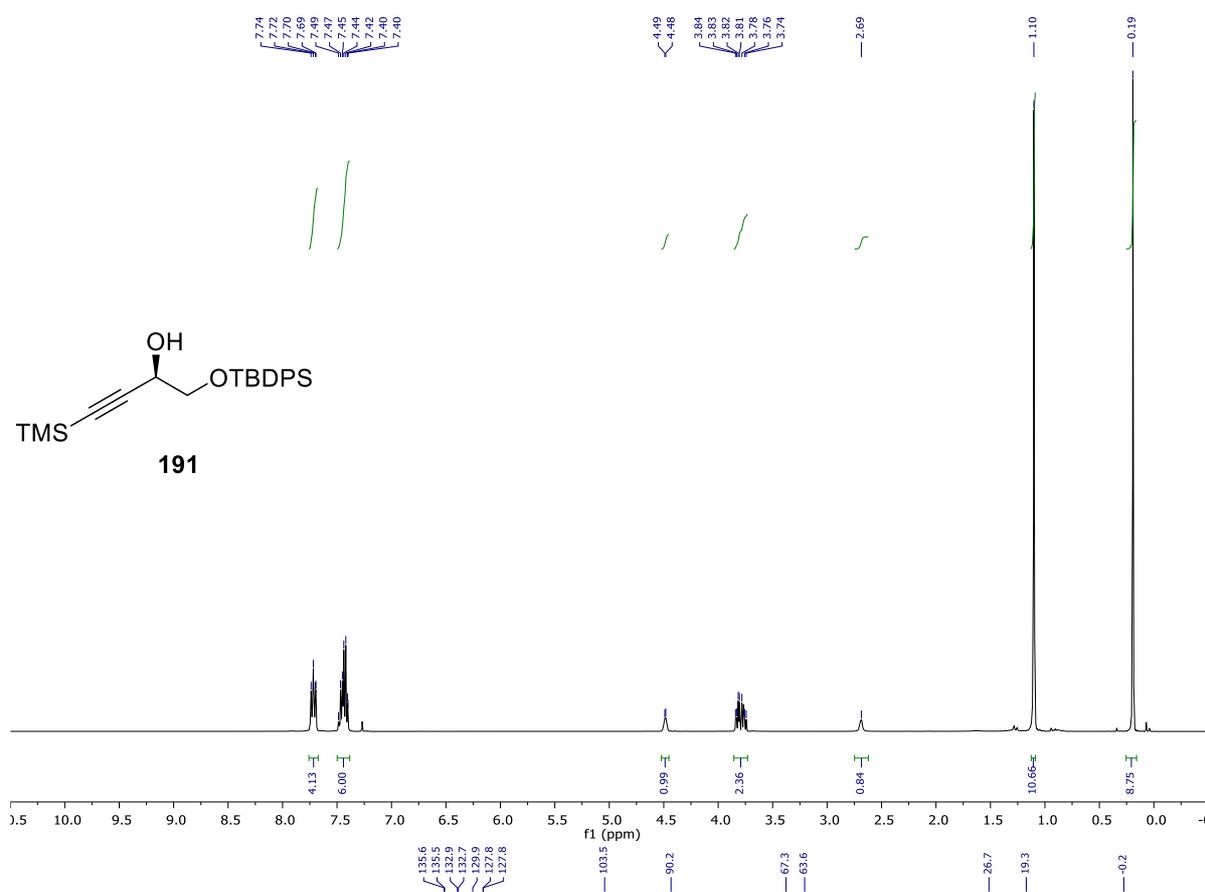


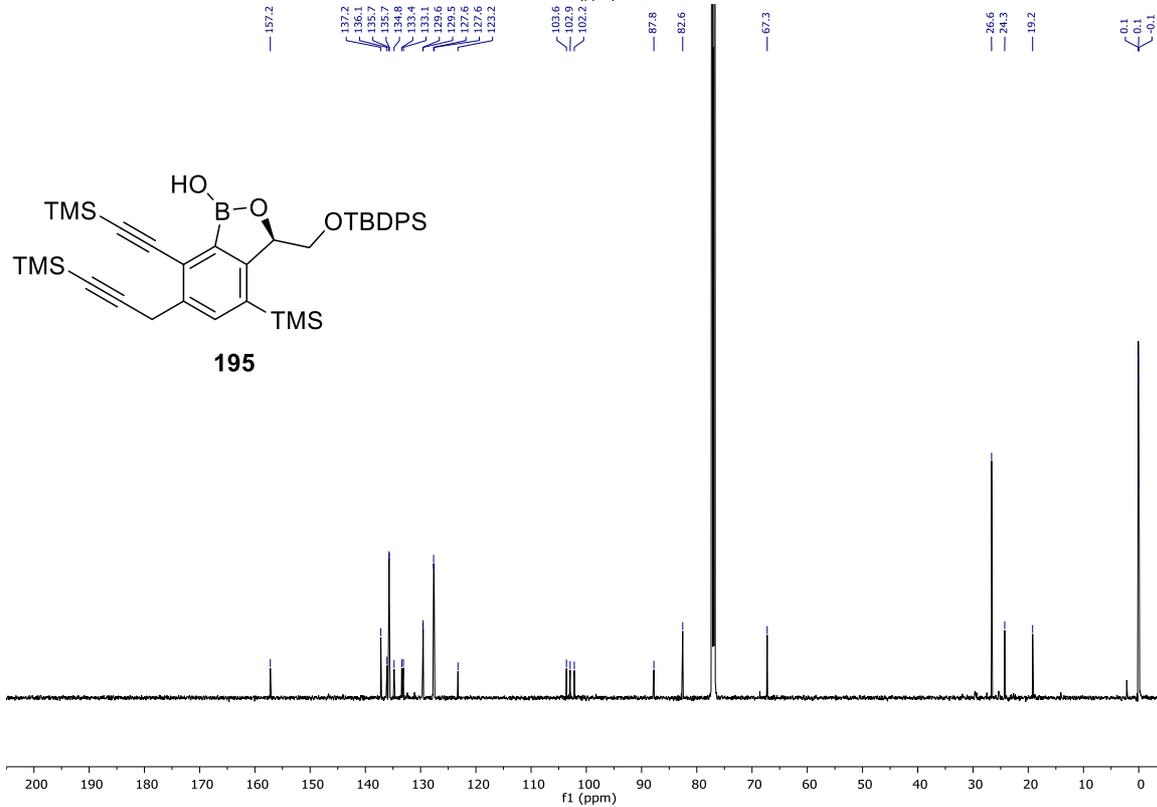
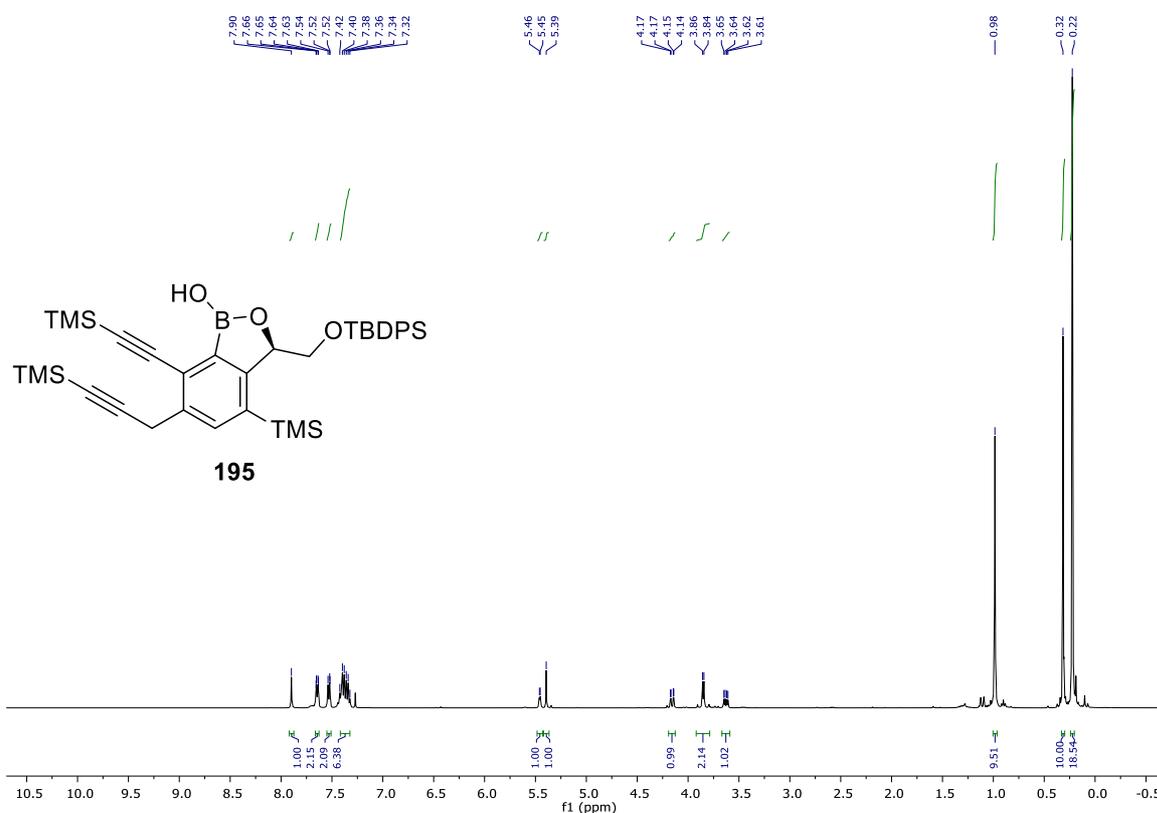


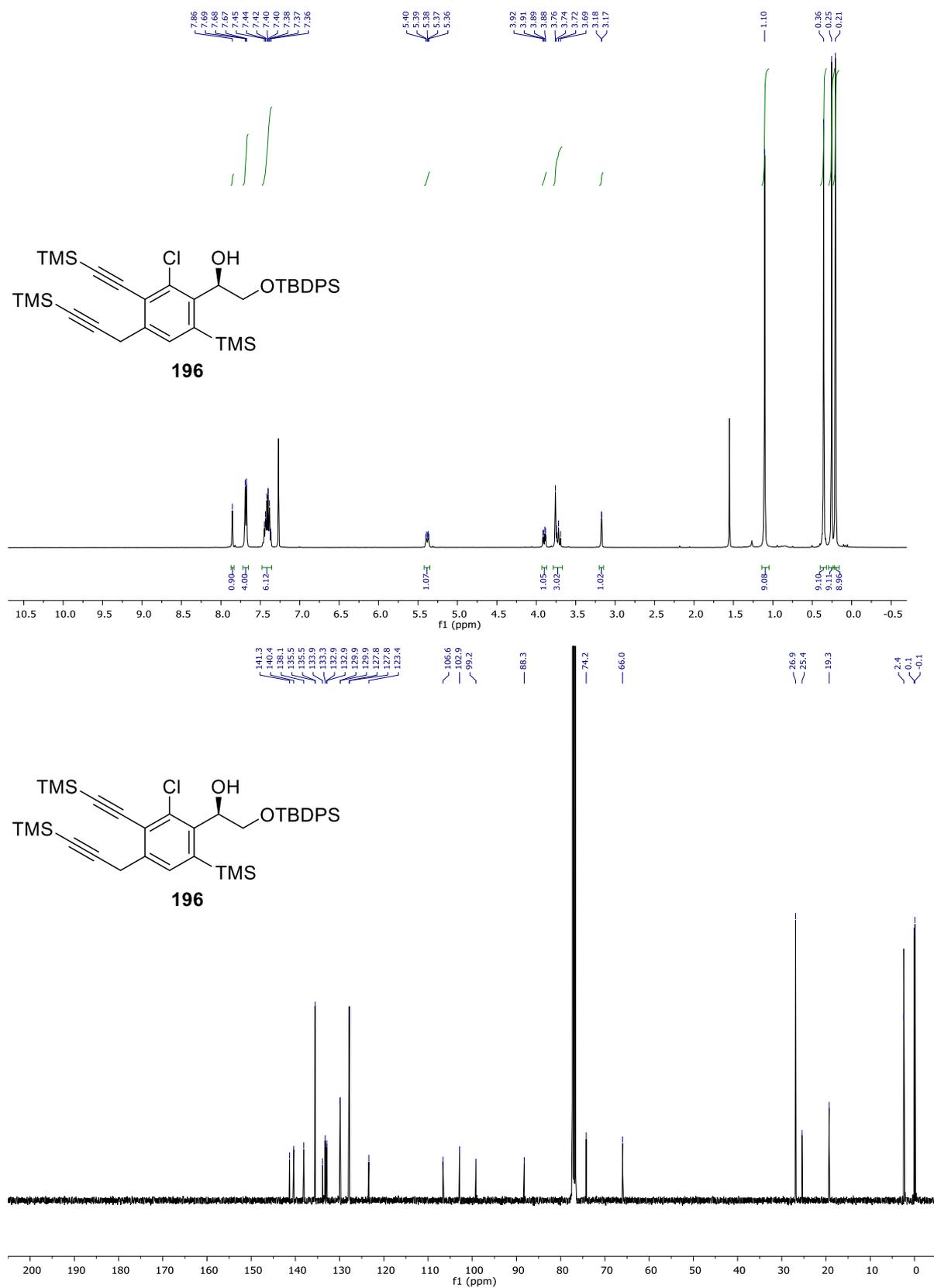


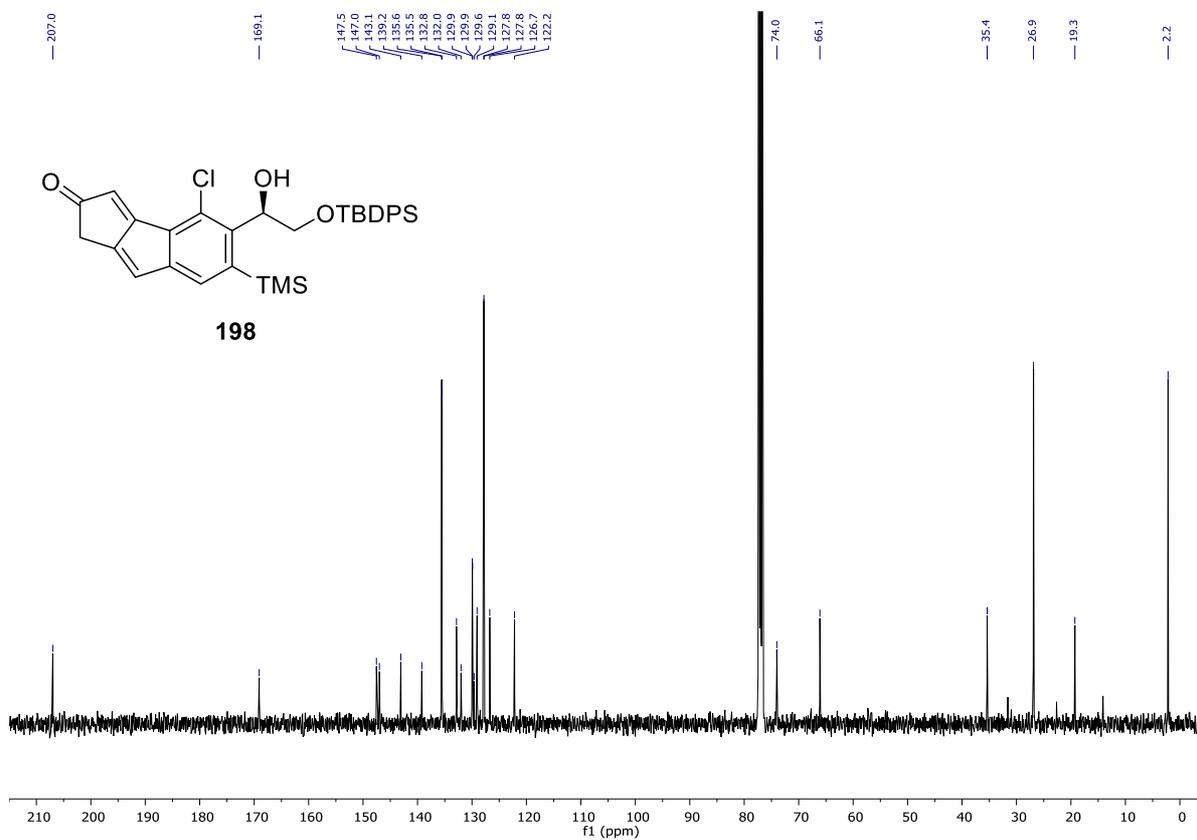
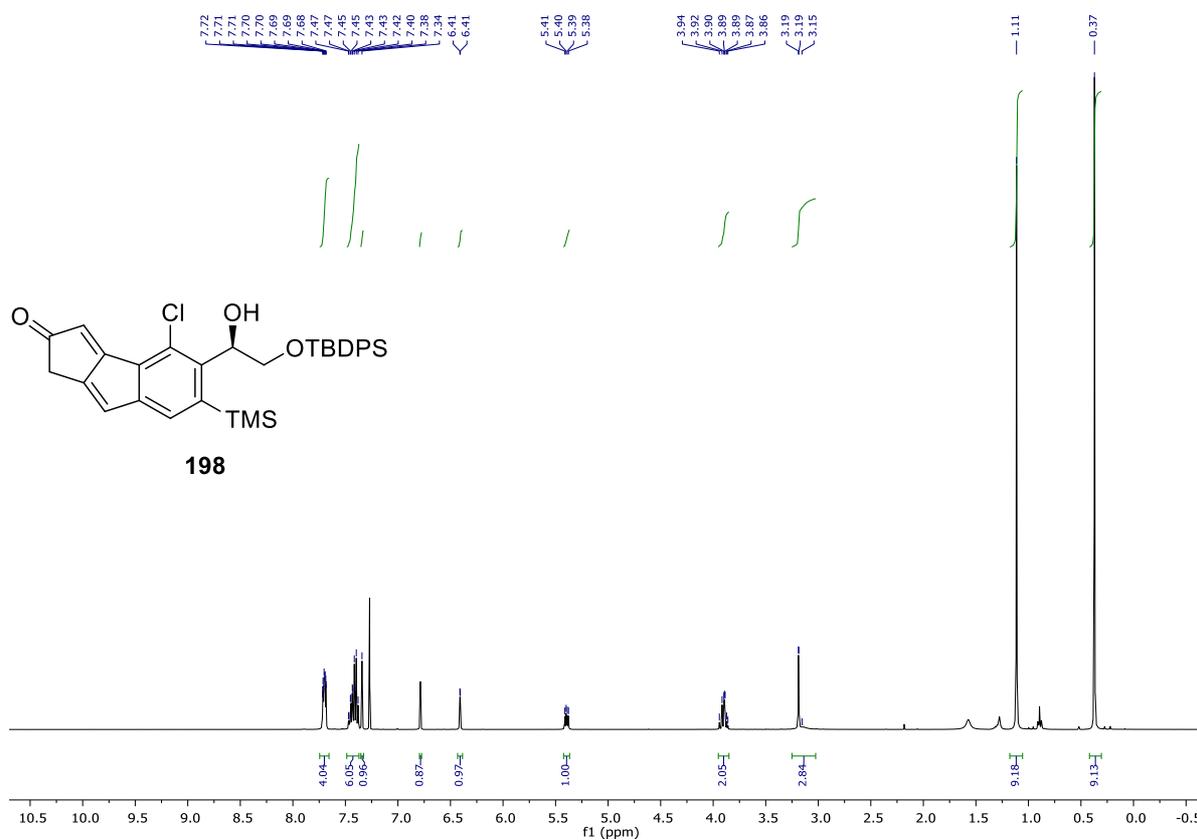




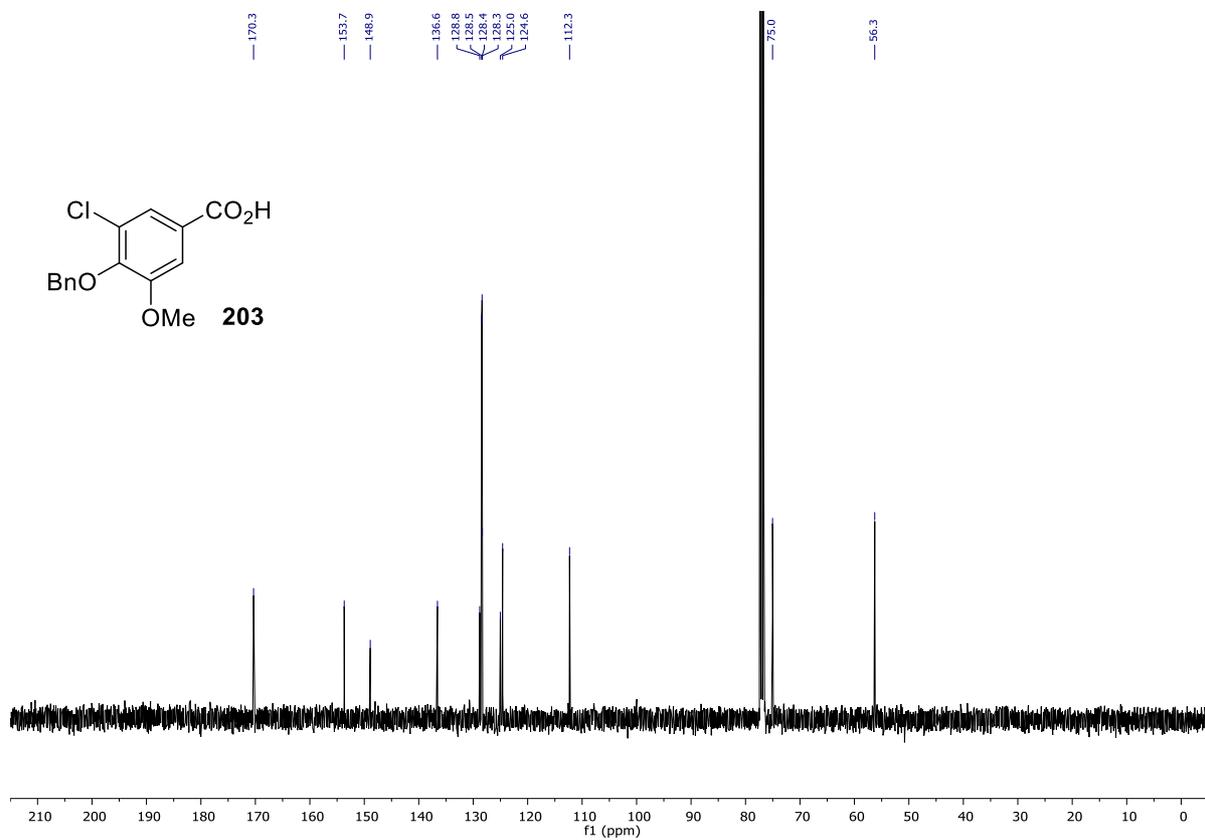
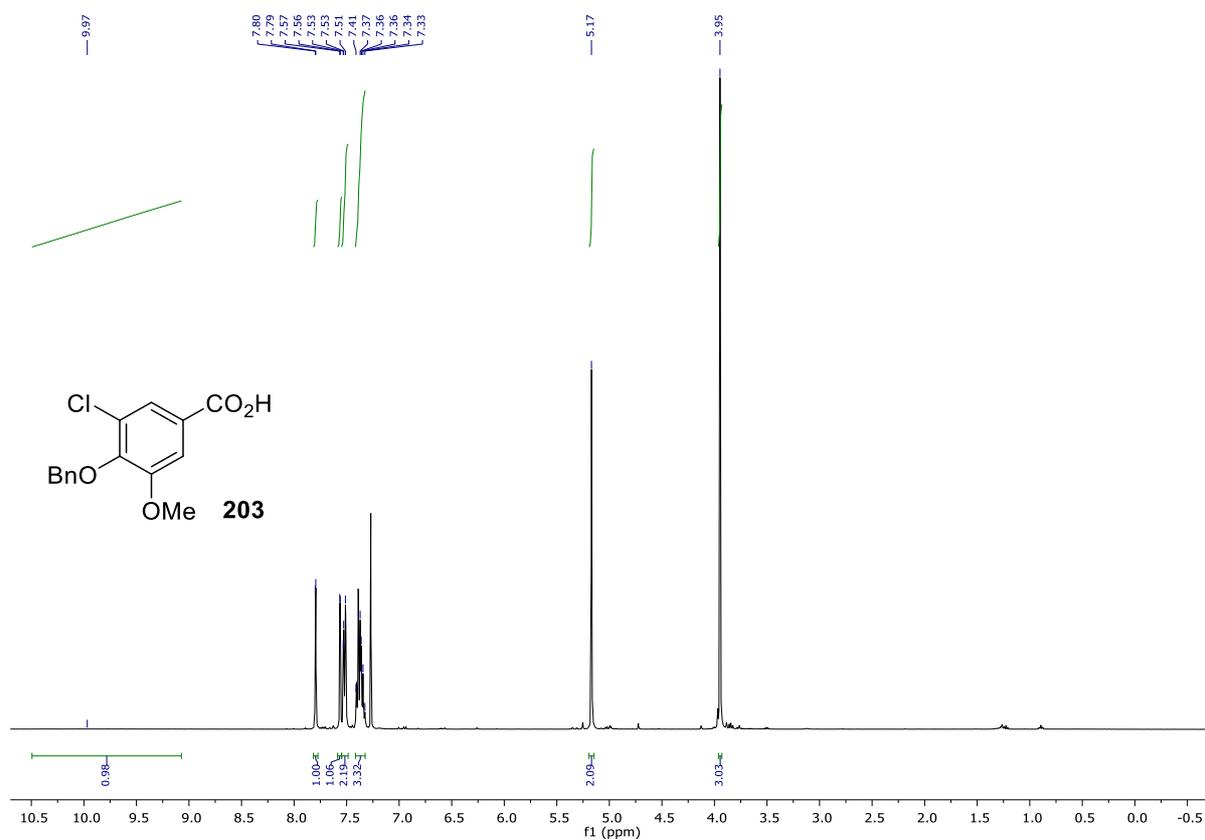


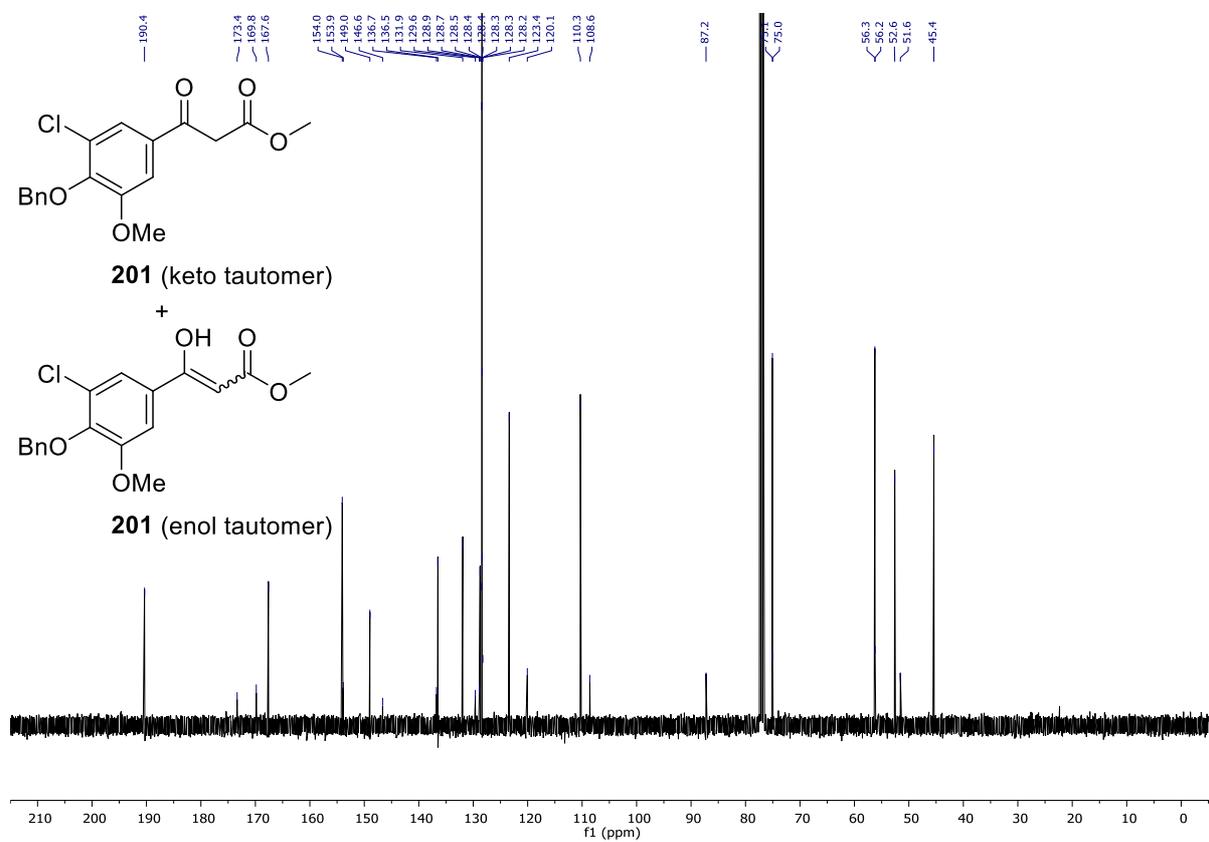
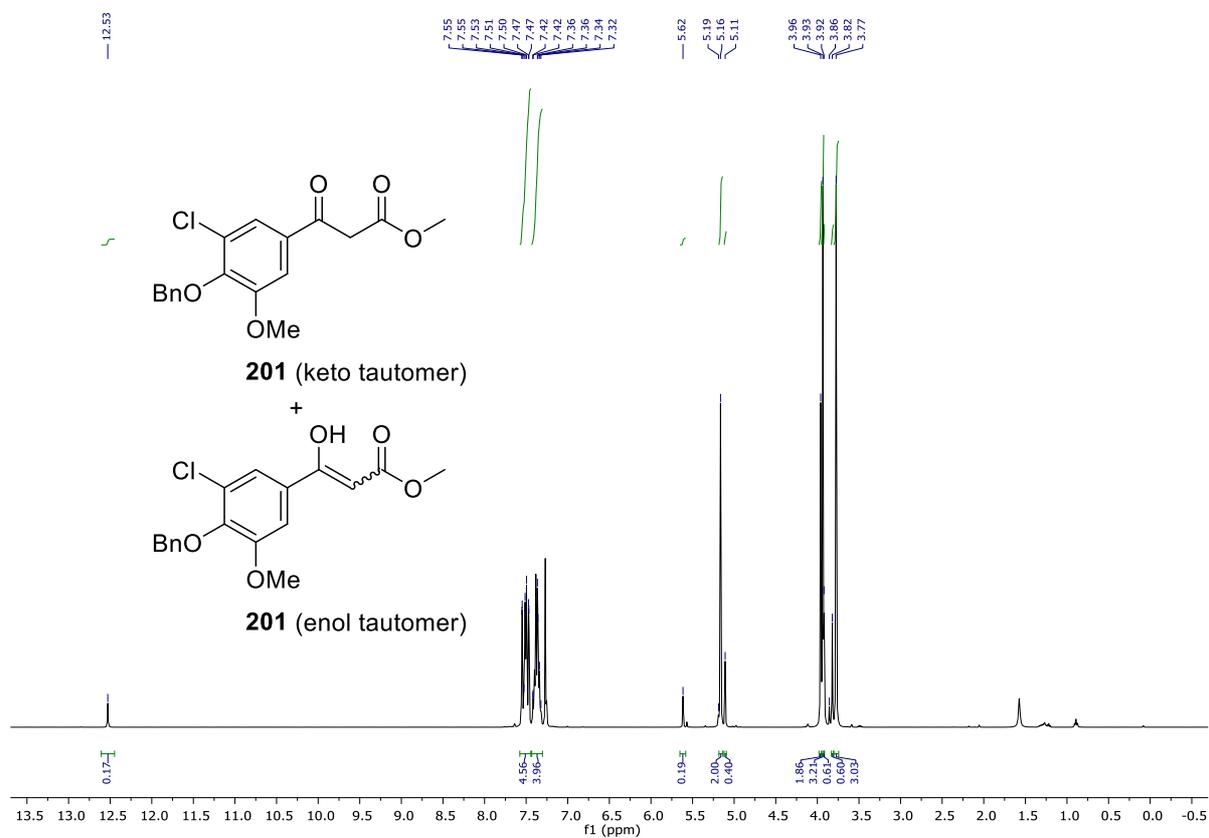


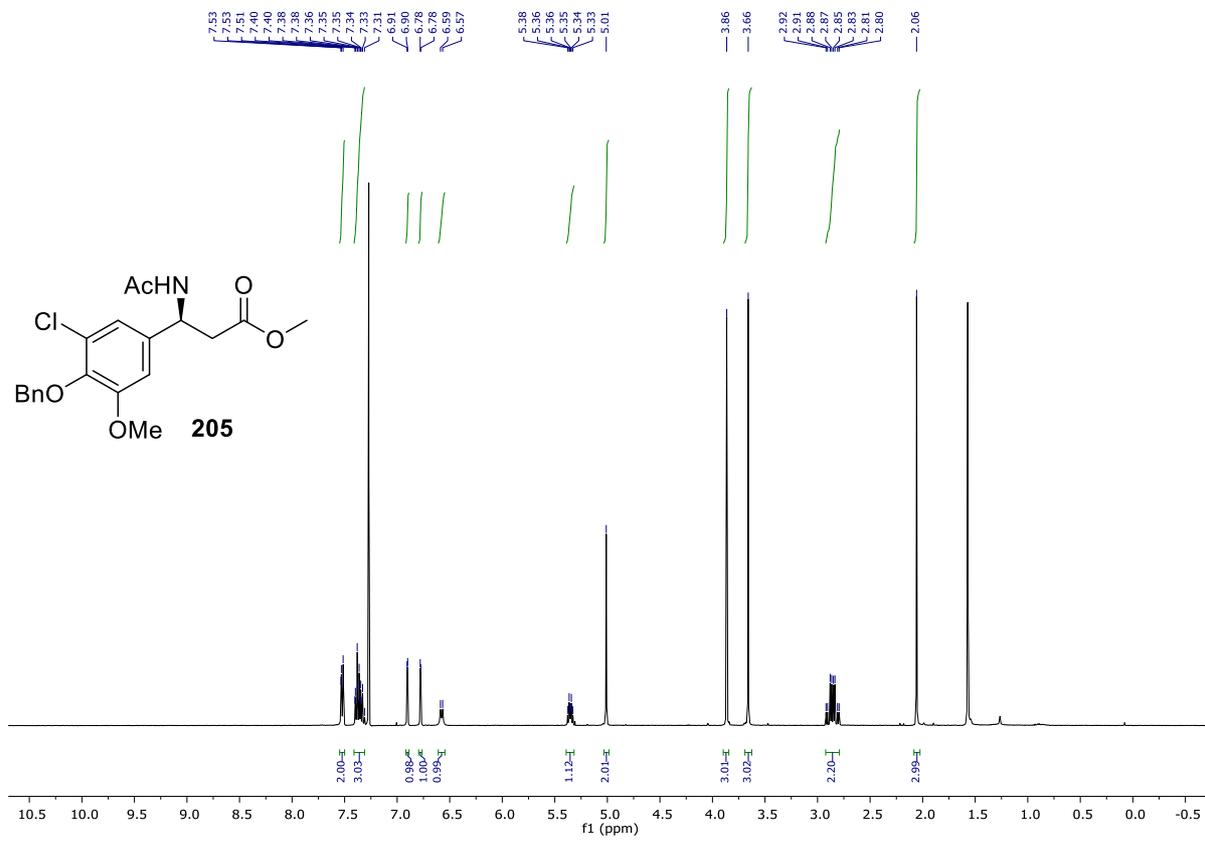
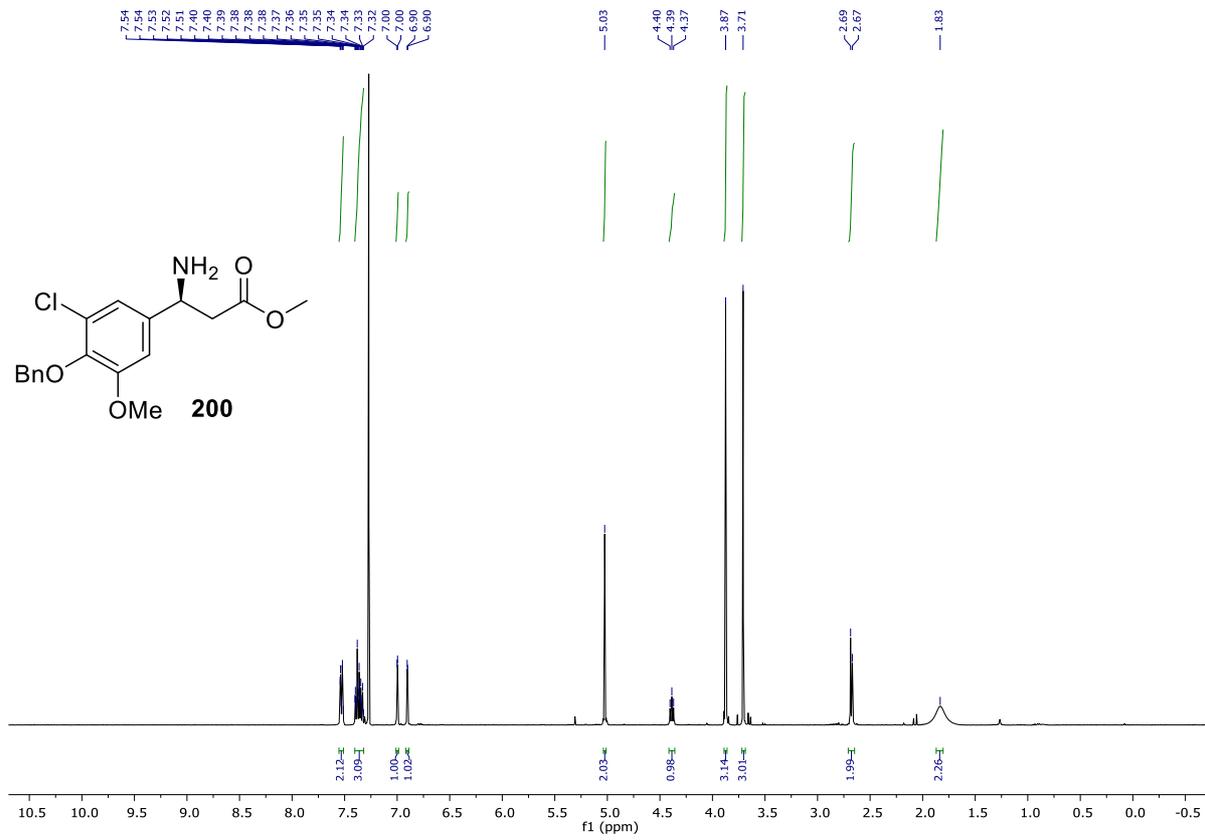


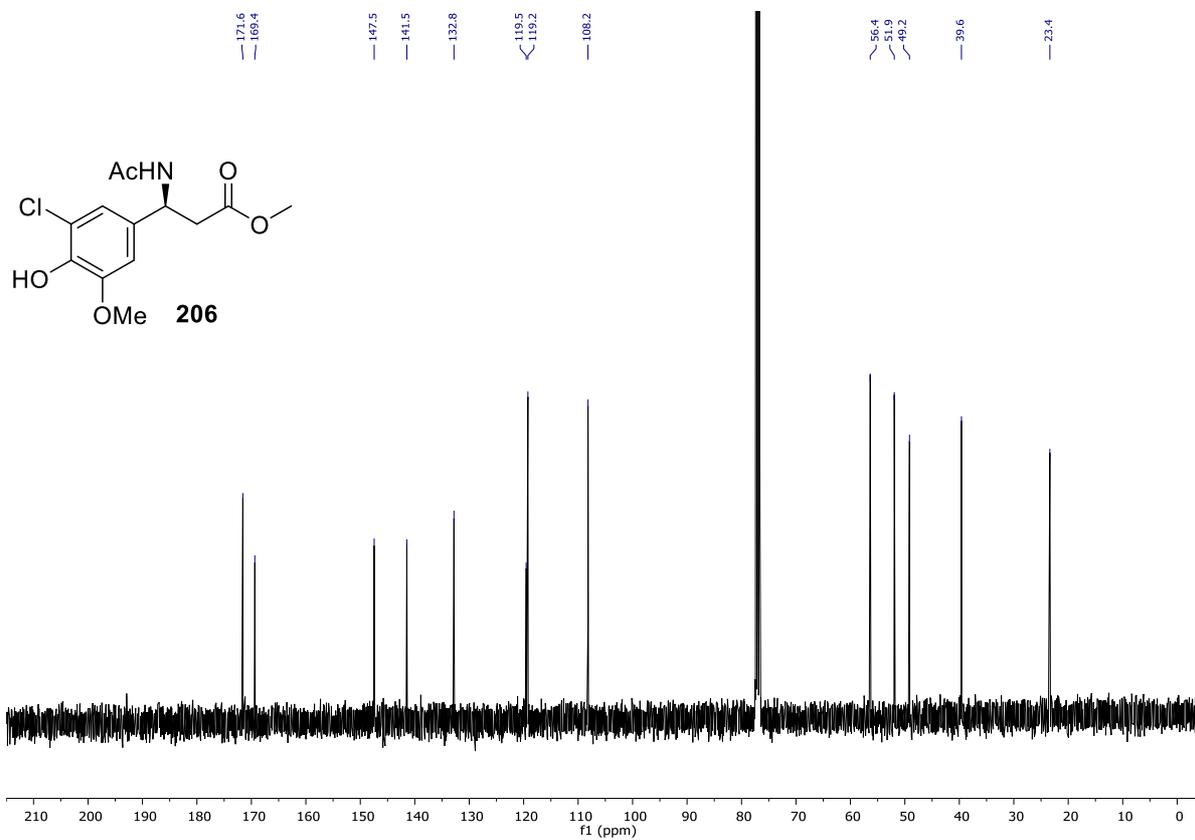
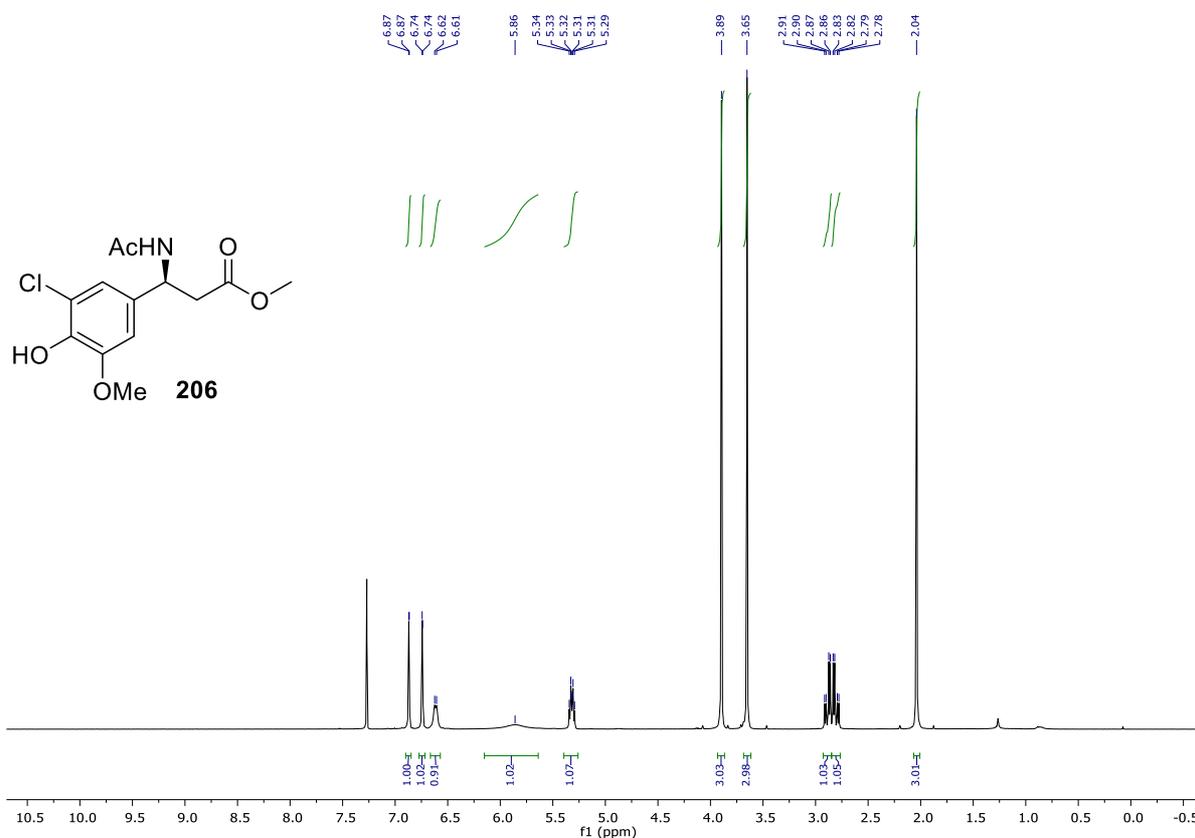


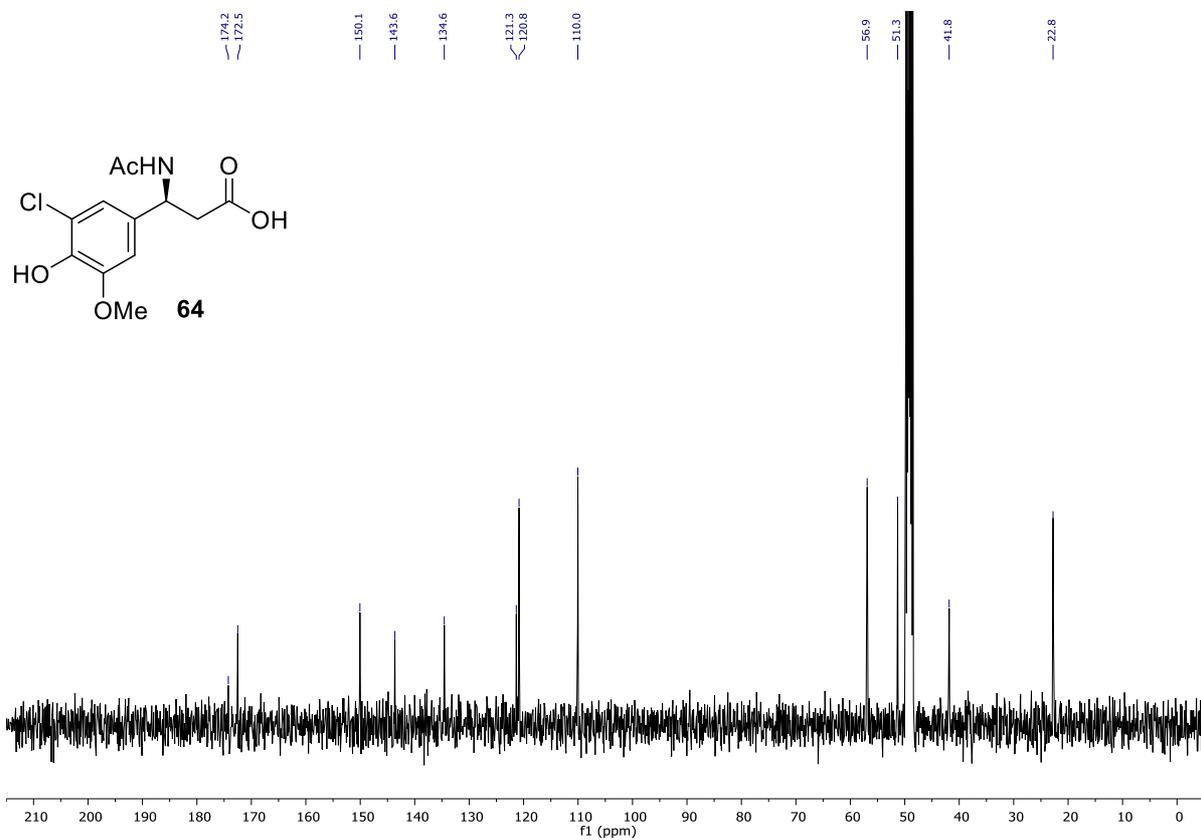
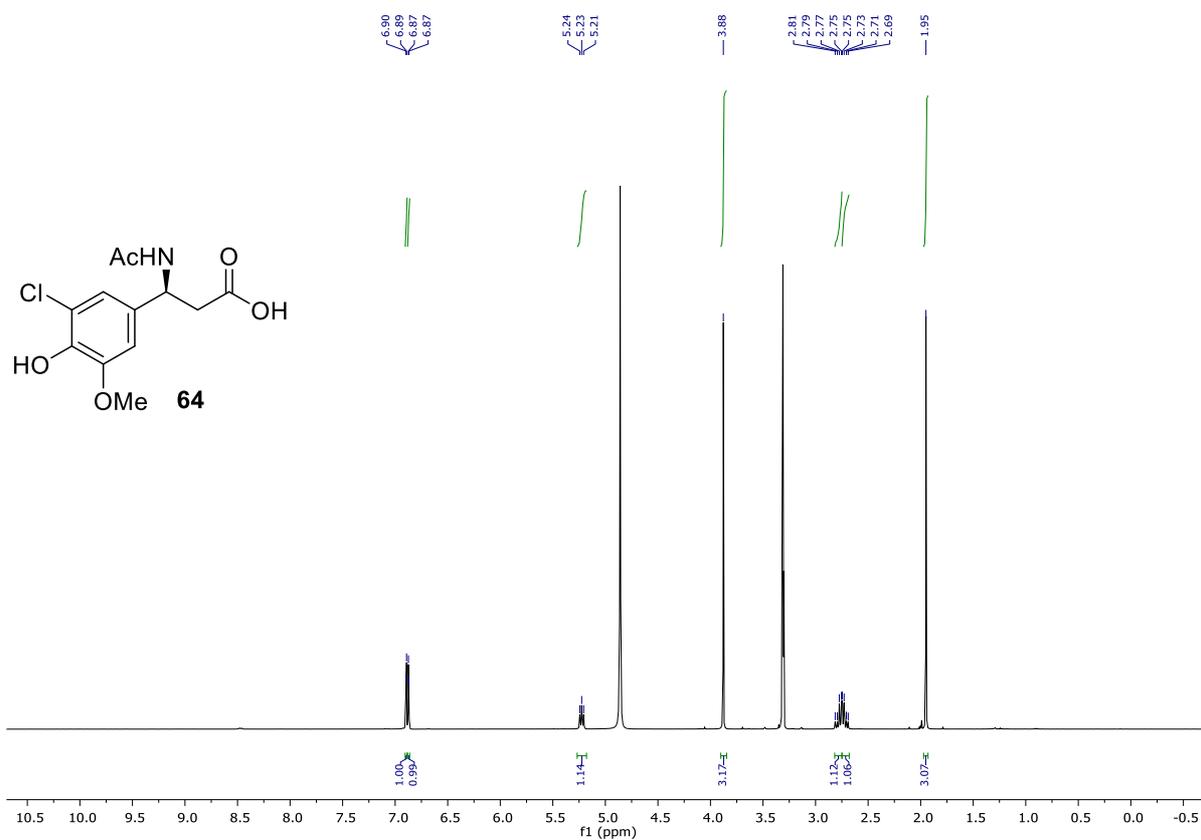


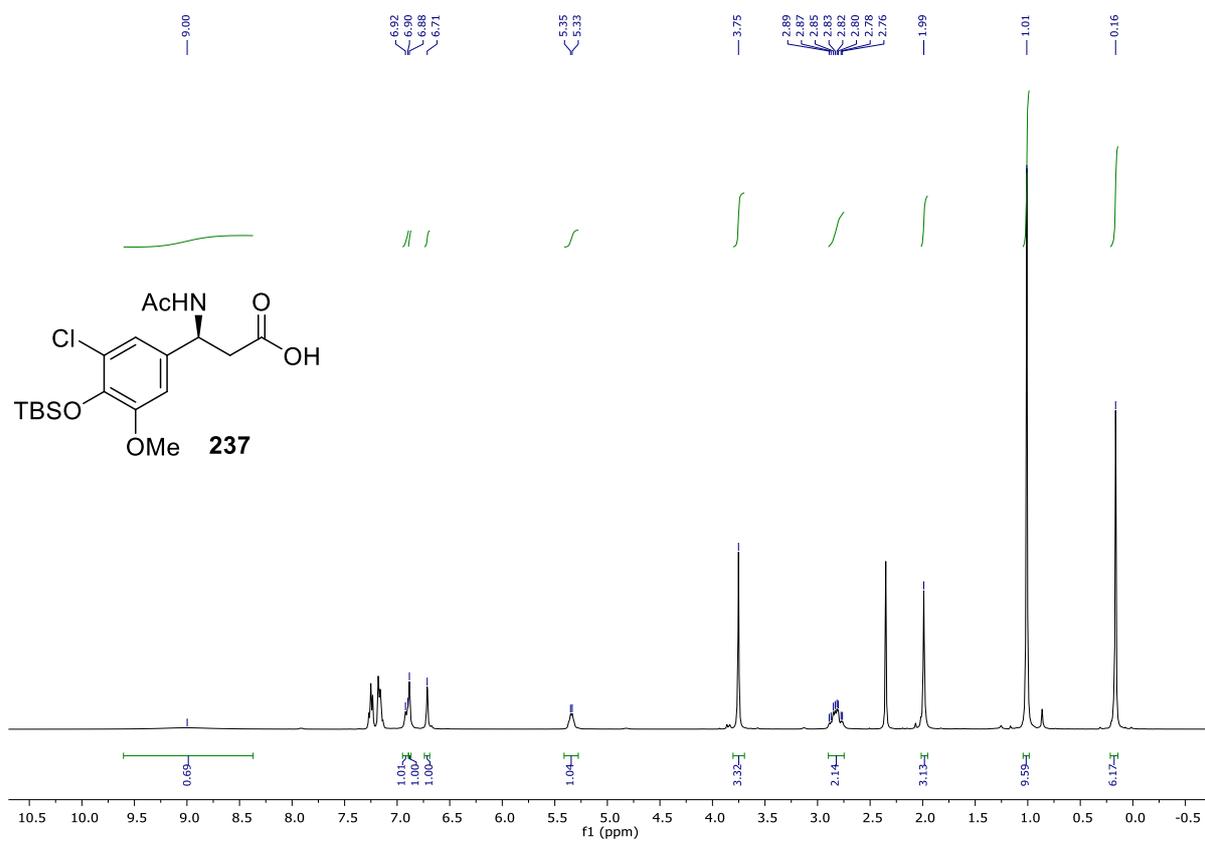


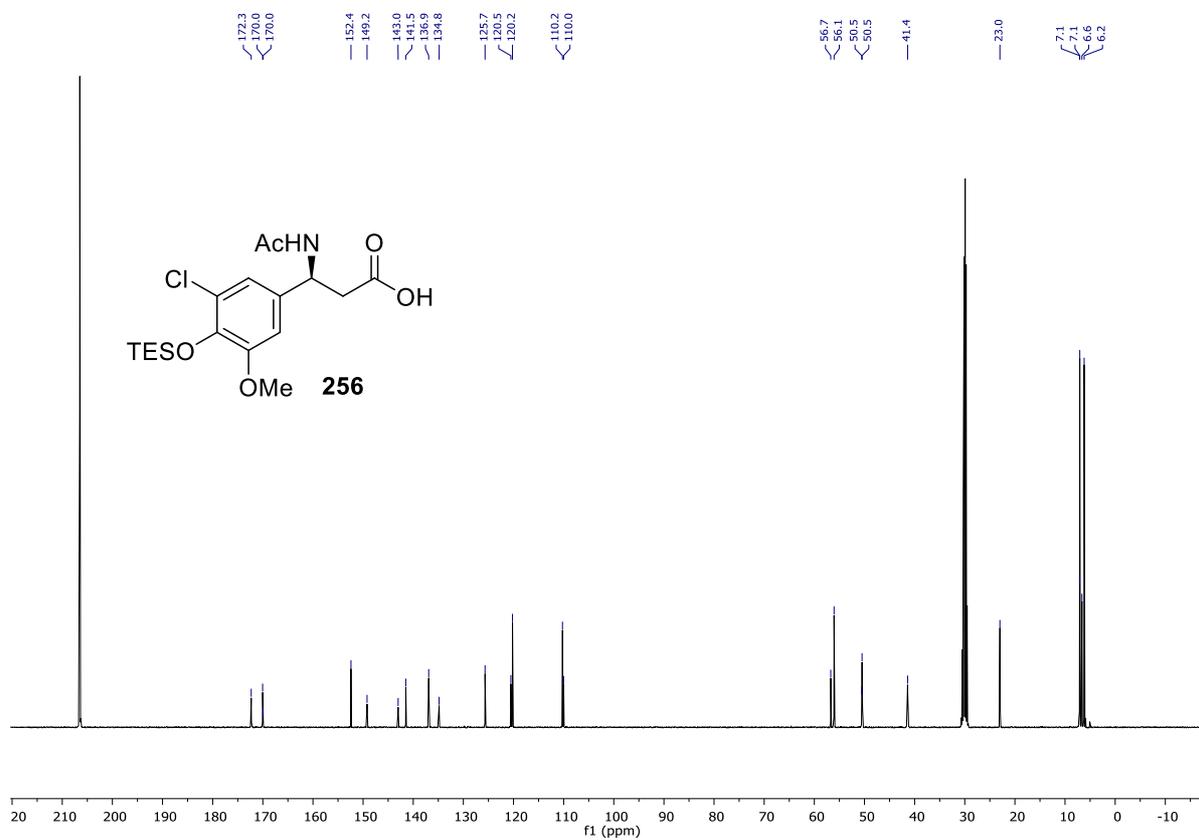
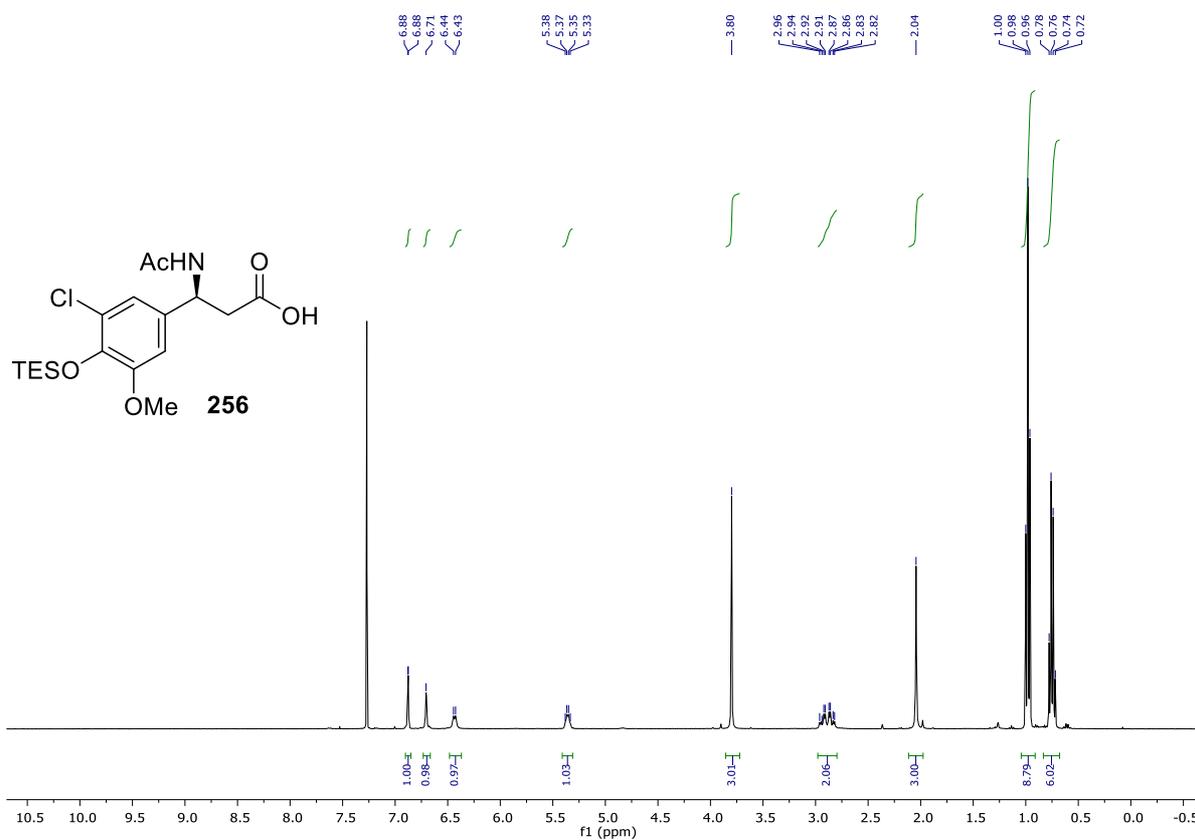


