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Indole Alkaloids

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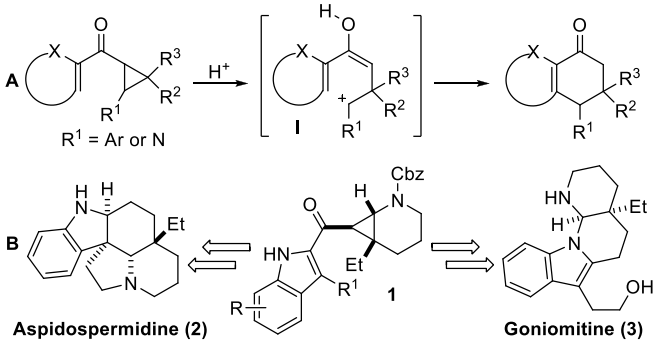
Catalytic Selective Cyclizations of Aminocyclopropanes: Formal Synthesis of Aspidospermidine and Total Synthesis of Goniomitine.**

*Filippo De Simone, Jürg Gertsch and Jérôme Waser**

((Dedication----optional))

Polyheterocyclic structures are present in most natural and synthetic molecules with important biological activity.[1] Therefore, the discovery of new efficient cyclization reactions is important to access natural products and to explore a broad range of complex scaffolds with potentially enhanced bioactivity.[2] We have recently reported the first catalytic formal homo-Nazarov cyclization of vinyl cyclopropyl ketones for the synthesis of cyclohexenones (**A**, Scheme 1).[3] In contrast to the well-established Nazarov cyclization of divinyl ketones to give cyclopentenones,[4] examples of homo-Nazarov cyclizations are rare and require stoichiometric amounts of strong Lewis acids and/or high temperatures.[5] The mild catalytic conditions developed in our work allowed us to apply our method to several unprecedented heterocyclic structures, but the scope of the reaction was limited by the required presence of an electron-rich aromatic group in order to stabilize the formed carbocationic intermediate **I**.

A heteroatom should also be able to stabilize the formed carbocation, as demonstrated by the rich chemistry of donor-acceptor cyclopropanes.[6] Aminocyclopropanes in particular may lead to the fused amino-cyclohexane core of numerous biologically relevant alkaloids (R^1 = N in Scheme 1). Cyclization of an acyl indole substituted amino cyclopropane **1** would constitute a general entry into the *Aspidosperma* alkaloids, such as aspidospermidine (**2**) (**B** in Scheme 1). The tetracyclic core obtained in the cyclization is not only present in the *Aspidosperma* family, but also in more complex natural products such as vinblastine or vincristine, which are front-line drugs in cancer therapy.[7] Although the combination of synthetically challenging structures and potential medical applications has resulted in a large number of successful total syntheses of aspidospermidine in the past,[8] the development of more general and flexible synthetic approaches is still required in order to access new analogs. Herein, we report the first example of the formal homo-Nazarov cyclization of aminocyclopropanes and its application in the formal total synthesis of aspidospermidine (**2**). Additionally, we demonstrate how a simple modification in reaction conditions leads to the scaffold of goniomitine (**3**), an indole alkaloid isolated from the tree *Gonioma malagasy*,[9] starting from aminocyclopropane **1**. In contrast to the *Aspidosperma* scaffold, the goniomitine ring system is unique in natural products, and only two total syntheses have been reported so far.[9b,9c] Based on our cyclization strategy, an efficient total synthesis of goniomitine (**3**) was accomplished and we present here the first study of its bioactivity, revealing significant cytotoxicity against several cancer cell lines, including vinblastine and taxol resistant P-glycoprotein (Pgp, MDR-1) overexpressing cells.



Scheme 1. Formal homo-Nazarov reaction and applications in the synthesis of polyheterocyclic natural products.

We began our research by examining the cyclization of a simple model system **4** containing the aminocyclopropane derived from the unsubstituted tetrahydro pyridine ring and a *N*-methylindole (Scheme 2).[10] Our standard conditions developed for the catalytic homo-Nazarov cyclization were highly successful and the reaction occurred in 90% yield with high diastereoselectivity for the *cis*-fused product **5**.[11] This result demonstrated that carbamates were also excellent activating group for the cyclization reaction.

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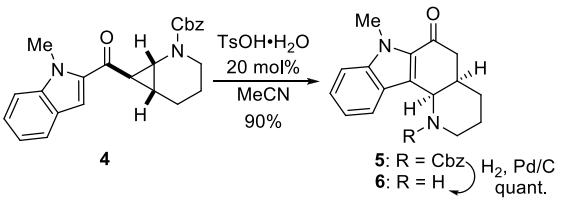
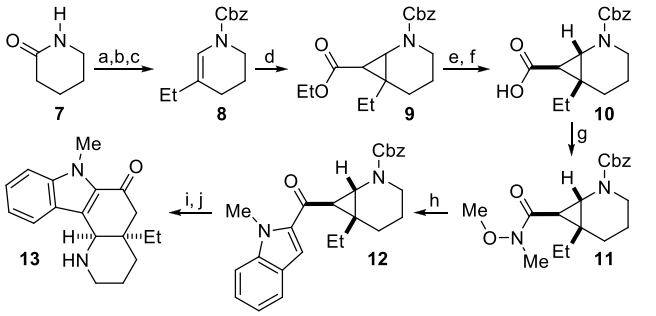
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Model study for the cyclization of aminocyclopropane **4**.

Encouraged by this promising result, we then synthesized the ethyl substituted cyclopropane **12** required for the core of the *Aspidosperma* alkaloids (Scheme 3). The synthesis of carboxylic acid **10** was accomplished using a slightly modified procedure of Grieco.[12] δ-Valerolactam (**7**) was Cbz-protected and alkylated in one pot. Reduction and dehydratation led to dehydropiperidine **8**. Enamide **8** was converted into aminocyclopropane **9** via cyclopropanation using CuOTf as catalyst.[13] The low diastereoselectivity observed in the cyclopropanation reaction is inconsequential, as the diastereomeric mixture of esters equilibrated to the exo isomer in presence of BF_3.[12] The exo ester obtained was hydrolyzed to obtain **10** as a pure diastereoisomer.

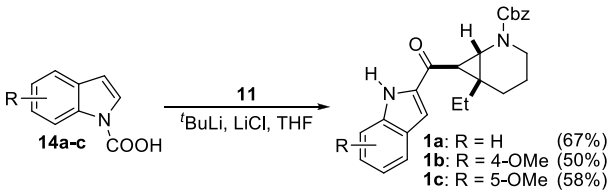
The choice of DMTMM[14] to convert the sensitive cyclopropane **10** into Weinreb amide **11** in good yield was crucial. The coupling reaction between amide **11** and 2-lithiated *N*-methyl indole afforded the precursor **12** of the homo-Nazarov reaction. To our delight, our catalytic conditions for the cyclization gave the tetracyclic core of *Aspidosperma* alkaloids as a single diastereoisomer **13** after removal of the Cbz protecting group.



Scheme 3. Synthesis and cyclization of aminocyclopropane **12**. Reagents and conditions: a) ^{n}BuLi, CbzCl, EtI, THF, –78 °C, 67%; b) $NaBH_4$, MeOH; c) H_2SO_4, THF, 93% overall; d) $(CuOTf)_2$•C_7H_8, N_2CHCO_2Et, DCM, 76% (dr: 1:1); e) BF_3•Et_2O, DCM; f) NaOH H_2O/THF/EtOH, 91% overall; e) DMTMM, NMM, THF, MeNHOMe•HCl, 93%; h) *N*-methylindole, ^{n}BuLi, ^{t}BuOK, THF, 48%; i) TsOH, MeCN, quant; j) H_2, Pd/C, quant.

The high diastereoselectivity observed is an important advantage of the formal homo-Nazarov cyclization. Other approaches based on aminocyclopropanes in intermolecular Friedel-Crafts reactions used for the synthesis of *Aspidosperma* alkaloids proceeded with low selectivity.[8d] If an enantioselective cyclopropanation method can be developed, an asymmetric synthesis will become possible.[15]

For the synthesis of aspidospermidine (**2**) a free NH indole was required. Therefore, we investigated the use of bis-lithiated *N*-carboxy indoles for the addition reaction to Weinreb amide **11** (Scheme 4).[16] The interest of carbon dioxide as protecting/directing group resides in its easy removal from the product, which already occurs upon aqueous work-up. However, its use has been limited to simple substrates.[16] We were therefore pleased to observe that the coupling procedure proceeded in moderate to good yields, leading directly to free NH indole **1a-c**. This approach was highly convergent and allowed the easy variation of coupling partners for the synthesis of analogs.



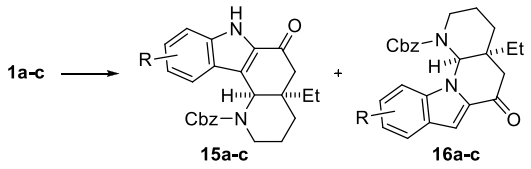
Scheme 4. Coupling of *N*-carboxylated indoles.

The obtained product **1a** was submitted to the standard conditions for the homo-Nazarov cyclization. We were surprised to observe the formation of two different products. The two compounds were identified as the desired product **15a** resulting from cyclization on the C3 position of indole, and the compound **16a** obtained via attack on the N1 position. The cyclic products were isolated in 74% yield and a ratio **15a** to **16a** of 1.6:1 (Table 1, Entry 1). In order to increase the selectivity for C-C cyclization, we examined several Brønsted and Lewis acids as catalysts (Entries 1-4). The use of soft Lewis acids instead of Brønsted acids allowed the preferred formation of **15a** as a pure diastereoisomer (Entries 2-3). Softer, milder Lewis acids could potentially exert an influence on the formation of the acyl iminium intermediate and favour the reaction of the softer C3 position of the indole ring. Deprotection of **15a** gave the free amine, concluding the successful formal total synthesis of aspidospermidine (**2**), as this intermediate had already been reported by Wenkert.[8d,17]

The N-cyclization product **16a** was also highly interesting, as it corresponded to the tetracyclic skeleton of goniomitine (**3**). When considering the rarity of this scaffold, the limited amount of synthetic approaches [9b,9c] and the absence of any study on his bioactivity, we found worthwhile to optimize the formation of the N1-cyclization product **16a**. We hypothesized that the use of a less polar solvent for the cyclization reaction could enhance the reactivity of the iminium intermediate and favorize a fast attack on the harder N1 position. Indeed, a strong influence of solvents on the cyclization was observed in the presence of Brønsted acids (Table 1, Entries 5-8). We were delighted to isolate the goniomitine scaffold **16a** in high yield and excellent selectivity using dichloromethane and toluene sulfonic acid as catalyst (Entry 9).

Cyclizations involving (acyl)iminium ions are important tools in the synthesis of alkaloids.[18] Examples involving a possible competition between N1 and C3 cyclization are rare, and it is difficult to control the regioselectivity and stereoselectivity of these reactions.[19] The ring-opening of aminocyclopropanes constitutes a new method for the generation of acyl iminium ions and the high level of control on the regio- and stereo- selectivity observed is unprecedented. To gain a first impression for the generality of the method, two methoxy indoles analogs **1b** and **1c** were examined, as similar electron-rich indoles are frequently encountered in natural products. Again, high yields and control of regioselectivity were achieved in these cases (Table 1, Entries 10-13).

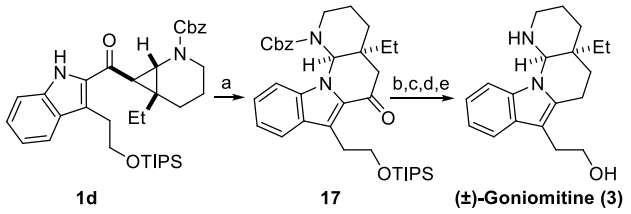
Table 1. Cyclization of Aminocyclopropanes **1**



Entry	R	Catalyst	Solvent	**15** : **16**	Yield
1	H	TsOH	MeCN	1.6 : 1[a]	74
2	H	$Cu(OTf)_2$	MeCN	8 : 1[b]	n.d.[c]
3	H	$Pd(CH_3CN)_4(BF_4)_2$	MeCN	11 : 1[b]	n.d.
4	H	$Cu(OTf)_2$	MeCN	7 : 1[a]	91
5	H	TsOH	$MeNO_2$	1.3 : 1[b]	n.d.
6	H	TsOH	THF	polymers[b]	n.d.
7	H	TsOH	DCM	1 : 18[b]	n.d.
8	H	TsOH	Toluene	1 : 16[b]	n.d.
9	H	TsOH	DCM	1: 21[a]	89
10	4-OMe	TsOH	DCM	1 : 22[a]	92
11	4-OMe	$Cu(OTf)_2$	MeCN	8 : 1[a]	88
12	5-OMe	TsOH	DCM	1: 20[a]	86
13	5-OMe	$Cu(OTf)_2$	MeCN	8 : 1[a]	95

[a] Yields and ratios obtained from isolated products. Reaction run with **1a-c** (40-100 mg, 90-250 µmol), 15-25 mol% catalyst and at a concentration of 0.025 M. [b] Ratios calculated by integration of ^{1}H NMR peaks in the crude mixture. Reaction carried out on a 10 mg (25 µmol) scale at a concentration of 0.025 M. [c] n.d. = not determined.

To finish the total synthesis of goniomitine (**3**) starting from **16a**, it would be necessary to introduce the lateral chain at C3 in presence of the sensitive aminal functionality. In order to avoid this difficult task, we envisaged a more convergent approach starting from cyclization precursor **1d** (Scheme 5). Indole **1d** was obtained from tryptophol via TIPS protection, carboxylation, lithiation and addition to Weinreb amide **11**.[20] Cyclopropane **1d** was cyclized in presence of catalytic amount of TsOH affording the tetracyclic core **17** of goniomitine (**3**) in 93% yield. The carbonyl group was reduced to the alcohol and acetylated. The acetate and the benzyl carbamate were cleaved in one step through hydrogenolysis. Deprotection of the primary alcohol gave goniomitine (**3**) in 77 % overall yield from **17**.[21] The total synthesis of (±)-goniomitine (**3**) was accomplished in a longer linear sequence of 13 steps (5 purifications by column chromatography) with an overall yield of 11%.



Scheme 5. Total synthesis of goniomitine (**3**). Reagents and conditions: a) TsOH, CH_2Cl_2, 93%; b) $NaBH_4$, MeOH; c) Ac_2O, pyridine; d) Pd/C, H_2, EtOH; e) TBAF, THF, 77% overall.

Somewhat surprisingly, we were unable to find any studies about the bioactivity of goniomitine (**3**). In a first biological assessment we therefore investigated the cytotoxicity of this natural product. Preliminary results are highly promising as goniomitine displays nM antiproliferative effects in several tumor cell lines (Table 2). Interestingly, unlike taxol and vinblastine, which are approximately 100-fold less effective in P-gp overexpressing cells (not shown), goniomitine did not lose its effect in the resistant MDR-1-MDCK cell line.

Table 2. Antiproliferative activity of goniomitine

Cell Lines	**IC**$_{50}$[a]
A549	205 ± 27 nM
MCF-7	239 ± 13 nM
HCT116	281 ± 29 nM
PC3	159 ± 24 nM
MDCK	247 ± 10 nM
MDR-1-MDCK	381 ± 17 nM

[a] IC_{50} values for inhibition of human tumor cell growth. A549: lung; MCF-7: breast; HCT-116: colon; PC-3M: prostate; MDCK canine kidney. MDR-1-MDCK is a human P-glycoprotein 170 (P-gp170)-overexpressing multidrug-resistant cell line.[22]

In conclusion, we have demonstrated the versatility of aminocyclopropanes as (acyl)iminium precursors for intramolecular cyclizations. The reaction proceeded under mild conditions and control about the regioselectivity was possible by the right choice of catalyst and solvent. The power of the methodology has been demonstrated in the efficient formal total synthesis of aspidospermidine (**2**) and the total synthesis of goniomitine (**3**). Preliminary studies on the bioactivity of goniomitine revealed its relatively potent cytotoxicity (antiproliferative effect) (IC_{50}: 150-400 nM) against several tumor cell lines. Preliminary data show that this natural product disrupts the microtubule network (not shown). Therefore, goniomitine is a potential new anticancer lead structure. In the future, the high convergence of our synthetic approach will allow us to access a large number of analogs of goniomitine (**3**) for structure-activity relationship studies. Applications of aminocyclopropanes as iminium precursors for other types of cyclization or addition reactions as well as the development of asymmetric cyclopropanation methods for enamides are currently under investigation in our laboratory and the results of this work will be reported in due course.

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[20] See supporting information.

[21] The values of 400-MHz ^{1}H NMR spectra of goniomitine (**3**) were identical to those of natural[9a] and synthetic[9b,9c] goniomitine. The obtained values for ^{13}C NMR fitted perfectly with the reported values for synthetic goniomitine, but small differences were apparent when compared with natural goniomitine. A comparison of the spectra is provided in the supporting information.

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Indole Alkaloids

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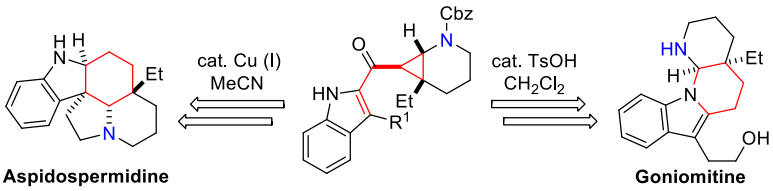
Catalytic Selective Cyclizations of Aminocyclopropanes: Formal Synthesis of Aspidospermidine and Total Synthesis of Goniomitine.



Mild Control: Selective cyclization of aminocyclopropanes on the N1 or C3 positions of indole was achieved by tuning the catalyst and solvent. The new strategy was applied to the formal synthesis of aspidospermidine and the total synthesis of goniomitine in 13 steps and 11% overall yield. The first studies on the bioactivity of goniomitine demonstrated significant cytotoxicity against several tumor cell lines (IC_{50}: 150-400 nM).

Supporting Information

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). NEt_3 and pyridine were distilled under nitrogen from KOH. 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 pressure. The deactivation of silica was obtained with a 1% solution of Et_3N in the indicated solvent. TLC was performed on Merck silica gel 60 F_{254} TLC glass plates or aluminium plates and visualized with UV light, permanganate stain, CAN stain or Anisaldehyde stain. Melting points were measured on a Büchi B-540 melting point apparatus using open glass capillaries, the data is uncorrected. ^{1}H-NMR spectra were recorded on a Brucker DPX-400 400 MHz and a Brucker AV-500 500 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 7.26 ppm, the internal DMSO signal at 2.50 ppm or the internal methanol signal at 3.30 ppm as standard. 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}C-NMR spectra were recorded with ^{1}H-decoupling on a Brucker DPX-400 100 MHz and a Brucker AV-500 125 MHz spectrometer in chloroform-d, DMSO-d_6 or CD_3OD, all signals are reported in ppm with the internal chloroform signal at 77.0 ppm, the internal DMSO signal at 39.5 ppm or the internal methanol signal at 49.0 ppm as standard. Infrared spectra were recorded on a JASCO FT-IR B4100 spectrophotometer with an ATR PRO410-S and a ZnSe prisma and are reported as cm^{-1} (w = weak, m = medium, s = strong, br = broad). Gas chromatographic and low resolution mass spectrometric measurements were performed on a Perkin-Elmer Clarus 600 gas chromatographer and mass spectrometer using a Perkin-Elmer Elite fused silica column (length: 30 m, diameter: 0.32 mm) and Helium as carrier gas. 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. HPLC measurement were done on a JASCO HPLC system with an AS2055 Autosampler, a PU 2089 Pump, a UV 2075 detector and a SEDEX 85 (SEDERE) detector using a CHIRALPAK IC column from DAICEL Chemical Industries Ltd. HPLC grade solvents from Sigma-Aldrich were used.

2 General Procedures

General procedure 1 (GP1): homo-Nazarov cyclization

Toluenesulfonic acid (0.2 equiv) was added to a solution of vinyl cyclopropyl ketone (0.04 M in anhydrous CH_3CN) at room temperature. The reaction was stirred during the indicated time. The solution was quenched with $NaHCO_3$ and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified as indicated.

General procedure 2 (GP2): nitrogen cyclization

Toluenesulfonic acid (0.15-0.20 equiv) was added to a solution of vinyl cyclopropyl ketone (0.02 M in anhydrous DCM). The reaction was stirred during the indicated time. The solution was quenched with $NaHCO_3$ and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The cyclization products are purified as indicated and deprotected via **GP4** for analysis (Cbz-protected products were difficult to analyze due to the presence of rotamers).

General procedure 3 (GP3): homo-Nazarov cyclization

A solution of Copper(II) triflate (0.15-0.20 equiv, 0.1 M in anhydrous CH_3CN) was added dropwise to a solution of a vinyl cyclopropyl ketone derivative (0.02 M in anhydrous CH_3CN). The reaction was stirred during the indicated time. The solution was quenched with $NaHCO_3$ and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The cyclization products are purified as indicated and deprotected via **GP4** for analysis (Cbz-protected products were difficult to analyze due to the presence of rotamers).

General procedure 4 (GP4): hydrogenolysis

To a solution (0.02 M in EtOH) of protected amine at room temperature Pd/C (0.10 equiv) was added portionswise. Hydrogen gas was bubbled into the solution until the conversion of all starting material (controlled by TLC)[1]. The suspension was filtered on celite (pre-washed with DCM), washed with DCM and AcOEt and dried over $MgSO_4$. The organic layer was evaporated on reduced pressure. No further purification was needed.

General procedure 5 (GP5): Carboxylation of indoles

Using a slight modification of a reported procedure,[2] ^{n}BuLi (2.5 M in pentane, 1.2 equiv) was added dropwise to a solution of substituted indole (0.2 M in Et_2O) at 0°C. The reaction was refluxed 2 hours then cooled to 0°C and CO_2 was bubbled in the solution during 30 minutes. The suspension was quenched with

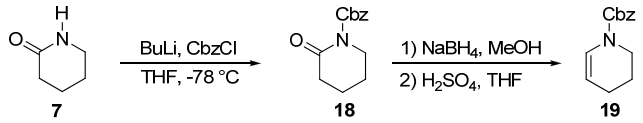
[1] A batch to batch dependency of the reaction time was observed (15 min to 5 h). It is consequently important to monitor the reaction carefully via TLC.

[2] D. A Shirley, P. A. Roussel, *J. Am. Chem. Soc.* **1953,** *75*, 375.

water and the organic layer was washed several times with water. The aqueous layer was acidified until pH = 2 and the precipitate was filtered and dried under vacuum.

3 Substrates synthesis

3,4-Dihydro-2*H*-pyridine-1-carboxylic acid benzyl ester (19)



Following a reported procedure,[3] δ-valerolactam (**7**) (3.00 g, 30.2 mmol, 1.00 equiv) was dissolved in THF (130 mL). The reaction mixture was cooled to -78 °C and ^{n}BuLi (2.5 M in hexane, 12 mL, 30 mmol, 1.0 equiv) was added dropwise to the resulting suspension. After 30 min at -78 °C, a solution of benzylchloroformate (4.3 mL, 30 mmol, 1.0 equiv) in THF (30 mL) was added dropwise. After 4 h at -78 °C, the reaction mixture was quenched with sat. NH_4Cl (40 mL) and warmed to 23 °C. The reaction mixture was extracted with Et_2O (3x50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure to give the crude Cbz protected lactam **18** (6.95 g, 29.8 mmol, 99%), which was used without further purification.

R_f 0.30 (PET/AcOEt 2:1, Anisaldehyde);

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47-7.28 (m, 5 H; PhH), 5.28 (s, 2 H; OCH_2), 3.74 (m, 2 H; CH_2N), 2.54 (m, 2 H; CH_2CO), 1.83 (m, 4 H; CH_2).

Following a reported procedure,[4] protected lactame **18** (2.82 g, 12.1 mmol, 1.00 equiv) was dissolved in methanol (52 mL) at 0 °C and sodium borohydride (0.46 g, 12 mmol, 1.0 equiv) was added portionswise. After the end of the addition, the reaction mixture was stirred at 0 °C for 15 min and poured onto ice-water (150 mL). The reaction mixture was extracted with AcOEt (3x100 mL). The combined organic layers were washed with brine (50 mL), the combined water layers were extracted with AcOEt (100 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

The residues were dried in HV for 15 min and dissolved in THF (25 mL). Conc. sulfuric acid (0.13 mL) was added and the reaction was monitored via TLC (PET/AcOEt 10:1-2:1). After 1 h the reaction mixture was poured onto sat. $NaHCO_3$ (100 mL) and extracted with AcOEt (3x100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 10:1-2:1) to yield enamide **19** (1.76 g, 8.11 mmol, 67%) as a colorless oil.

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[3] A. Giovannini, D. Savoia, A. Umani-Ronchi, *J. Org. Chem.* **1989**, *54*, 228.
[4] Y. Takeuchi, K. Azuma, M. Oshige, H. Abe, H. Nishioka, K. Sasaki, T. Harayama, *Tetrahedron* **2003**, *59*, 1639.

R_f 0.80 (PET/AcOEt 2:1, Anisaldehyde).

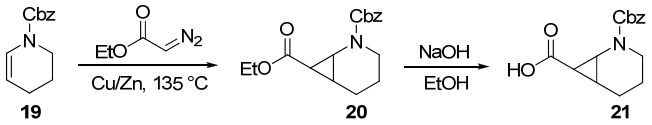
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43-7.27 (m, 5 H; PhH), 6.89 (d, *J* = 8.6 Hz, 0.4 H; alkene H), 6.80 (d, *J* = 8.6 Hz, 0.6 H; alkene H), 5.18 (s, 2 H; CH_2O), 4.97 (m, 0.4 H; alkene H), 4.86 (m, 0.6 H; alkene H), 3.63 (m, 2 H; CH_2N), 2.04 (m, 2 H; CH_2), 1.83 (m, 2 H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 151.7, 136.3, 128.5, 128.5, 128.2, 128.0, 128.0, 125.3, 124.8, 106.7, 106.4, 67.4, 67.3, 42.3, 42.2, 21.6, 21.4, 21.2.

IR ν 2951 (w), 1703 (s), 1653 (m), 1409 (s), 1347 (s), 1256 (s), 1227 (m), 1183 (w), 1108 (s), 1054 (m), 912 (m), 764 (m), 731 (s), 697 (s).

^{1}H NMR corresponded to the literature values.[4]

2-Benzyl 7-ethyl 2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (20) and 2-(benzyloxycarbonyl)-2-azabicyclo[4.1.0]heptane-7-carboxylic acid (21)



Following a reported procedure,[5] a mixture of enamide **19** (1.70 g, 7.82 mmol, 1.00 equiv) and copper/bronze (67 mg, prepared freshly as following: Zinc powder (0.20 g) was added to a solution of $CuSO_4$•$5H_2O$ (1.0 g) in water (2 mL) over 10 min at RT. The resulting suspension was filtered, the solid was washed with water (3x5 mL), ethanol (3x5 mL) and Et_2O (2x5 mL) and dried 1 h in HV) was heated to 135 °C. Ethyl diazoacetate (4.2 mL, 40 mmol, 5.0 equiv) was added via syringe pump over 90 min, and the reaction was stirred for further 30 min before cooling down to RT. The crude product was purified by two successive flash column chromatography (PET/AcOEt 10:1-2:1) to yield cyclopropane **20** (1.18 g, 3.89 mmol, 50%, R_f = 0.30 (PET/AcOEt 3:1), still containing some polymeric impurities) as a colorless oil.

The crude ester **20** (1.18 g, 3.89 mmol, 1.00 equiv) was dissolved in ethanol (4 mL) at 0 °C and NaOH (2.2 g, 55 mmol, 14 equiv) was added. The reaction mixture was stirred 1 h at 0 °C and 12 h at RT, diluted with water (10 mL), acidified to pH = 1 with 1 M HCl and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give nearly pure acid **21** (0.89 g, 3.2 mmol, 84%, 42 % from enamide **19**) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.26 (m, 5 H; CH-Ar), 5.26-5.11 (m, 2 H; OCH_2), 3.88 (dt, *J* = 12.5 Hz, 3.2 Hz, 0.7 H; NCH_2 or NCH rotamer A), 3.74 (s, 0.3 H; NCH_2 or NCH rotamer B), 3.57 (m, 0.3 H; NCH_2 or NCH rotamer B), 3.50 (dd, *J* = 8.6 Hz, 2.6 Hz, 0.7 H; NCH_2 or NCH rotamer A), 2.77 (dd, *J* = 1.3

[5] P. A. Grieco, M. D. Kaufman, *J. Org. Chem.* **1999,** *64*, 7586.

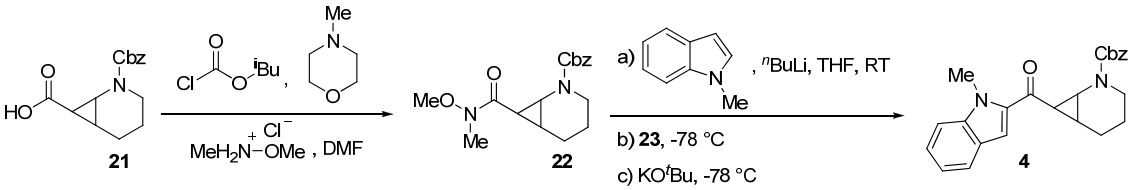
Hz, 0.6 Hz, 0.3 H; NCH_2 or NCH rotamer B), 2.67 (td, J = 12.5 Hz, 2.2 Hz, 0.7 H; NCH_2 or NCH rotamer A), 2.08-1.78 (m, 3 H; CHCO and CH_2), 1.77-1.58 (m, 2 H; CH or CH_2), 1.40-1.20 (m, 1 H; CH or CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 178.0, 177.0, 156.4, 136.5, 136.3, 128.8, 128.6, 128.5, 128.3, 127.7, 127.6, 127.5, 127.2, 126.7, 126.4, 68.4, 67.0, 39.8, 39.7, 38.1, 38.0, 26.5, 26.4, 25.5, 25.4, 22.8, 22.6, 19.6, 19.4.

