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Intramolecular Palladium-Catalyzed Alkene Carboalkynylation

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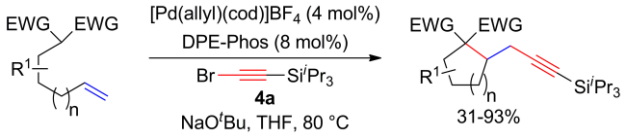

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Intramolecular Palladium-Catalyzed Alkene Carboalkynylation

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ABSTRACT

Carbocycles are essential building blocks for the synthesis of natural and synthetic bioactive compounds. Herein, we report the first example of palladium-catalyzed intramolecular carboalkynylation of non-activated olefins. Using activated carbonyl compounds as nucleophiles and an alkynyl bromide as an electrophile, the reaction gives access to cyclopentanes in 44-93% yield and one example of cyclohexane in 31% yield with simultaneous formation of a SP^3-SP C-C bond. The reaction therefore combines ring formation with the introduction of a versatile triple bond for further functionalization.

1. Introduction

Carbocycles confer a well-defined tridimensional structure to organic molecules and therefore allow more selective interactions with biological targets (Figure 1). This can already be achieved with a single five-membered ring, like in prostaglandin (**1**), or with more complex polycyclic frameworks, like the classical 6,6,6,5 ring system of the steroid cholesterol (**2**). Although five- and six-membered rings are most often encountered, other ring sizes can add further structural diversity, as exemplified by the diterpene ingenol (**3**) featuring three-, five- and seven-membered rings.[1] The importance of the exact cyclic structure of bioactive terpenes is also apparent from their biosynthesis via a cyclase and an oxidase phase, an approach which has also inspired synthetic chemists.[2] The development of new cyclization or annulation reactions to construct saturated carbocycles has consequently been an intensively investigated field of organic chemistry.

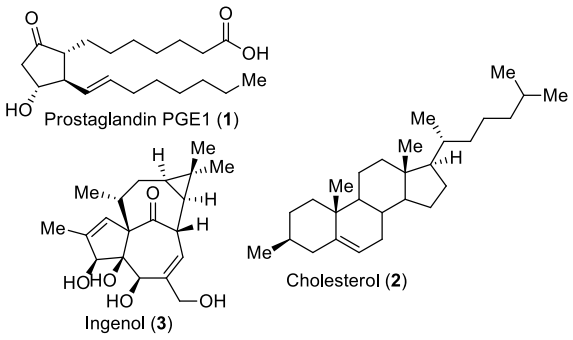
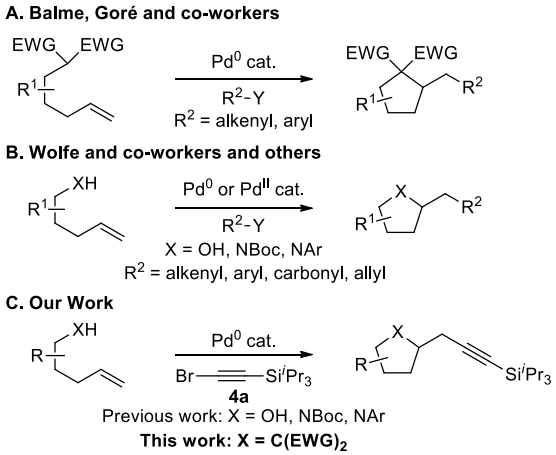


Figure 1. Carbocycles in bioactive compounds.

In this context, the palladium-catalyzed cyclization of carbon-nucleophiles onto alkenes is a powerful method to construct efficiently five- and six-membered rings.[3] If ring-formation can be accompanied by a second C-C bond formation in a domino reaction, the efficiency of the process will be greatly increased.[4] Nevertheless, the selective formation of two different C-C bonds in a single reaction sequence is challenging, and has been realized only in few rare cases. Most impressive are the reports of Goré, Balme and co-workers on the cyclization of activated carbonyl compounds combined with arylation or vinylation (Scheme 1, **A**).[5] However, this method remains underdeveloped in comparison to the oxy- or amino-carbofunctionalization reactions, which have been intensively investigated in the last decade, in particular by Wolfe and co-workers (Scheme 1, **B**).[6]

Scheme 1. Pd-catalyzed intramolecular carbofunctionalization of olefins.

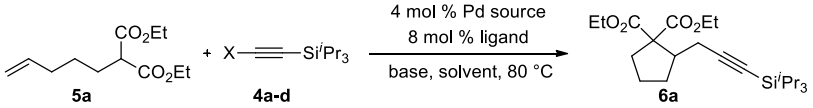


Since 2010, our group has been particularly interested in the hetero-alkynylation of alkenes,[7] as alkynes are among the most useful functional groups in organic chemistry.[8] We have developed both a Pd^{II}-[7a-b] and a Pd^0-catalyzed[7c-d] intramolecular oxy/amino-alkynylation of olefins using EBX (Ethynylbenziodoxolone) hypervalent iodine reagents and alkynyl bromides respectively. Herein, we would like to report the first use of activated carbonyls as nucleophiles in a Pd^0-catalyzed carboalkynylation of olefins (Scheme 1, **C**). The method could be applied to the synthesis of five- and six-membered rings and was also successful in the case of 5,5-, 5,6- and 5,7-bicyclic ring systems.

2. Results and Discussion

We started our investigations by examining the cyclization-alkynylation of diester **5a** with triisopropylsilylethynyl bromide (**4a**)[9] using the conditions developed previously for oxyalkynylation ($Pd_2(dba)_3$ with DPE-Phos as ligand, Table 1). Gratifyingly, the desired carboalkynylation product was obtained in 44% yield (entry 1). We then decided to systematically vary the palladium source, the phosphine ligand, the solvent, the base and the alkynylation reagent **4** in order to improve the yield. The palladium source used had a strong influence on the yield (entries 1-6).

Table 1. Optimization of the carboalkynylation reaction



5a **4a-d** **6a**

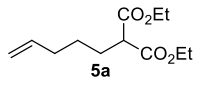
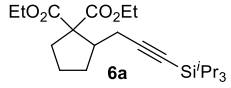
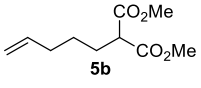
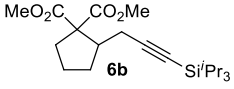
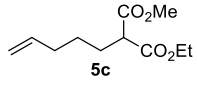
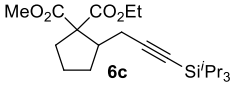
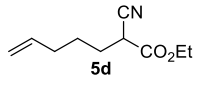
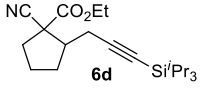
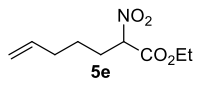
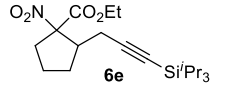
entry	Pd source	Ligand/bite angle	base	solvent	X	Yield[a]
1	$Pd_2(dba)_3$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	44%
2	$Pd(dba)_2$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	14%
3	$Pd(PPh_3)_4$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	3%
4	$Pd(OAc)_2$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	25%
5	$PdCl_2(PPh_3)_2$	DPE-Phos/102°	NaO^{t}Bu	THF	Br	72%
6	**[Pd(allyl)(cod)]BF$_4$**	**DPE-Phos/102°**	**NaO^{t}Bu**	**THF**	**Br**	**86%**
7	[Pd(allyl)(cod)]BF$_4$	dppe/76°	NaO^{t}Bu	THF	Br	5%
8	[Pd(allyl)(cod)]BF$_4$	dppp/86°	NaO^{t}Bu	THF	Br	<1%
9	[Pd(allyl)(cod)]BF$_4$	dppf/99°	NaO^{t}Bu	THF	Br	40%
10	[Pd(allyl)(cod)]BF$_4$	XANT-Phos/111°	NaO^{t}Bu	THF	Br	9%
11	[Pd(allyl)(cod)]BF$_4$	SEG-Phos/67°	NaO^{t}Bu	THF	Br	<1%
12	[Pd(allyl)(cod)]BF$_4$	BINAP/93°	NaO^{t}Bu	THF	Br	14%
13	[Pd(allyl)(cod)]BF$_4$	Ru-Phos	NaO^{t}Bu	THF	Br	37%
14	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	LiO^{t}Bu	THF	Br	83%
15	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	KO^{t}Bu	THF	Br	64%
16	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaHMDS	THF	Br	27%
17	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaH	THF	Br	19%
18	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	DBU	THF	Br	74%
19	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	Cs_2CO_3	THF	Br	0%
20	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	dioxane	Br	83%
21	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	trifluorotoluene	Br	57%
22	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	toluene	Br	22%
23	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	dichloroethane	Br	3%
24	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	acetonitrile	Br	1%
25	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	DMSO	Br	<1%
26	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	NMP	Br	<1%
27	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	THF	Cl	67%
28	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	THF	I	43%
29	[Pd(allyl)(cod)]BF$_4$	DPE-Phos/102°	NaO^{t}Bu	THF	BX	<1%

[a]Reaction conditions: 0.10 mmol **5a**, 0.15 mmol **4**, 4 mol % Pd source, 8 mol % ligand, 0.15 mmol base, 0.5 mL solvent, 80 °C. Yield determined by GC-MS. BX = Benziodoxolone.

Low yields were obtained with $Pd(dba)_2$, $Pd(PPh_3)_4$ or $Pd(OAc)_2$ (entries 2-4). With $PdCl_2(PPh_3)_2$, the yield could be improved to 72% (entry 5). Finally, the best result (86% yield) was obtained with $[Pd(allyl)(cod)]BF_4$[10] as precursor (entry 6). When other biphosphine ligands were tested (entries 7-12), only dppf, which has a bite angle similar to DPE-Phos (99 vs 102°) gave a substantial yield of **6a** (40%, entry 9). With the bulky monophosphine Ru-Phos, the carboalkynylation product **6a** could be obtained in 37% yield (entry 13). Up to now, no ligand superior to DPE-Phos could be found. Examination of the base confirmed that sodium *tert*-butoxide was the best (entries 14-19). Lithium *tert*-butoxide gave a similar yield (83%, entry 14), whereas **6a** was obtained in 64% yield with potassium *tert*-butoxide (entry 15). Stronger (entries 16 and 17) and weaker (entries 18 and 19) bases gave lower yields. Interestingly, product **6a** could still be obtained in 74% yield using DBU as a base (entry 18). The solvent effect was then examined (entries 20-26). A comparable yield was obtained in dioxane (83%, entry 20). Moderate yields were still observed in trifluorotoluene and toluene (entries 21 and 22), but no desired product could be obtained in dichloroethane, acetonitrile, NMP and DMSO (entries 23-26). It is interesting to note that highly polar solvents such as NMP and DMSO, which gave the best results for the related carboarylation reaction,[5a] did not work in this case. To conclude our optimization studies, we turned to variation of the alkynylation reagent (entries 27-29). The use of chloro- or iodo-alkynes **4b** and **4c** gave lower yields (entries 27 and 28). Finally, the use of the hypervalent iodine reagent TIPS-EBX (**4d**) was not successful (entry 29).

On preparative scale, cyclopentane **6a** was obtained in 85% yield (Table 2, entry 1). We then investigated which types of activated carbonyl compounds could be used in the cyclization reaction.[11] Dimethylmalonate derivative **5b** gave the desired product **6b** in 62% yield (entry 2). The reaction was also successful in the case of mixed malonate **5c** and cyano ester **5d**, although in this case mixtures of diastereoisomers were obtained (entries 3 and 4). No product was observed when using nitro ester **5e** (entry 5).

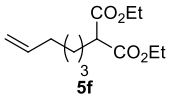
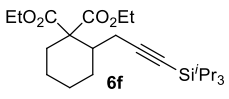
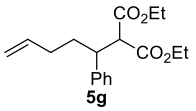
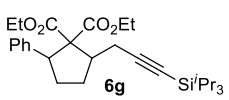
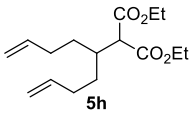
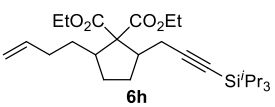
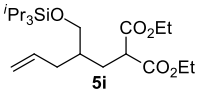
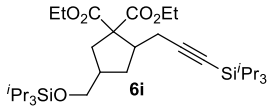
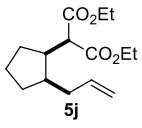
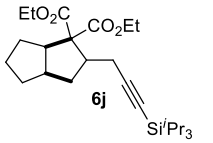
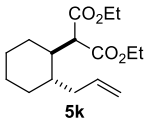
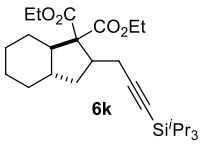
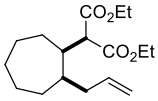
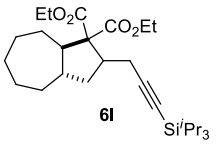
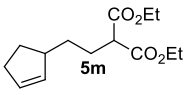
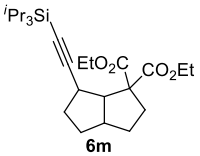
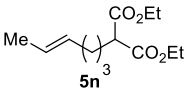
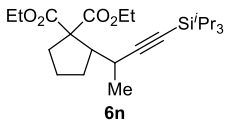
Table 2. Scope of activated carbonyl compounds.

entry	starting material	product	yield[a]
1	 **5a**	 **6a**	85%
2	 **5b**	 **6b**	62%
3	 **5c**	 **6c**	53%[b]
4	 **5d**	 **6d**	82%[b]
5	 **5e**	 **6e**	-

[a]Reaction conditions: 0.40 mmol **5**, 0.60 mmol **4a**, 0.015 mmol $[Pd(allyl)(cod)]BF_4$, 0.03 mmol DPE-Phos, 0.60 mmol NaO^{t}Bu, 2 mL THF, 80 °C. Isolated yields after column chromatography are given. [b]Obtained as a mixture of diastereoisomer (<2:1 dr), the diastereoselectivity could not be determined exactly due to peaks overlap.

We then turned to further modification of the diethyl malonate substrates (Table 3). Cyclohexane **6f** could be obtained in 31% yield, demonstrating that the synthesis of six-membered rings was also possible, albeit in lower yield (entry 1).

Table 3. Scope of substituents on the diethylmalonate substrates.

entry	starting material	product	yield[a]
1	 **5f**	 **6f**	31%
2	 **5g**	 **6g**	60%[b,c]
3	 **5h**	 **6h**	44%[b,c]
4	 **5i**	 **6i**	78%[b]
5	 **5j**	 **6j**	60%[b,c]
6	 **5k**	 **6k**	86%[b]
7	 **5l**	 **6l**	93%[b]
8	 **5m**	 **6m**	-
9	 **5n**	 **6n**	-

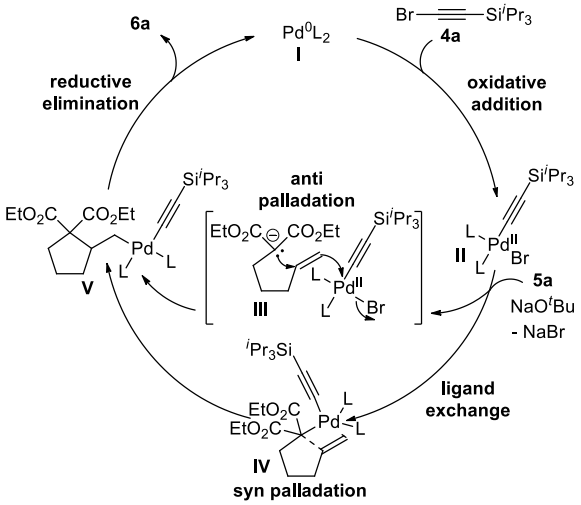
[a]Reaction conditions: 0.40 mmol **5**, 0.60 mmol **4a**, 0.015 mmol $[Pd(allyl)(cod)]BF_4$, 0.03 mmol DPE-Phos, 0.60 mmol NaO^{t}Bu, 2 mL THF, 80 °C. Isolated yields after column chromatography are given. [b]Obtained as a mixture of diastereoisomer (<2:1 dr), the diastereoselectivity could not be determined exactly due to peaks overlap. [c]Compound obtained in about 90% purity as determined by ^{1}H NMR.

Substituents in β or γ positions of the malonates were well tolerated (entries 2-4). However, a low diastereoselectivity (<2:1) was observed. Substituted five-, six-, and seven- membered rings were then examined in order to access important bicyclic systems (entries 5-7). The reaction proceeded in 60-93% yield and gave a mixture of diastereoisomers at the newly formed stereocenter. Currently, the method is limited to terminal alkenes, as no product was observed when using cyclic or acyclic internal

alkenes (entries 8 and 9). In addition, a complex mixture of compounds was obtained when aliphatic or aryl alkynyl bromides were used under these conditions.

At this early stage of research, only a very speculative proposal for the reaction mechanism can be made based on previous works in the field (Scheme 2).[5-7] Under the reaction conditions, a Pd^0-phosphine complex **I** is probably first generated. Oxidative addition on alkynyl bromide **4a** then gives Pd^{II} intermediate **II**. At this point, two mechanisms can be envisaged for carbopalladation: *anti* palladation via transition state **III** to give alkyl palladium complex **V**, or first ligand exchange resulting in formation of intermediate **IV**, followed by *syn* palladation to give **V**. The strong dependence on base strength indicates that deprotonation of malonate **5a** is required for the reaction to proceed. In our previous work on oxyalkynylation, we could demonstrate through the use of internal alkenes as substrates that the reaction proceeded via *syn* palladation.[7c-d] On the other hand, Balme, Goré and co-workers reported strong evidence for an *anti* palladation mechanism for the related carboarylation reaction.[5a] As the reaction did not work for internal olefins under our conditions, the stereochemistry of the carbopalladation step unfortunately cannot yet be established.[12] Nevertheless, the low diastereoselectivity observed would be more in agreement with an *anti* palladation process. Finally, reductive elimination with formation of the C(SP)-C(SP^3) bond gives product **6a** and regenerates the active Pd^0 complex **I**.

Scheme 2. Speculative mechanism for the carboalkynylation reaction.



In conclusion, we have described the first example of intramolecular carboalkynylation of alkenes using activated carbonyl compounds as nucleophiles and triisopropylsilylalkynyl bromide (**4a**). The reaction proceeded in good yields for the formation of five-membered rings and tolerated a broad range of substitution patterns on the alkyl chain between the olefin and the carbonyl compound. The formation of a six-membered ring was also possible, albeit only in moderate yields. Future investigations will focus on increasing the diastereoselectivity of the process, extending the scope to internal alkenes and other types of alkynylation reagents, as well as on in-depth understanding of the reaction mechanism.

3. Experimental section

3.1 General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, Karl-Fischer titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar reduced pressure. TLC was performed on Merck silica gel 60 F254 TLC glass plates or aluminium plates and visualized with UV light, permanganate stain or anisaldehyde stain. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d and all signals are reported in ppm with the internal chloroform signal at 7.26 ppm The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation). ^{13}CNMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prism and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API. All starting materials were synthesized using adapted reported procedures.[11]

3.2 General procedure for carboalkynylation

The starting material **5** (0.40 mmol) was introduced into a sealed tube containing $[Pd(allyl)(cod)]BF_4$ (5.2 mg, 0.015 mmol, 0.04 equiv), DPE-Phos (17 mg, 0.030 mmol, 0.08 equiv.), NaO^{t}Bu (57 mg, 0.60 mmol, 1.5 equiv), dry THF (2.0 mL) and TIPS acetylene bromide (**4a**) (0.17 g, 0.60 mmol, 1.5 equiv). The vial was heated to 80 °C and the reaction stirred until complete conversion of the starting material (analysis by TLC). The mixture was then allowed to cool to room temperature, silica gel was added and the solvent was removed under reduced pressure. The crude product adsorbed on silica gel was directly put on column chromatography for purification, eluting with PET:Et_2O, 15:1.

3.3 Characterization data for cyclization products

3.3.1 Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (6a)

The product was isolated as a yellow oil (0.138 g, 3.84 mmol, 85%) Rf: 0.5 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25-4.08 (m, 4H, $CO_2CH_2CH_3$), 2.80-2.72 (m, 1H, ring proton), 2.57 (dd, *J* = 16.5, 3.9 Hz, 1H, propargylic H), 2.46-2.38 (m, 1H, ring proton), 2.17-2.01 (m, 2H, ring protons), 2.11 (dd, *J* = 16.5, 11.2 Hz, 1H, propargylic H), 1.89-1.78 (m, 1H, ring proton), 1.70-1.56 (m, 2H, ring protons), 1.25 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.07-1.03 (m, 21H, TIPS protons). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 170.8, 107.3, 81.1, 62.8, 61.2, 61.1, 45.1, 34.4, 30.7, 22.5, 22.1, 18.6, 14.1, 14.0, 11.3. IR (neat), 2946(m), 2868(m), 2173 (w), 1731 (s), 1462 (m), 1372 (w), 1259 (s), 1200 (m), 1068 (m), 1027 (m), 881 (w). HRMS (ESI) calc for $C_{23}H_{42}O_4Si^+$ $[M+H]^+$ 409.27741; found 409.2778.

3.3.2 Dimethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (6b)

The product was isolated as a yellow oil (93.4 mg, 0.246 mmol, 62%) Rf: 0.42 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, CO_2*Me*), 3.70 (s, 3H, CO_2*Me*), 2.81-2.73 (m, 1H, ring proton), 2.55 (dd, *J* = 16.5 Hz, 4.0 Hz, 1H, propargylic H), 2.47-2.39 (m, 1H, ring proton), 2.16-2.03 (m, 3H, ring protons and propargylic H), 1.88-1.80 (m, 1H, ring protons), 1.71-1.58 (m, 2H, ring protons), 1.09-1.00 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 171.2, 107.0, 81.3, 62.8, 52.6, 52.3, 45.2, 34.4, 30.6, 22.5, 22.1, 18.6, 11.3. IR (neat), 2943 (m), 2865 (m). 2173 (m), 1732 (s), 1464 (m), 1463 (m), 1260 (s), 1205 (m), 1155 (m), 883 (s). HRMS (ESI) calcd for $C_{21}H_{36}NaO_4Si^+$ $[M+Na]^+$ 403.2275; found 403.2274.

3.3.3 1-Ethyl 1-methyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (6c)

The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr < 2:1, 83.6 mg, 0.212 mmol, 53%). Rf: 0.48 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz $CDCl_3$) δ 4.23-4.08 (m, 4H, CO_2*CH*$_2$CH$_3$), 3.71 (s, 3H, CO_2*CH*$_3$), 3.69 (s, 3H, CO_2*CH*$_3$), 2.81-2.72 (m, 2H, ring protons), 2.59-2.51 (m, 2H, propargylic H), 2.46-2.39 (m, 2H, ring protons), 2.14-2.01 (m, 6H, ring protons and propargylic H), 1.88-1.79 (m, 2H, ring protons), 1.71-1.55 (m, 4H, ring protons), 1.26-1.21 (m, 6H, CO_2CH_2*CH*$_3$), 1.09-1.02 (m, 42H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 171.9, 171.3, 170.7, 107.2, 107.1, 81.1, 62.9, 62.8, 61.3, 61.2, 52.5, 52.2, 45.2, 45.0, 34.3, 30.7, 30.6, 22.5, 22.2, 22.1 18.6, 14.2, 14.1, 11.3. Not all signals for each diastereoisomer could be resolved. IR (neat), 2941 (m), 2865 (m), 2173 (m), 1731 (s), 1464 (m), 1367 (w), 1258 (s), 1202 (m), 1153 (m), 1075 (m), 1029 (m), 996 (m), 883 (m). HRMS (ESI) calcd for $C_{22}H_{38}NaO_4Si^+$ $[M+Na]^+$ 417.2432; found 417.2413.

3.3.4 Ethyl 1-cyano-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentanecarboxylate (6d)

The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr: < 2:1, 0.123 g, 0.339 mmol, 82%). Rf: 0.40 (PET:Et_2O/15:1). ^{1}H NMR (400MHz $CDCl_3$) δ 4.24 (q, *J* = 7.0 Hz, 2H, CO_2*CH*$_2$CH$_3$), 2.74-2.44 (m, 3H, ring protons and propargylic H), 2.36-2.14 (m, 3H, ring protons and propargylic H), 2.04-1.65 (m, 3H, ring protons), 1.37-1.31 (m, 3H, CO_2CH_2*CH*$_3$) 1.08-0.97 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 167.8, 120.7, 118.1, 105.3, 104.9, 82.6, 82.0, 62.8, 62.6, 52.6, 50.5, 50.2, 47.9, 37.9, 36.7, 30.7, 30.6, 23.2, 22.6, 22.4, 21.4, 18.5, 18.4, 14.1, 14.0, 11.3, 11.2. IR (neat), 2943 (s), 2866 (s), 2243(w), 2176 (m), 2121 (m), 2062 (w), 1742 (s), 1464 (s), 1384 (w), 1369 (m), 1257 (s), 1222 (s), 1020 (s), 921 (m), 883 (s). HRMS (ESI) calcd $C_{21}H_{36}NO_2Si^+$ $[M+H]^+$ 362.2515; found 362.2516.