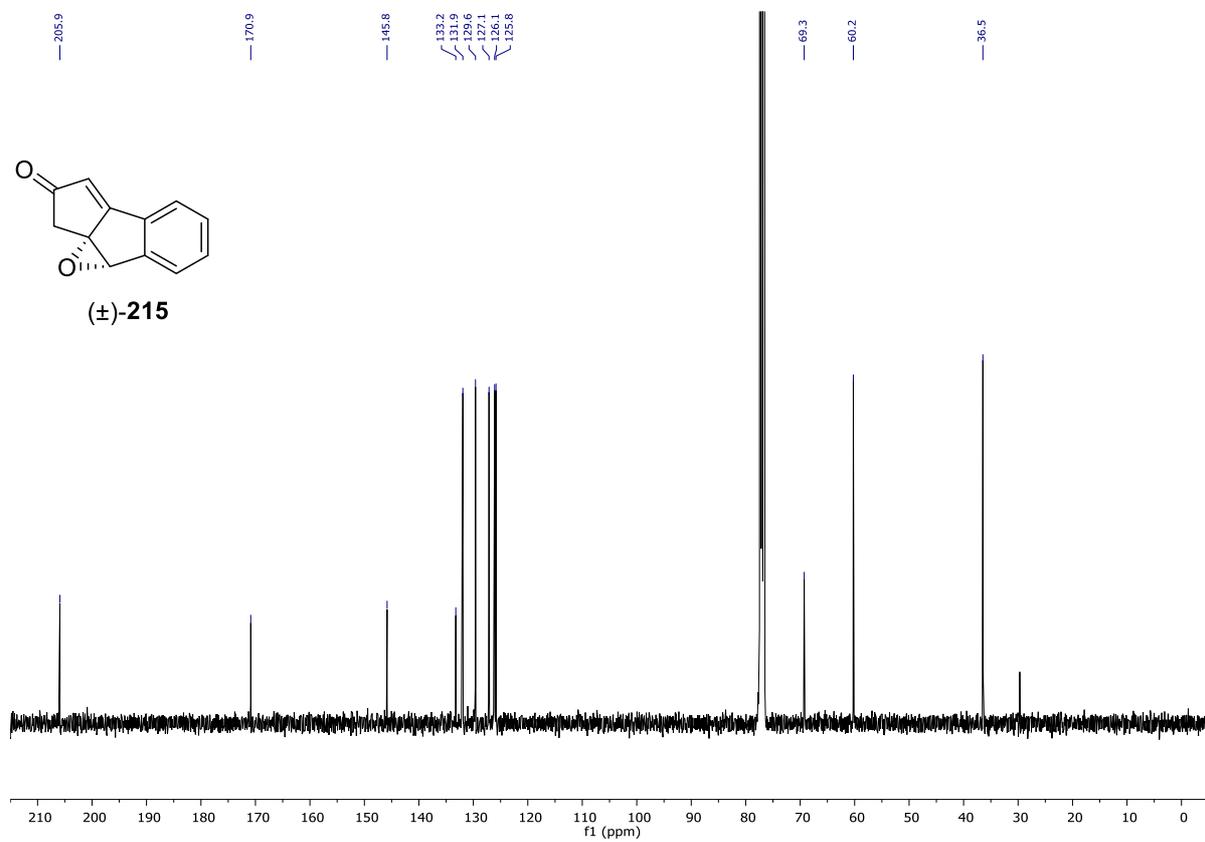
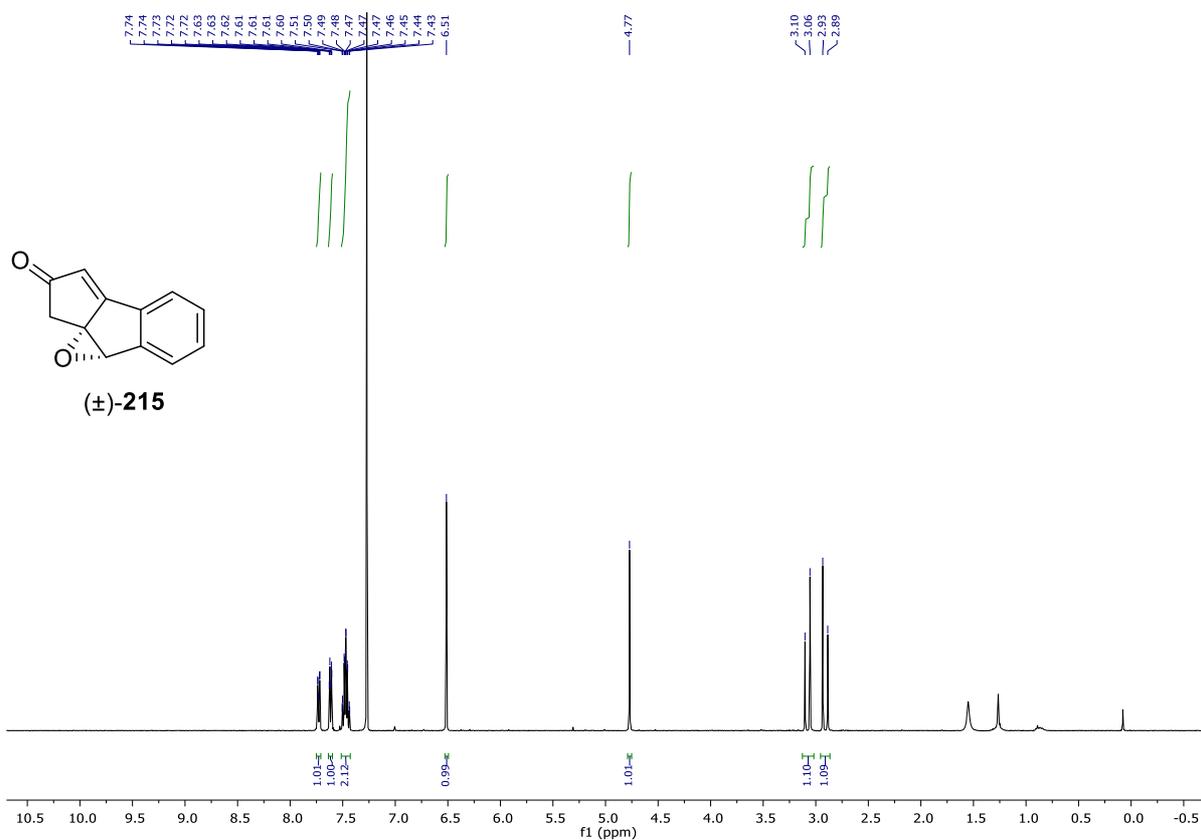


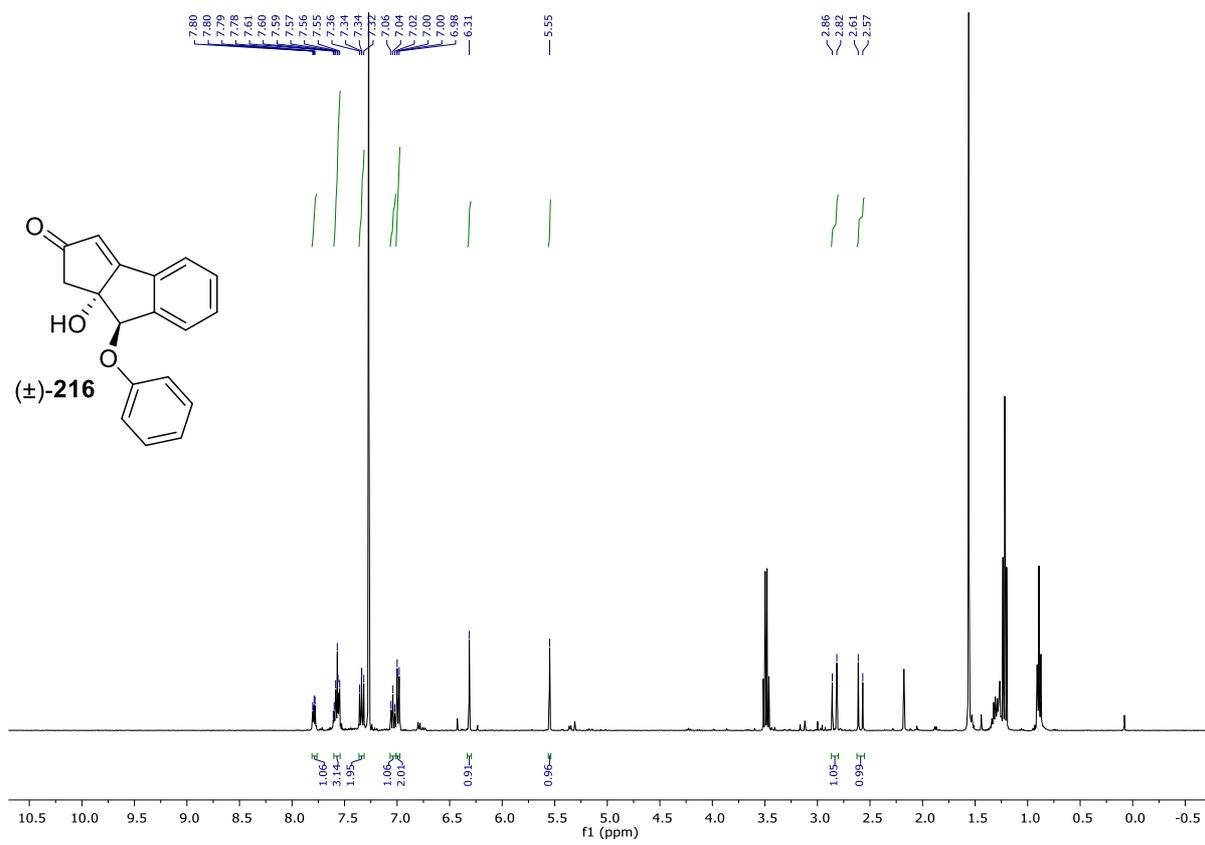


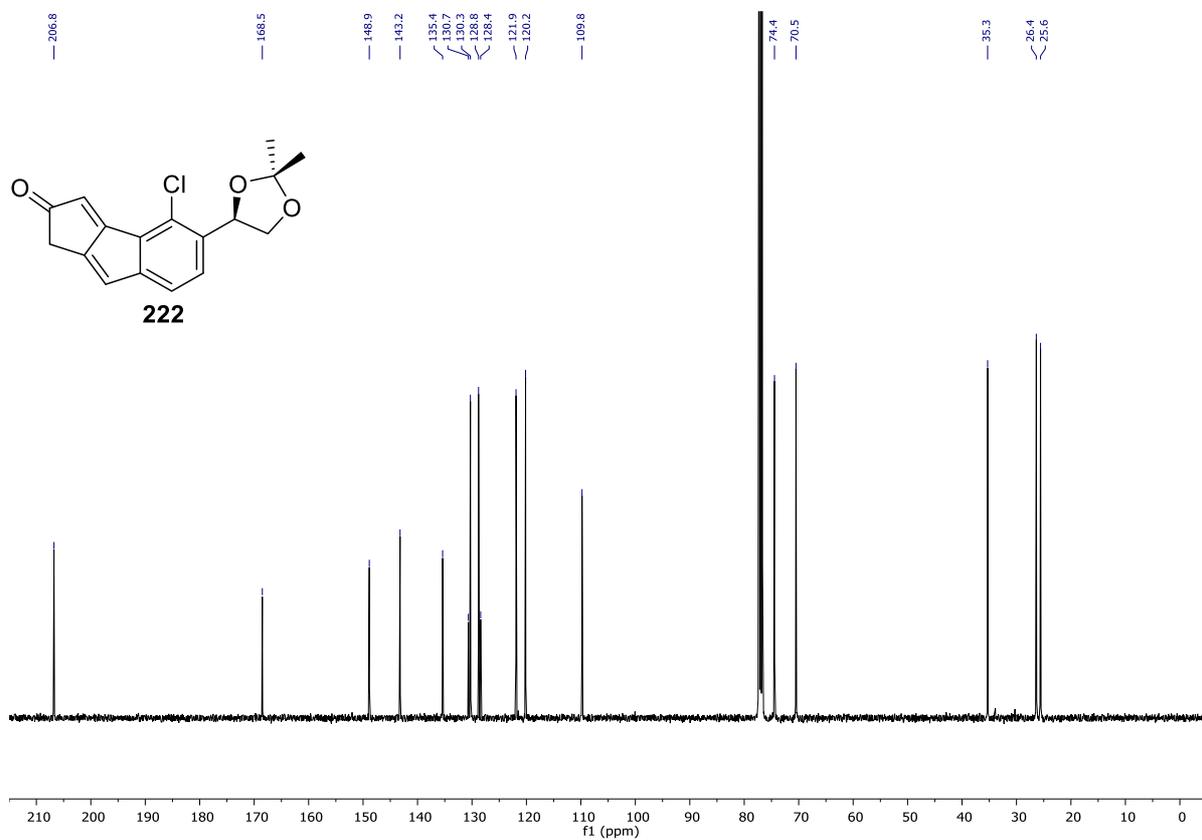
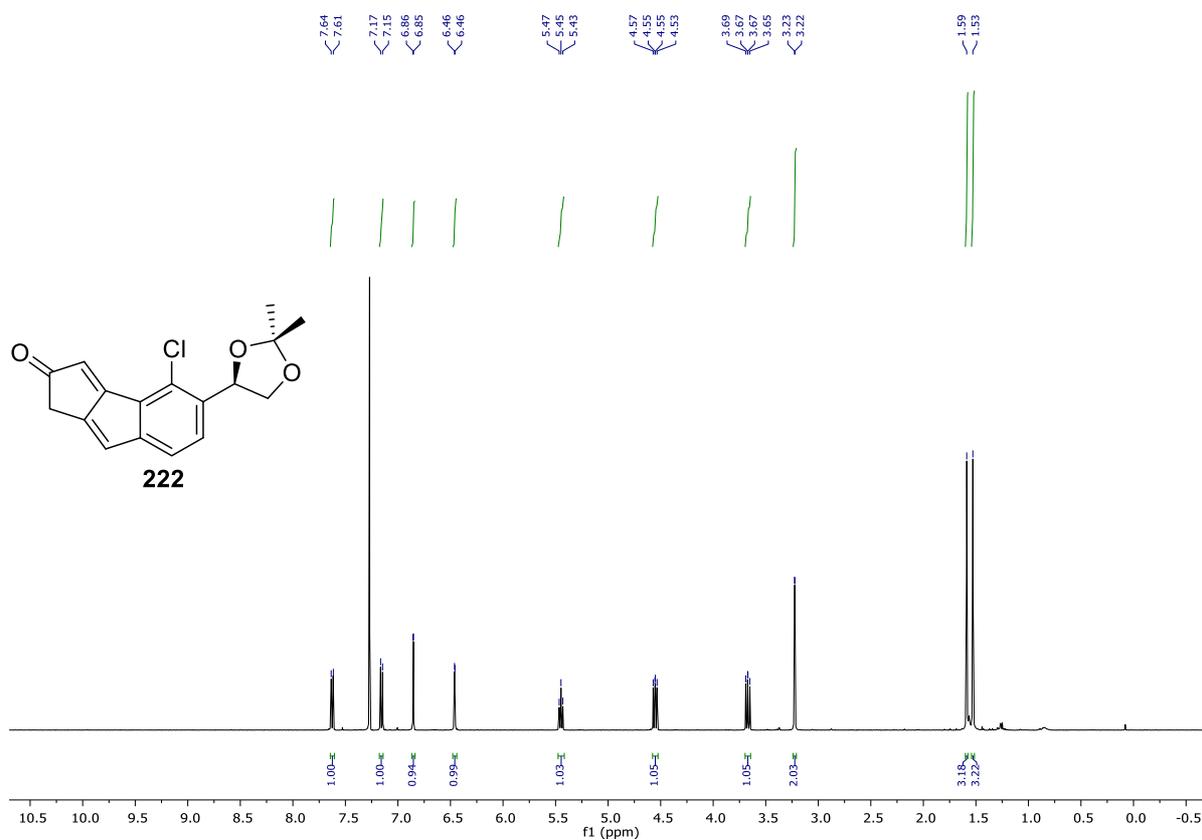


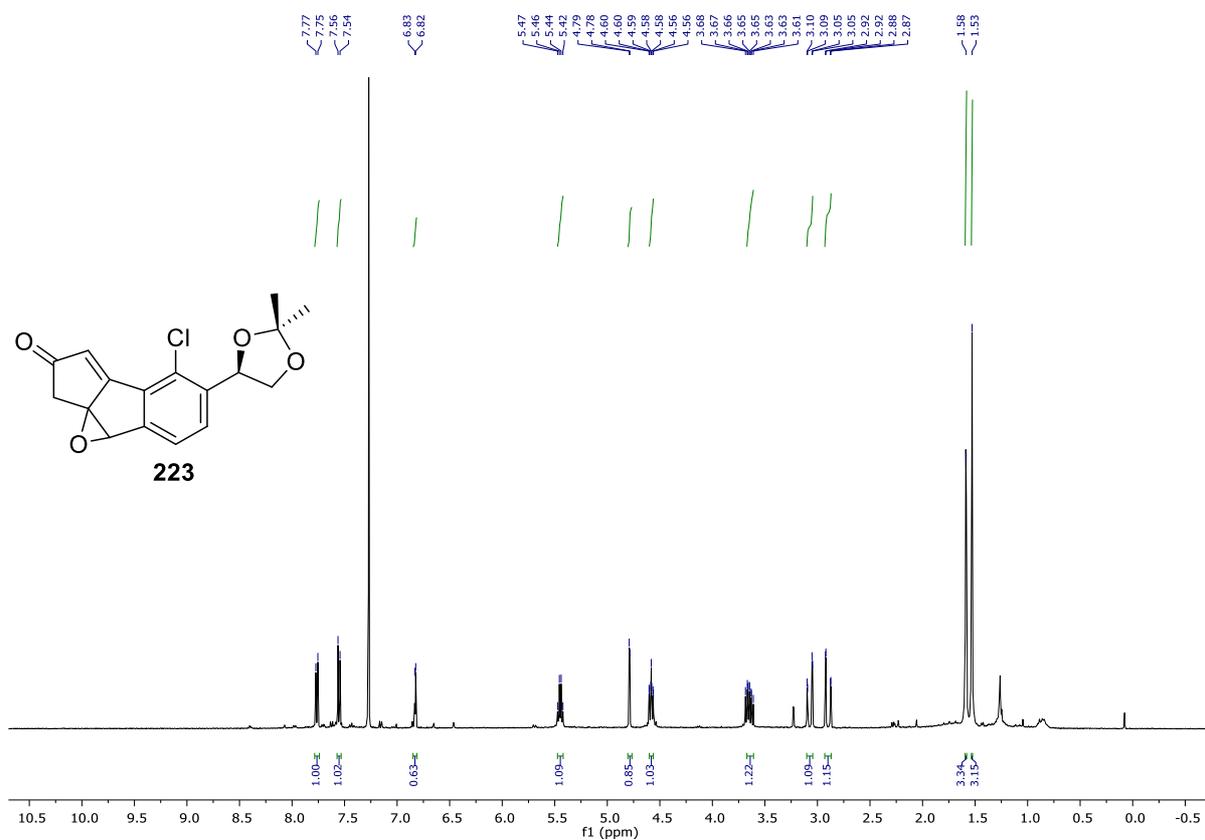


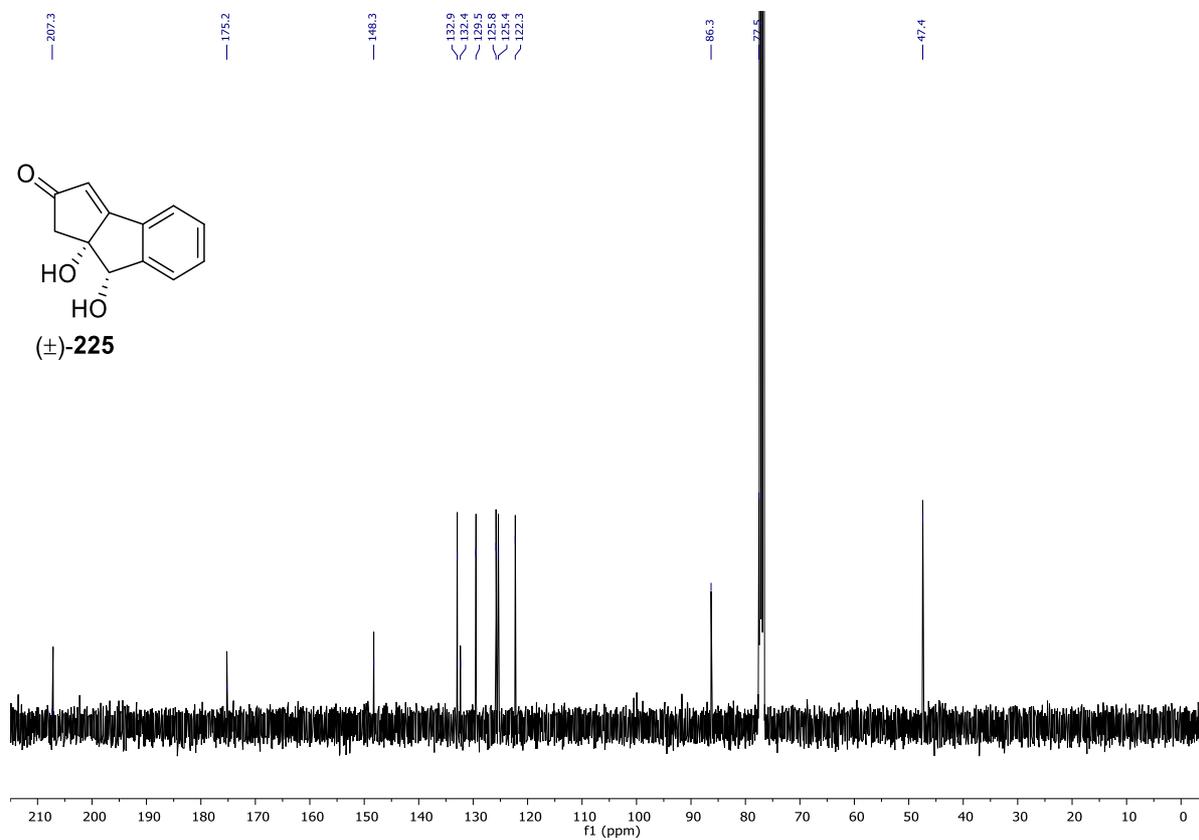
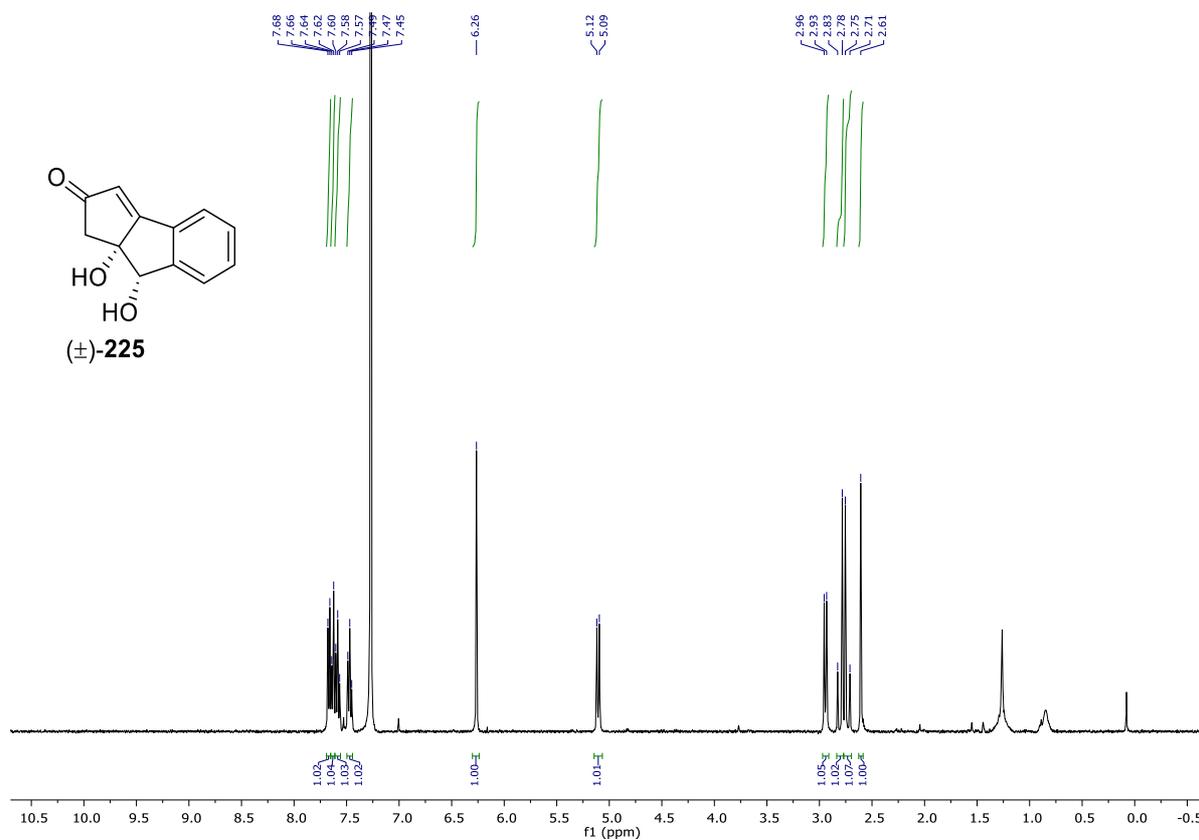


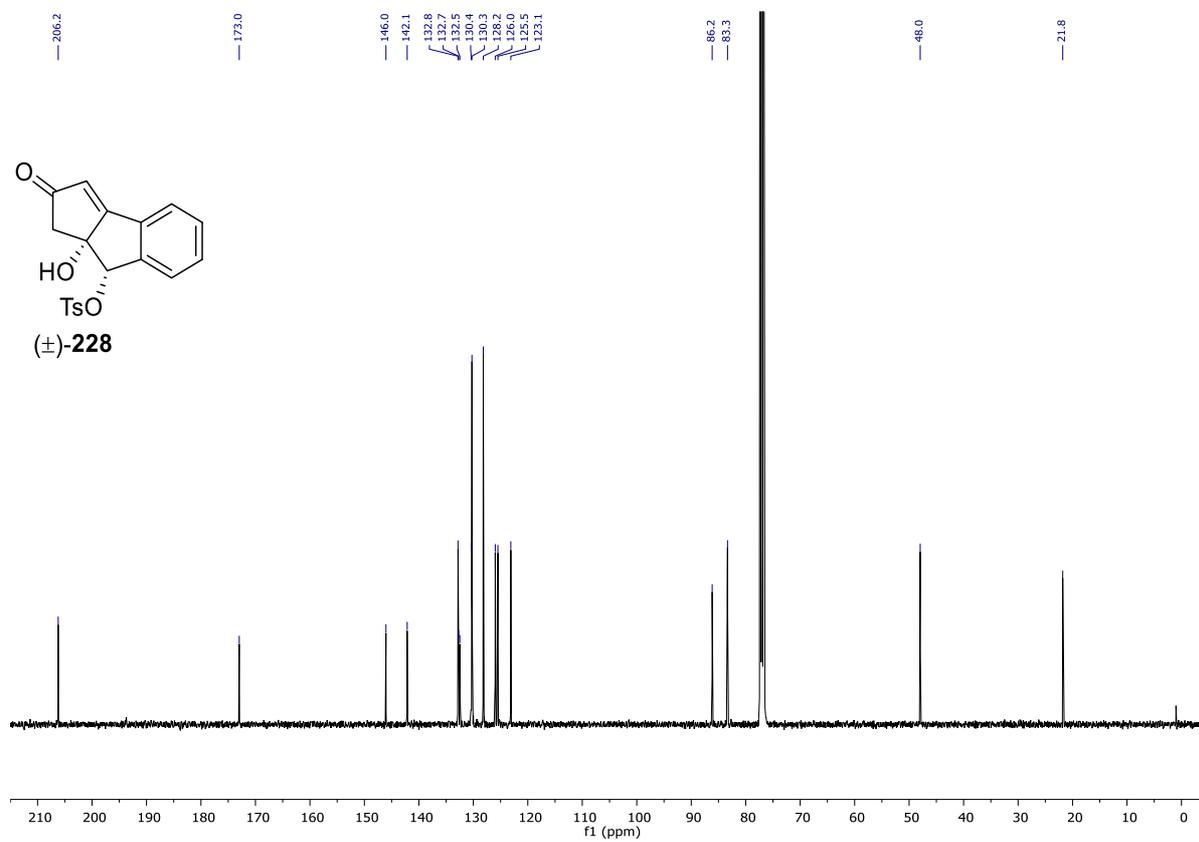
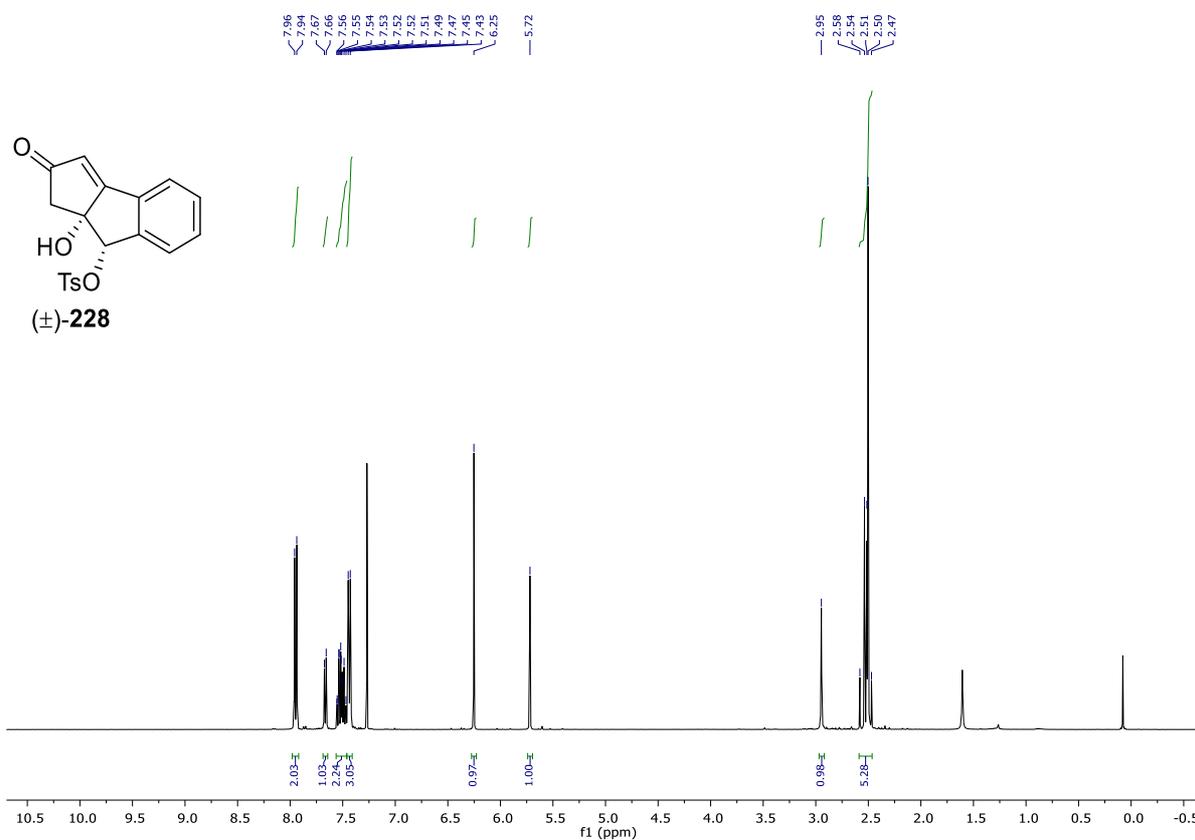


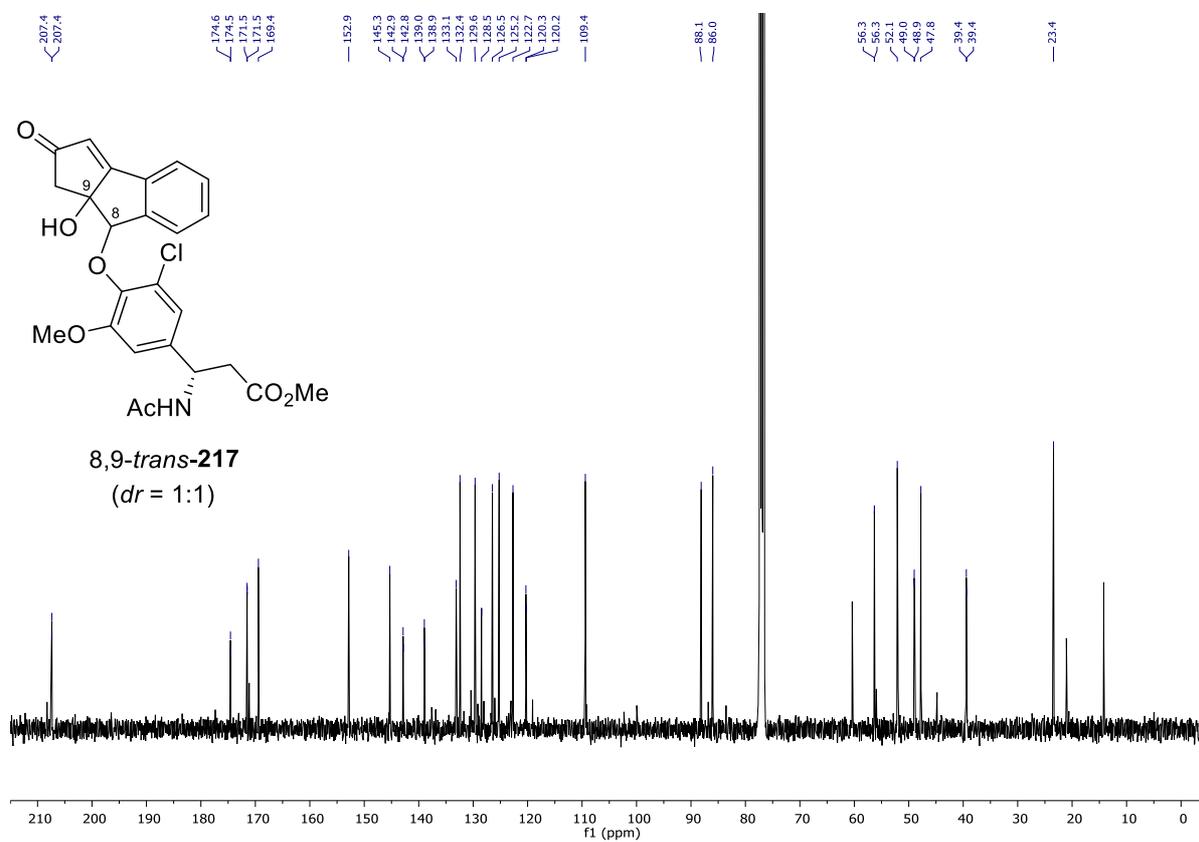
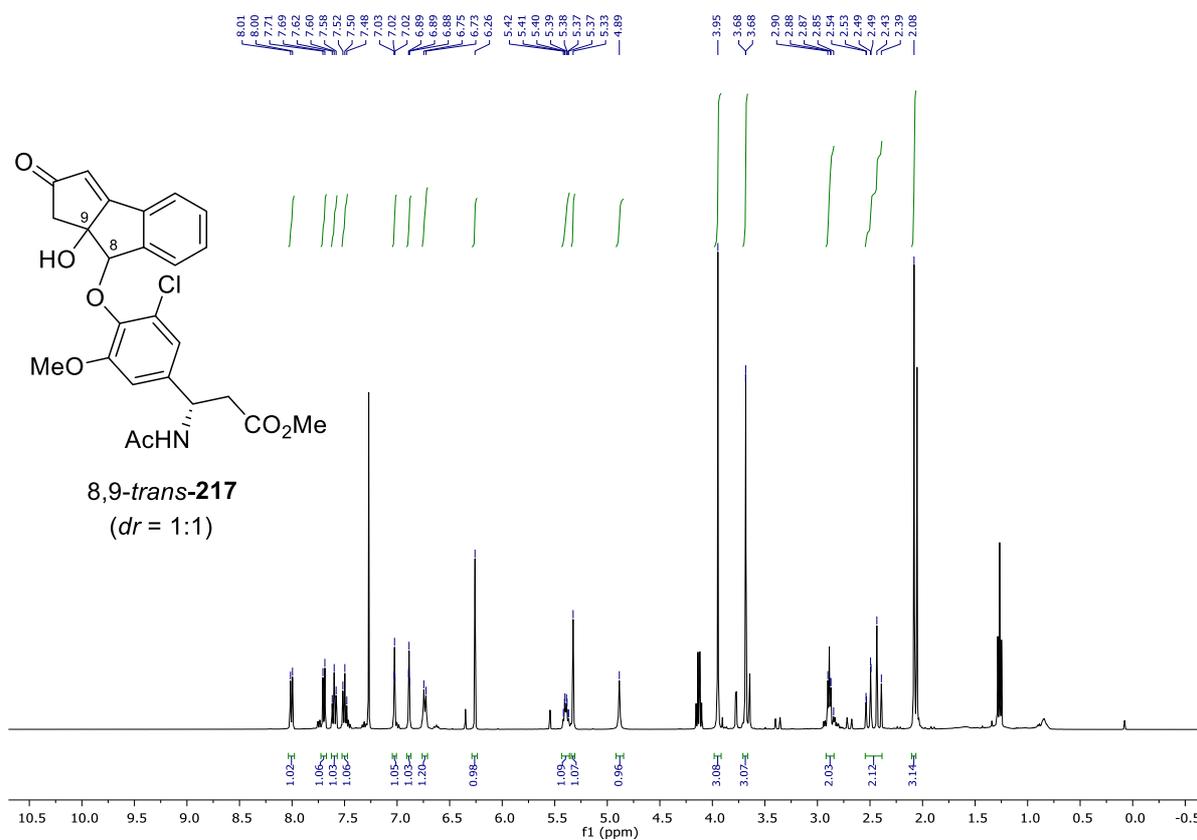


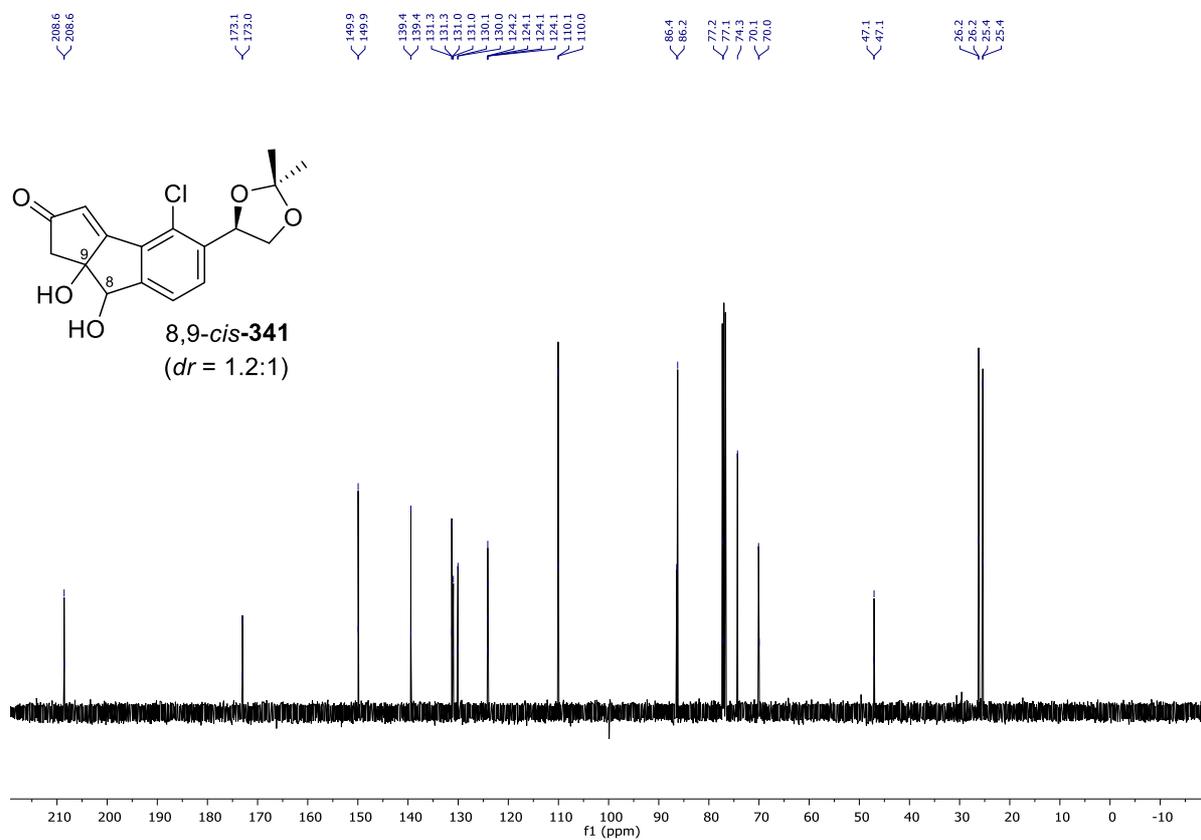
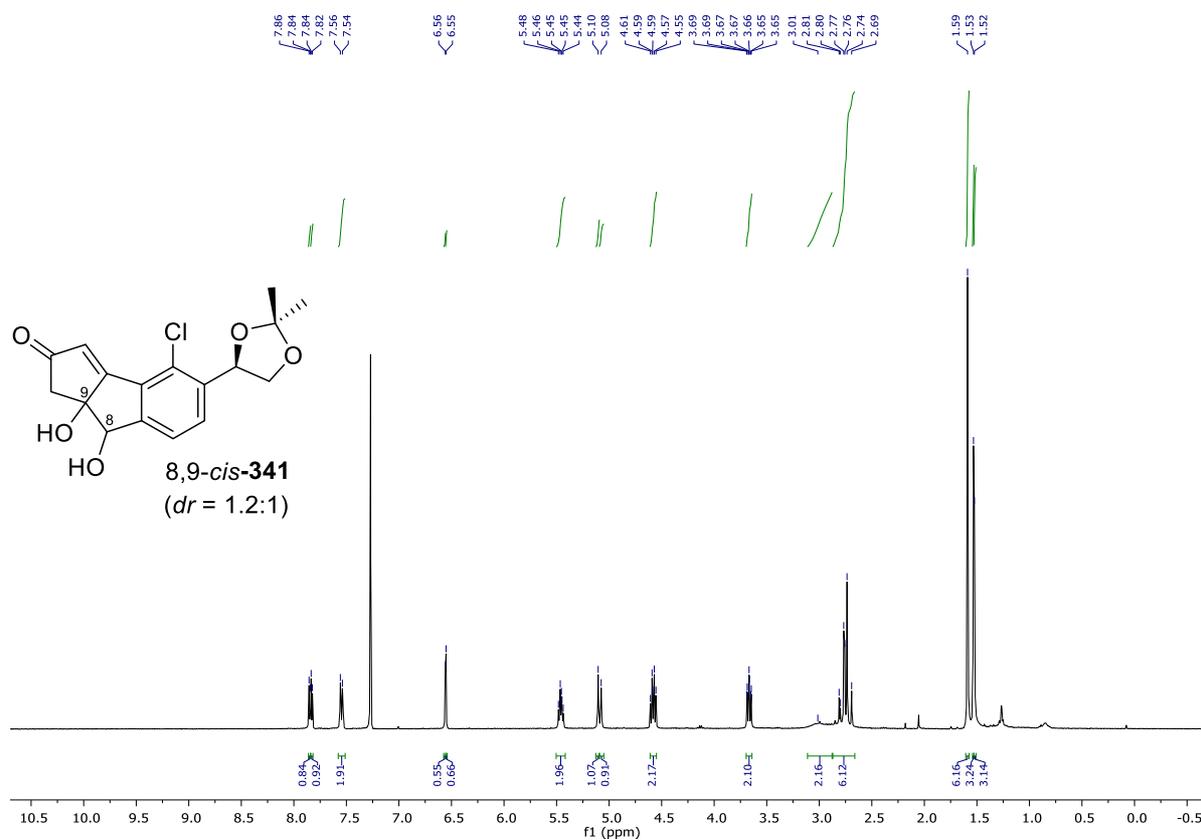


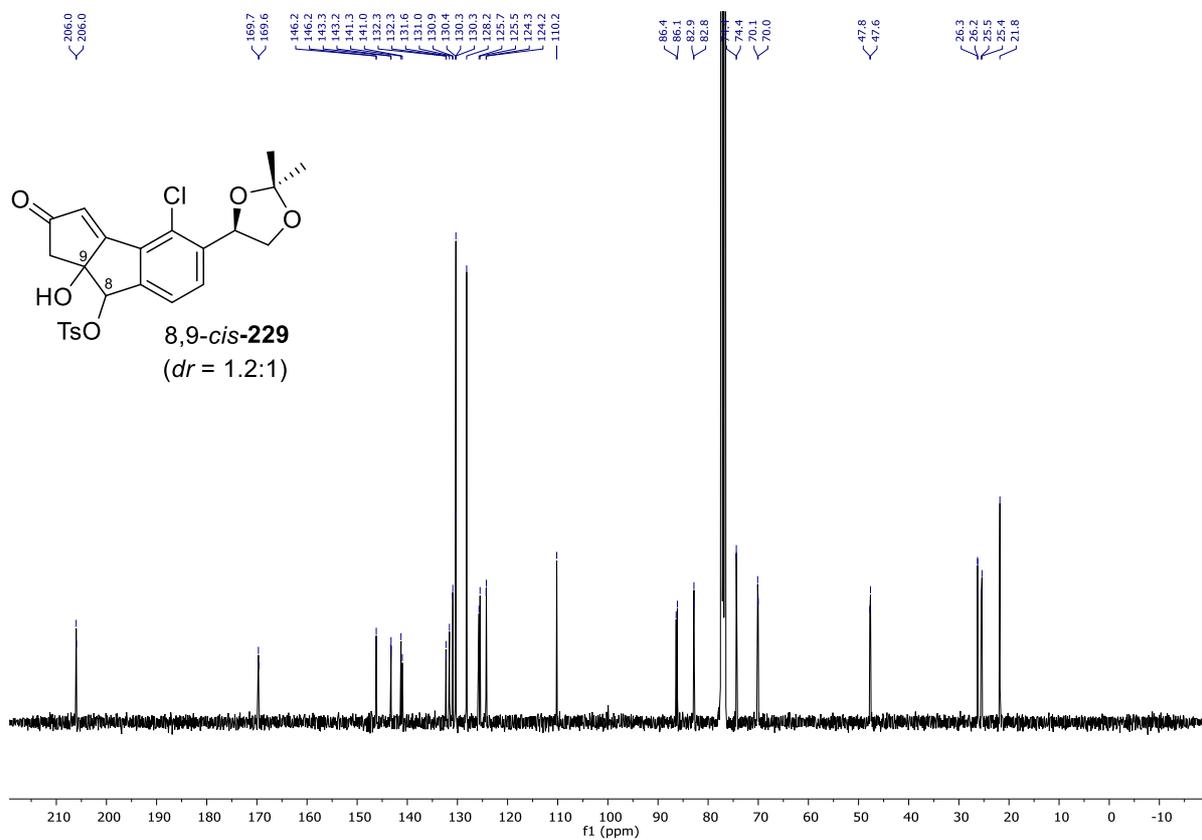
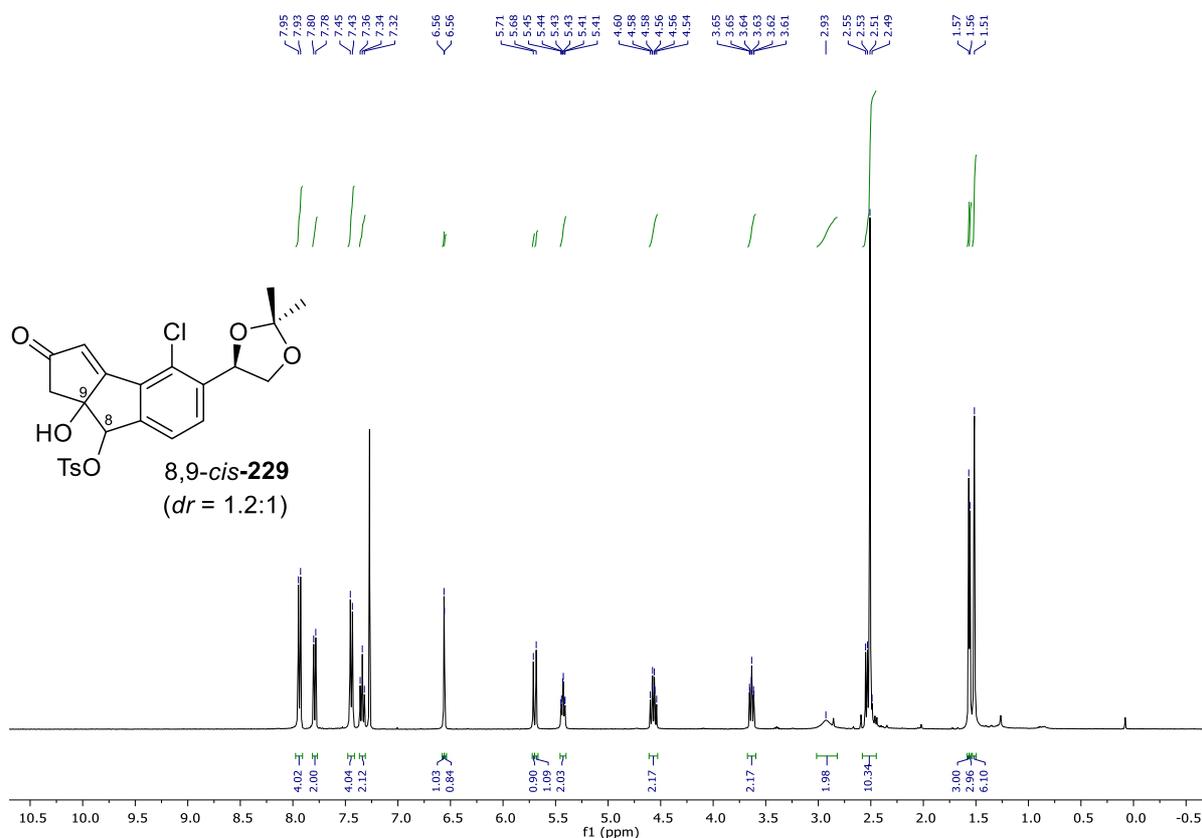


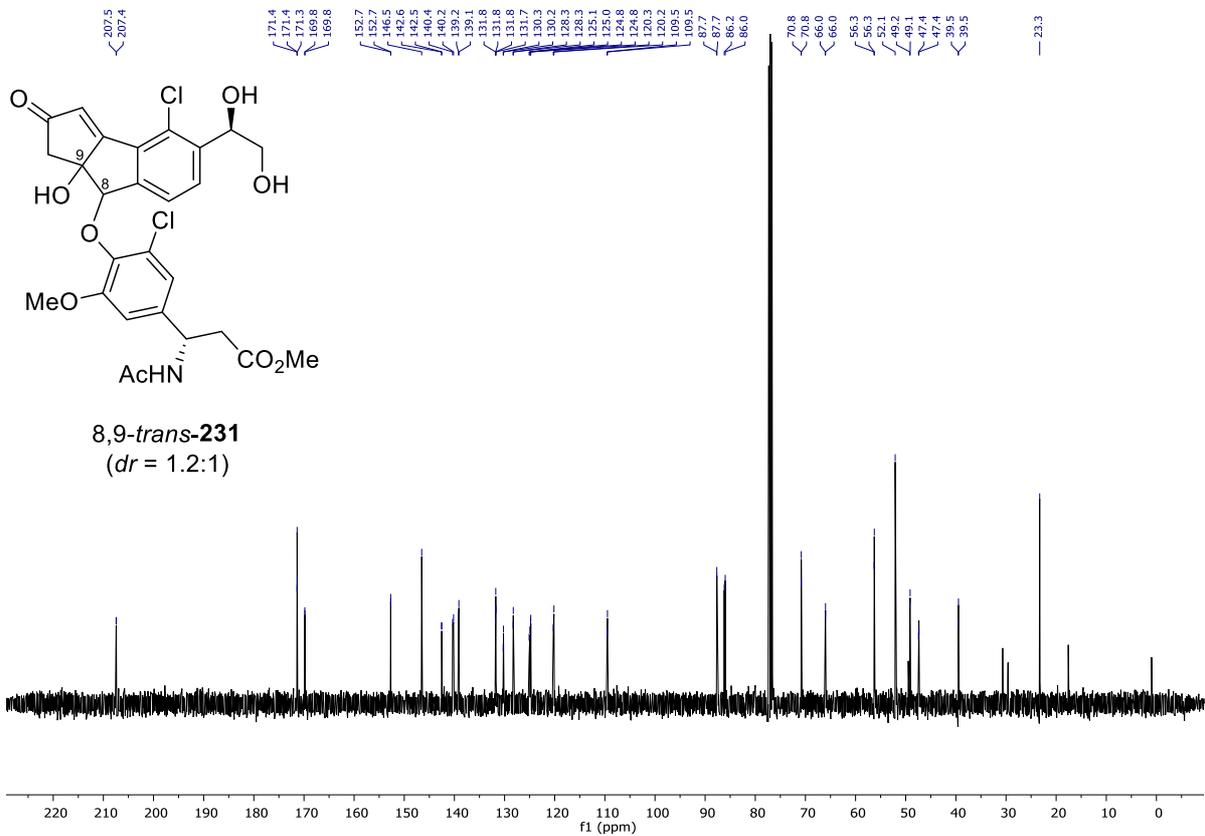
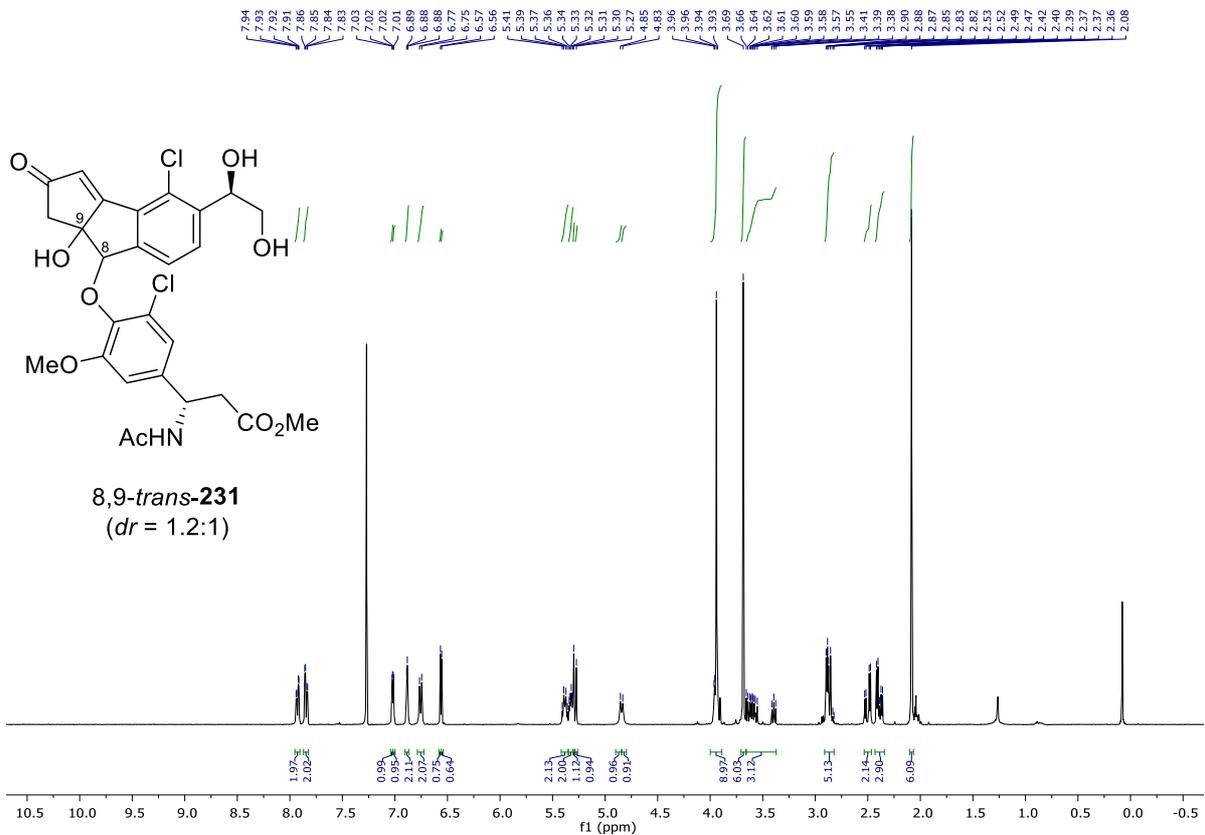


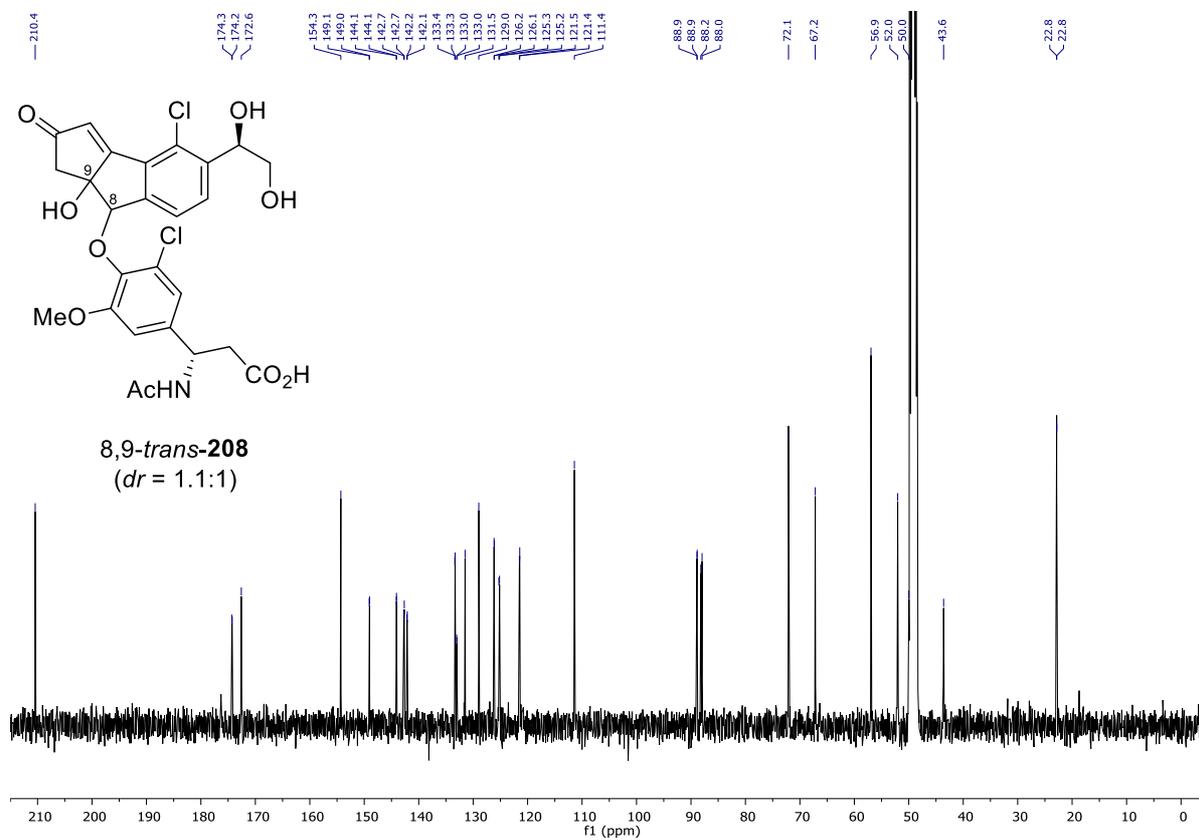
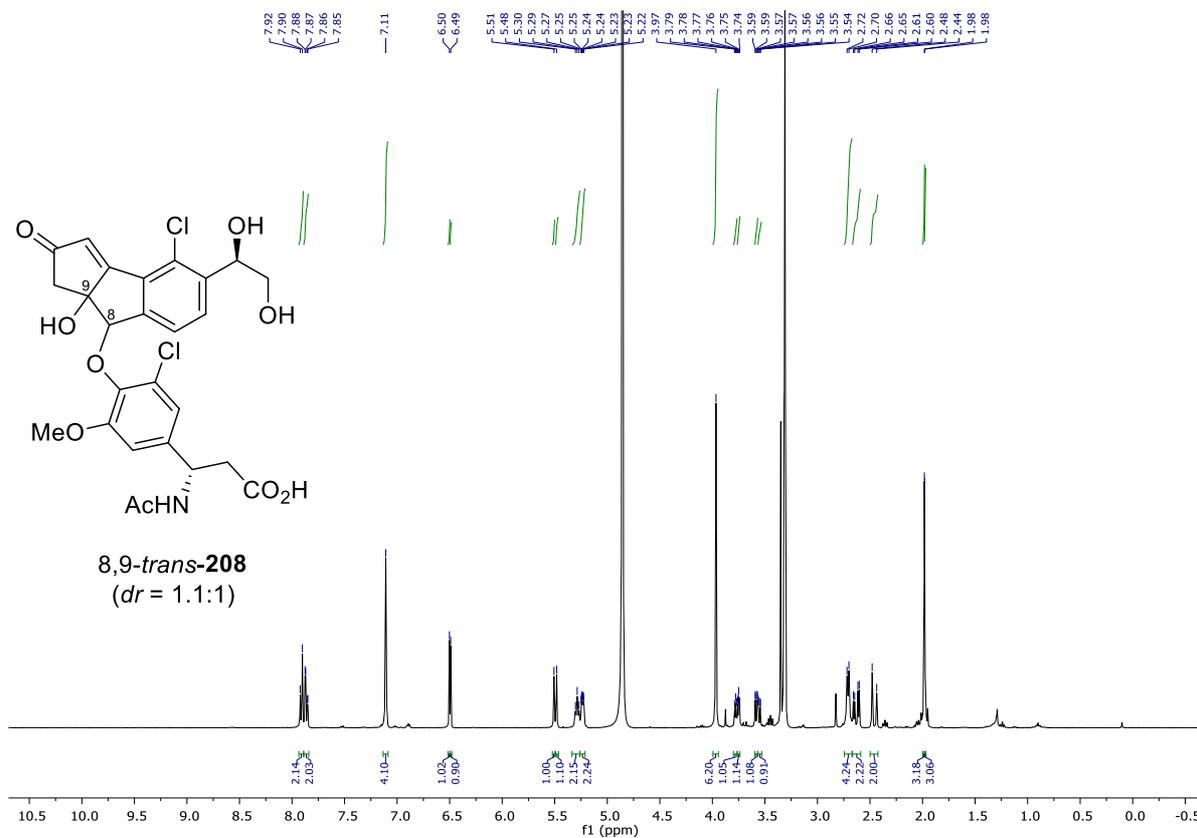