IR ν 3062 (w), 2946 (w), 2870 (w), 1689 (m), 1448 (w), 1423 (m), 1350 (w), 1302 (w), 1266 (m), 1195 (m), 1135 (w), 1098 (w), 1041 (w), 1002 (w), 909 (w), 731 (s), 699 (s).

HRMS(ESI) calcd for $C_{15}H_{18}NO_4^+$ (M+H) 276.1236, found 276.1232.

Benzyl 7-(methoxy(methyl)carbamoyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (22) and benzyl 7-(1-methyl-*1H*-indole-2-carbonyl)-2-azabicyclo[4.1.0]heptane-2-carboxylate (4)



Following a reported procedure,[6] *N*-methylmorpholine (0.40 mL, 3.6 mmol, 1.1 equiv) was added to a solution of acid **21** (0.90 g, 3.3 mmol, 1.0 equiv) in DMF (3.3 mL) at 0 °C. After 25 min, *iso*butylchloroformate (0.47 mL, 3.6 mmol, 1.1 equiv) was added dropwise at 0 °C. After 10 min, *N,O*-dimethylhydroxylamine hydrochloride (0.35 g, 3.6 mmol, 1.1 equiv) was added, followed by *N*-methylmorpholine (0.46 mL, 4.2 mmol, 1.3 equiv) and the reaction mixture was warmed to 23 °C. After 12 h, the reaction was quenched with 0.5 M HCl (6 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic layers were washed with 0.5 M NaOH (2x10 mL), brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 4:1-1:1) to yield Weinreb amide **22** (665 g, 2.09 mmol, 64%, R_f = 0.30 (PET/AcOEt 1:1) as a colorless oil, which was used directly in the next step.

N-Methyl indole (0.16 mL, 1.2 mmol, 1.2 equiv) was diluted in THF (4 mL) at 0 °C and ^{n}BuLi (0.47 mL, 1.2 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred 1 h at RT and cooled to -78 °C. Weinreb amide **22** (dried through 3 co-evaporation with toluene, 0.31 g, 0.97 mmol, 1.0 equiv) was added dropwise via cannula as a cooled (-78 °C) solution in THF (2 mL). After further stirring 2 h at -78 °C, a solution of KO^{t}Bu (0.22 g, 2.0 mmol, 2.0 equiv) in THF (2 mL) was added. After 2 h, the reaction mixture

[6] S. R. Nagarajan, H. F. Lu, A. F. Gasiecki, I. K. Khanna, M. D. Parikh, B. N. Desai, T. E. Rogers, M. Clare, B. B. Chen, M. A. Russell, J. L. Keene, T. Duffin, V. W. Engleman, M. B. Finn, S. K. Freeman, J. A. Klover, G. A. Nickols, M. A. Nickols, K. E. Shannon, C. A. Steininger, W. F. Westlin, M. M. Westlin, M. L. Williams, *Bioorg. Med. Chem.* **2007**, *15*, 3390.

was warmed to 0 °C, whereas the yellow suspension became an orange solution. After 5 min at 0 °C, the reaction mixture was quenched with sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (3x10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 5:1-3:1) to yield indole **4** (251 mg, 0.646 mmol, 67%) as a colorless solid.

R_f 0.30 (PET/AcOEt 3:1, Anisaldehyde).

Mp 119-121 °C.

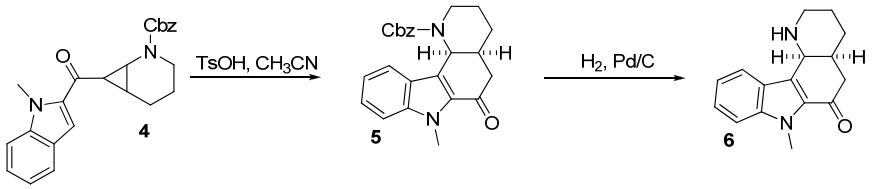
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 8.0 Hz, 1 H; CH-Ar), 7.43-7.28 (m, 4 H; CH-Ar), 7.22-7.14 (m, 1 H; CH-Ar), 7.10-7.02 (m, 2 H; CH-Ar), 6.99-6.89 (m, 2 H; CH-Ar), 5.16 (d, *J* = 12.5 Hz, 1 H; OCH_2), 4.99 (d, *J* = 12.5 Hz, 1 H; OCH_2), 4.06 (s, 0.8 H; CH_3 rotamer B), 4.00 (s, 2.2 H; CH_3 rotamer A), 3.95 (t, *J* = 3.8 Hz, 0.8 H; NCH or NCH_2 rotamer A), 3.84 (m, 0.2 H; NCH or NCH_2 rotamer B), 3.67 (m, 0.2 H; NCH or NCH_2 rotamer B), 3.55 (dd, *J* = 8.3 Hz, 2.2 Hz, 0.8 H; NCH or NCH_2 rotamer A), 2.85 (t, *J* = 12.5 Hz, 0.2 H; NCH or NCH_2 rotamer B), 2.76 (td, *J* = 12.5 Hz, 2.2 Hz, 0.8 H; NCH or NCH_2 rotamer B), 2.63 (dd, *J* = 5.8 Hz, 2.2 Hz, 1 H; COCH), 2.28 (m, 1 H; CH_2CH), 2.06-1.90 (m, 2 H; CH_2), 1.81-1.71 (m, 1 H; CH_2), 1.48 (m, 1 H; CH_2).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 189.9, 156.4, 140.0, 136.2, 135.4, 128.4, 128.0, 127.5, 127.5, 126.8, 125.9, 125.7, 125.5, 122.8, 122.6, 120.6, 120.3, 111.3, 111.1, 110.2, 67.1, 65.1, 41.6, 41.0, 33.5, 32.8, 32.0, 29.6, 23.8, 21.8, 19.9.

IR ν 2941 (w), 2866 (w), 1702 (s), 1639 (s), 1615 (w), 1513 (m), 1428 (s), 1407 (s), 1347 (s), 1299 (m), 1264 (m), 1195 (s), 1152 (m), 1129 (s), 1095 (m), 1034 (s), 908 (m), 794 (w), 769 (w), 752 (s), 731 (s), 698 (s), 648 (w).

HRMS(ESI) calcd for $C_{24}H_{25}N_2O_3^+$ (M+H) 389.1865, found 389.1854.

Benzyl 7-methyl-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-*1H*-pyrido[3,2-c]carbazole-1-carboxylate (5) and 7-methyl-3,4,4a,5,7,11c-hexahydro-*1H*-pyrido[3,2-c]carbazol-6(*2H*)-one (6)



The reaction was performed following **GP1**, starting from cyclopropane **4** (50 mg, 0.13 mmol, 1.0 equiv) and tosic acid (4.9 mg, 0.030 mmol, 0.20 equiv). The reaction was quenched after 12 h. Purification by flash chromatography (PET/AcOEt, 3:7) afforded **5** (45 mg, 0.12 mmol, 90 %) as yellow oil. R_f 0.60 (PET/AcOEt 7:3, Anisaldehyde). The indole derivative **5** (35 mg, 0.090 mmol, 1.0 equiv) was deprotected following general procedure **GP4**, using Pd/C (10 mg, 10% w/w) in Et_2O (3.5 mL) and a H_2 balloon. The suspension was filtered on celite and washed with DCM to afford **6** as yellow oil in quantitative yield (23 mg, 0.090 mmol, 1.0 equiv).

R_f 0.80 (DCM/MeOH/Et_3N 3:1:2%, Anisaldehyde).

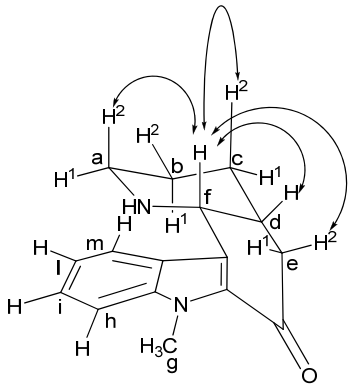
^{1}H NMR ($CDCl_3$, 400 MHz) 7.88 (d, J = 8.1 Hz, 1 H; H_m or H_h), 7.43-7.31 (m, 2 H; H_m or H_h and H_i or H_l), 7.18 (t, J = 7.4 Hz, 1 H; H_i or H_l), 4.35 (d, J = 3.3 Hz, 1 H; H_f), 4.06 (s, 3 H; $3H_g$), 3.23 (dd, J = 16.5 Hz, 12.0 Hz, 1 H; $H^1{}_e$), 2.96 (m, 1 H; $H^1{}_a$), 2.83 (m, 1 H; $H^2{}_a$), 2.52 (m, 1 H; H_d), 2.41 (dd, J = 16.5 Hz, 4.0 Hz, 1 H; $H^2{}_e$), 1.87-1.60 (m, 4 H; $H^1{}_c$ and/or $H^2{}_c$ and/or $H^1{}_b$ and/or $H^2{}_b$ and NH), 1.57-1.45 (m, 1 H; $H^1{}_b$ or $H^2{}_b$ or $H^1{}_c$).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2, 139.7, 130.2, 126.6, 123.9, 121.4 120.7, 110.3, 110.3, 51.4, 45.3, 41.0, 35.9, 31.5, 29.7, 28.5.

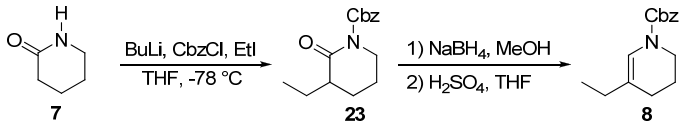
IR ν 3299 (w), 2926 (s), 2855 (m), 2149 (w), 1662 (s), 1616 (w), 1469 (m), 1432 (m), 1419 (w), 1386 (w), 1245 (m), 1062 (w), 758 (s), 746 (s), 732 (w), 655 (m).

HRMS(ESI) calcd for $C_{16}H_{19}N_2O^+$ (M+H) 255.1497, found 255.1490.

Important correlations ROESY: H_f-$H_a{}^2$; H_f-$H_c{}^2$; H_f-H_d; H_f-$H_e{}^2$ (see the 2D spectra in section 6)



3,4-Dihydro-*2H*-3-ethylpyridine-1-carboxylic acid benzyl ester (8)



Following a reported procedure,[5] a 2.5 M solution of ^{n}BuLi in pentane (88.0 mL, 220 mmol 2.20 equiv) was added dropwise to a solution of δ-valerolactam (**7**) (10.0 g, 100 mmol, 1.00 equiv) in THF (200 mL) at 0°C. The reaction mixture was stirred during 30 min and distilled ethyl iodide (12.2 mL, 150 mmol, 1.50 equiv) was added. The solution was stirred for additional 20 minutes before benzylchloroformate (14.9 mL, 105 mmol, 1.05 equiv) in THF (50 mL) was added. The reaction was stirred further 20 minutes, diluted with ether (250 mL) and washed with brine (2x50 mL). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (PET/AcOEt 5:1) to yield lactame **23** (17.4 g, 66.5 mmol, 67%) as colorless oil.

R_f 0.25 (PET/AcOEt 5:1, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (m, 2H; CH-Ar), 7.39-7.28 (m, 3 H; CH-Ar), 5.27 (s, 2 H; OCH_2), 3.81 (m, 1 H; NCH_2), 3.69 (m, 1 H; NCH_2), 2.35 (m, 1 H; CHCO), 2.07-1.73 (m, 4 H; CH_2CH_2), 1.58-1.46 (m, 2H; CH_2CH_3), 0.96 (t, J = 7.5 Hz, 3H; CH_3).

Following a reported procedure,[4] sodium borohydride (829 mg, 21.9 mmol, 1.05 equiv) was added portionswise into a solution of lactame **23** (5.45 g, 20.9 mmol, 1.00 equiv) in methanol (100 mL) at 0 °C. After the end of the addition, the reaction mixture was stirred at 0 °C for 15 min and poured onto ice-water (150 mL). The reaction mixture was extracted with AcOEt (3x100 mL). The combined organic layers were washed with brine (50 mL), the combined water layers were extracted with AcOEt (100 mL) and the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (50 mL) and 0.5 mL of concentrated sulfuric acid was added dropwise. The reaction was stirred at RT for 1 hour then quenched with K_2CO_3 and dried on Na_2SO_4.The suspension was filtered and concentrated to afford **8** (4.75 g, 19.4 mmol, 93% overall) without further purification as a colorless oil.

R_f 0.36 (PET/AcOEt 9:1, Anisaldehyde).

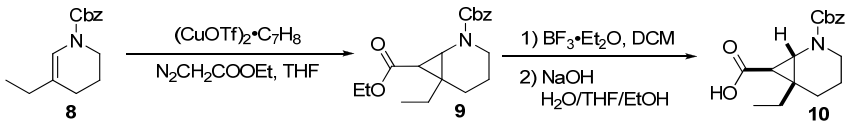
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.28 (m, 5 H; CH-Ar), 6.70 (s, 0.45 H; alkene-H rotamer A), 6.60 (s, 0.55 H; alkene-H rotamer B), 5.19 (s, 1.1 H; OCH_2 rotamer B), 5.17 (s, 0.9 H; OCH_2 rotamer A), 3.57 (m, 2 H; NCH_2), 2.07-1.94 (m, 4 H; allylic CH_2), 1.82 (m, 2 H; CH_2CH_2), 1.06-0.97 (m, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 153.4, 153.0, 136.5, 136.4, 128.3, 127.9, 127.8, 121.0, 120.6, 119.1, 118.7, 67.1, 67.0, 41.9, 41.8, 28.1, 28.1, 24.8, 24.7, 21.6, 21.6, 12.6, 12.4.

IR ν 2962 (w), 2934 (w), 2880 (w), 1703 (s), 1499 (w), 1409 (s), 1345 (m), 1313 (m), 1258 (s), 1202 (m), 1176 (m), 1111 (m), 1041 (m), 988 (m), 914 (m), 882 (m), 761 (m), 738 (m), 698 (m), 635 (m), 607 (m).

HRMS(ESI) calcd for $C_{15}H_{20}NO_2^+$ (M+H) 246.1494, found 246.1496.

1-Benzyloxycarbonyl-5-ethyl-1-azabicyclo[4.1.0]heptan-7-carboxylic acid ethyl ester (9) 1-Benzyloxycarbonyl-5-ethyl-1-azabicyclo[4.1.0]heptan-7-carboxylic acid (10)



Following a slight modification of a reported procedure,[7] a solution of ethyl diazoacetate (6.2 mL, 59 mmol, 4.0 equiv) in DCM (15 mL) was added to a solution of enamine **8** (3.64 g, 14.9 mmol, 1.00 equiv) and copper triflate (I) toluene complex (192 mg, 0.370 mmol, 0.0200 equiv) in DCM (15mL) over 18 h (1.3 mL/h) via syringe pump. After the addition was complete, the reaction was concentrated and purified by flash column chromatography (PET/AcOEt 15:1 until PET/AcOEt 9:1) to yield **9** (3.74 g, 11.3 mmol, 76%) as colorless oil. Following a reported procedure,[5] the mixture of exo and endo esters (1.50 g, 4.53 mmol, 1.00 equiv) in dichlorometane (20 mL) at -20°C was treated with BF_3•Et_2O (96 mg, 0.68 mmol, 0.15 equiv). The reaction was allowed to warm at 0°C and stirred at the same temperature until the isomerization was finished (from R_f 0.28-0.32 PET/AcOEt 9:1 to R_f 0.30 PET/AcOEt 9:1, Anisaldehyde). Triethylamine (1 mL) was added dropwise to the reaction and the mixture was diluted with Et_2O (50 mL) and washed with water and brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give a pale yellow oil (1.50 g) which was used directly in the next step.

The crude oil (1.50 g, 4.53 mmol, 1.00 equiv) was dissolved in a solution of water/THF/EtOH 1/1/3 (25 mL total) at 0°C and NaOH (1.63 g, 40.3 mmol, 9.00 equiv) was added portionswise. The reaction was heated to 60°C and stirred during 2 hours. The solution was concentrated, then diluted with water (30 mL) and washed with Et_2O (3x20 mL). The aqueous layer was acidified with HCl (1 M aqueous solution) until pH 2 and extracted with DCM (3x20 mL) to give **10** as a colorless oil which turns solid upon storage (1.25 g, 4.12 mmol, 91% overall). No further purification was needed.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.21 (m, 5 H; CH-Ar), 5.23-5.09 (m, 2 H; OCH_2), 3.86 (dt, J = 12.5 Hz, 3.1 Hz, 0.7 H; NCH_2 rotamer A), 3.73 (m, 0.3 H; NCH_2 rotamer B), 3.55 (d, J = 3.5 Hz, 0.3 H; NCH rotamer B), 3.49 (d, J = 3.6 Hz, 0.7 H; NCH rotamer A), 2.77 (dt, J = 12.5 Hz, 1.7 Hz, 0.3 H; NCH_2 rotamer B), 2.66 (dt, J = 12.5 Hz, 3.4 Hz, 0.7 H; NCH_2 rotamer A), 2.05 (m, 1 H; CHCO), 1.93-1.12 (m, 6 H; CH_2), 0.99 (t, J = 7.2 Hz, 1 H; CH_3 rotamer B), 0.93 (t, J = 7.4 Hz, 2 H; CH_3 rotamer A).

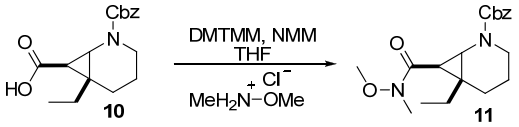
[7] R. Beumer, C. Bubert, C. Cabrele, O. Vielhauer, M. Pietzsch, O. Reiser, *J. Org. Chem.* **2000,** *65*, 8960.

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 177.2, 176.9, 156.2, 136.5, 128.5, 128.4, 128.1, 127.7, 127.2, 67.1, 67.0, 44.9, 44.8, 41.5, 41.1, 34.7, 34.0, 31.1, 30.6, 25.9, 25.7, 21.5, 21.3, 20.9, 10.3, 9.9.

IR ν 2956 (w), 2939 (w), 2864 (w), 1704 (s), 1584 (w), 1456 (s), 1423 (s), 1348 (m), 1270 (m), 1240 (m), 1214 (s), 1129 (m), 1036 (m), 1017 (w), 948 (w), 909 (m), 883 (m), 752 (m), 736 (s), 698 (m), 676 (m), 668 (m), 635 (m).

HRMS(ESI) calcd for $C_{17}H_{22}NO_4^+$ (M+H) 304.1549, found 304.1548.

***N*-Methoxy-*N*-methylcarbamo-6-yl-5-ethyl-1-azabicyclo[4.1.0]heptanes-1-benzylcarboxylate (11)**



Dimethoxytriazin-*N*-methylmorpholinium chloride[8] (DMTMM, 900 mg, 3.24 mmol, 1.50 equiv) was suspended into a solution of acid **10** (655 mg, 2.16 mmol, 1.00 equiv) in THF (7.5 mL) and the reaction mixture was stirred at RT during 60 min. *N,O*-dimethylhydroxylamine hydrochloride (97.5 mg, 2.16 mmol, 1.00 equiv) was added, followed by *N*-methylmorpholine (475 µL, 4.32 mmol, 2.00 equiv) and the reaction mixture was stirred during 36 hours. The reaction was quenched with a 5% aqueous solution of citric acid and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography (AcOEt/PET 3:7) to afford **11** (695 mg, 2.00 mmol, 93%) as colorless oil.

R_f 0.30 (PET/AcOEt 7:3, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.19 (m, 5 H; CH-Ar), 5.23 (d, J = 12.9 Hz, 0.8 H; OCH_2 rotamer A), 5.14 (d, J = 12.5 Hz, 0.2 H; OCH_2 rotamer B), 5.07 (d, J = 13.0 Hz, 1 H; OCH_2), 3.84 (dt, J = 12.5 Hz, 3.4 Hz, 0.8 H; NCH_2 rotamer A), 3.71 (m, 0.2 H; NCH_2, rotamer B), 3.64 (s, 0.6 H; OCH_3 rotamer B), 3.58-3.52 (m, 2.4 H; OCH_3 rotamer A and NCH rotamer B), 3.49 (d, J = 3.7 Hz, 0.8 H; NCH rotamer A), 3.15 (s, 0.6 H; NCH_3 rotamer B), 3.12 (s, 2.4 H; NCH_3 rotamer A), 2.73 (t, J = 11.7 Hz, 0.2 H; NCH_2 rotamer B), 2.64 (dt, J = 12.5 Hz, 2.2 Hz, 0.8 H; NCH_2 rotamer A), 2.09-1.87 (m, 2 H; CHCO and CH_2), 1.77-1.54 (m, 4 H; CH_2), 1.36 (m, 1 H; CH_2), 0.85 (t, J = 7.4 Hz, 3 H; CH_3).

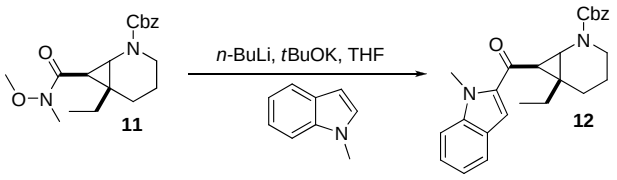
[8] M. Kunishima, C. Kawachi, F. Iwasaki, K. Terao, S. Tani, *Tetrahedron Letters* **1999**, *40*, 5327.

^{13}C NMR ($CDCl_3$, 100 MHz) δ (rotamers!) 171.2, 156.2, 136.8, 128.2, 128.1, 127.8, 127.8, 127.4, 127.0, 66.8, 66.5, 61.2, 42.9, 42.7, 41.5, 41.0, 33.0, 32.4, 29.1, 28.5, 26.0, 25.9, 25.2, 21.6, 10.3.

IR ν 2964 (w), 2937 (w), 2876 (w), 1703 (s), 1651 (s), 1458 (m), 1417 (s), 1384 (m), 1358 (m), 1344 (m) (m), 1295 (m), 1266 (m), 1209 (m), 1180 (m), 1123 (m), 1016 (m), 913 (m), 769 (w), 734 (s), 700 (w).

HRMS(ESI) calcd for $C_{19}H_{27}N_2O_4^+$ (M+H) 347.1971, found 347.1978.

6-(1-Methyl-*1H*-indol-2-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (12)



A solution of *N*-methylindole (13 μL, 0.10 mmol, 1.3 equiv) in THF (0.5 mL) was stirred at 0° C. Then a solution of ^{n}BuLi (2.5 M in pentane, 38 μL, 0.10 mmol, 1.2 equiv) diluted in THF (0.2 mL) was added dropwise. The solution was warmed to RT, stirred for 1 hour and then cooled to -78° C. From a separate flask, a solution of Weinreb amide **11** (27 mg, 0.080 mmol, 1.0 equiv) in THF (0.4 mL) was added via cannula into the solution. The mixture was stirred 2 hours at -78° C, then a solution of ^{t}BuOK in THF (0.3 mL) was added dropwise. The reaction was stirred 2 hours at -78° C and 5 min at 0° C, quenched with $NaHCO_3$ and extracted with Et_2O (5x3 mL). The organic layers were dried over Na_2SO_4, evaporated on reduced pressure and purified on flash chromatography (AcOEt/PET 1:5) to give **12** (16 mg, 0.038 mmol 48%) as a yellow oil.

R_f 0.60 (PET/AcOEt 7:3, Anisaldehyde).

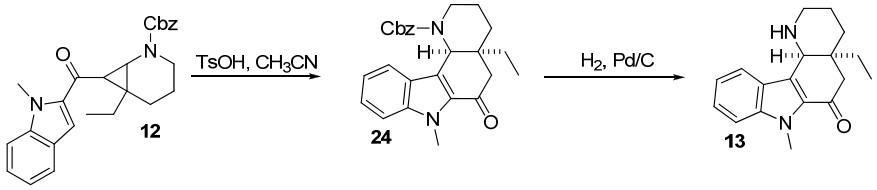
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.1 Hz, 1 H; CH-Ar), 7.45-7.29 (m, 4 H; CH-Ar), 7.25-7.00 (m, 5 H; CH-Ar), 5.19 (d, J = 12.7 Hz, 1 H; OCH_2), 5.04 (d, J = 12.7 Hz, 1 H; OCH_2), 4.08 (s, 0.6 H; CH_3 rotamer B), 3.97 (s, 2.4 H; CH_3 rotamer A), 3.95 (dt, J = 13.2 Hz, 3.4 Hz, 0.8 H; NCH_2, rotamer A), 3.88-3.82 (m, 0.2 H; NCH_2, rotamer B), 3.77 (d, J = 3.4 Hz, 1 H; NCH), 2.83 (t, J = 11.9 Hz, 0.2 H; NCH_2, rotamer B), 2.74 (dt, J = 12.0 Hz, 1.9 Hz, 0.8 H; NCH_2, rotamer A), 2.68 (d, J = 3.1 Hz, 0.2 H; COCH; rotamer B), 2.65 (d, J = 3.6 Hz, 0.8 H; COCH; rotamer A), 2.18 (m, 1 H; CH_2), 1.90-1.48 (m, 5 H; CH_2), 0.85 (t, J = 7.4 Hz, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 190.8, 157.3, 140.9, 137.6, 137.5, 129.4, 129.1, 128.5, 128.2, 126.9, 126.6, 126.3, 123.7, 121.7, 111.7, 111.3, 67.9, 46.2, 45.9, 42.3, 42.6, 39.2, 38.8, 38.4, 33.0, 27.3, 27.0, 26.0, 23.0, 22.8 11.7, 11.5.

IR ν 3064 (w), 3033 (w), 2938 (w), 2876 (w), 1703 (s), 1646 (s), 1614 (w), 1512 (m), 1464 (s), 1428 (s), 1408 (s), 1348 (s), 1268 (m), 1211 (s), 1196 (s), 1163 (m), 1129 (m), 1049 (m), 1027 (m), 910 (m), 769 (m), 737 (s), 698 (m).

HRMS(ESI) calcd for $C_{26}H_{29}N_2O_3^+$ (M+H) 417.2178, found 417.2181.

Benzyl 4a-ethyl-7-methyl-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-1*H*-pyrido[3,2-c]carbazole-1-carboxylate (24) and 4a-ethyl-7-methyl-3,4,4a,5,7,11c-hexahydro-1*H*-pyrido[3,2-c]carbazol-6(2*H*)-one (13)



The reaction was performed following general procedure **GP1**, starting from cyclopropane **12** (14 mg, 0.034 mmol, 1.0 equiv) and tosic acid (1 mg, 7 μmol, 0.2 equiv). The reaction was quenched after 5 min to give **24** (14 mg, 0.034 mmol, quant) without further purification as yellow oil (R_f 0.65 (PET/AcOEt 7:3, Anisaldehyde)). The indole derivative **24** (14 mg, 34 μmol, 1.0 equiv) was deprotected following general procedure **GP2**, using Pd/C (3 mg 10% w/w) in Et_2O (1.5 mL) and H_2 balloon. The suspension was filtered on celite and washed with DCM to afford **13** as green oil in quantitative yield (9.6 mg, 34 μmol).

R_f 0.75 (DCM/MeOH/Et_3N 3:1:2%, Anisaldehyde).

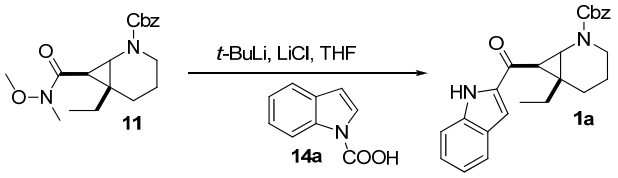
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, J = 8.2 Hz, 1 H; CH-Ar), 7.45-7.32 (m, 2 H; CH-Ar), 7.22 (t, J = 7.2 Hz, 1 H; CH-Ar), 4.16 (s, 1 H; CHN), 4.08 (s, 3 H; NCH_3), 3.53 (d, J = 17.0 Hz, 1 H; CH_2CO), 2.52 (m, J = 14.6 Hz, 2 H; CH_2N), 2.26 (d, J = 16.8 Hz, 1 H; CH_2CO), 1.87-1.21 (m, 7 H; CH_2 and NH), 0.75 (t, J = 7.4 Hz, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.6, 139.8, 129.9, 126.6, 124.3, 121.5, 120.8, 110.3, 110.3, 55.6, 45.0, 44.0, 40.2, 32.6, 31.6, 31.2, 29.7, 27.5.

IR ν 3300 (w), 2960 (m), 2935 (m), 2902 (w), 1702 (s), 1662 (s), 1615 (w), 1601 (w), 1542 (w), 1448 (m), 1411 (m), 1314 (m), 1252 (m), 1179 (w), 1117 (w), 1070 (w), 751 (m), 698 (m), 641 (m), 627 (m), 607 (m).

HRMS(ESI) calcd for $C_{18}H_{23}N_2O^+$ (M+H) 283.1810, found 283.1813.

6-(*1H*-indol-2-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (1a)



^{t}BuLi (1.6 M in pentane, 38 μL, 0.80 mmol, 2.2 equiv) was added dropwise into a solution of carboxylindole **14a** prepared following **GP5** (64 mg, 0.40 mmol, 1.1 equiv) and LiCl[9] (17 mg, 0.40 mmol, 1.1 equiv) in THF (1 mL) at -78° C. The solution was stirred for 3 hours and then transferred via cannula into a solution of amide **11** (125 mg, 360 μmol, 1.00 equiv) in THF (1 mL) at -78°C. The reaction was allowed to warm to -20°C over 5 hours then transferred via cannula into saturated aqueous $NaHCO_3$ solution (10 mL) at 0°C. The aqueous phase was extracted with Et_2O (5x10 mL). The organic layers were dried over Na_2SO_4, evaporated under reduced pressure and purified on flash chromatography with deactivated silica (AcOEt/PET 1:9) to give **1a** (97 mg, 24 mmol, 67%) as yellow oil.