3.3.5 Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclohexane-1,1-dicarboxylate (6f)

The product was isolated as a yellow oil (52.2 mg, 0.124 mmol, 31%). Rf: 0.49 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.21-4.15 (m, 4H, CO_2*CH*$_2$CH$_3$), 2.54-2.49 (m, 1H, propargylic H), 2.31-2.24 (m, 2H, ring protons and propargylic H), 2.17-2.10 (m, 1H, ring proton), 2.07-2.00 (m, 1H, ring proton), 1.88-1.81 (m, 1H, ring proton), 1.63-1.58 (m, 1H, ring proton), 1.52-1.30 (m, 4H, ring protons), 1.26-1.23 (m, 6H, CO_2CH_2*CH*$_3$), 1.07-1.02 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 170.5, 108.9, 81.1, 61.2, 60.9, 58.4, 41.0, 31.2, 26.4, 23.4, 22.6, 22.1, 18.6, 14.1, 11.3 (2C). IR (neat), 2942 (m), 2865 (m), 2172 (m), 1730 (s), 1261 (m), 1368 (m), 1245 (s), 1197 (m), 1142 (m), 1022 (m), 883 (m). HRMS (ESI) calcd for $C_{24}H_{43}O_4Si^+$ $[M+H]^+$ 423.2925; found 423.2938.

3.3.6 Diethyl 2-phenyl-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (6g)

The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr: 2:1, 0.116 g, 0.250 mmol, 60%, > 90% pure). The dr was calculated by integrating the peaks at 3.92 and 3.76 ppm in the ^{1}H NMR. Rf: 0.44 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.32 (m, 1H, Ar-H, both diastereoisomers), 7.23-7.17 (m, 6.5H, Ar-H, both diastereoisomer), 4.30-4.07 (m, 4H, CO_2*CH*$_2$CH$_3$ both diastereoisomer and benzylic CH major diastereoisomer), 3.98-3.87 (m, 1H, benzylic H, minor diastereoisomer and 1H, CO_2*CH*$_2$CH$_3$, minor diastereoisomer), 3.76 (dq, *J* = 10.7, 7.1, Hz, 1H, CO_2*CH*$_2$CH$_3$, major diastereoisomer), 3.65 (dq, *J* = 10.7, 7.2 Hz, 0.5H, CO_2*CH*$_2$CH$_3$, minor diastereoisomer), 3.36 (dq, *J*=10.7, 7.2 Hz, 1H, CO_2*CH*$_2$CH$_3$, major diastereoisomer), 3.16-3.08 (m, 1H, ring proton), 2.77 (dd, *J* = 15.6, 2.5 Hz, 0.5H, propargyl CH_2, minor diastereoisomer), 2.67-2.50 (m, 2H, propargyl CH_2, major diastereoisomer and ring proton), 2.38-2.52 (m, 3H, ring protons), 2.18-2.05 (m, 1H, ring proton), 2.10 (dd, *J* = 16.5, 10.3 Hz, 1H, propargyl CH_2, major diastereoisomer), 2.02-1.91 (m, 1H, ring proton), 1.75-1.62 (m, 1H, ring proton), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2C*H*$_3$, major diastereoisomer), 1.21 (t, *J* = 7.1 Hz, 1.5H, OCH_2C*H*$_3$, minor diastereoisomer), 1.09-1.05 (m, 31.5H, TIPS), 0.88 (t, *J* = 7.2 Hz, 1.5H, OCH_2C*H*$_3$, minor diastereoisomer), 0.77 (t, *J* = 7.2 Hz, 3H, OCH_2C*H*$_3$, major diastereoisomer). ^{13}C NMR (101 MHz, $CDCl_3$), δ 170.6, 170.1, 142.0, 139.8, 128.9, 128.7, 127.9, 127.7, 127.0, 126.8, 106.9, 81.3, 68.0, 67.6, 61.2, 61.1, 60.7, 60.5, 52.3, 51.7, 48.5, 45.1, 31.6, 30.4, 29.6, 29.0, 22.6, 21.8, 18.6, 14.1, 14.0, 13.6, 13.3, 11.4, 11.3. Not all peaks of the minor diastereoisomer could be resolved for the alkyne and the TIPS. IR (neat), 2961 (broad, s), 2172 (w), 1724 (s), 1462 (m), 1377 (m), 1252 (s), 1057 (s), 881 (m). HRMS (ESI) calcd for $C_{29}H_{45}O_4Si$ $[M+H]^+$ 485.3082; found 485.3062.

3.3.7 Diethyl 2-(but-3-en-1-yl)-5-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (6h)

The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr < 2:1, 81.2 mg, 0.180 mmol, 44%, >90% purity by ^{1}H NMR). Rf: 0.50 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.72 (m, 1H, CH_2*CH*=CH_2), 5.03-4.93 (m, 2H, CH_2CH=*CH*$_2$), 4.28-4.08 (m, 4H, CO_2*CH*$_2$CH$_3$), 2.92-2.76 (m, 1H), 2.71-1.80 (m, 7 H), 1.72-1.60 (m, 1H), 1.38-1.24 (m, 9 H), 1.11-1.00 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 171.0, 170.9, 170.4, 138.5 (2C), 114.6. 114.5, 106.9, 81.2, 66.6, 66.5, 61.0, 60.9, 47.2, 44.6, 44.0, 32.5, 32.3, 31.3, 30.8, 29.2, 29.0, 28.9, 28.2, 23.2, 18.6, 18.0, 14.2, 14.1, 11.3. Not all peaks of the minor diastereoisomer could be resolved. IR (neat), 2969 (br, s), 2173 (w), 1726 (s), 1464 (m), 1394 (m), 1252 (m), 1190 (m), 1067 (s), 883(m). HRMS (ESI) calcd for $C_{27}H_{47}O_4Si^+$ $[M+H]^+$ 463.3238; found 463.3243.

3.3.8 Diethyl 4-(((triisopropylsilyl)oxy)methyl)-2-(3-(triisopropylsilyl)prop-2-yn-1-yl)cyclopentane-1,1-dicarboxylate (6i)

The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr < 2:1, 0.186 g, 0.313 mmol, 78%). Rf: 0.51 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23-4.09 (m, 4H, CO_2*CH*$_2$CH$_3$), 3.71-3.54 (m, 2H, O*CH*$_2$), 2.90-2.72 (m, 1H), 2.63 (dd, *J* = 16.5, 3.8 Hz, 0.4H, propargylic H, *minor diastereoisomer*), 2.56-2.52 (m, 1.6H), 2.30-1.96 (m, 4H), 1.87-1.78 (m, 1H), 1.46-1.36 (m, 1H), 1.26-1.22 (m, 6H, CO_2CH_2C*H*$_3$), 1.08-1.02 (m, 42H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 171.8, 170.9, 170.8, 107.3, 107.2, 81.2, 81.0, 66.8, 66.6, 63.0, 62.5, 61.4, 61.3, 61.1, 44.6, 44.5, 39.9, 38.4,

37.1, 36.9, 34.6, 33.3, 22.5, 21.9, 18.7, 18.1, 14.1, 14.0, 12.0, 11.3. Not all signals for each diastereoisomer could be resolved. IR (neat), 1942 (m), 2892 (m), 2865 (s), 2173 (w), 1731 (s), 1464 (m), 1367 (m), 1254 (m), 1195 (m), 1098 (m), 1015 (m), 883 (s). HRMS (ESI) calcd for $C_{33}H_{63}O_5Si_2^+$ $[M+H]^+$ 595.4209; found 595.4217.

3.3.9 Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)hexahydropentalene-1,1(2H)-dicarboxylate (6j)

The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr < 2:1, 0.106 g, 0.237 mmol, 60%, >90% purity). Rf: 0.53 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22-4.07 (m, 4H, $CO_2CH_2CH_3$), 3.19-3.12 (m, 0.5H), 3.04-2.95 (m, 0.3H), 2.91-2.75 (m, 1H), 2.71-2.20 (m, 3.2 H), 2.17-1.87 (m, 1H), 1.85-1.40 (m, 6H), 1.26-1.22 (m, 7H, ring proton and $CO_2CH_2CH_3$), 1.06-1.02 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 170.7, 170.0, 108.1, 107.7, 80.9, 80.3, 66.1, 65.4, 61.1, 61.0, 60.7, 60.5, 51.9, 50.3, 50.2, 42.4, 42.3, 40.4, 37.9, 36.5, 35.5, 32.6, 30.7, 29.3, 28.1, 27.4, 21.8, 21.3,18.6, 14.2, 14.0, 11.3. Not all signals for each diastereoisomer could be resolved. IR (neat), 2943 (m), 2865 (m), 2173 (w), 1728 (s), 1464 (m), 1368 (m), 1252 (s), 1203 (m), 1098 (m), 1021 (m), 884 (m). HRMS (ESI) calcd for $C_{22}H_{44}NaO_4Si^+$ $[M+Na]^+$ 423.2901; found 423.2922.

3.3.10 Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydro-1H-indene-1,1-dicarboxylate (6k)

Reaction done using 0.0810 g (0.290 mmol) of the starting malonate. The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr < 2:1, 0.111 g, 0.240 mmol, 86%). Rf: 0.53 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27-4.06 (m, 4H, $CO_2CH_2CH_3$), 3.08-3.01 (m, 0.6H), 2.60-2.50 (m, 1H), 2.42 (dd, *J* = 16.4, 4.3 Hz, 0.6H, propargylic H, major diastereoisomer), 2.17 (dd, *J* = 16.3, 9.8 Hz, 0.6H, propargylic H, major diastereoisomer), 2.25-2.12 (m, 0.6H), 2.08-1.60 (m, 6H), 1.35-1.20 (m, 9H, ring protons and $CO_2CH_2CH_3$), 1.07-1.02 (m, 23H, TIPS and ring protons), 0.87-0.77 (m, 0.6H). ^{13}C NMR (101 MHz, $CDCl_3$,) δ 171.5, 171.4, 170.2, 169.2, 108.5, 106.5, 81.6, 80.1, 65.3, 65.0, 61.0, 60.9, 60.8, 60.5, 53.3, 51.1, 45.1, 41.4, 41.2, 41.1, 37.8, 35.6, 32.7, 32.2, 28.9, 28.1, 26.3, 26.2, 26.1, 25.8, 23.5, 22.5, 18.6, 14.2, 14.1, 14.1, 14.0, 11.3, 11.3. The methyl peaks at 18.6 ppm for the TIPS groups of both isomers were overlapping. IR (neat), 2928 (m), 2864 (m), 2173 (w), 1726 (s), 1464 (m), 1367 (w), 1250 (s), 1193 (s), 1088 (w), 1017 (m), 883 (m). HRMS (ESI) calcd for $C_{27}H_{47}O_4Si^+$ $[M+H]^+$ 463.3238; found 463.3239.

3.3.11 Diethyl 2-(3-(triisopropylsilyl)prop-2-yn-1-yl)octahydroazulene-1,1(2H)-dicarboxylate (6l)

The product was isolated as a yellow oil as a mixture of inseparable diastereoisomers (dr < 2:1, 0.176 g, 0.370 mmol, 93%). Rf: 0.54 (PET:Et_2O/15:1). ^{1}H NMR (400 MHz, $CDCl_3$), δ 4.28-4.07 (m, 4H, CO_2CH_2), 2.94-2.86 (m, 0.4H), 2.82 (dd, *J* = 16.4, 3.3 Hz, 0.6H, propargylic H, major diastereoisomer), 2.76-2.68 (m, 0.4H), 2.68-2.60 (m, 0.6H), 2.54-2.44 (m, 1H), 2.41 (dd, *J* = 16.7, 3.9 Hz, 0.4H, propargylic H, minor diastereoisomer), 2.36-2.20 (m, 1.4H), 2.09 (dd, *J* = 16.4, 5.2 Hz, 0.6H, propargylic H, major diastereoisomer), 2.20-1.74 (m, 4.6H), 1.66-1.45 (m, 3H), 1.29-1.13 (m, 10H, ring protons and $CO_2CH_2CH_3$), 1.07-1.02 (m, 21H, TIPS). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.0, 170.6, 169.6, 107.8, 107.3, 81.2, 80.5, 68.4, 66.5, 61.0, 60.9, 60.6, 60.5, 51.7, 48.5, 46.5, 43.8, 41.7, 40.8, 39.0, 38.1, 33.4, 32.0, 31.4, 31.2, 30.6, 29.7, 29.6, 29.2, 28.0, 27.8, 22.1, 21.5, 18.6, 14.2, 14.1, 13.9, 11.3. The signals for the TIPS and for one methyl group on the esters for each diastereoisomer could not be resolved. IR (neat), 2921 (m), 2865 (m), 2173 (m), 1726 (s), 1464 (m), 1367 (m), 1252 (s), 1204 (m), 1182 (s), 1101 (m), 1076 (m), 1019 (s), 883 (s). HRMS (ESI) calcd for $C_{28}H_{49}O_4Si^+$ $[M+H]^+$ 477.3395; found 477.3411.

Acknowledgments

EPFL, F. Hoffmann-La Roche Ltd and SNF (grant number 200021_119810) are acknowledged for financial support. The Institute of Chemical Sciences and Engineering (ISIC) at EPFL is acknowledged for the support of the master thesis of P. S.

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Supplementary Material

Detailed synthesis procedures, characterization data for starting materials and copies of NMR and IR spectra for new compounds.

Supporting Information for:

Intramolecular Palladium-Catalyzed Alkene Carboalkynylation

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(40 pages)

Table of Content

1. General Methods

All reactions were carried out in oven dried glassware under an atmosphere of nitrogen, unless stated otherwise. For quantitative flash chromatography technical grade solvents were used. For flash chromatography for analysis, HPLC grade solvents from Sigma-Aldrich were used. THF, Et_2O, CH_3CN, toluene, hexane and CH_2Cl_2 were dried by passage over activated alumina under nitrogen atmosphere (H_2O content < 10 ppm, Karl-Fischer titration). All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used as such unless stated otherwise. Chromatographic purification was performed as flash chromatography using Macherey-Nagel silica 40-63, 60 Å, using the solvents indicated as eluent with 0.1-0.5 bar reduced pressure. TLC was performed on Merck silica gel 60 F254 TLC glass plates or aluminium plates and visualized with UV light, permanganate stain or anisaldehyde stain. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz spectrometer in chloroform-d and all signals are reported in ppm with the internal chloroform signal at 7.26 ppm The data is being reported as (s = singlet, d = doublet, t = triplet, q = quadruplet, qi = quintet, m = multiplet or unresolved, br = broad signal, app = apparent, coupling constant(s) in Hz, integration, interpretation).^{13}CNMR spectra were recorded with 1H-decoupling on a Brucker DPX-400 100 MHz spectrometer in chloroform-d, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prism and are reported as cm-1 (w = weak, m = medium, s = strong, br = broad). High resolution mass spectrometric measurements were performed by the mass spectrometry service of ISIC at the EPFL on a MICROMASS (ESI) Q-TOF Ultima API.

2.Synthesis and Characterization of the Starting Materials

General Procedures

Procedure A: Grignard addition to an epoxide.[1]

In a dried two-neck flask equipped with a reflux condenser, allyl magnesium bromide (1.0 M solution in Et_2O, 2.5 equivalents) was diluted with Et_2O to give a 0.50 M solution with respect to the Grignard reagent. The epoxide was then added dropwise over 10 minutes at room temperature and the resulting solution was heated to reflux and monitored by TLC. After completion of the reaction (ca. 3 hours), the solution was cooled to room temperature and a sat. aq. NH_4Cl solution was carefully added until there was no more effervescence and the solution had become colourless. Water was then added to dissolve the solids. The aqueous layer was extracted three times with Et_2O; the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was then removed under reduced pressure and gave products of sufficient purity for the following steps.

Procedure B: Bromination of alcohols:[2] To a 0.40 M solution of alcohol in Et_2O and of PPh_3 (1.5 equiv) at

(1) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.
(2) Seemann, M.; Schöller, M.; Kudis, S.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, *2003*, 2122.

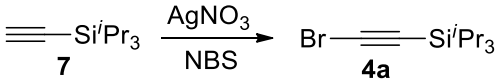
0 °C was added CBr_4 (1.5 equiv) in portions over 10 minutes. The suspension was then stirred at 0 °C for 30 minutes and then at room temperature until the reaction went to completion (often overnight). Pentane was then added and the mixture was stirred until complete precipitation of Ph_3PO. The solids were filtered off, washed with pentane and the resulting organic solution was concentrated *in vacuo* to afford the crude product which was then purified through column chromatography.

Procedure C: Mesylation of alcohols:[3] To an ice cooled 0.12 M solution of alcohol in DCM containing NEt_3 (7.0 equiv) and DMAP (0.1 equiv)was added MsCl (2.4 equiv) dropwise. The solution was stirred for 30 minutes before being allowed to warm to room temperature; it was then stirred at room temperature until completion. The reaction was quenched by the slow addition of water. The layers were separated and the aqueous one was extracted three times with DCM; the combined organics were washed with aq. 1M $KHSO_4$, sat. aq. $NaHCO_3$ and brine before being dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was then purified through column chromatography.

Procedure D: Alkylation of Malonates

Na (1.05 equiv) was added to dry EtOH and the resulting mixture was stirred until the complete consumption of Na, in order to generate a 12 M solution of NaOEt. The latter was then warmed to 50 °C and diethyl malonate (1.0 equiv) and the substrate (1.0 equiv) were successively added. The resulting mixture was heated to 80 °C until completion of the reaction as determined by TLC analysis. The solution was left to cool to rt and 1 M aq. HCl was slowly added (1 mL per mmol substrate). The aqueous layer was separated and extracted with ether. Then the organic layers were combined, washed with H_2O and dried over $MgSO_4$. Removal of the solvent under reduced pressure then afforded the crude product, which was then purified by column chromatography.

2-Bromo-1-tri*iso*propylsilyl acetylene[4] **(4a)**



7 **4a**

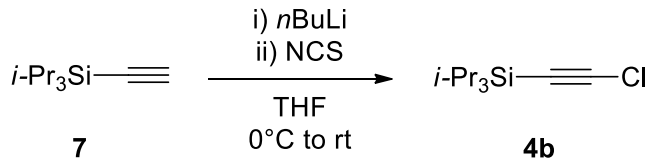
Tri*iso*propyl acetylene (**7**) (3.65 g, 20.0 mmol, 1.00 equiv) was dissolved in acetone (120 mL). NBS (4.13 g, 23.5 mmol, 1.16 equiv) was added followed by silver(I) nitrate (0.350 g, 2.00 mmol, 0.10equiv) under vigorous stirring. After 3 hours of stirring the reaction was quenched by addition of ice, which upon melting was extracted with pentane (3 x 120 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to yield **4a** (5.04 g, 19.2 mmol, 97%) as a colourless oil, which was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 21 H, TIPS); ^{13}C NMR (101 MHz, $CDCl_3$) δ 83.4, 61.7, 18.5, 11.3.

The values were in good agreement with the literature.[4]

(3) Ma, D.; Yang, J. *J. Am. Chem. Soc.* **2001**, *123*, 9706.
(4) Jiang, M. X.-W.; Rawat, M.; Wulff, W. D. *J. Am. Chem. Soc.* **2004**, *126*, 5970.

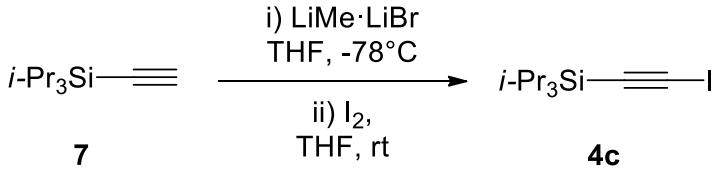
(Chloroethynyl)tri*iso*propylsilane (4b)



Following a reported procedure,[5] tri*iso*propyl silyl acetylene (**7**) (2.2 mL, 10 mmol, 1.0 equiv) was dissolved in THF (12.5 mL) and the solution was stirred at 0 °C for 5 min. *n*BuLi (2.5 M in hexanes, 4.4 mL, 11 mmol, 1.1 equiv) was added dropwise and the resulting mixture was stirred at 0 °C for 30 min. *N*-chloro succinimide (1.6 g, 12 mmol, 1.2 equiv) was added and the mixture was stirred at 0 °C for 5 min and then at room temperature overnight. The reaction was then quenched by the addition of water (12.5 mL). The two layers were separated and the aqueous one was extracted with EtOAc (3 x 12 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, hexane) afforded 2-iodo-1-tri*iso*propylsilyl acetylene (**4b**) (1.67 mg, 7.70 mmol, 77% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14-1.06 (m, 21 H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 80.0, 71.2, 18.5, 11.3. The values for the characterization of **5d** correspond to the ones reported in literature.[5]

2-Iodo-1-tri*iso*propylsilyl acetylene (4c)

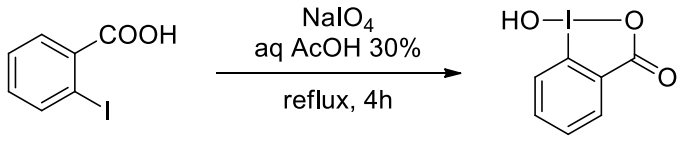


Following a reported procedure,[6] MeLi•LiBr (1.5 M in diethyl ether, 1.1 mL, 1.6 mmol, 1.0 equiv) was added to a stirred solution of tri*iso*propylsilylacetylene (**7**) (0.36 mL, 1.6 mmol, 1.0 equiv) in dry THF (1.8 mL), cooled at -78 °C, and the mixture was allowed to react for 1 h at that temperature. A solution of I_2 (457 mg, 1.80 mmol, 1.25 equiv) in dry THF (2.7 mL) was then added dropwise and the mixture was stirred for 1.5 h at -78 °C. The mixture was then diluted with brine (6 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ (3 x 20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexane) afforded 2-iodo-1-tri*iso*propylsilyl acetylene (**1c**) (0.470 g, 1.52 mmol, 94% yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10-1.04 (m, 21 H, TIPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.8, 18.5, 11.4 (one acetylene carbon was not resolved); the reported values correspond to the ones in literature.[6]

1-Hydroxy-1,2-benziodoxol-3-(1*H*)-one (9)

(5) Wada, T. ; Masayuki, J.; Azusa, K.; Hideki, Y.; Oshima, K. *Chem. Eur. J.* **2010**, *16*, 10671.
(6) López S.; Fernández-Trillo F.; Midón P.; Castedo L.; Saá *J. Org. Chem.*, **2005**, *70*, 6346.

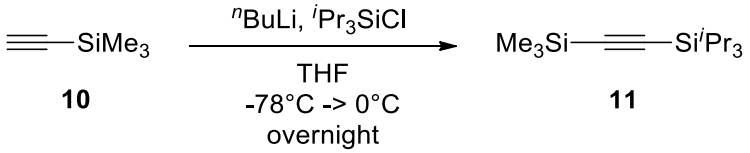


8 **9**

Following the reported procedure,[7] $NaIO_4$ (7.24 g, 33.8 mmol, 1.05 equiv) and 2-iodobenzoic acid (**8**) (8.00 g, 32.2 mmol, 1.00 equiv) were suspended in 30% (v:v) aq. AcOH (48 mL). The mixture was vigorously stirred and refluxed for 4 h. The reaction mixture was then diluted with cold water (180 mL) and allowed to cool to room temperature, protecting it from light. After 1 h, the crude product was collected by filtration, washed on the filter with ice water (3 x 20 mL) and acetone (3 x 20 mL), and air-dried in the dark to give the pure product **9** (8.3 g, 31 mmol, 98%) as a colorless solid.