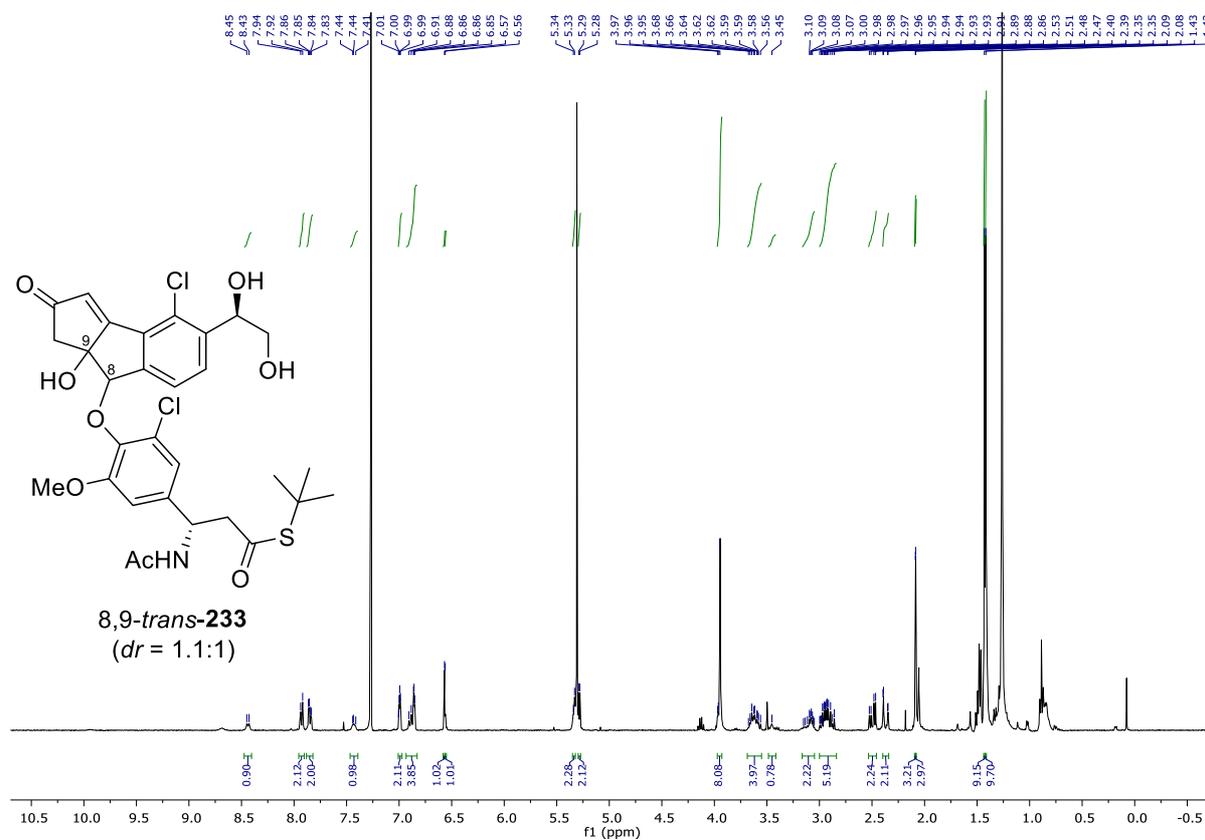


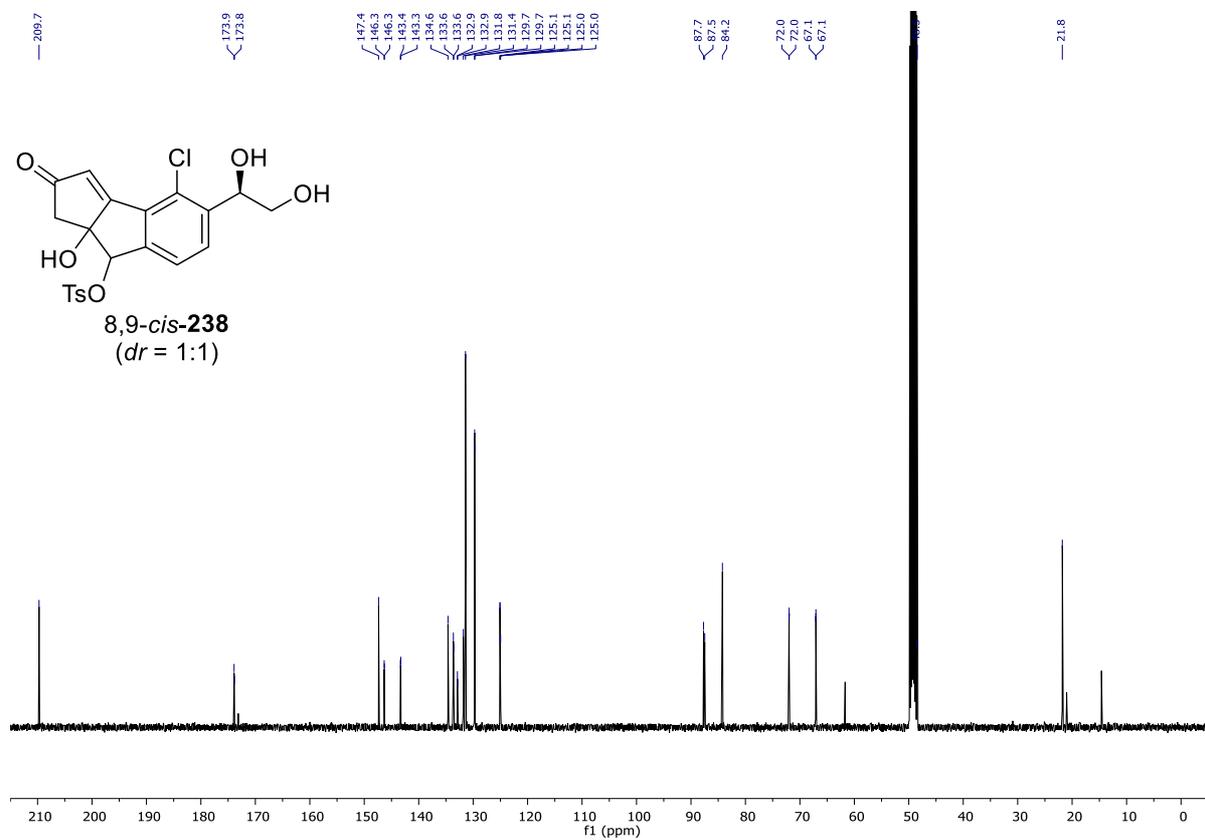
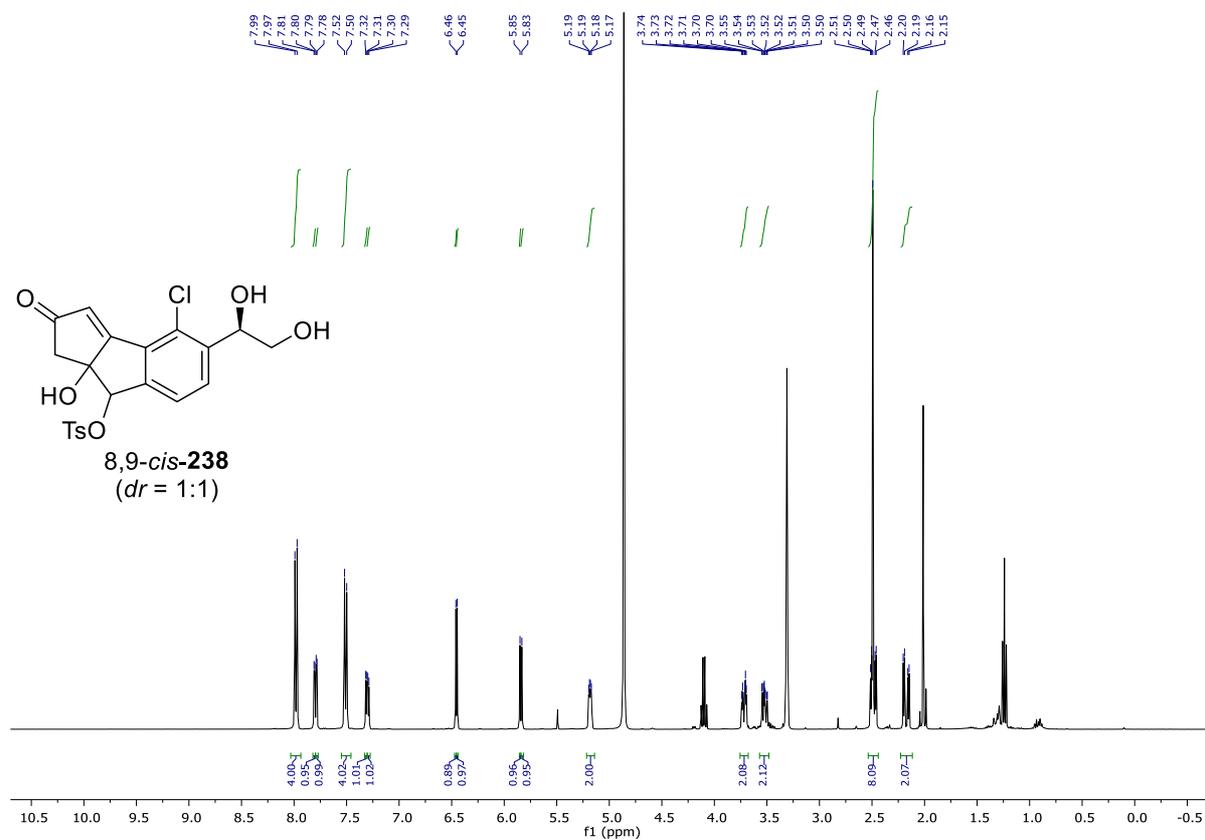


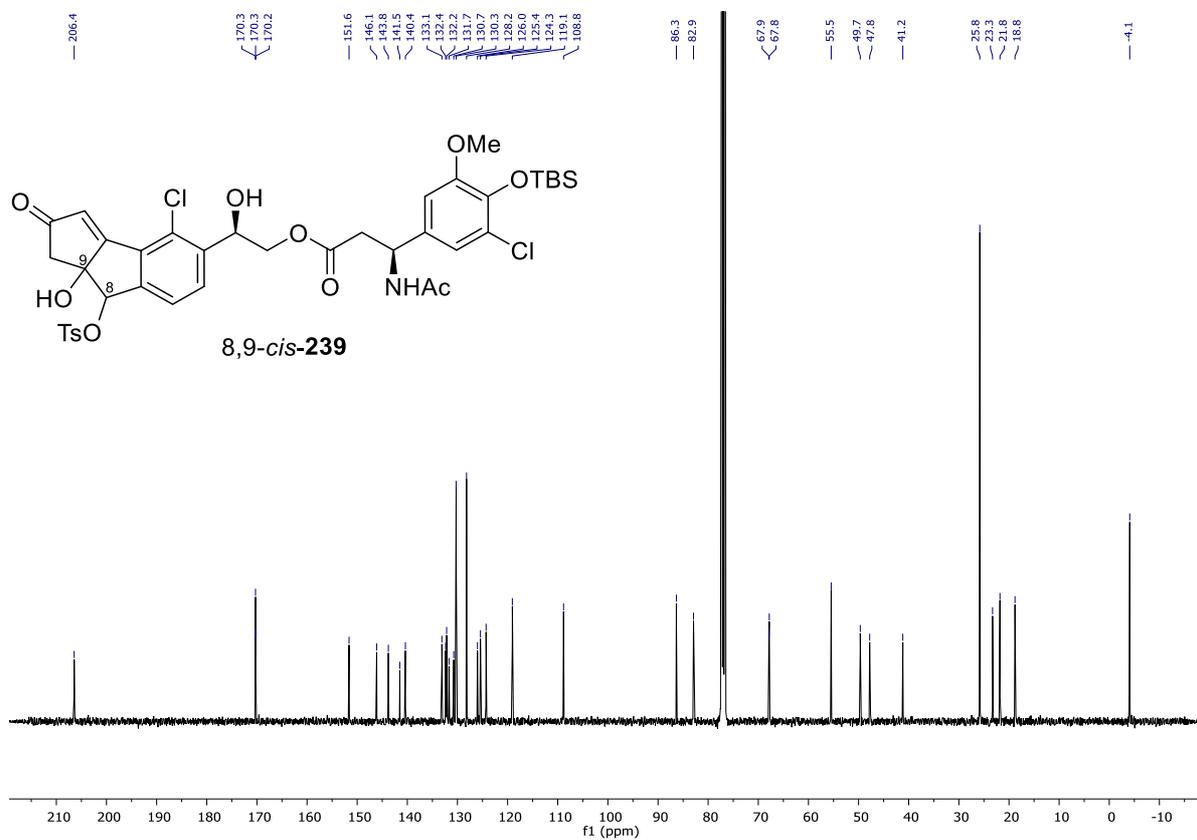
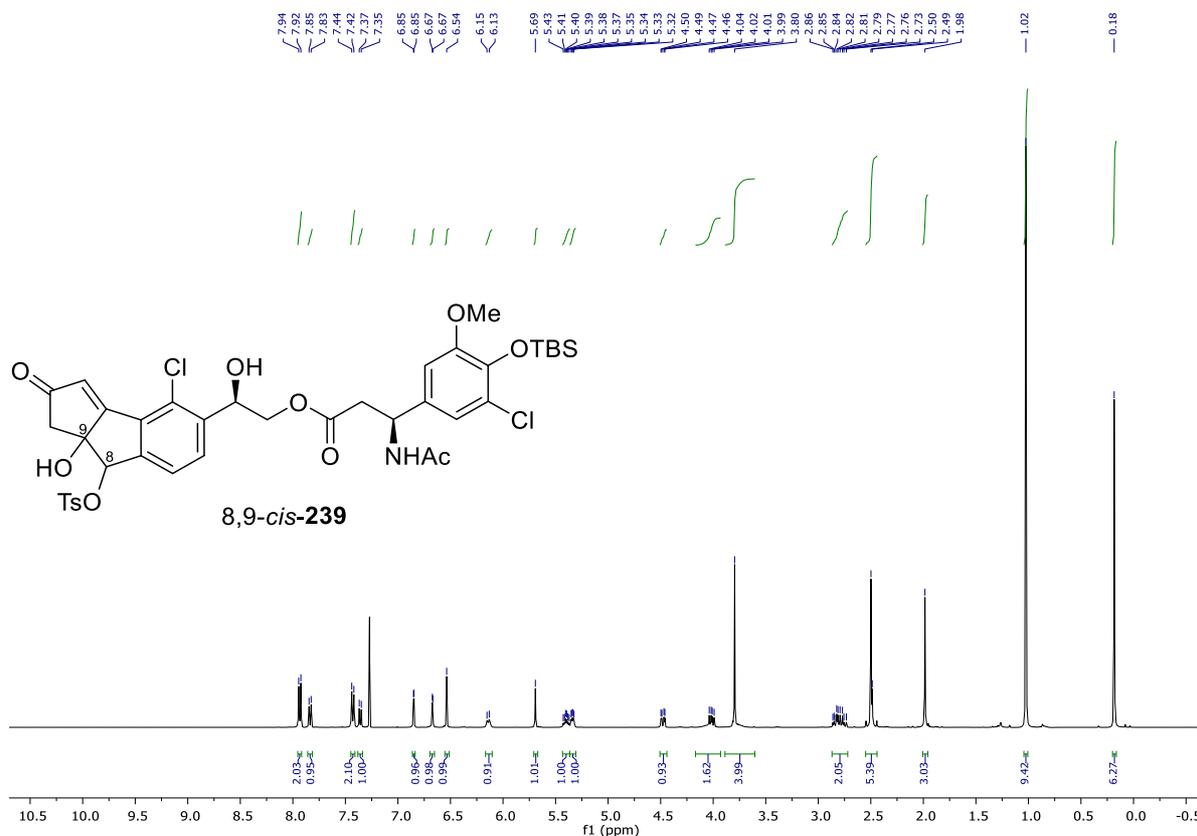


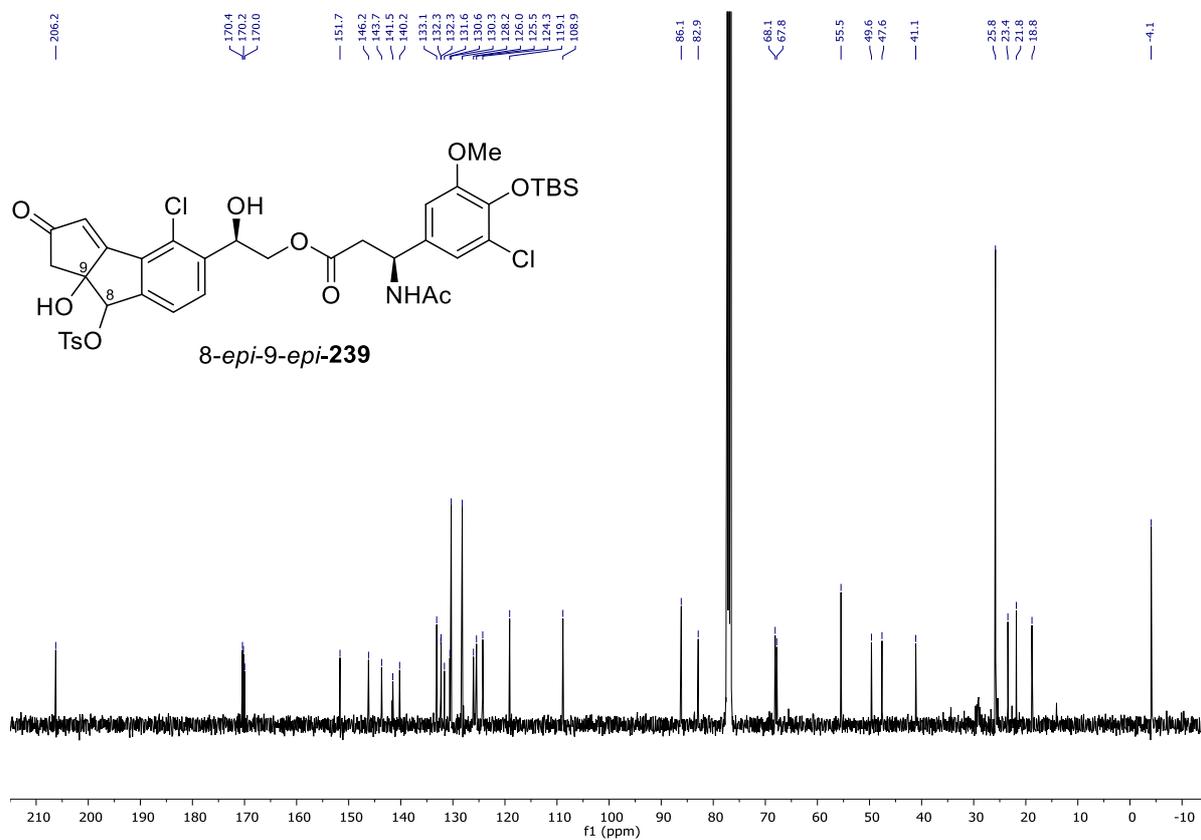
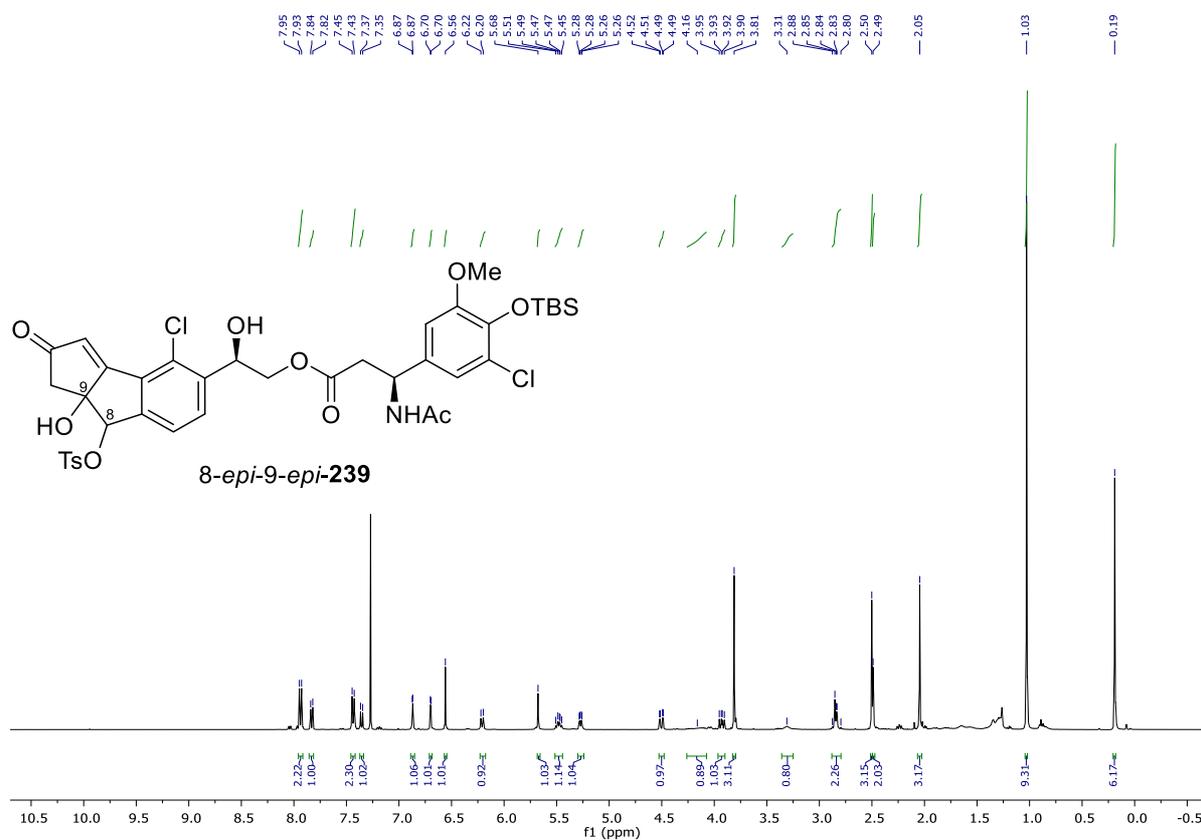


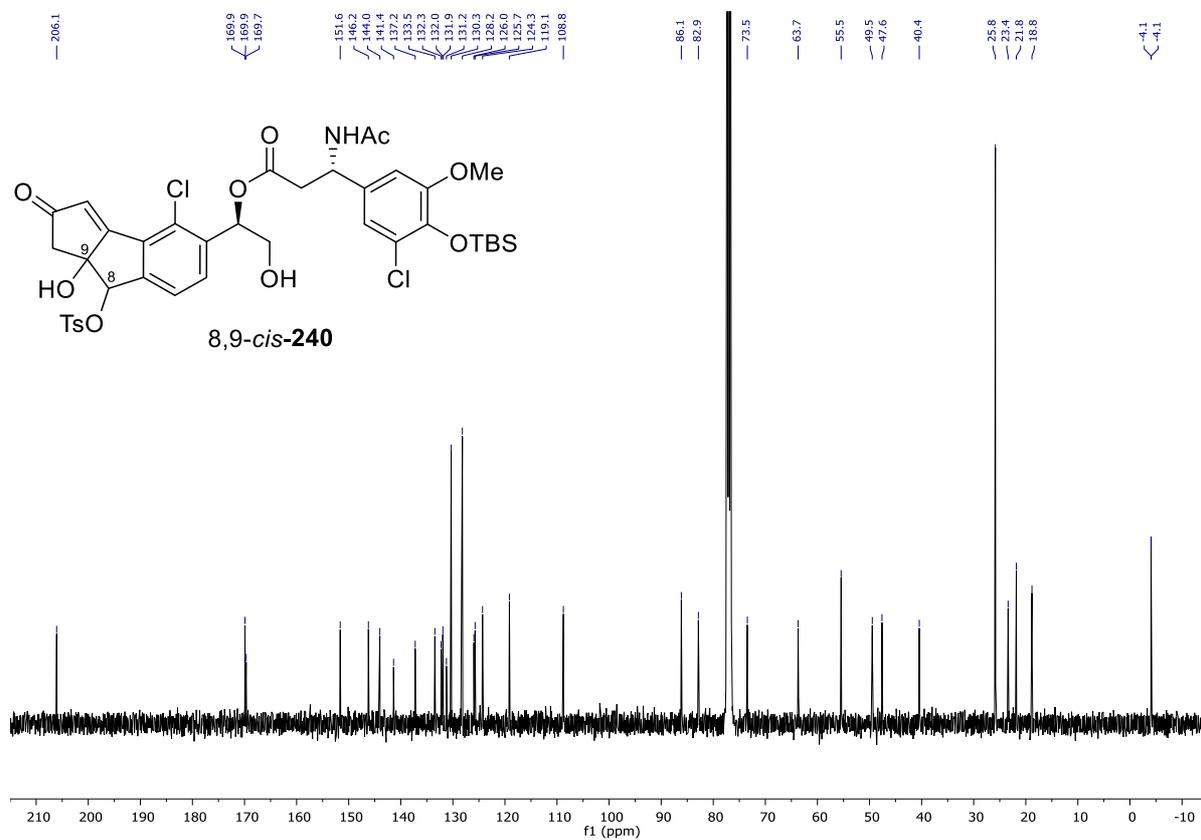
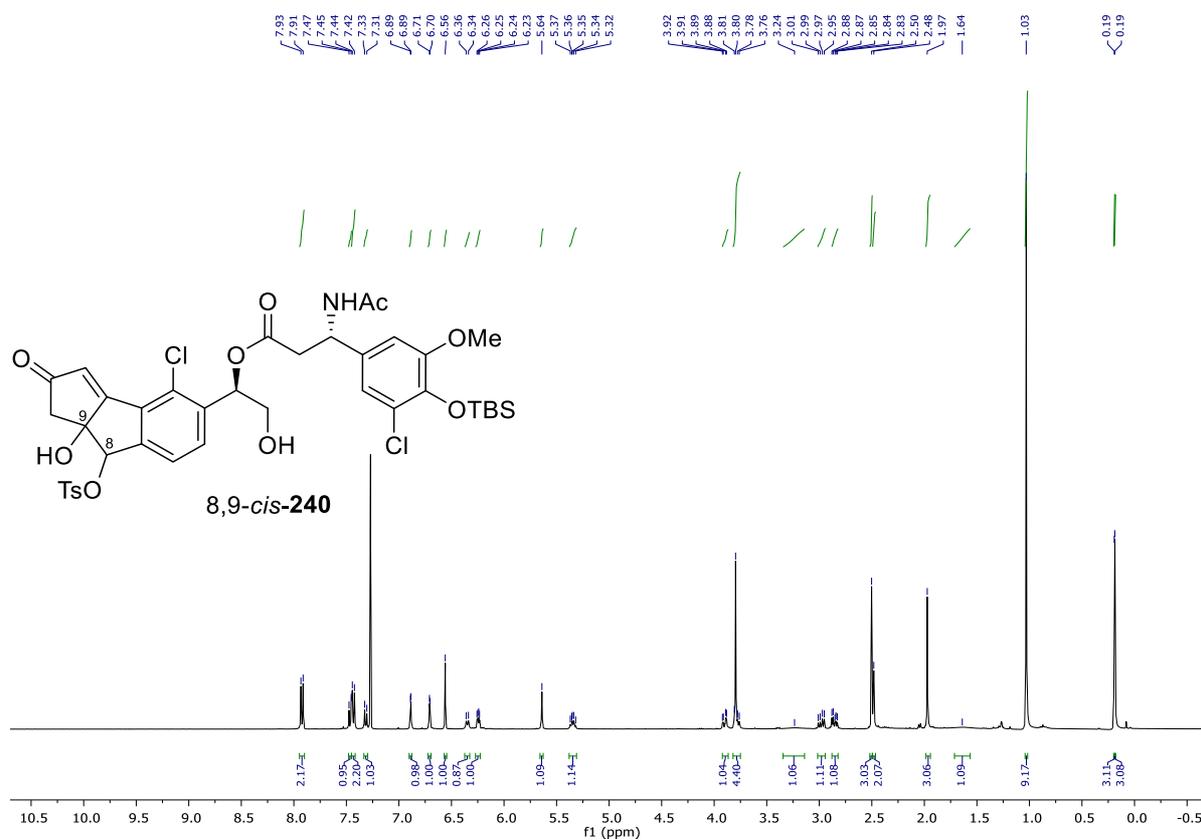


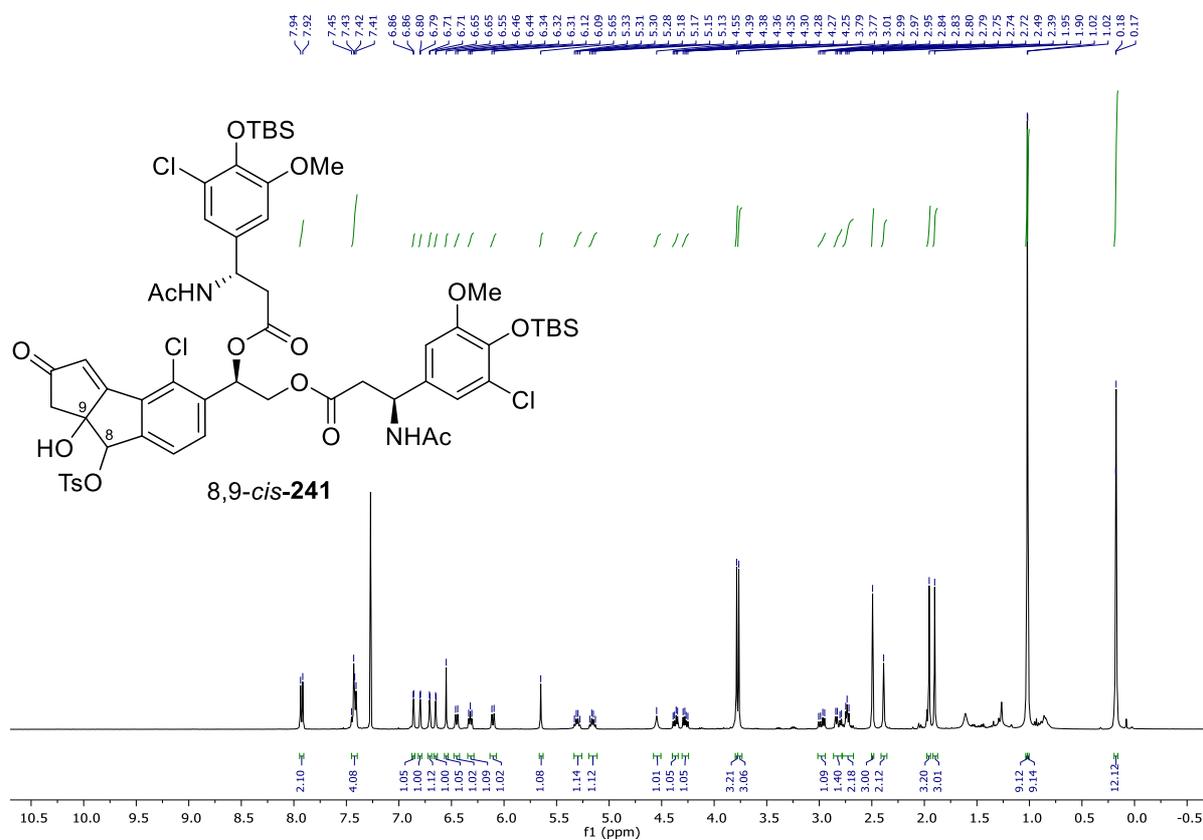


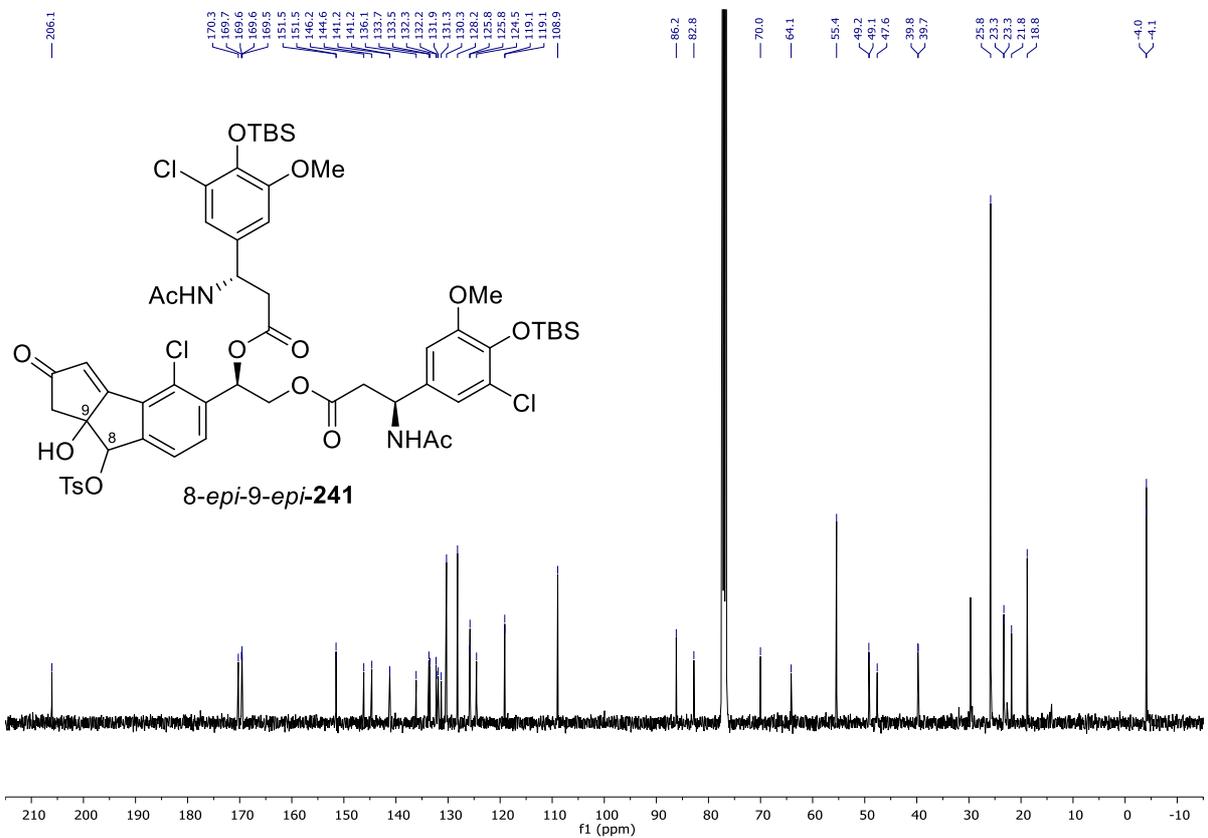
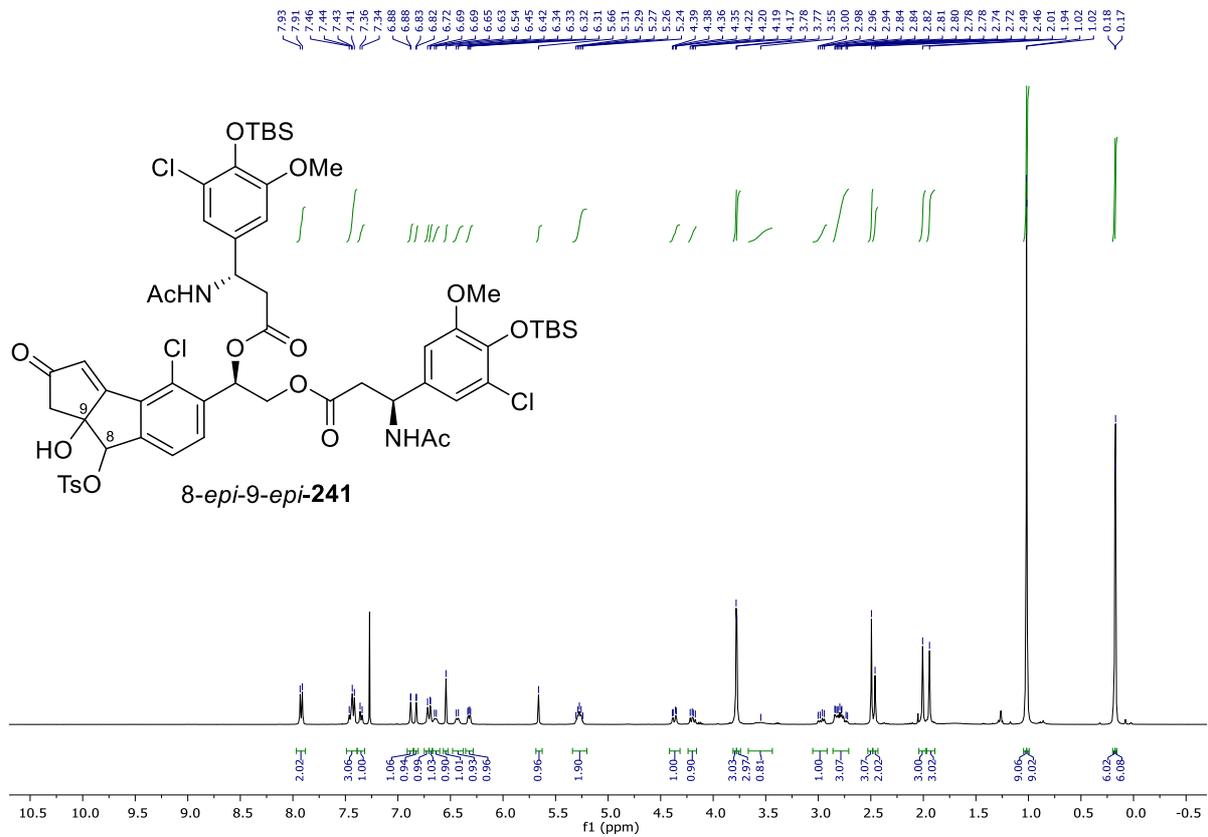


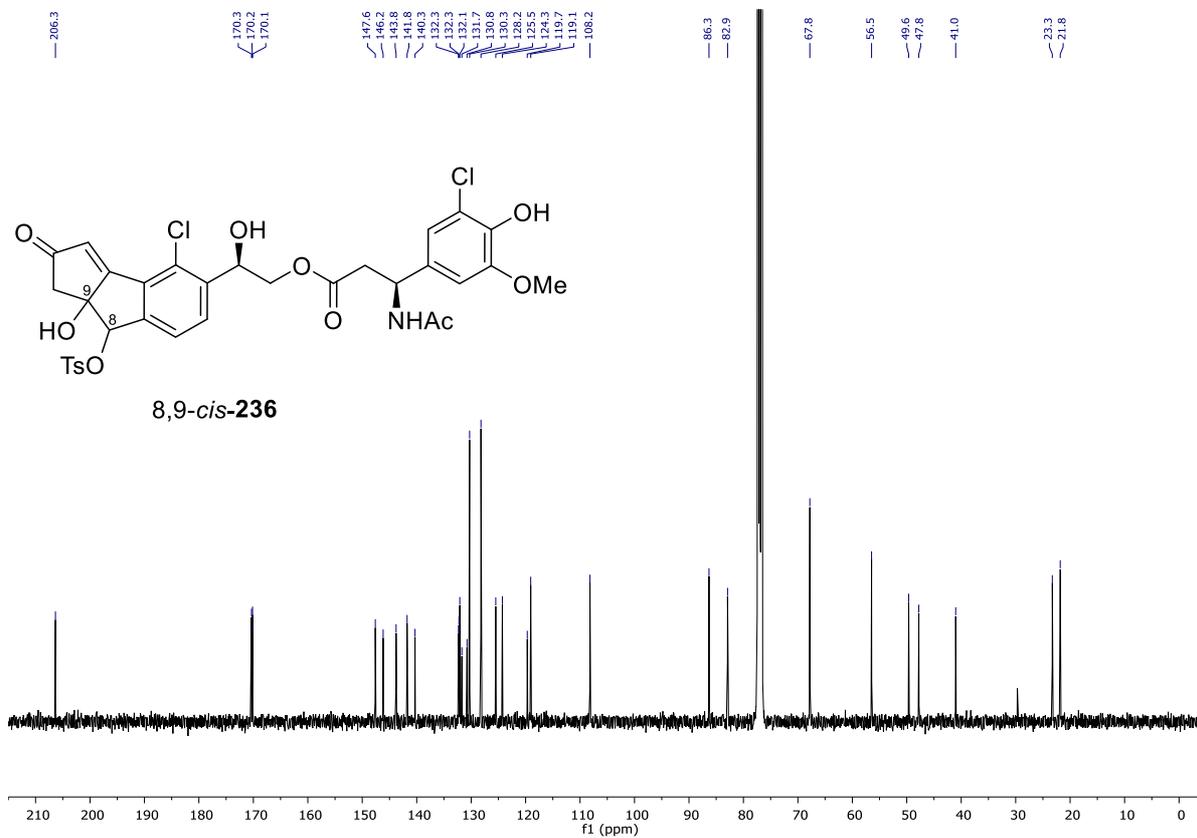
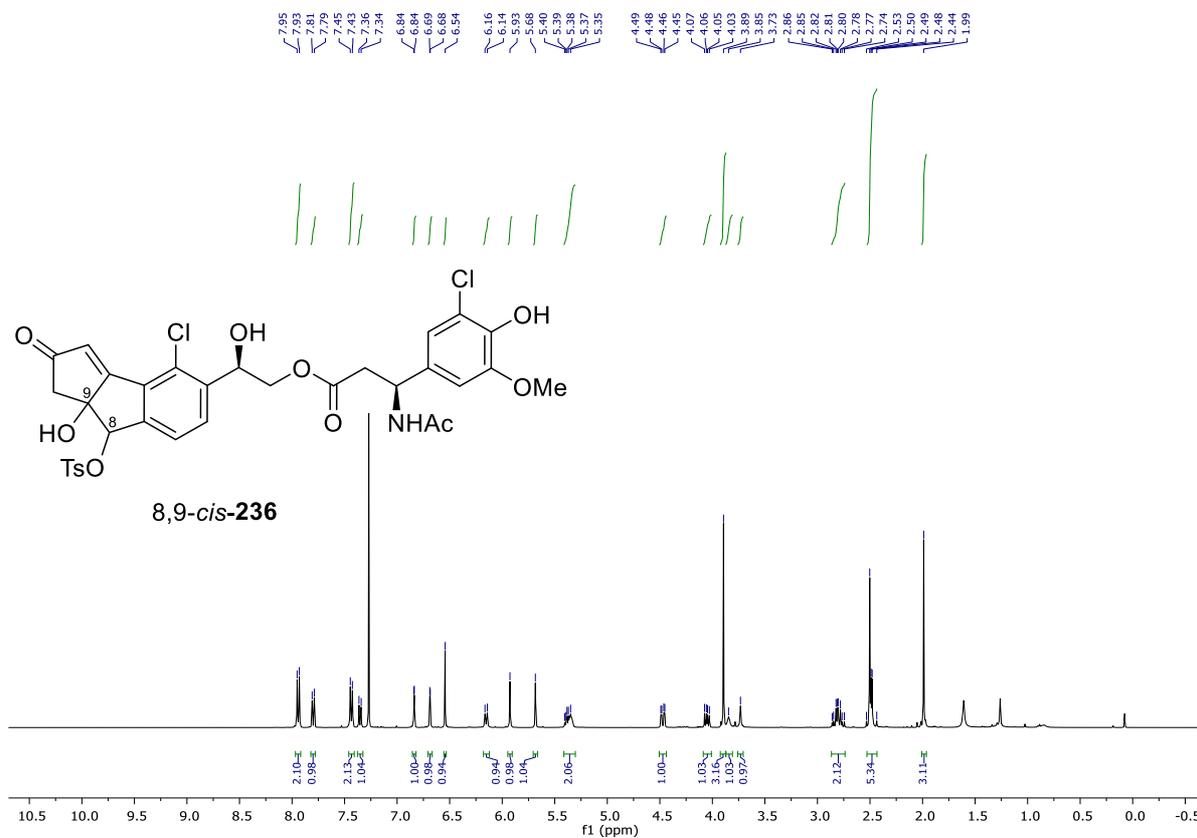


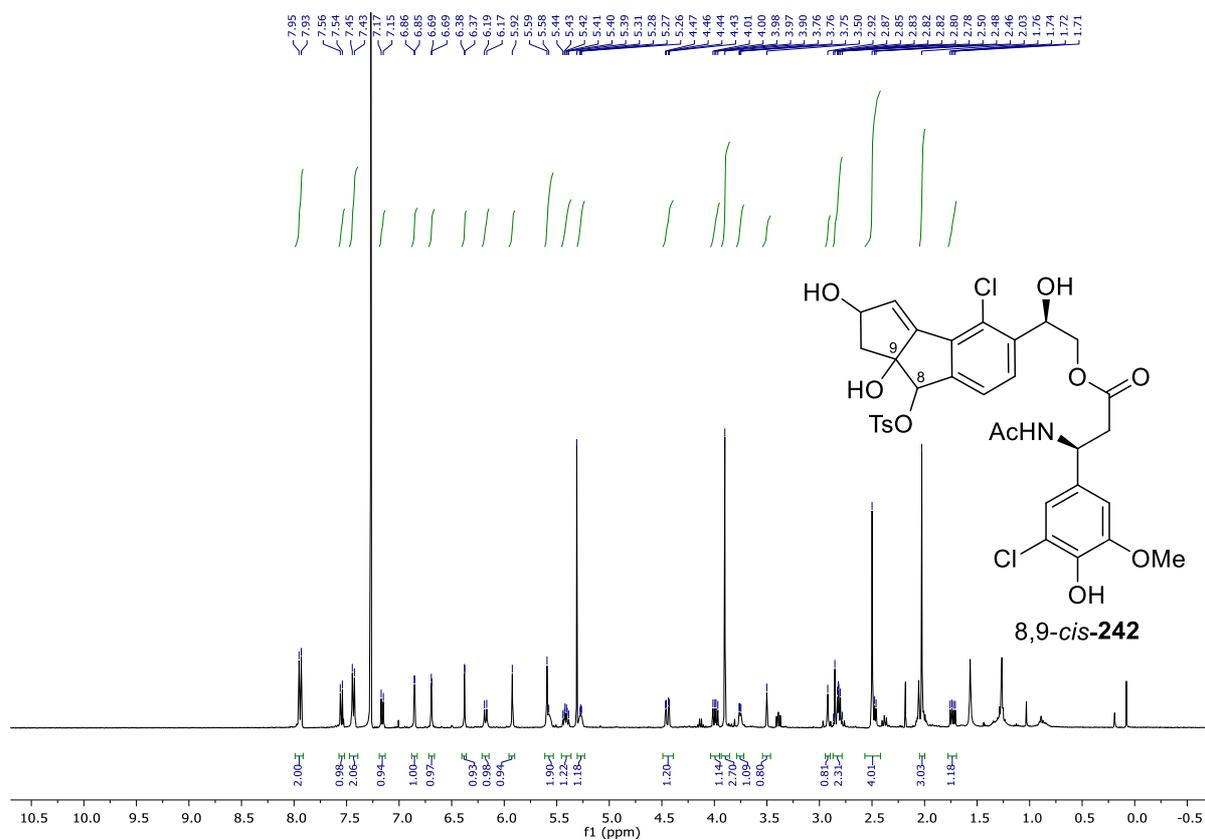


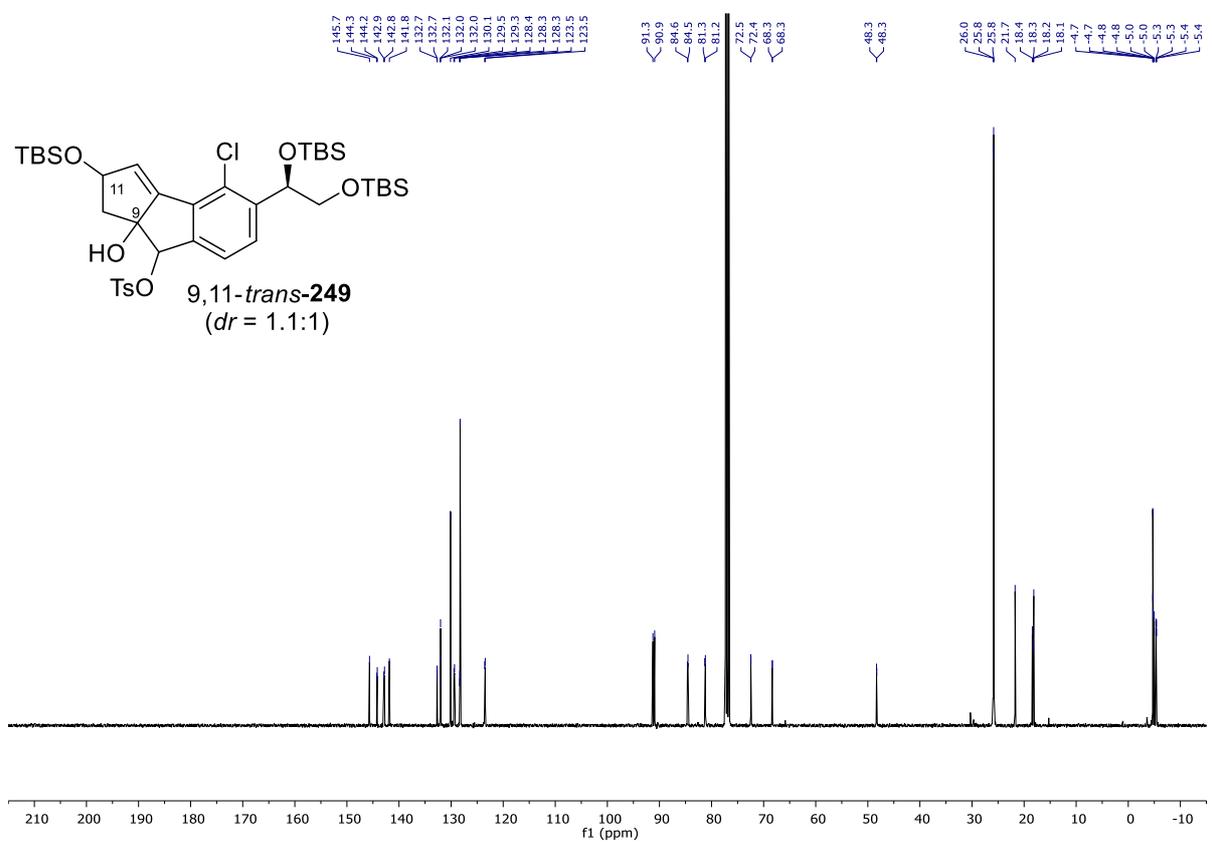
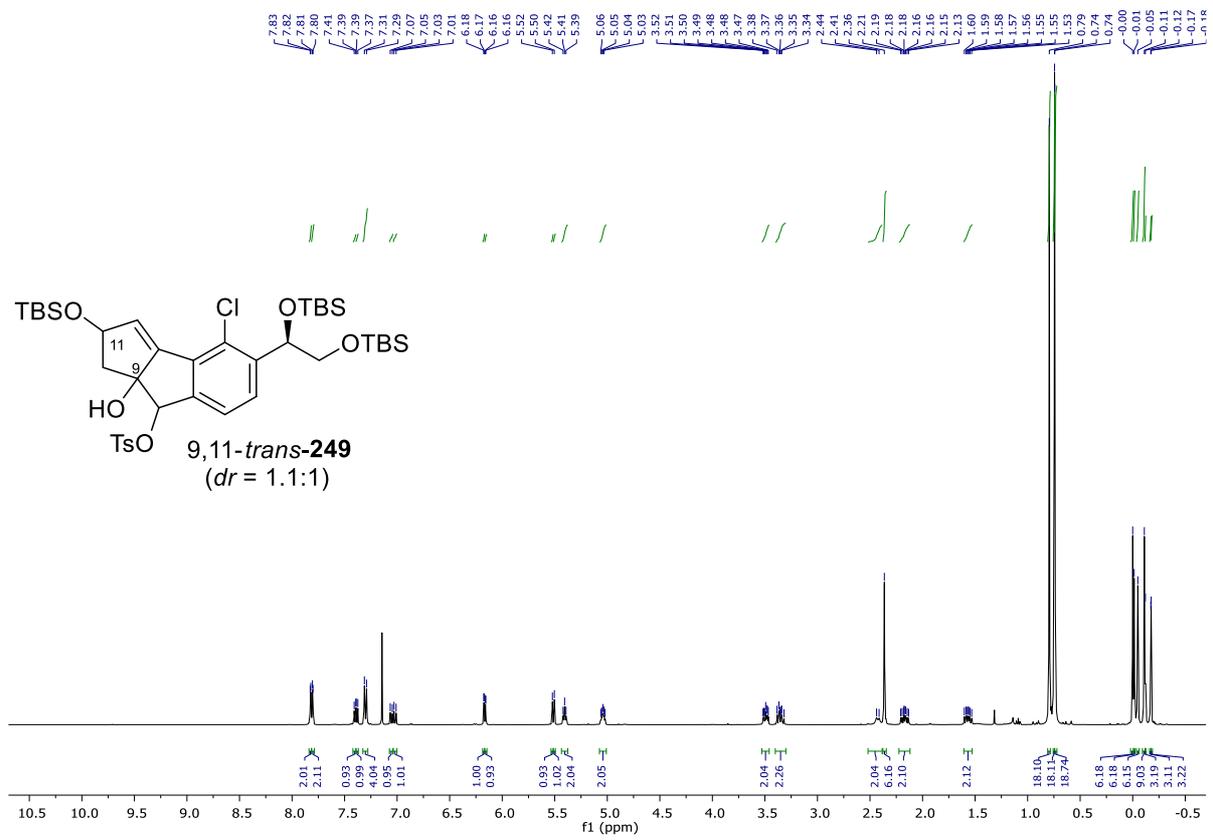


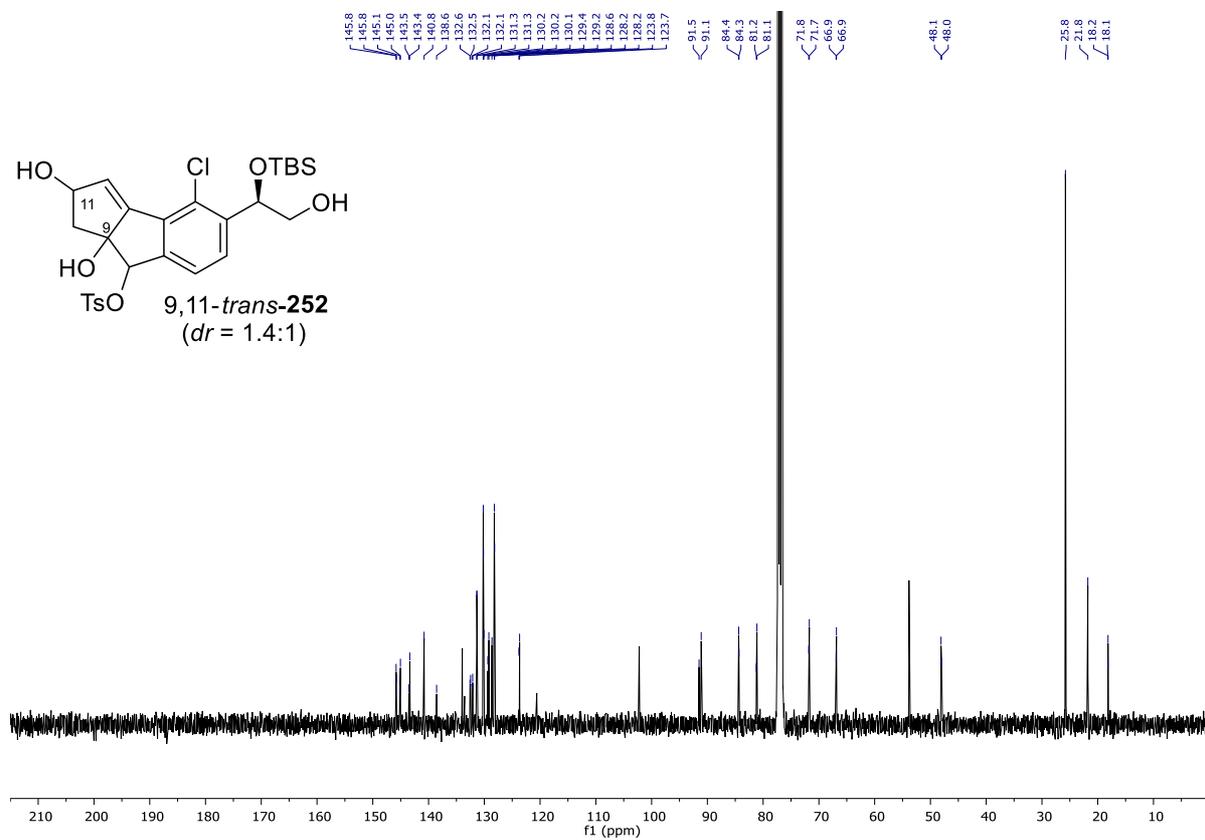
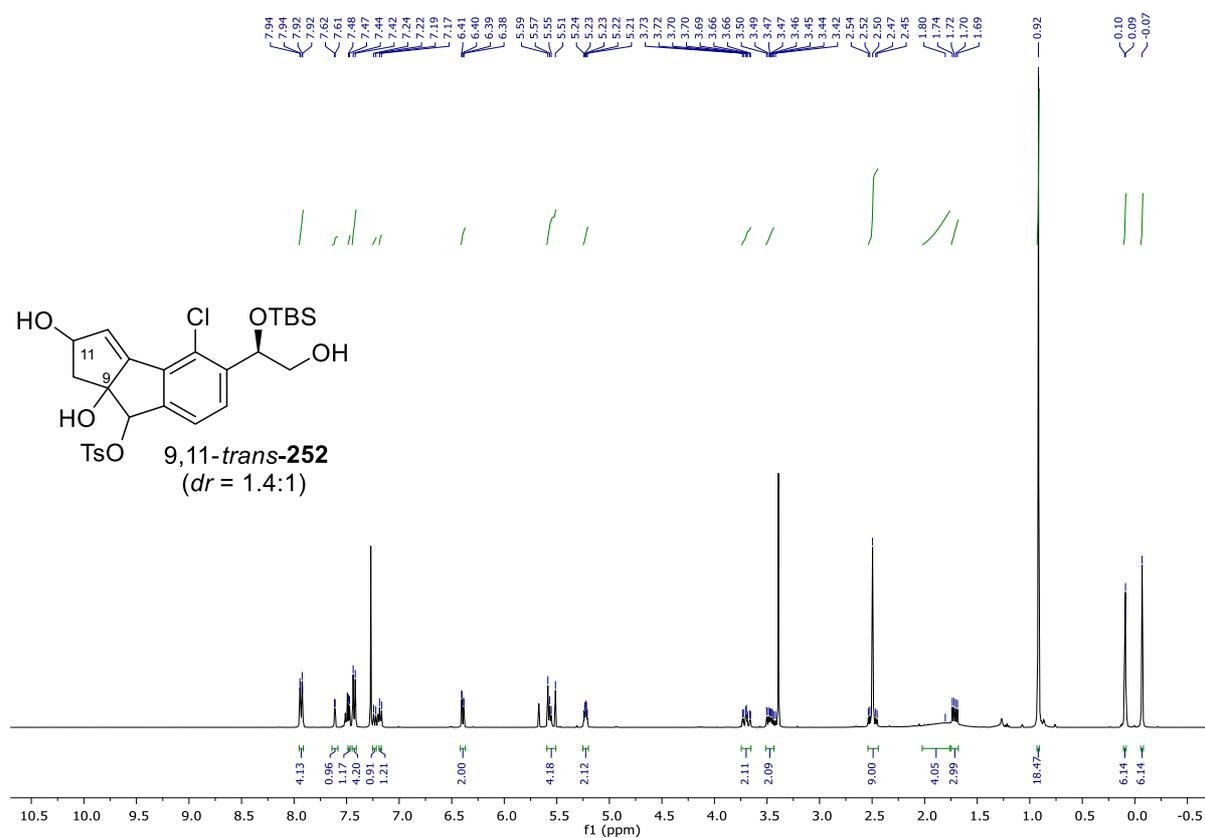