R_f 0.70 (PET/AcOEt 7:3, Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (d, J = 0.4 Hz, 0.2 H; NH rotamer B), 9.29 (m, 0.8 H; NH rotamer A), 7.72 (d, J = 8.0 Hz, 1 H; CH-Ar), 7.45 (m, 1 H; CH-Ar), 7.36 (m, 2 H; CH-Ar), 7.16 (m, 4 H; CH-Ar), 7.02 (m, 2 H; CH-Ar), 5.21-5.08 (m, 0.4 H; OCH_2 rotamer B), 5.15 (d, J = 12.7 Hz, 0.8 H; OCH_2 rotamer A) 5.02 (d, J = 12.7 Hz, 0.8 H; OCH_2 rotamer A), 3.93 (m, 1 H; NCH_2), 3.81 (d, J = 3.3 Hz, 1 H; NCH), 2.84 (t, J = 12.2 Hz, 0.2 H; NCH_2 rotamer B), 2.75 (t, J = 12.1 Hz, 0.8 H; NCH_2 rotamer A), 2.61 (d, J = 3.3 Hz, 1 H; COCH), 2.15 (m, 1 H; CH_2), 1.77 (m, 4 H; CH_2), 1.54 (m, 1 H; CH_2), 0.91 (m, 0.6 H; CH_3 rotamer B), 0.82 (t, J = 7.3 Hz, 2.4 H; CH_3 rotamer A).

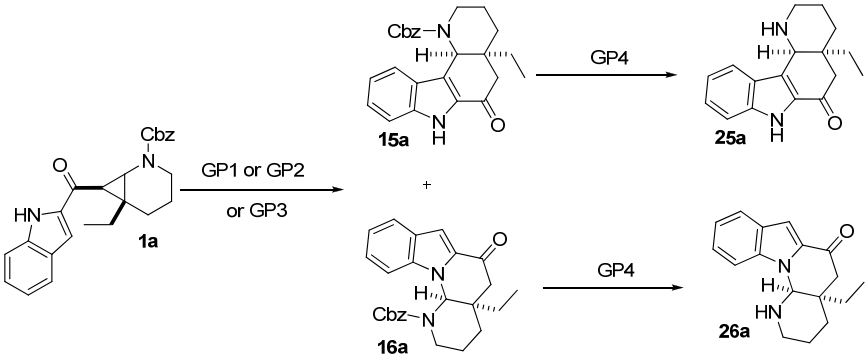
^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 188.6, 156.3, 137.1, 136.6, 136.5, 128.5, 128.1, 128.1, 127.7, 127.5, 127.3, 126.1, 122.9, 122.7, 120.9, 120.7, 112.1, 108.6, 108.4, 66.9, 46.0, 45.6, 41.7, 41.3, 38.3, 36.7, 36.0, 26.3, 26.1, 25.0, 21.9, 21.8, 10.7, 10.6.

IR ν 3309 (w), 2960 (w), 2936 (w), 2876 (w), 1700 (s), 1629 (s), 1521 (m), 1446 (m), 1409 (s), 1349 (s), 1313 (w), 1299 (w), 1268 (m), 1232 (w), 1210 (m), 1192 (m), 1164 (m), 1140 (s), 1080 (w), 1034 (w), 1010 (w), 978 (w), 911 (m), 799 (w), 746 (s), 736 (s), 698 (m), 606 (w).

[9] LiCl was dried under HV (< 0.05 Torr), warmed at 600° C (Mp) and stirred. It was then cooled down to RT and dissolved into 1mL of dry THF.

HRMS(ESI) calcd for $C_{25}H_{27}N_2O_3^+$ (M+H) 403.2022, found 403.2034.

Benzyl 4a-ethyl-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-*1H*-pyrido[3,2-c]carbazole-1-carboxylate (15a); 4a-ethyl-7-3,4,4a,5,7,11c-hexahydro-1*H*-pyrido[3,2-c]carbazol-6(2*H*)-one (25a); benzyl 4a-ethyl-6-oxo-2,3,4,4a,5,6-hexahydroindolo[1,2-a][1,8]naphthyridine-1(*12aH*)-carboxylate (16a); 4a-ethyl-1,2,3,4,4a,5-hexahydroindolo[1,2-a][1,8]naphthyridin-6(*12aH*)-one (26a)



The reaction was performed following general procedure **GP1**, starting from cyclopropane **1a** (35 mg, 0.087 mmol, 1.0 equiv) and tosic acid (3.0 mg, 16 µmol, 0.20 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 9:1, Anisaldehyde) to give the product **15a** (*Rf* 0.65, 16 mg, 39 µmol, 45 %) and the product **16a** (*Rf* 0.75, 10 mg, 25 µmol, 29%). The tetracyclic compound **15a** (16 mg, 16 µmol, 1.0 equiv) was deprotected following the general procedure **GP4** to give **25a** (10 mg, 38 µmol, 97 %) as a yellow oil without further purification. Product **16a (**10 mg, 25 µmol, 1.0 equiv) was deprotected following the general procedure **GP4** to give **26a** (6.7 mg, 25 µmol, 99 %) as a yellow oil without further purification.

The reaction was performed using general procedure **GP2**, starting from cyclopropane **1a** (100 mg, 0.250 mmol, 1.00 equiv) and copper (II) triflate (9.0 mg, 25 µmol, 0.10 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 7:3, Anisaldehyde) to give the product **15a** (*Rf* 0.65, 80 mg, 0.20 mmol, 80 %) and the product **16a** (*Rf* 0.75, 11 mg, 30 µmol, 11%). The tetracyclic compound **15a** (70 mg, 0.17 mmol, 1.0 equiv) was deprotected following the general procedure **GP4** to give **25a** (45 mg, 0.17 mmol, quant.) as a yellow oil without further purification.

The reaction was performed following general procedure **GP3**, starting from cyclopropane **1a** (0.10 g, 0.25 mmol, 1.0 equiv) and tosic acid (4.7 mg, 25 µmol, 0.1 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 7:3, Anisaldehyde) to give the product **15a** (*Rf* 0.65, 4.0 mg, 10 µmol, 4 %) and the product **16a** (*Rf* 0.75, 85 mg, 0.22 mmol, 85 %). The tetracyclic compound **16a** (50 mg, 0.12 mmol, 1.0 equiv) was deprotected following the general procedure GP4 to give **26a** (33 mg, 0.12 mmol, quant.) as a yellow oil without further purification.

25a

R_f 0.0 (AcOEt/PET 6:4, Anisaldehyde).

^{1}H NMR (CD_3OD, 400 MHz) δ 7.91 (d, J = 8.2 Hz, 1 H; CH-Ar), 7.51 (d, J = 8.4 Hz, 1 H; CH-Ar), 7.40 (d, J = 7.2 Hz, 1 H; CH-Ar), 7.23 (t, J = 7.5 Hz, 1 H; CH-Ar), 4.61 (s, 1 H; CHN), 3.40-3.11 (m, 3 H; CH_2N and CH_2CO), 2.37 (d, J = 17.6 Hz, 1 H; CH_2CO), 2.16 (s, 1 H; NH), 1.92 (m, 2 H; CH_2), 1.80 (m, 2 H; CH_2), 1.45 (m, 2 H; CH_2), 0.83 (t, J = 7.5 Hz, 3 H; CH_3).

^{13}C NMR (CD_3OD, 100 MHz) δ 191.2, 140.0, 132.6, 128.2, 126.1, 122.4, 122.0, 121.6, 114.1, 55.6, 45.3, 42.7, 41.5, 33.0, 32.7, 20.4, 7.8.

IR ν 2961 (s), 2943 (s), 2866 (s), 2142 (m), 1660 (w), 1543 (w), 1493 (m), 1464 (m), 1366 (w), 1263 (w), 1167 (m), 1105 (m), 1073 (m), 1021 (m), 884 (m), 804 (m), 751 (m), 673 (s), 635 (s).

HRMS(ESI) calcd for $C_{17}H_{21}N_2O^+$ (M+H) 269.1654, found 269.1655.

In order to obtain a crystalline compound, a solution of **25a** was treated with an excess of HCl (4 M in dioxane). The solvents were removed under reduced pressure and the colorless solid obtained was recrystallized by slow diffusion of hexane into a solution in dichloromethane. For X-ray image see the spectra in section 6 (CCDC number: 777832).

26a

R_f 0.4 (AcOEt/PET 3:7 Anisaldehyde).

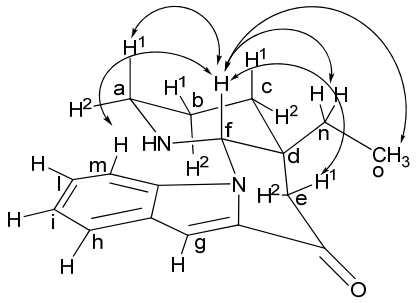
^{1}H NMR (CD_3OD, 400 MHz) δ 7.71 (d, J = 8.1 Hz, 1 H; H_h), 7.63 (d, J = 8.4 Hz, 1 H; H_m), 7.43 (t, J = 7.9 Hz, 1 H; H_i or H_l), 7.28 (s, 1 H; H_g), 7.18 (t, J = 7.7 Hz, 1 H; H_i or H_l), 5.22 (s, 1 H; H_f), 3.36 (d, J = 17.6 Hz, 1 H; H_e^2), 3.12 (m, 1 H; H_a^2), 2.97 (m, 1 H; H_a^1), 2.32 (d, J = 17.6 Hz, 1 H; H_e^1), 1.87-1.60 (m, 5 H; H_b^1 ; H_b^2 ; H_c^1; H_c^2 and NH), 1.31 (q, J = 7.6 Hz, 2 H; $2H_n$), 0.80 (t, J = 7.5 Hz, 3 H; $3H_o$).

^{13}C NMR (CD_3OD, 100 MHz) δ 192.9, 138.5, 133.1, 128.6, 127.5, 124.3, 122.8, 111.7, 107.4, 70.7, 45.9, 41.4, 40.2, 33.6, 31.6, 22.1, 7.4.

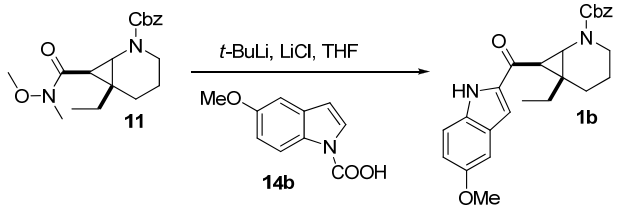
IR ν 2934 (w), 2861 (w), 1676 (s), 1532 (s), 1446 (w), 1407 (w), 1360 (w), 1322 (m), 1247 (w), 1196 (w), 1173 (w), 1146 (w), 1119 (w), 1044 (w), 929 (w), 894 (w), 872 (w), 846 (w), 811 (w), 740 (m), 634 (w).

HRMS(ESI) calcd for $C_{17}H_{21}N_2O^+$ (M+H) 269.1654, found 269.1652.

Important correlations NOESY: H_f-H_a^1; H_f-$2H_n$; H_f-$3H_o$; H_f-H_e^1; H_f-H_m (see the 2D spectra in section 6)



6-(5-methoxy-*1H*-indol-2-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (1b)



^{t}BuLi (1.6 M in pentane, 0.65 mL, 1.0 mmol, 2.6 equiv) was added dropwise into a solution of 5-metoxy-carboxylindole **14b** (100 mg, 0.520 mmol, 1.30 equiv) prepared following **GP5** and LiCl[9] (44.0 mg, 1.04 mmol, 2.60 equiv) in THF (3.5 mL) at -78° C. The solution was stirred over 3 hours then transferred via cannula into a solution of amide **11** (139 mg, 0.400 mmol, 1.00 equiv) in THF (3.5 mL) at 0°C over 20 minutes. The reaction was stirred at 0°C over 20 minutes then transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (10 mL) at 0°C. The aqueous layer was extracted with Et_2O (5x10 mL). The organic layers were dried over Na_2SO_4, evaporated under reduced pressure and purified on flash chromatography with deactivated silica (AcOEt/toluene 1:9) to give **1b** (99.8 mg, 23.0 mmol, 58%) as a yellow oil with tendency to solidify and amide **11** (53 mg, 0.15 mmol, 38%).

R_f 0.25 (AcOEt/toluene 9:1, Anisaldehyde).

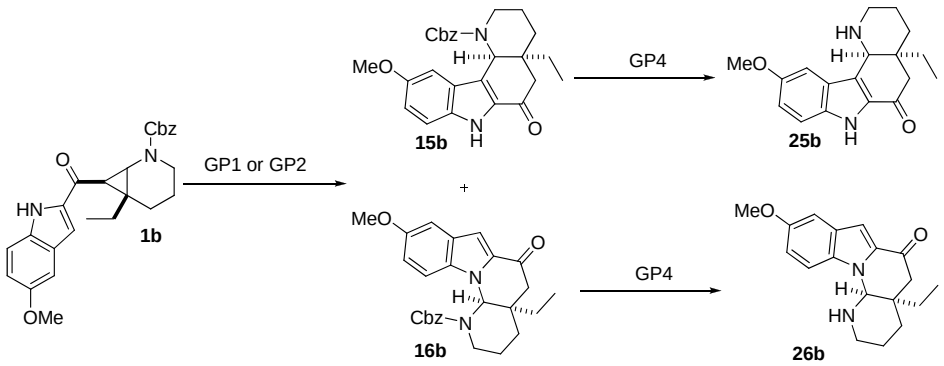
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.82 (s, 0.8 H; NH rotamer A), 9.74 (s, 0.2 H; NH rotamer B), 7.58-6.92 (m, 9 H; CH-Ar), 5.32-5.10 (m, 0.4 H; OCH_2 rotamer B), 5.17 (d, J = 12.8 Hz, 0.8 H; OCH_2 rotamer A), 5.03 (d, J = 12.6 Hz, 0.8 H; OCH_2 rotamer A), 3.98 (m, 1 H; NCH_2), 3.92-3.83 (m, 4 H; OCH_3 and NCH), 2.87 (t, J = 11.5 Hz, 0.2 H; NCH_2 rotamer B), 2.78 (t, J = 11.9 Hz, 0.8 H; NCH_2 rotamer A), 2.64 (d, J = 3.2 Hz, 1 H; COCH), 2.17 (m, 1 H; CH_2), 1.94-1.73 (m, 4 H; CH_2), 1.58 (m, 1 H; CH_2), 0.85 (t, J = 6.9 Hz, 3 H; CH_3)

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 188.6, 156.3, 154.6, 137.1, 136.4, 132.9, 128.4, 128.2, 128.0, 127.9, 127.4, 127.2, 118.0, 117.7, 117.4, 112.9, 112.9, 109.7, 108.3, 108.0, 102.9, 67.2, 66.9, 55.6, 45.9, 45.3, 41.7, 41.2, 38.1, 36.7, 36.0, 26.3, 26.0, 25.0, 21.9, 10.7.

IR ν 3303 (w), 2941 (w), 2866 (w), 1778 (w), 1703 (m), 1626 (m), 1525 (s), 1458 (m), 1414 (m), 1352 (m), 1296 (w), 1269 (w), 1211 (s), 1171 (m), 1124 (m), 1029 (w), 911 (w), 742 (m), 677 (w), 630 (w).

HRMS(ESI) calcd for $C_{26}H_{29}N_2O_4^+$ (M+H) 433.2127, found 433.2113.

Benzyl ethyl-10-methoxy-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-*1H*-pyrido[3,2-c]carbazole-1-carboxylate (15b); ethyl-10-methoxy-3,4,4a,5,7,11c-hexahydro-*1H*-pyrido[3,2-c]carbazol-6(*2H*)-one (25b); benzyl 4a-ethyl-9-methoxy-6-oxo-2,3,4,4a,5,6-hexahydroindolo[1,2-a][1,8]naphthyridine-1(*12aH*) carboxylate (16b) and 4a ethyl-9-methoxy-1,2,3,4,4a,5-hexahydroindolo[1,2-a][1,8]naphthyridin-6(*12aH*)-one (26b)



The reaction was performed using general procedure **GP2**, starting from cyclopropane **1b** (74 mg, 0.17 mmol, 1.0 equiv) and copper (II) triflate (9.2 mg, 25 μmol, 0.15 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 8:2, Anisaldehyde) to give the product **15b** (*Rf* 0.3, 62 mg, 0.14 mmol, 84 %) and the product **16b** (*Rf* 0.4, 8.0 mg, 80 μmol, 11%). The tetracyclic compound **15b** (50 mg, 0.12 mmol, 1.0 equiv) was deprotected following the general procedure **GP4** to give **25b** (35 mg, 0.12 mmol, quant.) as a yellow oil without further purification.

The reaction was performed following general procedure **GP3**, starting from cyclopropane **1b** (67 mg, 0.16 mmol, 1.0 equiv) and tosic acid (4.0 mg, 23 μmol, 0.15 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 8:2, Anisaldehyde) to give the product **15b** (*Rf* 0.3, 3 mg, 7 μmol, 4 %) and the product **16b** (*Rf* 0.4, 55 mg, 0.13 mmol, 82%). The tetracyclic compound **16b** (53 mg, 0.12 mmol, 1.0 equiv) was deprotected following the general procedure **GP4** to give **26b** (36 mg, 0.12 mmol, quant.) as a yellow oil without further purification.

25b

R_f 0.0 (AcOEt/PET 6:4 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.29 (s, 1 H; NH indole), 7.30 (d, *J* = 9.0 Hz, 1 H; CH-Ar), 7.15 (s, 1 H; CH-Ar), 7.01 (dd, *J* = 8.9 Hz, 1.9 Hz, 1 H; CH-Ar), 4.01 (s, 1 H; CHN), 3.86 (s, 3 H; OCH_3), 3.16 (d, *J* =

16.8 Hz, 1 H; CH_2CO), 3.06 (m, 1 H; CH_2N), 2.83 (m, 1 H; CH_2N), 2.27 (d, *J* = 16.8 Hz, 1 H; CH_2CO), 1.92 (br s, 1 H; NH amine), 1.79-1.62 (m, 2 H; CH_2), 1.52 (m, 2 H; CH_2), 1.42-1.17 (m, 2 H; CH_2), 0.81 (t, *J* = 7.5 Hz, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.4, 154.7, 133.6, 131.0, 127.5, 125.9, 118.5, 113.6, 100.9, 56.4, 55.7, 45.4, 42.8, 40.7, 33.0, 31.0, 22.7, 7.7.

IR ν 3281 (w), 2936 (w), 2857 (w), 1652 (s), 1540 (w), 1487 (m), 1464 (w), 1439 (w), 1335 (w), 1297 (w), 1264 (m), 1218 (s), 1169 (m), 1121 (w), 1105 (w), 1030 (w), 909 (m), 809 (w), 733 (s), 628 (w).

HRMS(ESI) calcd for $C_{18}H_{23}N_2O^+$ (M+H) 299.1760, found 299.1755.

26b

R_f 0.2 (AcOEt/PET 4:6 Anisaldehyde).

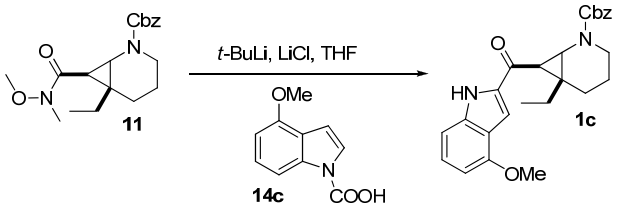
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (d, *J* = 9.0 Hz, 1 H; CH-Ar), 7.19 (s, 1 H; CH-Ar), 7.10 (d, *J* = 2.0 Hz, 1 H; CH-Ar), 7.06 (dd, *J* = 9.0 Hz, 2.3 Hz, 1 H; CH-Ar), 4.91 (s, 1 H; CHN), 3.85 (s, 3 H; OCH_3), 3.32 (d, *J* = 17.0 Hz, 1 H; CH_2CO), 3.13 (m, 1 H; CH_2N), 2.87 (td, *J* = 11.6 Hz, 2.5 Hz, 1 H; CH_2N), 2.30 (d, *J* = 17.0 Hz, 1 H; CH_2CO), 1.88-1.50 (m, 5H; CH_2 and NH), 1.32 (m, 2 H; CH_2), 0.81 (t, *J* = 7.5 Hz, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7, 155.0, 132.6, 132.1, 127.6, 118.0, 110.6, 105.3, 103.0, 70.7, 55.6, 45.4, 40.7, 39.2, 33.0, 30.3, 21.8, 7.2.

IR ν 2931 (w), 2862 (w), 2834 (w), 1672 (s), 1531 (s), 1447 (m), 1406 (w), 1351 (w), 1316 (w), 1267 (w), 1223 (s), 1179 (m), 1120 (w), 1032 (w), 918 (w), 860 (w), 845 (w), 799 (m), 740 (s).

HRMS(ESI) calcd for $C_{18}H_{23}N_2O_2^+$ (M+H) 299.1760, found 299.1749.

6-(4-methoxy-*1H*-indol-2-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (1c)



^{t}BuLi (1.6 M in pentane, 0.65 mL, 1.0 mmol, 2.6 equiv) was added dropwise into a solution of 4-metoxy-carboxylindole **14c** (100 mg, 0.520 mmol, 1.30 equiv) prepared following **GP5** and LiCl[9] (44 mg, 1.0

mmol, 2.6 equiv) in THF (3.5 mL) at -78° C. The solution was stirred over 3 hours then transferred via cannula into a solution of amide **11** (139 mg, 0.400 mmol, 1.00 equiv) in THF (3.5 mL) at 0°C over 25 minutes. The reaction was stirred at 0°C over 25 minutes then transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (10 mL) at 0°C. The aqueous layer was extracted with Et_2O (5x10 mL). The organic layers were dried over Na_2SO_4, evaporated under reduced pressure and purified on flash chromatography with deactivated silica (AcOEt/toluene 1:9) to give **1c** (86 mg, 20 mmol, 50%) as a yellow oil with tendency to solidify.

R_f 0.20 (AcOEt/PET 3:7, Anisaldehyde).

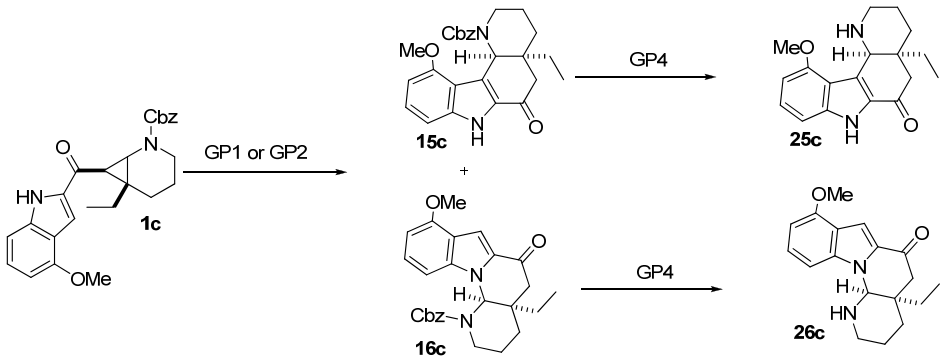
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.36 (s, 1 H; NH), 7.44-6.96 (m, 8 H; CH-Ar), 6.52 (m, 1 H; CH-Ar), 5.21-5.07 (m, 0.4 H; OCH_2 rotamer B), 5.14 (*J* = 12.9 Hz, 0.8 H; OCH_2 rotamer A), 5.02 (d, *J* = 12.7 Hz, 0.8 H; OCH_2 rotamer A), 3.96 (m, 4 H; OCH_3 and NCH_2), 3.81 (d, *J* = 3.1 Hz, 1 H; CHN), 2.83 (t, *J* = 12.0 Hz; 0.2 H; NCH_2 rotamer B), 2.74 (t, *J* = 12.1 Hz, 0.8 H; NCH_2 rotamer A), 2.63 (d, *J* = 3.1 Hz, 1H; COCH), 2.15 (d, *J* = 14.1 Hz, 1 H; CH_2), 1.89-1.64 (m, 4 H; CH_2), 1.57 (m, 1 H; CH_2), 0.81 (t, *J* = 7.0 Hz, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 188.3, 156.3, 154.8, 138.4, 136.5, 135.6, 128.4, 128.1, 128.0, 127.5, 127.2, 127.2, 126.9, 119.2, 106.3, 106.0, 105.2, 105.1, 99.6, 99.5, 67.2, 66.9, 55.3, 45.8, 45.5, 41.7, 41.3, 38.0, 36.5, 35.8, 26.3, 26.1, 25.1, 21.9, 21.8, 10.8.

IR ν 3304 (w), 2959 (w), 2936 (w), 2875 (w), 1703 (s), 1620 (m), 1580 (m), 1517 (s), 1457 (m), 1410 (s), 1364 (s), 1305 (w), 1259 (s), 1239 (w), 1208 (m), 1191 (m), 1162 (s), 1126 (m), 1108 (m), 1079 (w), 1030 (w), 1010 (w), 981 (w), 911 (m), 824 (w), 776 (m), 735 (s), 699 (w).

HRMS(ESI) calcd for $C_{26}H_{29}N_2O_4^+$ (M+H) 433.2127, found 433.2110.

Benzyl ethyl-11-methoxy-6-oxo-2,3,4,4a,5,6,7,11c-octahydro-*1H*-pyrido[3,2-c]carbazole-1-carboxylate (15c); ethyl-11-methoxy-3,4,4a,5,7,11c-hexahydro-*1H*-pyrido[3,2-c]carbazol-6(*2H*)-one (25c); benzyl 4a-ethyl-8-methoxy-6-oxo-2,3,4,4a,5,6-hexahydroindolo[1,2-a][1,8]naphthyridine-1(*12aH*) carboxylate (16c) and 4a-ethyl-8-methoxy-1,2,3,4,4a,5-hexahydroindolo[1,2-a][1,8]naphthyridin-6(*12aH*)-one (26c)



The reaction was performed using general procedure **GP2**, starting from cyclopropane **1c** (40 mg, 92 µmol, 1.0 equiv) and copper (II) triflate (5.0 mg, 14 µmol, 0.15 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 7:3, Anisaldehyde) to give the product **15c** (*Rf* 0.18, 31 mg, 72 µmol, 78 %) and the product **16c** (*Rf* 0.20, 4 mg, 9 µmol, 10%). The tetracyclic compound **15c** (30 mg, 70 µmol, 1.0 equiv) was deprotected following the general procedure **GP4** to give **25c** (20 mg, 70 µmol, quant.) as a pale yellow oil without further purification.

The reaction was performed following general procedure **GP3**, starting from cyclopropane **1c** (40 mg, 92 µmol, 1.0 equiv) and tosic acid (2.6 mg, 14 µmol, 0.15 equiv). The reaction was quenched after 15 min and the crude oil was purified by column chromatography (PET/AcOEt 8:2, Anisaldehyde) to give the product **15c** (*Rf* 0.18, 1.7 mg, 4 µmol, 4 %) and the product **16c** (*Rf* 0.2, 35 mg, 81 µmol, 88 %). The tetracyclic compound **16c** (30 mg, 70 µmol, 1.0 equiv) was deprotected following the general procedure **GP4** to give **26c** (20 mg, 68 µmol, quant) as a yellow oil without further purification.

25c

R_f 0.0 (AcOEt/PET 6:4 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.44 (s br, 1 H; NH indole), 7.18 (t, *J* = 8.0 Hz, 1 H; CH-Ar), 6.92 (d, *J* = 8.2 Hz, 1 H; CH-Ar), 6.47 (d, *J* = 7.8 Hz, 1 H; CH-Ar), 4.24 (s, 1 H; CHN), 3.97 (s, 3 H; OCH_3), 3.29 (d, *J* = 16.9 Hz, 1 H; CH_2CO), 3.19 (m, 1 H; CH_2N), 2.85 (d, *J* = 11.3 Hz, 1 H; CH_2N), 2.24 (d, *J* = 16.9 Hz, 1 H; CH_2CO), 1.75 (m, 2 H; CH_2), 1.62-1.41 (m, 3 H; CH_2 and NH amine), 1.30 (m, 2 H; CH_2), 0.80 (t, *J* = 7.5 Hz, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.1, 155.4, 139.5, 129.5, 127.8 116.6, 105.7, 99.9, 57.1, 55.5, 45.8, 42.1, 40.3, 33.4, 31.5, 21.8, 7.7. (1 C in aromatic region is not resolved)

IR ν 3267 (w), 2960 (w), 2932 (w), 1650 (s), 1620 (w), 1582 (m), 1543 (w), 1518 (w), 1470 (m), 1424 (w), 1391 (w), 1354 (m), 1266 (w), 1254 (m), 1166 (w), 1108 (s), 977 (w), 919 (w), 873 (w), 785 (m), 740 (s), 637 (m), 617 (s).

HRMS(ESI) calcd for $C_{18}H_{23}N_2O^+$ (M+H) 299.1760, found 299.1754.

26c

R_f 0.2 (AcOEt/PET 4:6 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (s, 1 H; CH-Ar), 7.30 (t, *J* = 8.1 Hz, 1 H; CH-Ar), 6.99 (d, *J* = 8.3 Hz, 1 H; CH-Ar), 6.51 (d, *J* = 7.7 Hz, 1 H; CH-Ar), 4.92 (s, 1 H; CHN), 3.94 (s, 3 H; OCH_3), 3.35 (d, *J* = 17.1 Hz, 1 H; CH_2CO), 3.13 (m, 1 H; CH_2N), 2.87 (t, *J* = 11.8 Hz, 1 H; CH_2N), 2.29 (d, *J* = 17.1 Hz, 1 H; CH_2CO), 1.87-1.49 (m, 5 H; CH_2 and NH), 1.33 (m, 2 H; CH_2), 0.80 (t, *J* = 7.5 Hz, 3 H; CH_3).

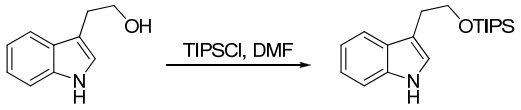
^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.5, 155.5, 138.0, 131.2, 127.1, 118.9, 103.8, 102.4, 100.2, 70.7, 55.4, 45.5, 40.8, 39.2, 32.9, 30.3, 21.7, 7.1.