^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 8.02 (dd, 1 H, *J* = 7.7, 1.4 Hz, Ar*H*), 7.97 (m, 1 H, Ar*H*), 7.85 (dd, 1 H, *J* = 8.2, 0.7 Hz, Ar*H*), 7.71 (td, 1 H, *J* = 7.6, 1.2 Hz, Ar*H*); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 167.7, 134.5, 131.5, 131.1, 130.4, 126.3, 120.4; IR ν 3083 (w), 3060 (w), 2867 (w), 2402 (w), 1601 (m), 1585 (m), 1564 (m), 1440 (m), 1338 (s), 1302 (m), 1148 (m), 1018 (w), 834 (m), 798 (w), 740 (s), 694 (s), 674 (m), 649 (m); the reported values correspond to the ones in literature.[7]

Tri*iso*propylsilyl trimethylsilylacetylene (11)



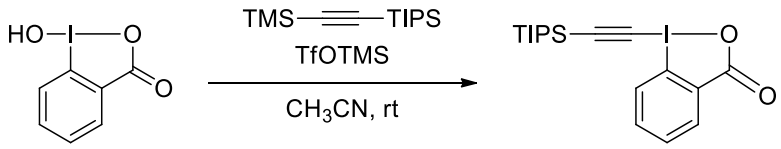
10 **11**

Following a reported procedure,[8] *n*-butyllithium (2.5 M in hexanes, 12.0 mL, 29.9 mmol, 0.98 equiv) was added dropwise to a stirred solution of ethynyltrimethylsilane (**10**) (3.0 g, 30 mmol, 1.0 equiv) in THF (48 mL) at -78 °C. The mixture was then warmed to 0 °C and stirred for 5 min. The mixture was then cooled back to -78 °C and chlorotri*iso*propylsilane (6.4 mL, 30 mmol, 1.0 equiv) was added dropwise. The mixture was then allowed to warm to room temperature and stirred overnight. A saturated solution of ammonium chloride (40 mL) was added, and the reaction mixture was extracted with diethyl ether (2 x 60 mL). The organic layer was washed with water and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure to obtain a colorless liquid which was further purified by Kugelrohr distillation (56-57°C/0.25 mmHg) to yield **11** (7.16 g, 28.0 mmol, 92% yield) as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 1.08 (m, 21 H, TIPS), 0.18 (s, 9 H, TMS). IR ν 2959 (m), 2944 (m), 2896 (w), 2867 (m), 1464 (w), 1385 (w), 1250 (m), 996 (w), 842 (s), 764 (s), 675 (m), 660 (m). Characterization data of **8** corresponded to the literature values.[8]

1-[(Tri*iso*-propylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX, 4d)

(7) Kraszkiewicz, L.; Skulski, L. *Arkivoc*. **2003**, *6*, 120.
(8) Helal, C J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938.

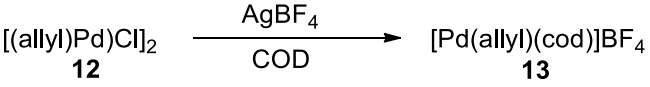


9 **4d**

Following a reported procedure,[9] 2-iodosylbenzoic acid (**9**) (21.7 g, 82.0 mmol, 1.0 equiv) was charged in oven-dried three-neck 1L flask equipped with a magnetic stirrer. After 3 vacuum/nitrogen cycles, anhydrous acetonitrile (500 mL) was added via cannula and cooled to 4 °C. Trimethylsilyltriflate (16.4 mL, 90.0 mmol, 1.1 equiv) was added dropwise via a dropping funnel over 30 min (no temperature increase was observed). After 15 min, (trimethylsilyl)(tri*iso*propylsilyl)acetylene (**11**) (23.0 g, 90.0 mmol, 1.1 equiv) was added via canula over 15 min (no temperature increase was observed). After 30 min, the suspension became an orange solution. After 10 min, pyridine (7.0 mL, 90 mmol, 1.1 equiv) was added via syringe. After 15 min, the reaction mixture was transferred in a one-neck 1L flask and reduced under vacuum until a solid was obtained. The solid was dissolved in DCM (200 mL) and transferred in a 1L separatory funnel. The organic layer was added and washed with aq. 1 M HCl (200 mL) and the aqueous layer was extracted with CH_2Cl_2 (200 mL). The organic layers were combined, washed with a saturated solution of $NaHCO_3$ (2 x 200 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. Recrystallization from acetonitrile (*ca* 120 mL) afforded **4d** (30.1 g, 70.2 mmol, 86%) as colorless cristals.

^{1}H NMR (400 MHz, CDCl3) δ 8.44 (m, 1 H, Ar*H*), 8.29 (m, 1 H, Ar*H*), 7.77 (m, 2 H, Ar*H*), 1.16 (m, 21 H, TIPS). ^{13}C NMR (100 MHz, CDCl3) δ 166.4, 134.6, 132.3, 131.4, 131.4, 126.1, 115.6, 114.1, 64.6, 18.4, 11.1. IR ν 2943 (m), 2865 (m), 1716 (m), 1618 (m), 1604 (s), 1584 (m), 1557 (m), 1465 (m), 1439 (w), 1349 (m), 1291 (m), 1270 (w), 1244 (m), 1140 (m), 1016 (m), 999 (m), 883 (m), 833 (m), 742 (m), 702 (s), 636 (m); Melting point (Dec.) 170-176°C; The values for the characterization of **TIPS-EBX (1d)** correspond to the ones reported in literature.[9]

[Pd(allyl)(cod)]BF_4 (13)



Following a reported procedure,[10] Pd dimer **12** (300 mg, 0.820 mmol, 1.0 equiv) and $AgBF_4$ (316 mg, 1.62 mmol, 2.0 equiv) were transferred into a 2-necked flask under N_2. DCM (8.0 mL) was then added and the solution stirred at room temperature for 15 minutes. COD (0.330 mL, 1.64 mmol, 2.0 equiv) was then added and the solution was stirred for 1 h. The white precipitate that forms was removed *via* filtration. Ether (50 mL) was added to precipitate out the product, which was removed by filtration, washed with ether (3 x 10 mL) and dried *in vacuo*. The solid was taken up in DCM and passed through a cotton wool plug, ether was again added to precipitate out the product. After washing with more ether the crude product was dried *in*

(9)Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304.

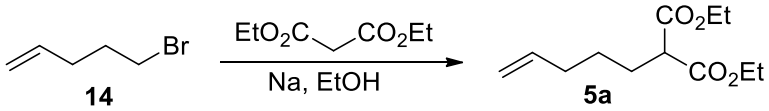
(10) White, D. A., Doyle, J. R. and Lewis, H. (2007) Cationic Diene Complexes of Palladium (II) and Platinum (II), in Inorganic Syntheses, Volume 13 (ed F. A. Cotton), John Wiley & Sons, Inc., Hoboken, NJ, USA, p. 55-56.

vacuo to give **13** (0.354 g, 1.04 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d broad, 4H, cod *C*=*CH*), 6.10 (tt, *J* = 13.4, 7.3 Hz, 1H, allyl C=*CH*), 4.98, (d, *J* = 7.3 Hz, 2H, allyl CH_2), 3.98 (d, *J* = 13.4 Hz, 2H, allyl CH_2), 2.75-2.55 (broad m, 6H, cod 3 x CH_2), 2.36 (broad s, 2H, cod, CH_2) .

The ^{1}H NMR values were in accordance with the literature.[11]

Diethyl 4-pentenylpropanedioate (5a)



14 **5a**

Following a reported procedure,[12] a 50 mL 2-neck round-bottom flask fitted with a reflux condenser was charged with dry ethanol (11 mL). Solid Na (3.08 g, 21.6 mmol, 1.08 equiv) was added and the mixture was vigorously stirred until the complete consumption of Na, upon which the solution was warmed to 50 °C. Diethyl malonate (3.03 mL, 20. 0 mmol, 1.00 equiv) and 5-bromo-1-pentene (**14**) (0.497 mL, 21.6 mmol, 1.08 equiv) were added. The solution was then heated to reflux for 3 hours, after which the consumption of the malonate was confirmed by TLC. The solvent was removed under reduced pressure. The resulting oil was then diluted with ether (20 mL) and washed with 1 M HCl (30 mL) and water (120 mL). The aqueous layers were extracted with ether and the organic ones were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. **5a** was obtained as a colourless oil (3.39 g, 14.9 mmol, 74%) upon purification by column chromatography (SiO_2, 97:3 to 95:5 pentane : EtOAc).

Rf: 0.5 (pentane:EtOAc/95:5);

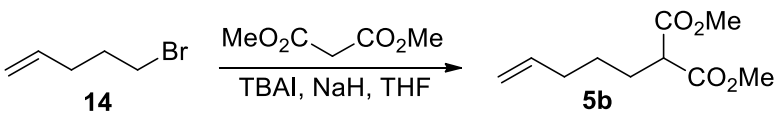
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82−5.72 (m, 1H, CH_2*CH*=CH_2), 5.04−4.94 (m, 2H, CH_2CH=*CH_2*), 4.19 (q, *J* = 7.3 Hz, 4H, CO_2*CH_2*CH_3), 3.31 (t, *J* = 7.5 Hz, 1H, $(CO_2Et)_2$*CH*), 2.15−2.08 (m, 2H, *CH_2*), 2.04−1.96 (m, 2H, *CH_2*), 1.47-1.39 (m, 2H, CH_2), 1.27 (t, *J* = 7.2 Hz, 6H, CO_2CH_2*CH_3*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 138.2, 115.2, 61.5, 52.1, 33.5, 28.4, 26.8, 14.3;

IR (neat), 3077 (w), 2982 (w), 2936 (w), 1734 (s), 1643 (w), 1455 (w), 1373 (w), 1149 (s), 1030 (m), 915 (m), 860 (w).

^{1}H NMR data was accordance with the values reported in literature.[12]

Dimethyl 2-(pent-4-en-1-yl)malonate (5b)



14 **5b**

Following an adapted procedure,[13] anhydrous NaH (0.225 g, 9.00 mmol, 1.20 equiv) and anhydrous THF (30 mL) were introduced into a 2-neck flask and the suspension was cooled to 0 °C. Dimethyl

(11) Carturan, G.; Biasiolo, M.; Daniele, S.; Mazzocchin, G. A.; Ugo, P. *Inorg. Chim. Acta* **1986**, *119*, 19.
(12) Salomon, R. G.; Coughlin, D. J.; Ghosh, S.; Zagorski, M. G. *J. Am. Chem. Soc.* **1982**, *104*, 998.
(13) Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405.

malonate (1.33 mL, 8.40 mmol, 1.13 equiv) was then added dropwise over 5 minutes. During this time, effervescence was observed and the suspension cleared. The ice bath was removed and the solution stirred at room temperature for a further 30 minutes. Tetrabutylammonium iodide (0.831 g, 2.25 mmol, 0.30 equiv) was added, followed by 5-bromopent-1-ene (**14**) (0.84 mL, 7.5 mmol, 1.0 equiv), the mixture was purged with Ar and refluxed at 80 ^{o}C overnight. The solution was then allowed to cool to room temperature and quenched by addition of aq. sat. NH_4Cl solution. Extraction of the aqueous layer with ether (3x10 mL), washing the combined organic layers with brine (10 mL), drying over $MgSO_4$ and removal of the solvent under reduced pressure gave the crude product, which was purified by column chromatography (SiO_2, 10:1 PET:Et_2O). **5b** was obtained as a colourless oil (1.24 g, 6.82 mmol, 82%).

Rf: 0.42 (PET:Et_2O/15:1);

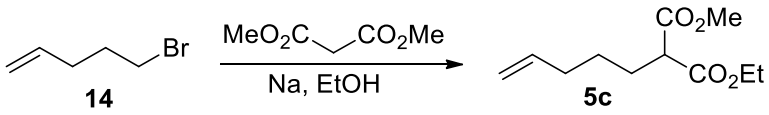
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.70 (m, 1H, CH_2*CH*=CH_2), 5.03-4.94 (m, 2H, CH_2CH=*CH_2*), 3.73 (s, 6H, CO_2*CH_3*), 3.37 (t, *J* = 7.5 Hz, 1H, malonate proton), 2.10-2.04 (m, 2H, *CH_2*), 1.93-1.88 (m, 2H, *CH_2*), 1.45-1.37 (m, 2H, CH_2);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 137.9, 115.1, 52.4, 51.5, 33.2, 28.2, 26.5;

IR (neat), 3072 (w), 2956 (m), 1733 (s), 1642 (w), 1437 (m), 1346 (w), 1219 (m), 1154 (s), 1102 (m), 915 (w).

The data were in agreement with the ones published in the literature.[13]

1-Ethyl 3-methyl 2-(pent-4-en-1-yl)malonate (5c)



14 **5c**

Solid Na (75.9 mg, 3.30 mmol, 1.1 equiv) was introduced into a tube, which was sealed and put under a N_2 atmosphere using Schlenk line techniques. Dry ethanol (1.5 mL) was then added dropwise and the vial heated to 50 ^{o}C and stirred until the Na fully reacted. Dimethyl malonate (0.52 mL, 3.3 mmol, 1.1 equiv) was added and the solution was stirred for 5 minutes before 5-bromopent-1-ene (**14**) was added. The vial was then heated at 80 ^{o}C for a further 5 hours. The reaction vessel was then cooled to room temperature and quenched with sat. NH_4Cl solution (15 mL), the aqueous layer was then extracted with ether (3x10 mL). The combined organic layers were dried over $MgSO_4$ and the solution was concentrated under reduced pressure. The crude prodcut was then purified by column chromatography (SiO_2, eluting with 10:1 PET :Et_2O) to afford **2c** (0.18 g, 0.78 mmol, 26%) as a colourless oil.

Rf: 0.40 (PET:Et_2O/15:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.72 (m, 1H, CH_2*CH*=CH_2), 5.03-4.95 (m, 2H, CH_2CH=*CH_2*),

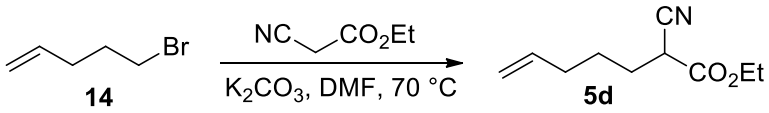
4.19 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.73 (s, 3H, CO_2CH_3), 3.34 (t, *J* = 7.5 Hz, 1H, malonate proton), 2.10-2.05 (m, 2H, CH_2), 1.93-1.88 (m, 2H, CH_2), 1.46-1.38 (m, 2H, CH_2), 1.27 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$);

^{13}C NMR (101 MHz, $CDCl_3$), δ170.0, 169.4, 137.9, 115.1, 61.4, 52.4, 51.8, 33.2, 28.3, 26.6, 14.1.

IR (neat), 3079 (w) 2956 (m), 1753 (s), 1731 (s), 1642 (w), 1473 (m), 1339 (m), 1217 (s), 1152 (s), 1028 (m), 914 (m);

HRMS (ESI) calcd for $C_{11}H_{19}O_4^+$ $[M+H]^+$ 215.1278; found 215.1268.

Ethyl 2-cyanohept-6-enoate (5d)



Following a reported procedure,[14] a dried flask was charged with dry DMF (6 mL), ethyl cyanoacetate (0.40 mL, 3.7 mmol, 1.5 equiv), 5-bromopent-1-ene (**14**) (0.30 mL, 2.5 mmol, 1.0 equiv) and dried K_2CO_3 (1.04 g, 7.50 mmol, 3.0 equiv). The flask was then heated at 70 ºC for 5 hours after which it was allowed to cool to room temperature. The reaction mixture was then concentrated under reduced pressure, before ether (40 mL) was added. The layers were separated and the aqueous solution was extracted with ether (3x15 mL); the organic layers were combined and washed with H_2O (5x25 mL) and once with brine (25 mL). After drying over $MgSO_4$, concentration under reduced pressure and purification by column chromatography (SiO_2, eluting with 10:1 PET:Et_2O) **5d** was obtained as a colourless oil (0.148 g, 0.815 mmol, 33%).

Rf:0.38 (PET:Et_2O/10:1);

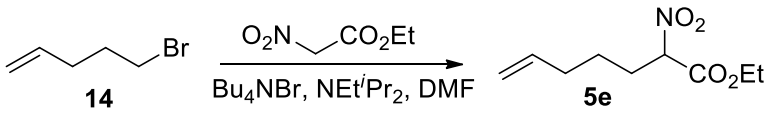
^{1}H NMR (400 MHz, $CDCl_3$), δ 5.83-5.72 (m, 1H, CH_2CH=CH_2), 5.07-5.00 (m, 2H, CH_2CH=CH_2), 4.27 (q, 2H, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.49 (t, *J* = 6.8 Hz, 1H, malonate proton), 2.15-2.09 (m, 2H, CH_2), 1.99-1.92 (m, 2H, CH_2), 1.65-1.58 (m, 2H, CH_2), 1.33 (t, 3H, *J* = 7.1 Hz, $COCH_2CH_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 137.2, 116.5, 115.8, 62.8, 37.5, 32.7, 29.2, 25.1, 14.0;

IR (neat), 3080 (w), 2982 (w), 2933 (w), 2251 (w), 1744 (s), 1643 (w), 1461 (w), 1371 (w), 1258 (m), 1198 (s), 1023 (m), 916 (m), 856 (w).

^{1}H NMR data were in agreement with the values in the literature.[14]

Ethyl 2-nitrohept-6-enoate (5e)



(14) Marsilje, T. H.; Hedrick, M. P.; Desharnais, J.; Tavassoli, A.; Zhang, Y.; Wilson, I. A.; Benkovic, S. J.; Boger, D. L. *Bioorg. Med. Chem.* **2003**, *11*, 4487.

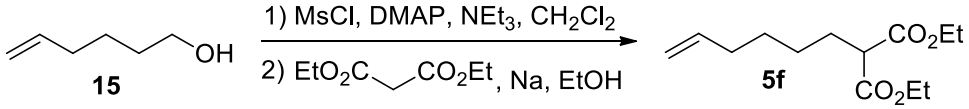
Following a reported procedure,[15] ethyl nitroacetate (0.330 mL, 3.00 mmol, 1.00 equiv), tetrabutyl ammonium bromide (0.100 g, 0.300 mmol, 0.100 equiv) and N*i*Pr$_2$Et (1.00 mL, 6.00 mol, 2.00 equiv) were added to dry DMF (2 mL). 5-bromopent-1-ene (**14**) (0.710 mL, 6.00 mmol, 2.00 equiv) was then added dropwise and the solution stirred overnight at room temperature. Purification through column chromatography (SiO_2 eluting with 5:1 PET:Et_2O) afforded **5e** as a colourless oil (0.040 g, 0.20 mmol, 6%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.70 (m, 1H, CH_2*CH*=CH_2), 5.10 (dd, *J* = 9.4 Hz, 5.4 Hz, 1H, *CH*NO_2), 5.06-5.00 (m, 2H, CH_2CH=*CH$_2$*), 4.28 (q, *J* = 7.2 Hz, 2H, CO_2*CH$_2$*CH_3), 2.33-2.23 (m, 1H, *CH$_2$*), 2.18-2.09 (m, 3H, CH_2), 1.51-1.38 (m, 2H, CH_2), 1.33 (t, *J* = 7.1 Hz, 3H, CO_2CH_2*CH$_3$*).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 137.0, 115.9, 88.0, 63.0, 32.7, 29.6, 24.7, 13.9.

The experimental data were in good agreement with published values.[16]

Diethyl 2-(hex-5-en-1-yl)malonate (5f)



Hex-5-ene-1-ol (**15**) (0.460 mL, 4.00 mmol) was converted into the corresponding mesylate using procedure **C**. After purification over SiO_2 with 1:1 PET:ether, the mesylate was isolated as a pale yellow oil (0.704 g, 3.95 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.71 (m, 1H, CH_2*CH*=CH_2), 5.05-4.97 (m, 2H, HC=C*H$_2$*), 4.24 (t, *J* = 6.5 Hz, 2H, C*H$_2$*OMs), 3.00 (s, 3H, SO_2*CH$_3$*), 2.13-2.07 (m, 2H, *CH$_2$*), 1.82-1.73 (m, 2H, *CH$_2$*), 1.55-1.49 (m, 2H, *CH$_2$*).

The mesylate (0.704 g, 3.95 mmol) was alkylated using procedure **D**. Purification through column chromatography (SiO_2 eluting with 5:1 PET:Et_2O) gave **5f** (0.322 g, 1.33 mmol, 34%) as a colourless oil.

Rf: 0.43 (PET:Et_2O/15:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.71 (m, 1H, CH_2*CH*=CH_2), 4.99-4.91 (m, 2H, CH_2CH=*CH$_2$*), 4.17 (q, *J* = 7.2 Hz, 4H, CO_2*CH$_2$*CH_3), 3.30 (t, *J* = 7.5 Hz, 1H, malonate proton), 2.06-2.01 (m, 2H, *CH$_2$*), 1.91-1.85(m, 2H, *CH$_2$*), 1.73-1.30 (m, 4H, *CH$_2$*), 1.25 (t, *J* = 7.1 Hz, 6H, CO_2CH_2*CH$_3$*).

^{13}C NMR (100Mz, $CDCl_3$) δ 169.6, 138.6, 114.6, 61.3, 52.1, 33.4, 28.6, 28.5, 26.8, 14.1.

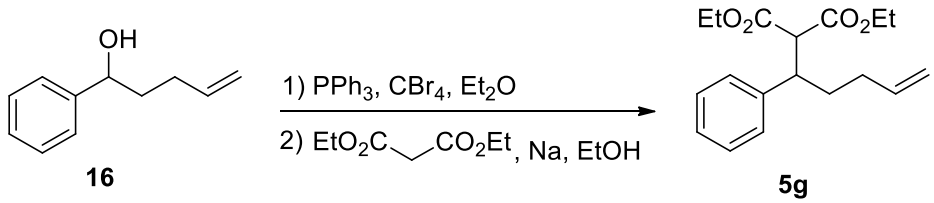
IR (neat), 3079 (w), 2982 (w), 2933 (w), 2860 (w), 1750 (s), 1732 (s), 1642 (w), 1464 (w), 1370 (w), 1151 (m), 1029 (m), 912 (m), 816 (w).

^{1}H NMR data were in good agreement with literature.[12]

(15) Fu, Y.; Hammarström, L. G. J.; Miller, T. J.; Fronczek, F. R.; McLaughlin, M. L.; Hammer, R. P. *J. Org. Chem* **2001**, *66*, 7118.

(16) Snider, B. B.; Che, Q. *Tetrahedron* **2002**, *58*, 7821.

Diethyl 2-(1-phenylpent-4-en-1-yl)malonate (5g)



16 (0.970 g, 6.00 mmol) was converted into the corresponding bromide using procedure **B**. Kugelrohr distillation failed to provide the pure product. Further purification was therefore performed through column chromatography (SiO_2 eluting with pentane) to give the corresponding bromide **(**0.450 g, 2.00 mmol, 33%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H, *ArH*), 5.83-5.73 (m, 1H, CH_2CH=CH_2), 5.07-4.94 (m, 3H, CH_2CH=CH_2 and benzylic proton), 2.25-2.12 (m, 2H, CH_2CH=CH_2) 1.32-1.23 (m, 2H, $BrCHCH_2$).

The bromide (0.56 g, 2.5 mmol) was converted using procedure **D**. Purification through column chromatography (SiO_2 eluting with 100:0 to 97:3 hexanes:EtOAc) gave **5g** (0.470 g, 1.54 mmol, 77%) as a colourless oil.

Rf: 0.37 (PET:Et_2O/15:1);

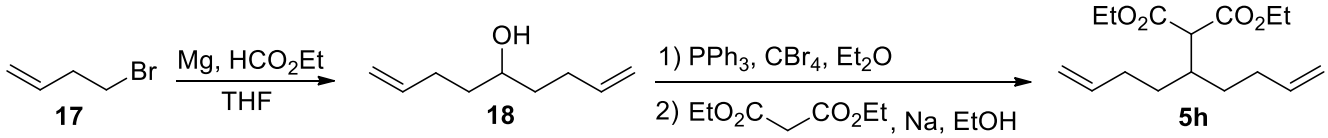
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.18 (m, 5H, ArH), 5.75-5.65 (m, 1H, CH_2CH=CH_2), 4.94-4.88 (m, 2H, CH_2CH=CH_2), 4.23 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.86 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 3.62 (d, *J* = 10.9 Hz, 1H, malonate proton), 3.38 (m, 1H, $ArCHCH_2$), 1.87-1.64 (m, 4H, CH_2), 1.28 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 0.92 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 167.8, 140.5, 137.9, 128.4, 128.3, 127.0, 115.0, 61.5, 61.1, 58.8, 45.0, 33.1, 31.1, 14.1, 13.7;

IR (neat), 3065 (broad, w), 3031 (w), 2982 (w), 2936 (w), 1731 (s), 1641 (w) 1455 (m), 1369 (m), 1304 (m), 1243 (m), 1143 (s), 1034 (s), 912 (m);

HRMS (ESI) calcd for $C_{18}H_{24}O_4$ $[M+H]^+$ 305.1753, found 305.1756.