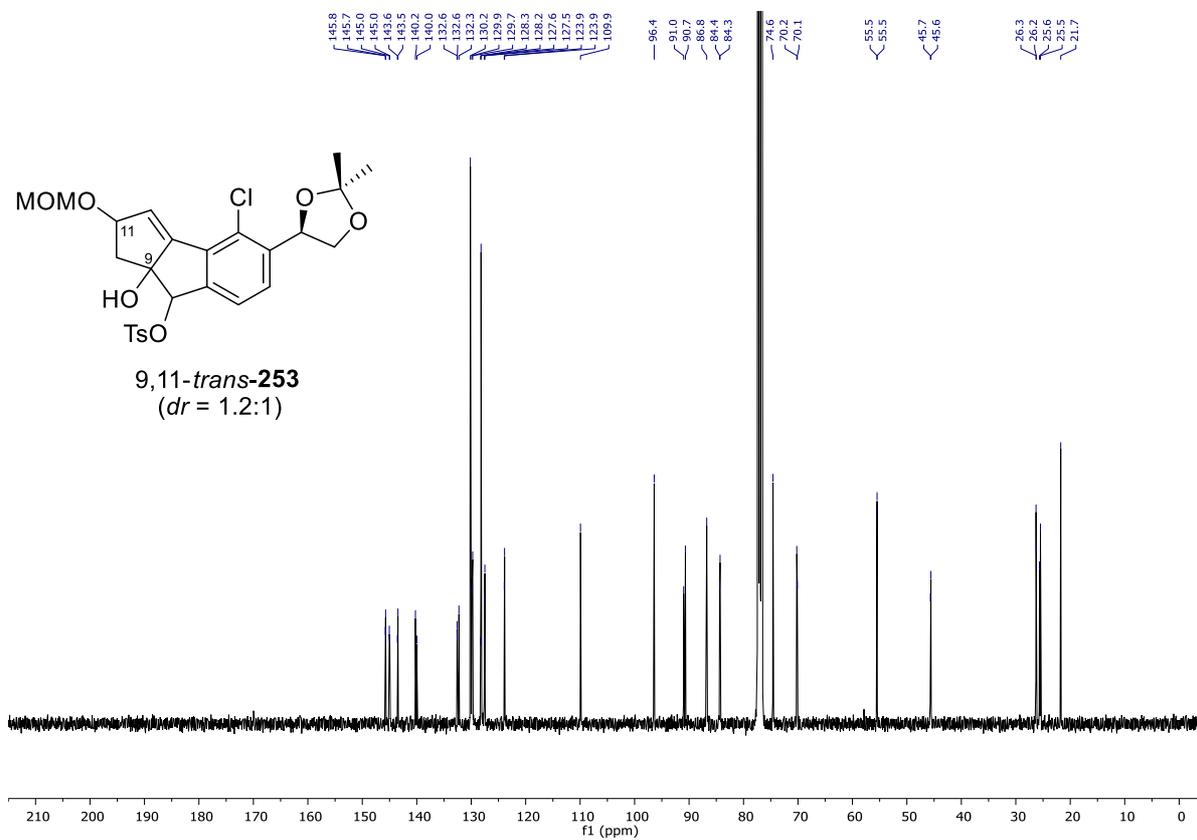
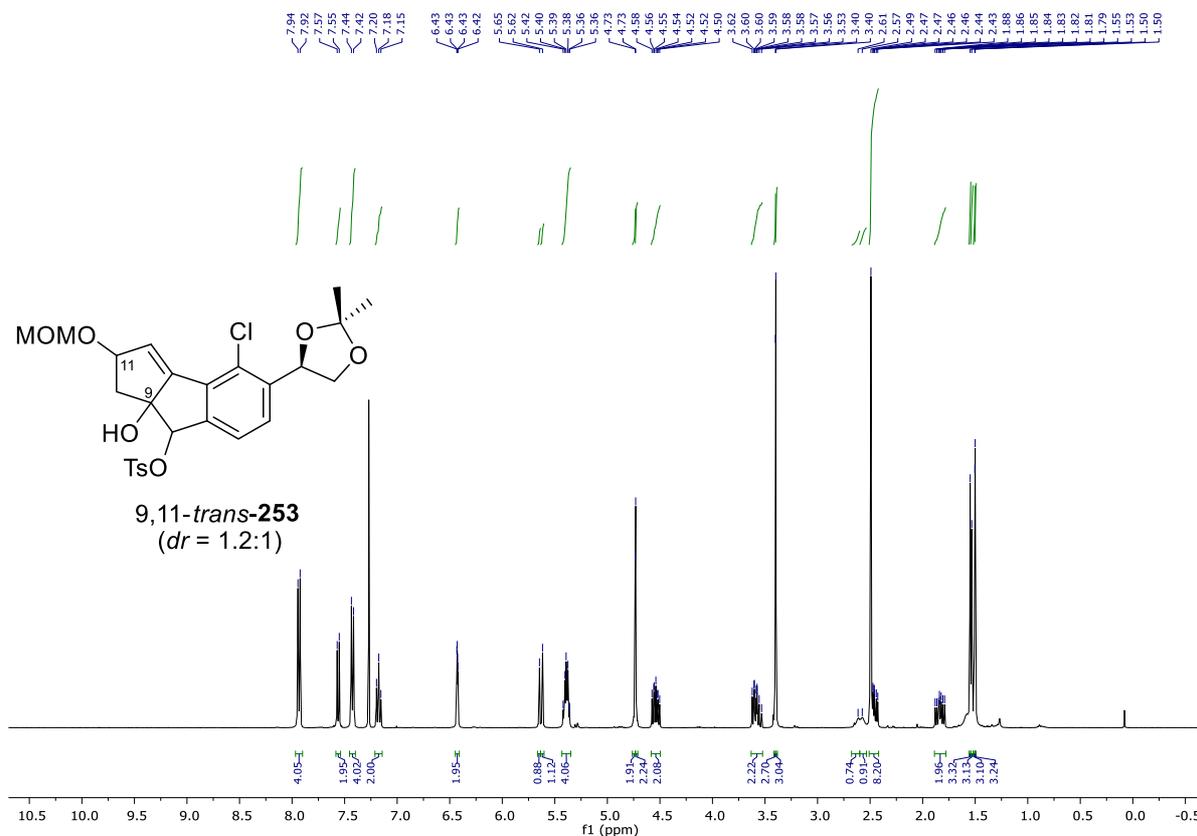


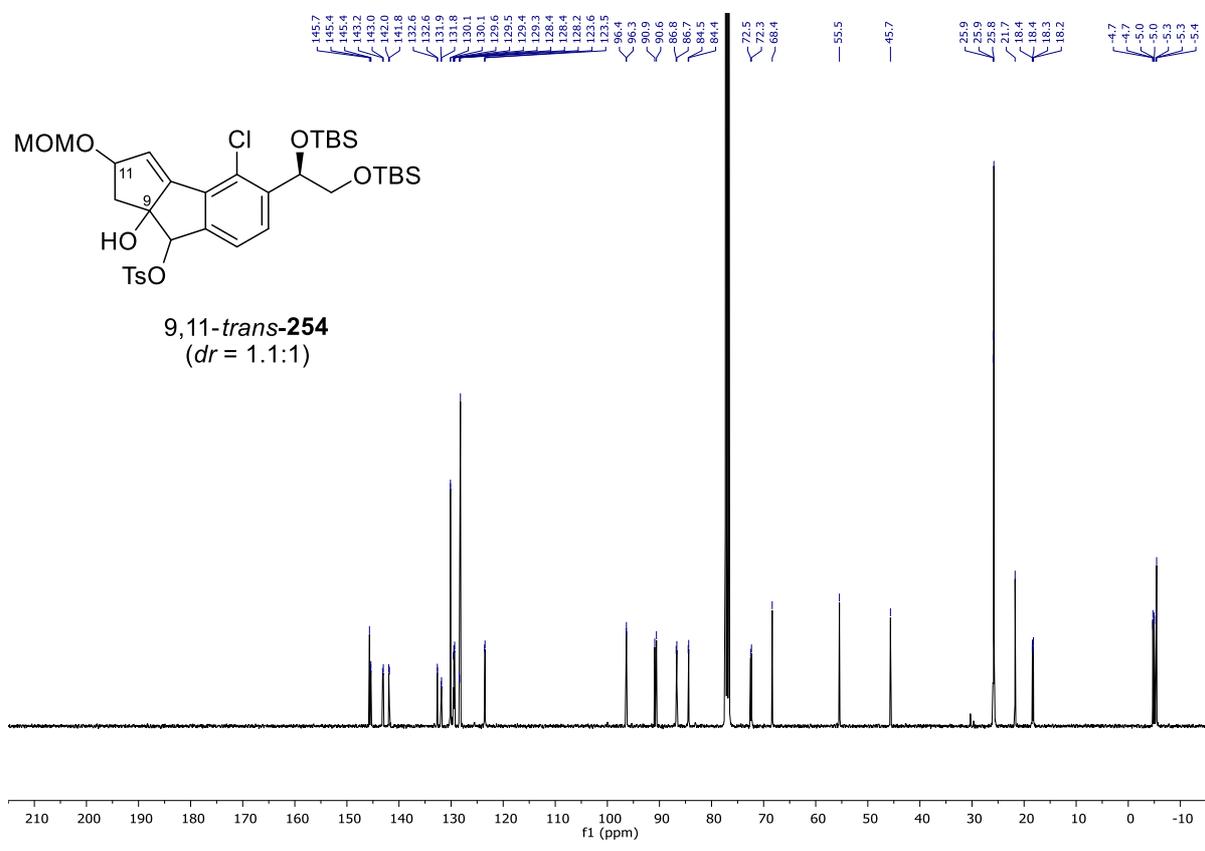
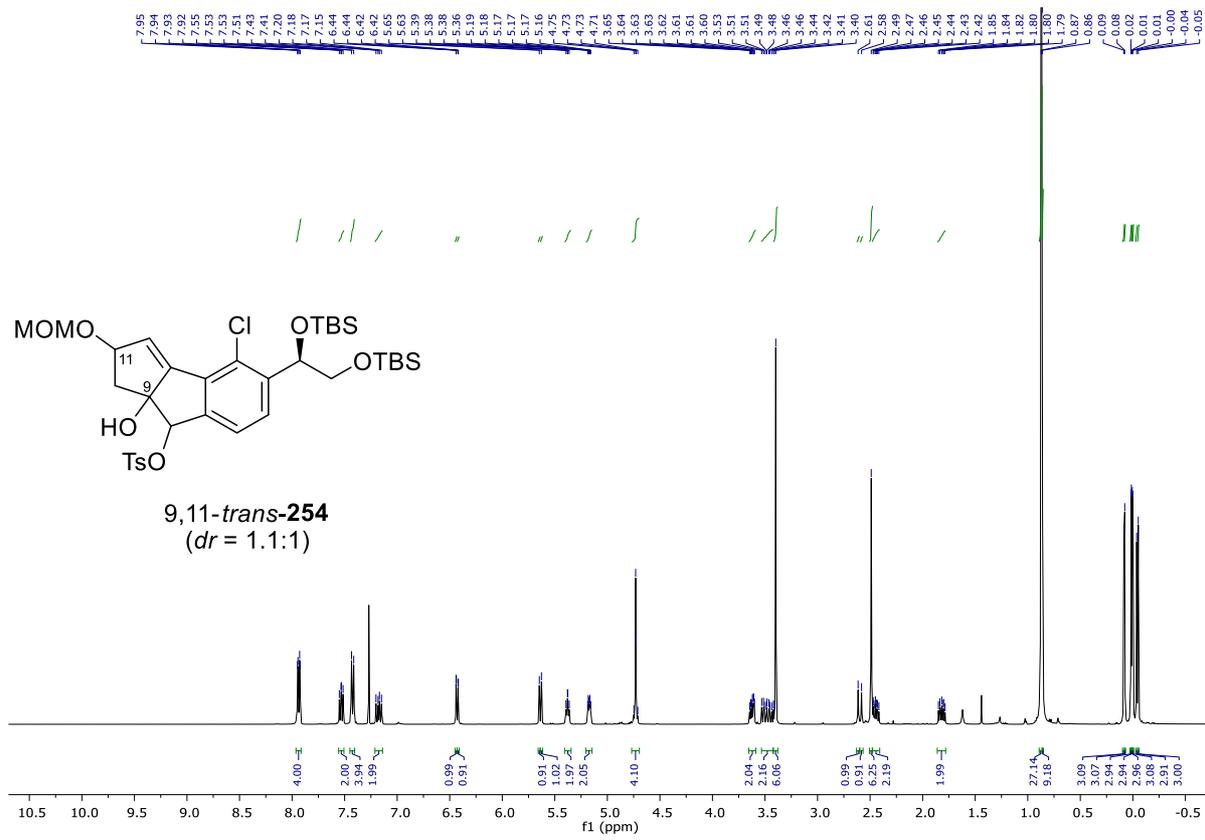


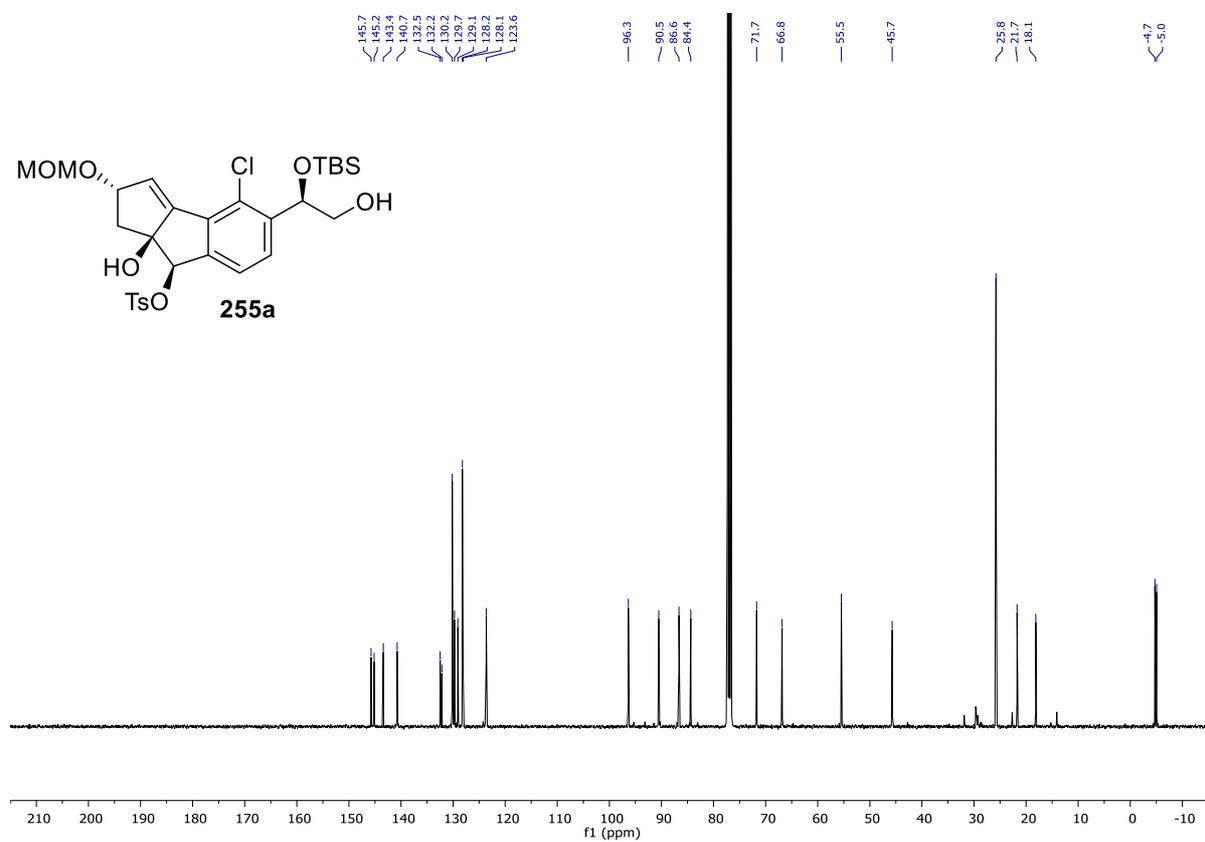
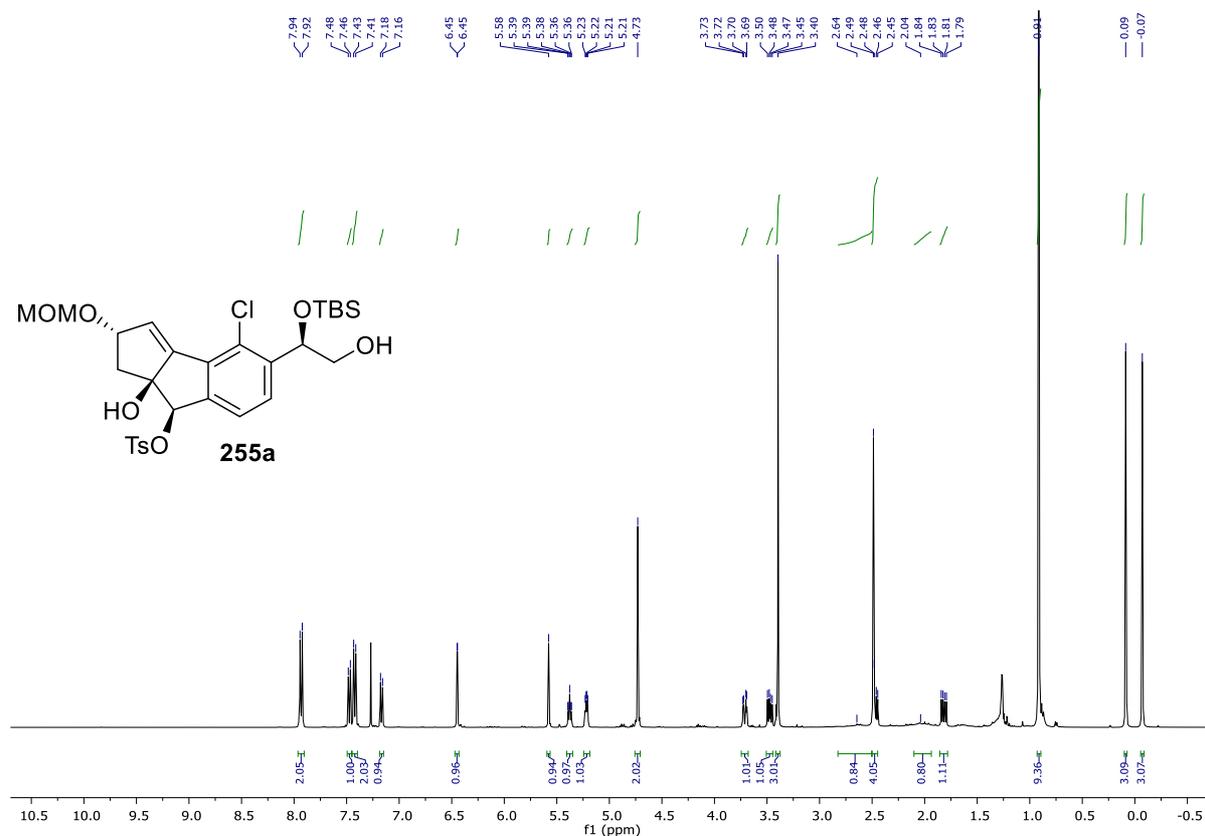


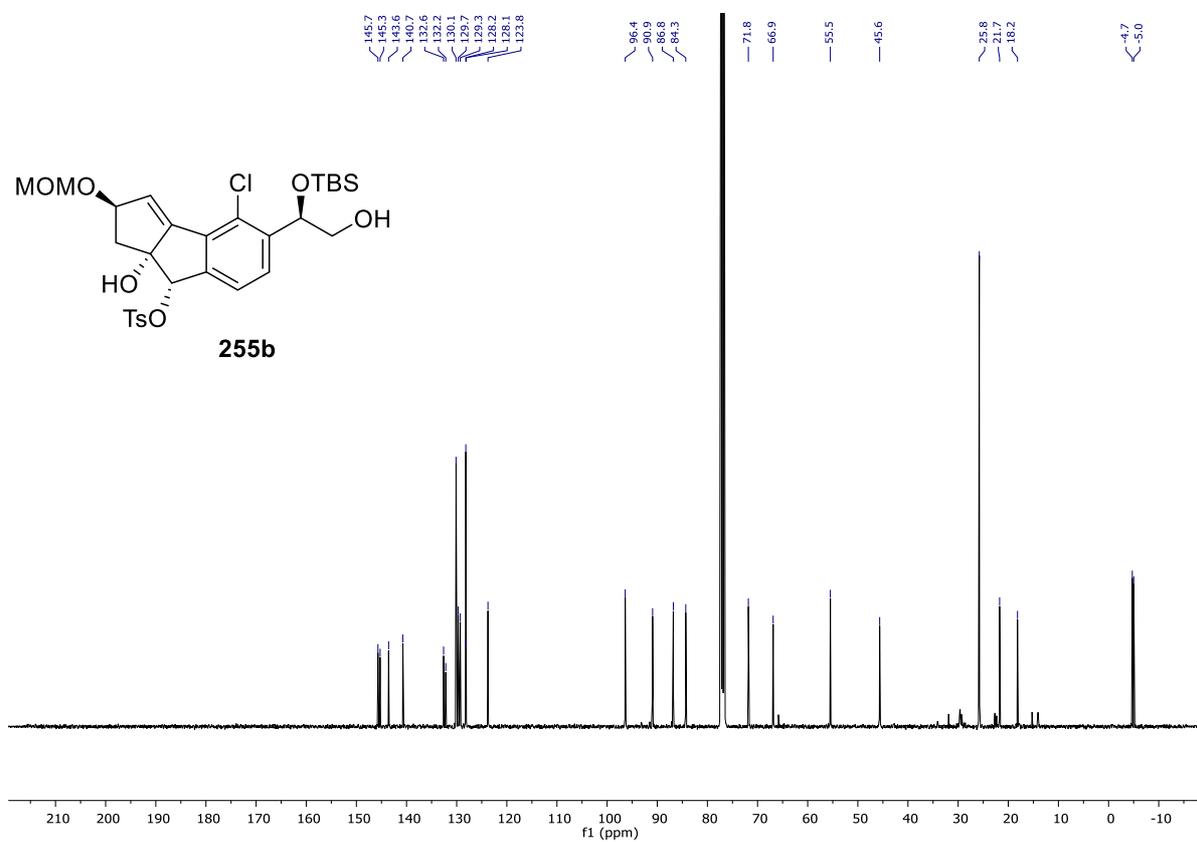
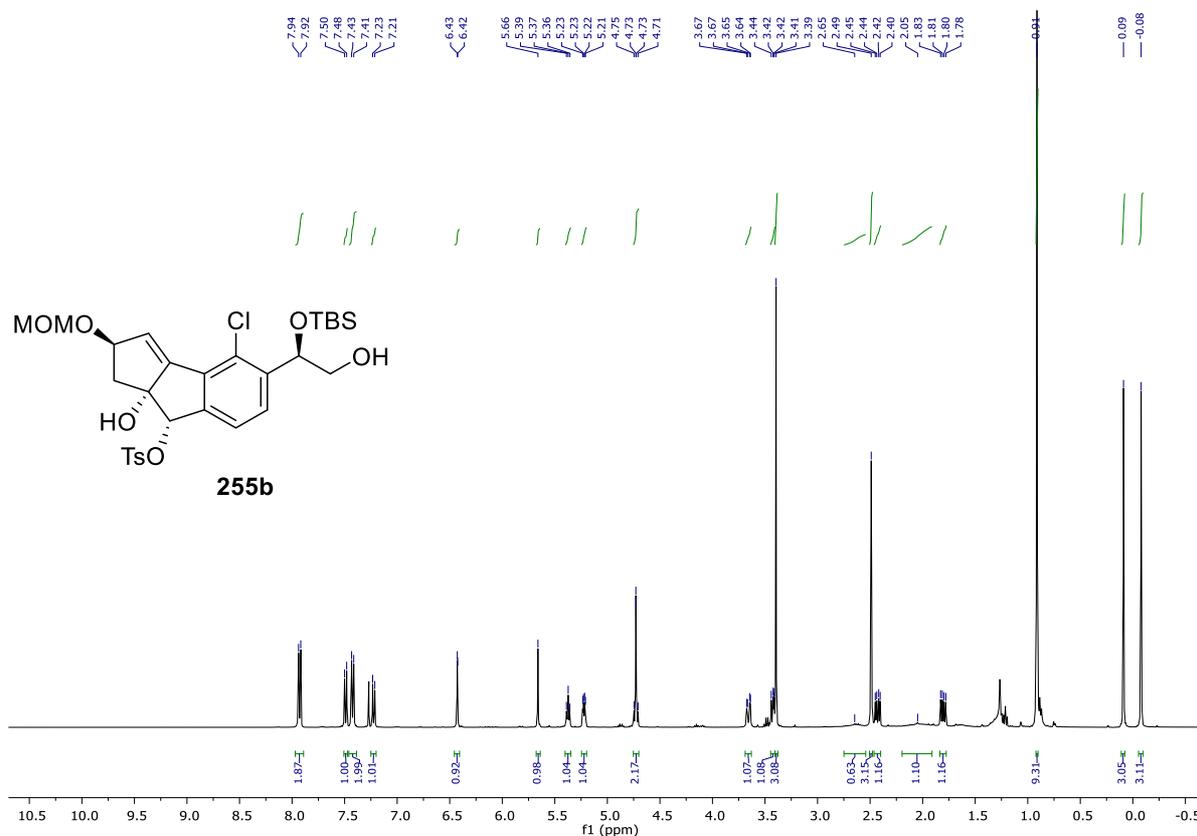


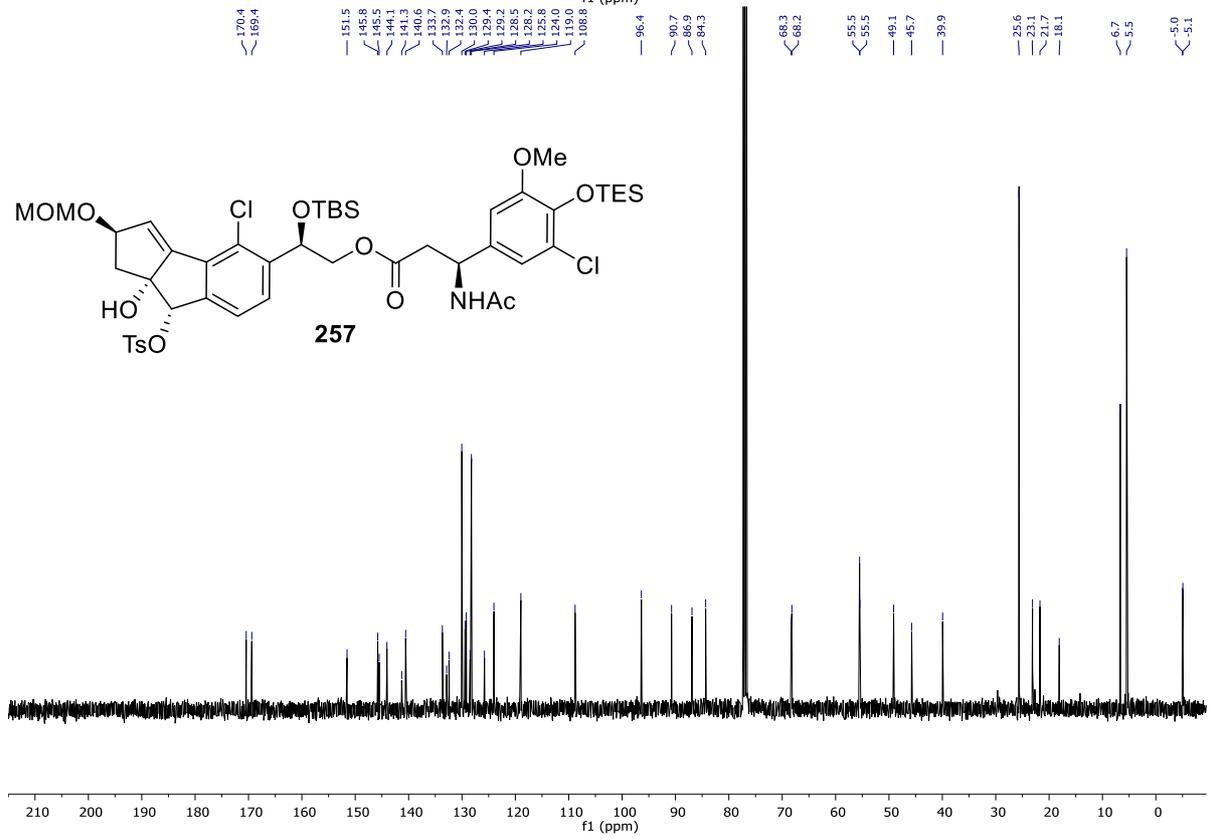
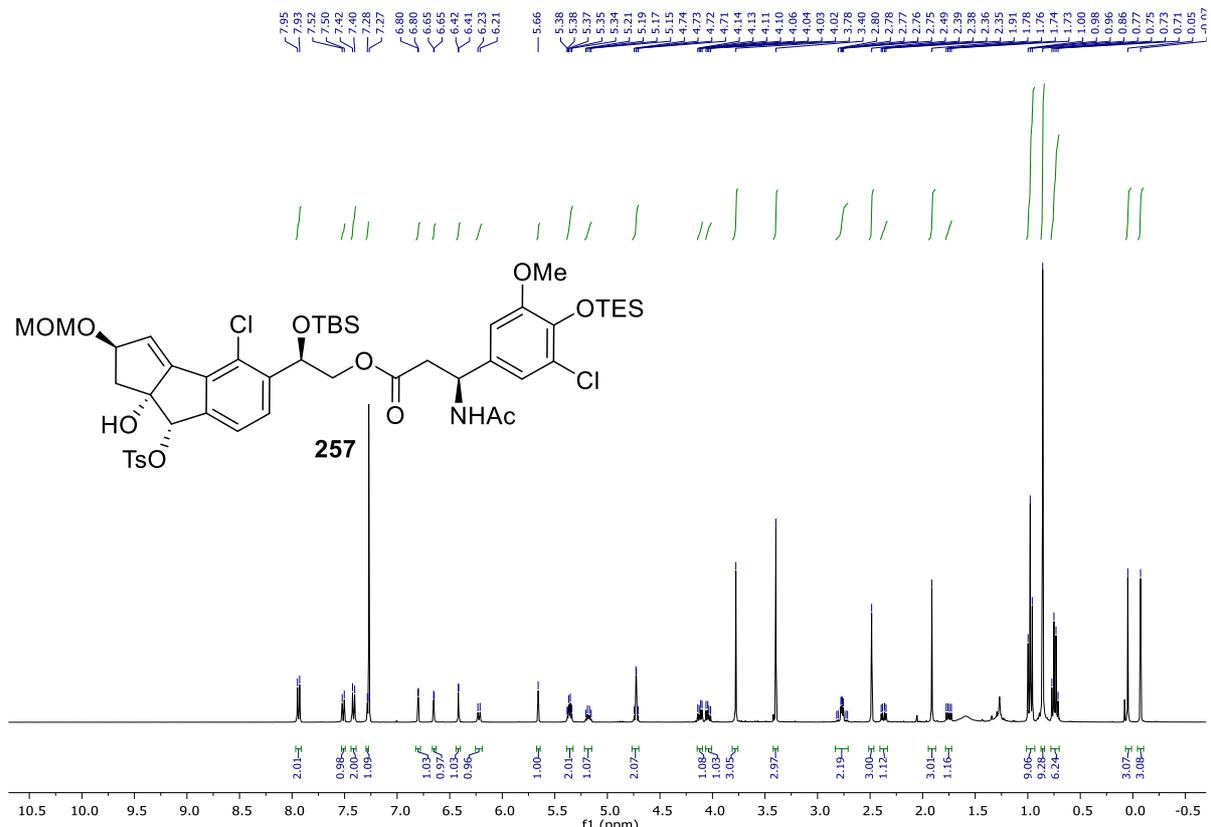




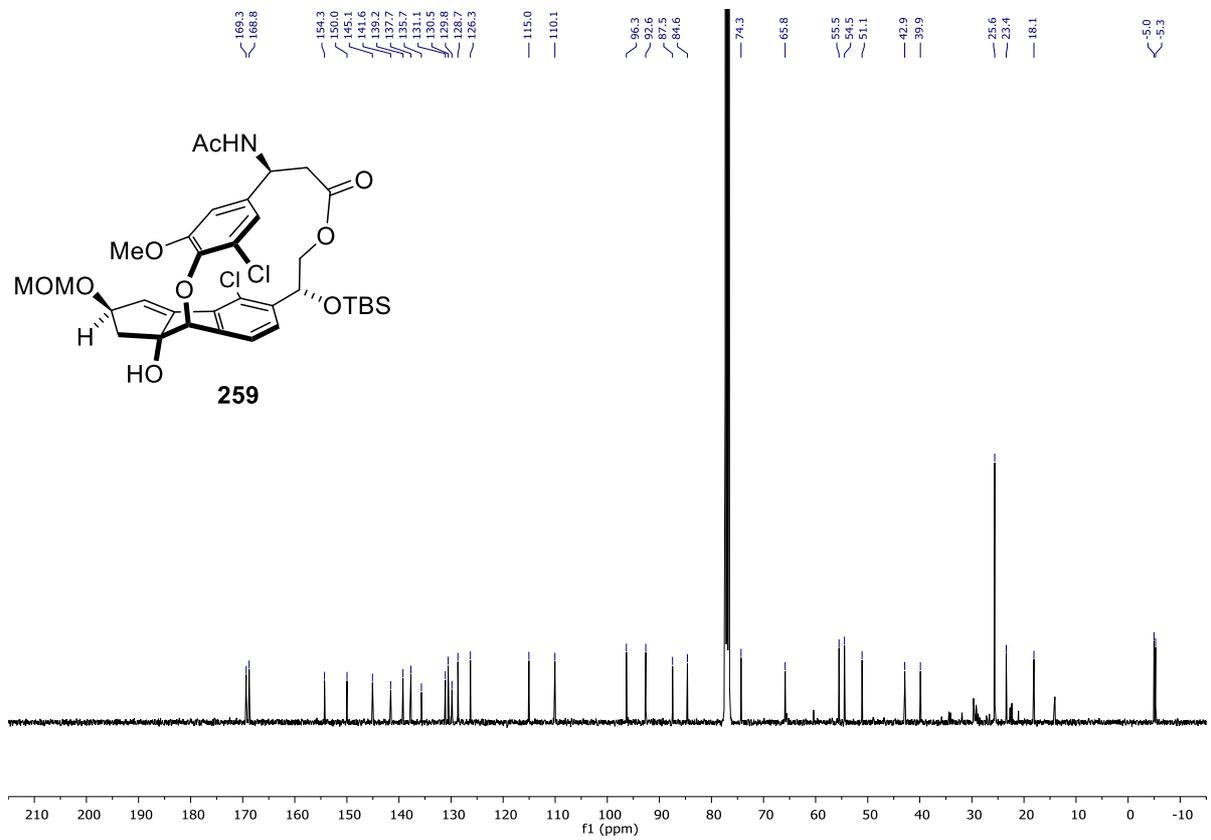
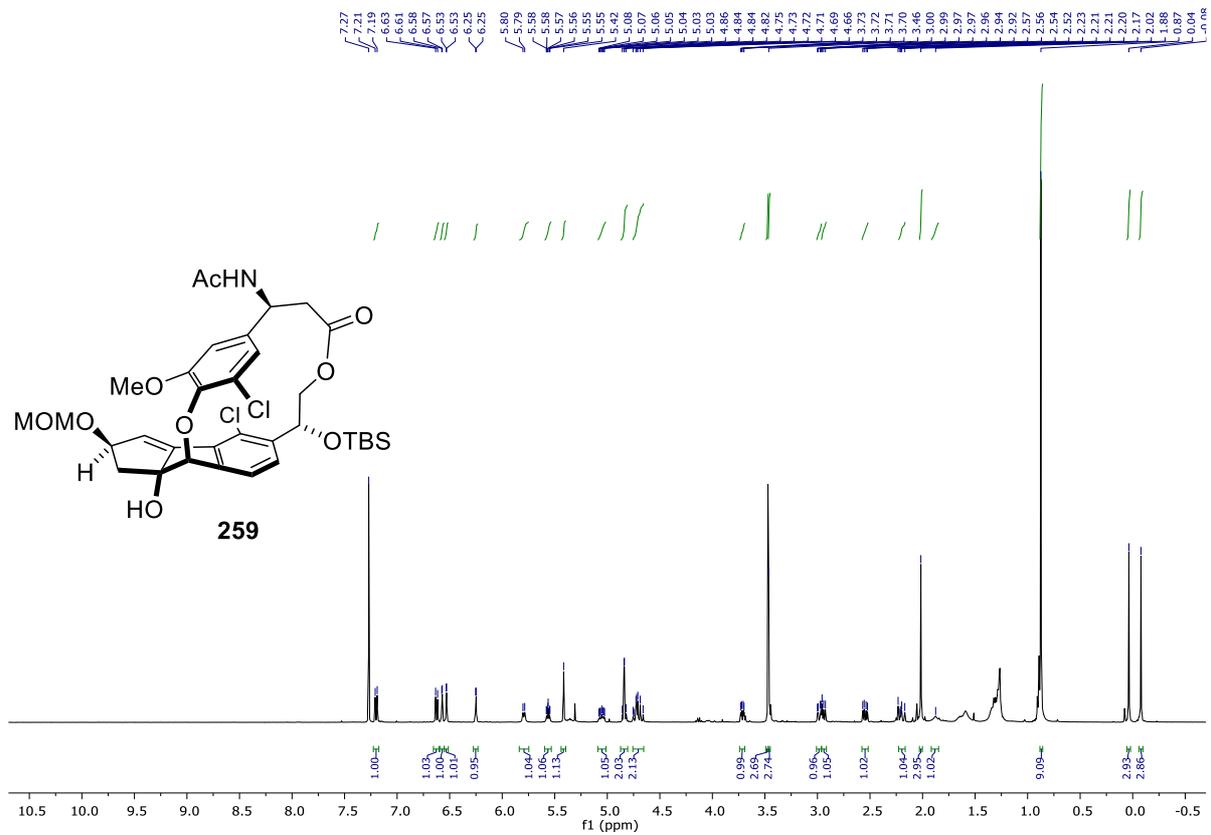


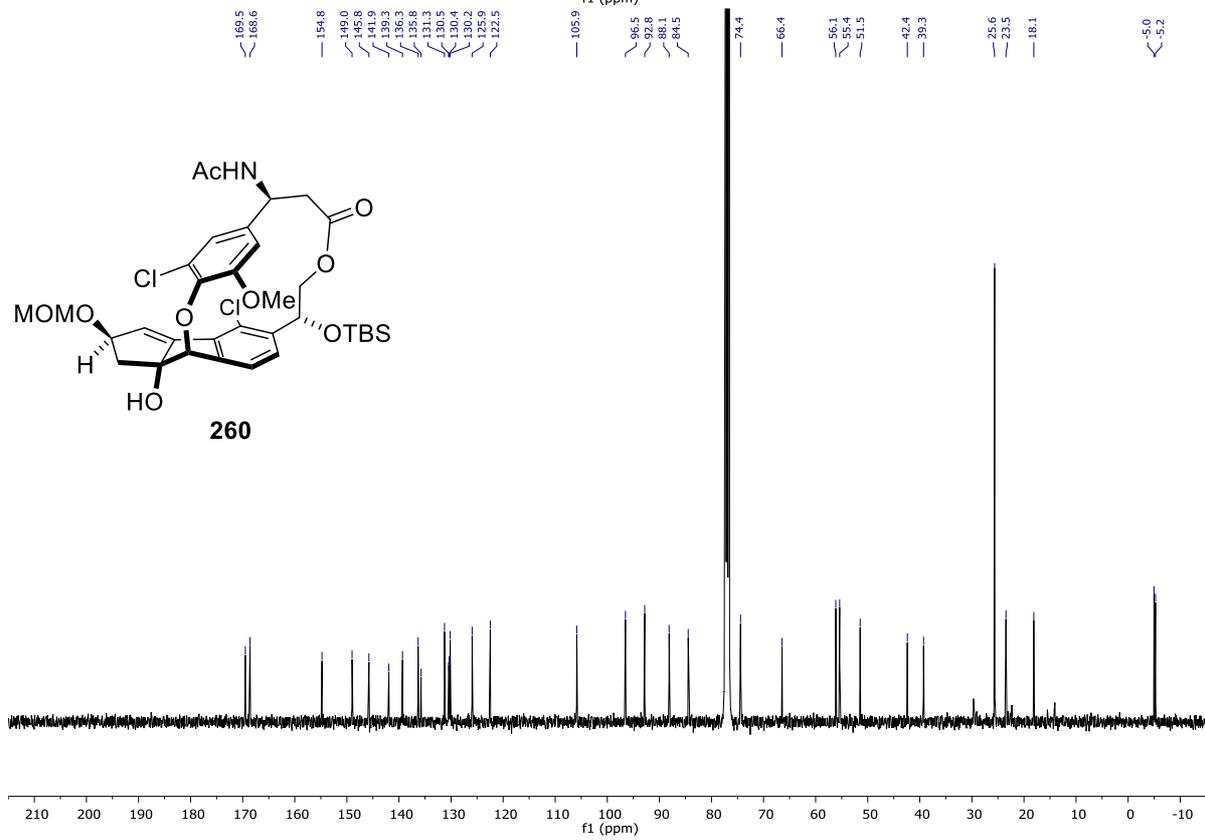
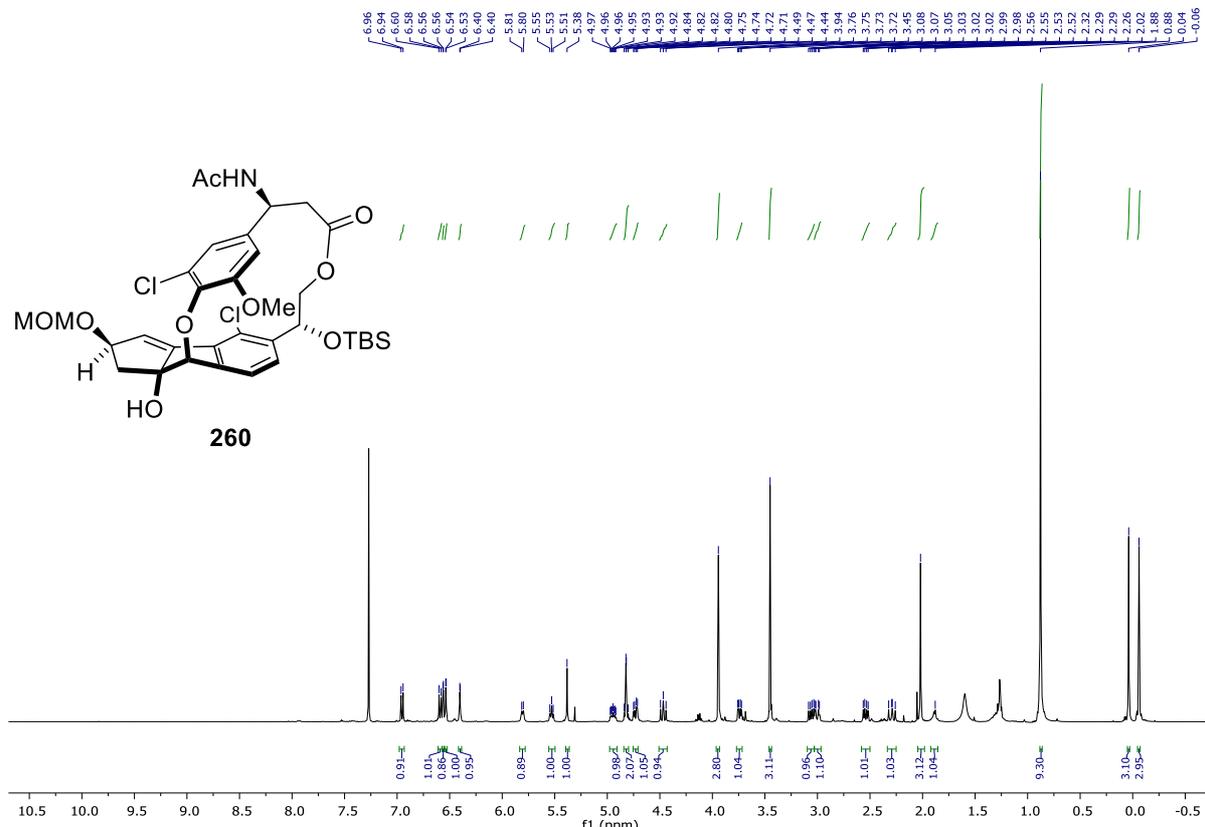


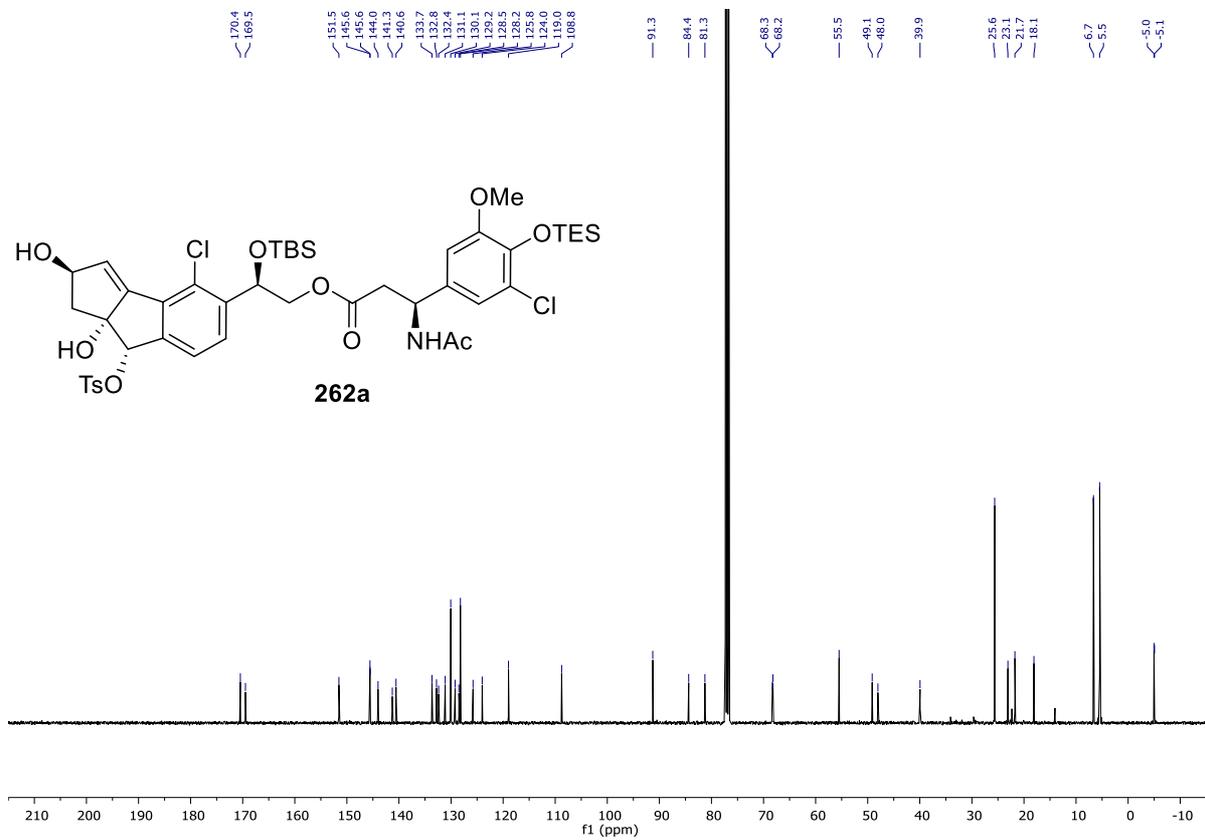
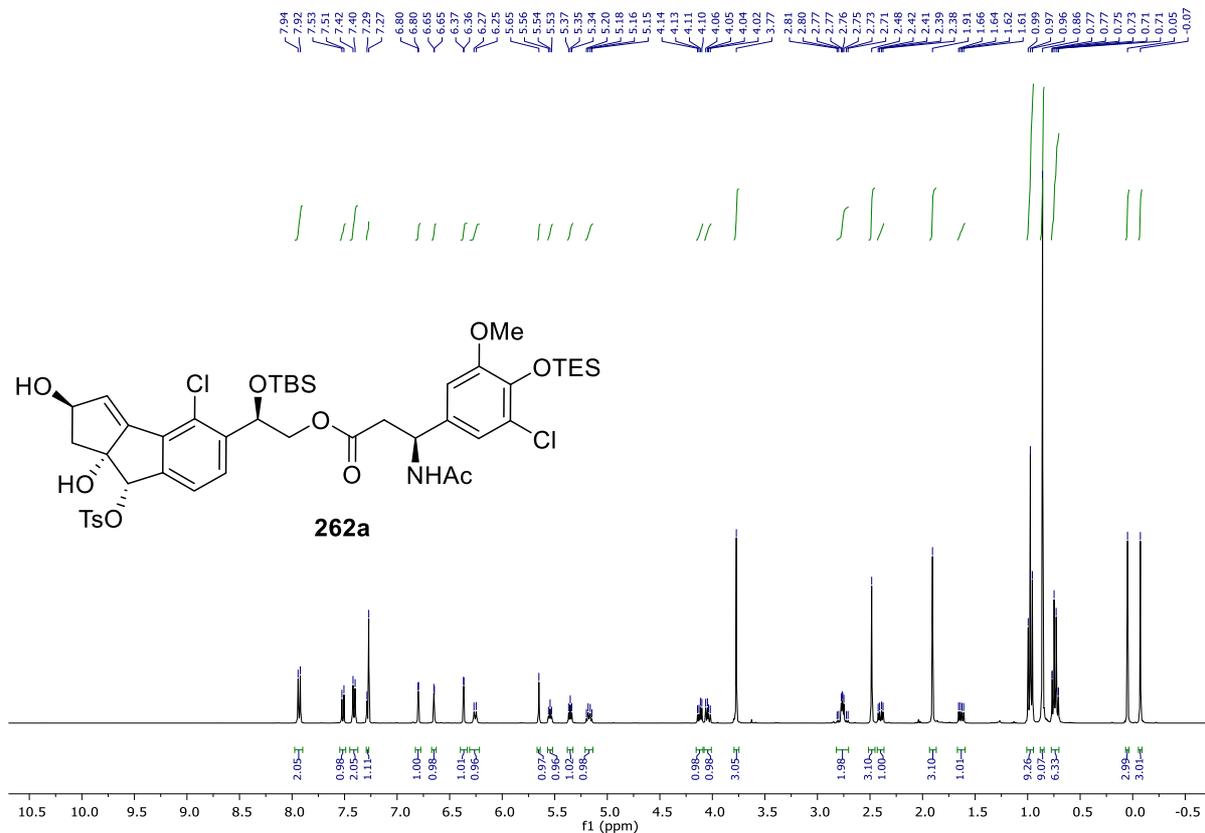


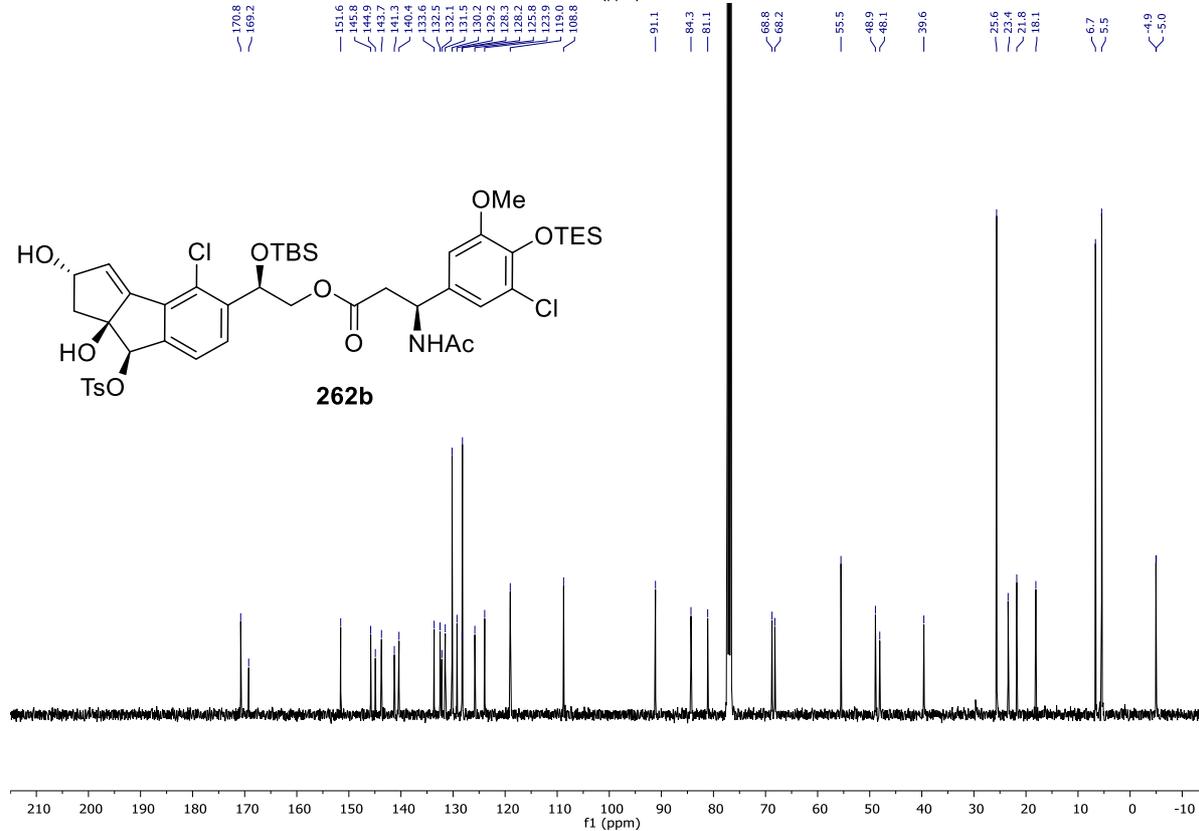
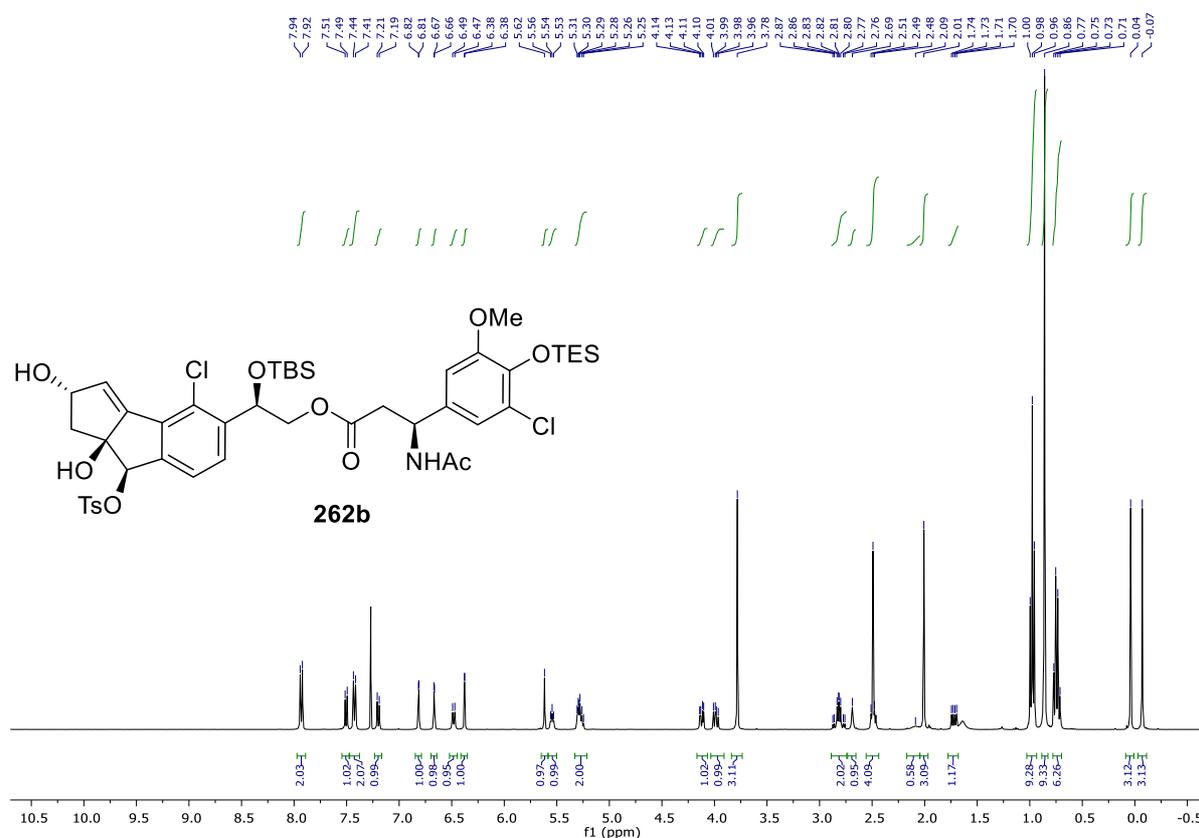