IR ν 2939 (w), 2862 (w), 1673 (s), 1615 (w), 1575 (w), 1525 (s), 1505 (w), 1463 (w), 1431 (w), 1368 (w), 1307 (m), 1261 (s), 1182 (m), 1094 (w), 1038 (w), 983 (w), 924 (w), 911 (m), 773 (m), 735 (s).

HRMS(ESI) calcd for $C_{18}H_{23}N_2O_2^+$ (M+H) 299.1760, found 299.1762.

4. Total synthesis of Goniomitine

3-Tri*iso*propylyloxyethyl-1*H*-indole (28)



27 28

Following a reported procedure,[10] TIPSCl (630 mg, 3.25 mmol, 1.05 equiv) was added to a solution of Tryptophol (**27**) (500 mg, 3.10 mmol, 1.00 equiv) and imidazole (440 mg, 6.50 mmol, 2.10 equiv) in DMF (3.5 mL) at RT. The reaction was stirred for 1 hour then quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The organic layer was dried on Na_2SO_4 and concentrated under reduced pressure. The crude oil was purified by column chromatography (AcOEt/PET 1:9) to give the product **28** (990 mg, 3.10 mmol, quant.) in quantitative yield.

R_f 0.85 (AcOEt/PET 2:8 Anisaldehyde).

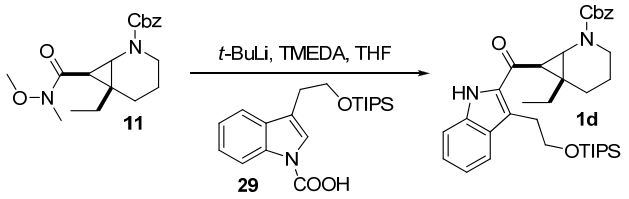
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (br s, 1H; NH), 7.61 (d, *J* = 7.9 Hz, 1H; CH-Ar), 7.35 (d, *J* = 8.1 Hz, 1 H; CH-Ar), 7.18 (ddd, *J* = 8.0 Hz, 7.1 Hz, 1.1 Hz, 1 H; CH-Ar), 7.11 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1 H; CH-

[10] T. Fukuda, R. Maeda, M. Iwao, *Tetrahedron*, **1999**, *55*, 9151.

Ar), 7.06 (d, *J* = 1.7 Hz, 1H; CH-Ar), 3.95 (t, *J* = 7.4 Hz, 2 H; OCH_2), 3.03 (m, 2 H; CH_2), 1.14-1.00 (m, 21 H; ^{i}Pr).

The ^{1}H NMR corresponded with literature.[10]

6-(3-Tri*iso*propyloxyethyl-1*H*-indol-2-carbonyl)-5-ethyl-1-azabicyclo[4.1.0]heptane-1-benzylcarboxylate (1d)



^{t}BuLi (1.6 M in pentane, 0.17 mL, 0.28 mmol, 3.0 equiv) was added dropwise into a solution of 3-triisopropyloxyethyl-*N*-carboxylindole **29** (50 mg, 0.14 mmol, 1.5 equiv) prepared following **GP5** and TMEDA (21 mg, 0.18 mmol, 2.0 equiv) in THF (1 mL) at -78° C. The solution was stirred over 3 hours then transferred via cannula into a solution of amide **11** (32 mg, 90 µmol, 1.0 equiv) in THF (1 mL) at 0°C over 20 minutes. The reaction was stirred at 0°C during 20 minutes then transferred via cannula into a saturated aqueous solution of $NaHCO_3$ (2 mL) at 0°C. The aqueous layer was extracted with Et_2O (5x5 mL). The organic layers were dried over Na_2SO_4, evaporated under reduced pressure and purified on flash chromatography with deactivated silica (AcOEt/PET 1:9) to give amide **11** (8.2 mg, 23 µmol, 25%) and **1d** (20 mg, 33 µmol, 36 % (48% brsm)) as a yellow oil.

R_f 0.40 (AcOEt/PET 3:7, Anisaldehyde).

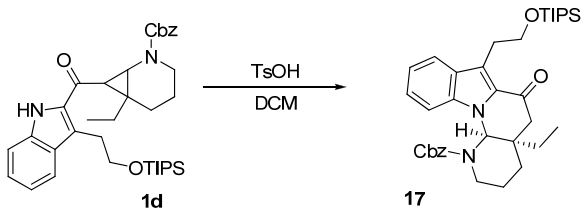
^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.84 (s, 0.2 H; NH rotamer B), 8.99 (s, 0.8 H; NH rotamer A), 7.70 (d, *J* = 8.1 Hz, 1 H; CH-Ar), 7.45-7.30 (m, 4 H; CH-Ar), 7.25 (m, 1 H; CH-Ar), 7.20-7.08 (m, 3 H; CH-Ar), 5.28-5.14 (m, 0.4 H; OCH_2 rotamer B), 5.18 (d, *J* = 12.7 Hz, 0.8 H; OCH_2 rotamer A), 5.09 (d, *J* = 12.8 Hz, 0.8 H; OCH_2 rotamer A), 4.06-3.81 (m, 4 H; CH_2O, NCH_2 and NCH), 3.52-3.25 (m, 2 H; CH_2C-Ar), 2.84 (m, 0.2 H; NCH_2 rotamer B), 2.83 (d, *J* = 3.4 Hz, 0.8 H; CHCO rotamer A), 2.75 (t, *J* = 11.5 Hz, 0.8 H; NCH_2 rotamer A), 2.66 (d, *J* = 3.2 Hz, 0.2 H; CHCO rotamer B), 2.29 (m, 1 H; CH_2), 1.91-1.55 (m, 5H; CH_2), 1.10-0.97 (m, 21 H; ^{i}Pr), 0.86 (m, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 189.2, 156.2, 156.1, 136.6, 136.5, 135.9, 135.8, 133.6, 133.4, 128.7, 128.5, 128.4, 128.4, 128.1, 128.0, 127.4, 127.2, 126.9, 126.0, 125.7, 120.9, 120.8, 120.1, 119.9, 118.5, 118.3, 112.1, 112.0, 67.3, 66.8, 65.2, 64.1, 45.9, 44.5, 43.6, 41.7, 41.2, 38.2, 38.1, 37.5, 35.6, 29.4, 29.2, 26.1, 25.9, 25.6, 25.3, 21.7, 21.3, 17.9, 17.8, 11.9, 10.7, 10.5.

IR ν 2943 (s), 2866 (m), 2852 (m), 1698 (s), 1556 (w), 1460 (m), 1432 (m), 1386 (w), 1340 (w), 1305 (w), 1268 (m), 1193 (w), 1101 (s), 1013 (w), 919 (w), 884 (w), 820 (w), 744 (s), 695 (m), 633 (s).

HRMS(ESI) calcd for $C_{36}H_{51}N_2O_4Si^+$ (M+H) 603.3618, found 603.3782.

Benzyl 4a-ethyl-6-oxo-7-(2-(tri*iso*propylsilyloxy)ethyl)-2,3,4,4a,5,6-hexahydroindolo[1,2-a][1,8]naphthyridine-1(*12aH*)-carboxylate (17)



The reaction was performed following general procedure **GP3**, starting from cyclopropane **1d** (60 mg, 0.10 mmol, 1.0 equiv) and tosic acid (3.8 mg, 20 μmol, 0.2 equiv). The reaction was quenched after 10 min, extracted with Et_2O (3x10 mL), washed with brine (2x10mL) and dried on Na_2SO_4. The organic layer was concentrate to give the cyclic product **17** (56 mg, 93 μmol, 93 %) as a yellow oil without further purification.

R_f 0.75 (AcOEt/PET 2:8 Anisaldehyde).

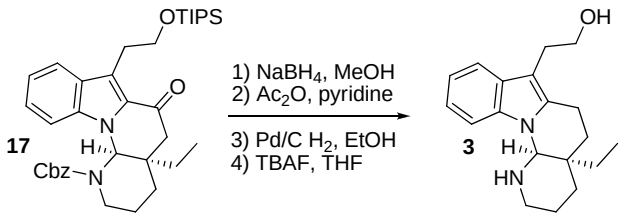
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, *J* = 8.0 Hz, 1 H; CH-Ar), 7.51-7.34 (m, 5 H; CH-Ar), 7.19-7.09 (m, 2 H; CH-Ar), 7.06 (d, *J* = 7.9 Hz, 1 H; CH-Ar), 6.43 (br s, 1 H; CHN), 5.39 (d, *J* = 11.3 Hz, 1 H; CH_2-Ar), 5.31 (d, *J* = 11.6 Hz, 1 H; CH_2-Ar), 4.06 (m, 1 H; CH_2N), 3.95 (m, 2 H; CH_2O), 3.40 (m, 2 H; CH_2C-Ar), 2.67 (d, *J* = 16.0 Hz, 1 H; CHCO), 2.49 (d, *J* = 16.0 Hz, 1H; CHCO), 2.28 (td, *J* = 12.9 Hz, 2.7 Hz, 1H; CH_2N), 1.84-1.52 (m, 5 H; CH_2), 1.30 (m, 1 H; CH_2), 1.13-0.83 (m, 24 H; ^{i}Pr and CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz) (rotamers!) δ 190.0, 155.4, 136.2, 135.6, 129.6, 128.8, 128.6, 128.4, 127.1, 126.7, 122.5, 122.0, 121.1, 121.0, 120.5, 112.2, 111.8, 68.9, 68.0, 63.6, 47.5, 39.0, 38.6, 28.6, 28.2, 27.4, 20.0, 17.9, 17.7, 11.9, 7.5.

IR ν 2927 (s), 2863 (m), 1707 (s), 1676 (s), 1545 (m), 1463 (m), 1426 (s), 1346 (m), 1322 (w), 1275 (s), 1217 (m), 1141 (w), 1114 (w), 1101 (s), 1055 (w), 1020 (w), 964 (w), 885 (w), 742 (s), 694 (m), 633 (m).

HRMS(ESI) calcd for $C_{18}H_{23}N_2O_2^+$ (M+H) 603.3618, found 603.3621.

2-(4a-Ethyl-1,2,3,4,4a,5,6,12a-octahydro-indolo[1,2-*a*][1,8]naphthyridin-7-yl)-ethanol (Goniomitine)(3)



$NaBH_4$ (49.0 mg, 1.30 mmol, 14.2 equiv) was added portionwise to a solution of tetracyclic compound **17** (55 mg, 91 µmol, 1.0 equiv) in MeOH (3 mL) at 0°C. The reaction was allowed to warm to RT and stirred during 3 hours before adding 5 mL of ice water and extracting with DCM (5x5 mL). The organic layer was dried on Na_2SO_4 and concentrated under reduced pressure. The white solid obtained was solubilized with pyridine (1.2 mL) at rt. and Ac_2O (0.8 mL) was added dropwise. The reaction was stirred overnight then quenched with $NaHCO_3$ (5 mL) and extracted with DCM (3x5 mL). The organic layer was dried with Na_2SO_4 and concentrated to give pale yellow oil which was dissolved in EtOH (7 mL) and deprotected following the general procedure **GP4**. The crude oil obtained was diluted in THF (5 mL). The solution was stirred at RT and TBAF (0.4 mL, 0.4 mmol, 4.4 equiv) was added dropwise. The reaction was stirred 30 min at RT then quenched with water and extracted with DCM (3x5 mL). The organic layer was dried on Na_2SO_4, concentrated and purified on flash chromatography with deactivated silica (AcOEt/PET 1:1) to give goniomitine **3** (21 mg, 70 µmol, 77 % overall).

R_f 0.2 (AcOEt/Hexane/Et_3N 29:70:1 Anisaldehyde).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, J = 7.7 Hz, 1 H; CH-Ar), 7.30 (d, J = 8.0 Hz, 1 H; CH-Ar), 7.14 (t, J = 7.2 Hz, 1 H; CH-Ar), 7.08 (t, J = 7.5 Hz, 1 H; CH-Ar), 4.79 (s, 1 H; NCH), 3.83 (t, J = 6.4 Hz, 2 H; OCH_2), 3.12-2.75 (m, 6 H; CH_2), 2.52 (td, J = 13.1 Hz, 6.7 Hz, 1 H; CH_2), 1.89 (d, J = 13.8 Hz, 1 H; CH_2), 1.80-1.41 (m, 7 H; CH_2 OH and NH), 1.21 (m, 1 H; CH_2), 0.88 (t, J = 7.5 Hz, 3 H; CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.3, 132.7, 129.0, 120.5, 119.5, 118.0, 108.2, 105.9, 71.6, 62.6, 45.6, 35.1, 34.0, 28.6, 27.8, 21.62, 21.58, 18.5, 7.1.

IR ν 3317 (w), 2934 (s), 2857 (m), 1735 (w), 1651 (w), 1564 (w), 1463 (s), 1420 (w), 1360 (m), 1313 (m), 1271 (w), 1240 (w), 1204 (w), 1118 (w), 1047 (m), 1017 (w), 910 (m), 872 (w), 740 (s), 648 (w).

HRMS(ESI) calcd for $C_{19}H_{27}N_2O^+$ (M+H) 299.2123, found 299.2119.

The obtained values for ^{1}H NMR fitted perfectly with the reported ones for natural[11] and synthetic[12] goniomitine. The obtained values for ^{13}C NMR fitted perfectly with the reported values for synthetic

[11] L. Randriambola, J. C. Quirion, C. Kanfan, H. P. Husson, *Tetrahedron Lett.* **1987**, *28*, 2123.
[12] a) S. Takano, T. Sato, K. Inomata, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1991**, 462; b) C. L. Morales, B. L. Pagenkopf, *Org. Lett.* **2008**, *10*, 157. We thank Prof. Pagenkopf for a copy of the original NMR data.

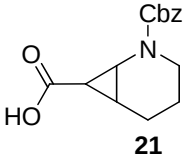
goniomitine, but small differences were apparent when compared with natural goniomitine, probably due to different conditions of measurement. A comparison of the spectra is provided in section 6.

5. Cell Assays[13]

The MCF-7 (breast cancer), HCT116 (colon carcinoma), A549 (lung cancer) and PC-3M (prostate cancer) cell lines originate from the American Type Culture (ATCC) and were obtained as a generous gift from Dr. Markus Wartmann, Novartis AG, Switzerland. Cells were seeded at 1.5×10^3 per well into 96-well microtiter plates and incubated overnight. Compounds were added in serial dilutions on day 1. Subsequently, the plates were incubated for 72 h and then fixed with 3.3 % v/v glutaraldehyde, washed with water and stained with 0.05 % methylene blue. After washing, the dye was eluted with 3 % v/v HCl and the optical density measured at 665 nm with a photometer. IC_{50} values were determined by the GraphPad Prim software (San Diego, USA) using the formula $(OD_{treated}-OD_{start})/(OD_{control}-OD_{start})\times100$. The IC_{50} is defined as the drug concentration which leads to 50 % of cells per well as compared to control cultures (100 %) at the end of the incubation period. Experiments were performed three times on different days. The MDCK cells (canine kidney) were obtained as a gift from Dr. Stefanie Krämer, ETH Zurich, Switzerland. The MDR-1-MDCK cells are a stably-transfected cell line expressing human P-glycoprotein.

[13] J. Gertsch, F. Feyen, A. Bützberger, B. Gerber, B. Pfeiffer, K. H. Altmann, *Chembiochem* **2009**, *10*, 2513.