Diethyl 2-(nona-1,8-dien-5-yl)malonate (5h)



Following a reported procedure,[17] solid Mg (0.660 g, 25.0 mmol, 2.50 equiv) was added to a flask and stirred for 5 minutes under N_2. 4-Bromo butane (**17**) (2.54 mL, 25.0 mmol, 2.50 equiv) in THF (20 mL) was very slowly added and the reaction mixture was stirred at room temperature for 1 hour. Following this, ethyl formate ester (0.810 mL, 10.0 mmol, 1.00 equiv) in THF (12.5 mL) was then slowly added over 30 minutes and the reaction was stirred overnight at room temperature. The Grignard was quenched by slow addition of an aq. sat. NH_4Cl solution until no effervescence or precipitation occurred. Water (15 mL) was then added and the layers separated. After extraction of the aqueous layer with ether (3x15 mL), the combined organics were dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification of the crude was carried out through column chromatography (SiO_2 eluting with 5:1 hexanes:EtOAc) and gave **18** (1.13 g, 8.10 mmol, 81%).as a colourless oil.

Rf: 0.5 (hexane:EtOAc /5:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91-5.81 (m, 2H CH_2CH=CH_2) δ 5.03 (m, 4H, CH_2CH=CH_2), 3.74-3.61 (m, 1H, $(CH_2)_2C$*(H)*OH), 2.28-2.11 (m, 4H, CH_2), 1.63-1.52 (m, 4H, CH_2).

Alcohol **18** (0.84 g, 6.0 mmol) was converted into the corresponding bromide following the procedure **B**. The crude product was purified though column chromatography (SiO_2 eluting with pentane) to furnish the desired product (0.576 g, 2.85 mmol, 48%) as a colourless oil.

Rf: 0.95 (pentane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83-5.73 (m, 2H CH_2CH=CH_2), 5.03 (m, 4H, CH_2CH=CH_2), 4.05-3.99 (m, 1H, $(CH_2)_2C$*(H)*Br), 2.34-2.18 (m, 4H, CH_2), 1.95-1.87 (m, 4H, CH_2).

The bromide (0.505 g, 2.50 mmol, 1.00 equiv) was then converted following procedure **D**. Purification though column chromatography (SiO_2 eluting with 100 : 0 to95 : 5 pentane : EtOAc) gave **5h** (0.370 g, 1.34 mmol, 54%) as a colourless oil.

Rf: 0.43 (PET:Et_2O/15:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.72 (m, 2H CH_2CH=CH_2), 5.03-4.94 (m, 4H, CH_2CH=CH_2), 4.19 (dq, *J* = 7.2 Hz, 0.8 Hz, 4H, OCH_2CH_3), 3.43 (d, *J* = 7.1 Hz, 1H, malonate proton), 2.24-2.15 (m, 1H, $CH(CO_2Et)_2$), 2.10-2.03 (m, 4H, CH_2), 1.57-1.41 (m, 4H, CH_2), 1.26 (t, *J* = 7.1 Hz, 6H, OCH_2CH_3);

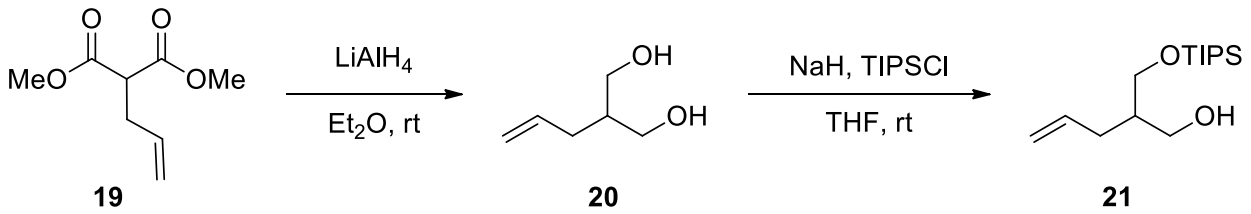
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 138.3, 114.8, 61.1, 55.0, 37.1, 30.8, 30.1, 14.1.

IR (neat), 3078(w), 2980 (w), 2935 (w), 1731 (s), 1642 (s), 1450 (w), 1370 (w), 1305 (w), 1244 (w), 1151 (s), 1304 (s), 911 (s);

(17) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993.

HRMS (ESI) calcd for $C_{16}H_{26}O_4$ $[M+H]^+$ 283.1904 found 283.1913.

2-((Triisopropylsilyloxy)methyl)pent-4-en-1-ol (21)



19 **20** **21**

According to a reported procedure,[18] a solution of dimethyl 2-allylmalonate (**19**) (1.77 mL, 11.0 mmol, 1.0 equiv) in Et_2O (25 mL) was added dropwise to a suspension of $LiAlH_4$ (1.25 g, 33.0 mmol, 3.0 equiv) in Et_2O (31 mL) at 0°C. The resulting mixture was stirred at room temperature for 3 h; it was then cooled back to 0°C and the reaction was quenched by slow addition of water (1.05 mL). The mixture was allowed to warm to rt and treated with aqueous NaOH (15%, 1.05 mL) and water (3.2 mL). The resulting white slurry was filtered through Celite and then washed with EtOAc (4 x 50 mL). After removal of the solvent by distillation under reduced pressure, the crude product was purified by column chromatography (SiO_2, eluting with Et_2O) to afford diol **20** as a colorless oil (744 mg, 6.40 mmol, 58% yield).

Following a reported procedure,[19] a solution of diol **20** (581 mg, 5.00 mmol, 1.0 equiv) in THF (4.0 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 120 mg, 5.00 mmol, 1.0 equiv) in THF (10 mL). The mixture was stirred at rt for 50 min and then a solution of triisopropyl silyl chloride (0.96 mL, 4.5 mmol, 0.9 equiv) in THF (4.0 mL) was slowly added. After stirring for 2 h, the reaction was quenched by treatment with aqueous K_2CO_3 (1.0 M, 15 mL). The aqueous layer was separated from the organic one and extracted with Et_2O (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by column chromatography (SiO_2, eluting with 95:5 pentane:EtOAc) afforded the monoprotected diol **21** as a colorless oil (1.15 g, 4.23 mmol, 85% yield).

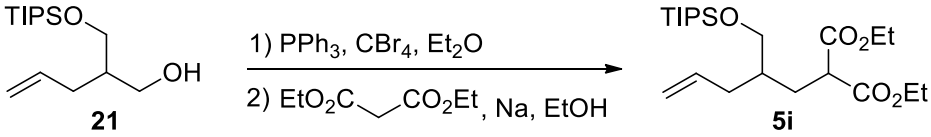
R_f 0.57 (Pentane/EtOAc 20/3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (ddt, 1 H, *J* = 17.2, 10.1, 7.2 Hz, *CH*=CH_2), 5.07-4.98 (m, 2 H, CH=*CH*$_2$), 3.88 (dd, 1 H, *J* = 9.8, 4.1 Hz, *CH*$_2$OTIPS), 3.79-3.58 (m, 3 H, *CH*$_2$OTIPS and *CH*$_2$OH), 2.96 (m, 1 H, *OH*), 2.03 (t, 2 H, *J* = 7.3 Hz, *CH*$_2$CH=CH_2), 1.86 (m, 1 H, *CH*CH_2OTIPS), 1.23-0.94 (m, 21 H, *TIPS*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.3, 116.3, 67.2, 66.3, 41.9, 32.4, 17.9, 11.7; IR 3419 (br, w), 3078 (w), 2943 (m), 2922 (m), 2892 (m), 2866 (m),

(18) Macsári, I.; Szabó, K. J. *Chem. Eur. J.* **2001**, *7*, 4097.
(19) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774.

2726 (w), 1642 (w), 1464 (m), 1442 (w), 1416 (w), 1385 (w), 1368 (w), 1249 (w), 1099 (m), 1040 (m), 1014 (m), 995 (m), 913 (m), 882 (s), 787 (m), 736 (w), 681 (s), 660 (s), 652 (s), 637 (s), 627 (m), 613 (w).

The data is in good agreement with published values.[20]

Diethyl 2-(2-(((triisopropylsilyl)oxy)methyl)pent-4-en-1-yl)malonate (5i)



Alcohol **21** (0.820 g, 3.00 mmol) was converted into the corresponding bromide using procedure **B**. Purification through column chromatography (SiO_2 eluting with pentane) gave the bromide (0.423 g, 1.27 mmol, 42%) as a colourless oil.

Rf: 0.90 (pentane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.70 (m, 1H, CH_2CH=CH_2), 5.12-5.05 (m, 2H, CH_2CH=CH_2), 3.76-3.64 (m, 2H, OCH_2), 3.58-3.50 (m, 2H, CH_2Br), 2.12 (m, 2H CH_2CH=C), 1.58-1.51 (m, 1H, $CH$$CH_2$Br), 1.12-1.04 (m, 21H, TIPS protons).

Alkylation of the bromide (0.350 g, 1.20 mmol) using procedure **D** gave the crude product **5i**, which was purified though column chromatography (SiO_2 eluting with 5:1 PET:Et_2O). **5i** (0.204 g, 0.490 mmol, 49%) was isolated as a colourless oil.

Rf: 0.43 (PET:Et_2O/15:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81-5.71 (m, 1H, CH_2CH=CH_2), 5.07-5.00 (m, 2H, CH_2CH=CH_2), 4.20-4.15 (m, 4H, $CO_2CH_2CH_3$), 3.66-3.54 (m, 3H, malonate proton and TIPSOCH_2), 2.22-2.03 (m, 2H, CH_2). 1.96-1.20 (m, 2H, CH_2), 1.62-1.56 (m, 1H, TIPSOCH$_2$CH), 1.26 (td, J = 7.1 Hz, 2.2 Hz, 6H, $CO_2CH_2CH_3$), 1.12-1.02 (m, 21H, TIPS);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 136.4, 116.5, 65.1, 61.2, 50.1, 38.4, 35.6, 30.4, 18.0, 14.1 12.0;

IR (neat), 3078 (w), 2939 (m), 2867(m), 1735(s), 1642(w), 1465(m), 1370(m), 1259 (s),1151(s), 1098(s), 1032(s), 916 (m), 813(m);

HRMS (ESI) calcd for $C_{22}H_{42}NaO_5Si^+$ $[M+Na]^+$ 437.2694; found 437.2685.

***Cis*-diethyl 2-(2-allylcyclopentyl)malonate (5j)**

(20) Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324.

Procedure **A** was used to convert cyclopentene oxide (**22**) (0.490 mL, 5.60 mmol) into alcohol **23 (**0.706 g, 5.60 mmol, quantitative), which was obtained as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.78 (m, 1H, CH_2*CH*=CH_2), 5.07-4.98 (m, 2H, CH_2CH=*CH_2*), 3.86 (app. q, *J* = 5.7 Hz, 1H, *CH*OH), 2.21-1.99 (m, 2H, *CH_2*CH=C), 1.95-1.85 (m, 2H, ring protons), 1.83-1.74 (m, 1H, ring proton), 1.73-1.69 (m, 1H, ring proton), 1.61-1.50 (m, 2H, ring protons), 1.27-1.17 (m, 1H, ring proton);

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 115.7, 78.6, 47.7, 38.1, 34.3, 29.7, 21.6.

Alcohol **23** (0.710 g, 5.60 mmol) was mesylated using procedure **C**. After purification though column chromatography (SiO_2 eluting with 5:1 PET:Et_2O) the mesylate (0.479 g, 2.34 mmol, 42%) was obtained as a yellow oil.

Rf:0.35 (PET:Et_2O/5:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73-5.71 (m, 1H, CH_2*CH*=CH_2), 5.09-5.03 (m, 2H, CH_2CH=*CH_2*), 4.76-4.72 (m, 1H, *CH*OMs), 2.98 (s, 3H, OMs), 2.26-2.16 (m, 2H, *CH_2*CH=CH_2), 2.08-1.90 (m, 3H, ring protons), 1.82-1.66 (m, 2H, ring protons), 1.33-1.26 (m, 2H, ring protons).

The mesylate (0.410 g, 2.00 mmol) was converted using procedure **D**. Purification though column chromatography (SiO_2 eluting with 10:1 to 5:1 PET:Et_2O) gave **5j** as a yellow oil (0.124 g, 0.503 mmol, 25%).

Rf: 0.47 (PET:Et_2O/15:1);

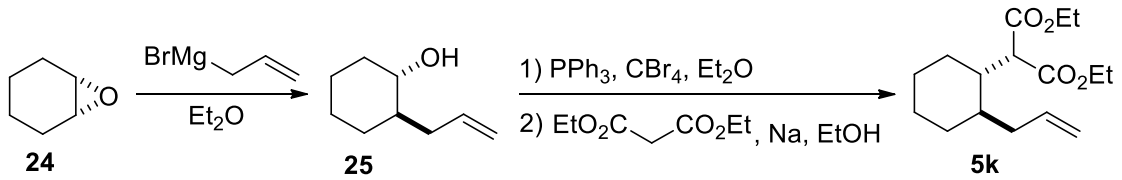
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73-5.63 (m, 1H, CH_2*CH*=CH_2), 5.01-4.96 (m, 2H, CH_2CH=*CH_2*), 4.19 (m, 4H, CO_2*CH_2*CH_3), 3.32 (d, *J* = 11.6 Hz, 1H, malonate proton), 2.61-2.52 (m, 1H , *CH*CH(CO_2Et)$_2$), 2.21-2.14 (m, 2H, *CH_2*CH=C), 2.09-2.04 (m, 1H, ring proton), 1.78-1.52 (m, 6H, ring protons), 1.26 (t, *J* = 7.1 Hz, 6H, CO_2CH_2*CH_3*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 168.9, 137.7, 116.4, 61.3, 53.6, 41.3, 39.8, 33.1, 29.5, 27.8, 21.8, 14.1;

IR (neat), 3078(w), 2979(w), 2871(w), 1754 (s), 1731(s), 1641(w), 1447(w), 1369(m) 1149(m), 1032(m), 911(m);

HRMS (ESI) calcd for $C_{15}H_{24}NaO_4^+$ $[M+Na]^+$ 291.1567; found 291.1569.

***Trans*-diethyl 2-(2-allylcyclohexyl)malonate (5k)**



24 **25** **5k**

Cyclohexene oxide (**24**) (0.700 mL, 7.00 mmol) was converted into alcohol **25** using procedure **A**. **25** (0.981 g, 7.00 mmol, quantitative) was obtained as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90-5.80 (m, 1H, CH_2*CH*=CH_2), 5.08-5.00 (m, 2H, CH_2CH=*CH_2*), 3.30-3.23 (m, 1H, *CH*OH), 2.48-2.41 (m, 1H, CH_2 or CH), 2.01-1.94 (m, 2H, CH_2 or CH), 1.79-1.72 (m, 2H, CH_2 or CH), 1.65-1.59 (m, 1H, CH_2 or CH), 1.37-1.10 (m, 4H, CH_2 or CH), 0.99-0.89 (m, 1H, CH_2 or CH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.5, 116.0, 74.7, 45.0, 37.5, 35.6, 30.4, 25.5, 24.9.

25 (0.490 g, 3.50 mmol) was converted into the corresponding alcohol following theprocedure **B**. Purification thorugh column chromatography (SiO_2 eluting with 95:5 PET:Et_2O) gave the corresponding bromide (0.461 g, 2.28 mmol, 65%) as a colourless oil

Rf : 0.9 (PET:Et_2O/95:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79-5.69 (m, 1H, CH_2*CH*=CH_2). 5.12-5.02 (m, 2H, CH_2CH=*CH_2*), 4.54 (m, 1H, *CH*Br), 2.20-1.99 (m, 2H, allyl or ring protons), 1.85-1.71 (m, 4H, allyl or ring protons), 1.53-1.25 (m, 5H, allyl or ring protons);

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0, 116.7, 61.5, 42.4, 39.7, 35.2, 27.1, 25.4, 21.1.

The bromide (0.400 g, 2.00 mmol) was reacted with diethyl malonate using procedure **D**. Purification though column chromatography (SiO_2 eluting with 10:1 to 5:1 PET:Et_2O) gave **5k** (0.105 g, 0.373 mmol, 19%) as a colourless oil.

Rf: 0.47 (PET:Et_2O/15:1);

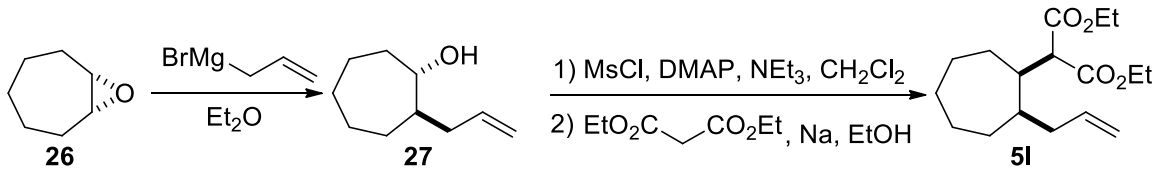
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80-5.69 (m, 1H, CH_2*CH*=CH_2), 5.03-4.99 (m, 2H, CH_2CH=*CH_2*), 4.21-4.16 (m, 4H, O*CH_2*CH_3), 3.71 (d, *J* = 5.2 Hz, 1H, malonate proton), 2.29-2.23 (m, 1H, allyl or ring protons), 2.02-1.90 (m, 2H, allyl or ring protons), 1.77-1.62 (m, 5H, ring protons), 1.47-1.38 (m, 4H, ring protons), 1.29-1.24 (m, 6H, CO_2CH_2*CH_3*);

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 168.7, 136.4, 116.3, 61.2, 60.8, 53.2, 41.5, 38.7, 37.7, 31.1, 27.8, 25.6, 25.3, 14.2, 14.1;

IR (neat), 3078 (w), 2980 (w), 2930 (m), 2859 (w), 1755 (s), 1731(s), 1640 (w), 1462 (m), 1368 (m), 1155 (m), 1032 (m), 911 (m);

HRMS (ESI) calcd for $C_{16}H_{27}O_4^+$ $[M+H]^+$ 283.1904; found 283.1894

***Cis*-diethyl 2-(2-allylcycloheptyl)malonate (5l)**

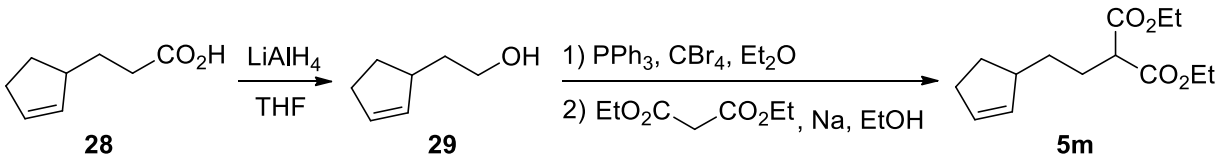


Cycloheptene oxide (**26**) (0.480 mL, 4.20 mmol) was converted into alcohol **27** following general procedure **A**. Alcohol **27** (0.646 g, 4.20 mmol, quantitative) was obtained as a colourless oil
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89-5.78 (m, 1H, CH_2CH=CH_2), 5.08-5.01 (m, 2H, CH_2CH=CH_2), 3.50 (m, 1H, *CH*OH), 2.40-2.33 (m, 1H, allyl or ring proton), 2.08-2.00 (m, 2H, allyl or ring proton), 1.76-1.38 (m, 10H, ring protons).

Alcohol **27** (0.647 g, 4.20 mmol) was mesylated using procedure **C**. After purification though column chromatography (SiO_2 eluting with 1:1 PET:Et_2O), the mesylate (0.821 g, 3.46 mmol, 82%) was isolated as a colourless oil.
Rf: 0.30 (PET:Et_2O/1:1);
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78-5.70 (m, 1H, CH_2CH=CH_2), 5.09-5.04 (m, 2H, CH_2CH=CH_2), 4.67-4.62 (m, 1H, *CH*OMs), 3.00 (s, 3H, SO_2CH_3), 2.36-2.30 (m, 1H, allyl or ring protons), 2.13-1.98 (m, 2H, allyl or ring protons), 1.95-1.79 (m, 2H, ring protons), 1.76-1.63 (m, 4H, ring protons), 1.57-1.51 (m, 1H, ring proton), 1.44-1.36 (m, 2H, ring protons), 1.30-1.20 (m, 1H, ring proton).

The mesylate (0.821 g, 3.46 mmol) was reacted with diethylmalonate following procedure **D**. Purification though column chromatography (SiO_2 eluting with 15:1 PET:Et_2O) gave **5l** (0.307 g, 1.04 mmol, 30%). as a colourless oil.
Rf: 0.4 (PET:Et_2O/15:1);
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73-5.64 (m, 1H, CH_2CH=CH_2), 5.04-4.95 (m, 2H, CH_2CH=CH_2), 4.19 (t, *J* = 7.1 Hz, 4H, OCH_2CH_3), 3.39 (d, *J* = 11.2 Hz, 1H, malonate proton), 2.52-2.47 (m, 1H, allyl or ring proton), 2.18-2.13 (m, 1H, allyl or ring proton), 2.00-1.89 (m, 1H, allyl or ring protons), 1.77-1.70 (m, 1H, ring proton), 1.65-1.45 (m, 8H, ring protons), 1.41-1.37 (m, 2H, ring protons), 1.26 (t, *J* = 7.1 Hz, 6H, $COCH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1, 168.9, 137.8, 115.7, 61.3, 57.1, 42.4, 38.5, 33.2, 32.2, 28.0, 27.4, 27.1, 24.3, 14.1;
IR (neat), 3079 (w), 2981 (w), 2932 (m), 2855 (w), 1755 (s), 1731 (s), 1640 (w), 1461 (m), 1368 (w), 1301 (m), 1155 (s), 1033 (s), 914 (s); HRMS (ESI) calcd for $C_{17}H_{29}O_4^+$ $[M+H]^+$ 297.2060; found 297.2071.

Diethyl 2-(2-(cyclopent-2-en-1-yl)ethyl)malonate (5m)



28 **29** **5m**

A solution of $LiAlH_4$ (1.51 g, 39.8 mmol, 2.50 equiv) in THF (60 mL) was cooled to 0 ºC and acid **28** (1.80 mL, 13.6 mmol, 1.00 equiv) was added dropwise. The suspension was then heated to reflux for 2 hours, TLC analysis showed an incomplete reaction and so an additional $LiAlH_4$ (0.23 g, 6.1 mmol, 0.45 equiv) was added and the suspension was stirred overnight at rt. The reaction was then quenched by successive additions of H_2O (2.1 mL), 10% aq. NaOH solution (4.2 mL) and H_2O (6.3 mL). The resulting mixture was then stirred at room temperature for 1 hour (until the mixture turned white) and the solids were filtered off. The solvents were removed under reduced pressure to give **29** (1.33 g, 11.9 mmol, 88%) as a yellow oil. NMR analysis showed that **29** was pure enough to use without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75-5.72 (m, 1H, C=*CH*), 5.70-5.67 (m, 1H, C=*CH*), 3.72-3.68 (m, 2H, *CH*$_2$OH), 2.81-2.73 (m, 1H, C=C*CH*), 2.40-2.23 (m, 2H, C=CCH_2), 2.11-2.03 (m, 1H, *CH*$_2$), 1.74-1.65 (m, 1H, *CH*$_2$), 1.62-1.55 (m, 1H, *CH*$_2$), 1.48-1.40 (m, 1H, *CH*$_2$).

Procedure **B** was used for the bromination of **29** (1.68 g, 15.0 mmol). The crude was then purified by column chromatography (SiO_2 eluting with 6:1 Pentane:EtOAc) to give the bromide (2.22 g, 12.8 mmol, 85%) as a pale yellow oil.