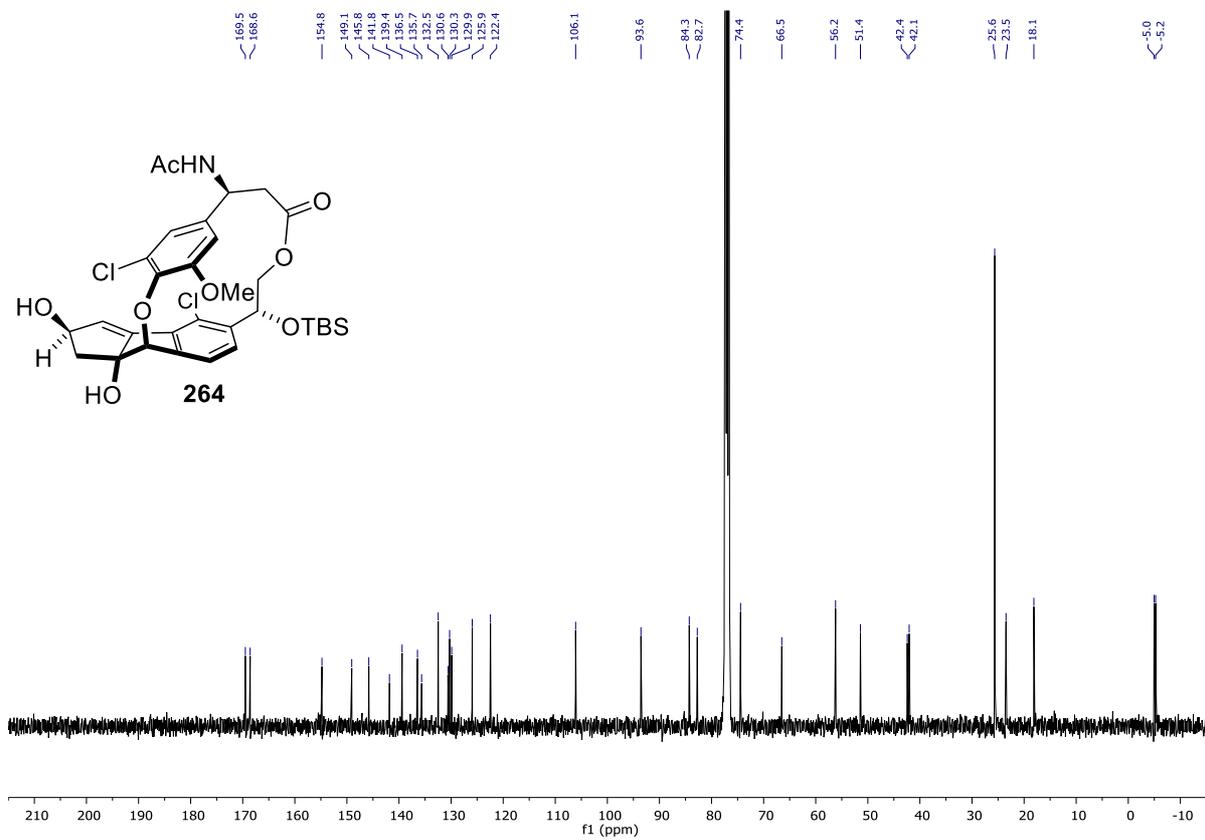
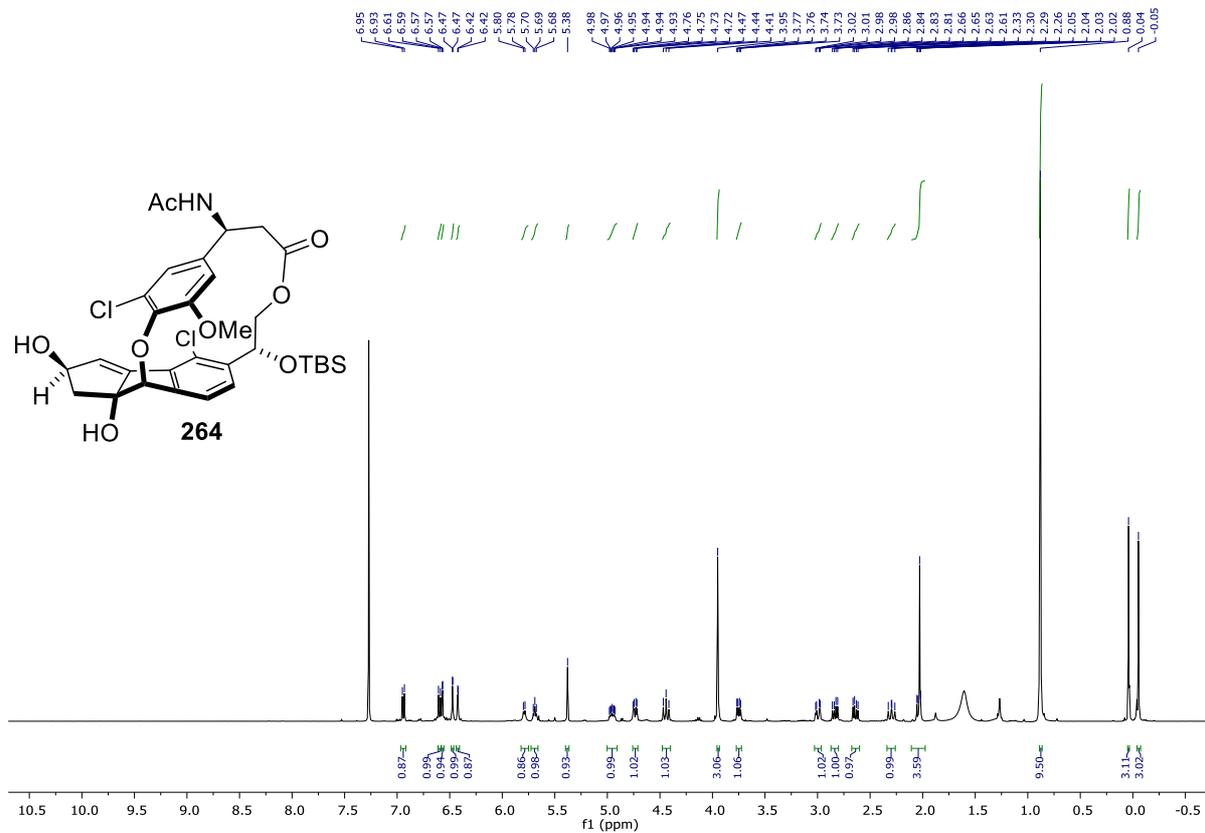


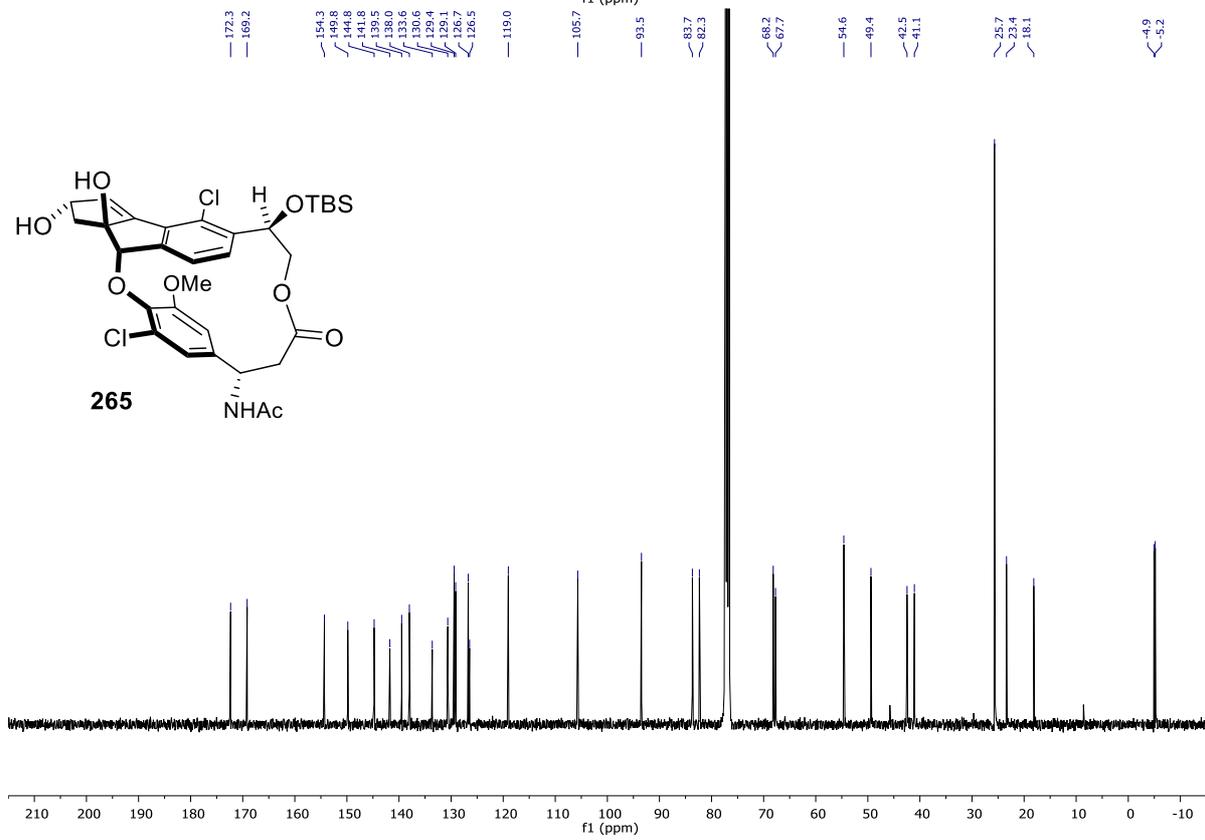
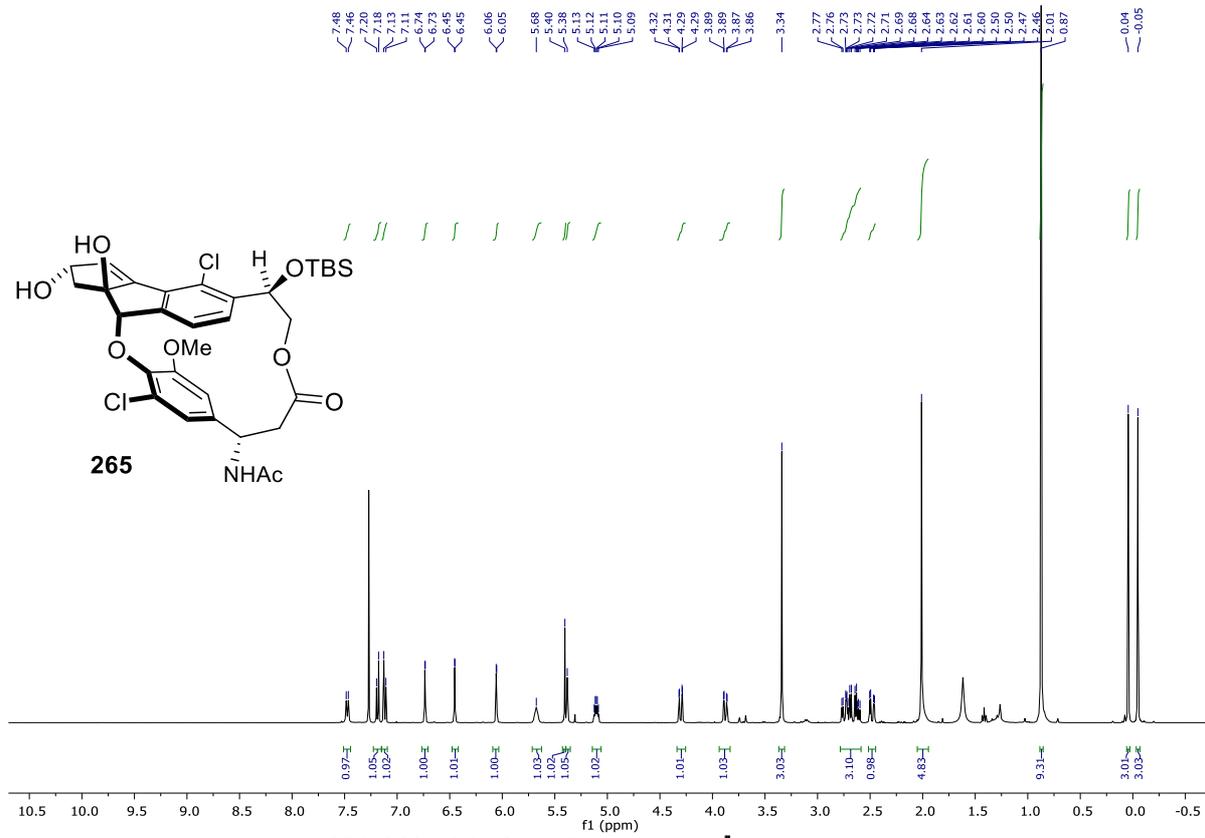


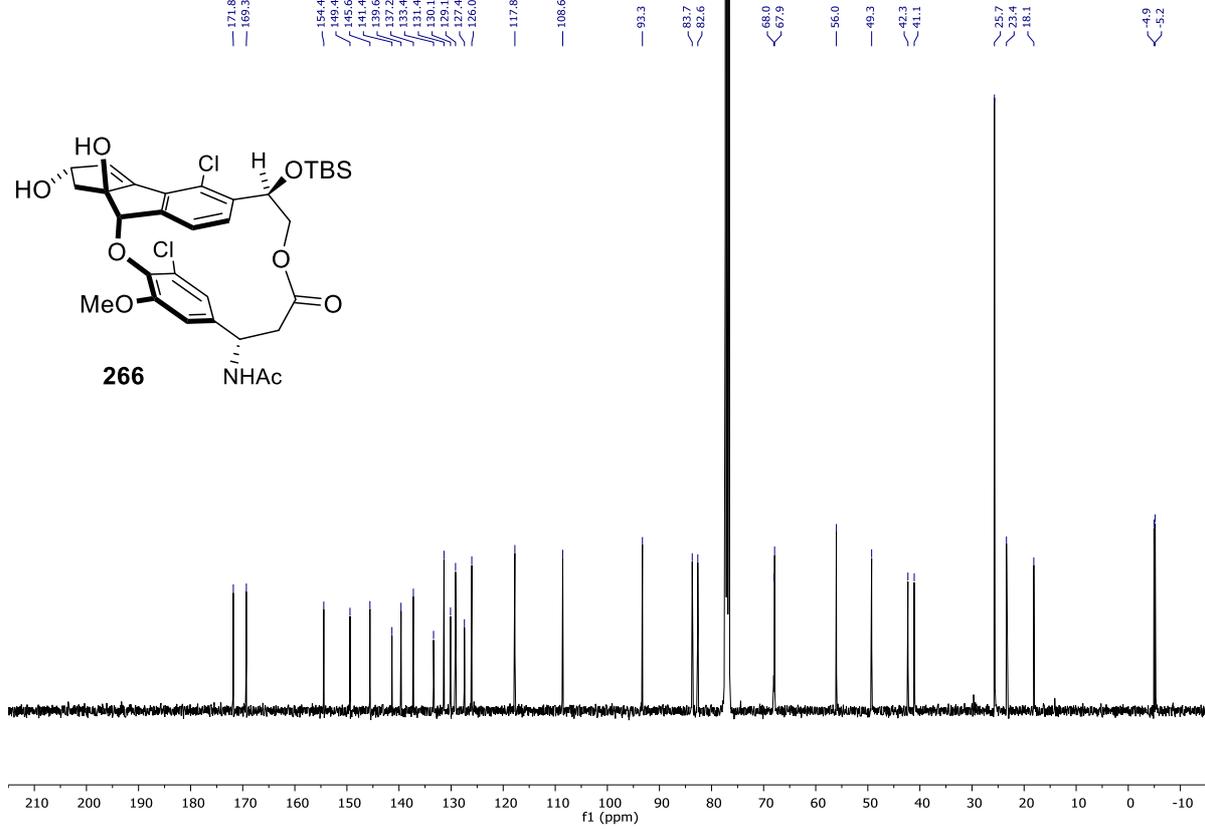
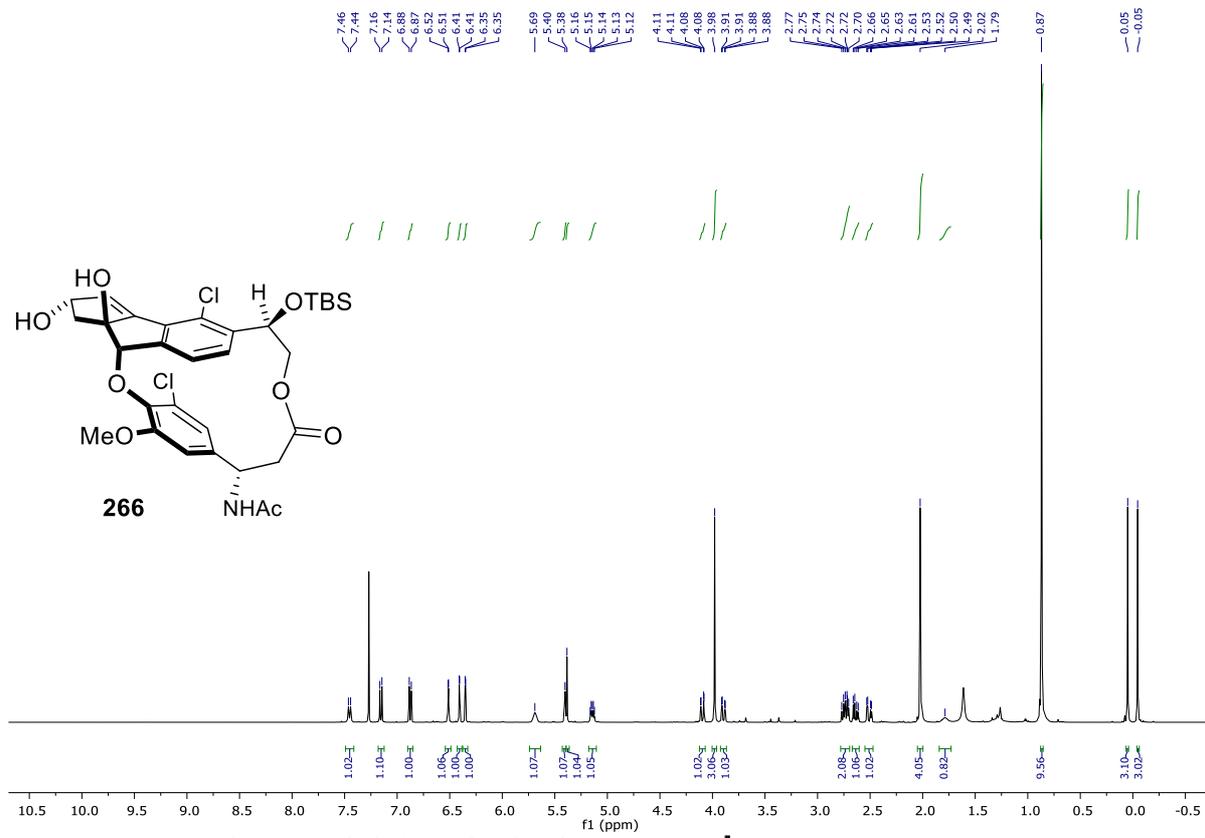


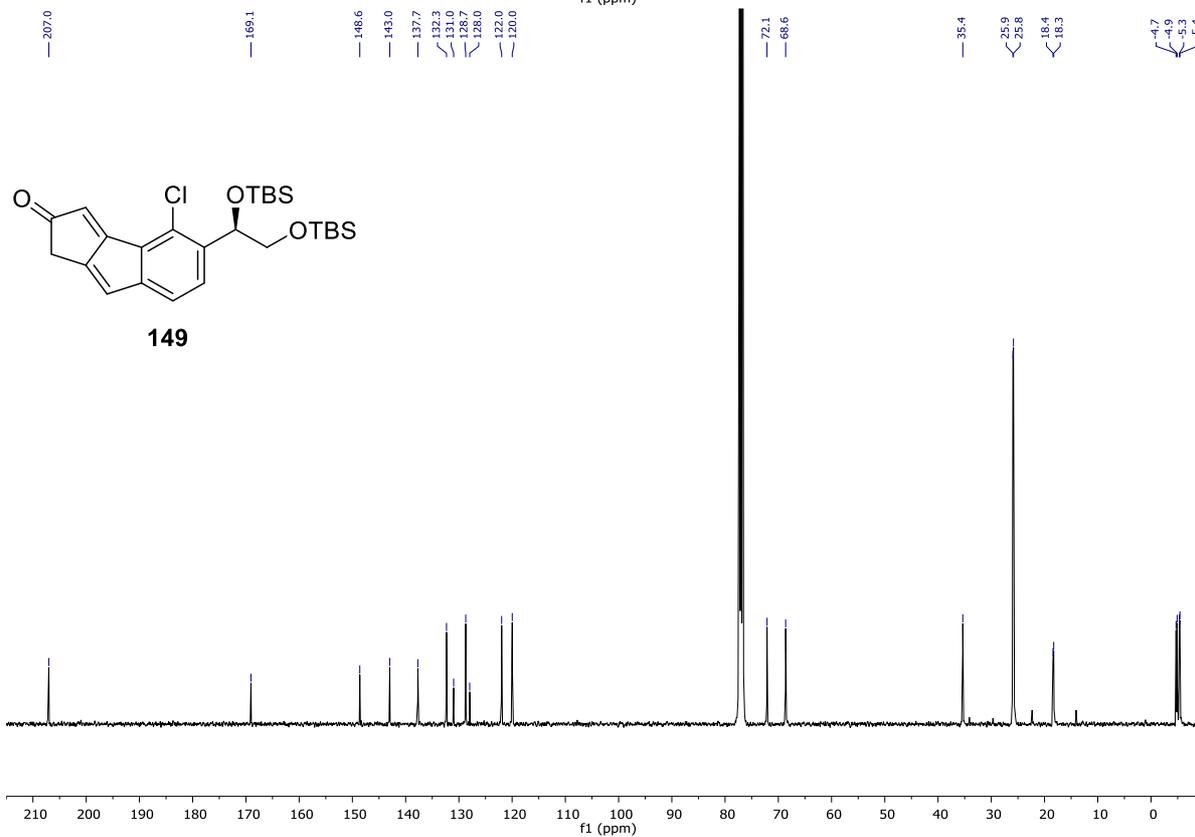
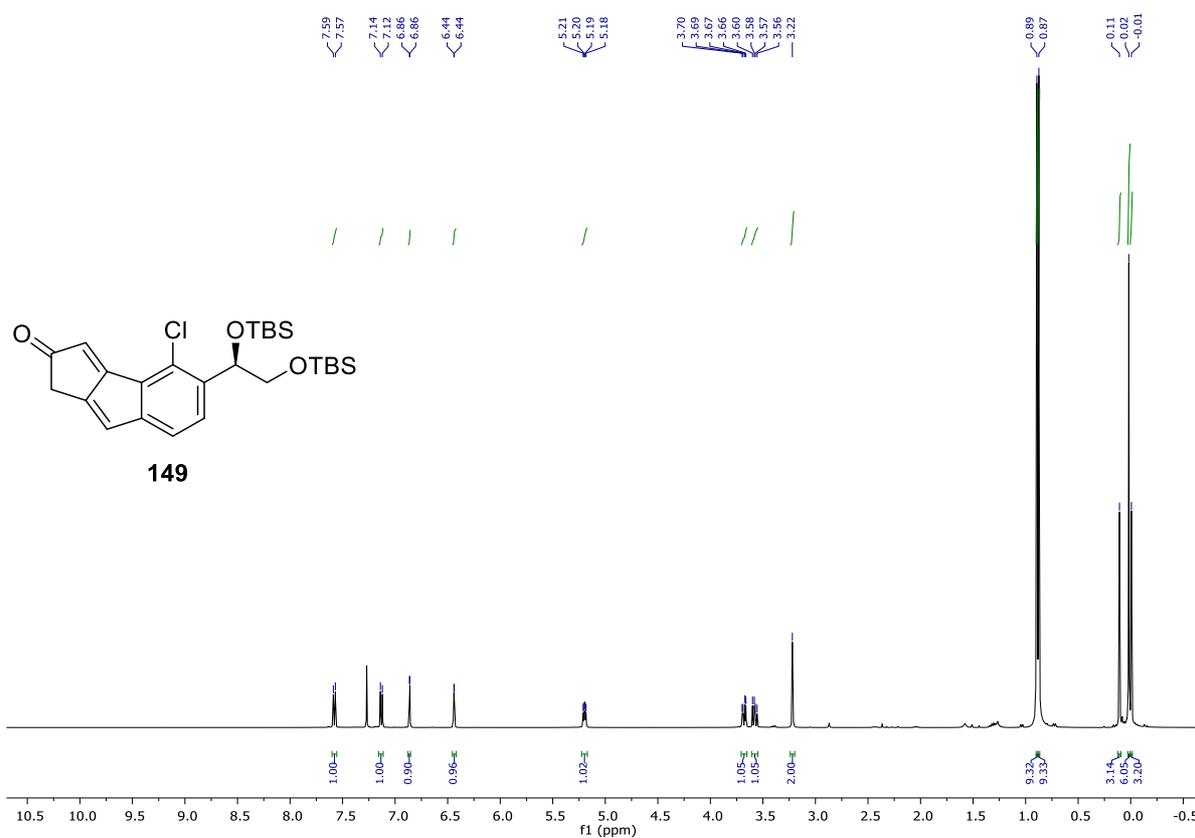


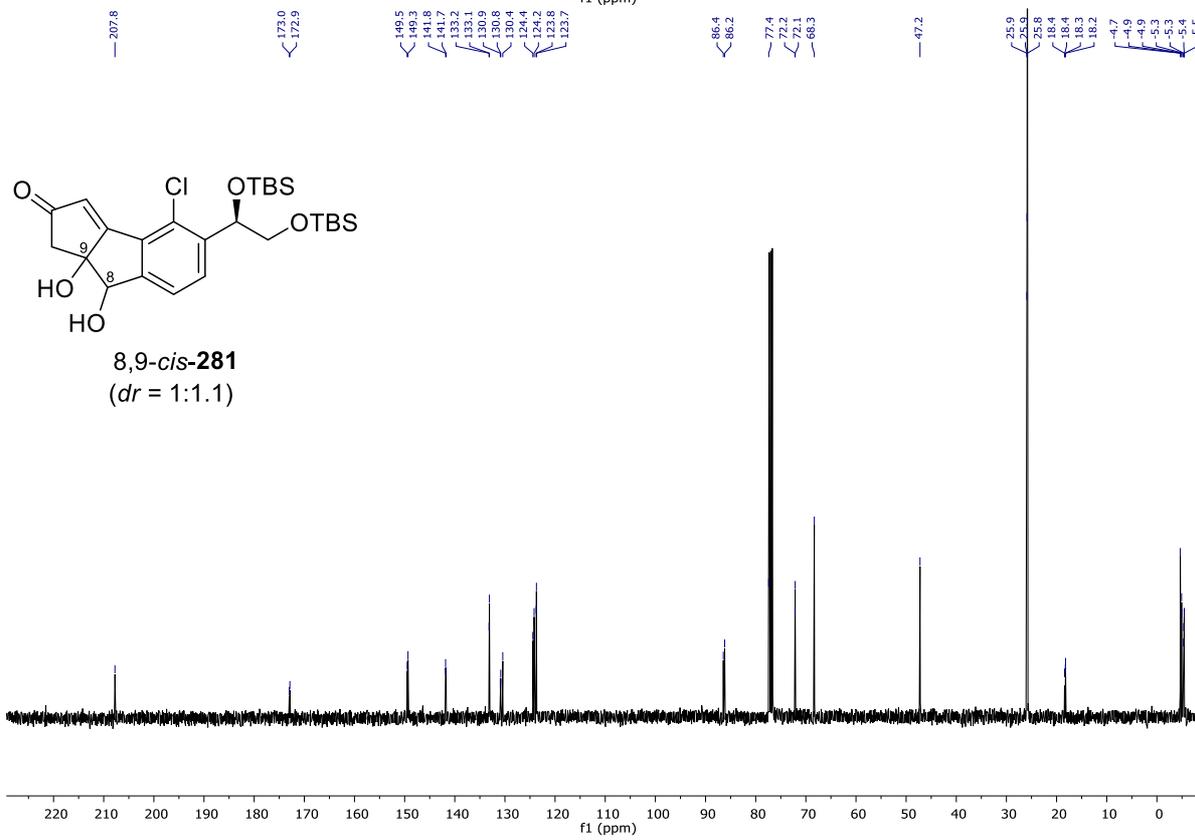
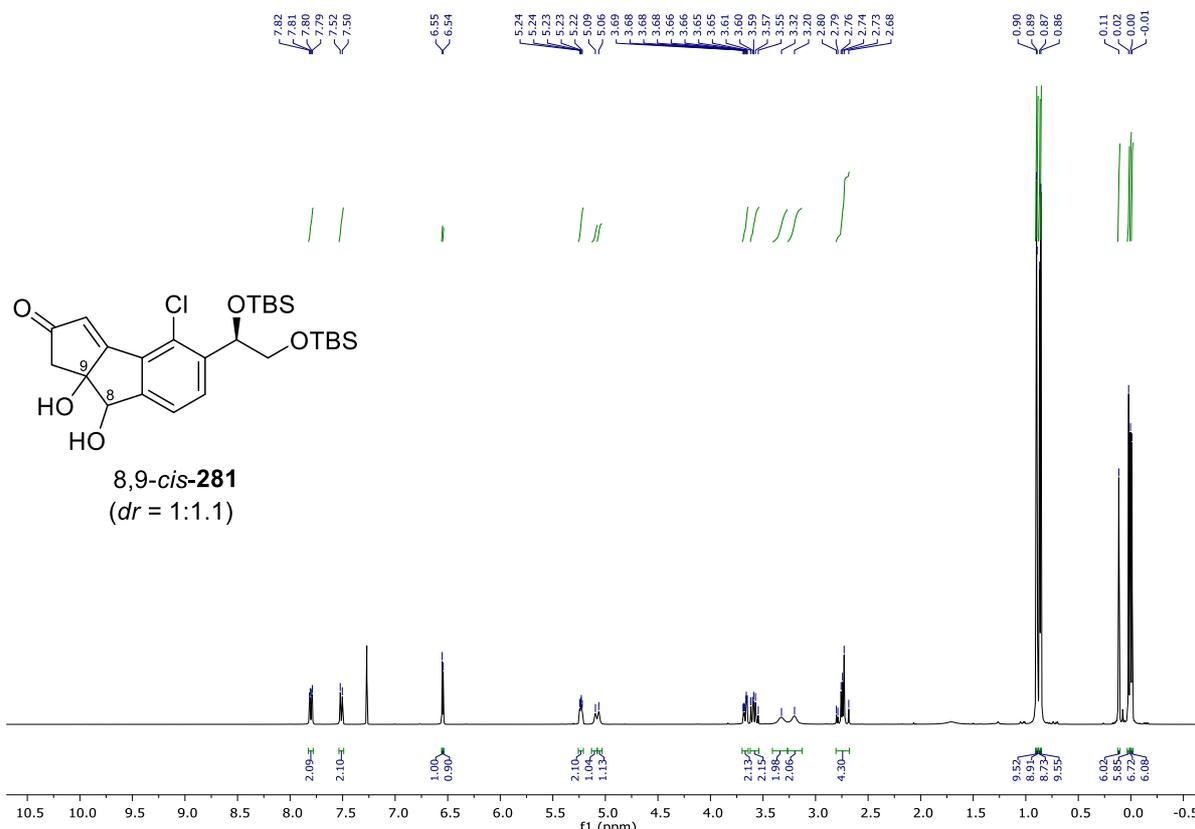


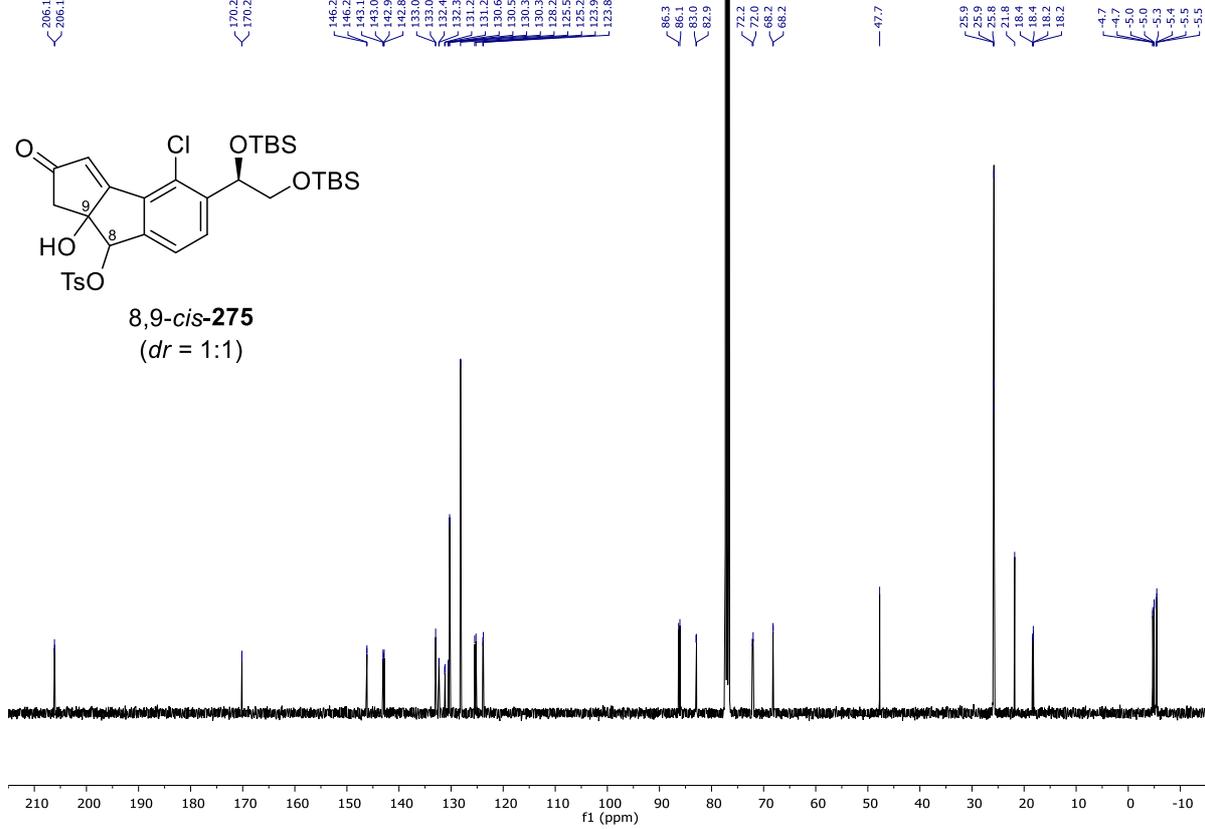
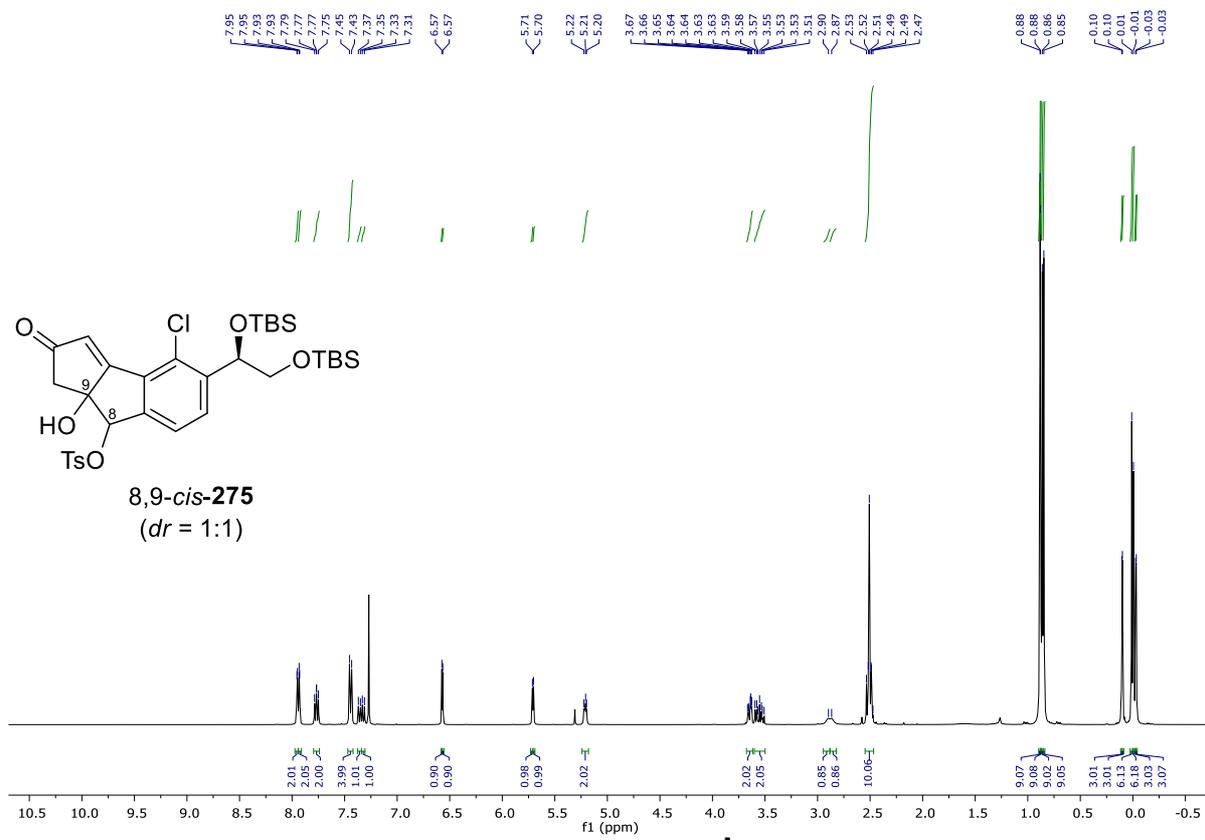


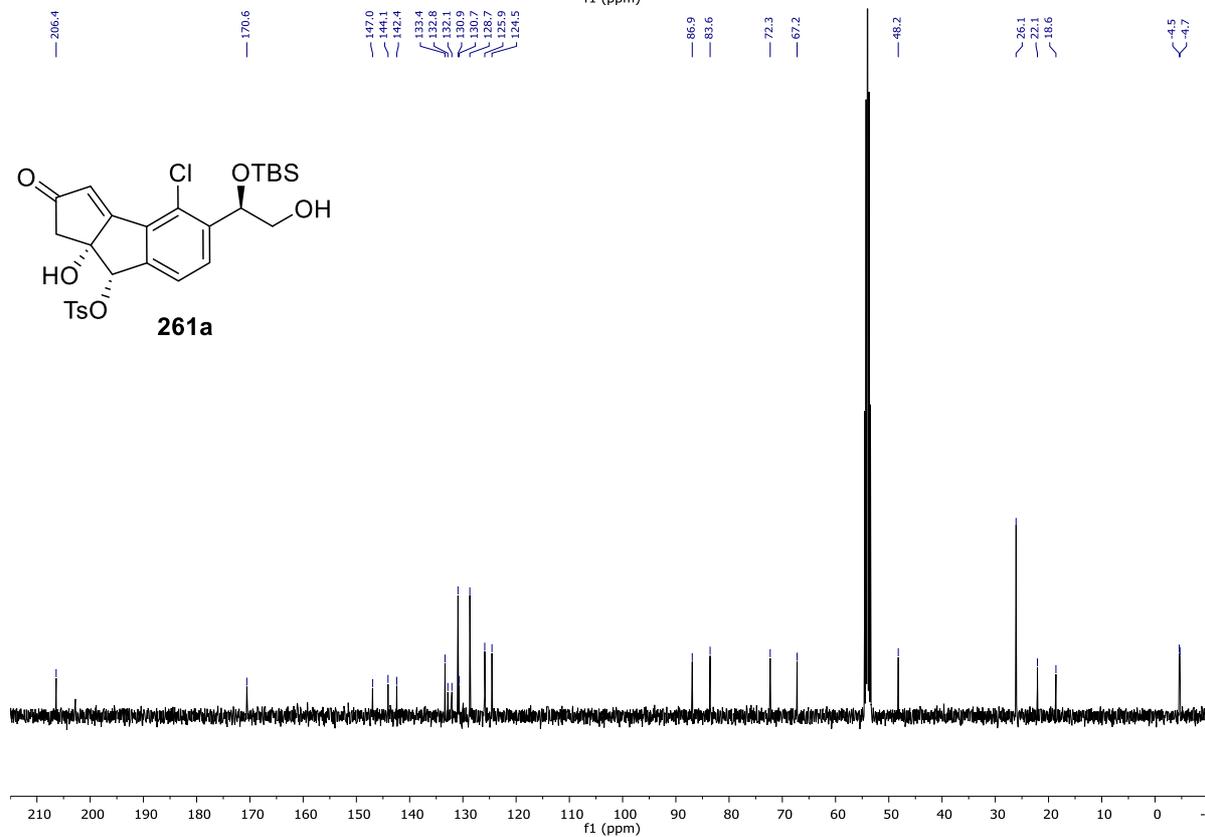
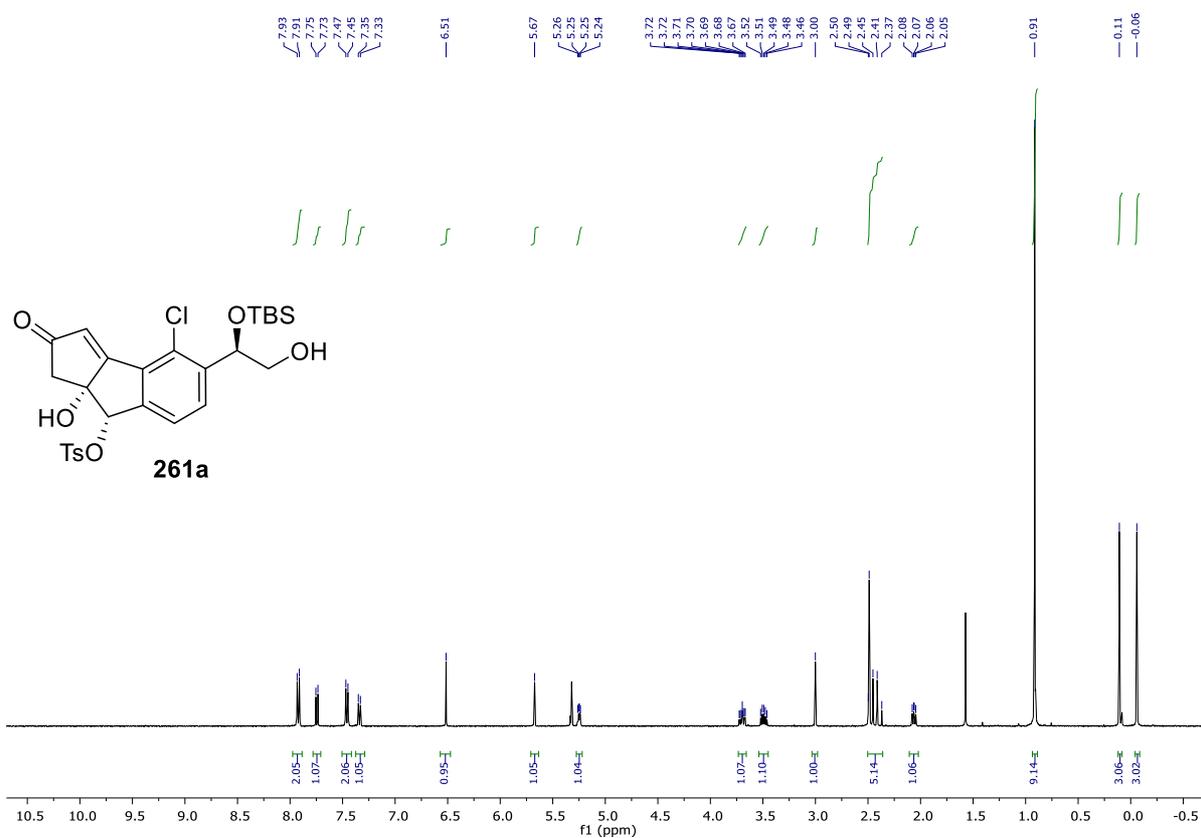


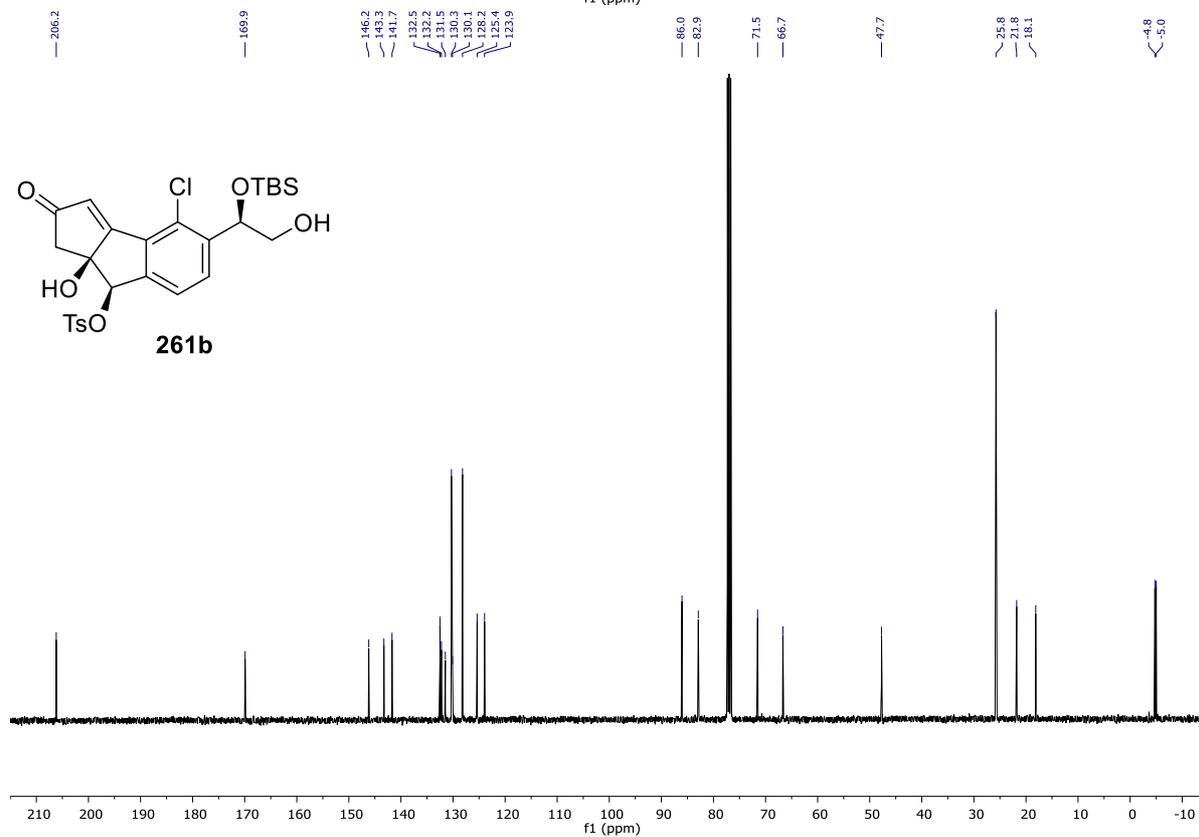
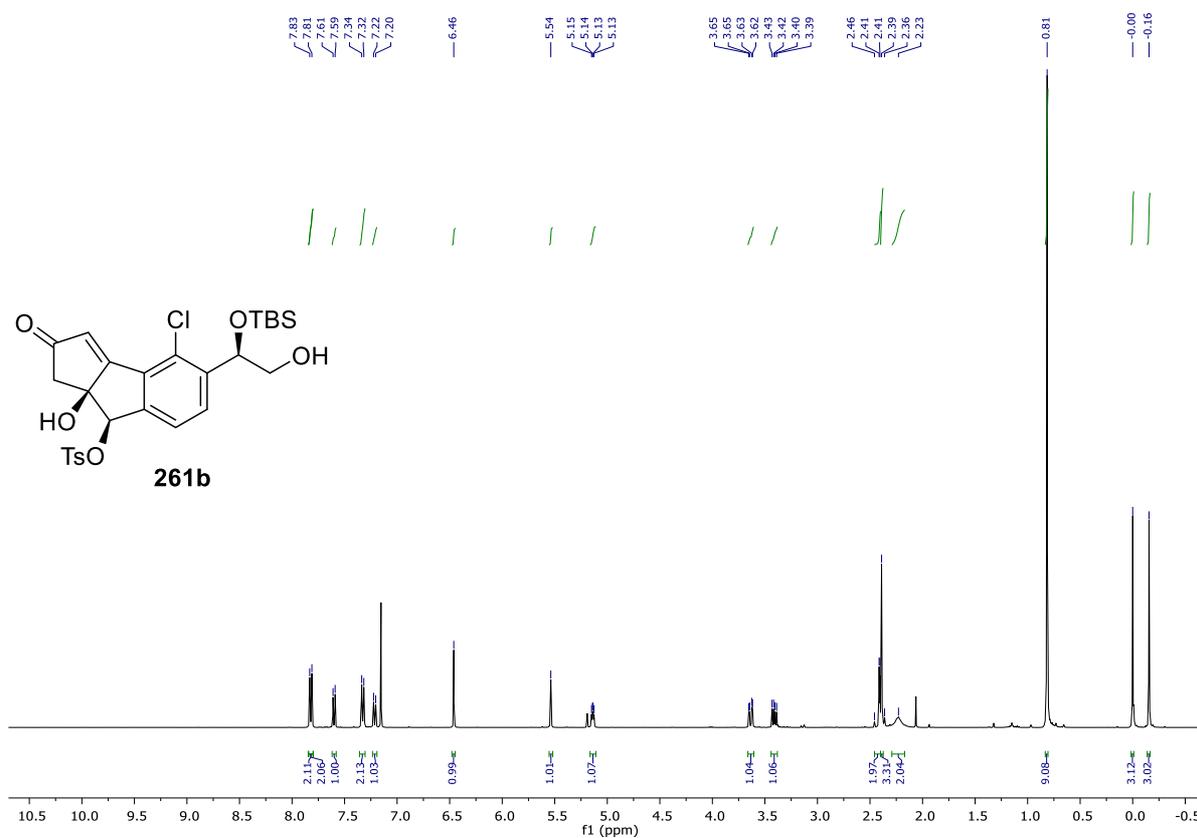


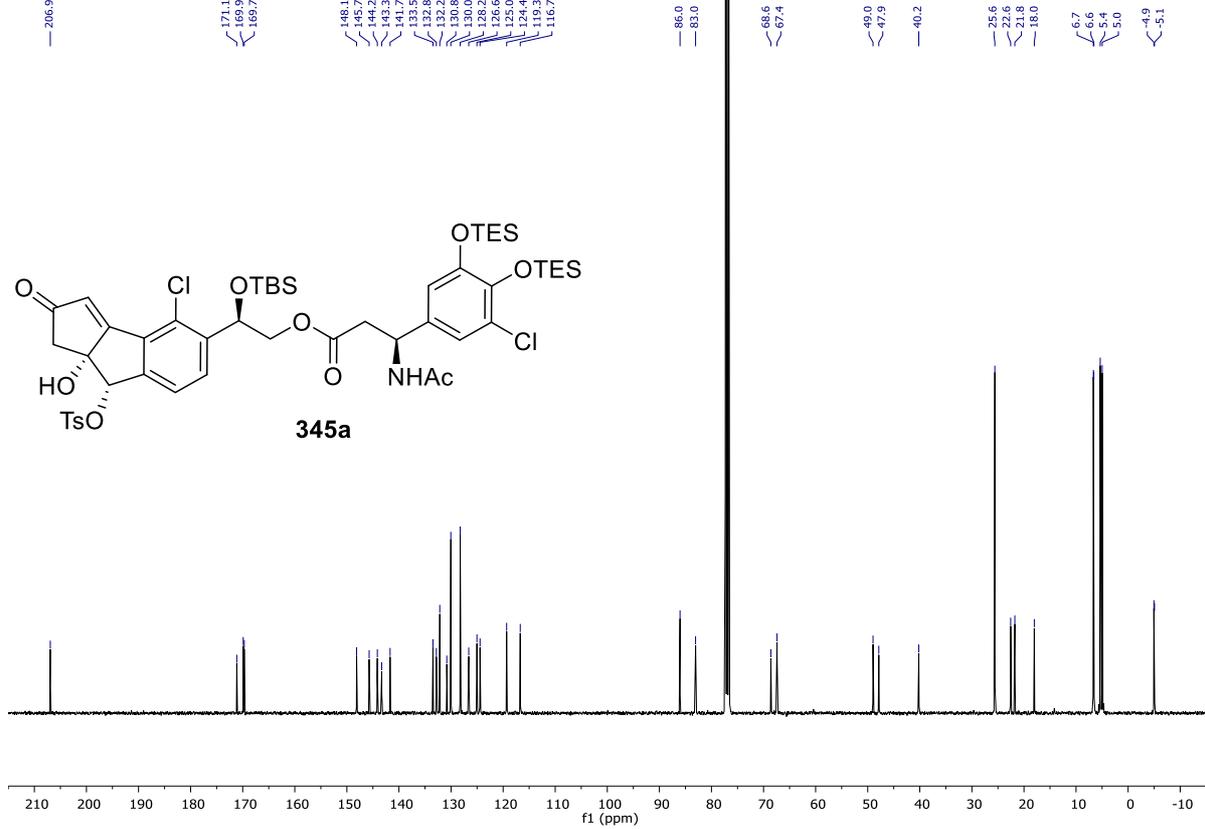
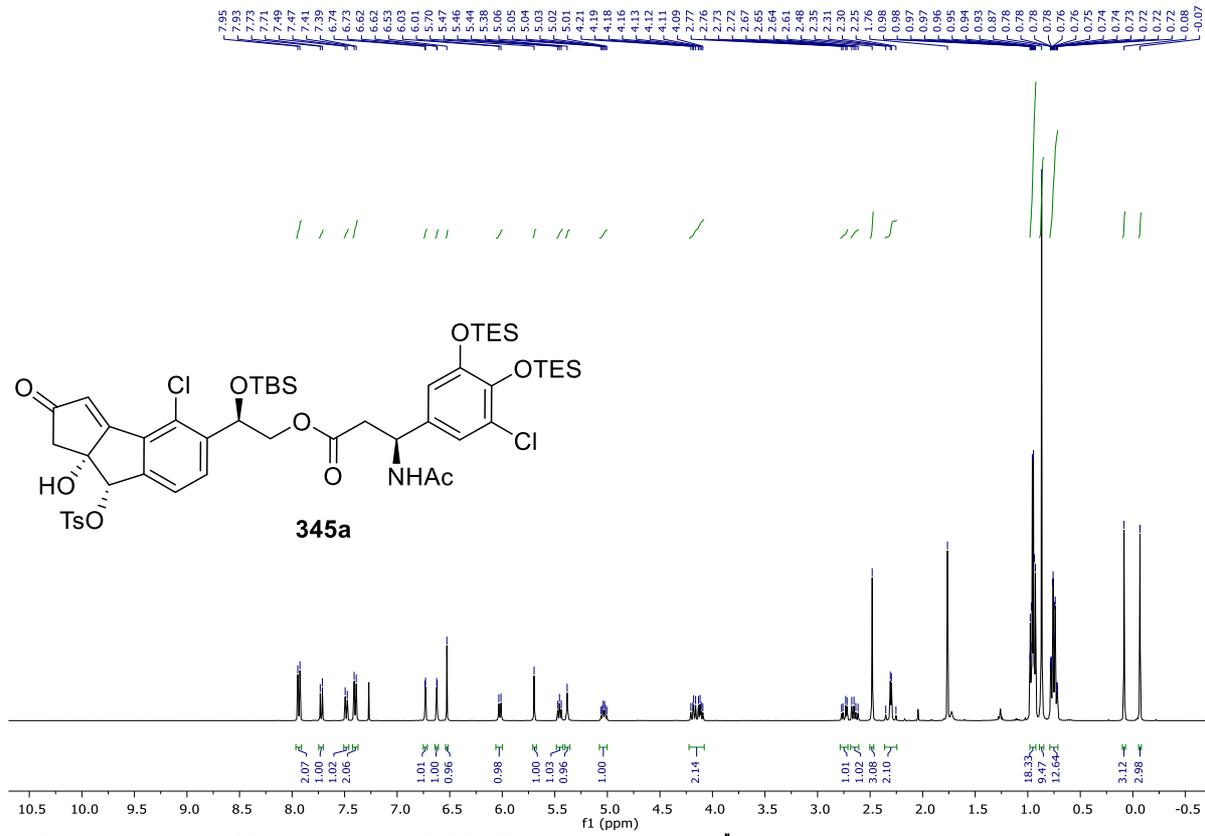


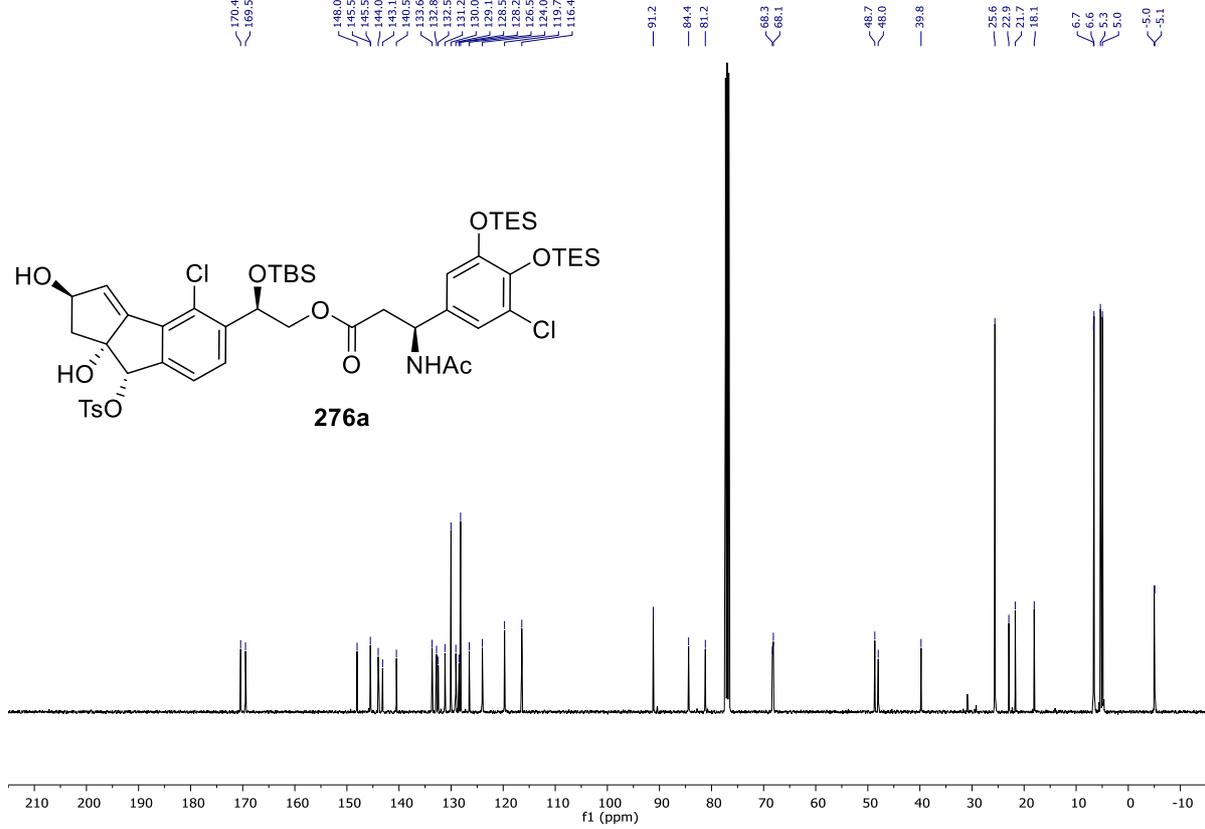
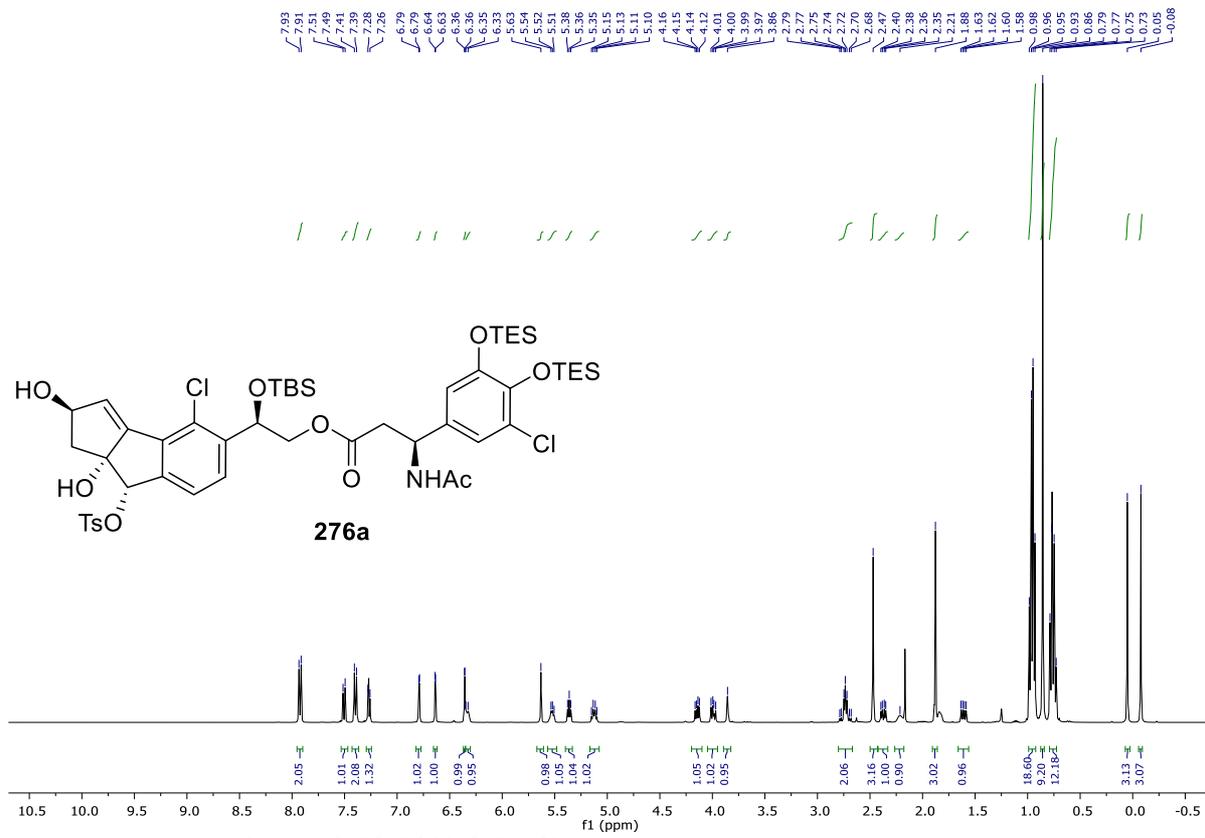