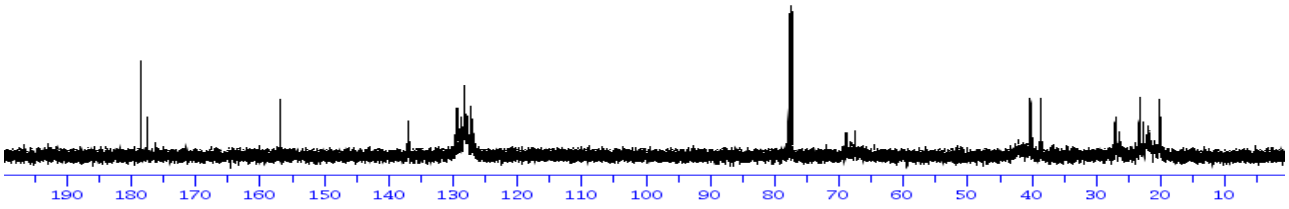
6 Spectra of New Compounds

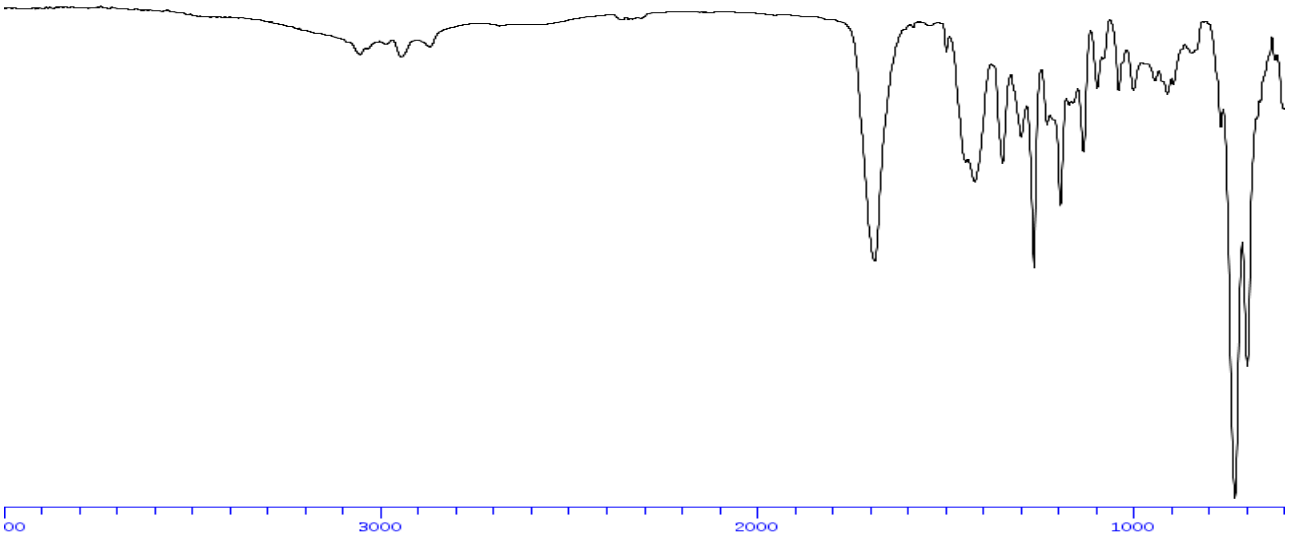


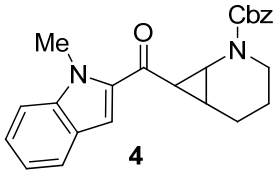
21

$CDCl_3$
400 MHz

$CDCl_3$
100 MHz



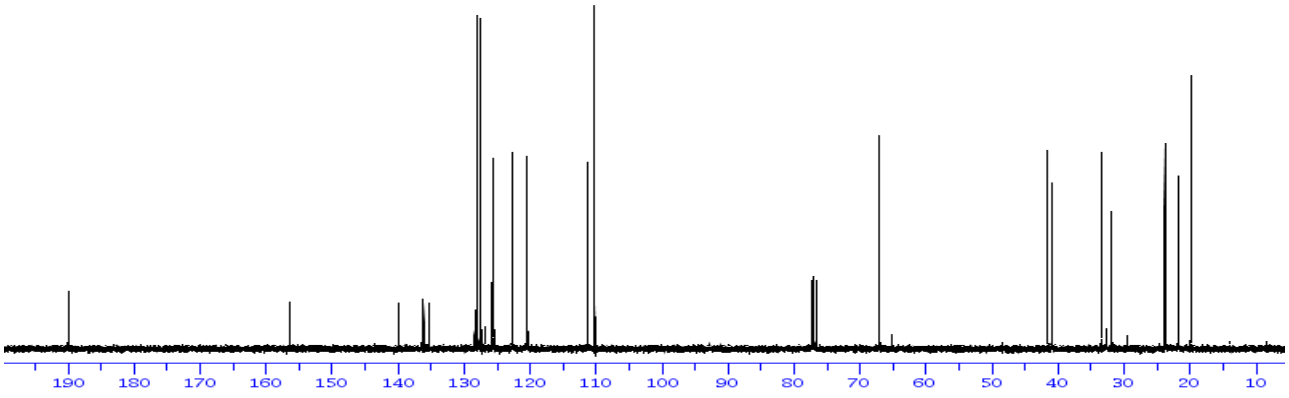


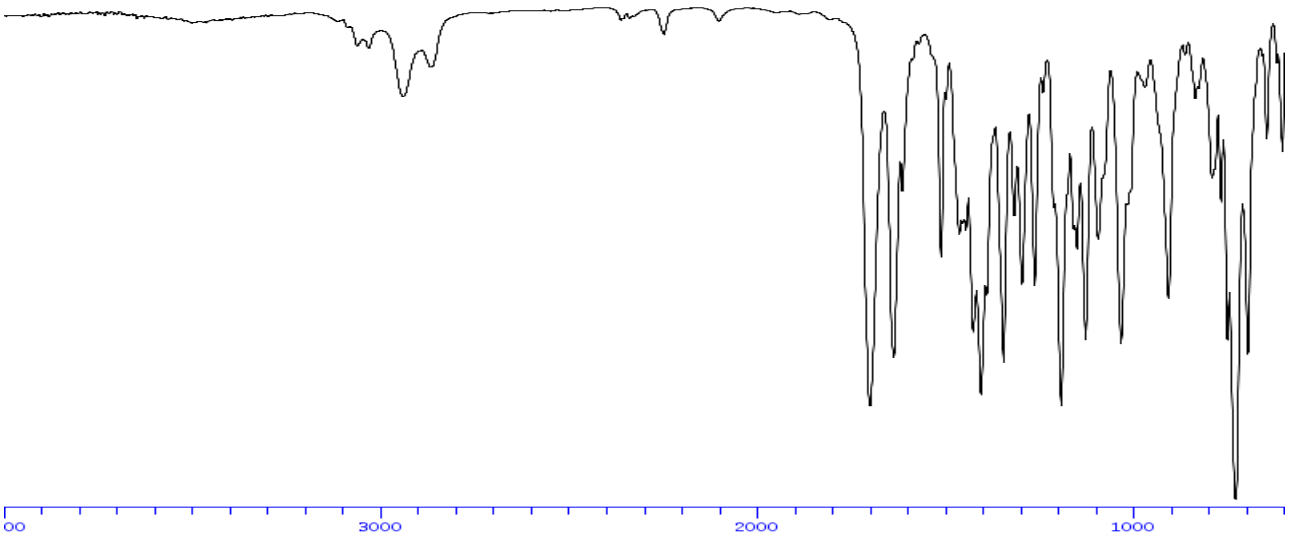


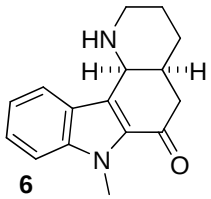
4

$CDCl_3$
400 MHz

$CDCl_3$
100 MHz

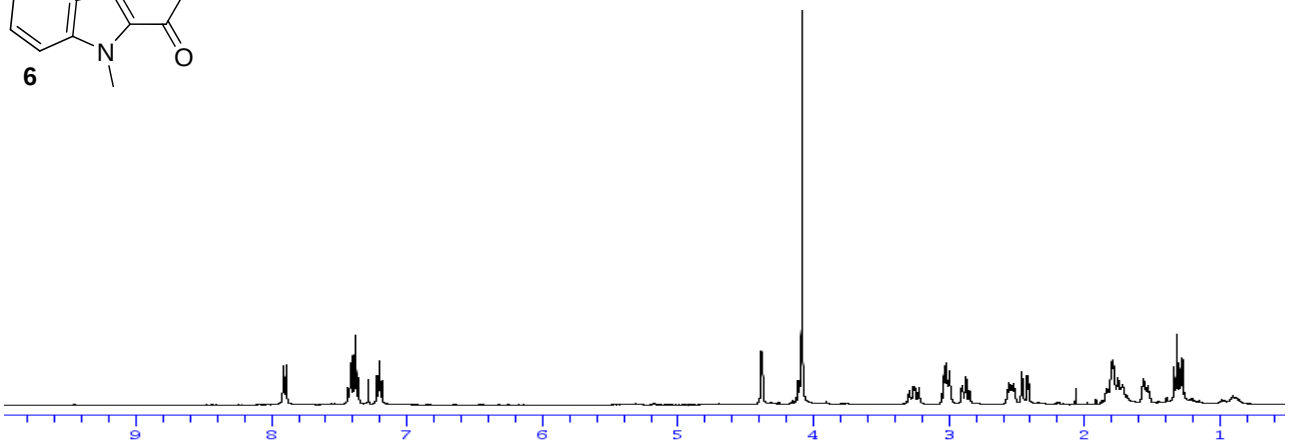




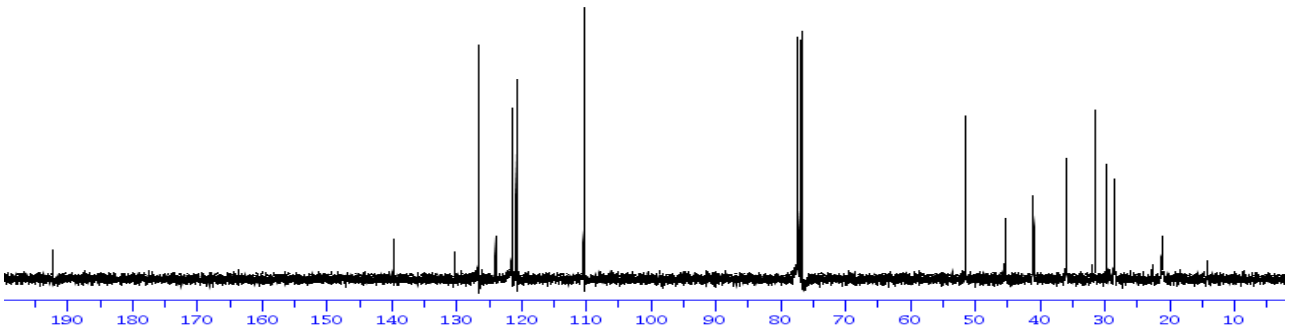


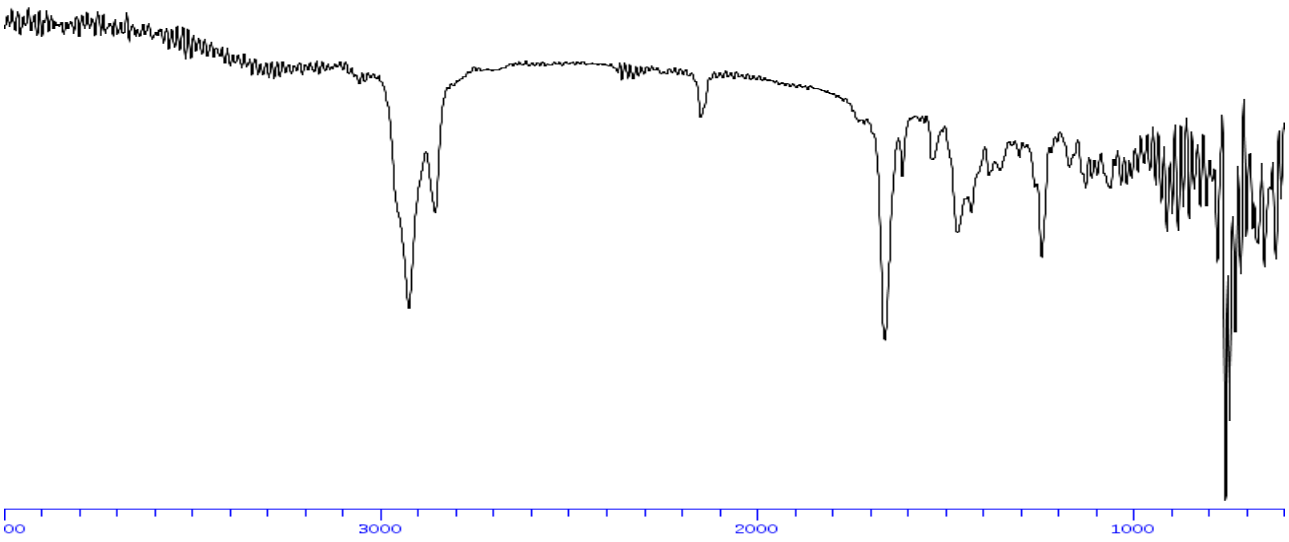
6

$CDCl_3$
400 MHz

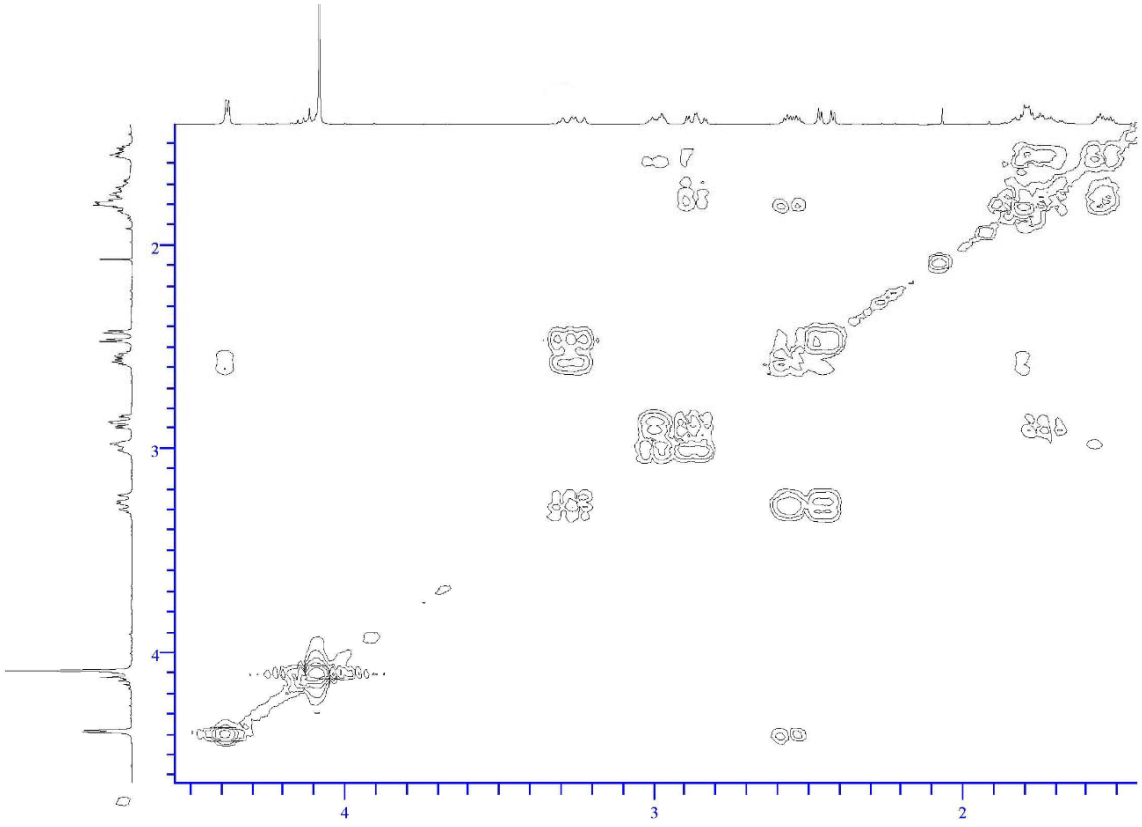


$CDCl_3$
100 MHz

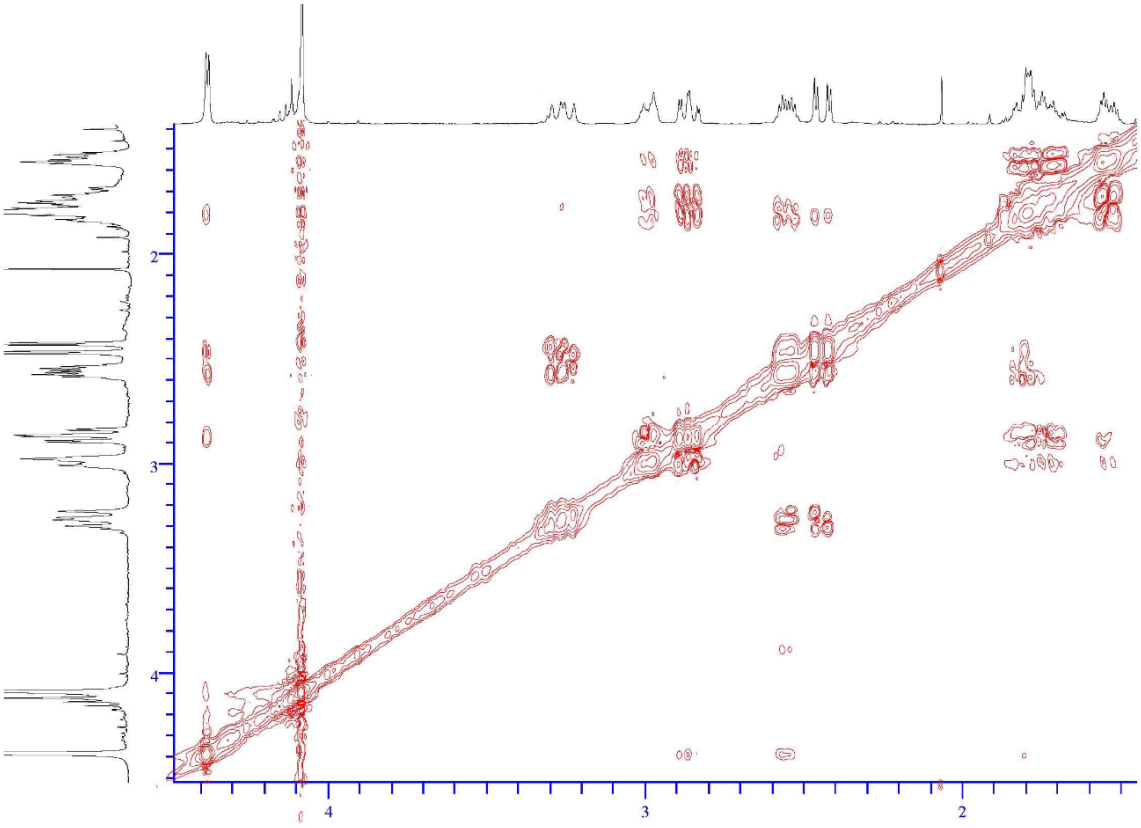


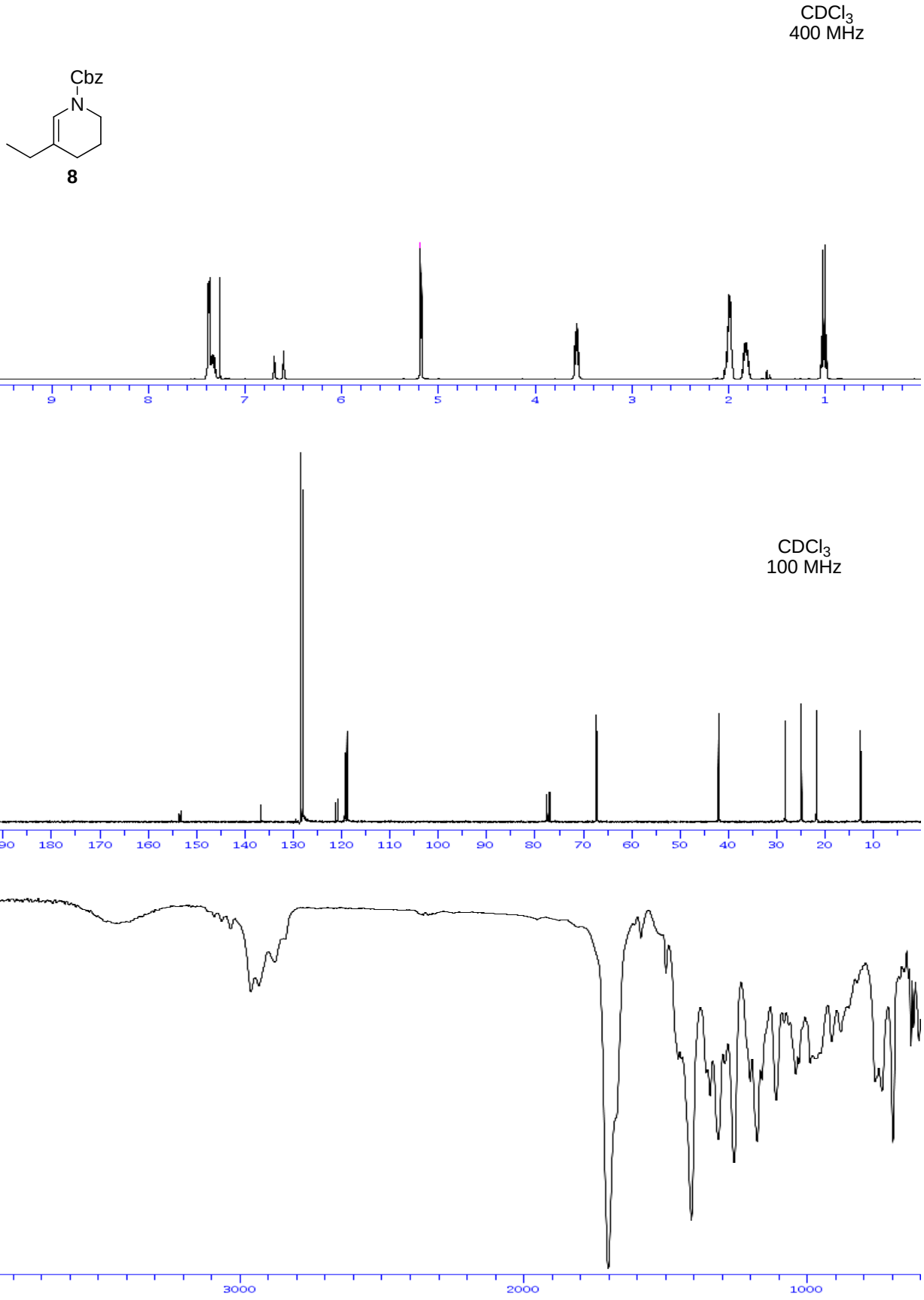


COSY



ROESY


2
3
4
4
3
2


CDCl3
400 MHz
Cbz
N
8
9
8
7
6
5
4
3
2
1
CDCl3
100 MHz
190
180
170
160
150
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120
110
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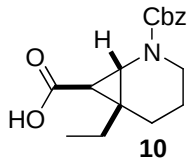
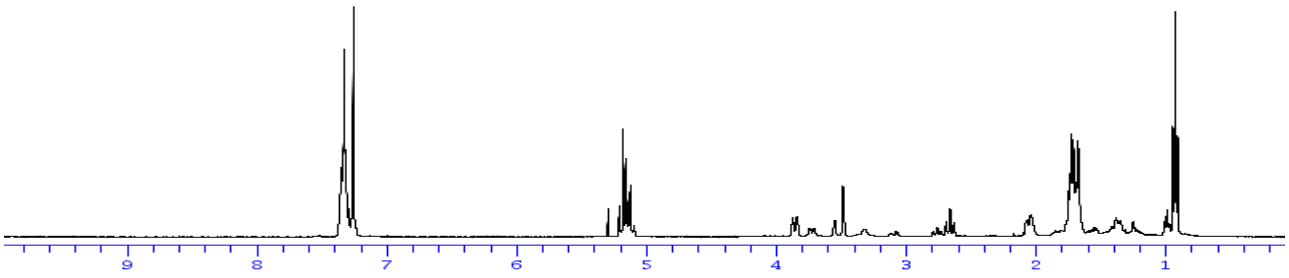
60
50
40
30
20
10
00
3000
2000
1000



10

$CDCl_3$
400 MHz



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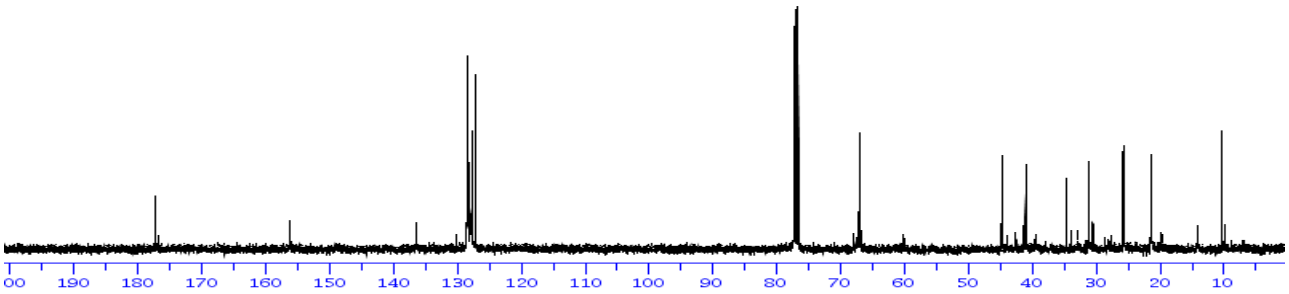
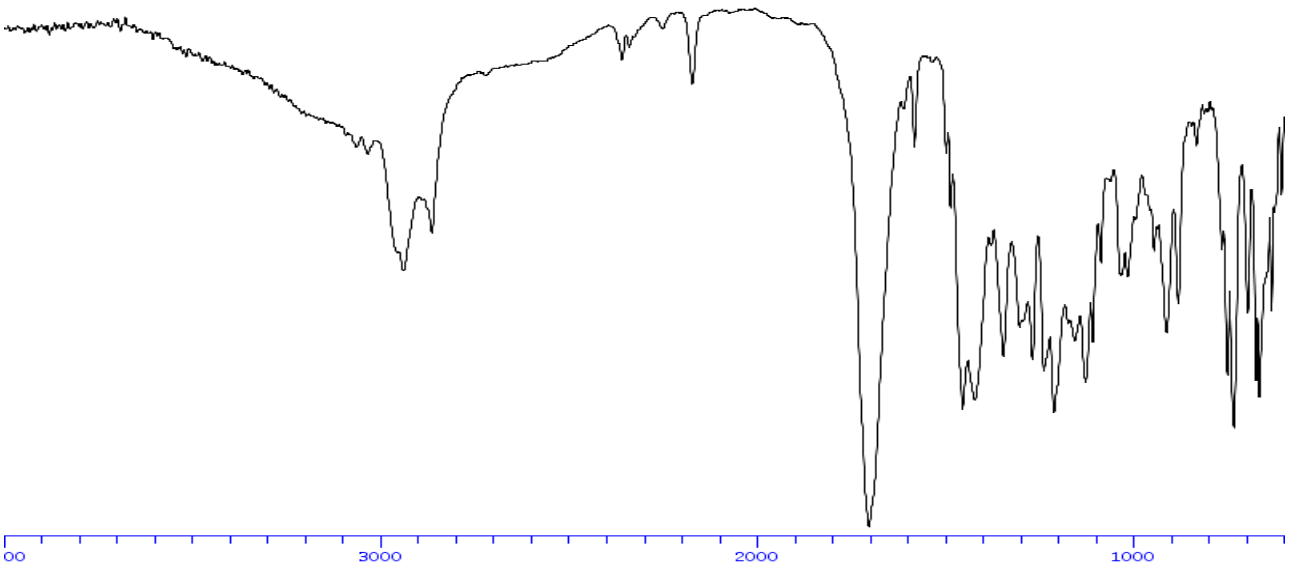
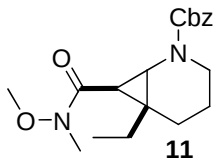
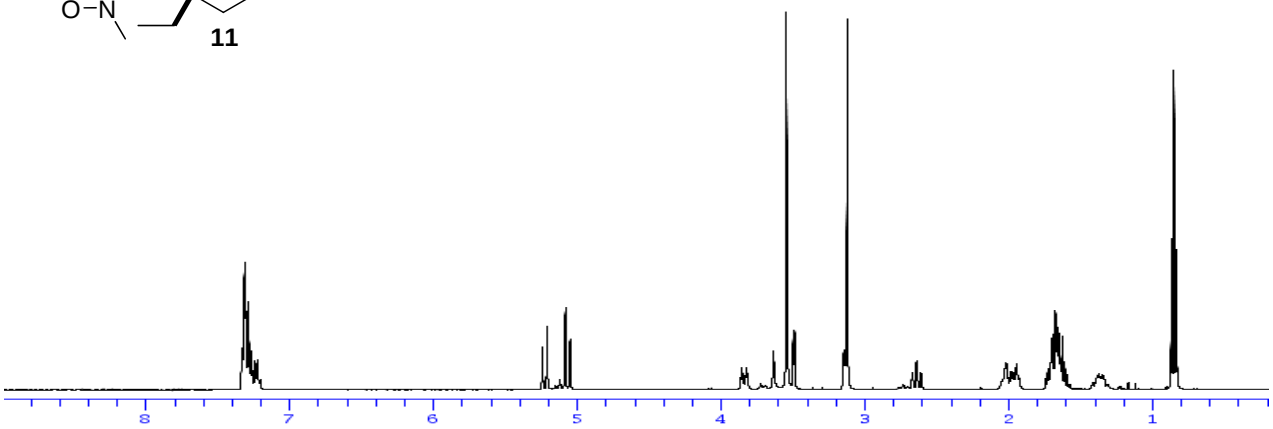






11

$CDCl_3$
400 MHz



$CDCl_3$
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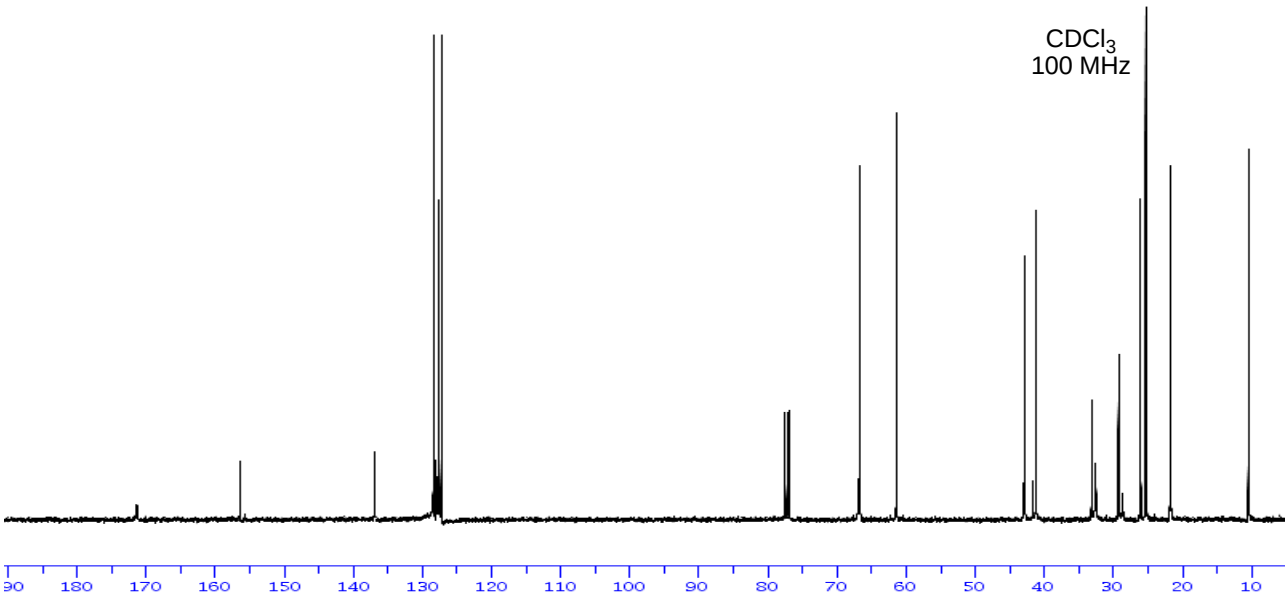
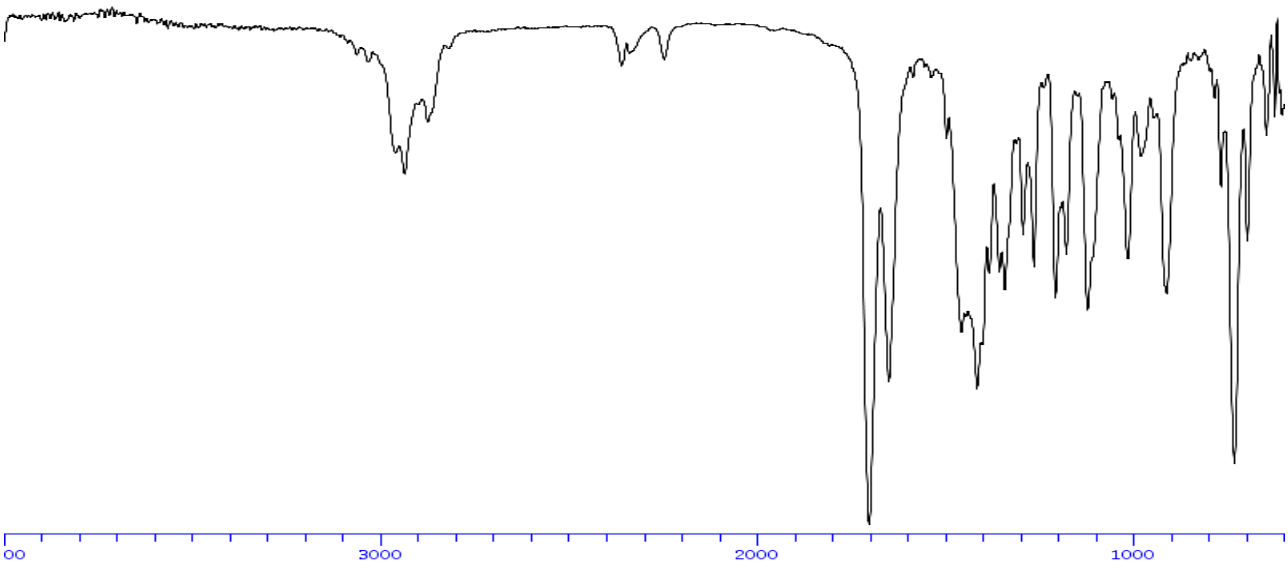
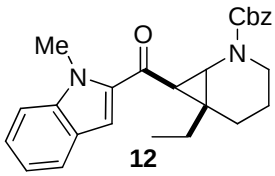
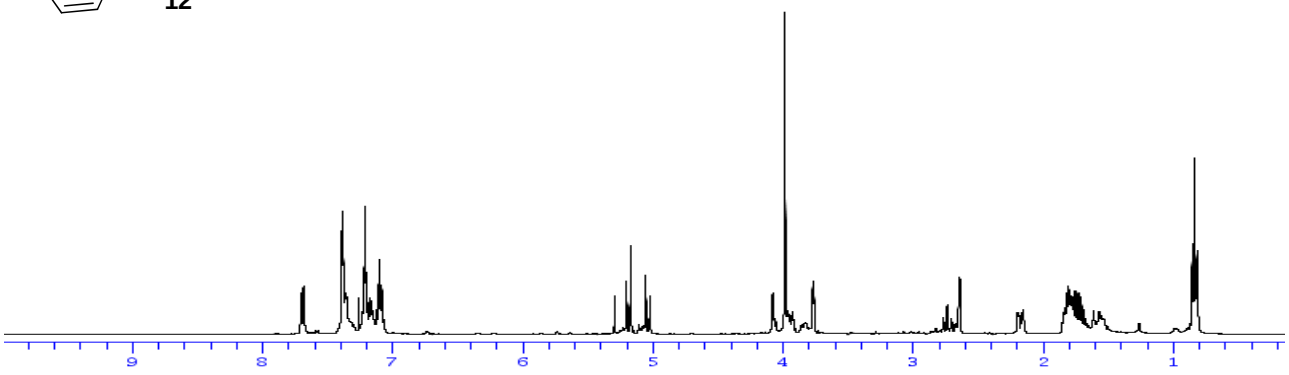




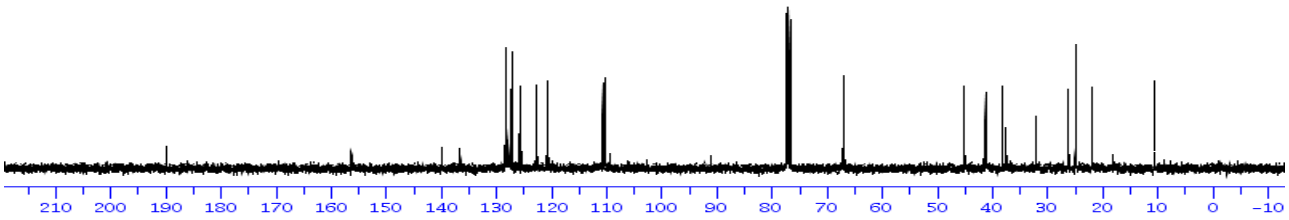


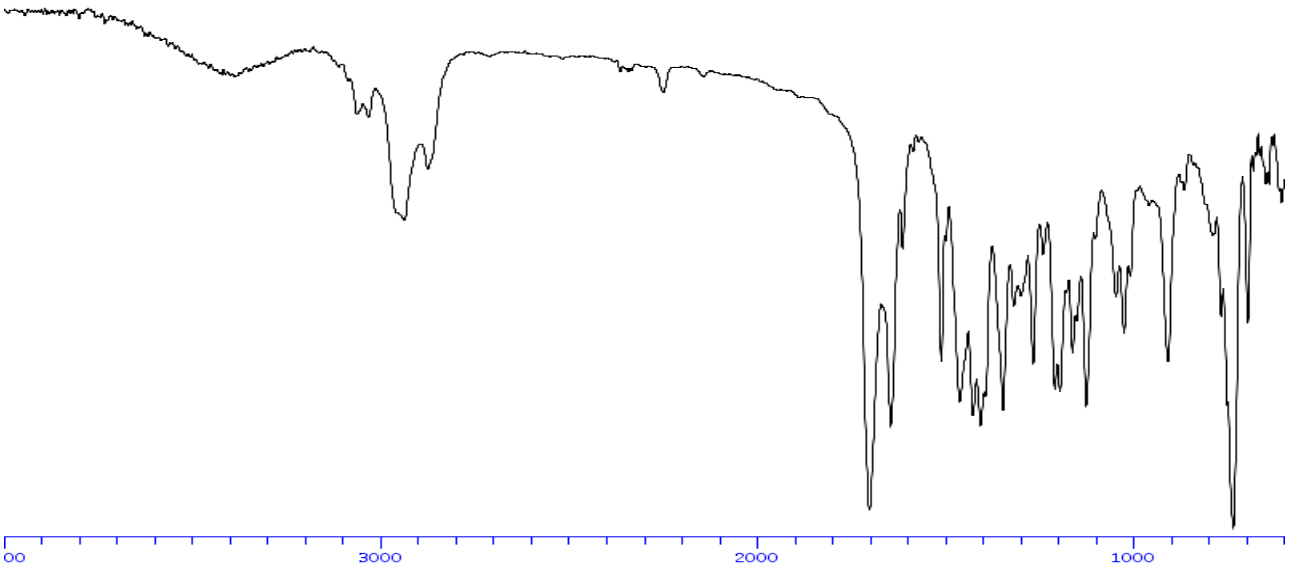
12

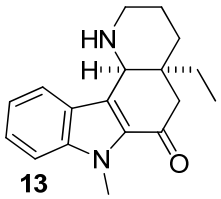
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

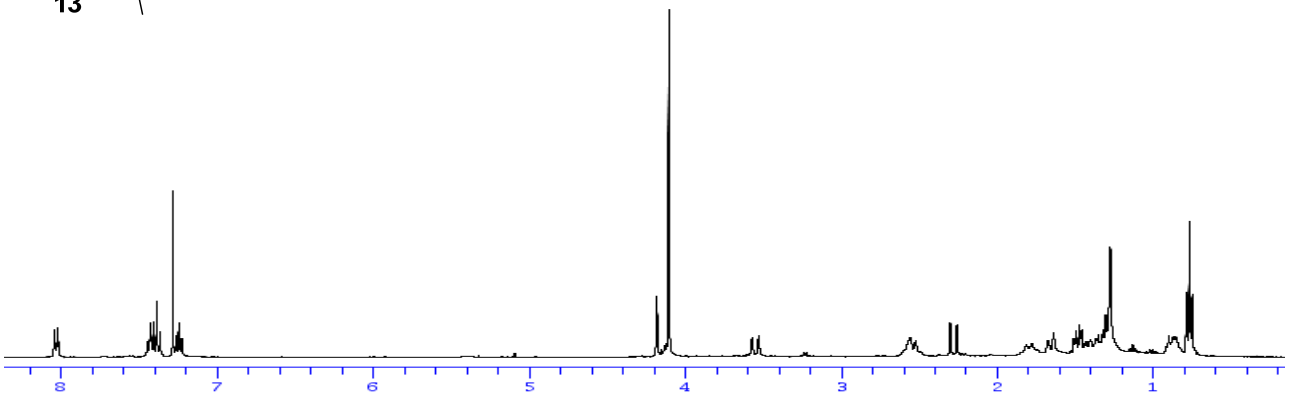




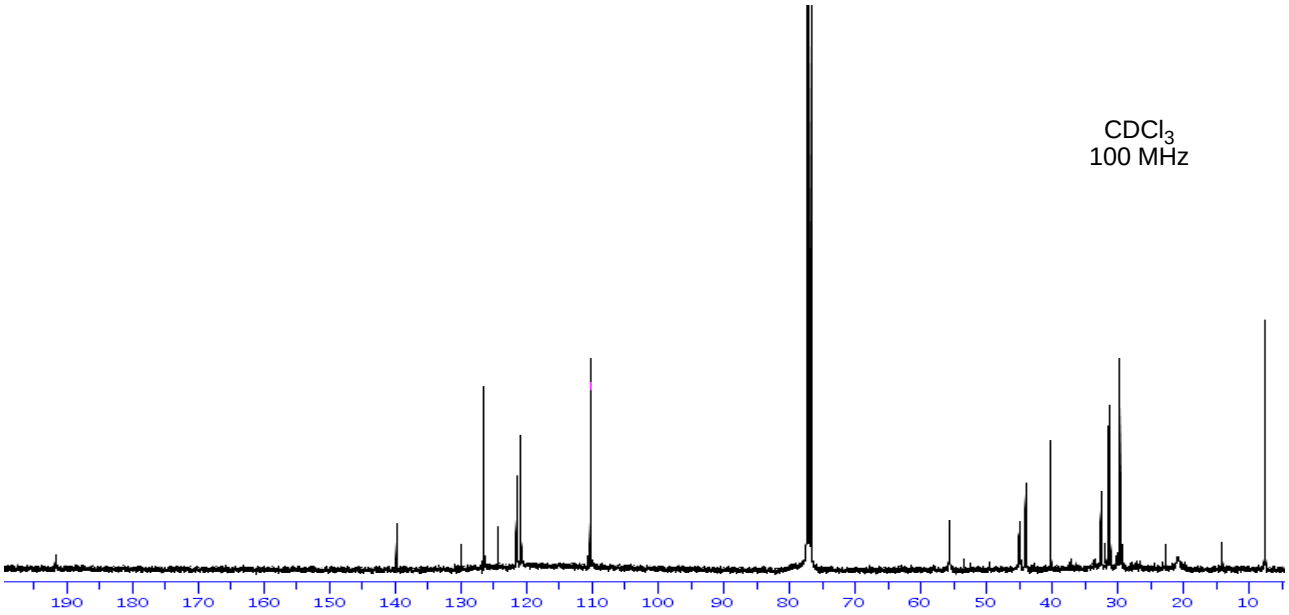


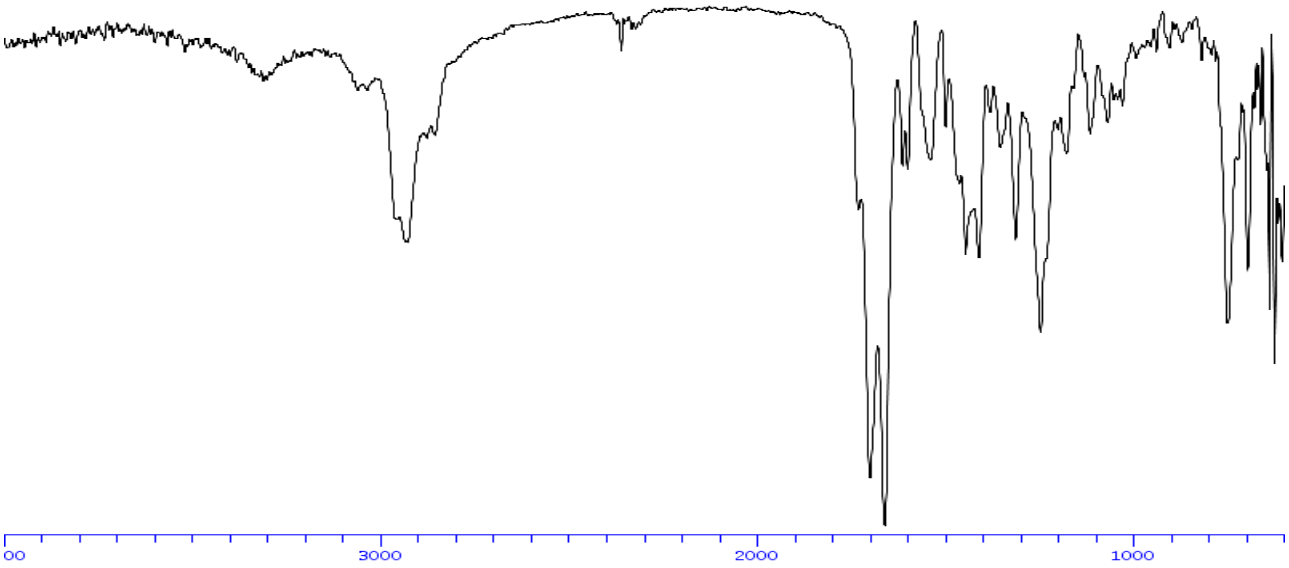
13

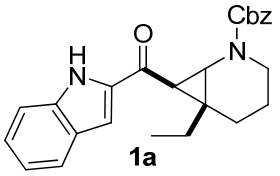
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