Rf: 0.9 (PET:EtOAc/6:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (m, 1H, C=*CH*), 5.66 (m, 1H, C=*CH*), 3.46-3.38 (m, 2H, *CH*$_2$Br), 2.83 (m, 1H, C=C*CH*$(CH_2)_2$Br). 2.38-2.26 (m, 2H, *CH*$_2$), 2.12-2.04 (m, 1H, *CH*$_2$), 2.01-1.93 (m, 1H, *CH*$_2$), 1.88-1.79 (m, 1H, *CH*$_2$), 1.45-1.36 (m, 1H, *CH*$_2$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 133.5, 131.3, 44.2, 39.0, 32.2, 31.9, 29.3.

The bromide (1.31 g, 6.50 mmol) was then reacted with diethylmalonate using procedure **D**. Purification of the crude though column chromatography (SiO_2 using 25:1 pentane:EtOAc) yielded **5m** (0.412 g, 1.60 mmol, 25% yield) as a colourless oil.

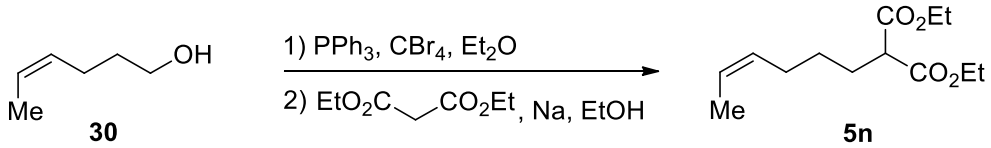
Rf: 0.5 (PET:Et_2O/15:1);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (m, 1H, C=*CH*), 5.66 (m, 1H, C=*CH*), 4.20 (dq, *J* = 7.1, 2.1 Hz, 4H, OC*H*$_2$CH$_3$), 3.30 (t, *J* = 7.5 Hz, 1H, malonate proton), 2.69-2.61 (m, 1H, allylic CH or CH_2), 2.38-2.21 (m, 2H, *CH*$_2$), 2.09-2.01 (m, 1H, *CH*$_2$), 1.95-1.88 (m, 2H, *CH*$_2$), 1.47-1.37 (m, 3H, *CH*$_2$), 1.26 (t, *J* = 7.1 Hz, 6H, OCH$_2$C*H*$_3$);

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 134.4, 130.9, 61.2, 52.2, 45.2, 33.6, 31.9, 29.5, 27.1, 14.1.

IR (neat), 3052 (w), 2984 (w), 2938 (w) 2852 (w), 1732 (s), 1454 (s), 1370 (s), 1147 (s), 1029 (s).
HRMS (ESI) calcd for $C_{14}H_{23}O_4$ $[M+H]^+$ 256.1591 found 256.1602.

(*Z*)-Diethyl hex-4-enylpropanedioate (5n)



Z-hex-4-ene-1-ol (**30**) (1.17 mL, 10.0 mmol) was brominated using procedure **B**. Purification though column chromatography (SiO_2 eluting with pentane) gave the bromide (1.54 g, 9.48 mmol, 95%), as a colourless oil.
Rf: 0.80 (pentane);^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55-5.48 (m, 1H, olefin CH), 5.37-5.30 (m, olefin CH), 3.41 (t, *J* = 6.6 Hz, 2H, C*H*$_2$Br), 2.20 (q, *J* = 6.7 Hz, 2H, C*H*$_2$CH=CH), 1.95-1.88 (m, 2H, C*H*$_2$), 1.63 (d, *J* = 6.5 Hz, 3H, C*H*$_3$);
^{13}C NMR (101 MHz, $CDCl_3$) δ 128.4, 125.6, 33.4, 32.5, 25.3, 12.9.

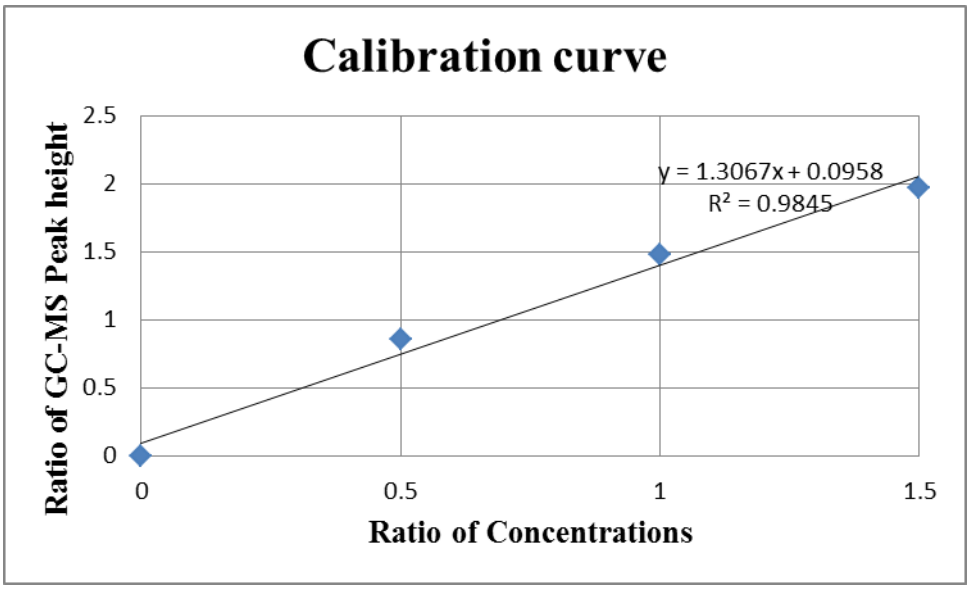
The bromide (0.970 g, 6.00 mmol) was reacted with diethylmalonate using procedure **D**. Purification though column chromatography (SiO_2 using 20:1 hexanes:EtOAc) gave **5n** (1.01 g, 4.20 mmol, 70%) as a colourless oil.
Rf: 0.42 (PET:Et_2O/15:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50-5.44 (m, 1H, C=*CH*), 5.38-5.31 (m, 1H, C=*CH*), 4.21 (q, *J* = 7.1 Hz, 4H, O*CH*$_2$CH$_3$), 3.32 (t, *J* = 7.5 Hz, 1H, malonate proton), 2.07 (dd, *J* = 7.2, 7.2 Hz, 2H, C*H*$_2$), 1.91 (m, 2H, C*H*$_2$), 1.60 (d, *J* = 6.6 Hz, 3H, =CH*Me*), 1.39 (m, 2H, C*H*$_2$), 1.26 (t, *J* = 7.1 Hz, 6H, CO_2CH_2*CH*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 129.7, 124.5, 61.2, 51.9, 29.3, 27.2, 26.4, 14.1, 12.7;
IR (neat), 2986 (broad, m), 1731 (s), 1450 (broad, w), 1370 (w), 1236 (m), 1150 (m), 1047 (m), 863 (w);
HRMS (ESI) calcd for $C_{13}H_{22}O_4$ $[M+H]^+$ 243.1596; found 243.1597.

3. Calibration procedure used for optimization

A 0.015 M solution of **5a** was prepared by dissolving 53.9 mg in 8.79 mL of HPLC grade DCM. Additionally a 0.15 M solution of the chosen internal standard, pentadecane, was also prepared by dissolving 25 μL pentadeceane in 6.04 mL of DCM. 3 solutions were then prepared:

- Solution A (0.015 M) containing 0.25 mL of the standard and 0.5 mL of the product
- Solution B (0.015 M) contained 0.5 mL of both the standard and product solutions
- Solution C (0.015 M) contained 0.75 mL of the standard and 0.5 mL of the product solutions

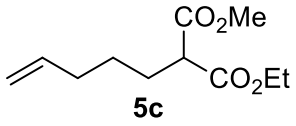
Then chromatograms for these solutions were then obtained. The ratio peaks for the standard (retention 15.96 min) and product (retention time 28.91 min) were calculated and a calibration graph was obtained



The general procedure for screening involved taking a 0.15 mL aliqout of the reaction mixture after 3 hours and diluting it with 0.85 mL of HPLC grade DCM. 1 µL of this solution was injected into the GC-MS and the following oven program was used: initial temperature: 50 °C, Ramp: 10.0 °C/min to 250 °C, hold 15 min at 250 °C. Each sample was run for 40 minutes.