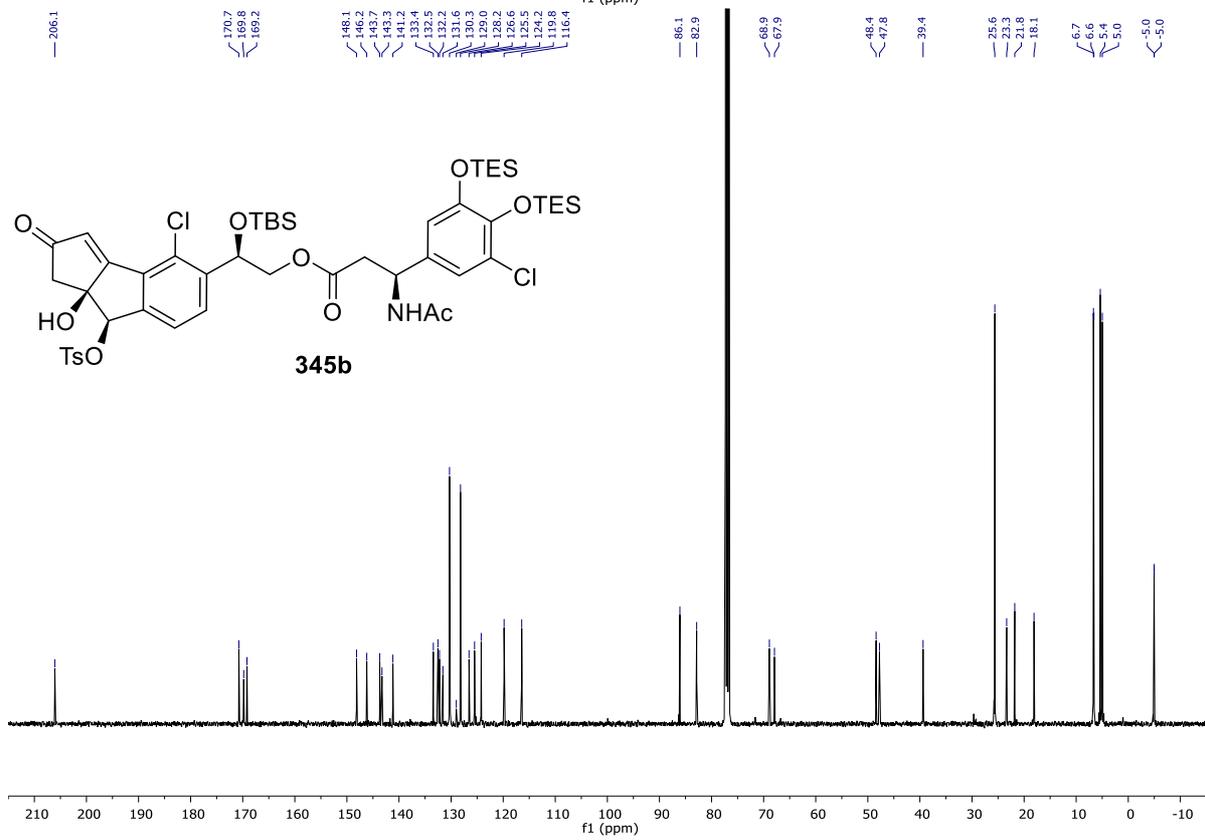
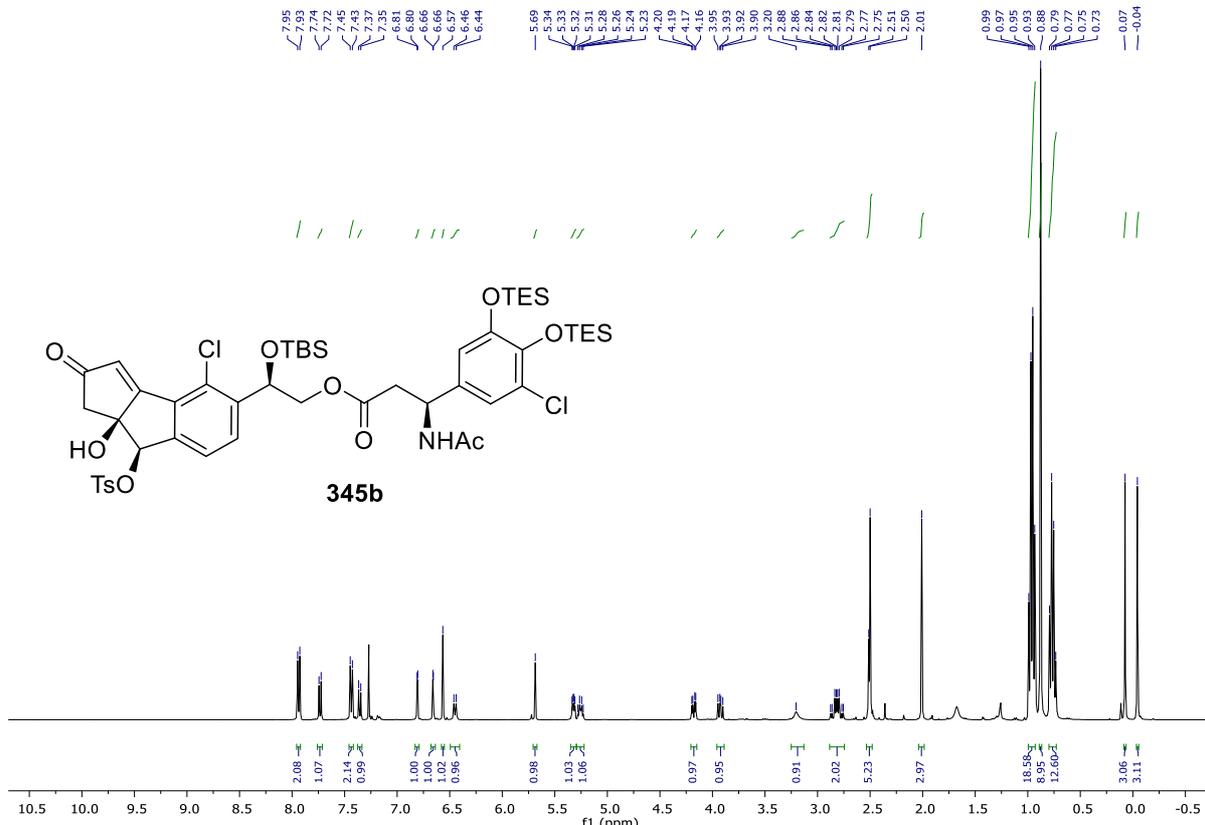




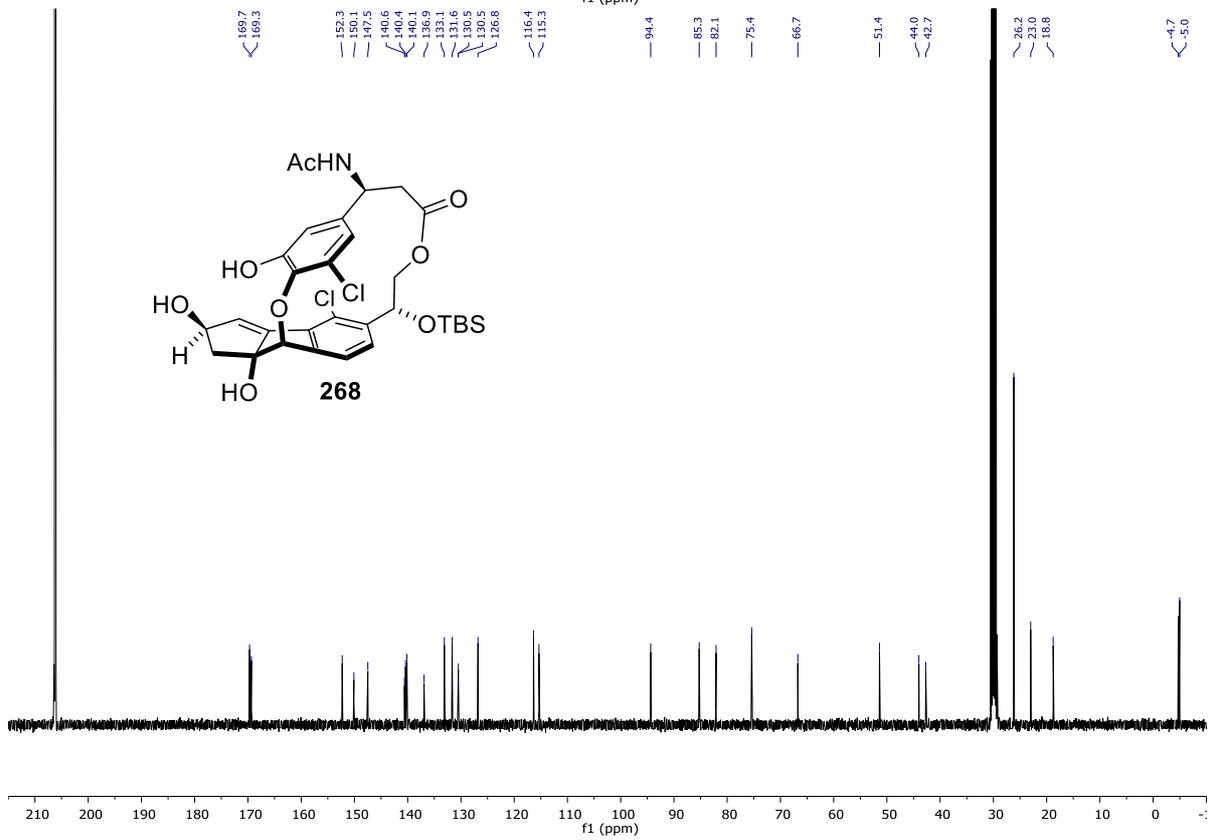
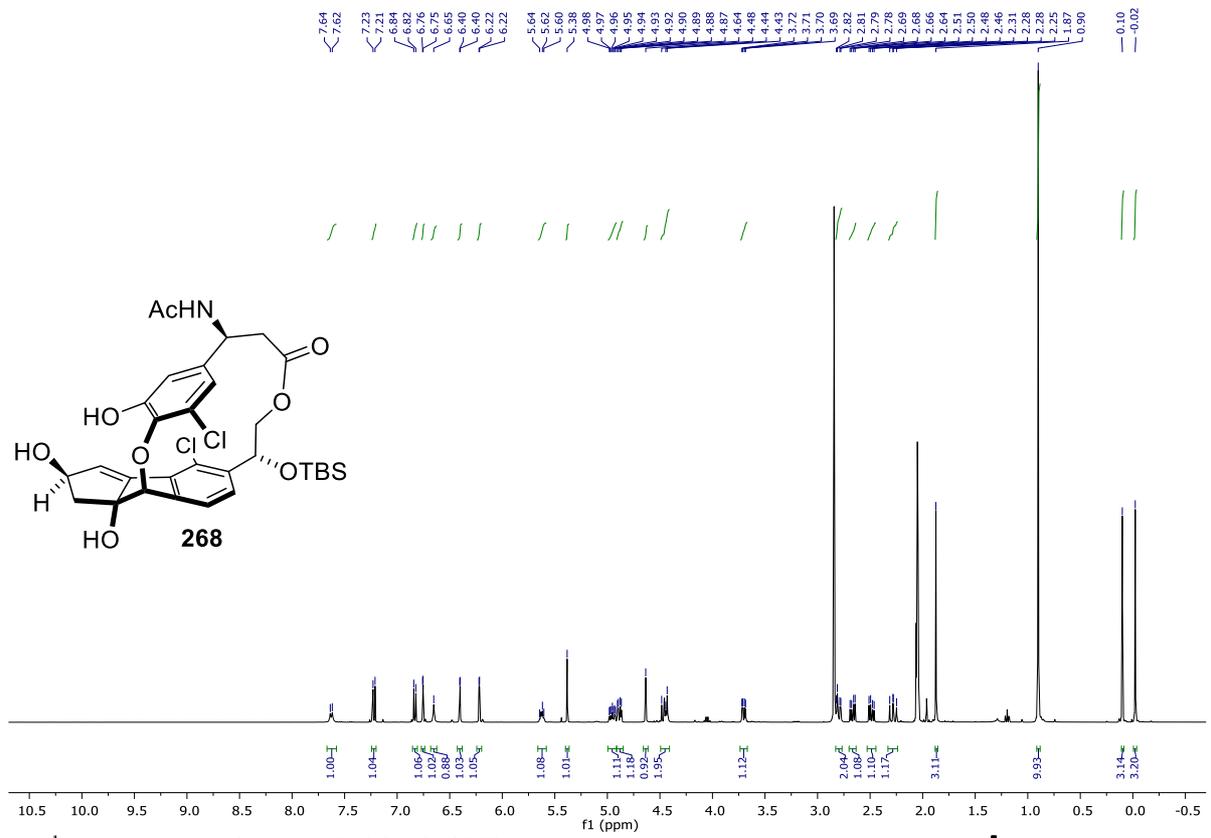


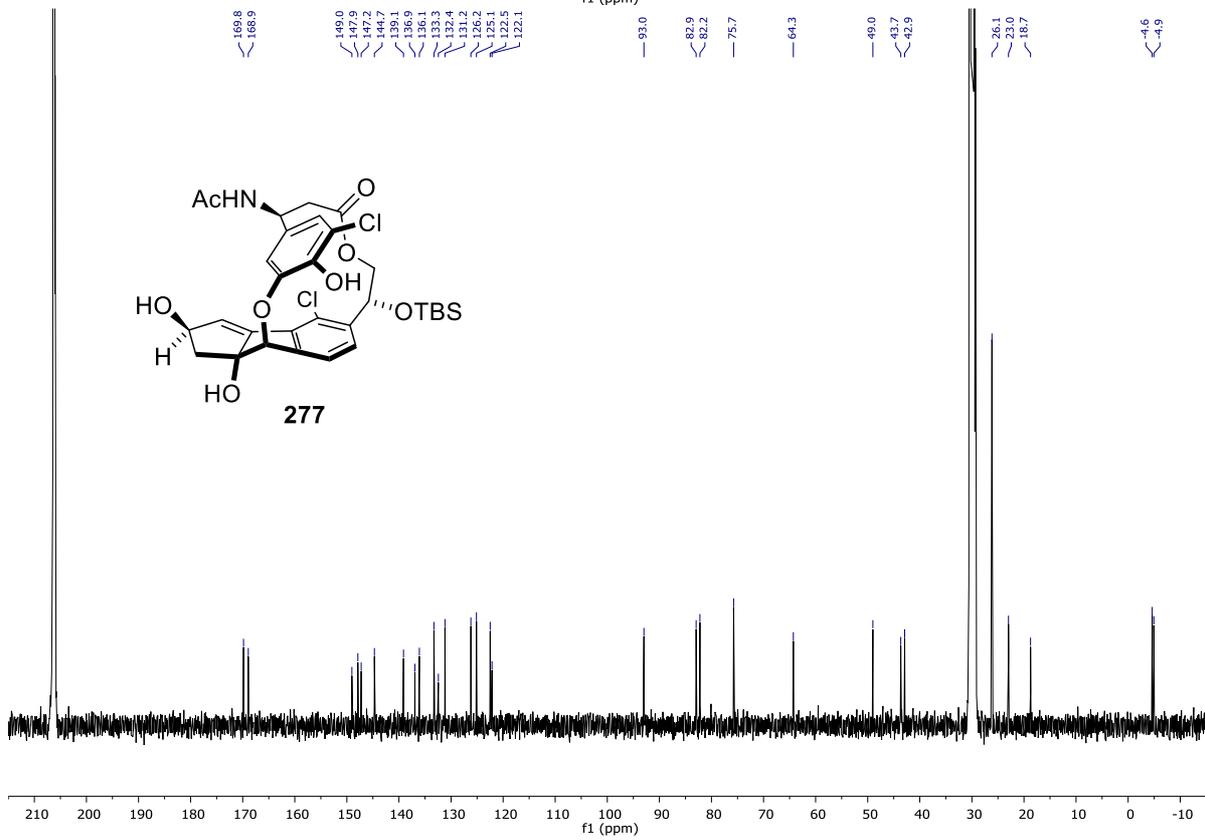
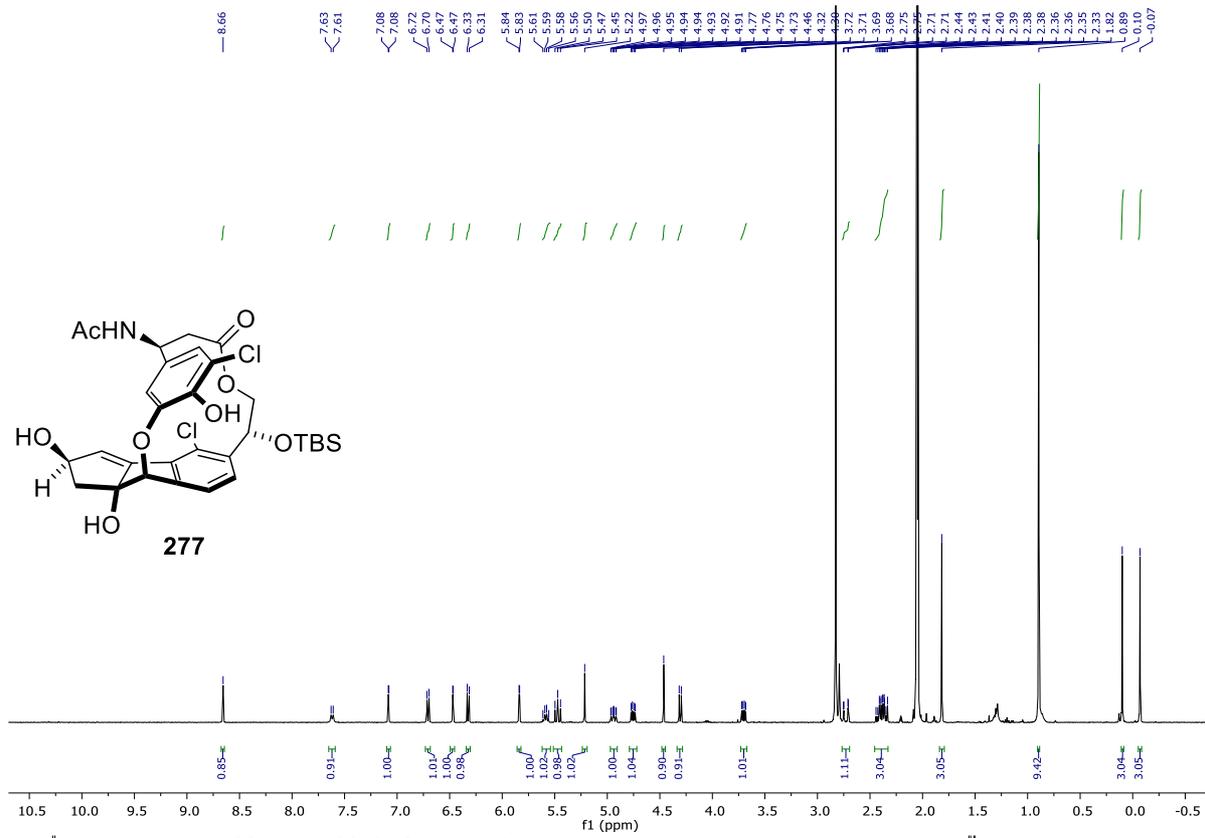


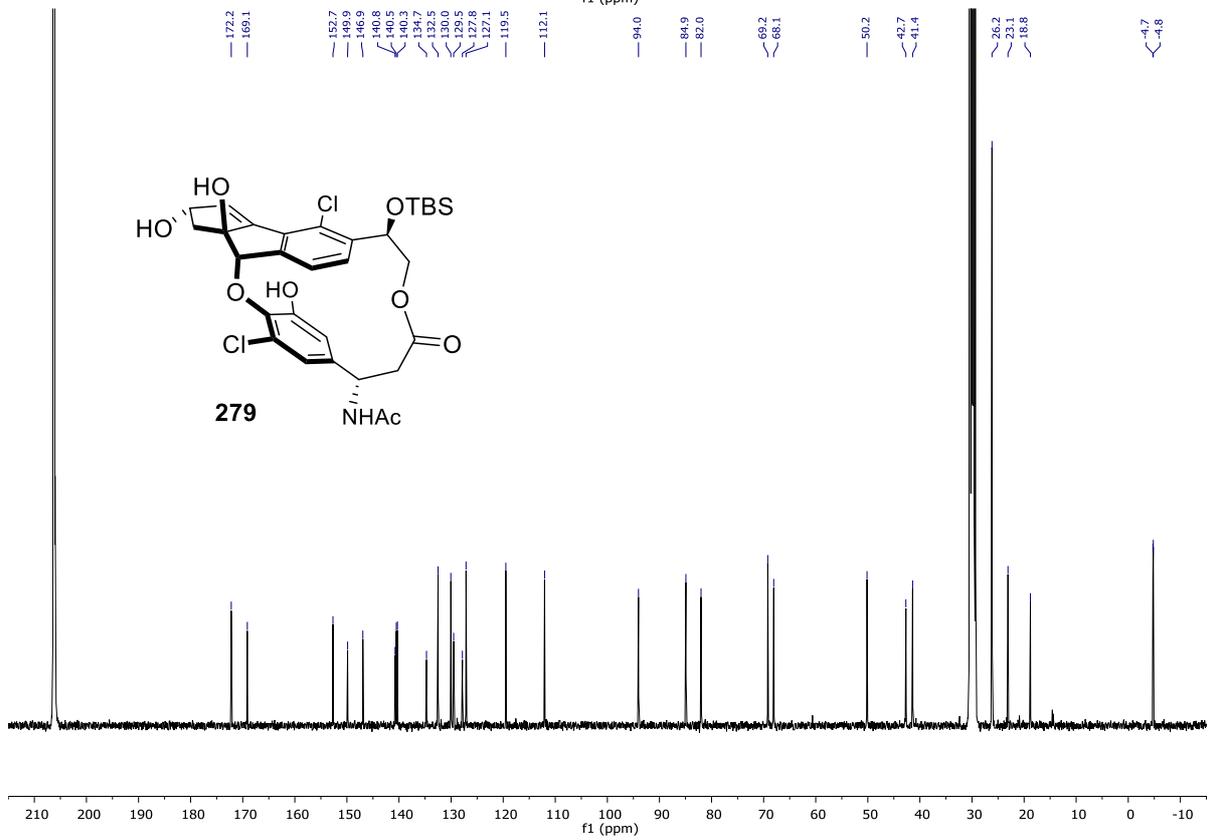
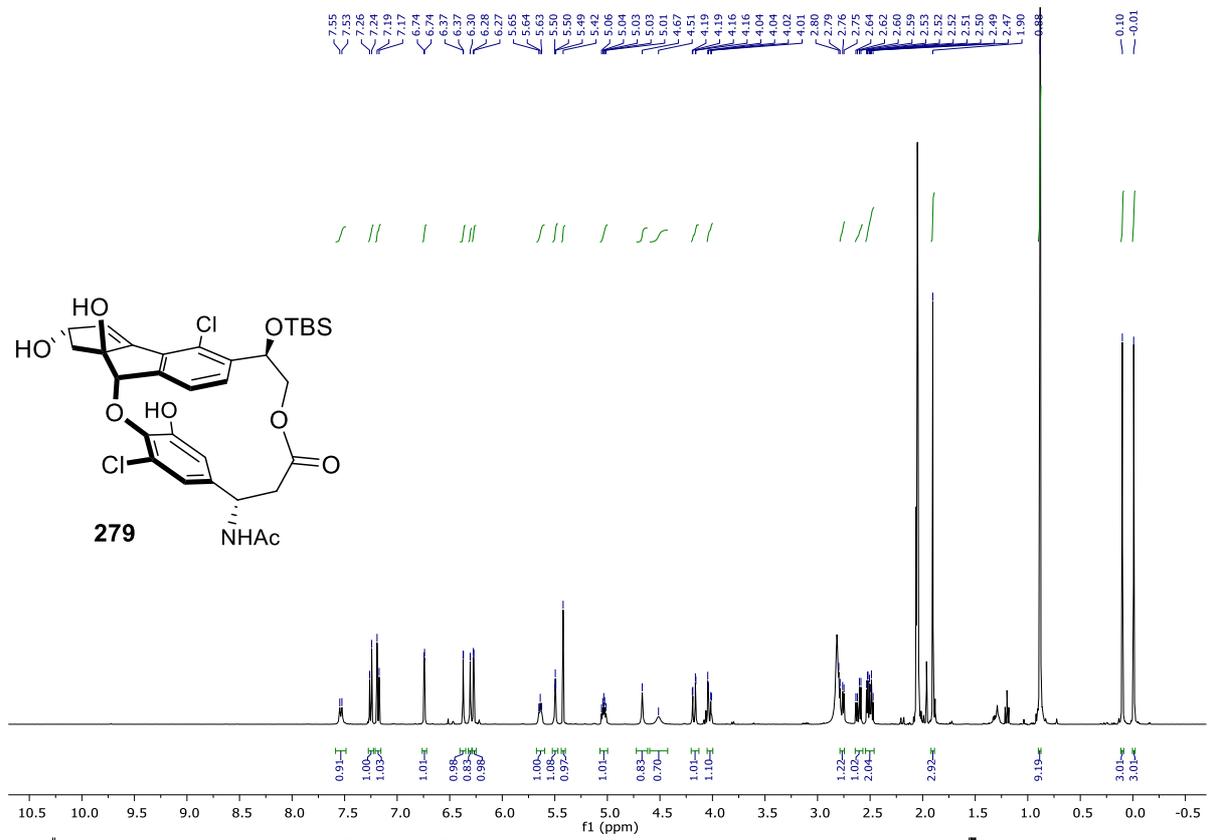




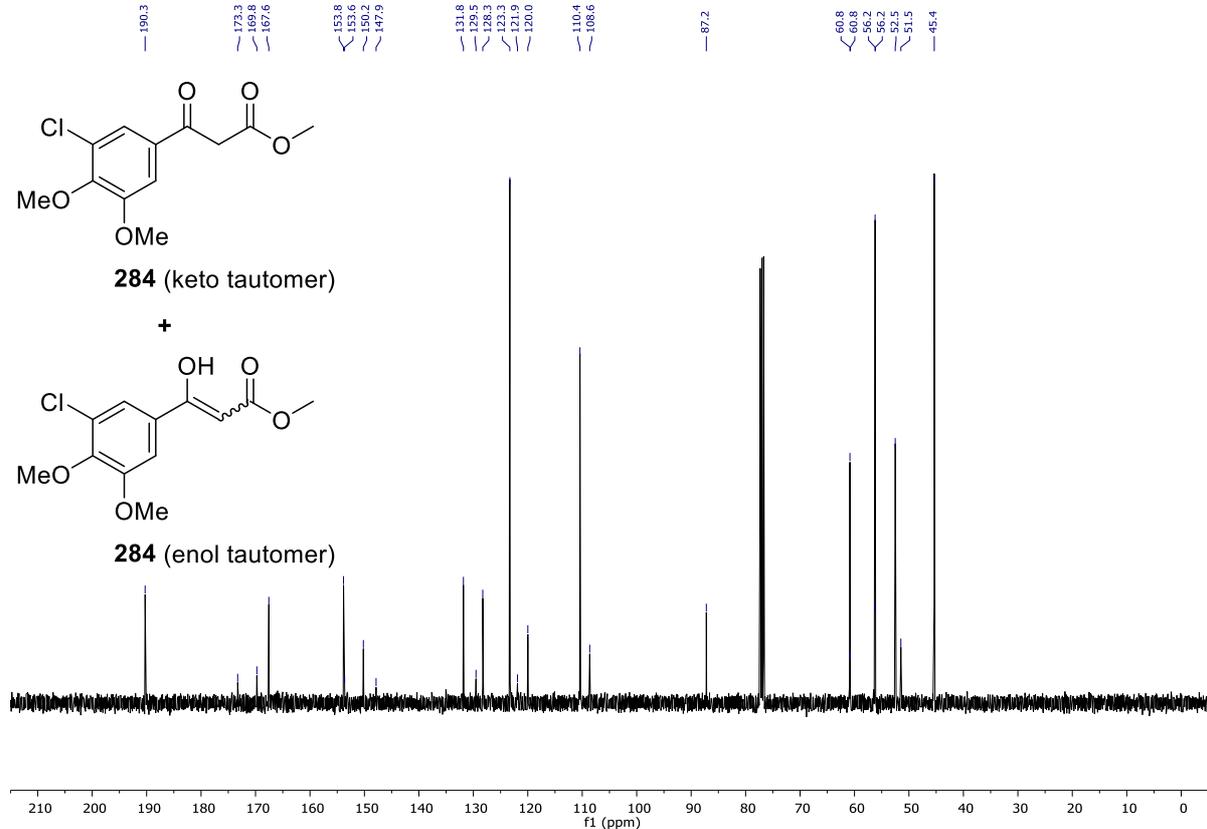
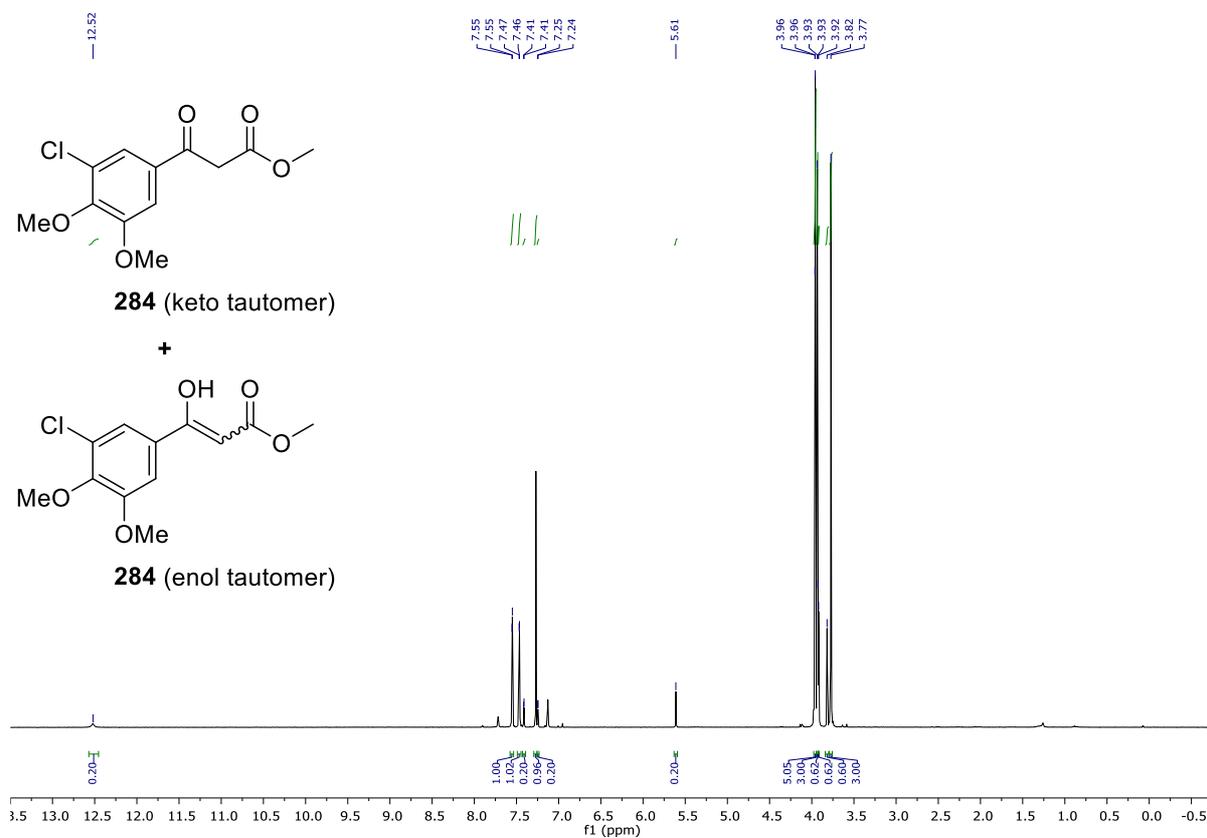


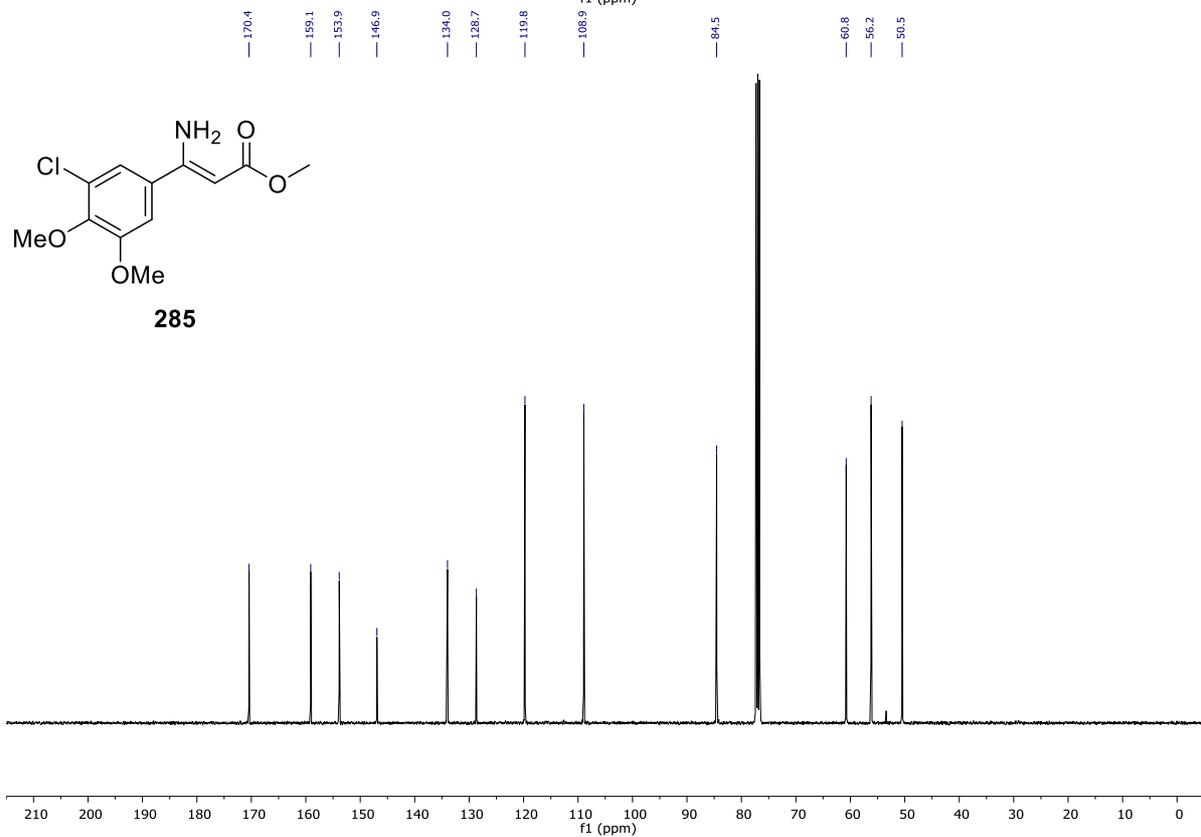
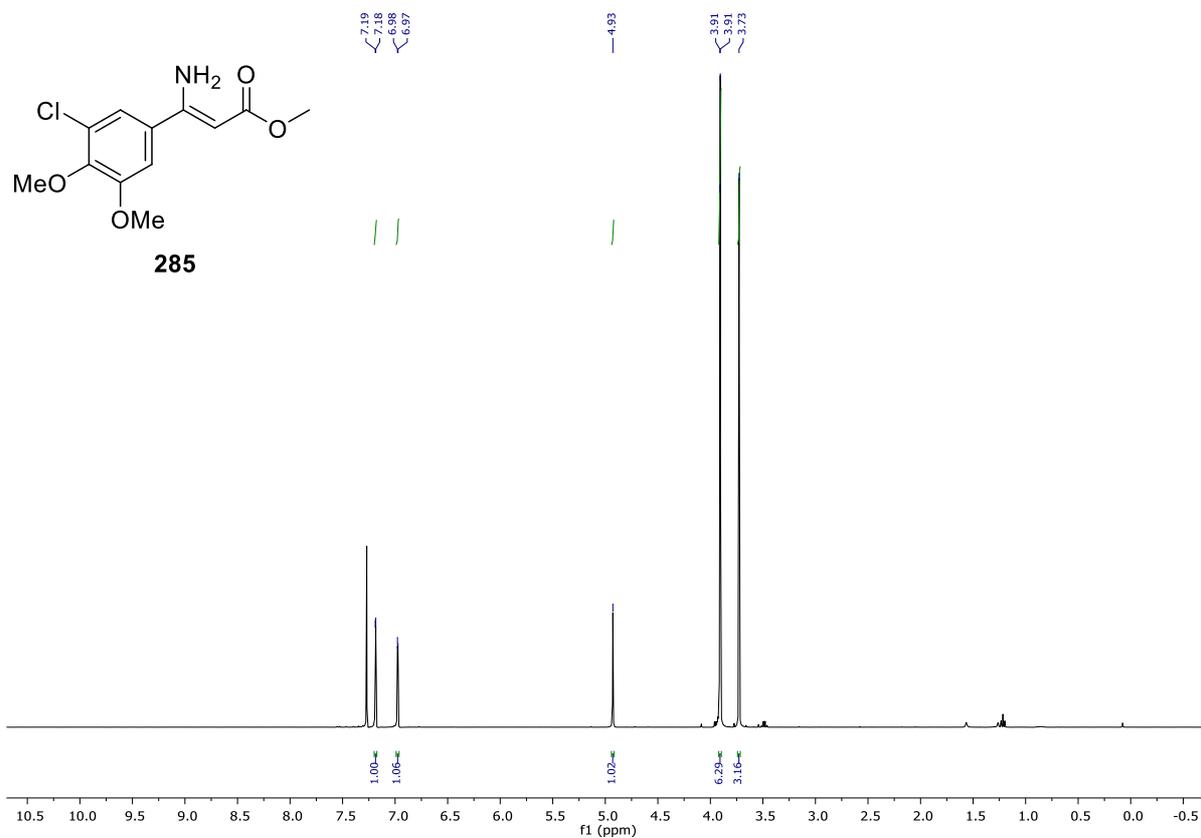


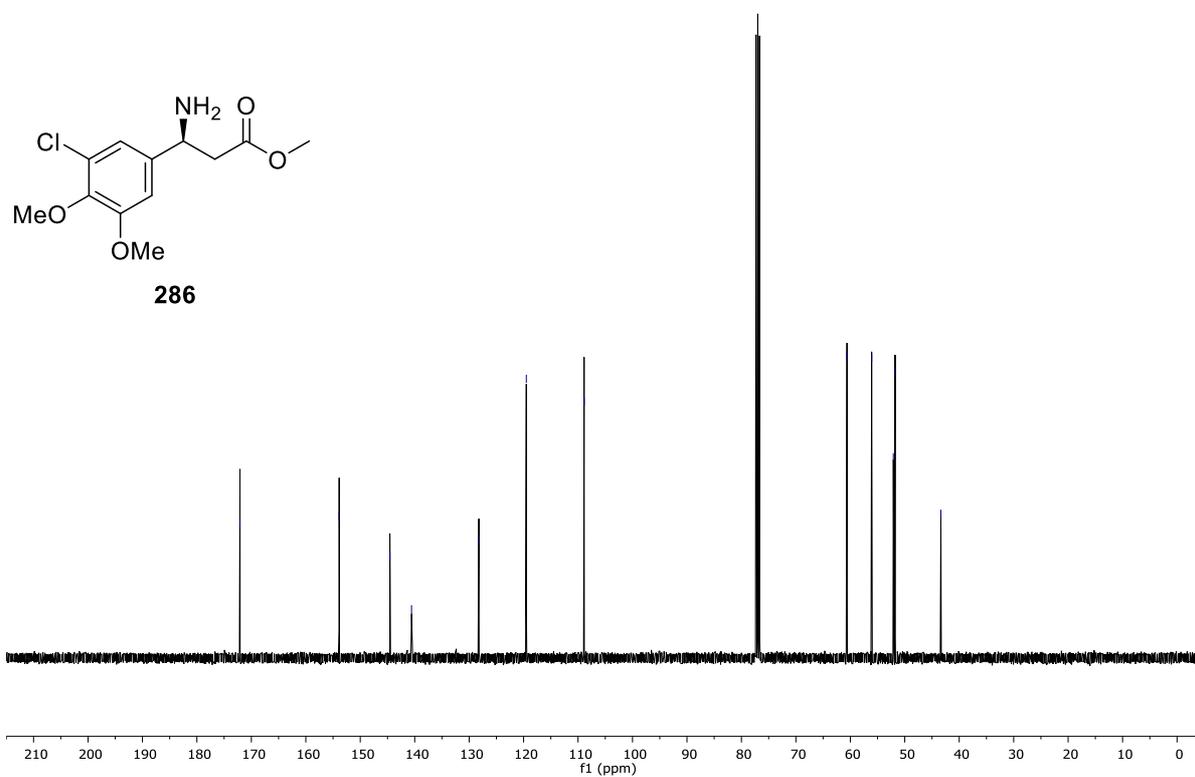
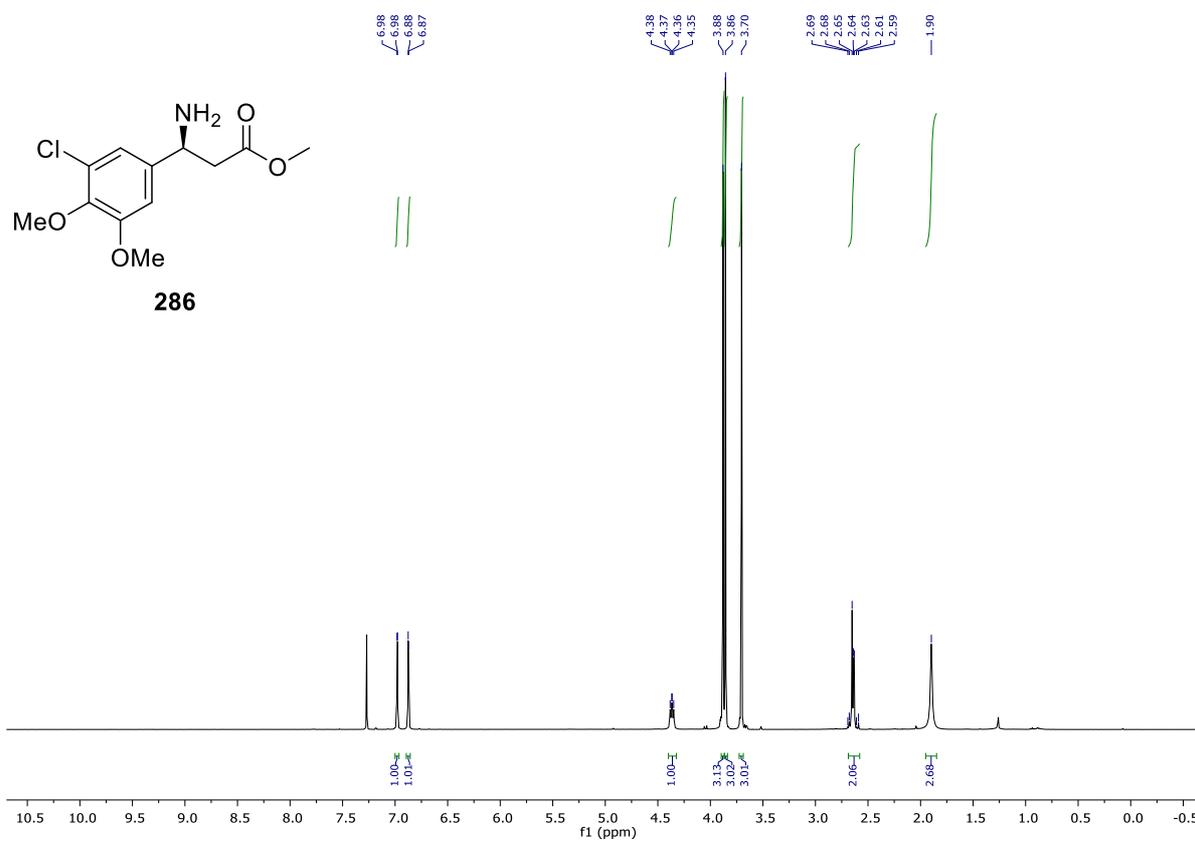


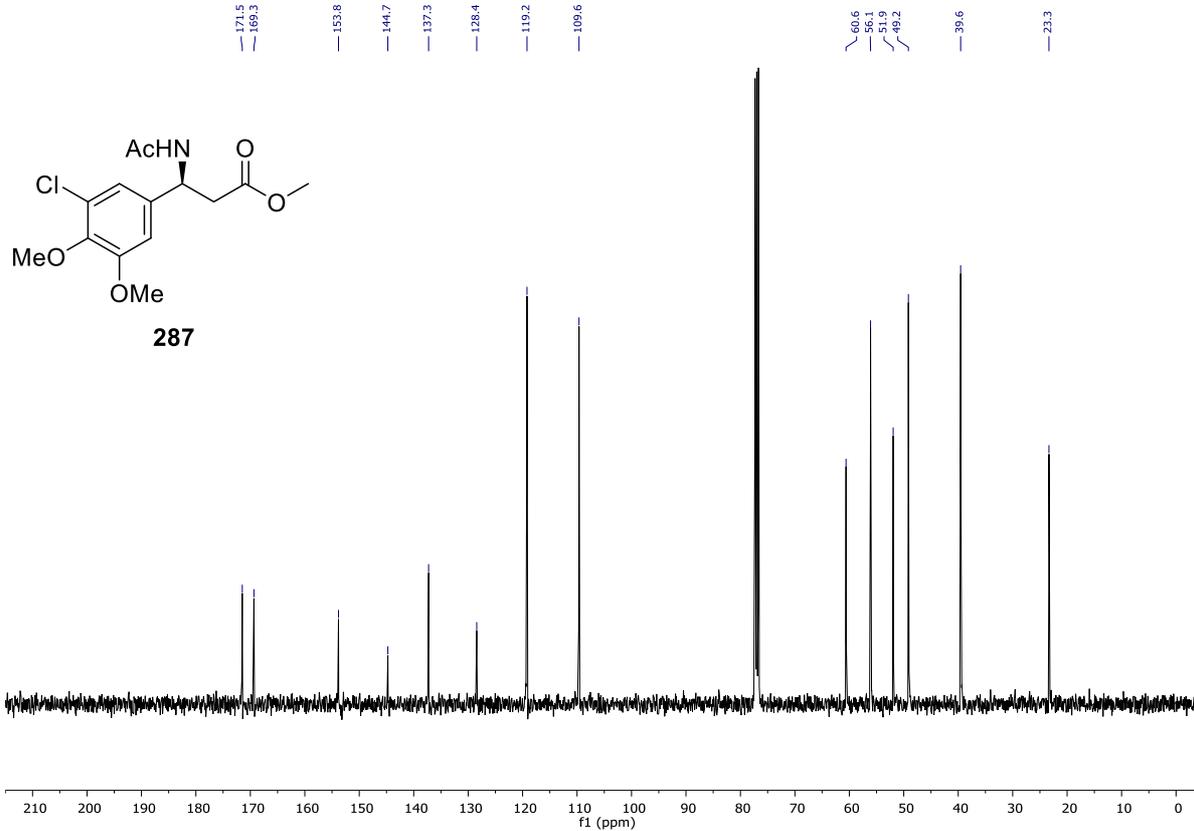
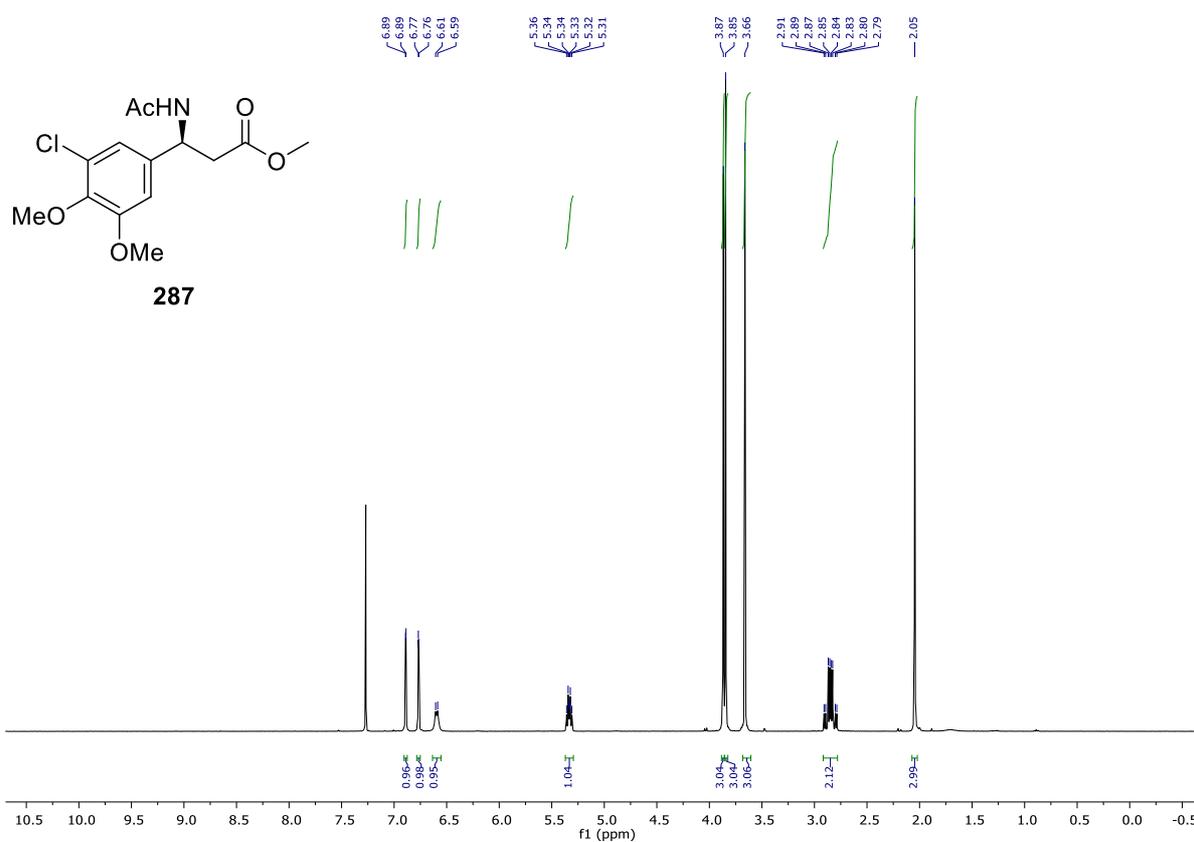


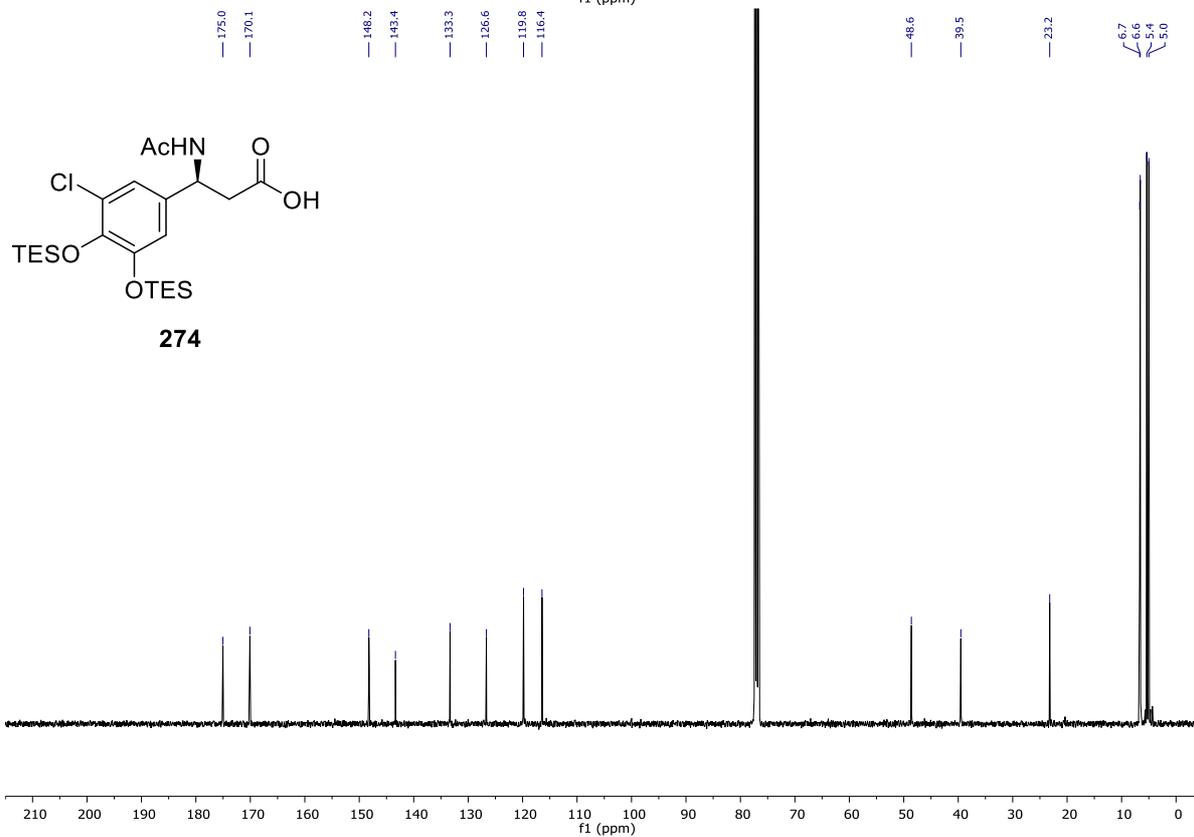
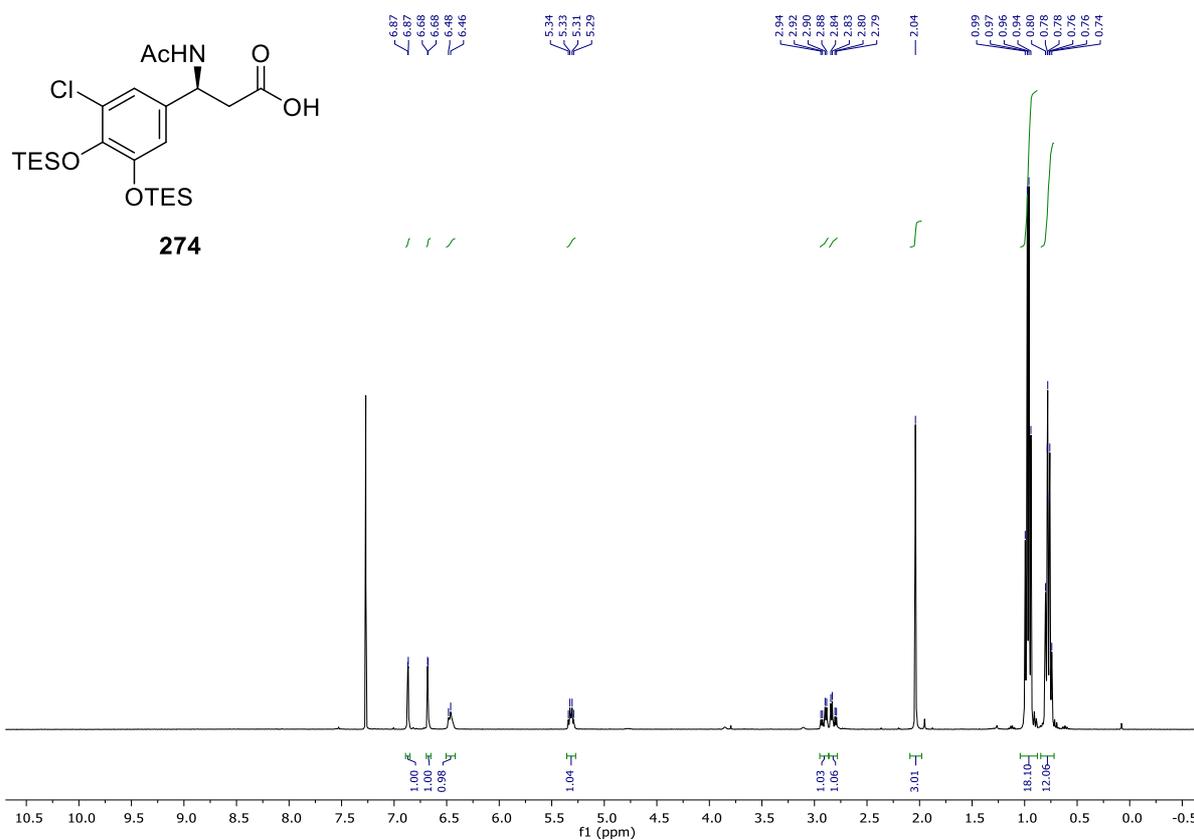