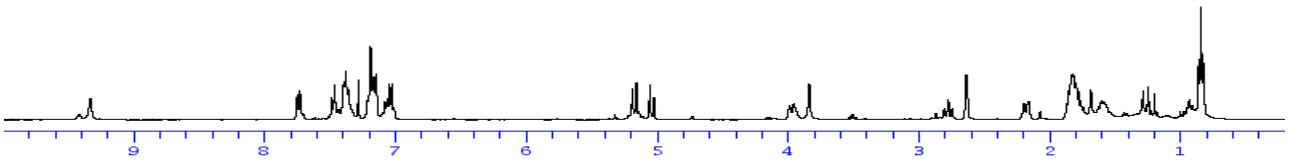






1a

$CDCl_3$
400 MHz



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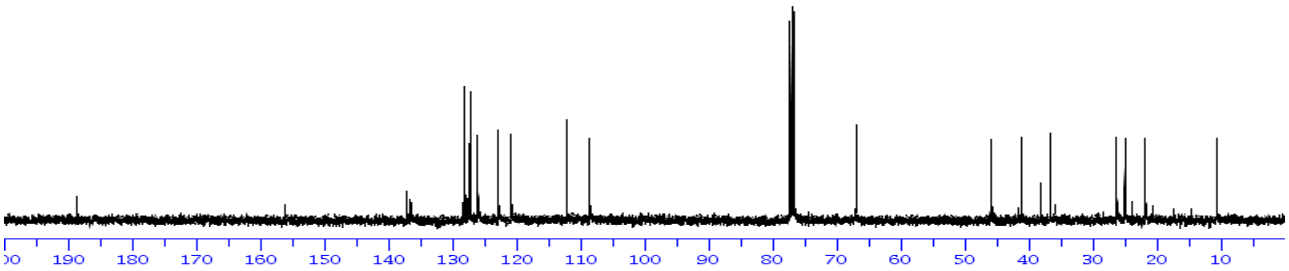

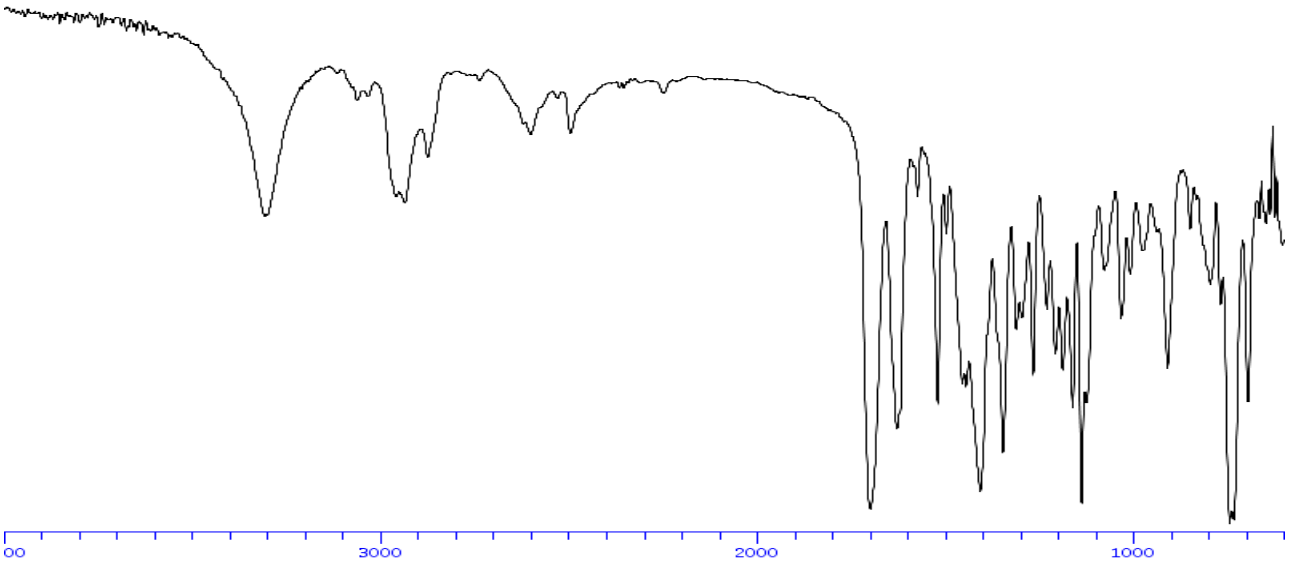

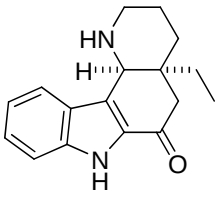

25a

CD_3OD
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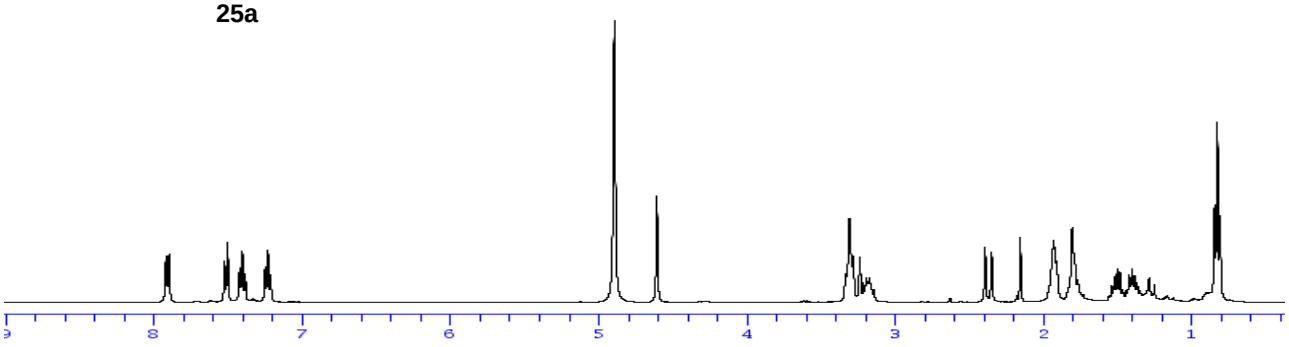
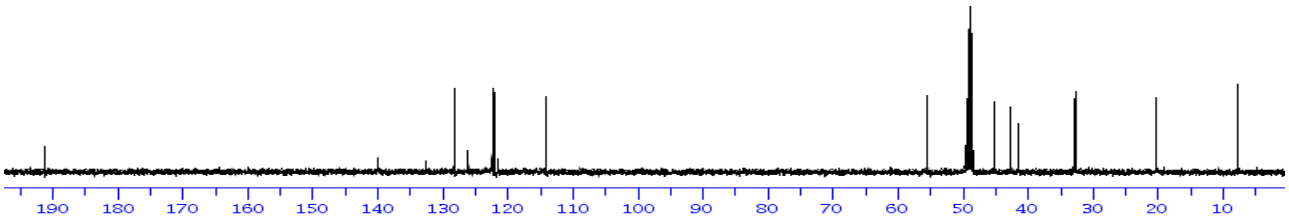
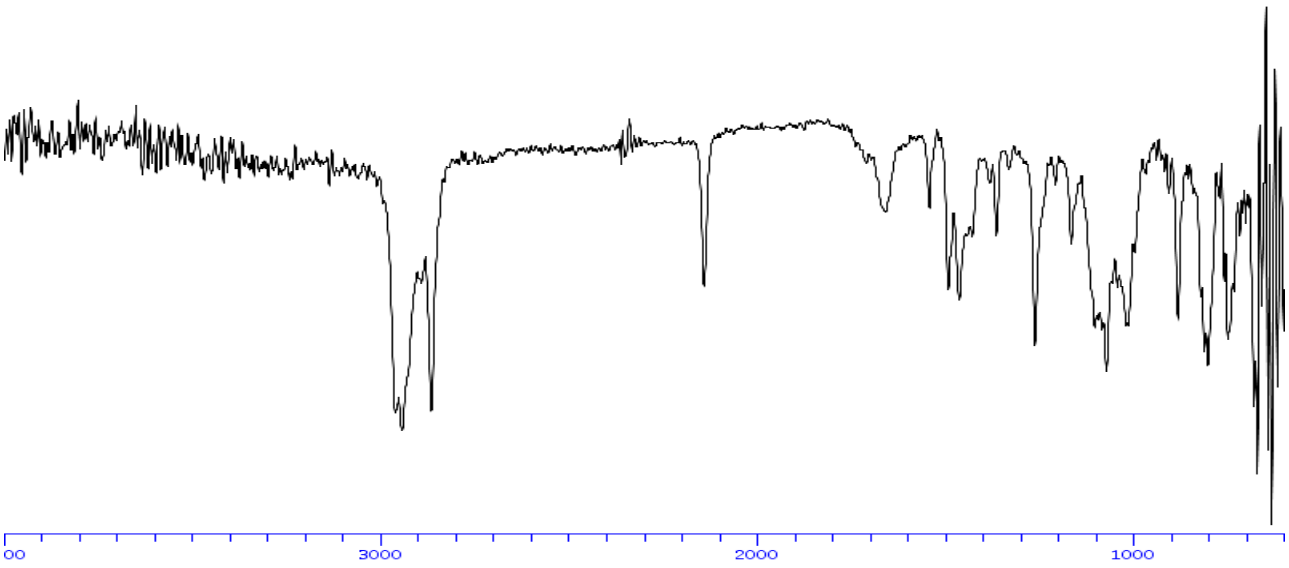






Crystallographic data

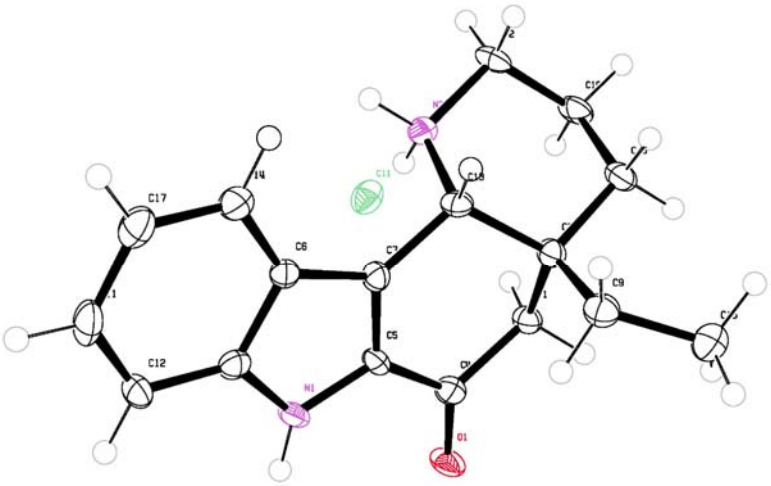


Table 1. Crystal data and structure refinement for fds330.

Identification code	fds330	
Empirical formula	C17 H21 Cl N2 O	
Formula weight	304.81	
Temperature	140(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 9.1506(10) Å	α= 90°.
	b = 15.3882(14) Å	β= 103.618(12)°.
	c = 10.9477(12) Å	γ = 90°.
Volume	1498.2(3) Å^3	
Z	4	
Density (calculated)	1.351 Mg/m^3	
Absorption coefficient	0.256 mm^{-1}	
F(000)	648	
Crystal size	0.15 x 0.11 x 0.09 mm^3	
Theta range for data collection	2.93 to 26.37°.	
Index ranges	-11<=h<=11, -19<=k<=19, -13<=l<=13	
Reflections collected	13092	
Independent reflections	3040 [R(int) = 0.0708]	
Completeness to theta = 26.37°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.92803	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3040 / 0 / 274	

Goodness-of-fit on F^2	0.967
Final R indices [I>2sigma(I)]	R1 = 0.0546, wR2 = 0.0992
R indices (all data)	R1 = 0.1022, wR2 = 0.1112
Largest diff. peak and hole	0.380 and -0.237 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for fds330. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	2806(1)	4005(1)	4618(1)	27(1)
O(1)	-709(2)	5221(1)	1532(2)	28(1)
N(1)	3748(3)	5933(2)	4836(2)	19(1)
N(2)	2019(3)	5647(2)	754(2)	20(1)
C(1)	2842(3)	6581(2)	3930(2)	17(1)
C(2)	3758(3)	6081(2)	6187(3)	23(1)
C(3)	2167(3)	6082(2)	6324(3)	24(1)
C(4)	1247(3)	6764(2)	5501(3)	21(1)
C(5)	1213(3)	6668(2)	4094(2)	18(1)
C(6)	273(3)	5867(2)	3555(2)	18(1)
C(7)	317(3)	5612(2)	2231(2)	20(1)
C(8)	1700(3)	5838(2)	1889(2)	17(1)
C(9)	2867(3)	6294(2)	2628(2)	17(1)
C(10)	3988(3)	6389(2)	1933(2)	17(1)
C(11)	3410(3)	5976(2)	759(2)	18(1)
C(12)	4208(3)	5956(2)	-184(3)	23(1)
C(13)	5577(3)	6356(2)	69(3)	27(1)
C(14)	6179(3)	6768(2)	1222(3)	26(1)
C(15)	5402(3)	6784(2)	2151(3)	22(1)
C(16)	521(3)	7495(2)	3402(3)	23(1)
C(17)	-898(3)	7839(2)	3712(3)	28(1)

Table 3. Bond lengths [Å] and angles [°] for fds330.

O(1)-C(7)	1.221(3)
N(1)-C(2)	1.495(3)
N(1)-C(1)	1.510(3)
N(1)-H(1A)	0.91(3)
N(1)-H(1B)	0.95(3)
N(2)-C(11)	1.369(3)

N(2)-C(8)	1.373(3)
N(2)-H(2)	0.88(3)
C(1)-C(9)	1.497(4)
C(1)-C(5)	1.548(3)
C(1)-H(1)	1.00(2)
C(2)-C(3)	1.498(4)
C(2)-H(2A)	0.94(3)
C(2)-H(2B)	0.93(3)
C(3)-C(4)	1.504(4)
C(3)-H(3A)	0.88(3)
C(3)-H(3B)	1.00(2)
C(4)-C(5)	1.541(4)
C(4)-H(4A)	0.98(2)
C(4)-H(4B)	0.96(3)
C(5)-C(16)	1.539(4)
C(5)-C(6)	1.540(4)
C(6)-C(7)	1.511(4)
C(6)-H(6A)	0.97(3)
C(6)-H(6B)	0.97(3)
C(7)-C(8)	1.444(4)
C(8)-C(9)	1.371(3)
C(9)-C(10)	1.422(4)
C(10)-C(15)	1.398(4)
C(10)-C(11)	1.420(4)
C(11)-C(12)	1.398(4)
C(12)-C(13)	1.364(4)
C(12)-H(12)	0.94(2)
C(13)-C(14)	1.404(4)
C(13)-H(13)	0.84(3)
C(14)-C(15)	1.371(4)
C(14)-H(14)	0.93(3)
C(15)-H(15)	0.99(3)
C(16)-C(17)	1.513(4)
C(16)-H(16A)	0.96(3)
C(16)-H(16B)	0.95(3)
C(17)-H(17A)	0.92(3)
C(17)-H(17B)	0.95(3)
C(17)-H(17C)	0.96(3)

C(2)-N(1)-C(1)	115.0(2)
C(2)-N(1)-H(1A)	104.3(15)

C(1)-N(1)-H(1A)	112.1(16)
C(2)-N(1)-H(1B)	106.6(19)
C(1)-N(1)-H(1B)	108.9(19)
H(1A)-N(1)-H(1B)	110(2)
C(11)-N(2)-C(8)	108.3(2)
C(11)-N(2)-H(2)	123(2)
C(8)-N(2)-H(2)	129(2)
C(9)-C(1)-N(1)	107.5(2)
C(9)-C(1)-C(5)	111.5(2)
N(1)-C(1)-C(5)	112.1(2)
C(9)-C(1)-H(1)	108.7(12)
N(1)-C(1)-H(1)	104.7(12)
C(5)-C(1)-H(1)	111.9(12)
N(1)-C(2)-C(3)	108.6(2)
N(1)-C(2)-H(2A)	105.5(15)
C(3)-C(2)-H(2A)	111.8(15)
N(1)-C(2)-H(2B)	103.2(15)
C(3)-C(2)-H(2B)	111.5(16)
H(2A)-C(2)-H(2B)	115(2)
C(2)-C(3)-C(4)	111.1(2)
C(2)-C(3)-H(3A)	105(2)
C(4)-C(3)-H(3A)	109.8(19)
C(2)-C(3)-H(3B)	107.9(14)
C(4)-C(3)-H(3B)	110.2(14)
H(3A)-C(3)-H(3B)	113(2)
C(3)-C(4)-C(5)	114.1(2)
C(3)-C(4)-H(4A)	109.8(13)
C(5)-C(4)-H(4A)	106.3(13)
C(3)-C(4)-H(4B)	107.8(16)
C(5)-C(4)-H(4B)	110.4(16)
H(4A)-C(4)-H(4B)	108(2)
C(16)-C(5)-C(6)	110.2(2)
C(16)-C(5)-C(4)	108.8(2)
C(6)-C(5)-C(4)	109.7(2)
C(16)-C(5)-C(1)	108.1(2)
C(6)-C(5)-C(1)	110.6(2)
C(4)-C(5)-C(1)	109.4(2)
C(7)-C(6)-C(5)	115.9(2)
C(7)-C(6)-H(6A)	103.7(14)
C(5)-C(6)-H(6A)	109.9(14)
C(7)-C(6)-H(6B)	109.7(14)

C(5)-C(6)-H(6B)	105.7(14)
H(6A)-C(6)-H(6B)	112(2)
O(1)-C(7)-C(8)	123.2(2)
O(1)-C(7)-C(6)	122.6(2)
C(8)-C(7)-C(6)	114.2(2)
C(9)-C(8)-N(2)	110.0(2)
C(9)-C(8)-C(7)	125.3(2)
N(2)-C(8)-C(7)	124.7(2)
C(8)-C(9)-C(10)	107.2(2)
C(8)-C(9)-C(1)	121.9(2)
C(10)-C(9)-C(1)	130.8(2)
C(15)-C(10)-C(11)	118.8(2)
C(15)-C(10)-C(9)	135.2(3)
C(11)-C(10)-C(9)	106.1(2)
N(2)-C(11)-C(12)	129.5(3)
N(2)-C(11)-C(10)	108.4(2)
C(12)-C(11)-C(10)	122.0(2)
C(13)-C(12)-C(11)	117.0(3)
C(13)-C(12)-H(12)	123.9(15)
C(11)-C(12)-H(12)	119.0(15)
C(12)-C(13)-C(14)	122.2(3)
C(12)-C(13)-H(13)	120.3(18)
C(14)-C(13)-H(13)	117.4(18)
C(15)-C(14)-C(13)	120.8(3)
C(15)-C(14)-H(14)	117.9(17)
C(13)-C(14)-H(14)	121.3(17)
C(14)-C(15)-C(10)	119.1(3)
C(14)-C(15)-H(15)	121.5(15)
C(10)-C(15)-H(15)	119.3(15)
C(17)-C(16)-C(5)	117.0(3)
C(17)-C(16)-H(16A)	106.6(16)
C(5)-C(16)-H(16A)	110.0(16)
C(17)-C(16)-H(16B)	109.6(17)
C(5)-C(16)-H(16B)	109.2(16)
H(16A)-C(16)-H(16B)	104(2)
C(16)-C(17)-H(17A)	109.4(17)
C(16)-C(17)-H(17B)	111.3(17)
H(17A)-C(17)-H(17B)	110(2)
C(16)-C(17)-H(17C)	110.1(17)
H(17A)-C(17)-H(17C)	108(2)
H(17B)-C(17)-H(17C)	108(2)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for fds330. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	20(1)	26(1)	35(1)	-2(1)	7(1)	-2(1)
O(1)	19(1)	45(1)	18(1)	-11(1)	3(1)	-12(1)
N(1)	17(1)	22(1)	17(1)	-1(1)	2(1)	-1(1)
N(2)	18(1)	31(1)	12(1)	-5(1)	3(1)	-4(1)
C(1)	15(1)	18(1)	16(2)	-2(1)	2(1)	-5(1)
C(2)	29(2)	26(2)	12(2)	-2(1)	1(1)	-2(1)
C(3)	26(2)	34(2)	11(2)	-2(1)	4(1)	-4(1)
C(4)	20(2)	26(2)	17(2)	-6(1)	6(1)	-6(1)
C(5)	16(1)	23(1)	17(2)	-3(1)	5(1)	-2(1)
C(6)	16(2)	22(2)	17(2)	-1(1)	5(1)	-2(1)
C(7)	21(2)	24(1)	15(2)	1(1)	4(1)	1(1)
C(8)	19(1)	23(1)	10(1)	-1(1)	4(1)	-1(1)
C(9)	17(1)	21(1)	14(1)	1(1)	6(1)	1(1)
C(10)	17(1)	20(1)	15(1)	4(1)	3(1)	4(1)
C(11)	17(1)	20(1)	17(1)	3(1)	1(1)	4(1)
C(12)	25(2)	30(2)	15(2)	1(1)	7(1)	5(1)
C(13)	24(2)	34(2)	28(2)	6(1)	18(2)	7(1)
C(14)	19(2)	31(2)	29(2)	4(1)	9(1)	-1(1)
C(15)	17(2)	26(2)	21(2)	0(1)	4(1)	-1(1)
C(16)	24(2)	23(2)	22(2)	-1(1)	5(1)	-3(1)
C(17)	23(2)	31(2)	29(2)	-1(2)	7(2)	1(2)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^{\ 3}$) for fds330.

	x	y	z	U(eq)
H(1A)	3400(30)	5384(17)	4680(20)	10(6)
H(1B)	4760(40)	5960(20)	4780(30)	50(10)
H(2)	1480(30)	5340(20)	120(30)	40(10)
H(1)	3410(20)	7140(14)	4114(19)	0(5)

H(2A)	4220(30)	6627(17)	6390(20)	17(7)
H(2B)	4290(30)	5608(17)	6590(20)	15(7)
H(3A)	2230(30)	6205(18)	7120(30)	33(9)
H(3B)	1730(30)	5493(17)	6090(20)	12(6)
H(4A)	1660(30)	7341(16)	5750(20)	9(6)
H(4B)	250(30)	6741(17)	5630(20)	23(7)
H(6A)	660(30)	5355(17)	4050(20)	14(7)
H(6B)	-750(30)	6003(16)	3590(20)	16(7)
H(12)	3810(30)	5644(16)	-930(20)	13(7)
H(13)	6110(30)	6345(16)	-460(20)	15(7)
H(14)	7100(30)	7047(18)	1370(30)	28(8)
H(15)	5840(30)	7044(16)	2990(20)	20(7)
H(16A)	1240(30)	7961(18)	3560(20)	28(8)
H(16B)	350(30)	7405(16)	2520(30)	24(8)
H(17A)	-1560(30)	7390(17)	3700(20)	21(8)
H(17B)	-1360(30)	8270(19)	3130(30)	28(8)
H(17C)	-670(30)	8095(18)	4530(30)	26(8)

Table 6. Torsion angles [°] for fds330.