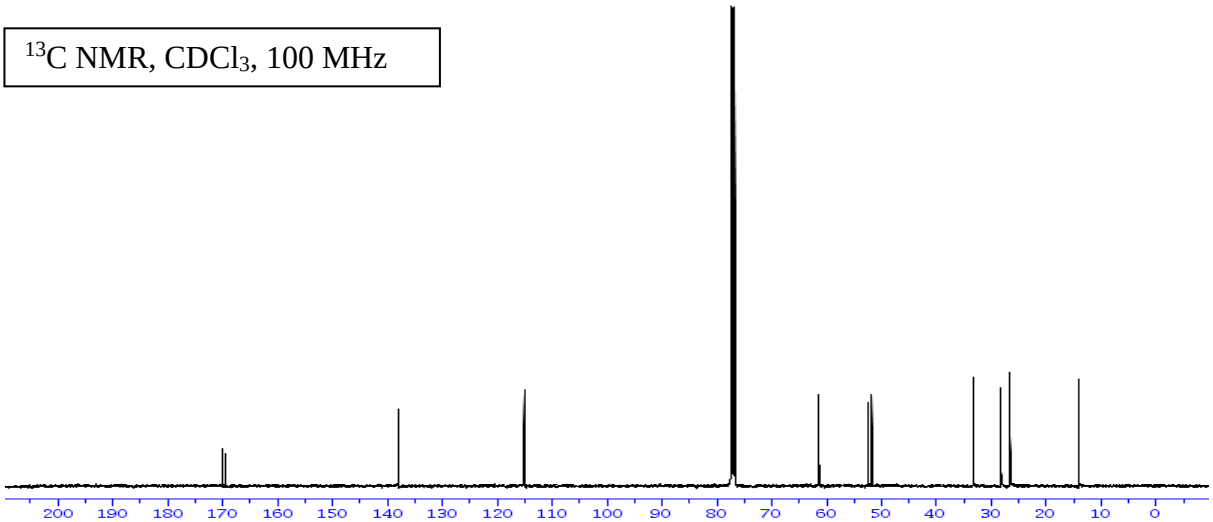
4. Spectra of new compounds

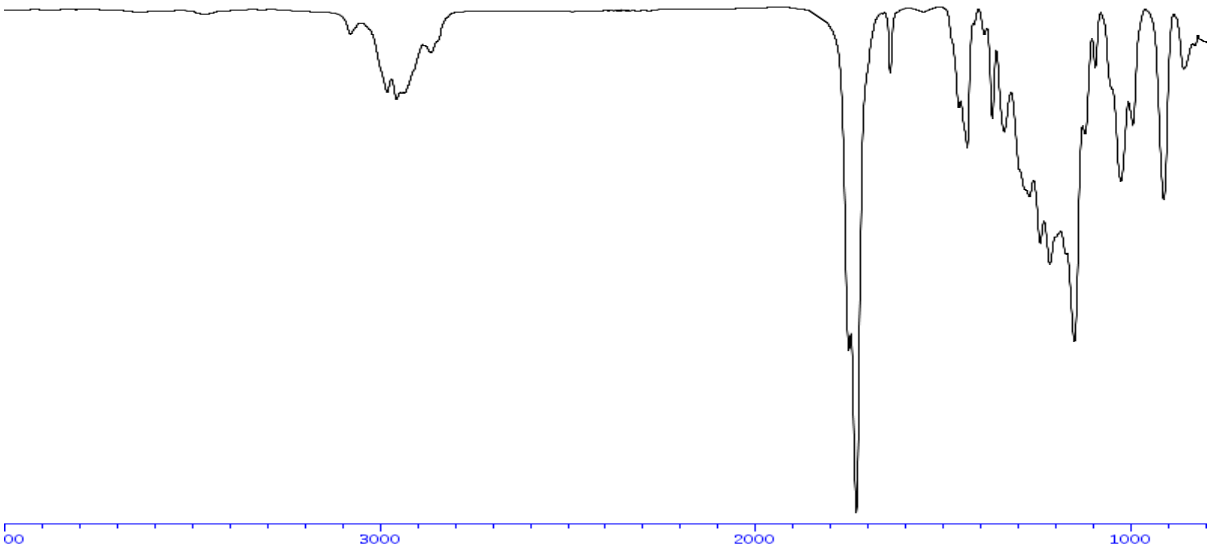
^{1}H NMR, $CDCl_3$, 400 MHz



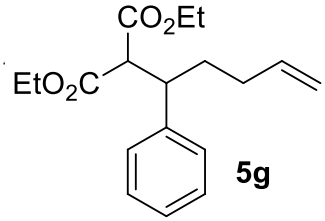
5c

^{13}C NMR, $CDCl_3$, 100 MHz



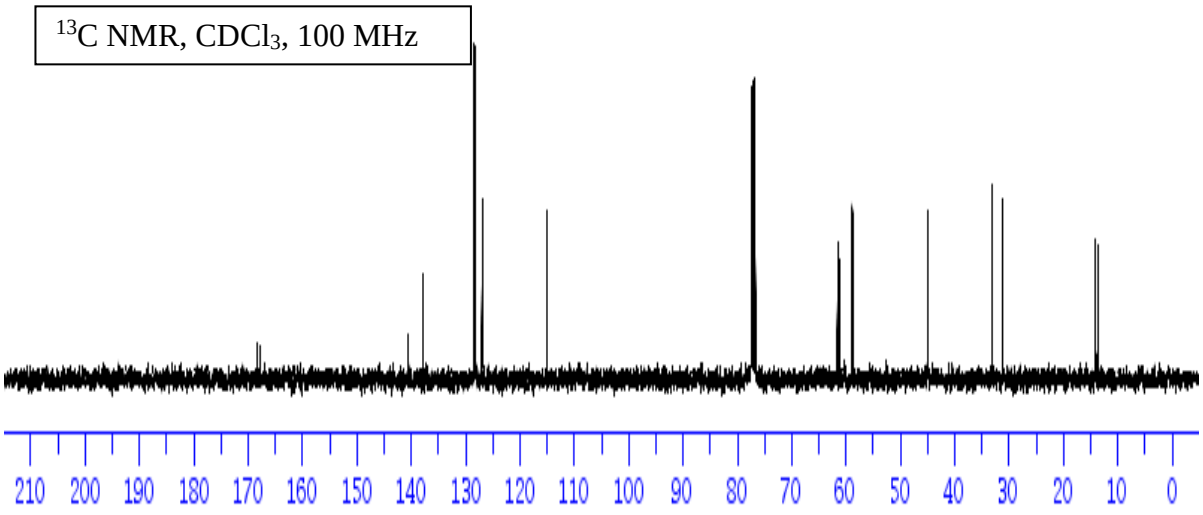


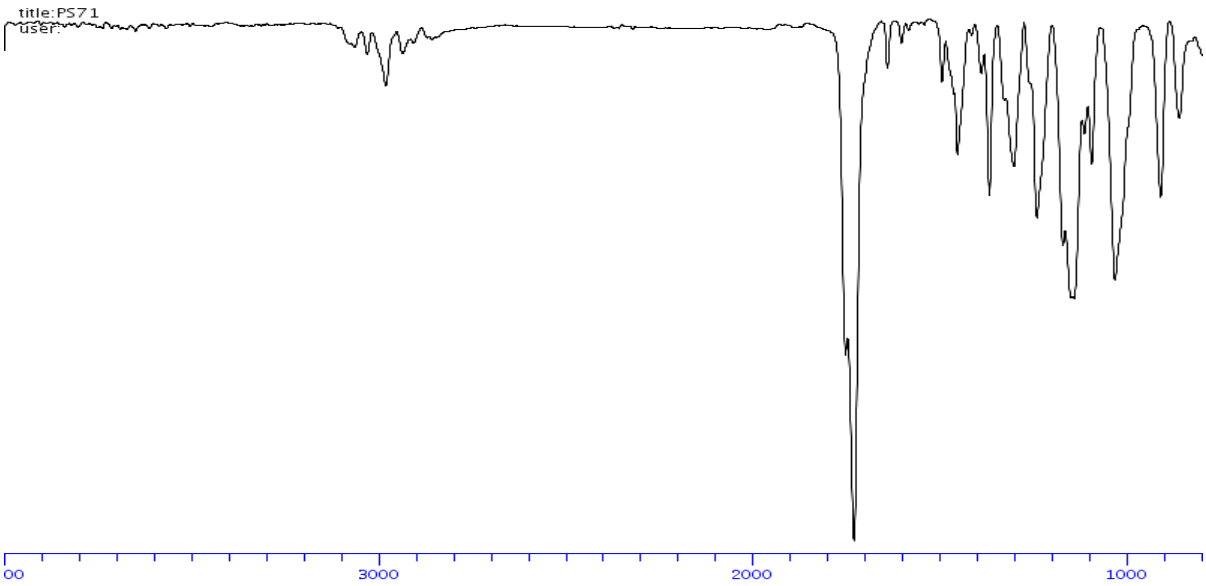
^{1}H NMR, $CDCl_3$, 400 MHz



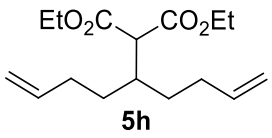
5g

^{13}C NMR, $CDCl_3$, 100 MHz



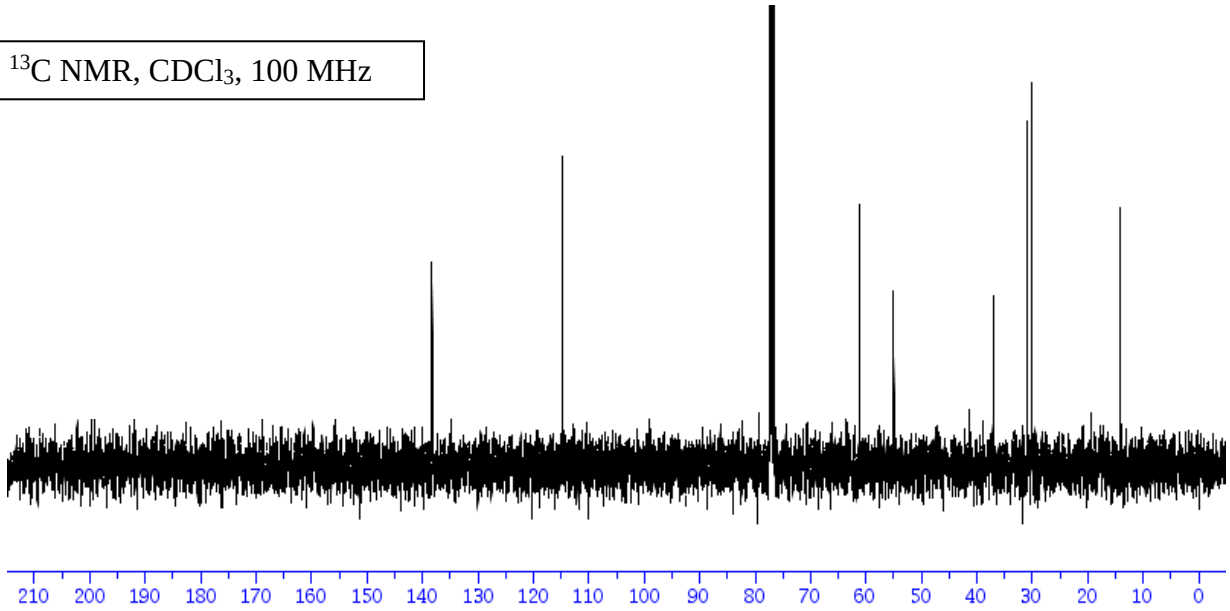


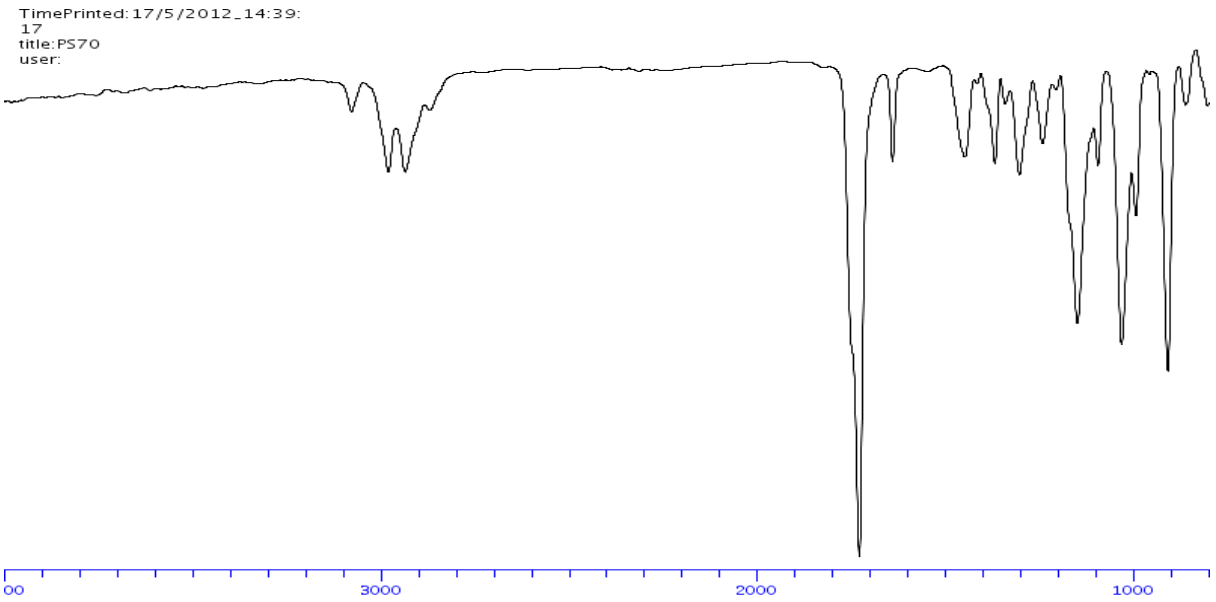
^{1}H NMR, $CDCl_3$, 400 MHz



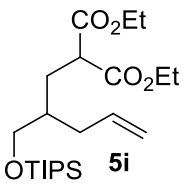
5h

^{13}C NMR, $CDCl_3$, 100 MHz



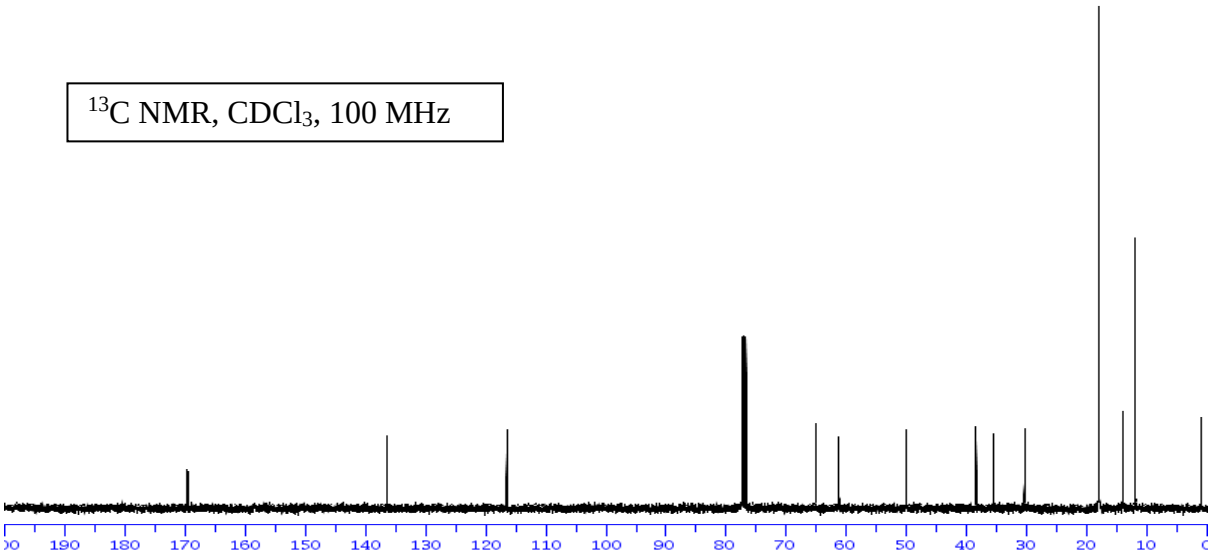


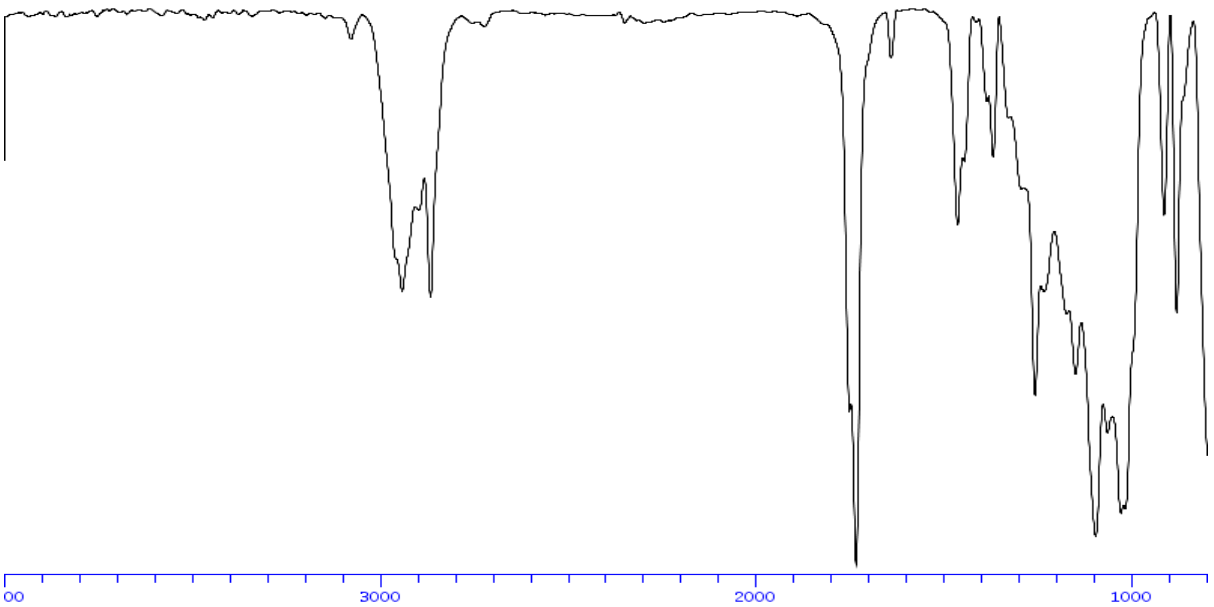
^{1}H NMR, $CDCl_3$, 400 MHz



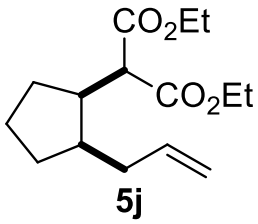
5i

^{13}C NMR, $CDCl_3$, 100 MHz



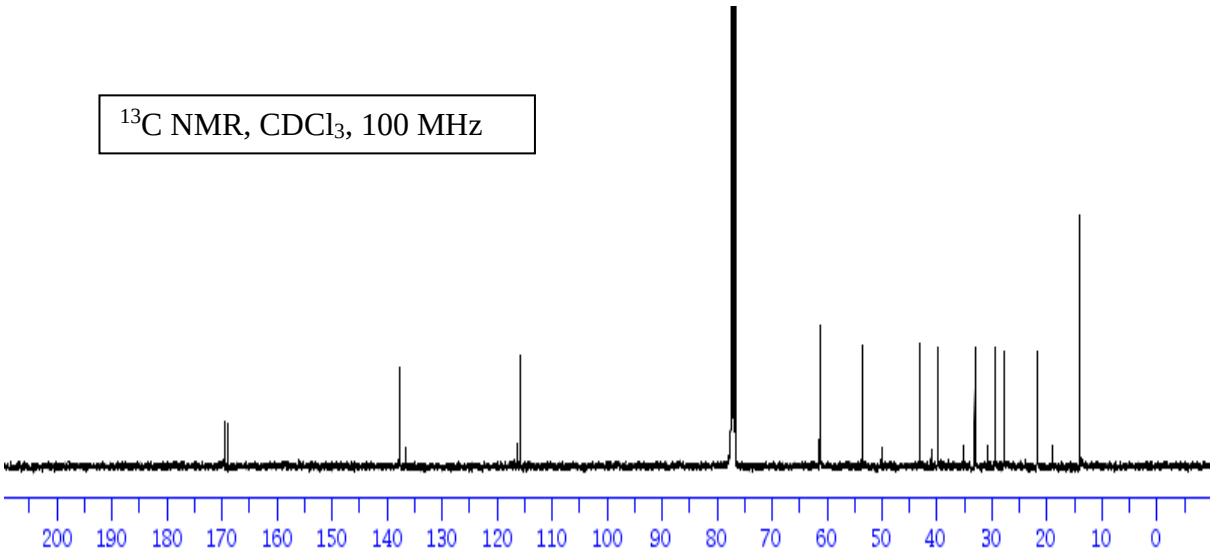


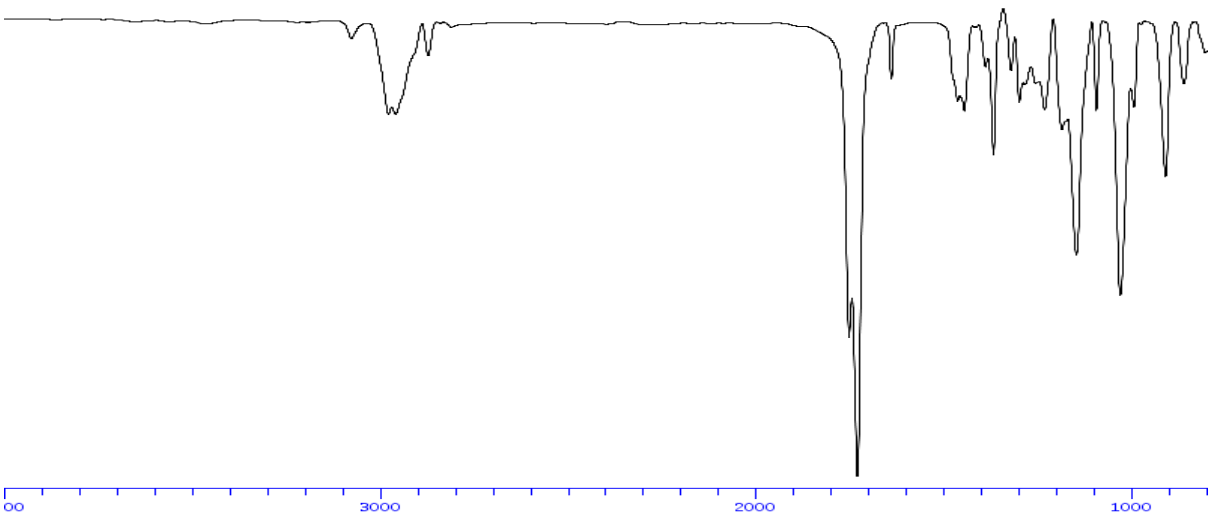
^{1}H NMR, $CDCl_3$, 400 MHz



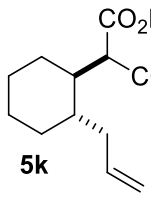
5j

^{13}C NMR, $CDCl_3$, 100 MHz



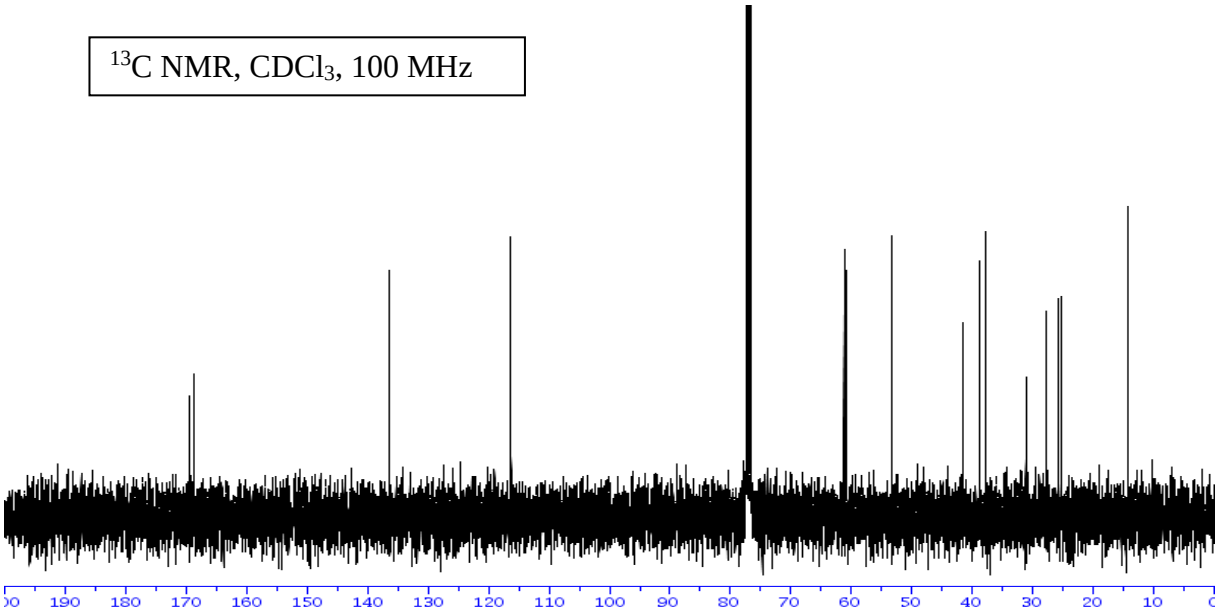


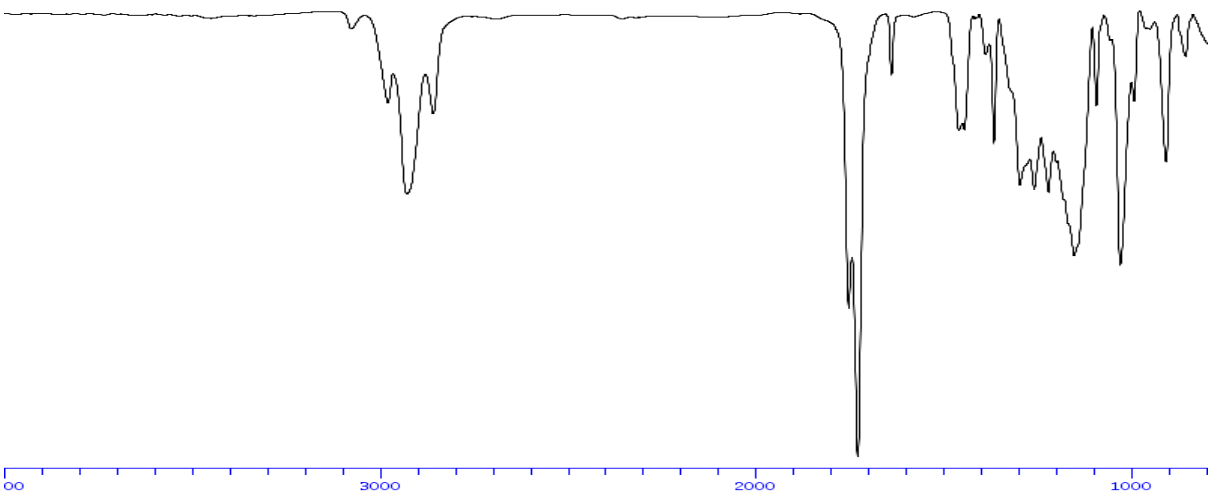
^{1}H NMR, $CDCl_3$, 400 MHz



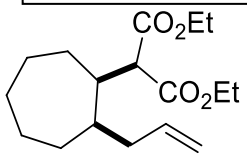
5k

^{13}C NMR, $CDCl_3$, 100 MHz



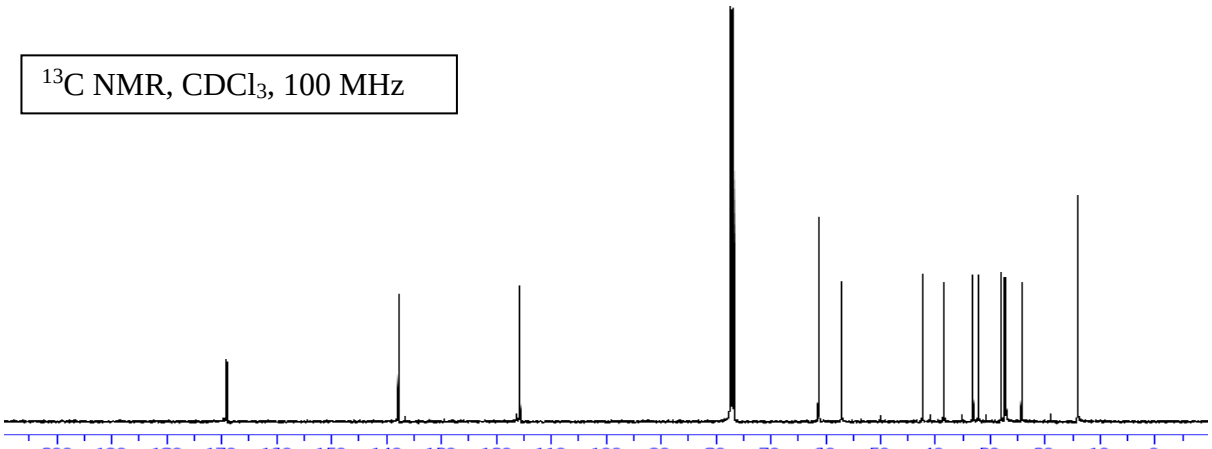