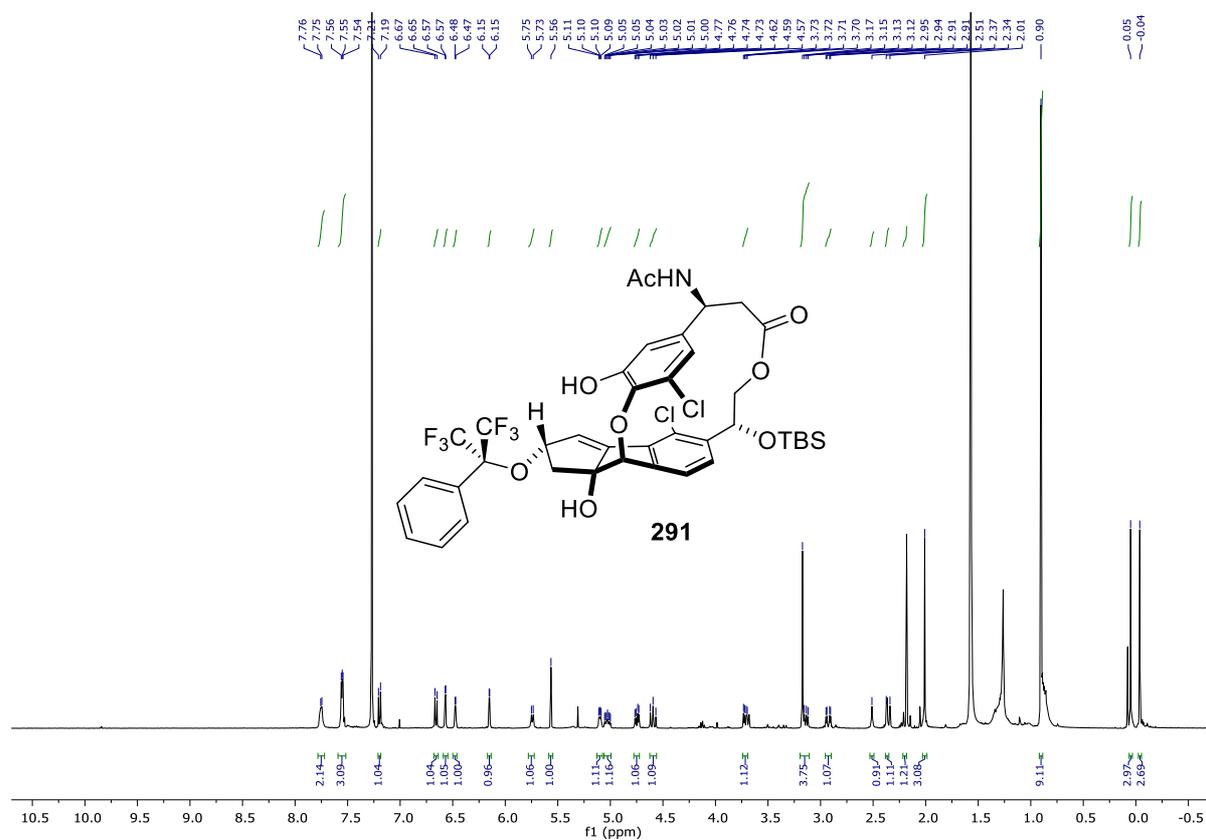


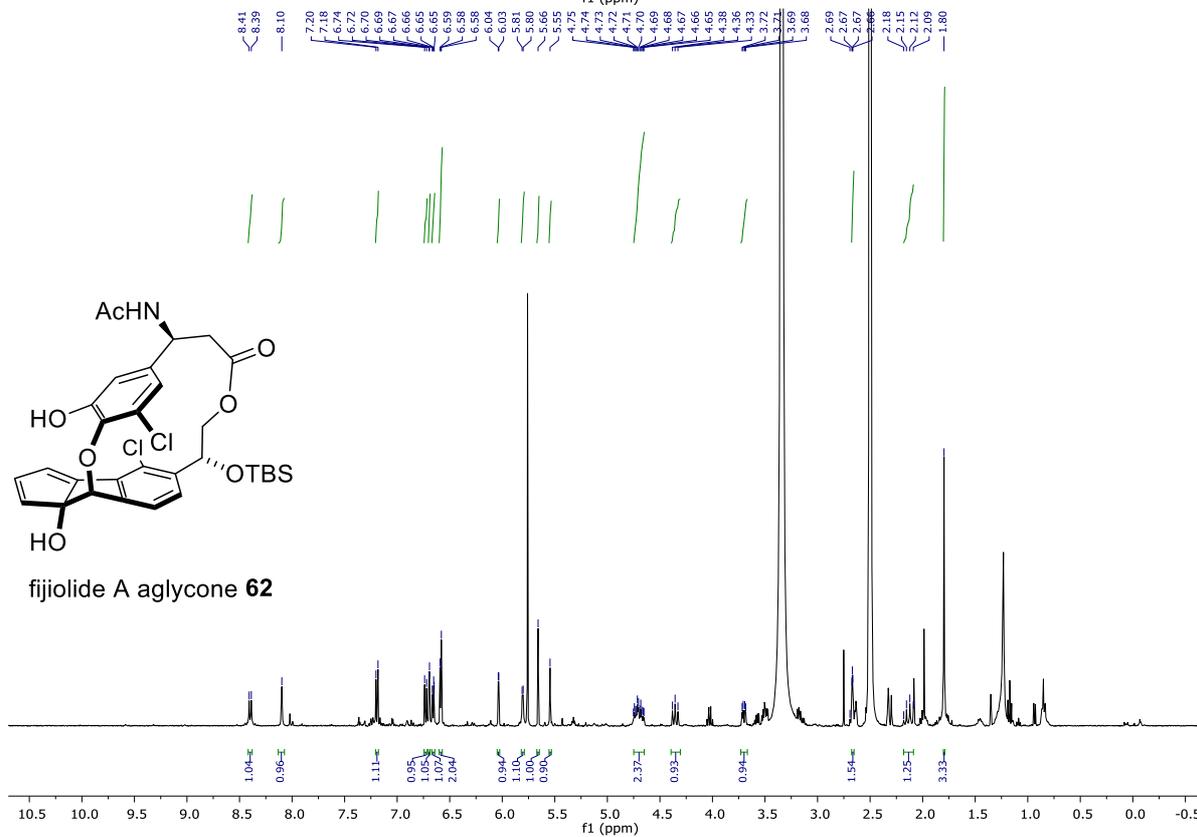
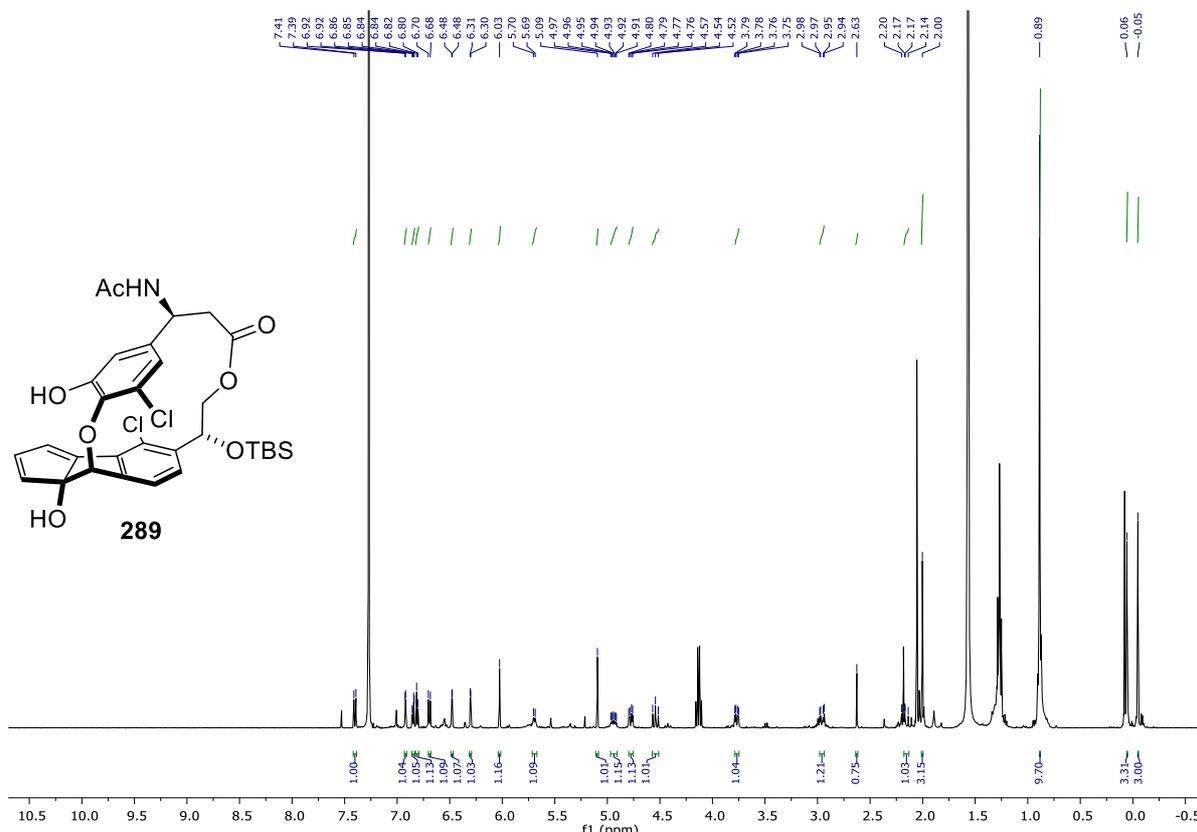




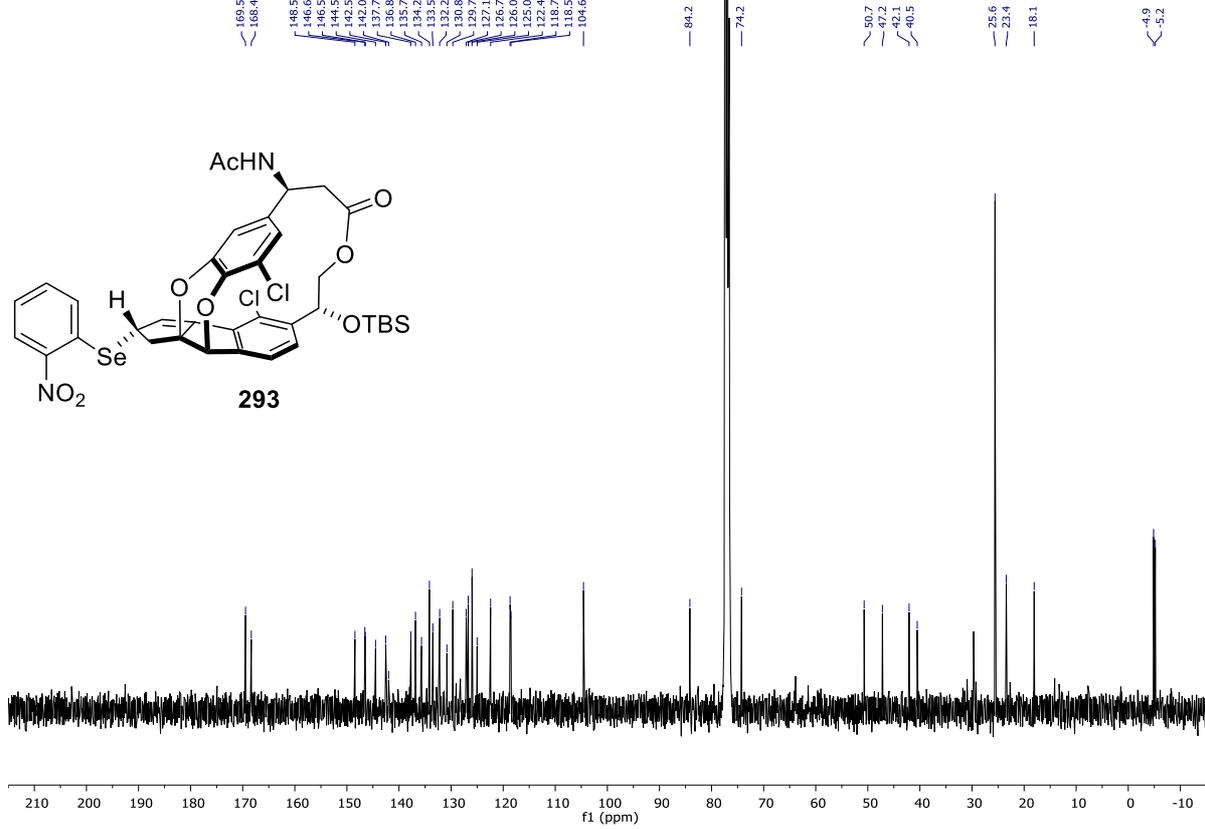
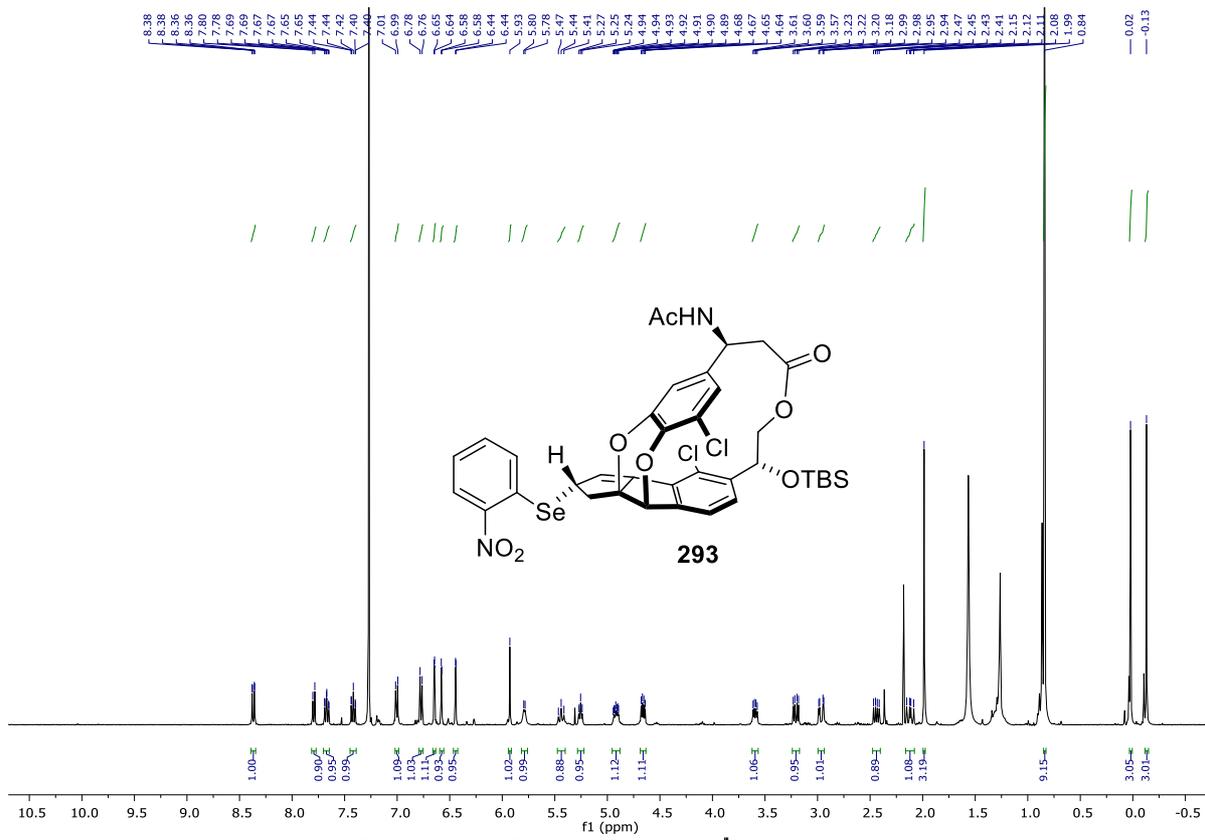




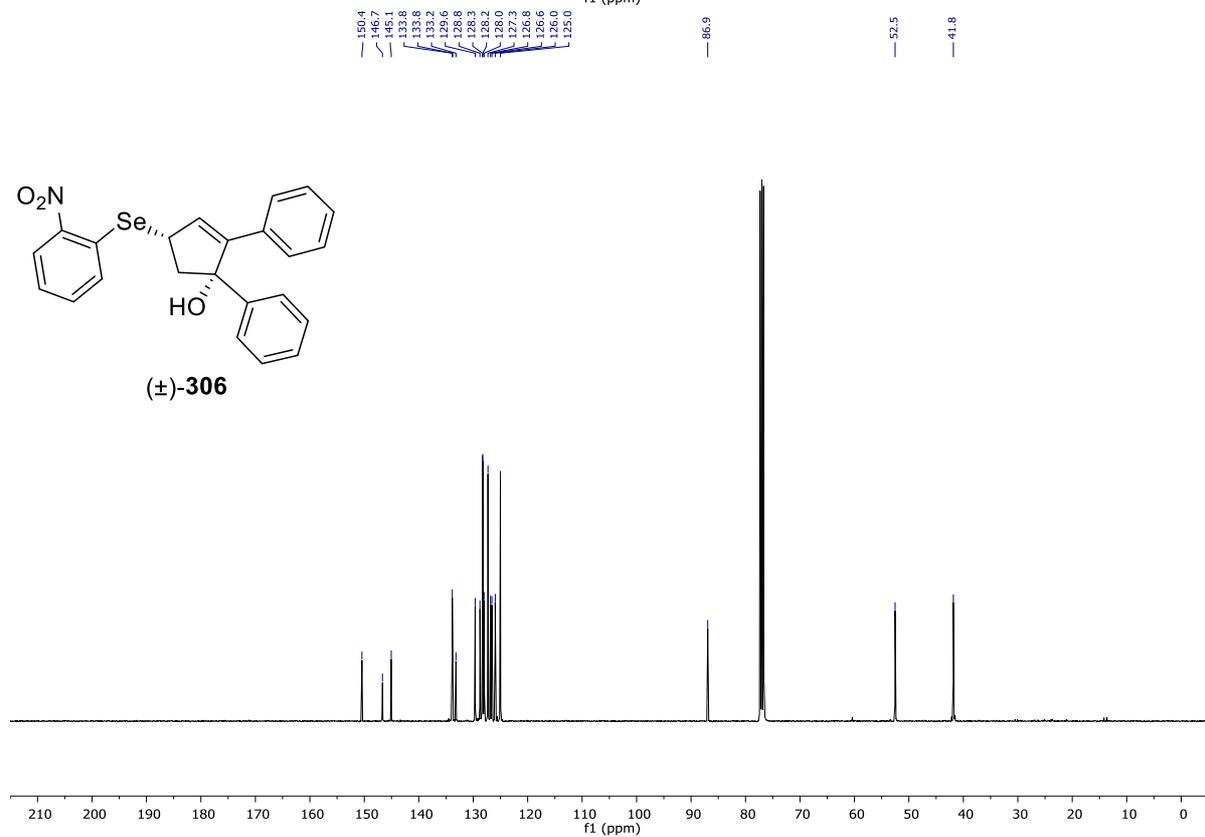
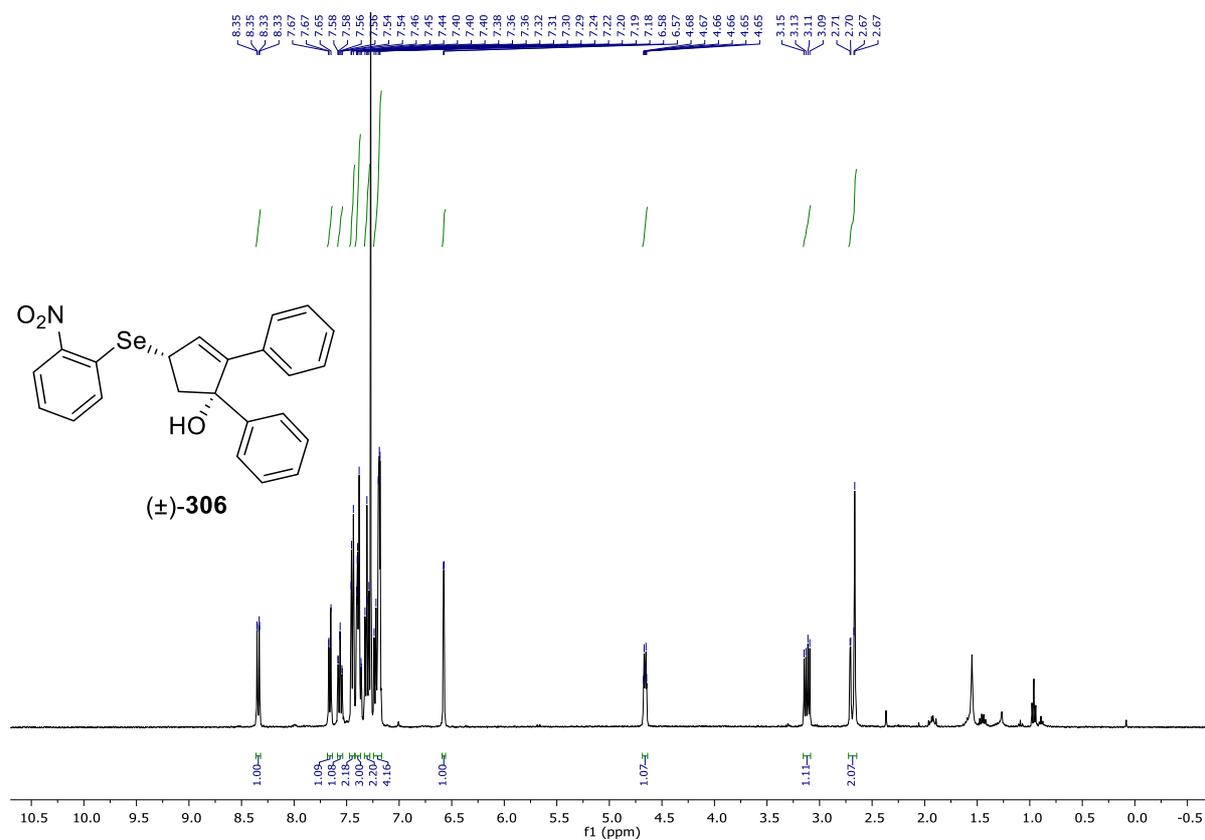


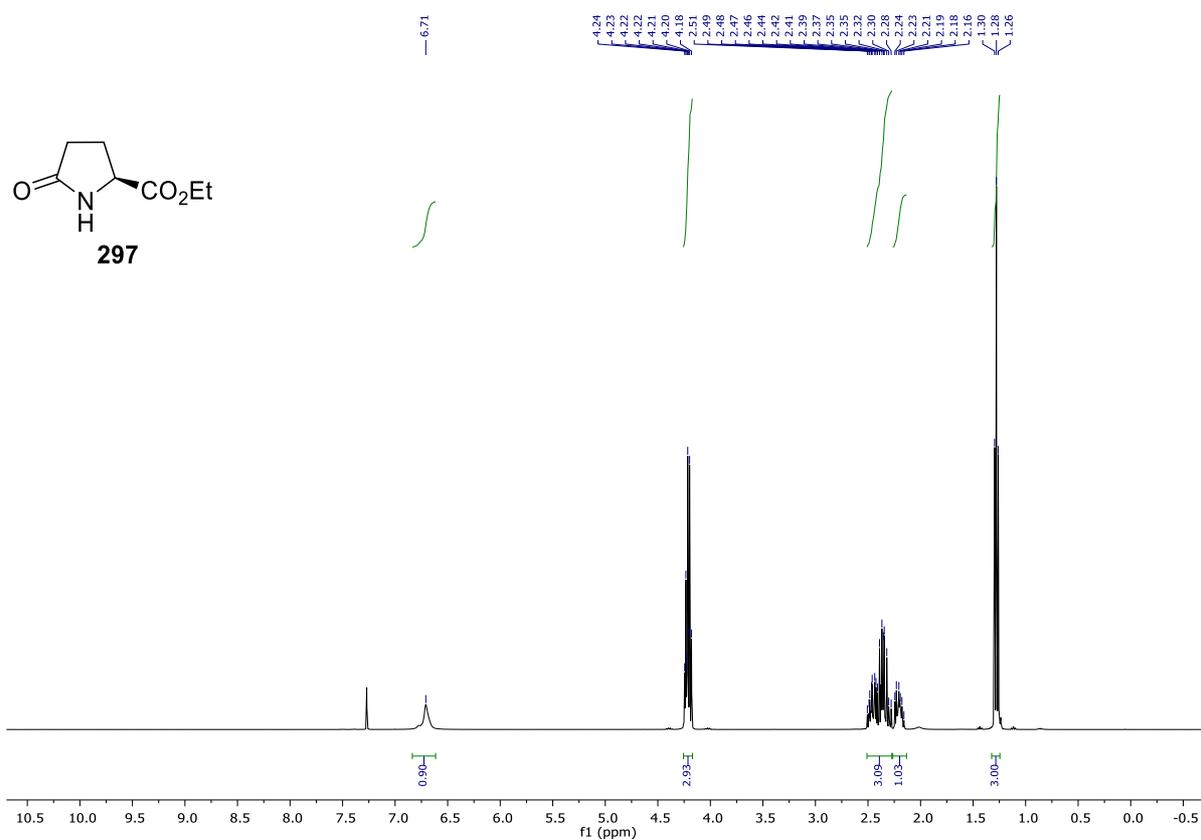


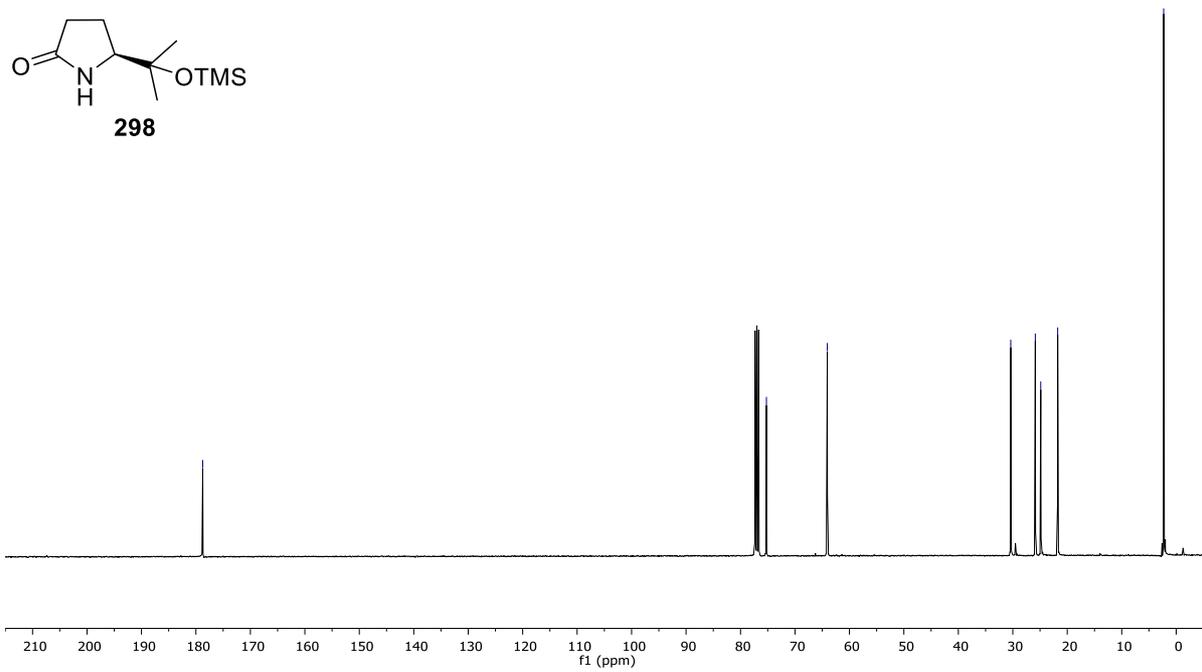
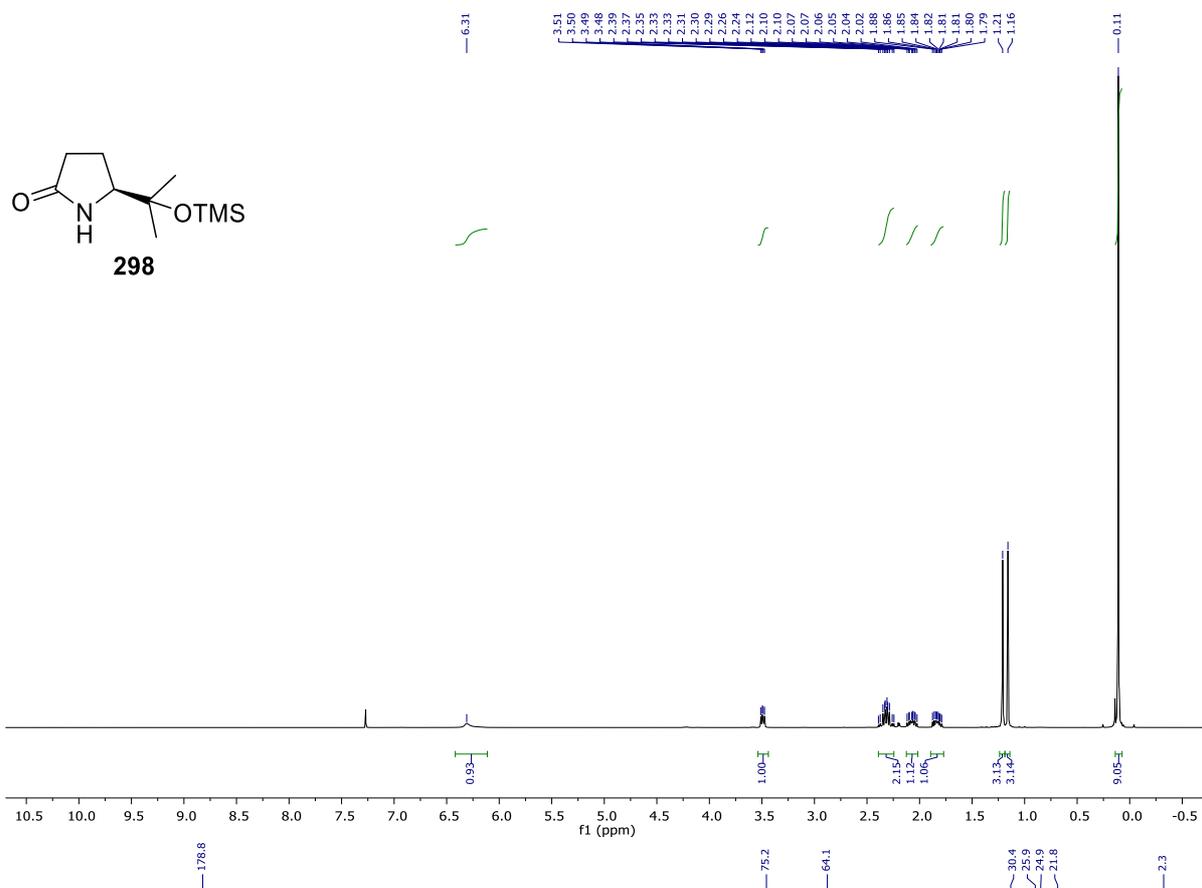




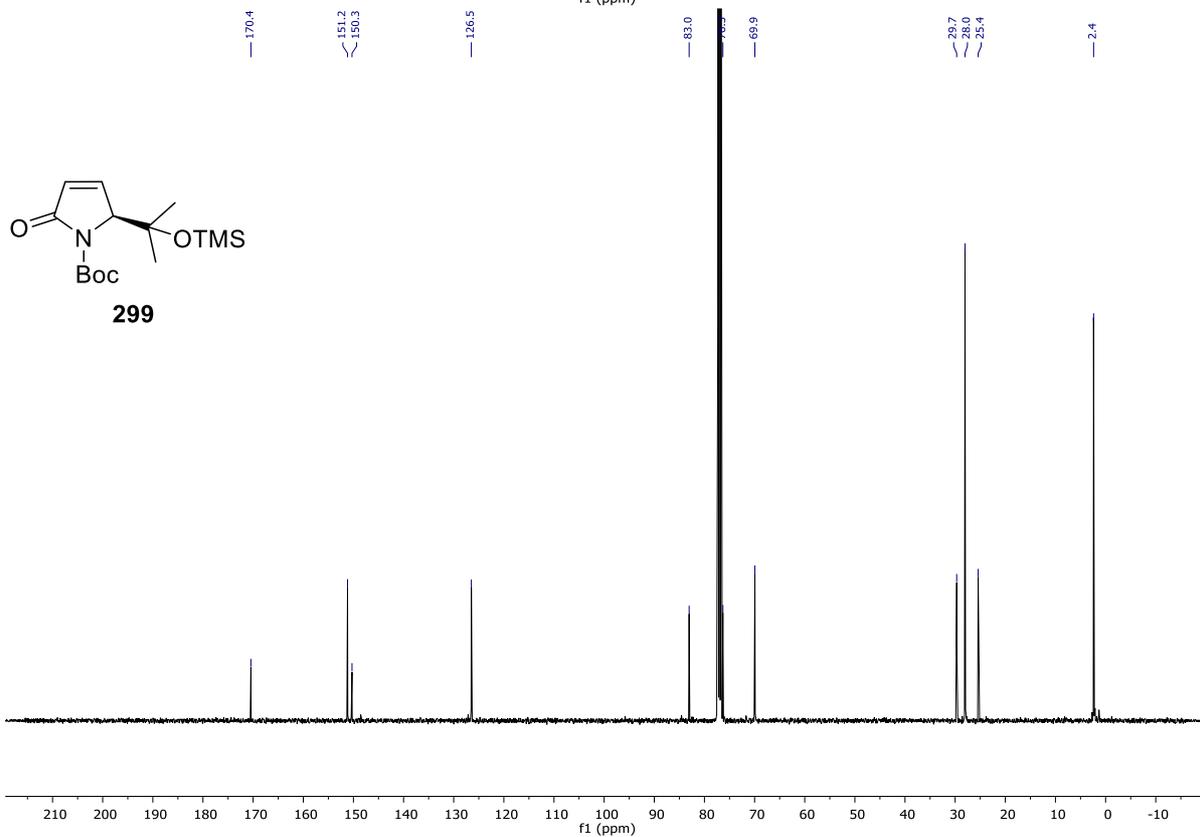
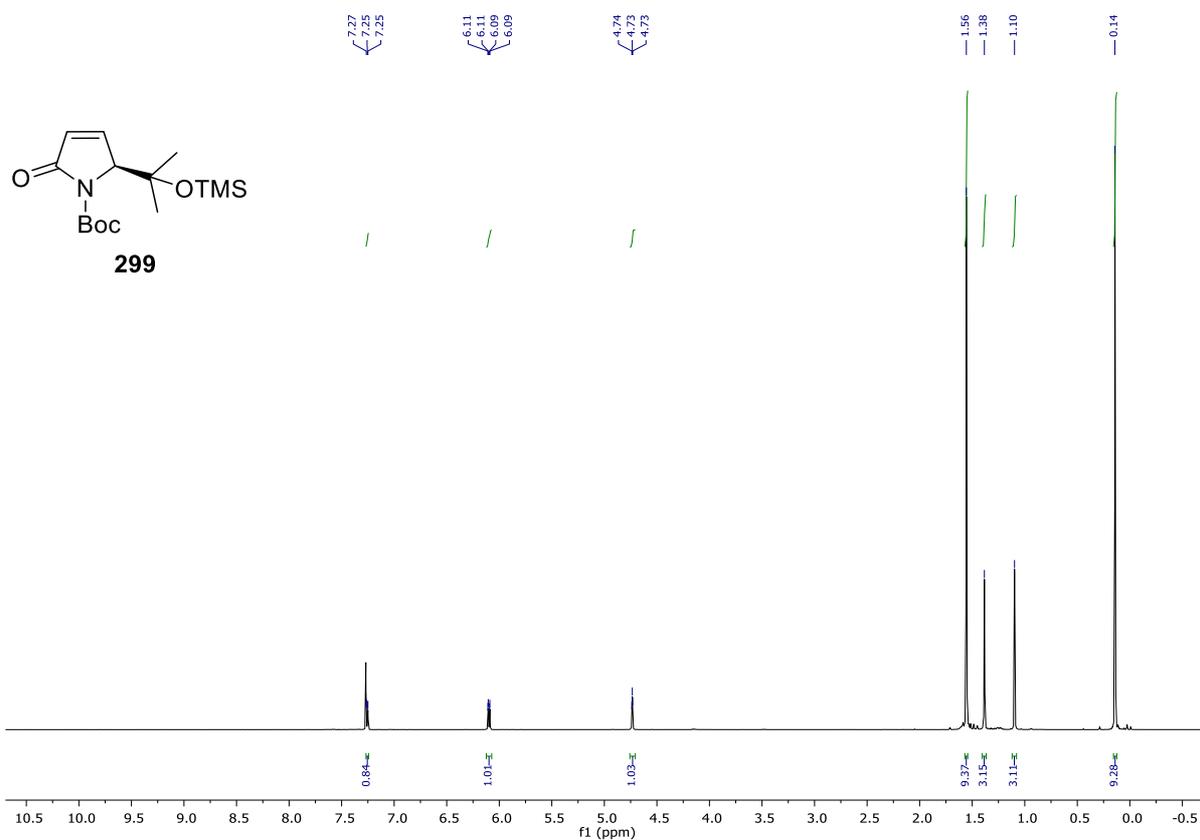


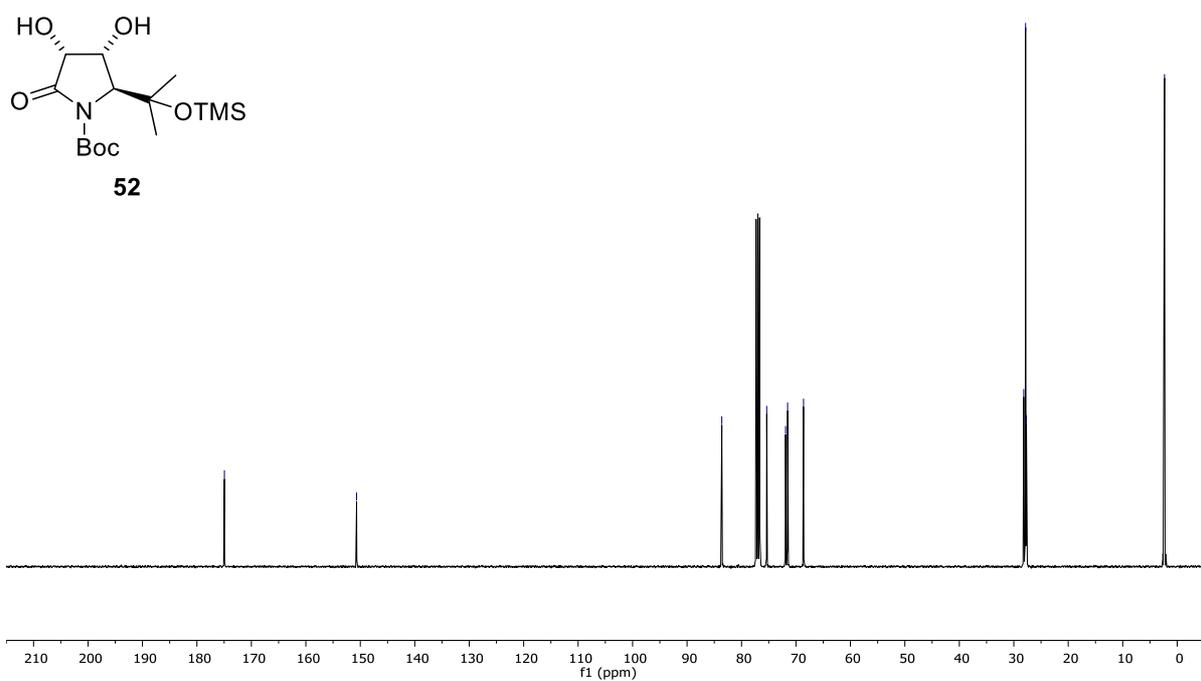
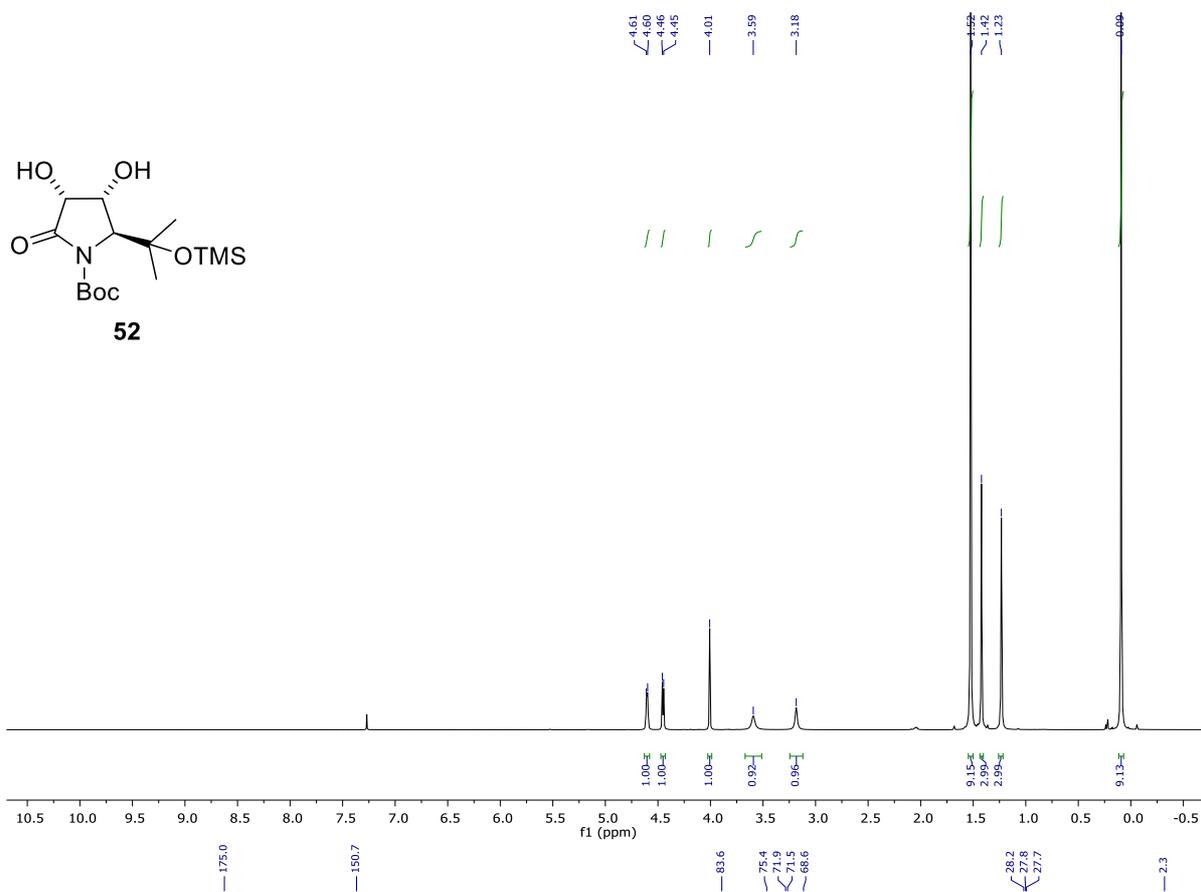


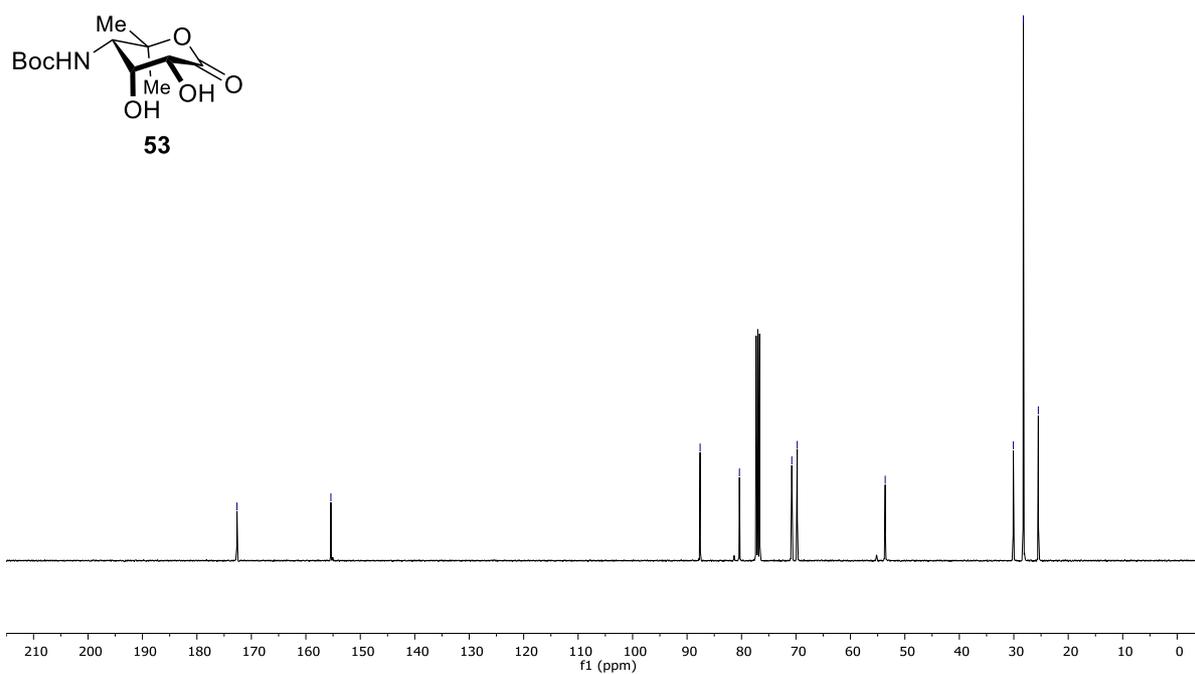
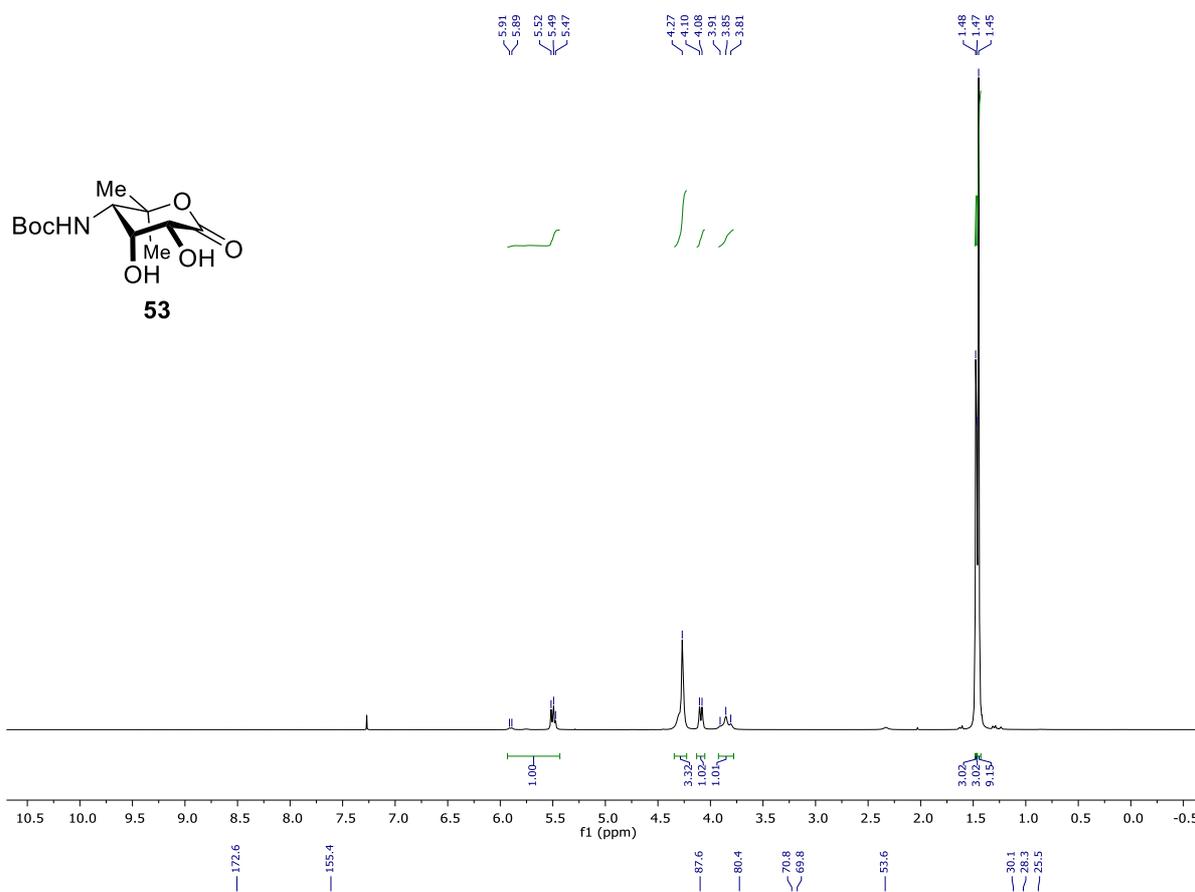


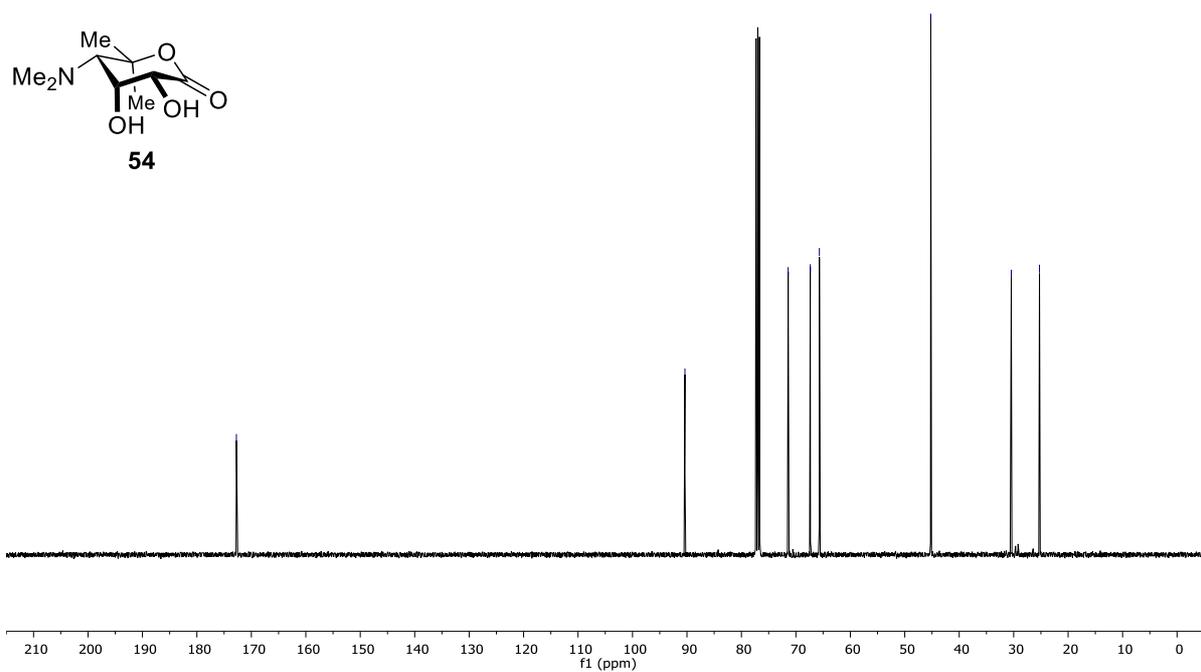
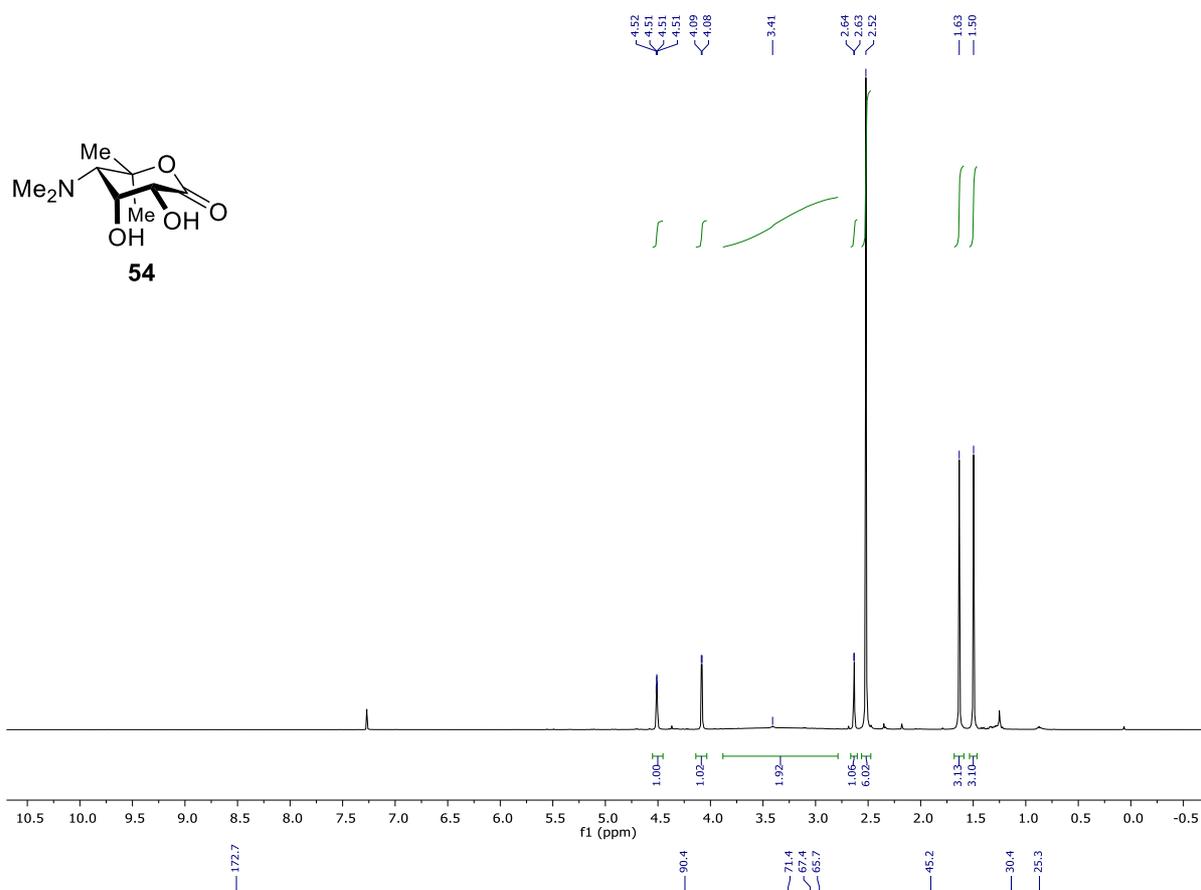


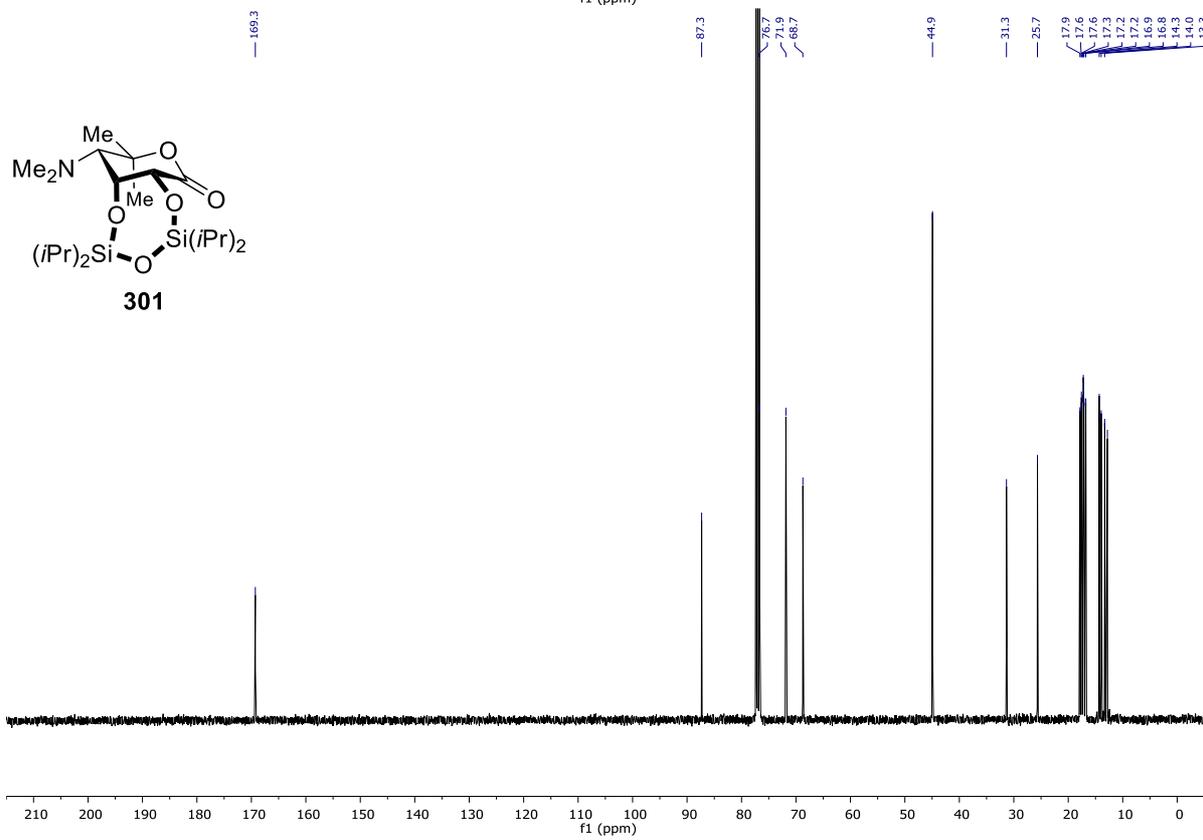
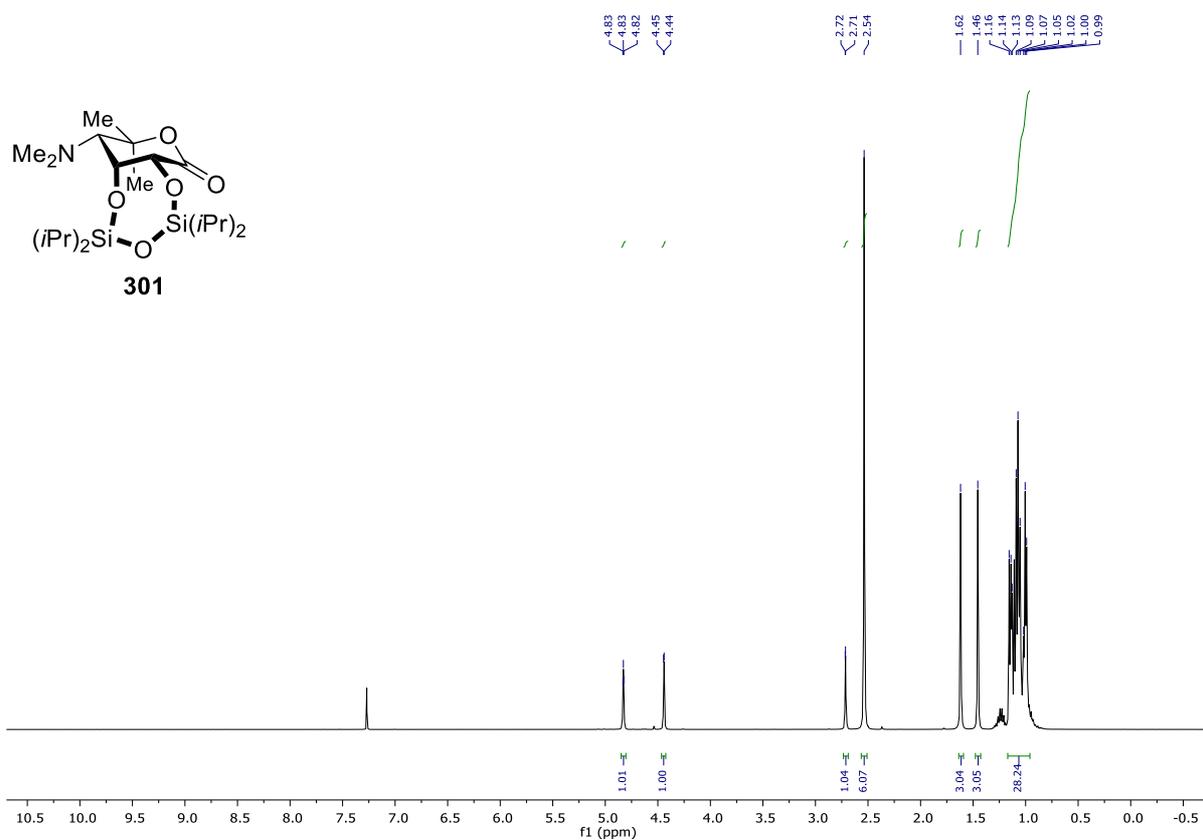