C(2)-N(1)-C(1)-C(9)	-175.9(2)
C(2)-N(1)-C(1)-C(5)	-52.9(3)
C(1)-N(1)-C(2)-C(3)	57.1(3)
N(1)-C(2)-C(3)-C(4)	-57.6(3)
C(2)-C(3)-C(4)-C(5)	57.6(3)
C(3)-C(4)-C(5)-C(16)	-168.6(2)
C(3)-C(4)-C(5)-C(6)	70.7(3)
C(3)-C(4)-C(5)-C(1)	-50.8(3)
C(9)-C(1)-C(5)-C(16)	-74.1(3)
N(1)-C(1)-C(5)-C(16)	165.3(2)
C(9)-C(1)-C(5)-C(6)	46.6(3)
N(1)-C(1)-C(5)-C(6)	-74.0(3)
C(9)-C(1)-C(5)-C(4)	167.5(2)
N(1)-C(1)-C(5)-C(4)	46.9(3)
C(16)-C(5)-C(6)-C(7)	68.6(3)
C(4)-C(5)-C(6)-C(7)	-171.6(2)
C(1)-C(5)-C(6)-C(7)	-50.9(3)
C(5)-C(6)-C(7)-O(1)	-153.3(3)
C(5)-C(6)-C(7)-C(8)	29.2(3)
C(11)-N(2)-C(8)-C(9)	0.5(3)

C(11)-N(2)-C(8)-C(7)	178.7(2)
O(1)-C(7)-C(8)-C(9)	178.3(3)
C(6)-C(7)-C(8)-C(9)	-4.2(4)
O(1)-C(7)-C(8)-N(2)	0.3(4)
C(6)-C(7)-C(8)-N(2)	177.8(2)
N(2)-C(8)-C(9)-C(10)	-0.6(3)
C(7)-C(8)-C(9)-C(10)	-178.9(2)
N(2)-C(8)-C(9)-C(1)	-179.2(2)
C(7)-C(8)-C(9)-C(1)	2.6(4)
N(1)-C(1)-C(9)-C(8)	98.6(3)
C(5)-C(1)-C(9)-C(8)	-24.6(3)
N(1)-C(1)-C(9)-C(10)	-79.6(3)
C(5)-C(1)-C(9)-C(10)	157.2(3)
C(8)-C(9)-C(10)-C(15)	179.4(3)
C(1)-C(9)-C(10)-C(15)	-2.2(5)
C(8)-C(9)-C(10)-C(11)	0.5(3)
C(1)-C(9)-C(10)-C(11)	178.9(2)
C(8)-N(2)-C(11)-C(12)	-179.1(3)
C(8)-N(2)-C(11)-C(10)	-0.1(3)
C(15)-C(10)-C(11)-N(2)	-179.4(2)
C(9)-C(10)-C(11)-N(2)	-0.3(3)
C(15)-C(10)-C(11)-C(12)	-0.3(4)
C(9)-C(10)-C(11)-C(12)	178.8(2)
N(2)-C(11)-C(12)-C(13)	178.7(3)
C(10)-C(11)-C(12)-C(13)	-0.2(4)
C(11)-C(12)-C(13)-C(14)	0.4(4)
C(12)-C(13)-C(14)-C(15)	0.0(4)
C(13)-C(14)-C(15)-C(10)	-0.5(4)
C(11)-C(10)-C(15)-C(14)	0.7(4)
C(9)-C(10)-C(15)-C(14)	-178.2(3)
C(6)-C(5)-C(16)-C(17)	74.6(3)
C(4)-C(5)-C(16)-C(17)	-45.7(3)
C(1)-C(5)-C(16)-C(17)	-164.4(3)

Symmetry transformations used to generate equivalent atoms:

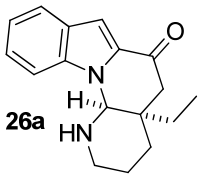
Table 7. Hydrogen bonds for fds330 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1A)...Cl(1)	0.91(3)	2.19(3)	3.082(3)	170(2)

N(1)-H(1B)...Cl(1)#1	0.95(3)	2.17(3)	3.069(2)	159(3)
N(2)-H(2)...O(1)#2	0.88(3)	1.98(3)	2.841(3)	164(3)

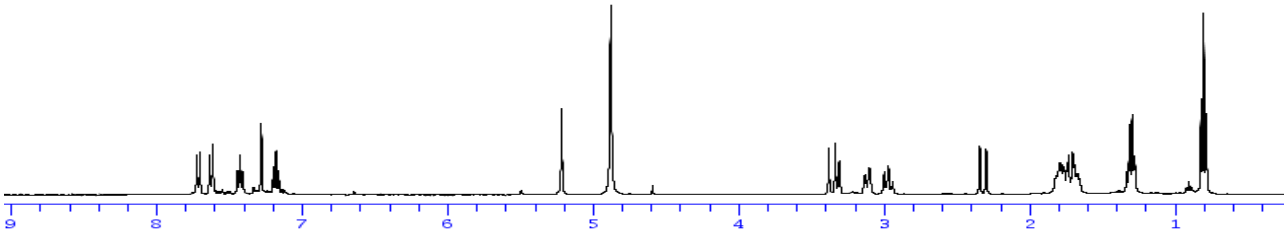
Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+1,-z+1 #2 -x,-y+1,-z

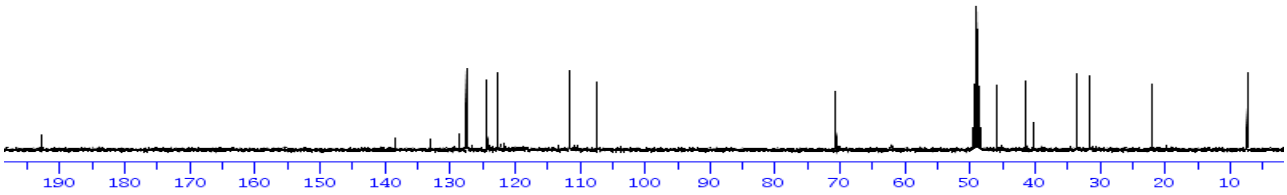


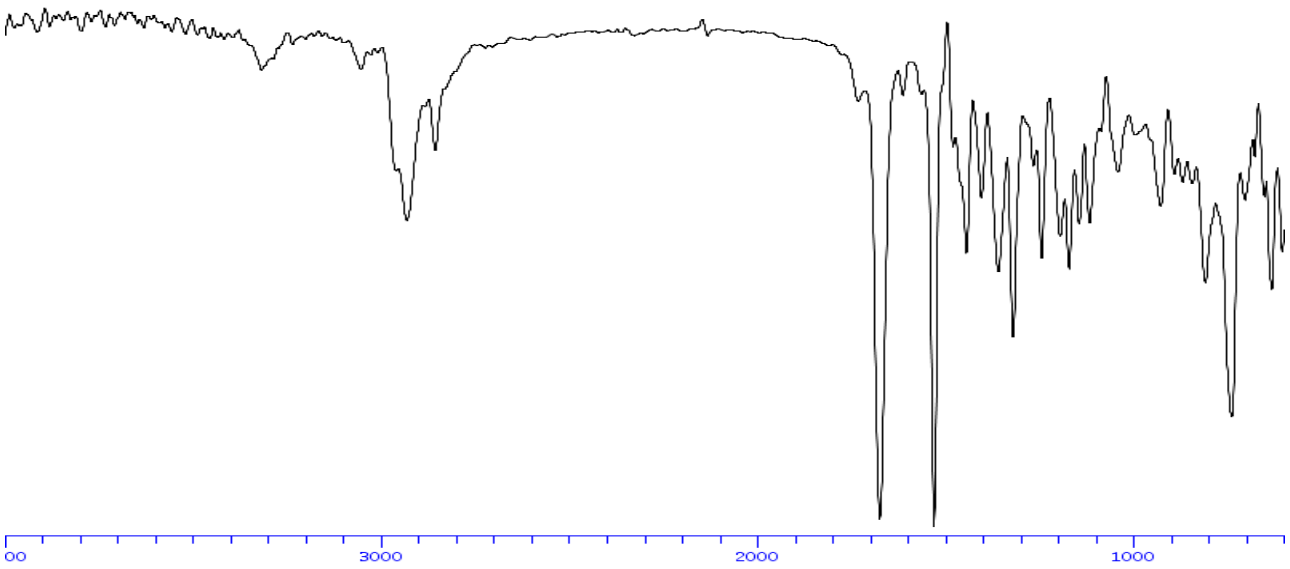
26a

CD_3OD
400 MHz

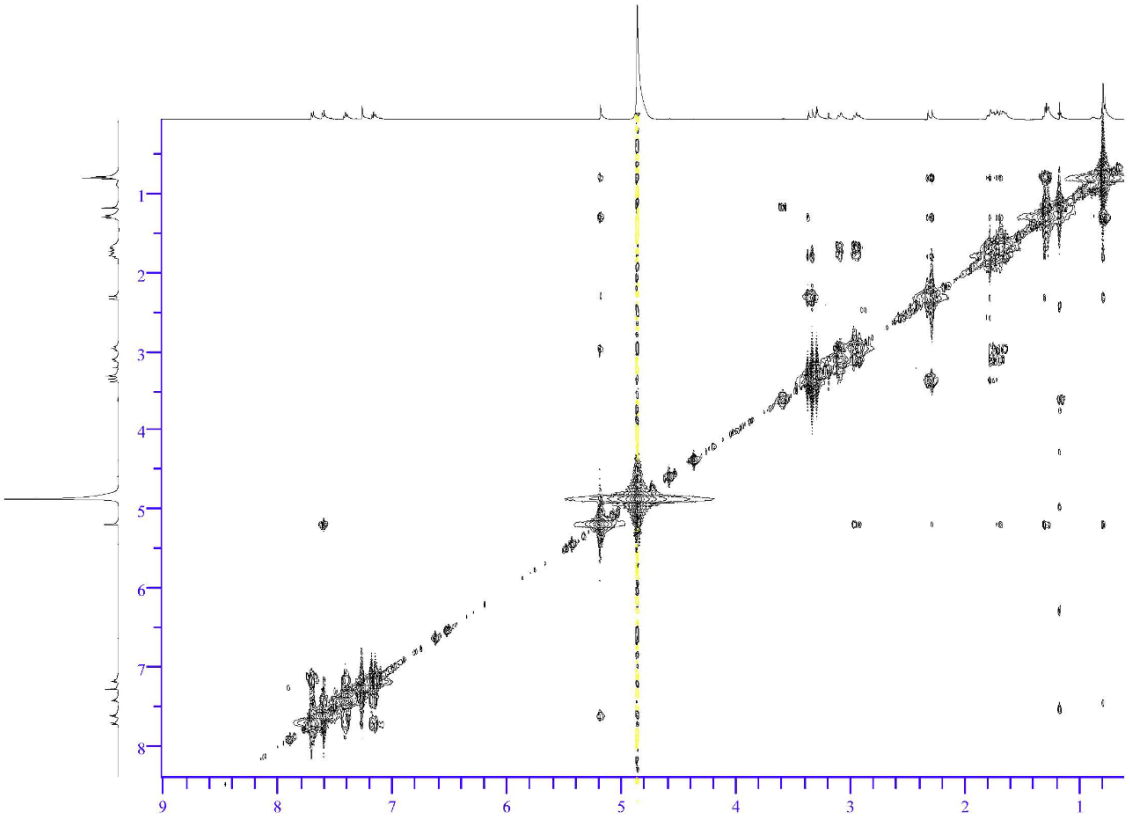


CD_3OD
125 MHz

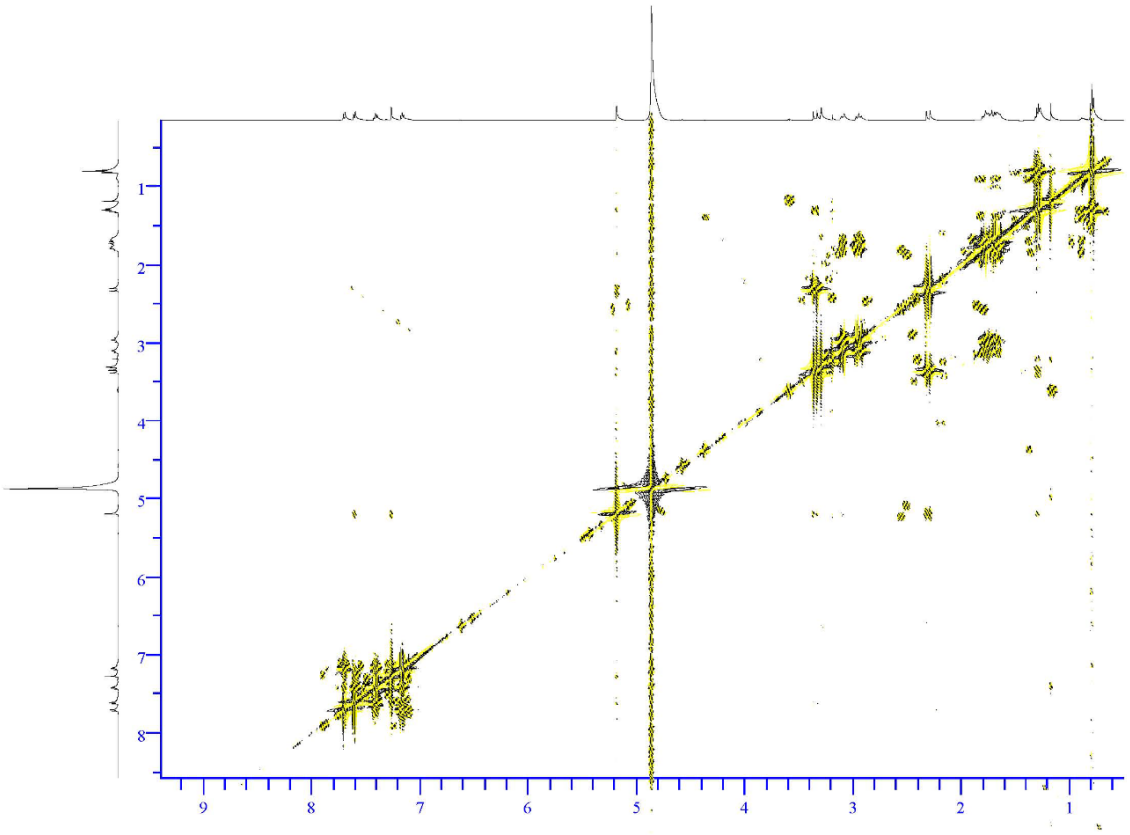


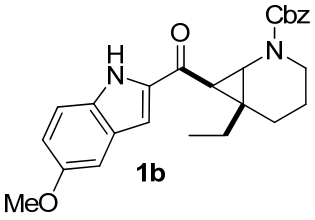


NOESY



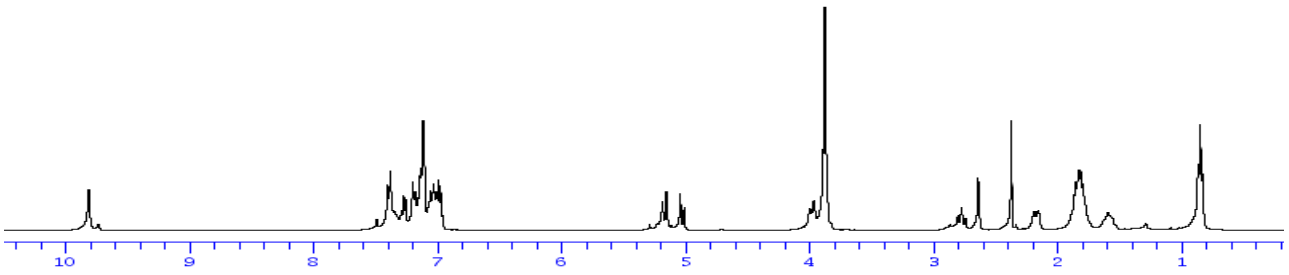
COSY



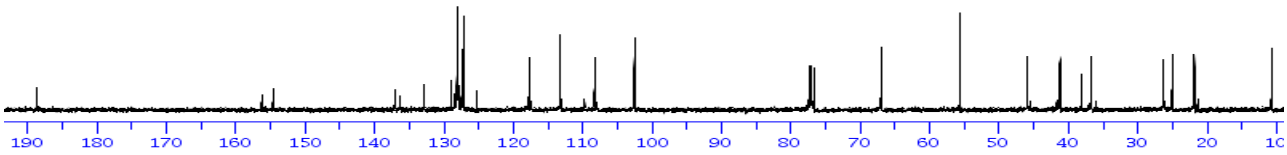


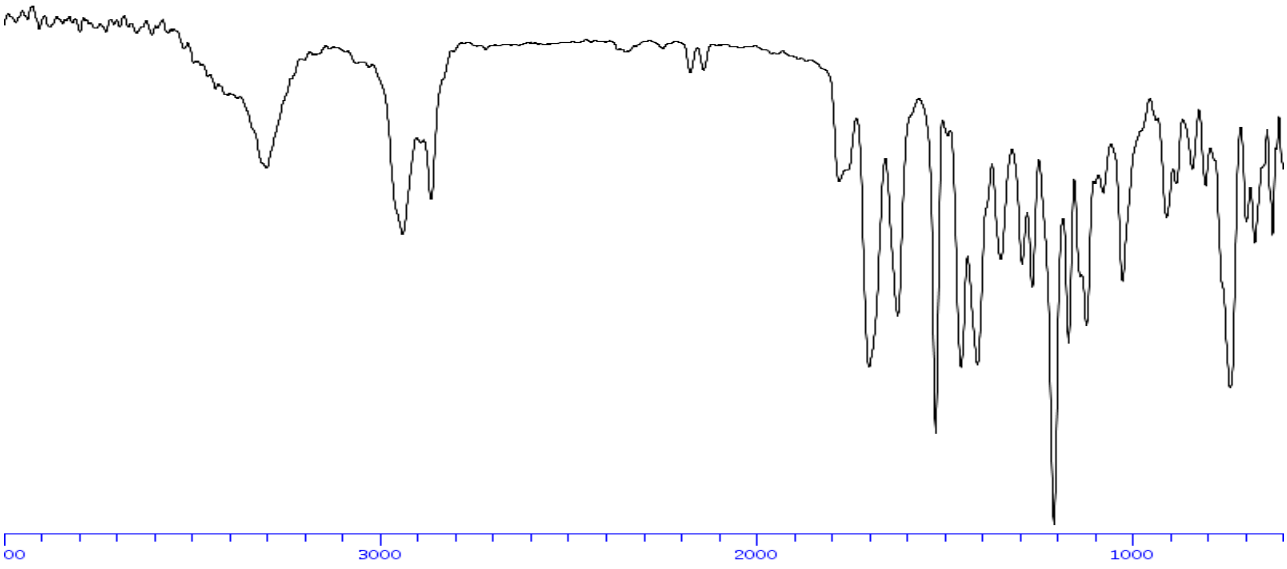
1b

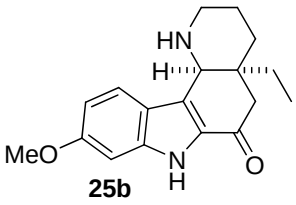
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

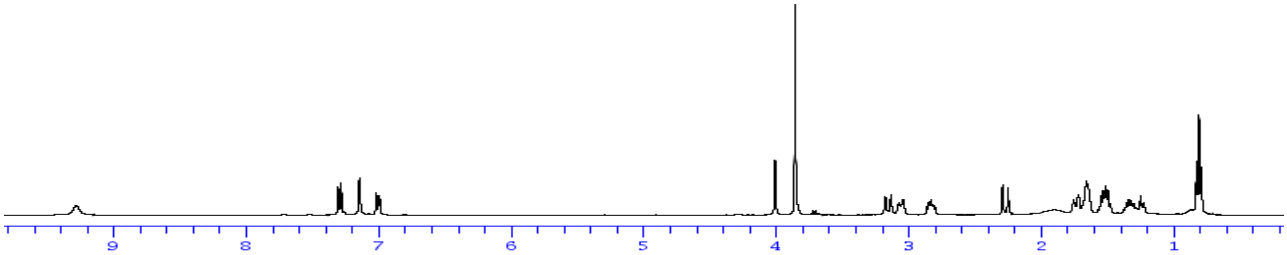




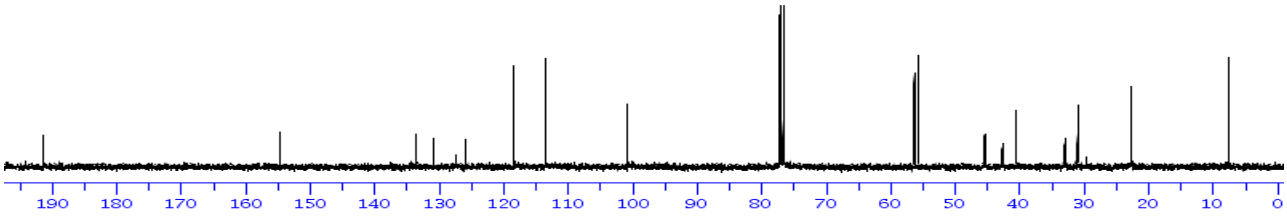


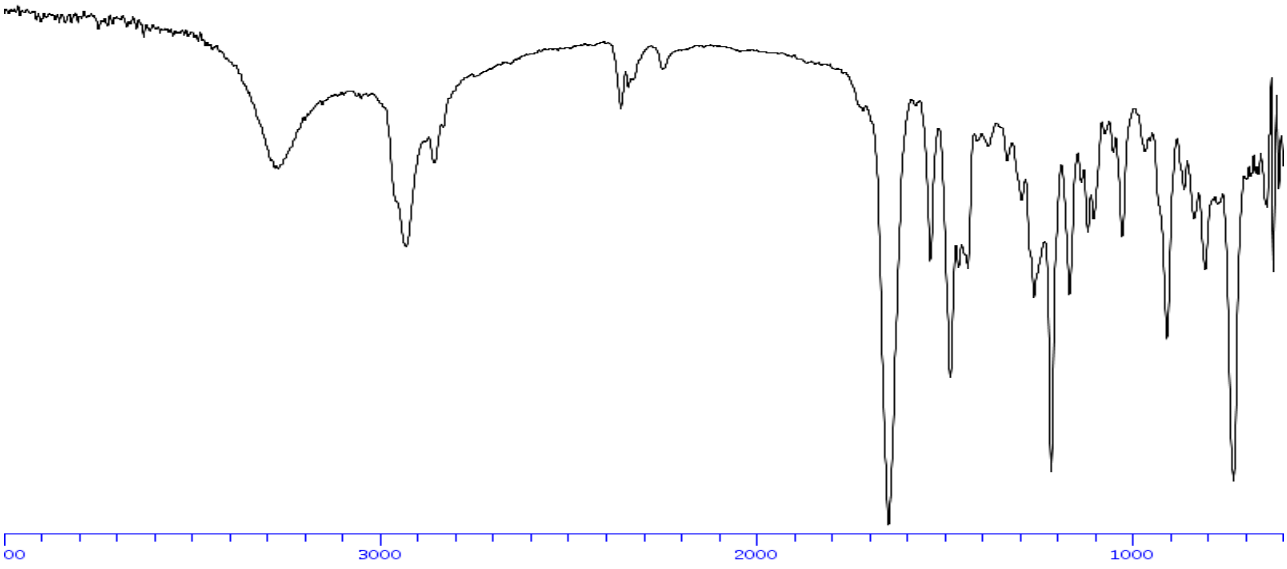
25b

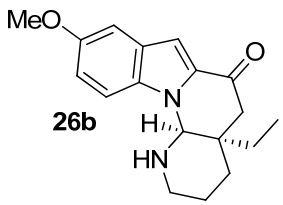
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

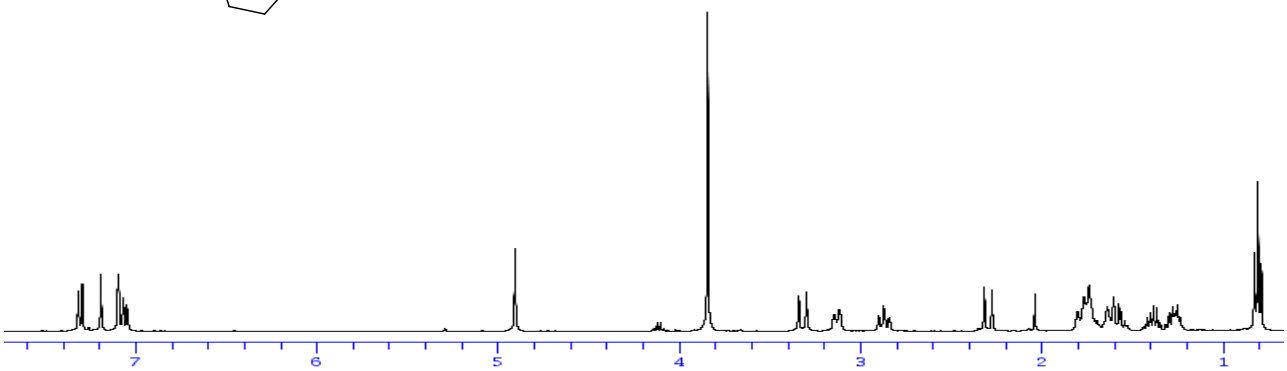




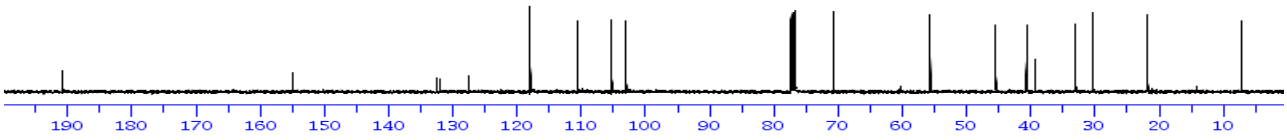


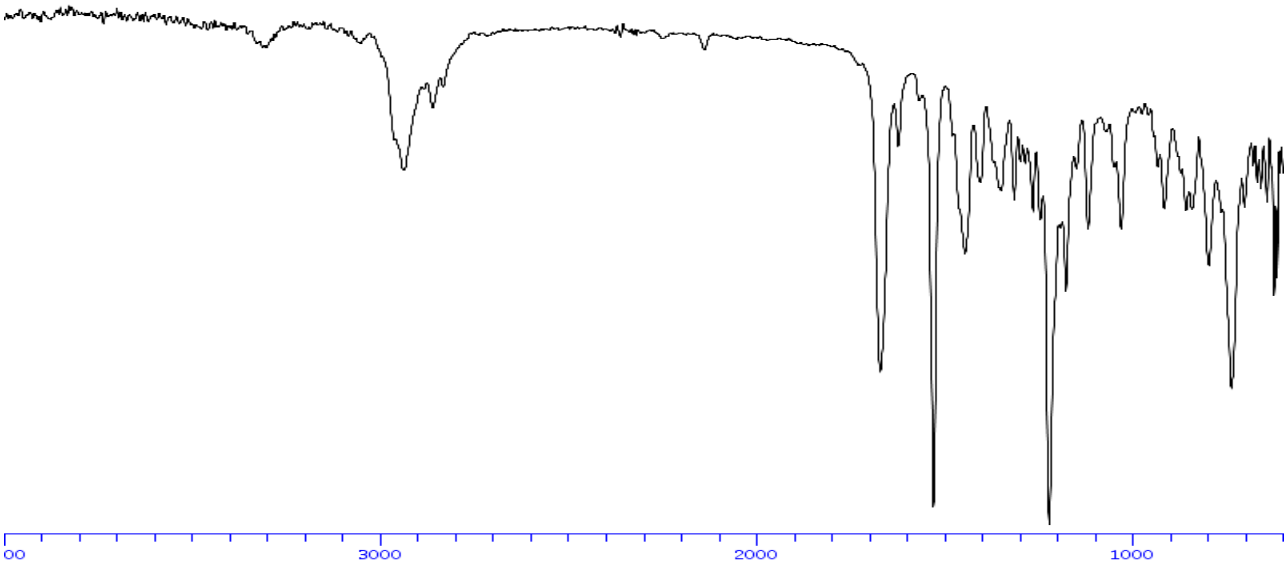
26b

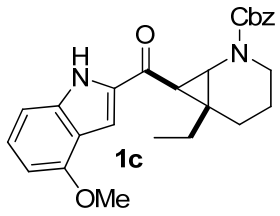
$CDCl_3$
400 MHz



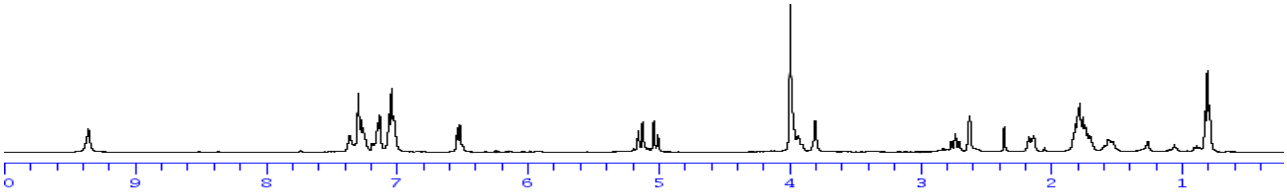
$CDCl_3$
100 MHz



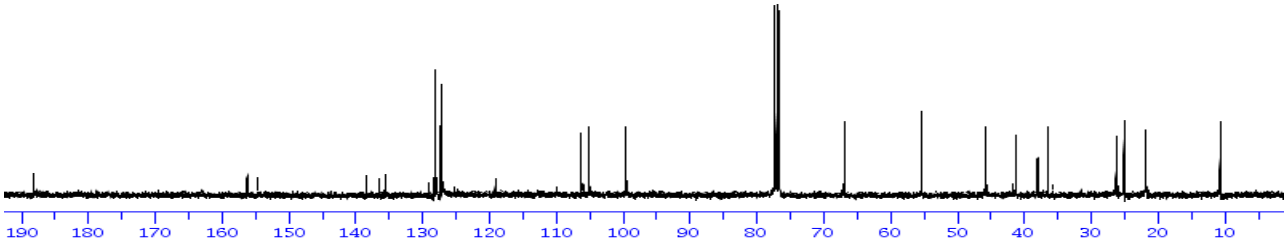


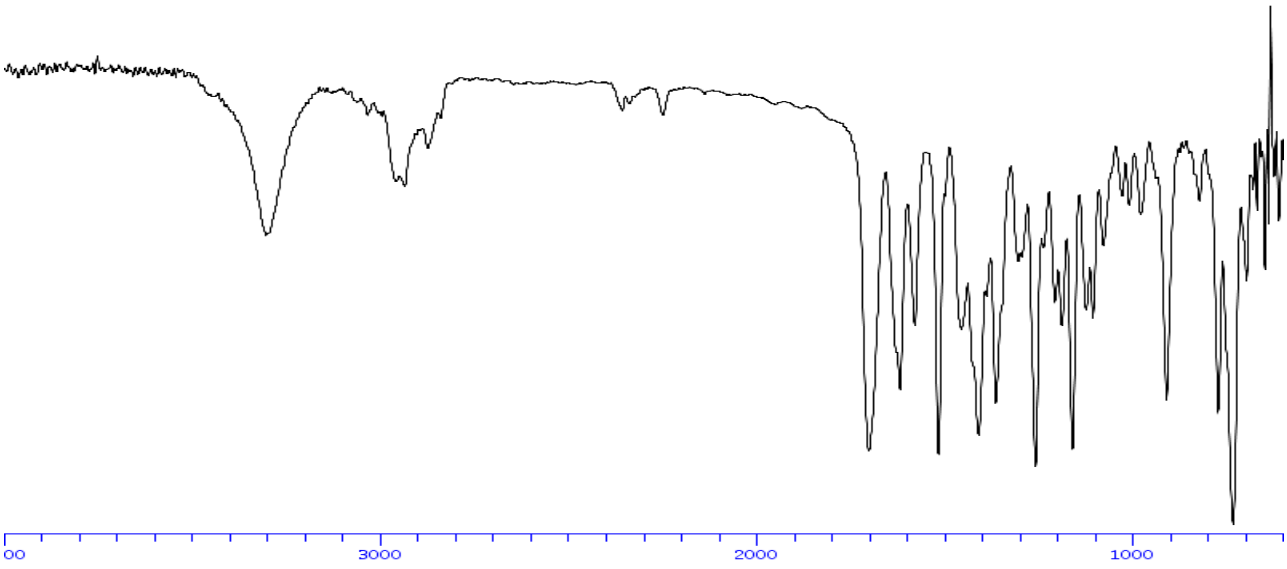


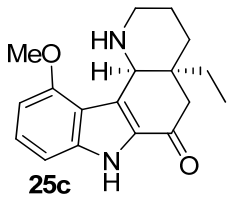
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz