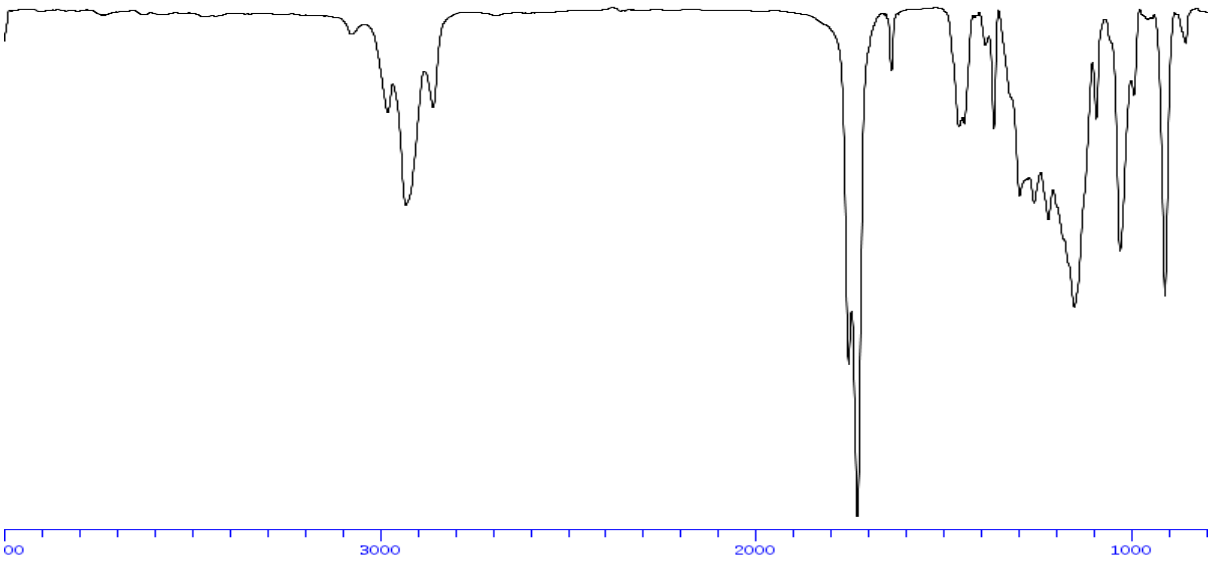
^{1}H NMR, $CDCl_3$, 400 MHz



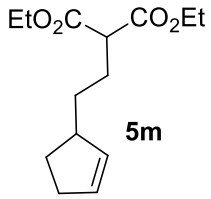
5l

^{13}C NMR, $CDCl_3$, 100 MHz

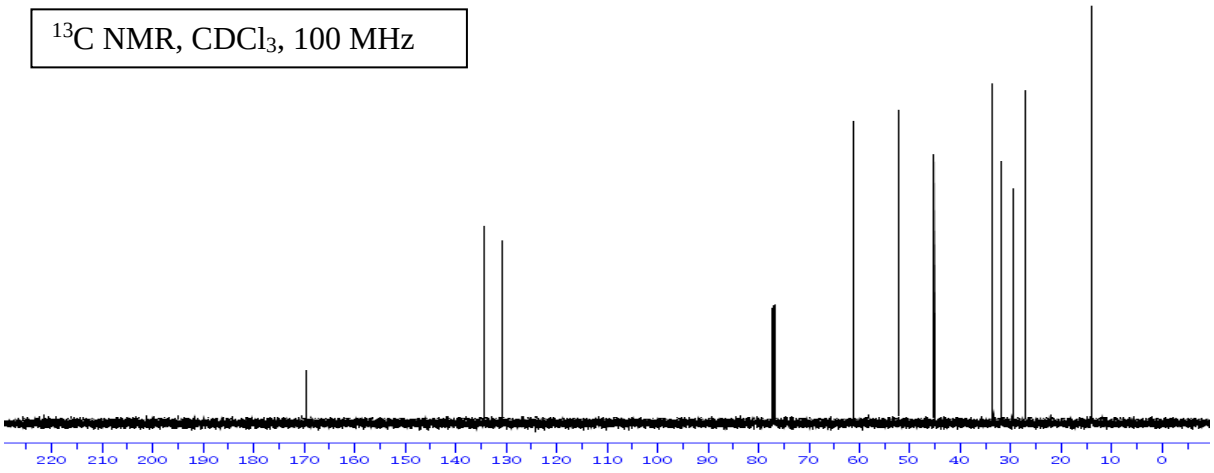


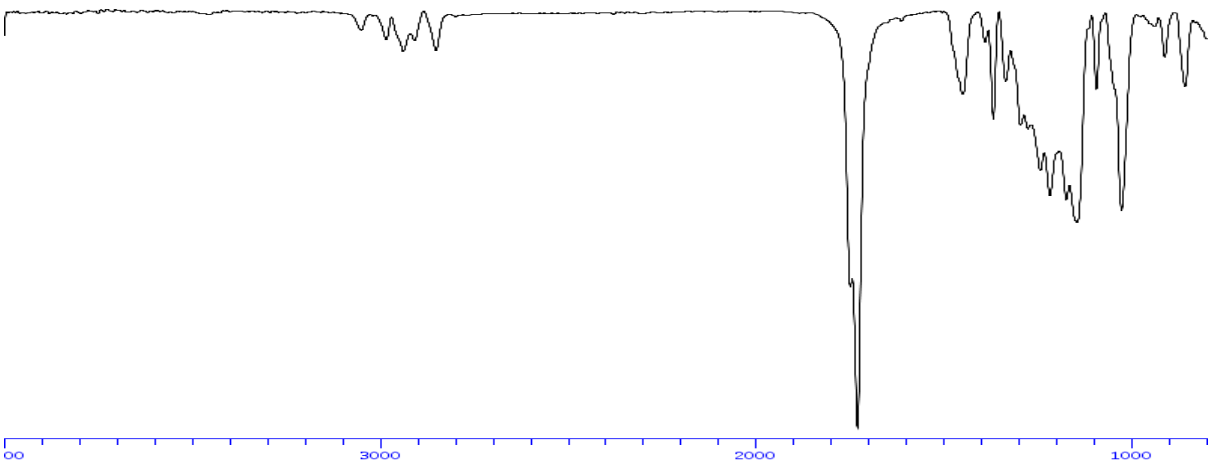


^{1}H NMR, $CDCl_3$, 400 MHz

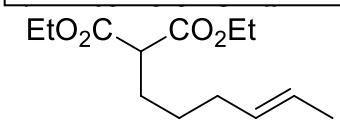


^{13}C NMR, $CDCl_3$, 100 MHz



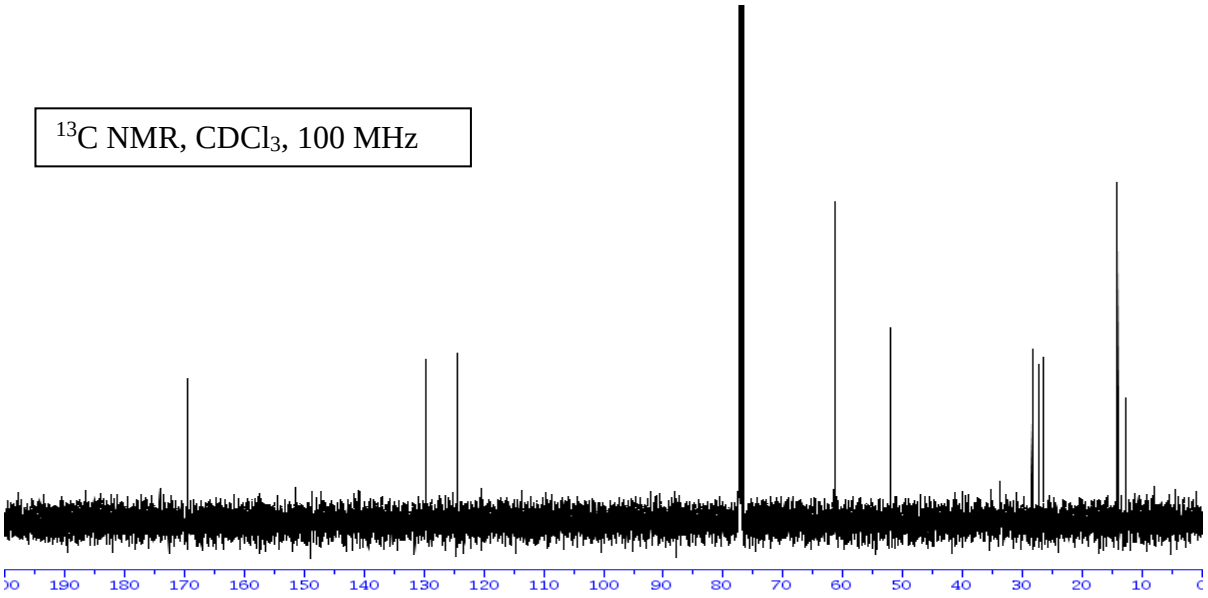


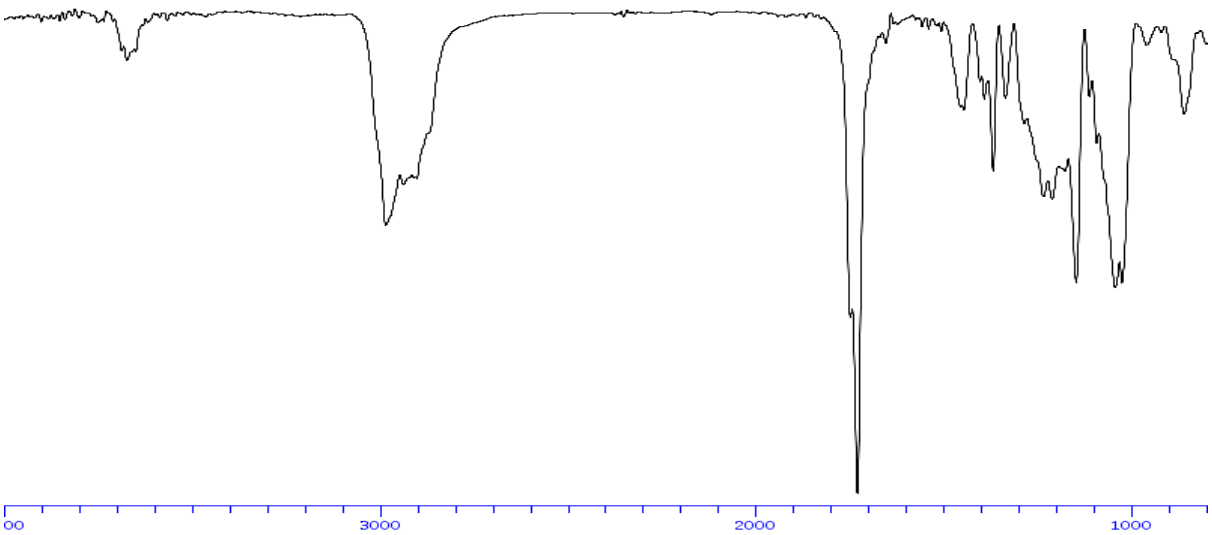
^{1}H NMR, $CDCl_3$, 400 MHz



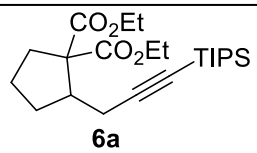
5n

^{13}C NMR, $CDCl_3$, 100 MHz



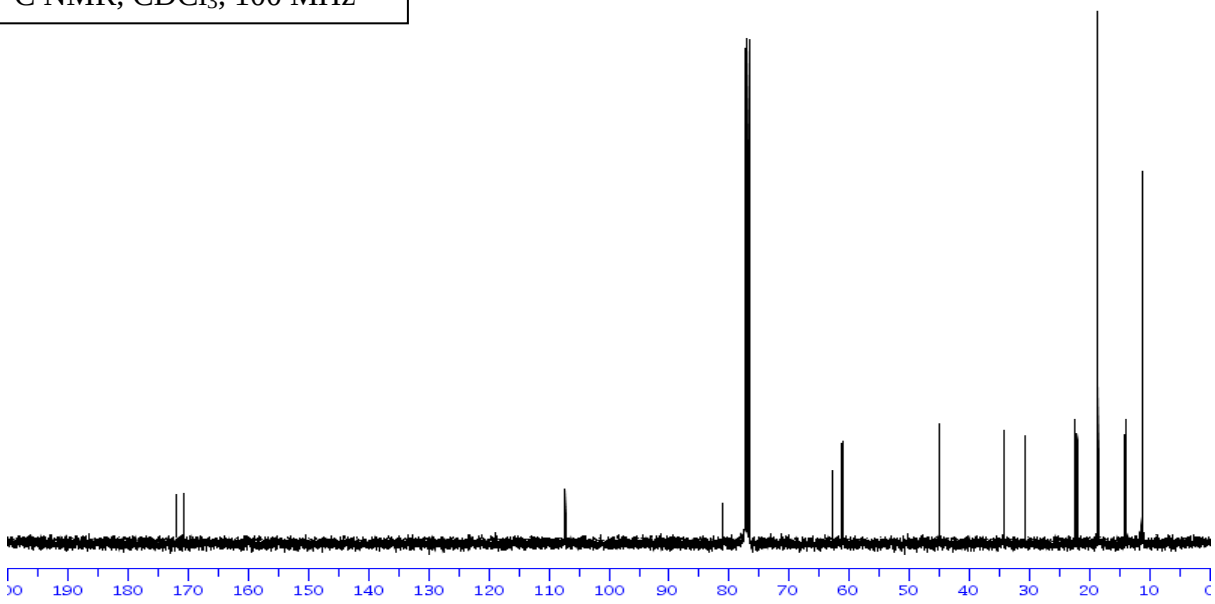


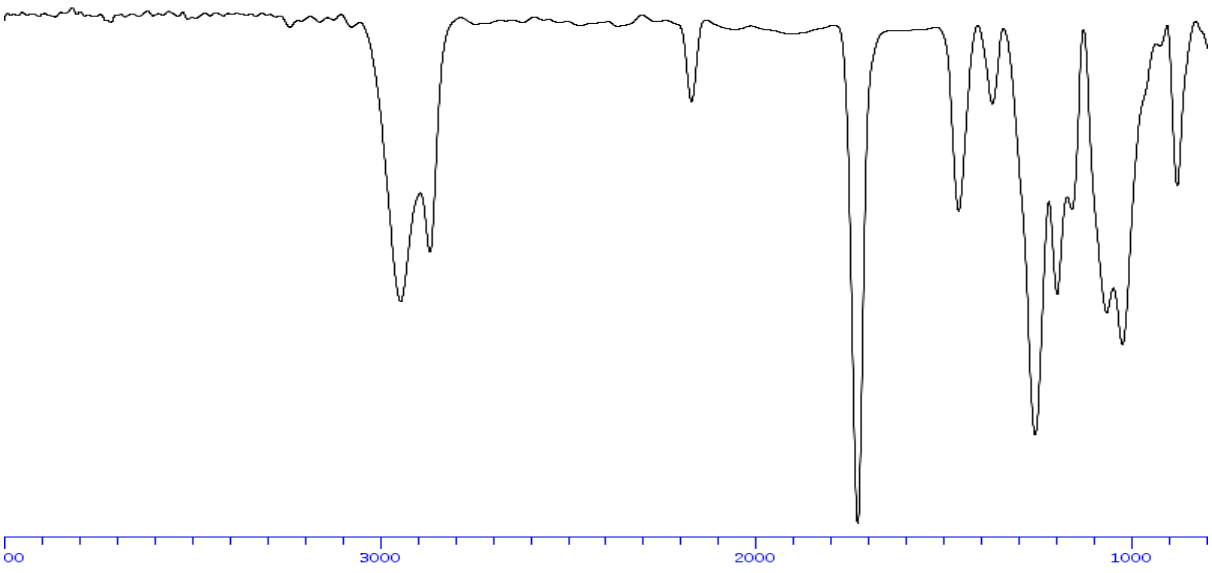
^{1}H NMR, $CDCl_3$, 400 MHz



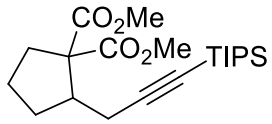
6a

^{13}C NMR, $CDCl_3$, 100 MHz



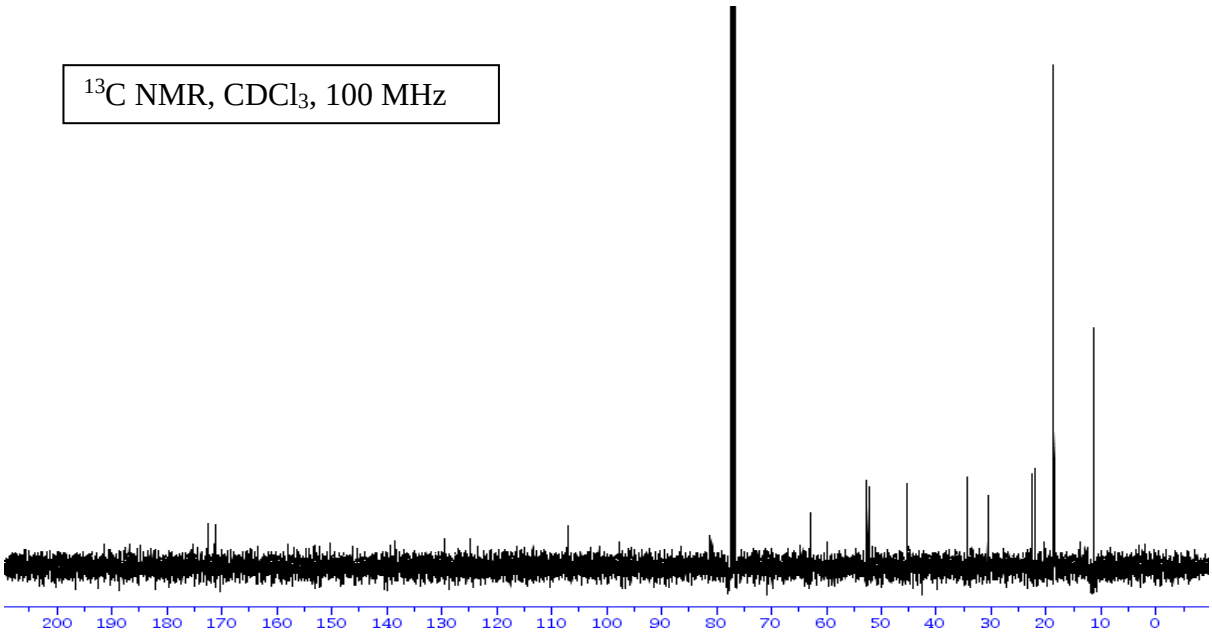


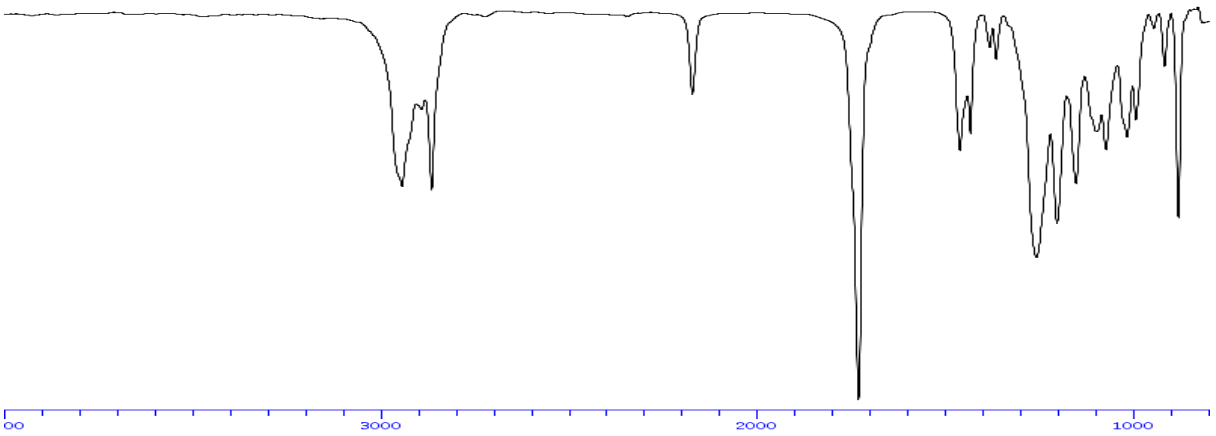
^{1}H NMR, $CDCl_3$, 400 MHz



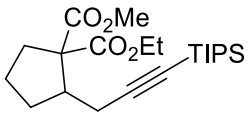
6b

^{13}C NMR, $CDCl_3$, 100 MHz



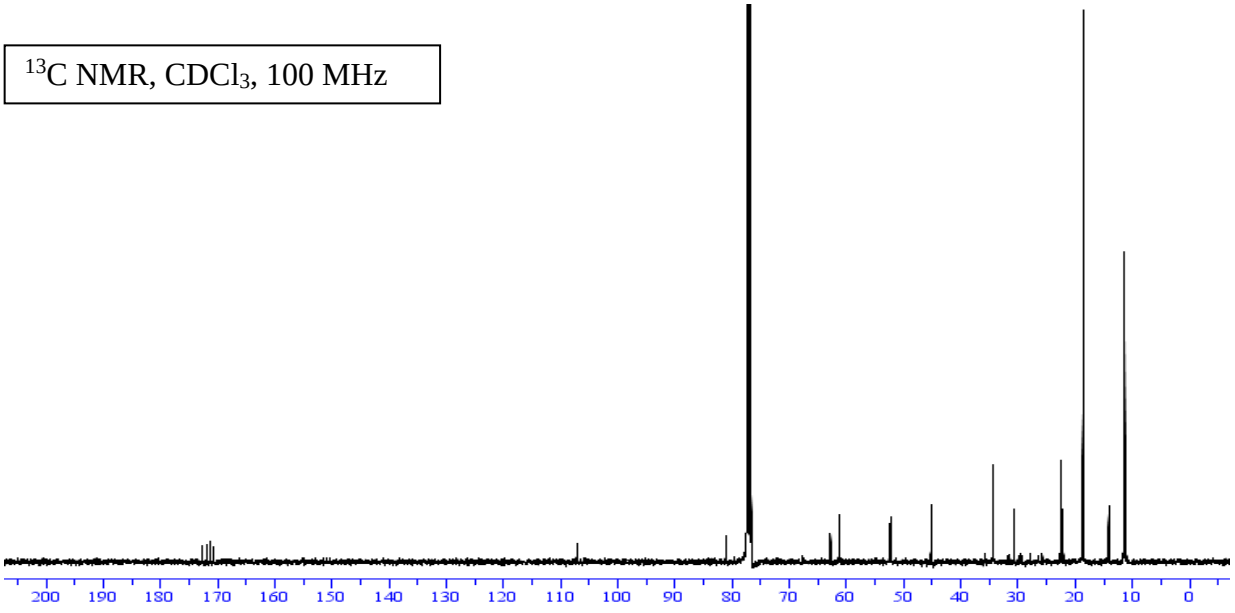


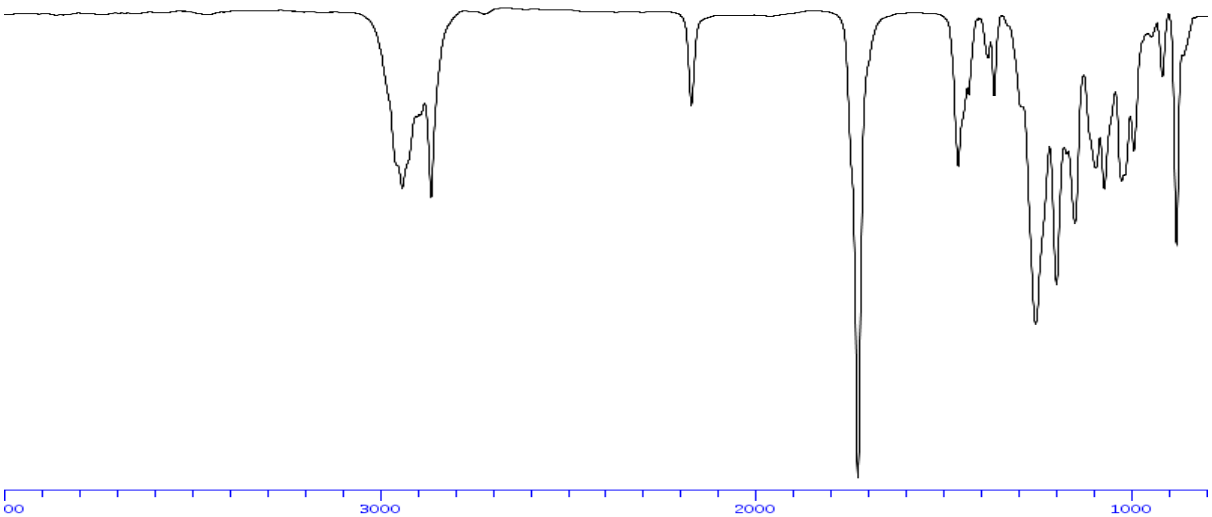
^{1}H NMR, $CDCl_3$, 400 MHz



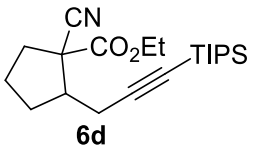
6c

^{13}C NMR, $CDCl_3$, 100 MHz



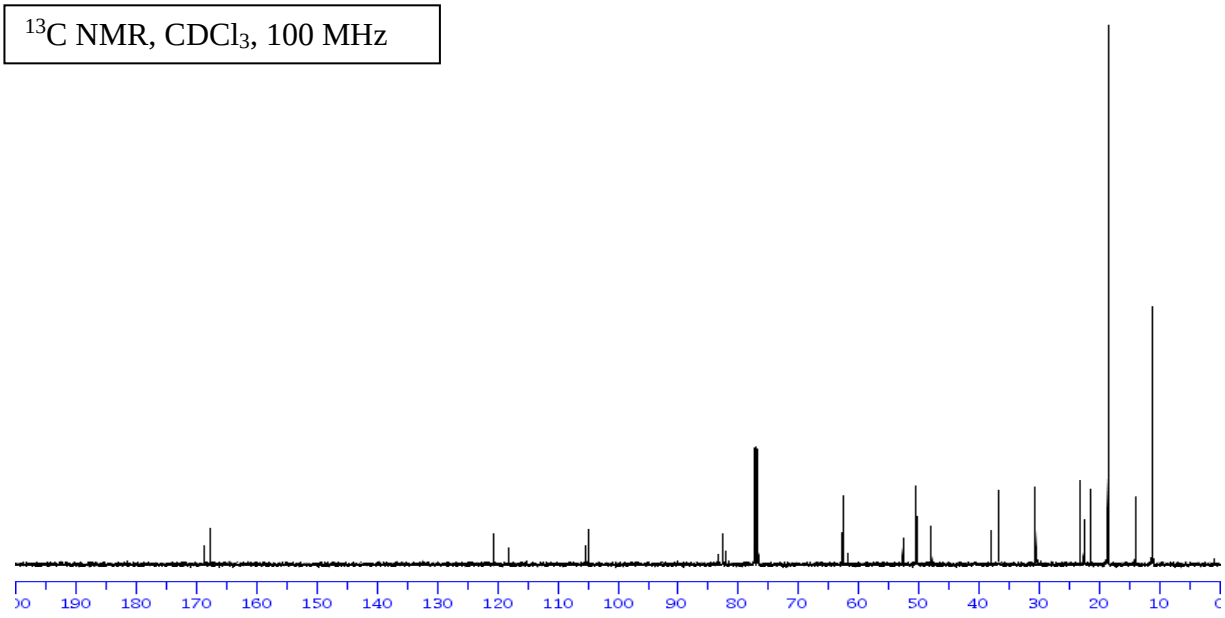


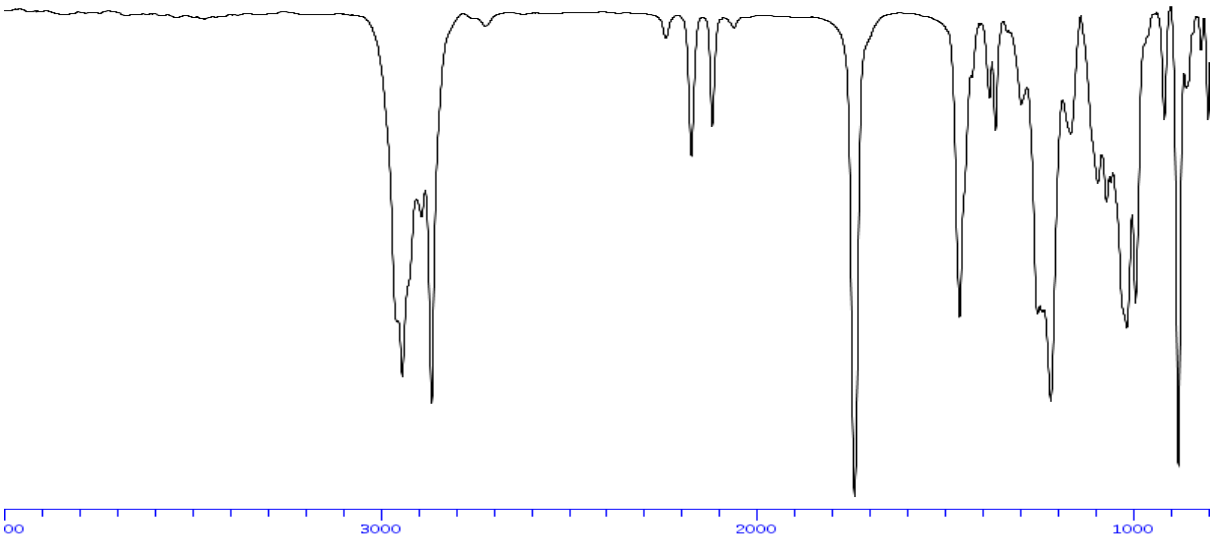
^{1}H NMR, $CDCl_3$, 400 MHz



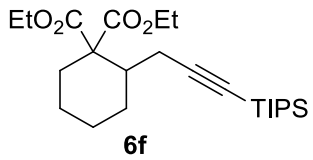
6d

^{13}C NMR, $CDCl_3$, 100 MHz



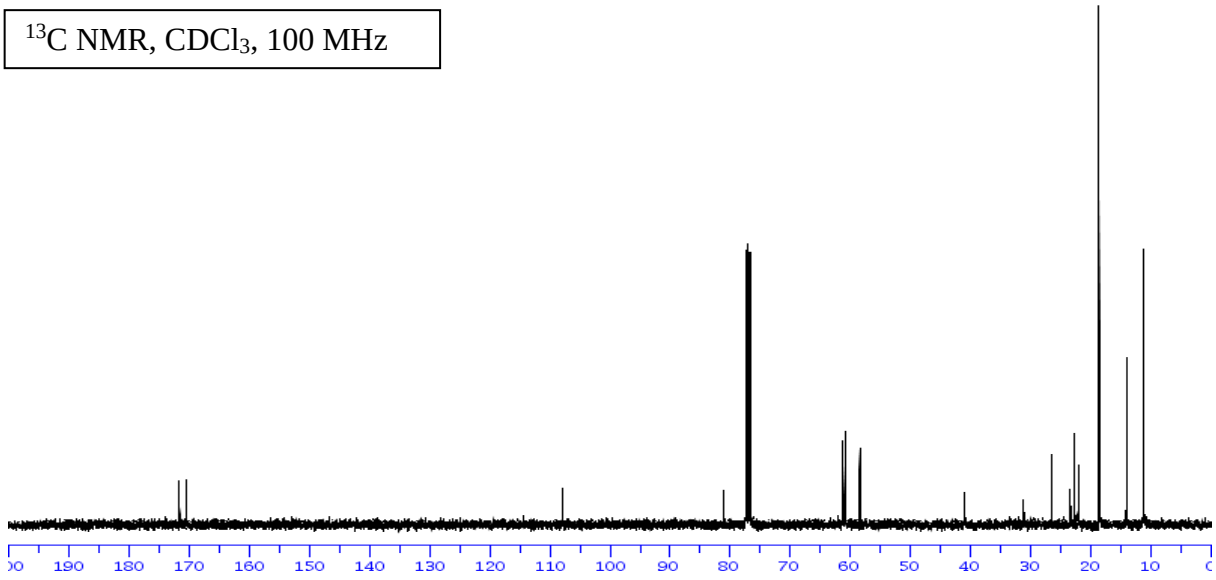


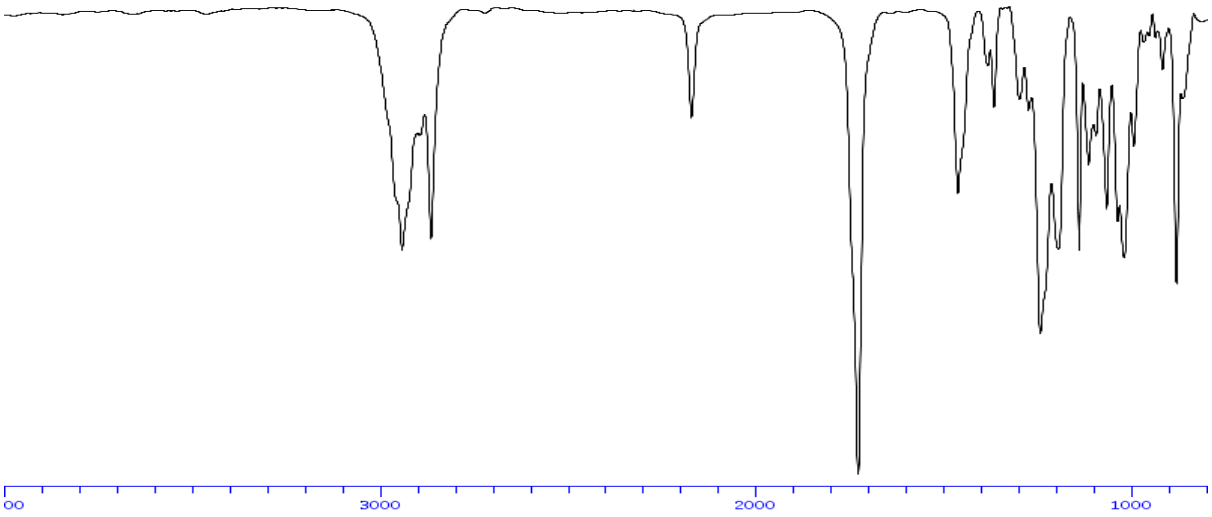
^{1}H NMR, $CDCl_3$, 400 MHz



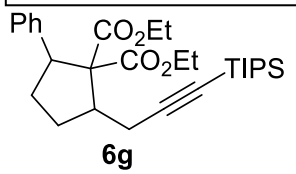
6f

^{13}C NMR, $CDCl_3$, 100 MHz



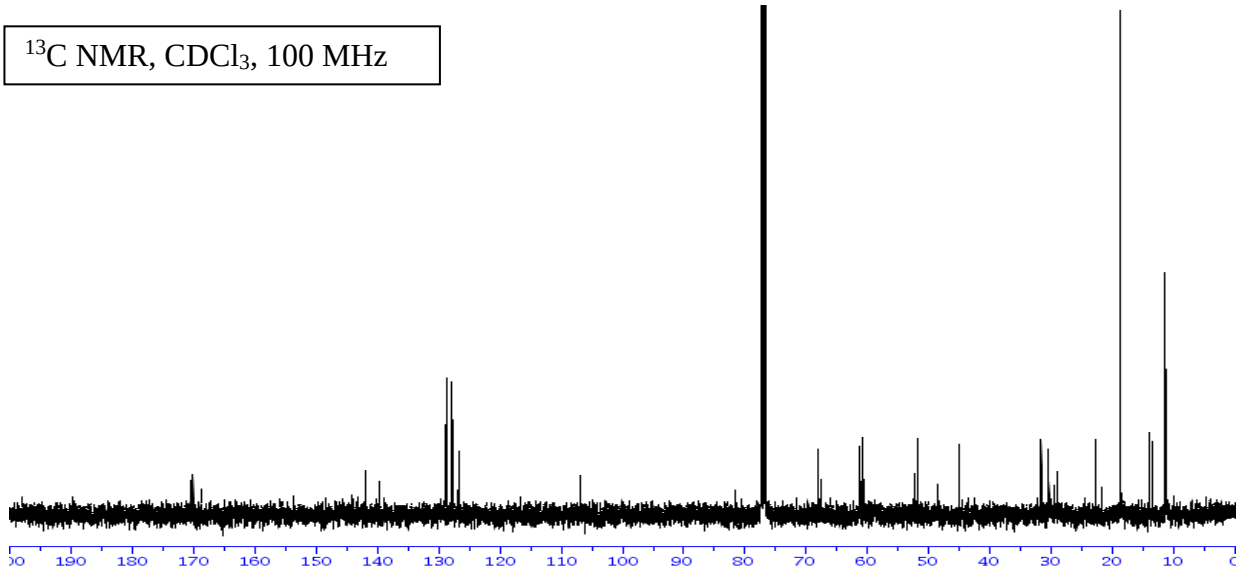


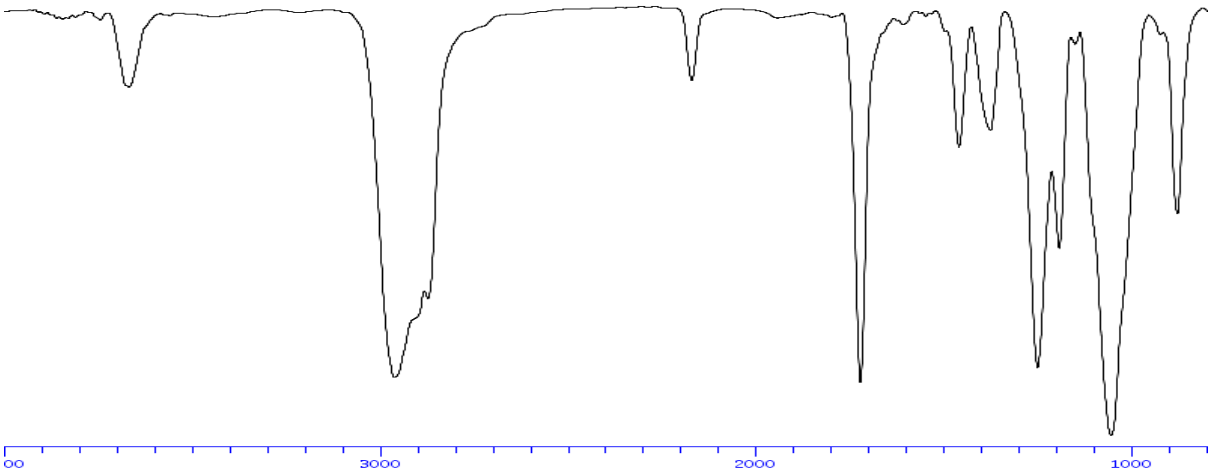
^{1}H NMR, $CDCl_3$, 400 MHz



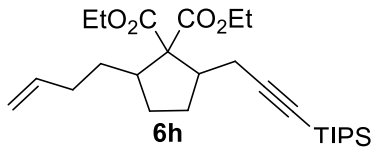
6g

^{13}C NMR, $CDCl_3$, 100 MHz



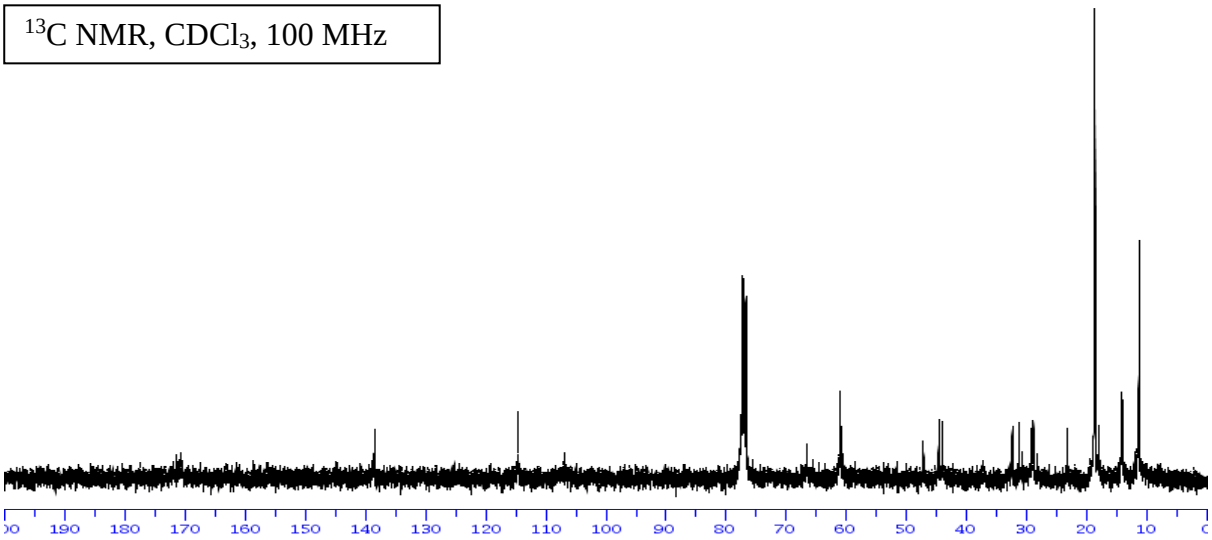


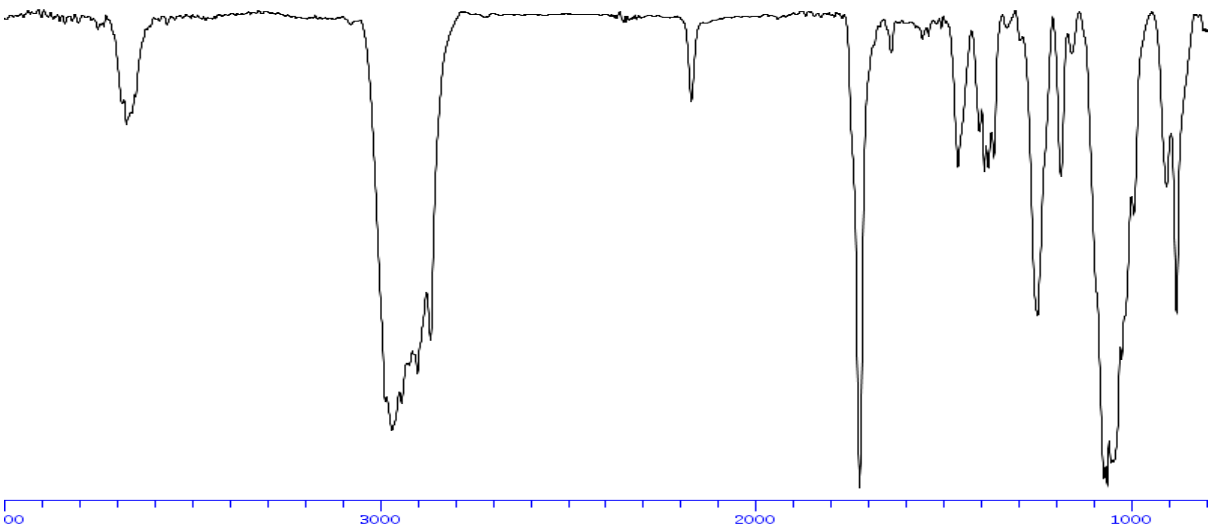
^{1}H NMR, $CDCl_3$, 400 MHz



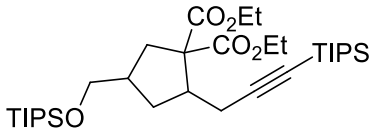
6h

^{13}C NMR, $CDCl_3$, 100 MHz



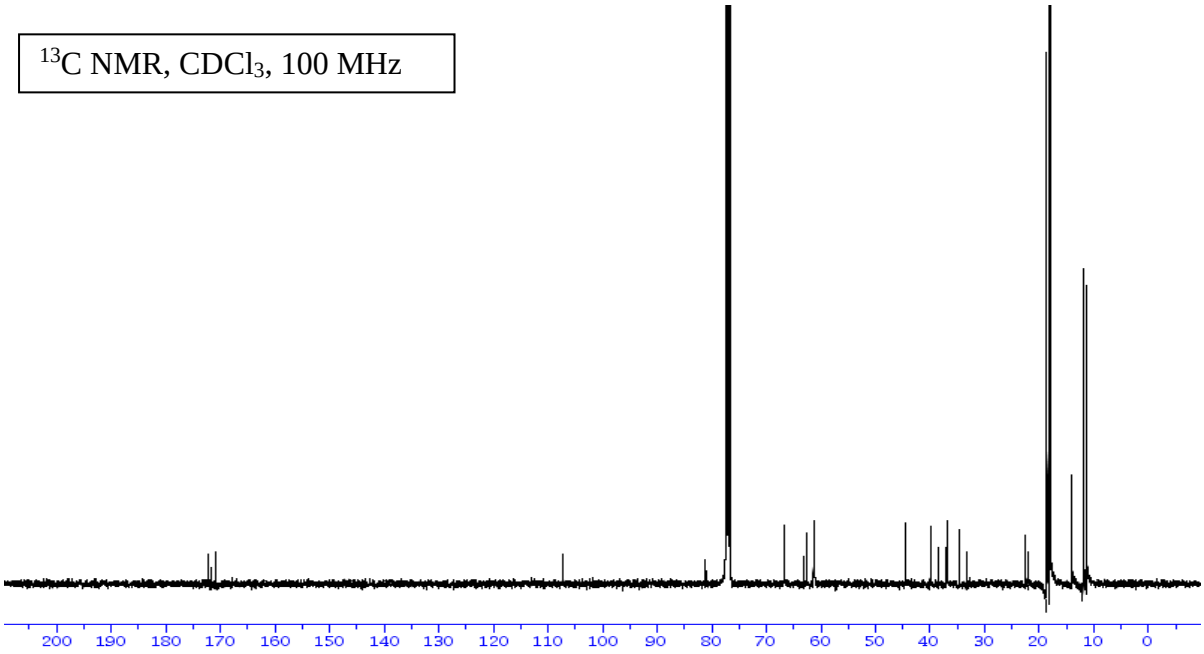


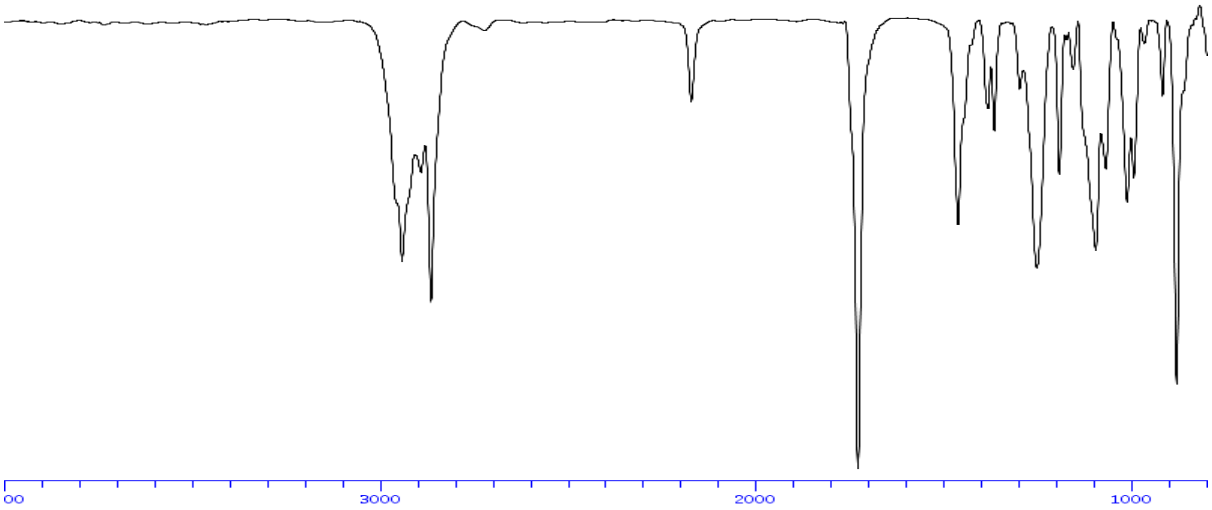
^{1}H NMR, $CDCl_3$, 400 MHz



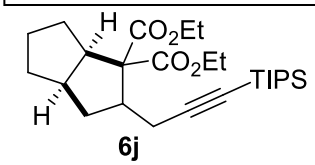
6i

^{13}C NMR, $CDCl_3$, 100 MHz



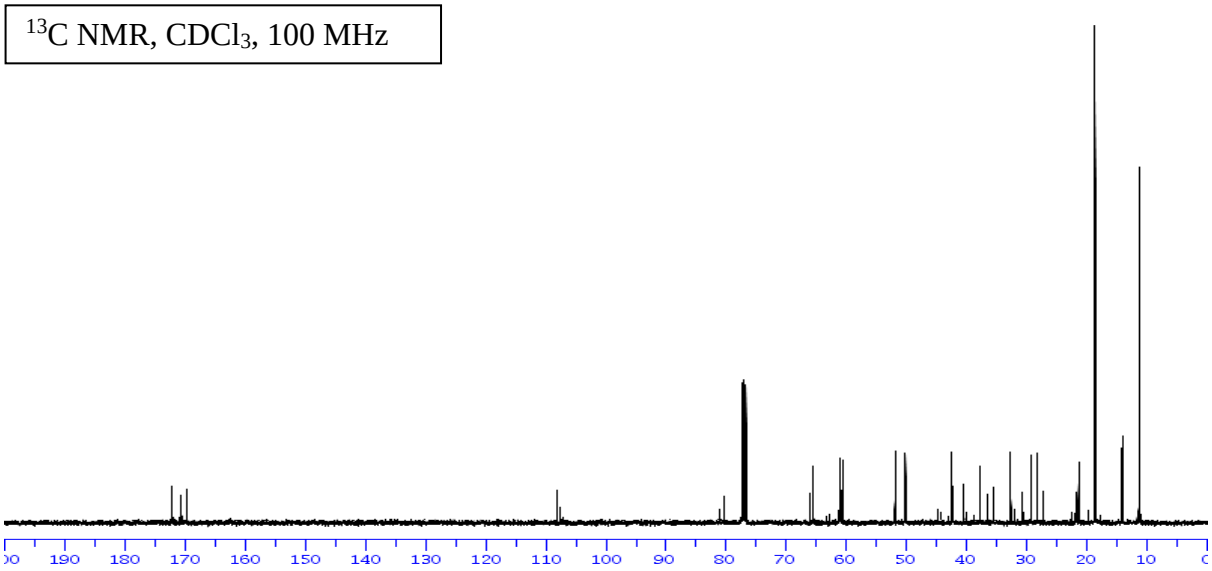


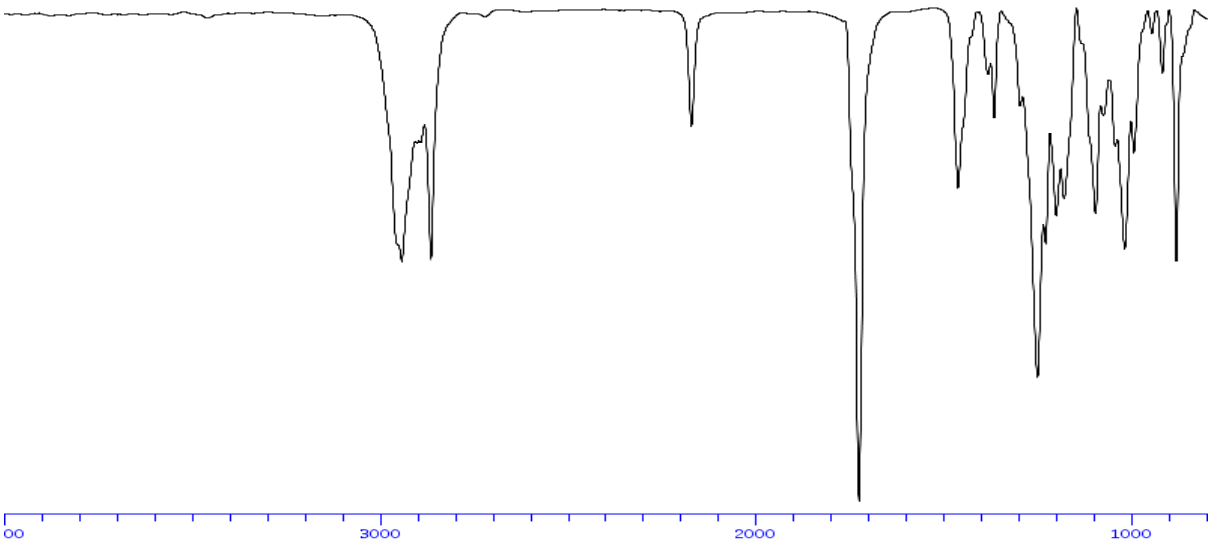
^{1}H NMR, $CDCl_3$, 400 MHz



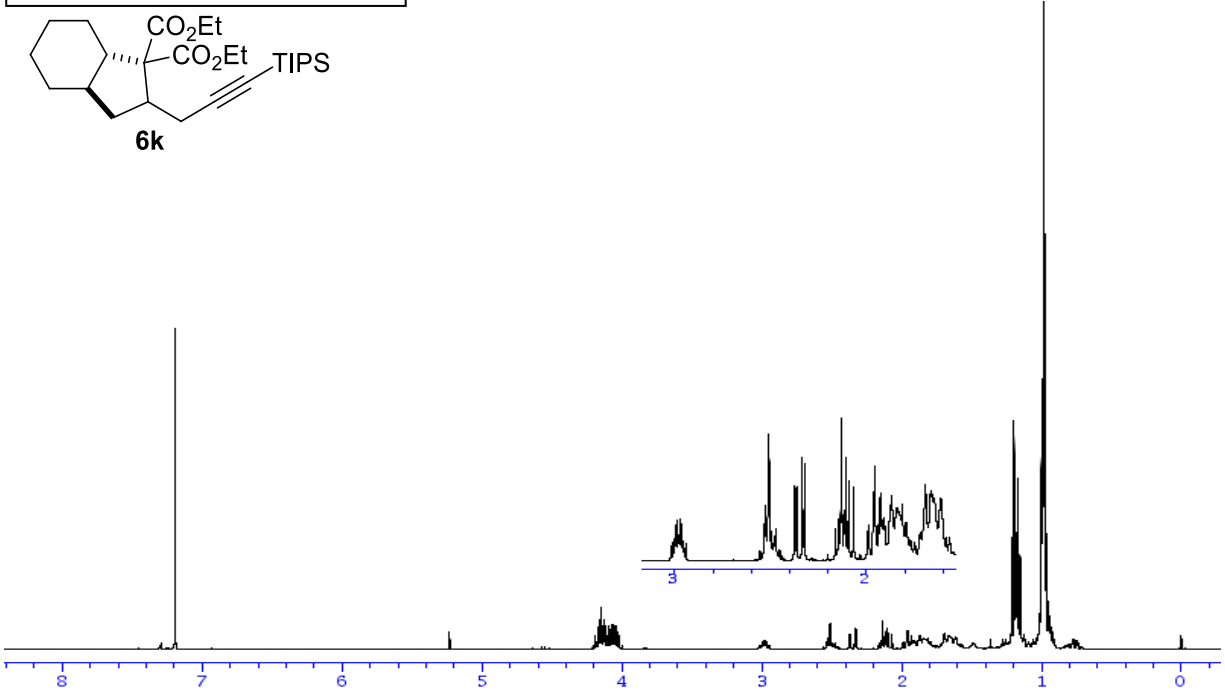
6j

^{13}C NMR, $CDCl_3$, 100 MHz

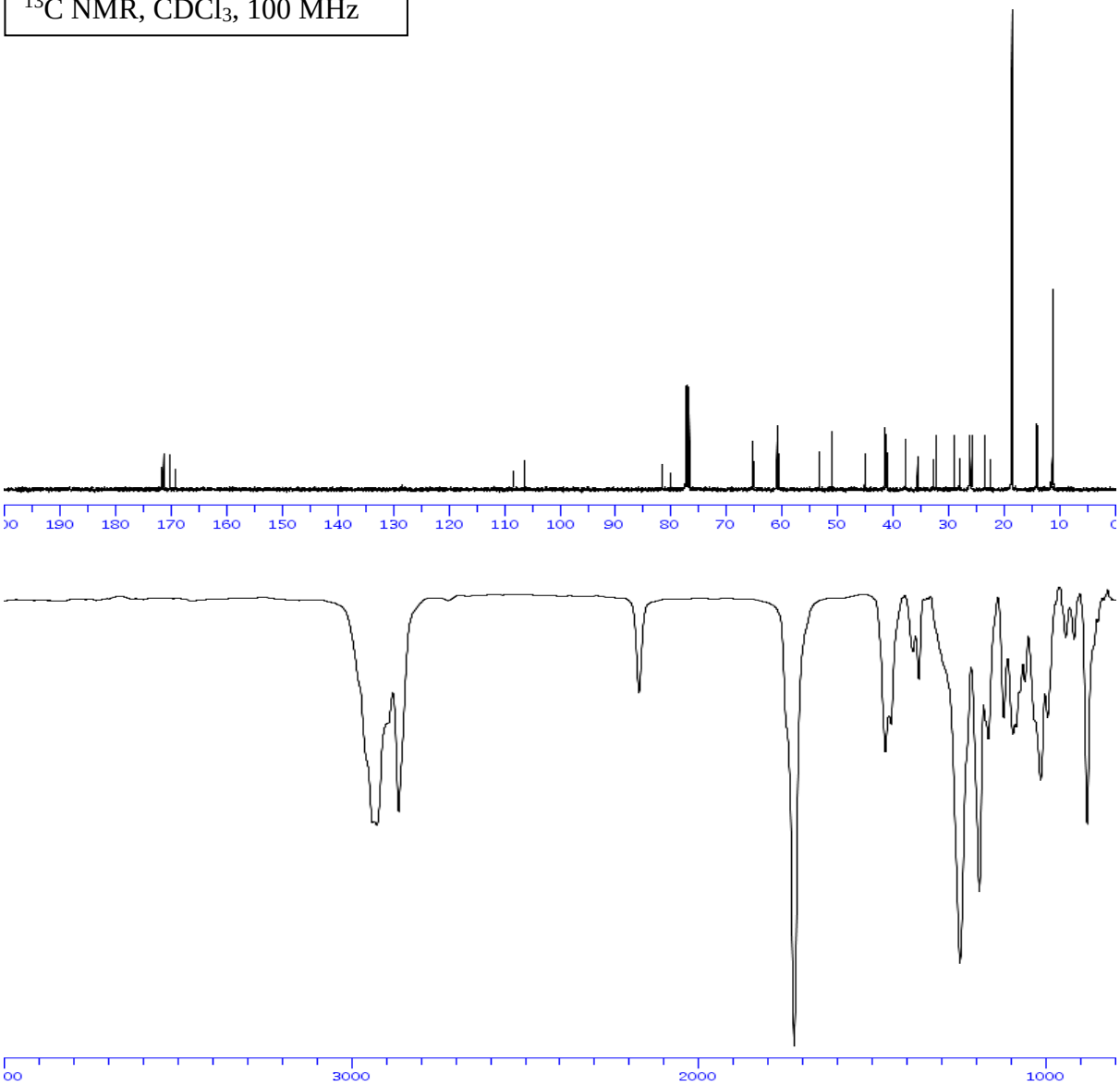




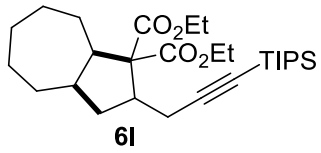
^{1}H NMR, $CDCl_3$, 400 MHz



^{13}C NMR, $CDCl_3$, 100 MHz



^{1}H NMR, $CDCl_3$, 400 MHz



6l

^{13}C NMR, $CDCl_3$, 100 MHz