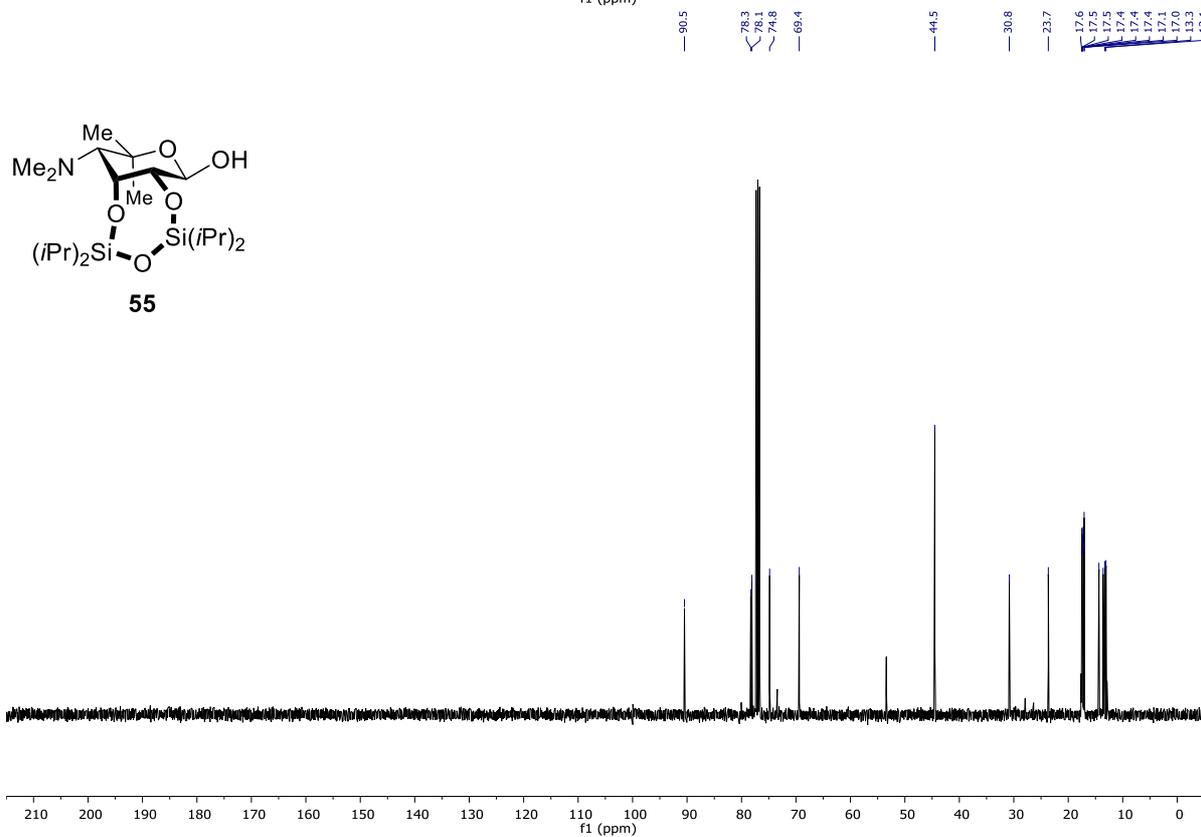
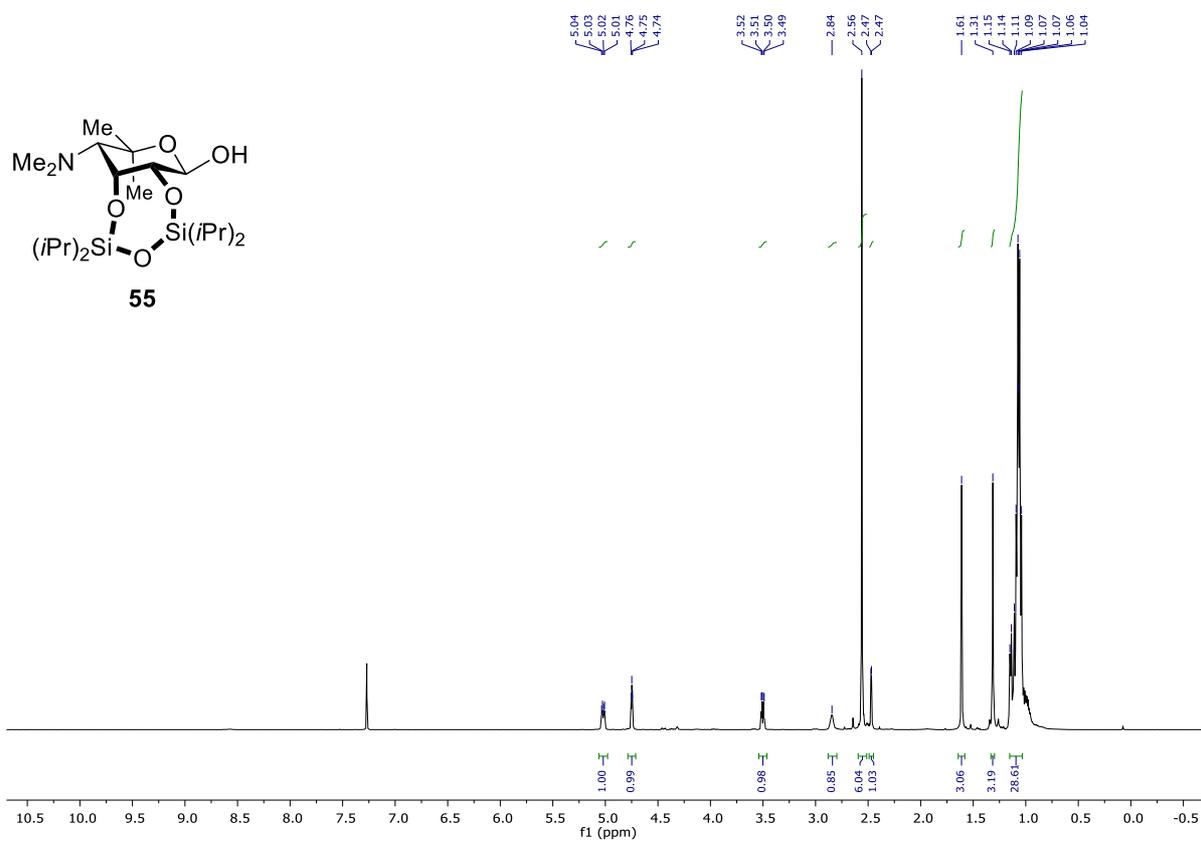


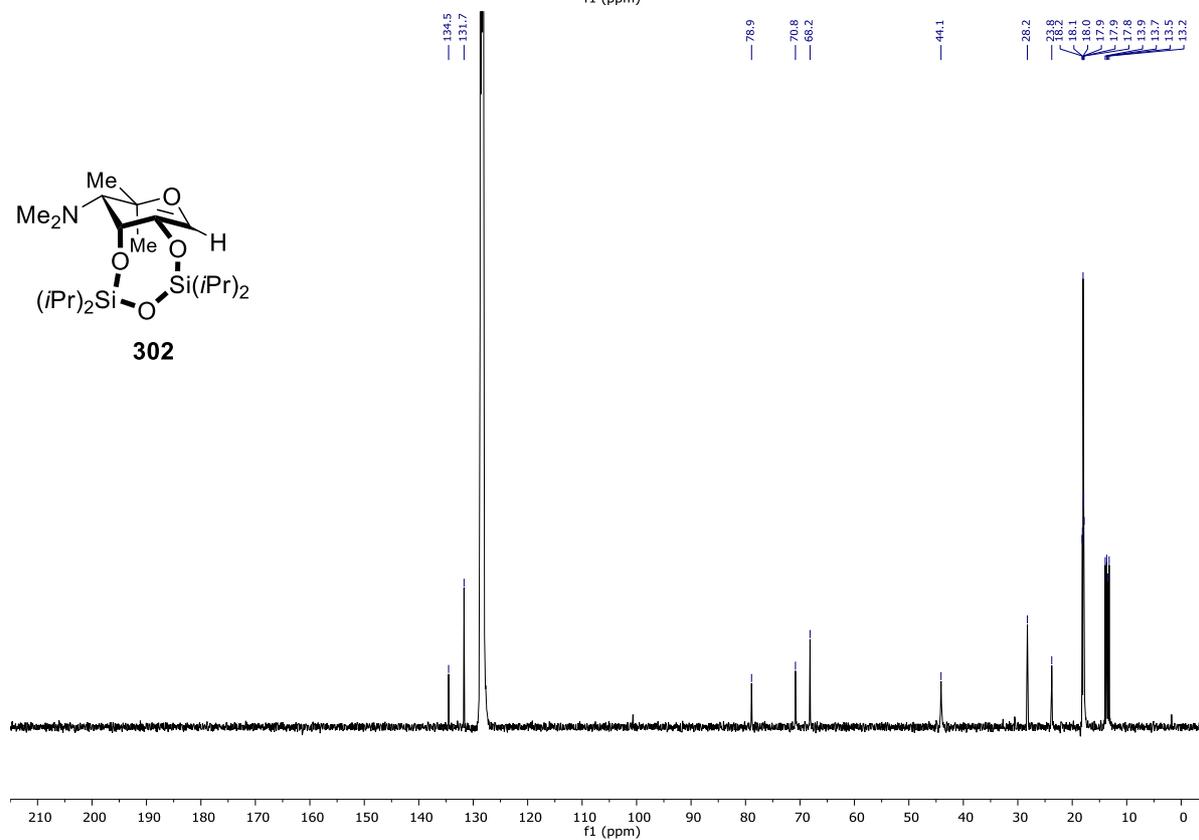
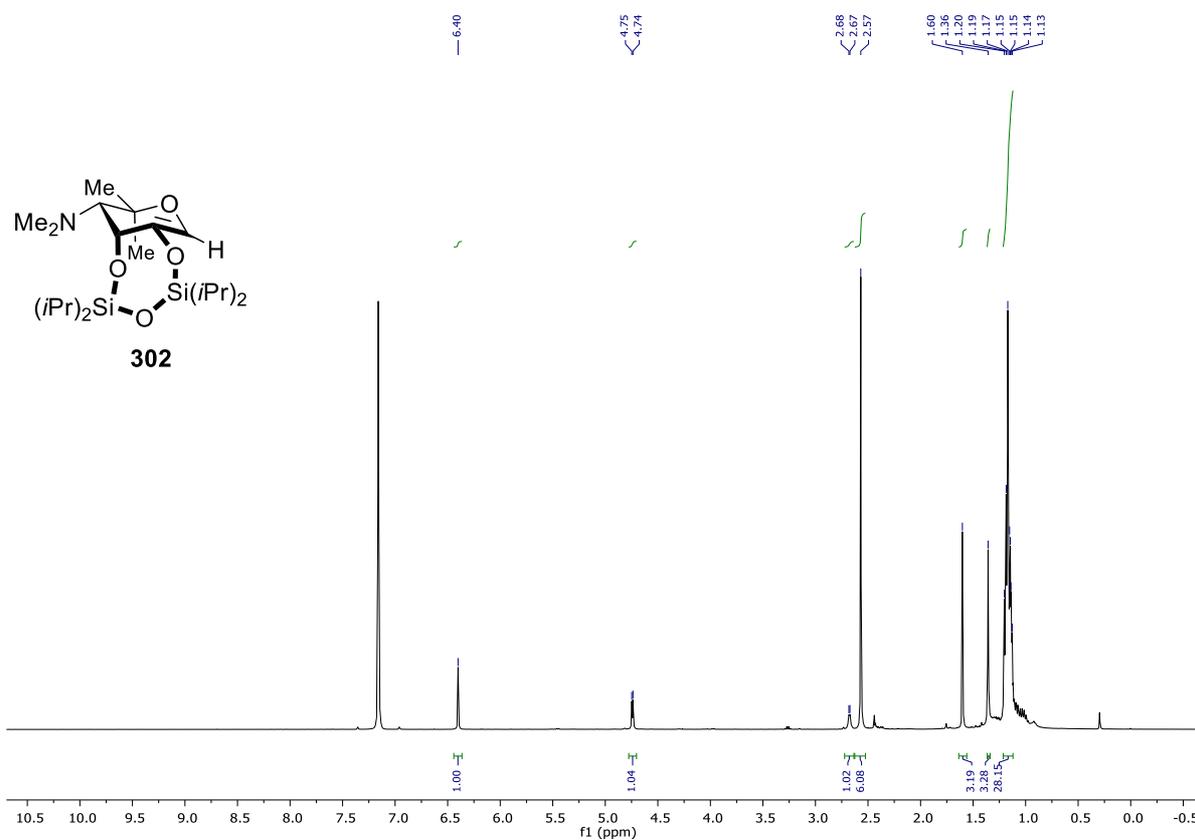


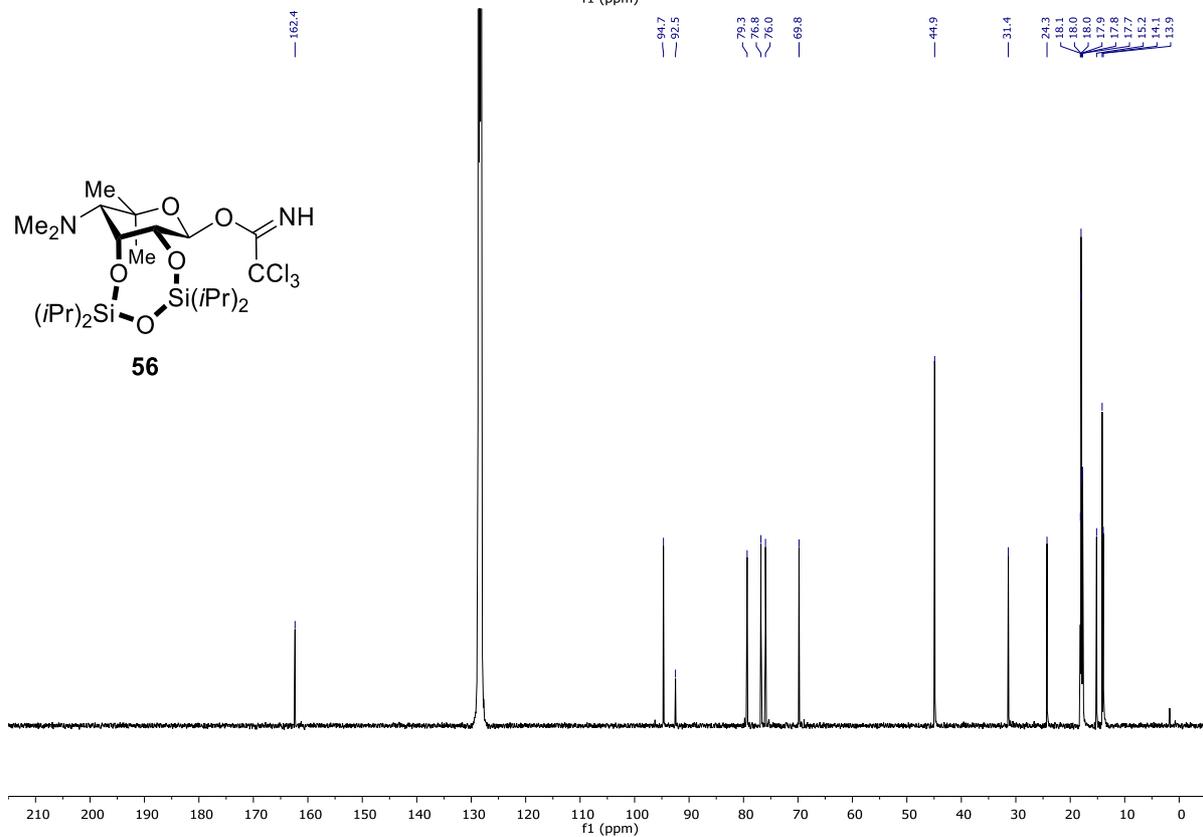
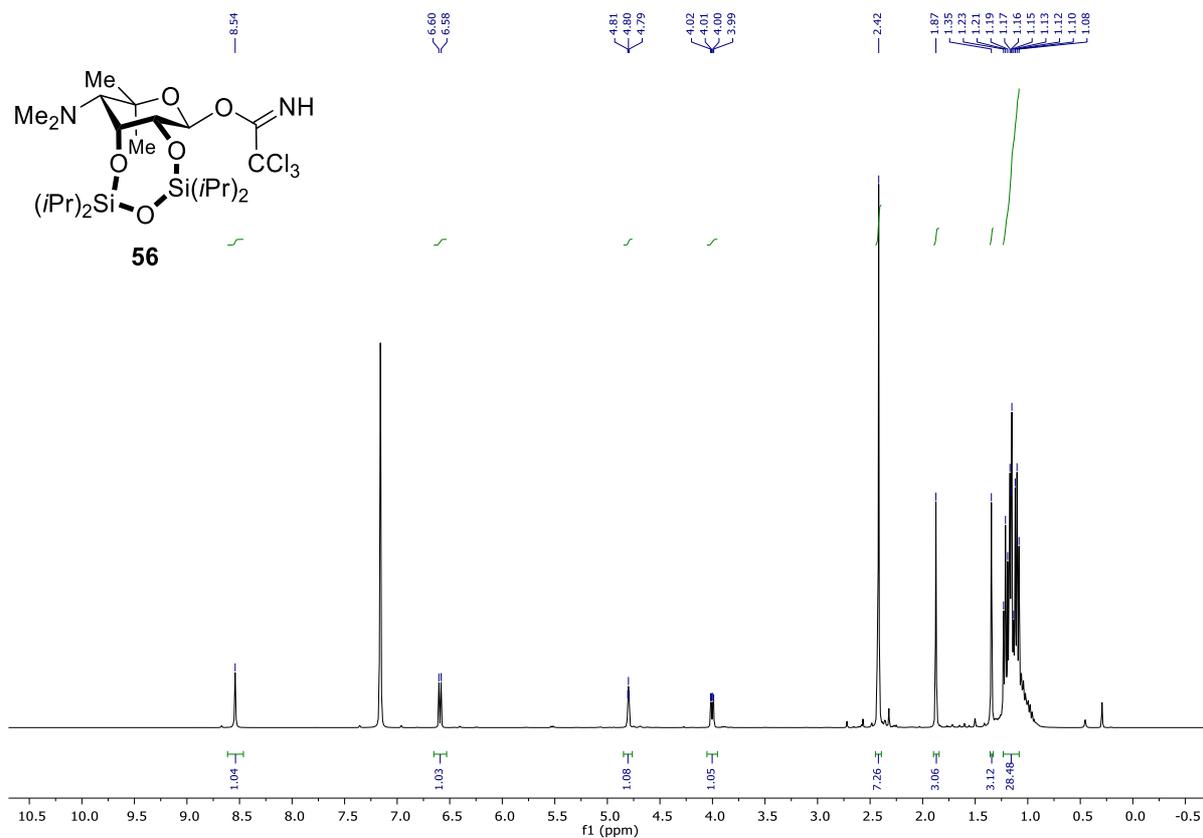


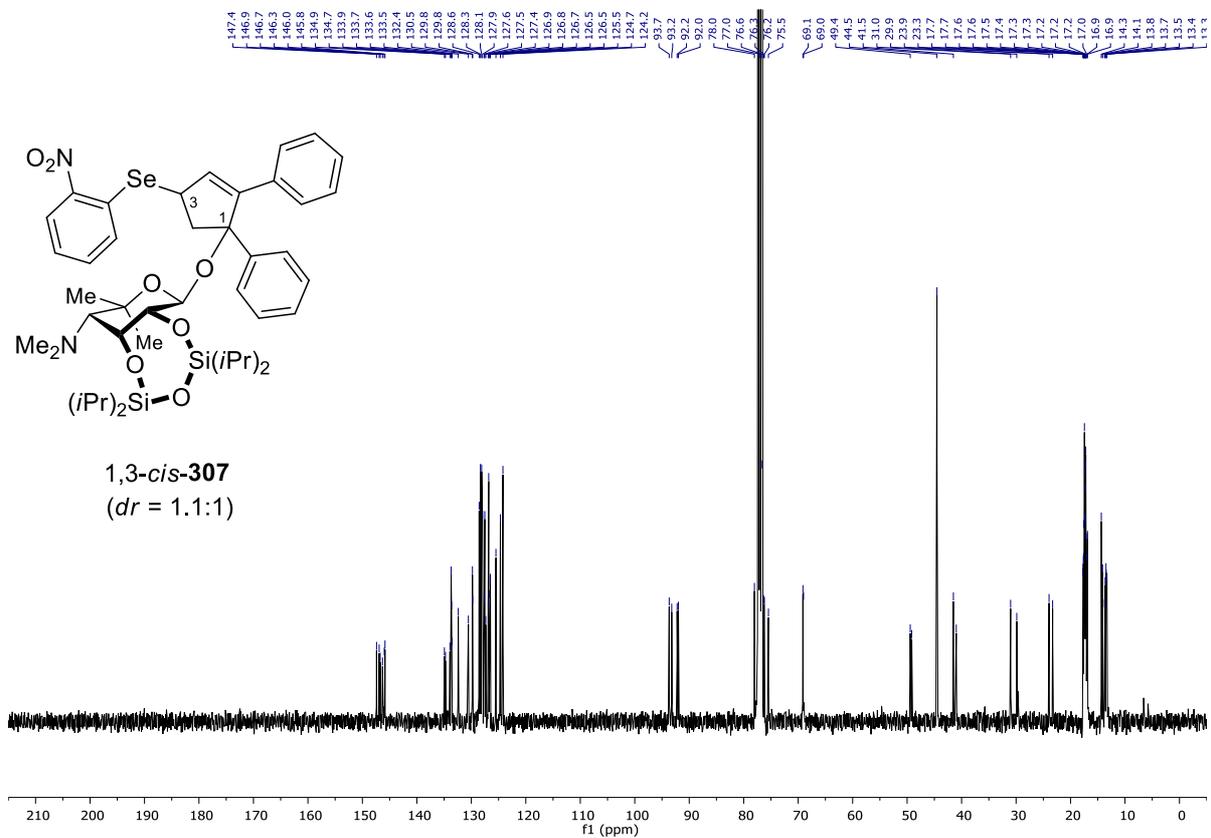
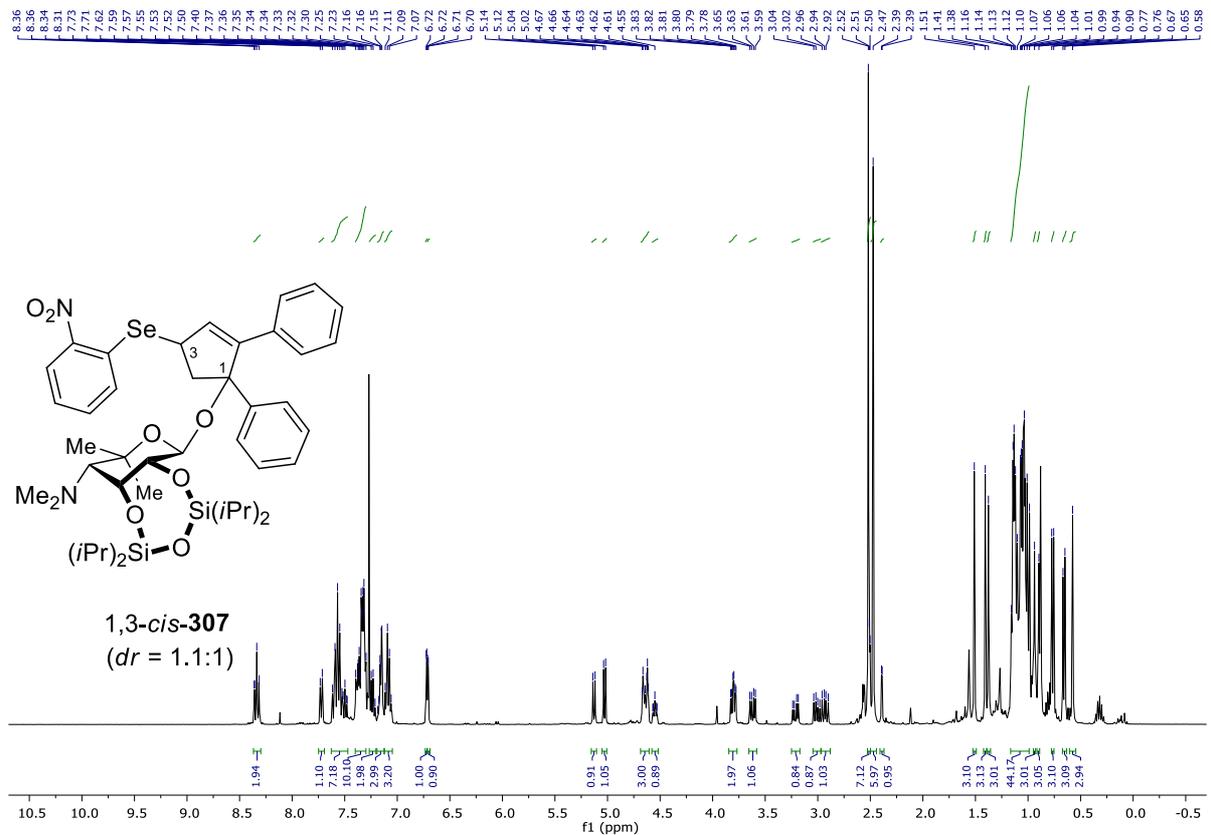


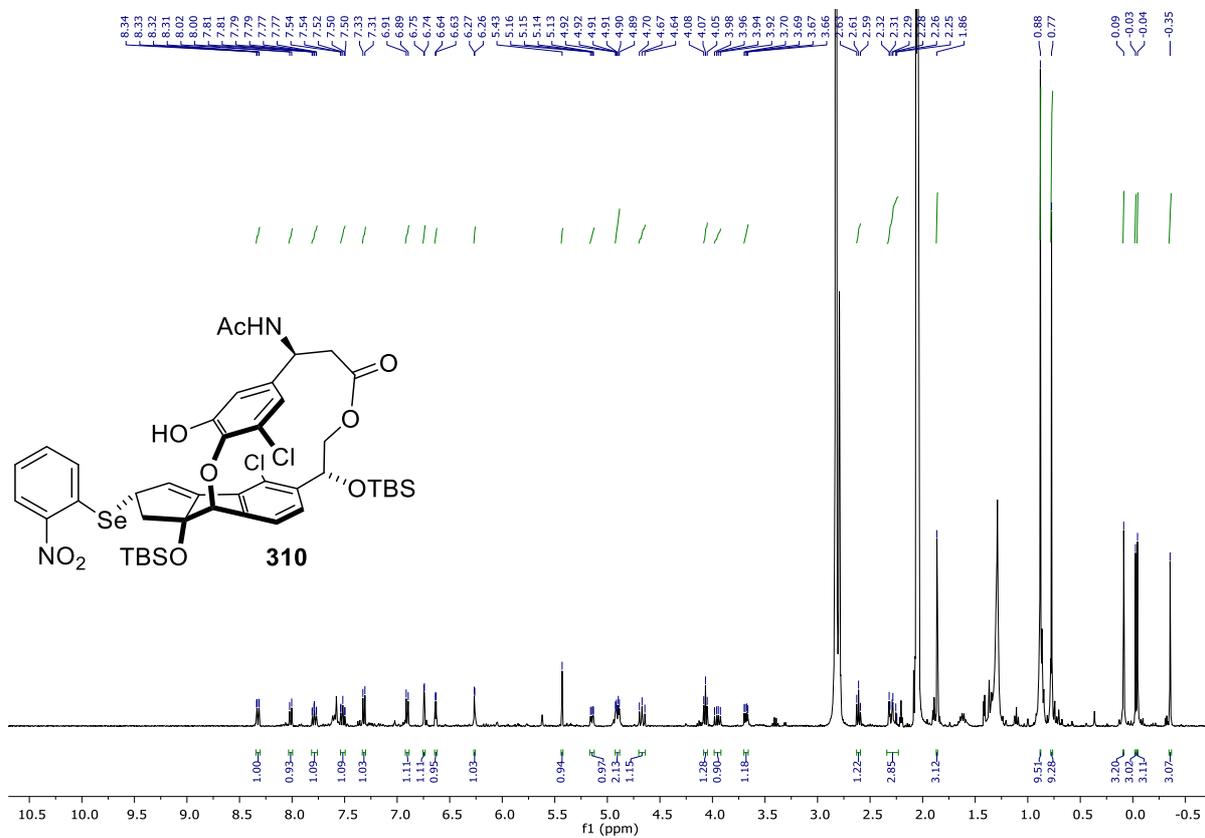
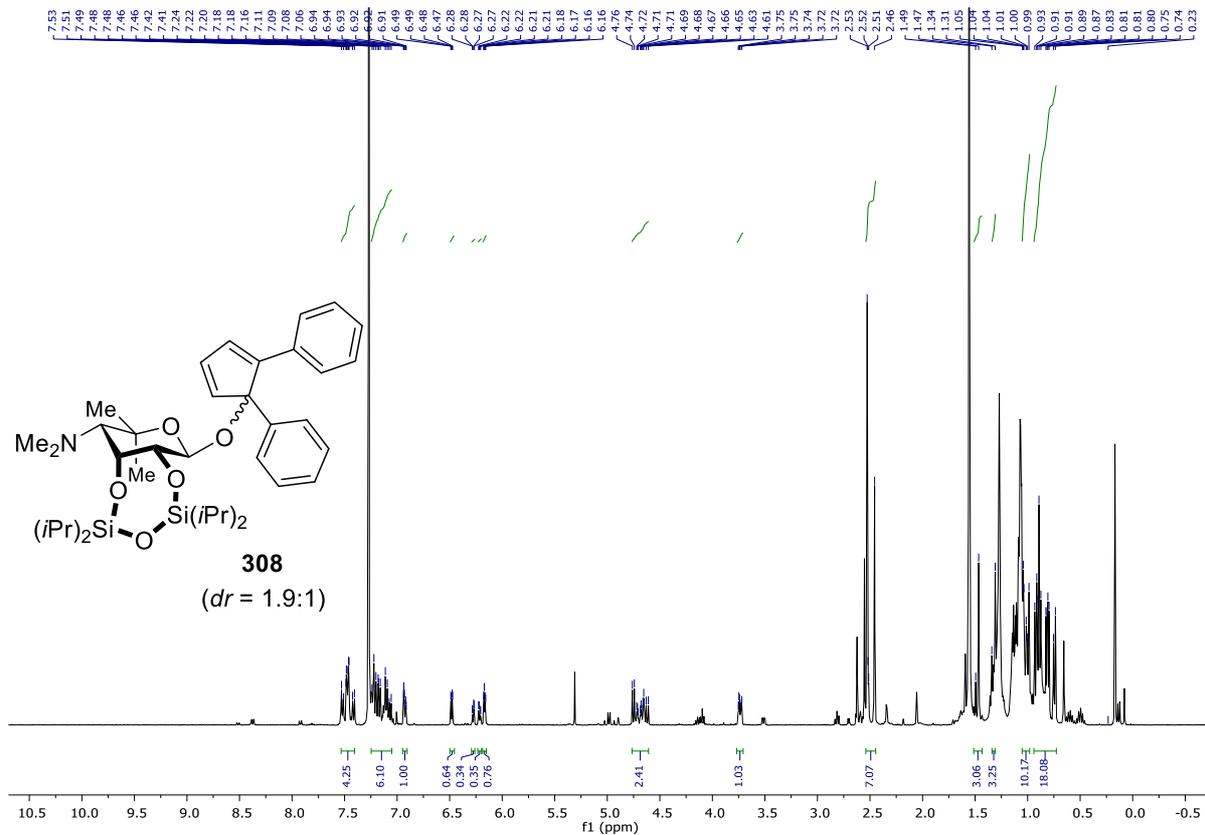


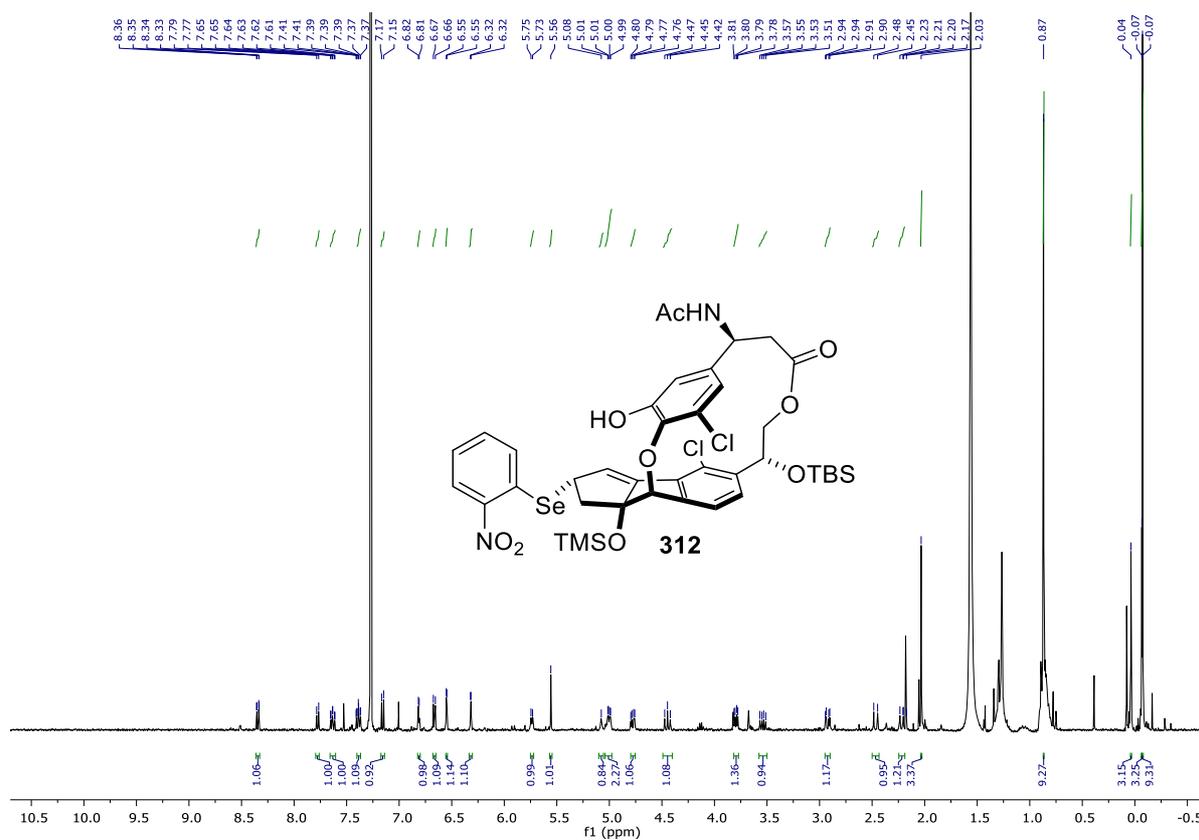


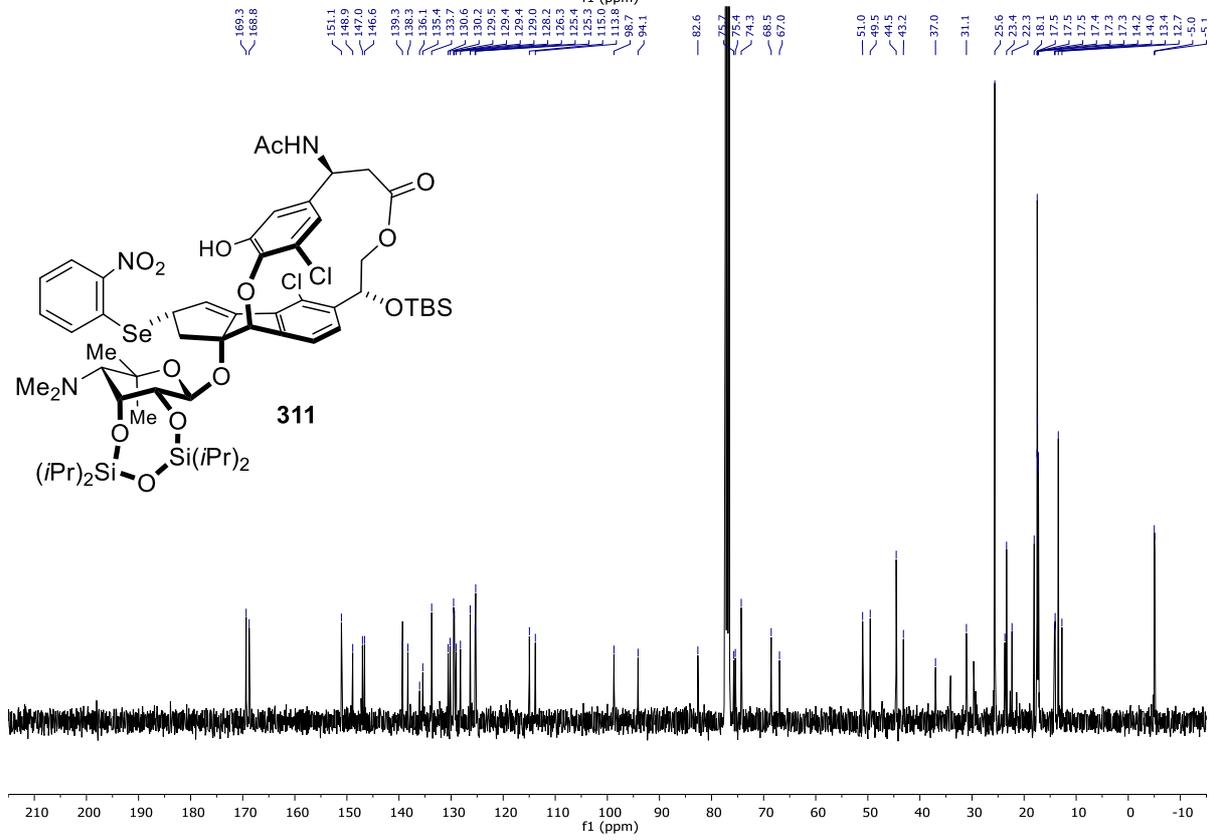
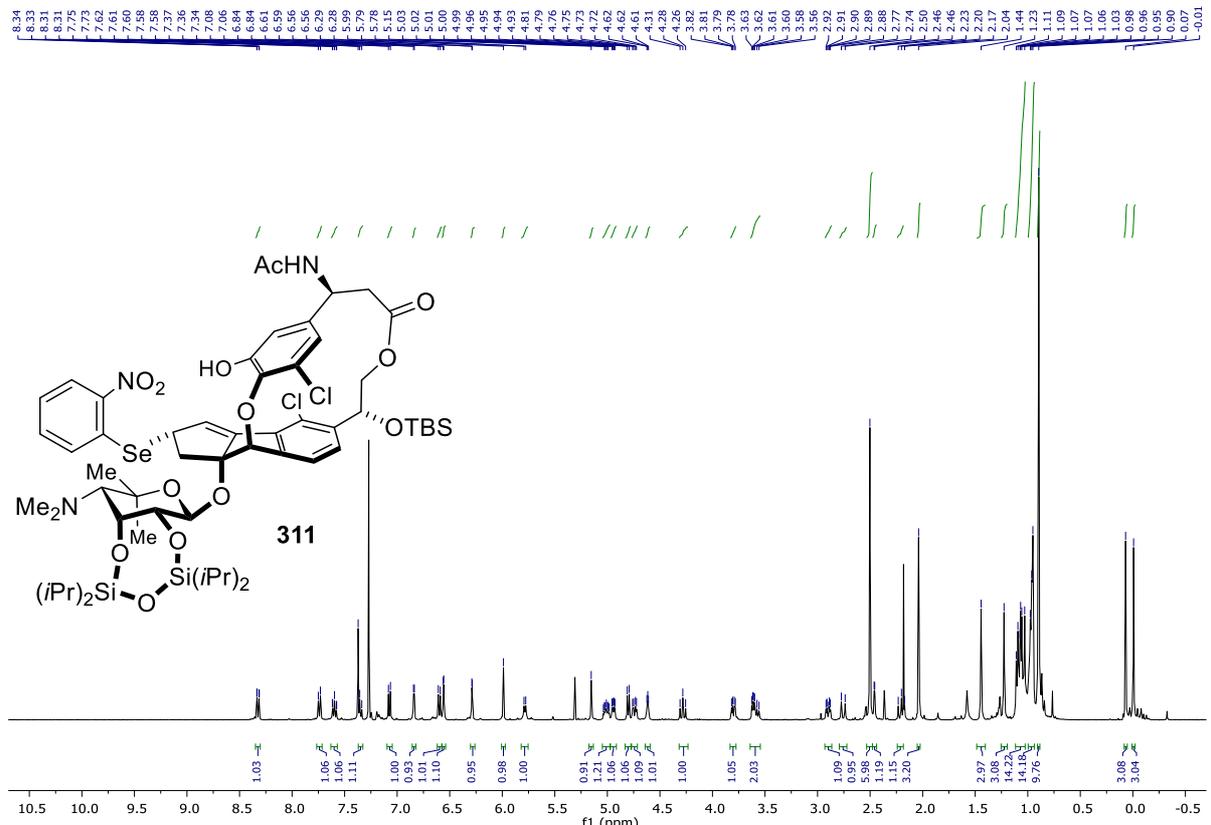




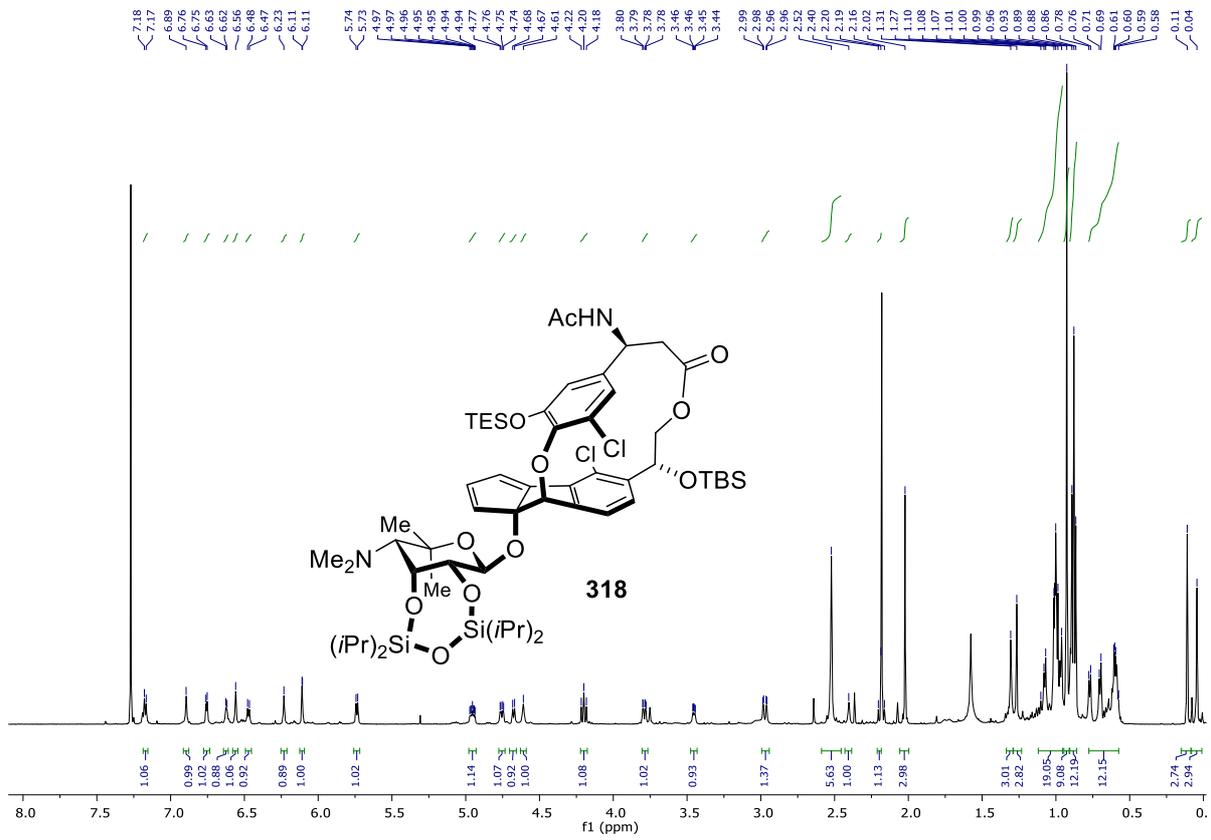


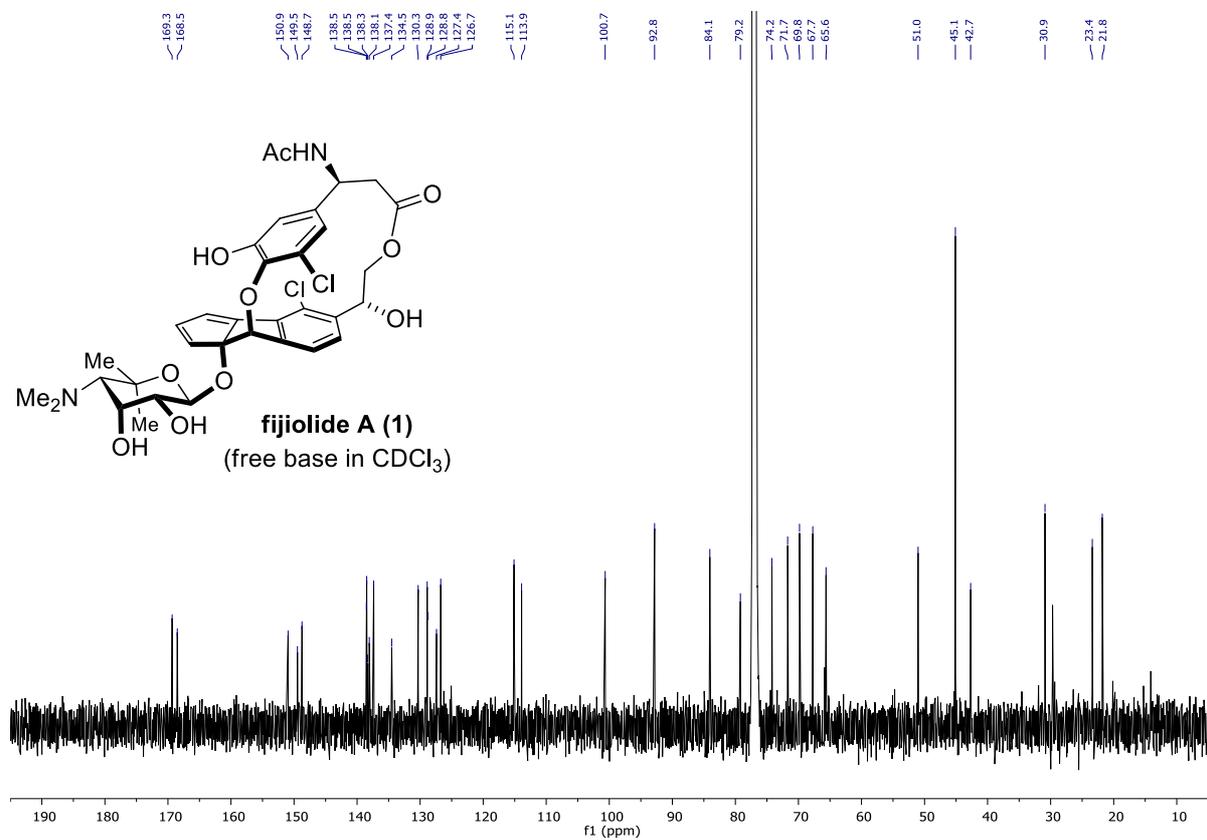
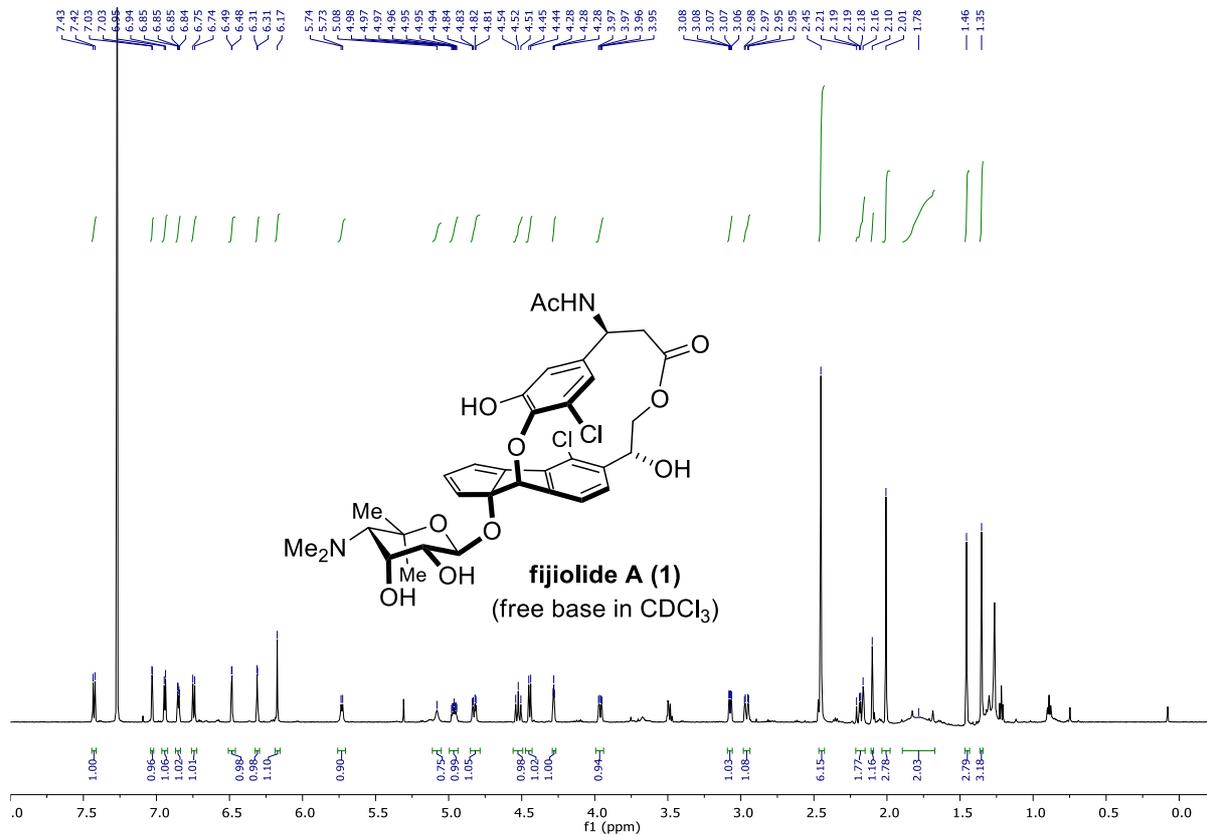


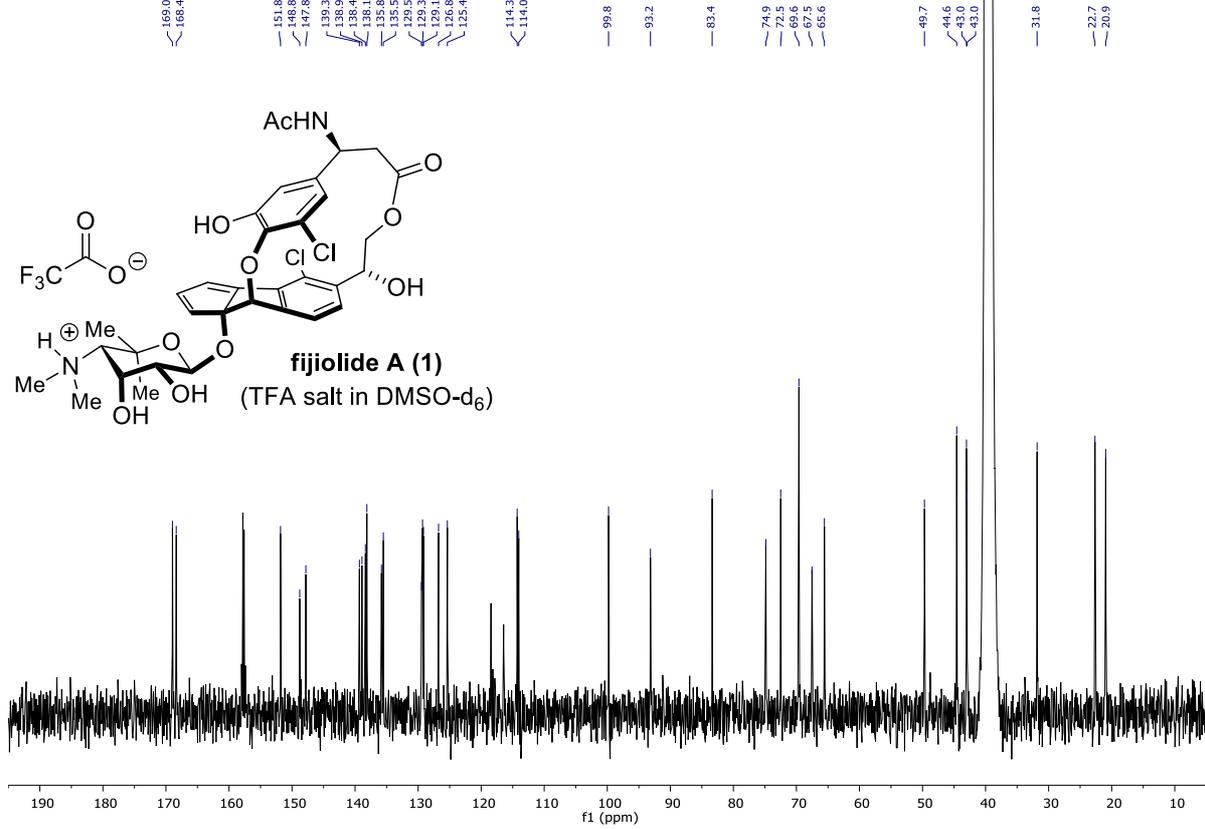
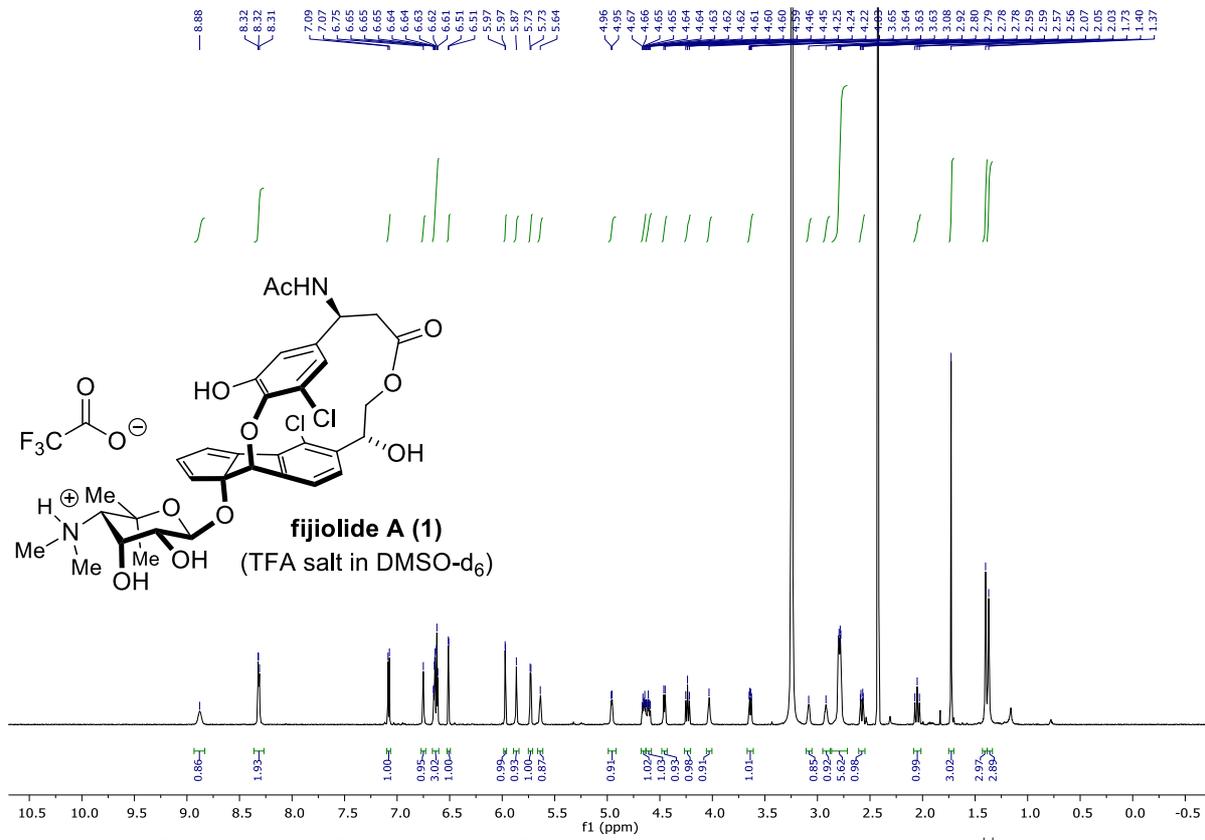














## *12. Curriculum Vitae*

**Christoph HEINZ***Curriculum Vitae*

Email: christoph.heinz@gmx.net  
 Phone: 0041-788345022  
 Date of Birth: August 10<sup>th</sup>, 1985  
 Address: Chemin de la Colline 11, 1007 Lausanne, Switzerland  
 Citizenship: German

**Education**

11/2011 – 02/2016	Doctoral Studies	<b>EPF Lausanne, Switzerland</b> PhD thesis in organic chemistry with Prof. N. Cramer: “ <i>Total Synthesis of Fijiolide A via an Atropselective Paracyclophane Formation.</i> ”
10/2009 – 09/2011	Master of Science in Chemistry (ranked 1/20)	<b>Technical University of Dortmund, Germany</b> Major in organic chemistry; Master thesis with Prof. M. Christmann: “ <i>Synthetic Studies Towards JBIR-22.</i> ” Grade obtained: 1.0 (“very good”)
10/2006 – 09/2009	Bachelor of Science in Chemistry (ranked 2/16)	<b>Technical University of Dortmund, Germany</b> Bachelor thesis with Prof. M. Christmann: “ <i>Synthesis of 1,4-Dienes by Allylic Substitution.</i> ” Grade obtained: 1.0 (“very good”)
08/1996 – 05/2005	German High School Diploma	St. Michael Gymnasium Ahlen, Germany advanced courses in Chemistry and Biology

**Work Experience**

02/2012 – 12/2014	Course Supervisor/ Teaching Assistant	Institute of Chemical Sciences & Engineering, EPFL <i>Supervision of undergraduate (practical) courses</i>
12/2008 – 02/2011	Student Assistant	Chair of Organic Chemistry, TU Dortmund <i>Tutor for Organic Chemistry I/II</i>  Chair of Technical Chemistry, TU Dortmund <i>Execution of high pressure reactions</i>  Chair of Inorganic Chemistry, TU Dortmund <i>Supporting elementary students in practical courses</i>
09/2005 – 05/2006	Community Service	St. Josef Parish, Ahlen <i>Youth leader, horticultural and charitable work</i>

## Publications and Awards

- *Synthesis of Fijiolide A via an Atropselective Paracyclophane Formation*, C. Heinz, N. Cramer, *J. Am. Chem. Soc.* **2015**, *137*, 11278-11281.
- *Transforming Terpene Feedstock into Polyketide Architecture*, P. Winter, C. Vaxelaire, C. Heinz, M. Christmann, *Chem. Commun.* **2011**, *47*, 394-396.
- *Early Postdoc.Mobilty Fellowship* awarded by the Swiss National Science Foundation
- *Best Poster Prize in Organic Chemistry* at the Swiss Chemical Society Fall Meeting 2015
- *Runner-up Poster Prize in Organic Chemistry* at the Swiss Chemical Society Fall Meeting 2014
- *Faculty Prize in Chemistry 2011*, Technical University of Dortmund

## Presentations

09/2015	Swiss Chemical Society Fall Meeting, Lausanne, Switzerland ( <i>poster</i> )
07/2015	44 <sup>th</sup> National Organic Chemistry Symposium, College Park, MD, USA ( <i>poster</i> )
09/2014	Swiss Chemical Society Fall Meeting, Zurich, Switzerland ( <i>poster</i> )
08/2013	Swiss Summer School on Synthesis and Catalysis, Villars, Switzerland ( <i>poster</i> )

## Extracurricular Experience

2004 – 2006	Youth Leader	Organization of childrens' and youth camps
2001 – 2008	School and Sports Event Technician	Technical support and organization of school events; Sub-group leader at the UCI ProTour cycle race "Deutschland Tour"

## Language Skills

German (native), English (fluent), French (basics)

## Interests

Handball, athletic sports, hiking, skiing, event technology

## Personal Profile

Reliable and responsible person, highly motivated to accomplish ambitious goals, team-oriented, able to identify and tackle (synthetic) problems.

*-References available upon request-*