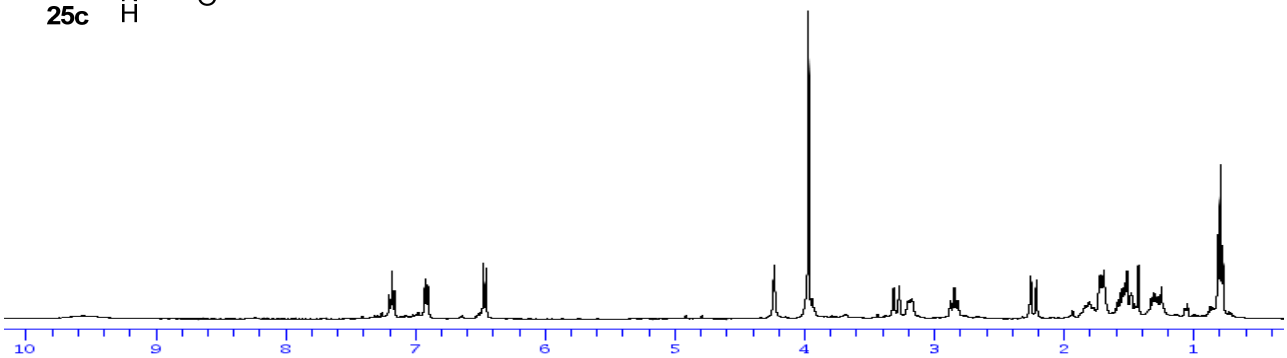




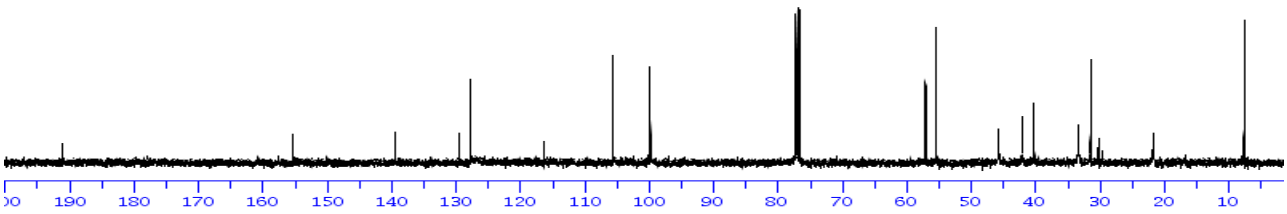


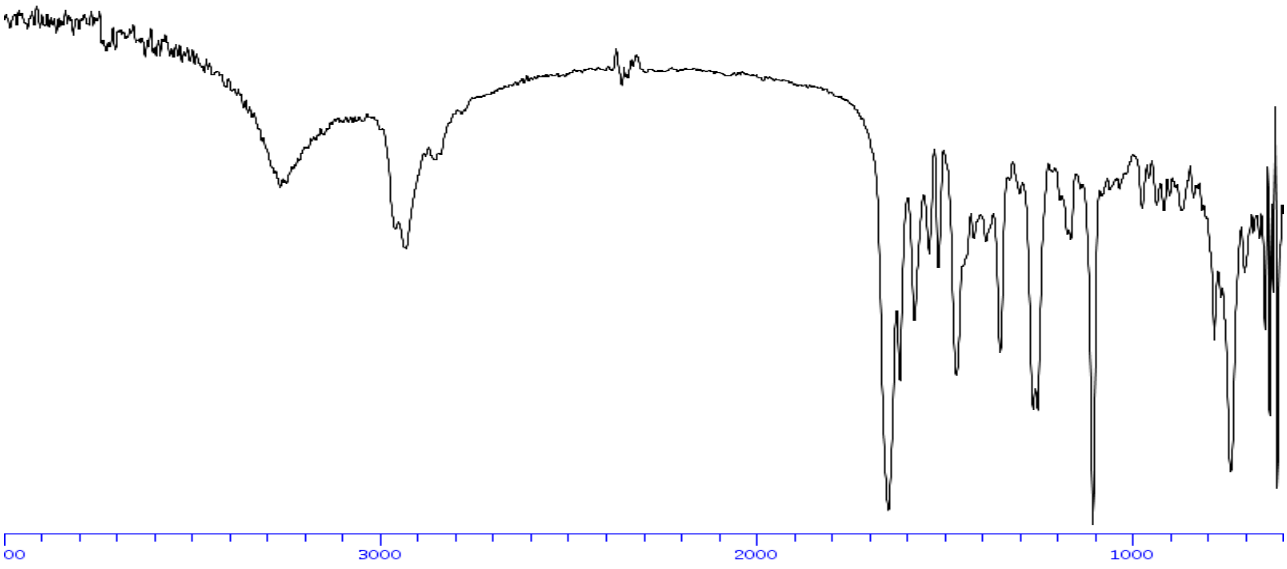
25c

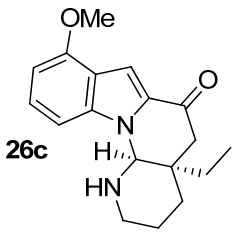
$CDCl_3$
400 MHz



$CDCl_3$
100 MHz



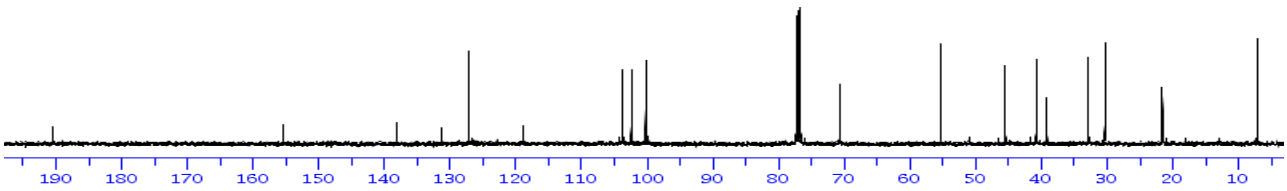


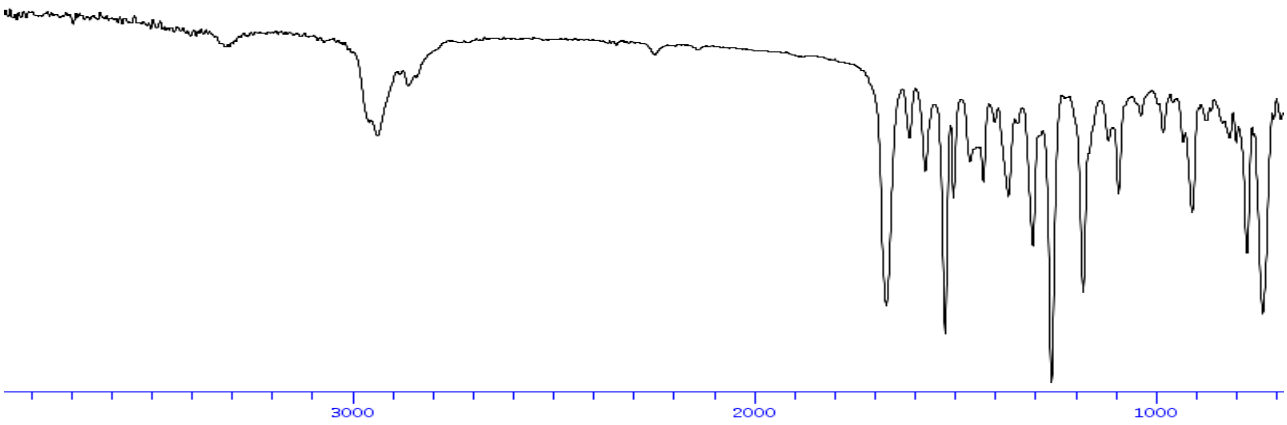


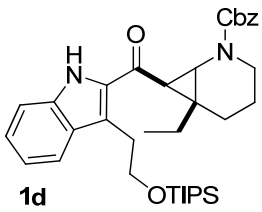
26c

$CDCl_3$
400 MHz

$CDCl_3$
100 MHz

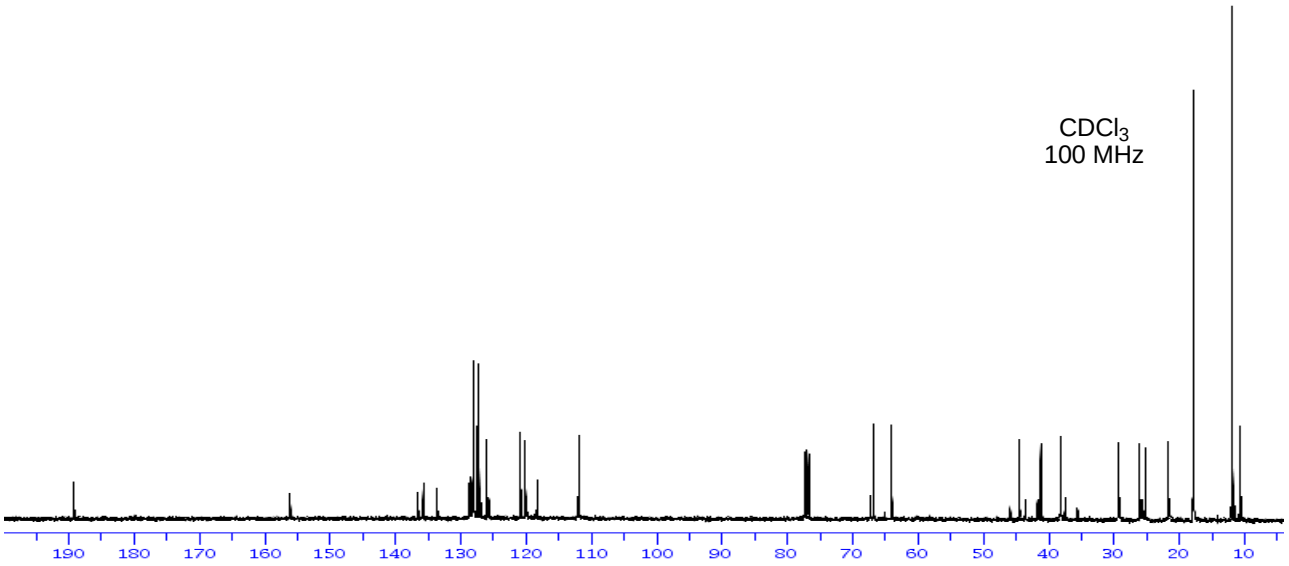


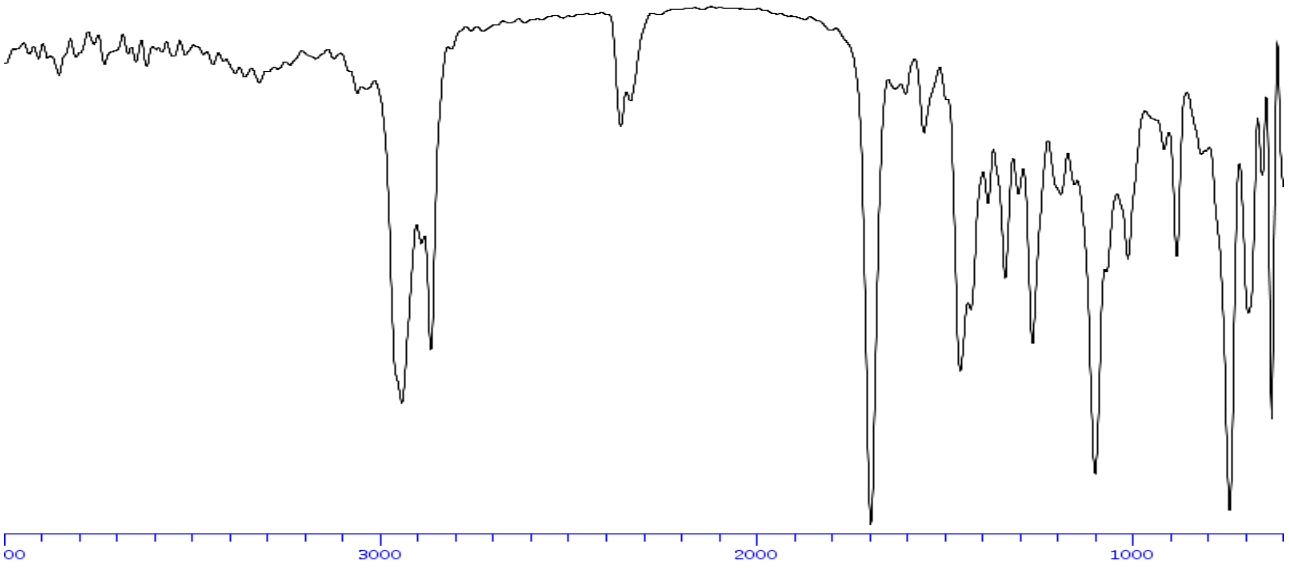


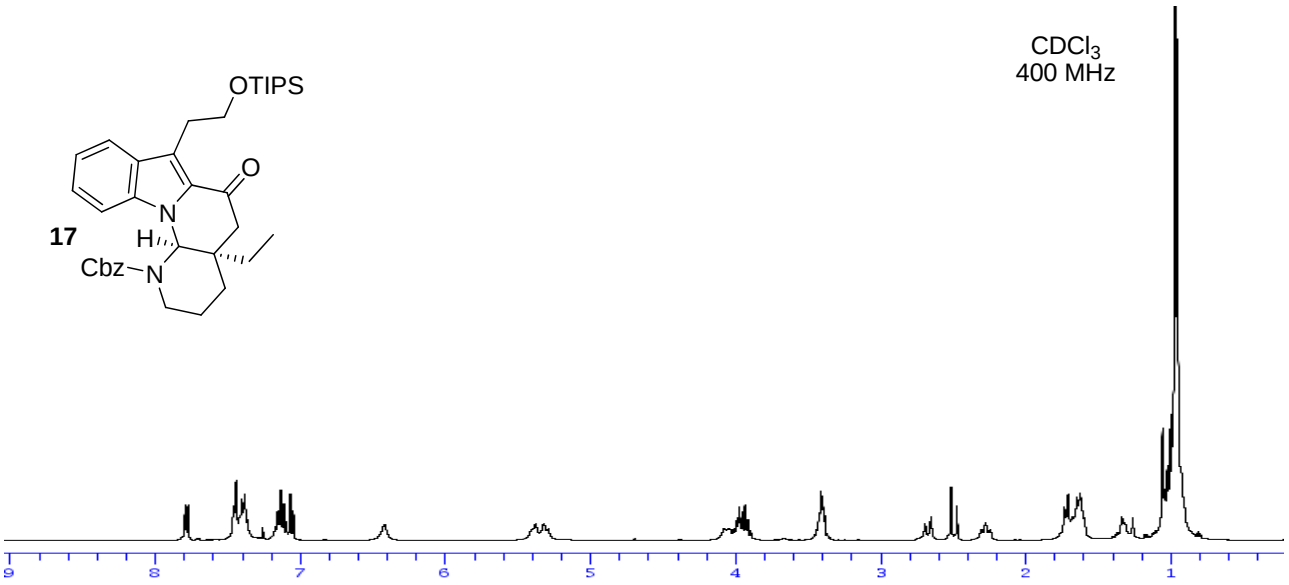


1d

$CDCl_3$
400 MHz

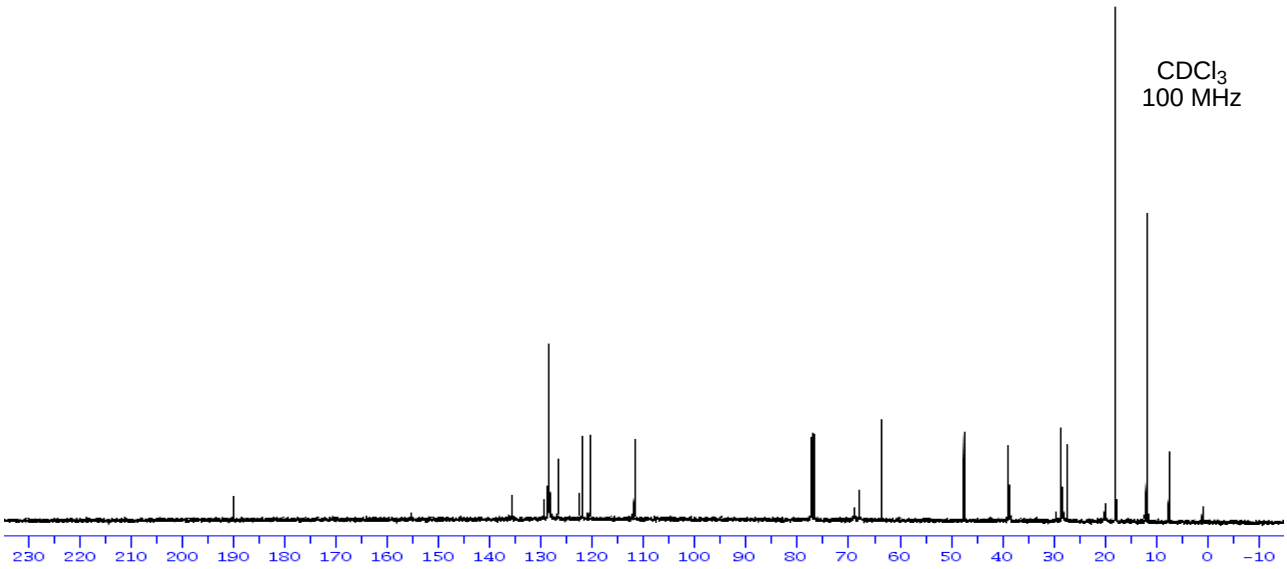

CDCl3
100 MHz
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10

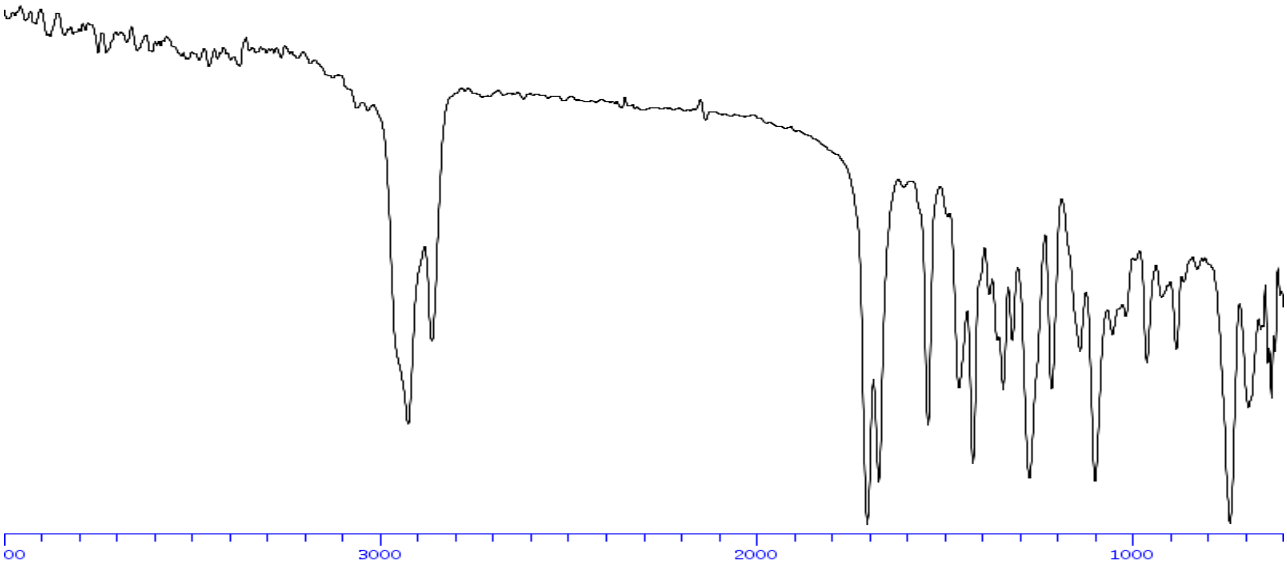

00 3000 2000 1000

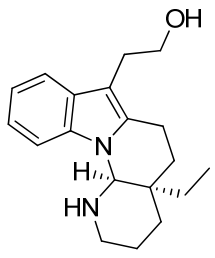

CDCl3
400 MHz
9 8 7 6 5 4 3 2 1

OTIPS
O
N
H
Cbz
N

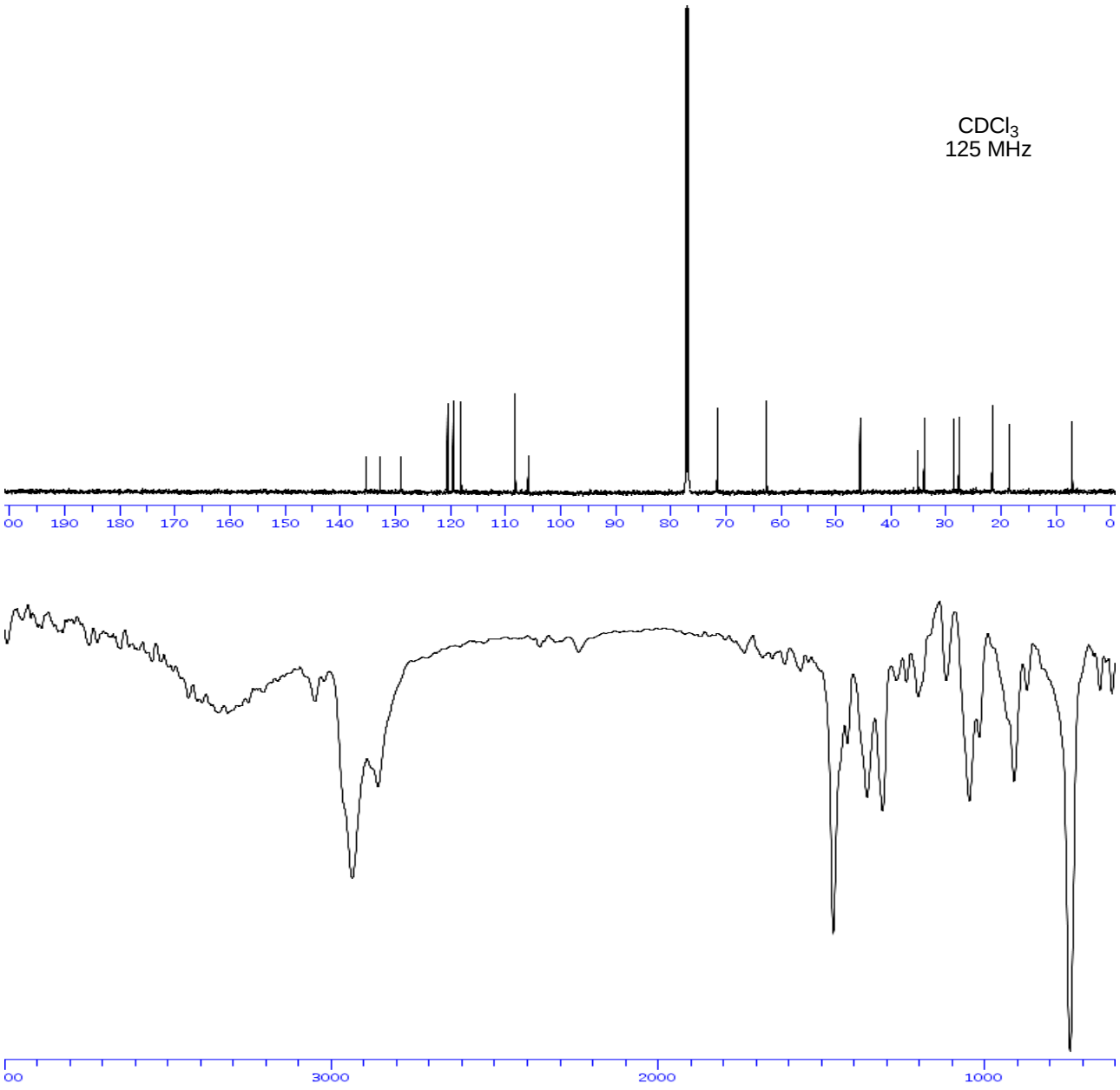
17

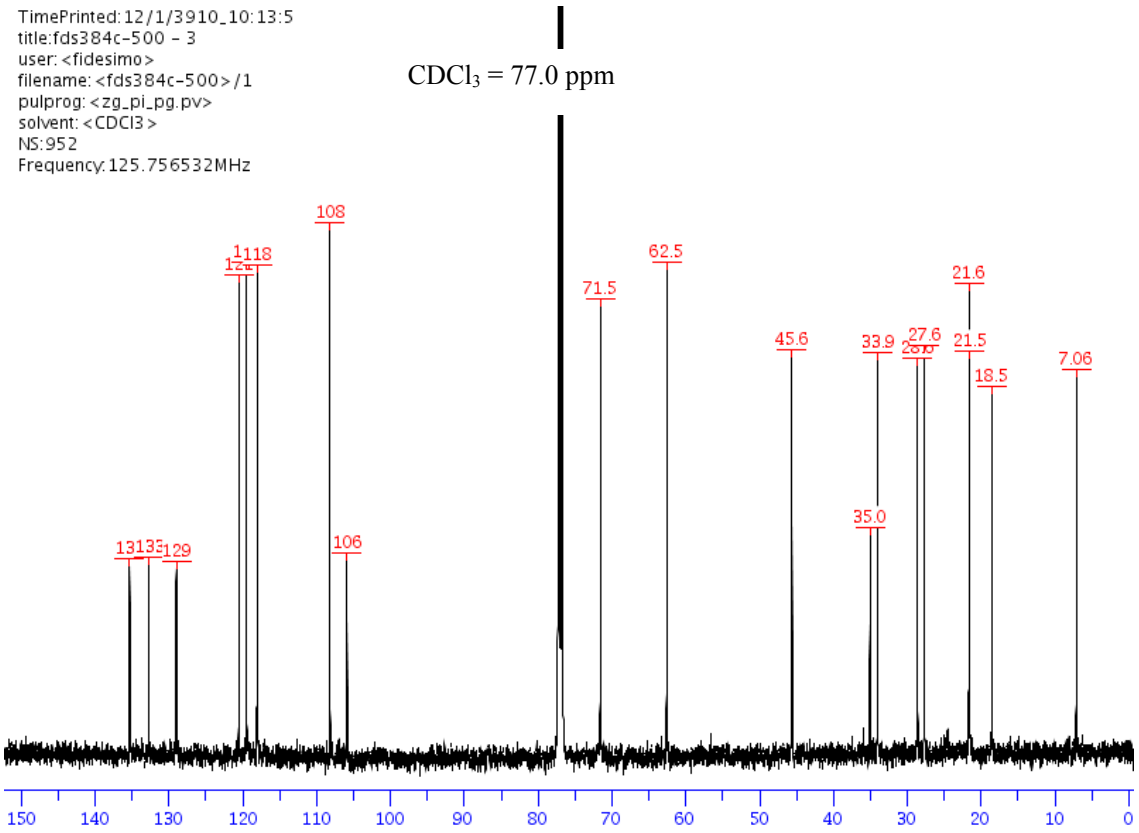






Goniomitine
(3)

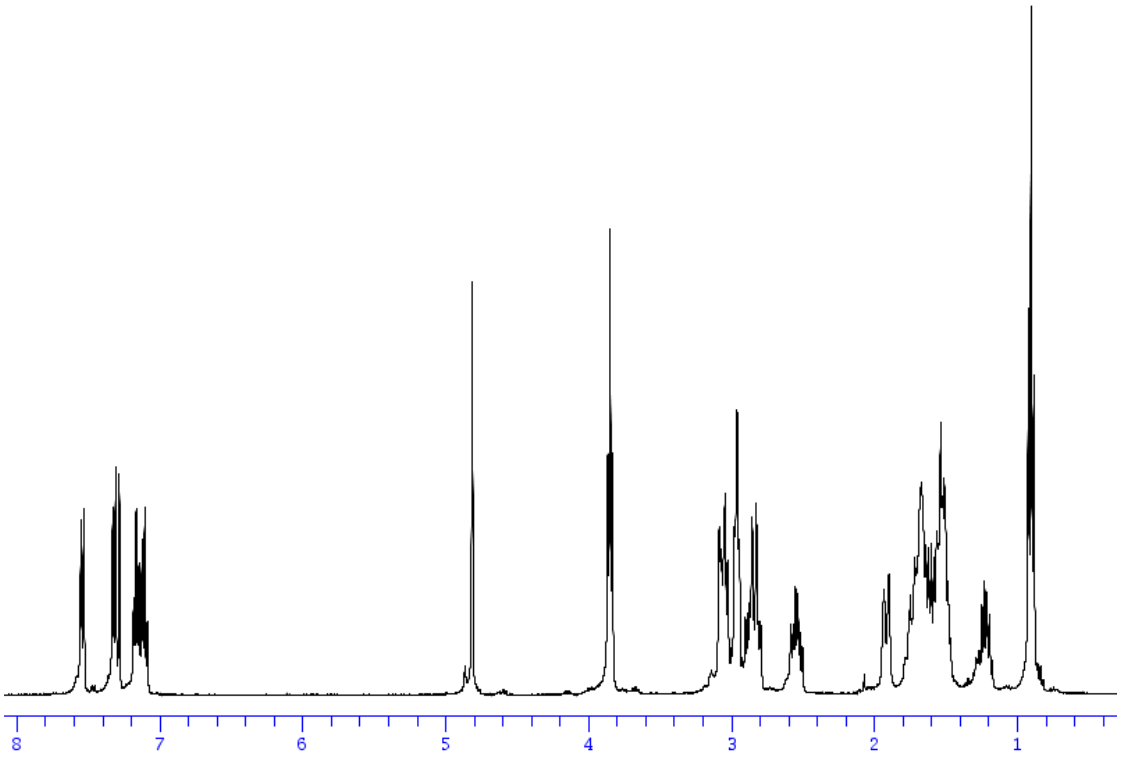

$CDCl_3$
125 MHz
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
00 3000 2000 1000



^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.34, 132.70, 129.01, 120.52, 119.50, 118.05, 108.20, 105.88, 71.55, 62.57, 45.62, 35.06, 33.99, 28.61, 27.68, 21.62, 21.58, 18.54, 7.07.

Pagenkopf (values kindly provided by Prof. Pagenkopf):[12b] ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.35, 132.70, 129.04, 120.51, 119.51, 118.05, 108.18, 105.99, 71.51, 62.52, 35.07, 33.98, 28.61, 27.67, 21.65, 21.55, 18.52, 7.05.

Husson:[11] ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 135.4, 132.6, 129.3, 120.8, 119.9, 118.1, 108.7, 106.8, 71.1, 62.6, 45.4, 35.3, 33.8, 28.7, 27.8, 21.8, 20.8, 18.5, 7.3.



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.52 (d, *J* = 7.7 Hz, 1 H; CH-Ar), 7.30 (d, *J* = 8.0 Hz, 1 H; CH-Ar), 7.14 (t, *J* = 7.2 Hz, 1 H; CH-Ar), 7.08 (t, *J* = 7.5 Hz, 1 H; CH-Ar), 4.79 (s, 1 H; NCH), 3.83 (t, *J* = 6.4 Hz, 2 H; OCH_2), 3.12-2.75 (m, 6 H; CH_2), 2.52 (td, *J* = 13.1 Hz, 6.7 Hz, 1 H; CH_2), 1.89 (d, *J* = 13.8 Hz, 1 H; CH_2), 1.80-1.41 (m, 7 H; CH_2 OH and NH), 1.21 (m, 1 H; CH_2), 0.88 (t, *J* = 7.5 Hz, 3 H; CH_3).

Copy of Spectra from Husson: