Synthesis of spongidine A, D and petrosaspongiolide L methyl ester using pyridine C-H functionalization

Florian Bartels,[a] Manuela Weber[b] and Mathias Christmann*[a]

An efficient strategy for the synthesis of the potent phospholipase A_2 inhibitors spongidine A and D is presented. The tetracyclic core of the natural products was assembled via an intramolecular hydrogen atom transfer-initiated Minisci reaction. A divergent late-stage functionalization of the tetracyclic ring system was also used to achieve a concise synthesis of petrosaspongiolide L methyl ester.

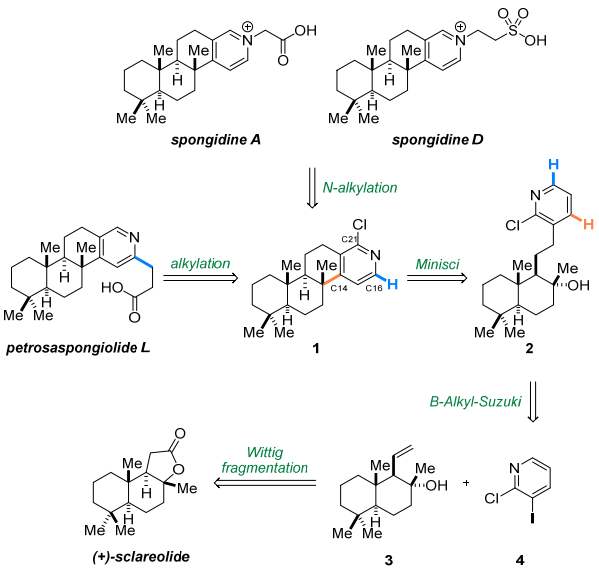
Spongidine A and D are tetracyclic pyridinium alkaloids with either acetic or ethanesulfonic acid side chains attached to the pyridine nitrogen. They were isolated in 1996 near the coast of Tongoa from an unidentified sponge and exhibit potent inhibitory activity against soluble phospholipase A_2 ($sPLA_2$). Remarkably, spongidines possess a higher selectivity toward $sPLA_2$ inhibition than the known PLA_2 inhibitor manoalide.[1, 2] Petrosaspongiolide L, a structurally related natural product, was isolated in 1987/88 from *Petrosaspongia Nigra* found near New Caledonia. In contrast to the spongidines, petrosaspongiolide L possesses a neutral pyridine with a propionic acid substituent at C16. Petrosaspongiolide L shows moderate cytotoxicity (5.6 μM) against non-small-cell lung carcinoma (NSCLC-N6).[3]

The pronounced biological activities within the spongidine class coupled with the challenging isolation from natural sources have spurred endeavors to establish more reliable access by chemical synthesis.[4, 5] Only recently, Basabe and co-workers reported the first synthesis of spongidine A and D.[6-9]

We initiated our program toward the synthesis of spongidine alkaloids with the aim to establish a short and flexible synthetic route to efficiently access the different substitution patterns found in these natural products. Despite advances in the development of new methods for late-stage C-H functionalization, application to the synthesis of complex target molecules remain rare.[10] Here, we show the selective C-H functionalization of pyridines enables the efficient synthesis of spongidine natural products.

Owing to the identical core structures of spongidines A and D as well as petrosaspongiolide L, we identified chloropyridine **1** as a key intermediate in our retrosynthetic analysis (Scheme 1). In the synthetic direction, the spongidine natural products should be accessible from this intermediate via hydrodehalogenation/*N*-alkylation, while petrosaspongiolide L should be attainable by a C-H functionalization of C16. An intramolecular Minisci reaction of a suitable tertiary radical derived from intermediate **2** was envisioned as the key step for forging the C8-C14 bond, setting the quaternary stereocenter at C8 and providing access to chloropyridine **1**. In order to direct the attack to C14, we decided to place a chlorine substituent at the C21 position of pyridine **2**. The C16 position appeared inaccessible to an intramolecular attack due to the formation of an energetically unfavorable eight-membered ring. Pyridine **2** could be obtained by *B*-alkyl Suzuki coupling between a suitable borane obtained from alkene **3** and pyridine **4**. These coupling partners are readily accessible from (+)-sclareolide and 3-amino-2-chloropyridine **5**, respectively.

The synthesis commenced with the preparation of alkene **3** from (+)-sclareolide using our previously established two-step procedure (Scheme 2).



Scheme 1. Retrosynthetic analysis.

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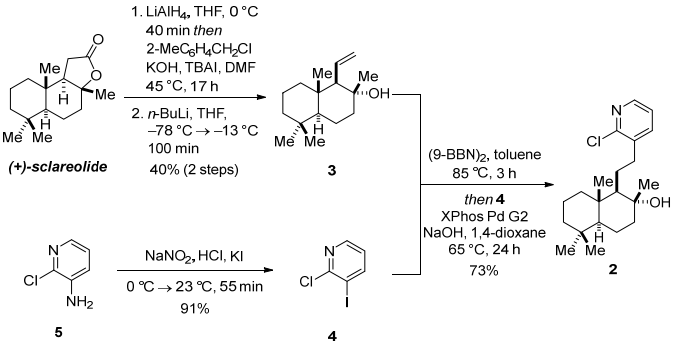
Electronic Supplementary Information (ESI) available: Detailed experimental procedures, spectral data, X-ray crystallographic data for **1** (CIF) [CCDC 1859575].

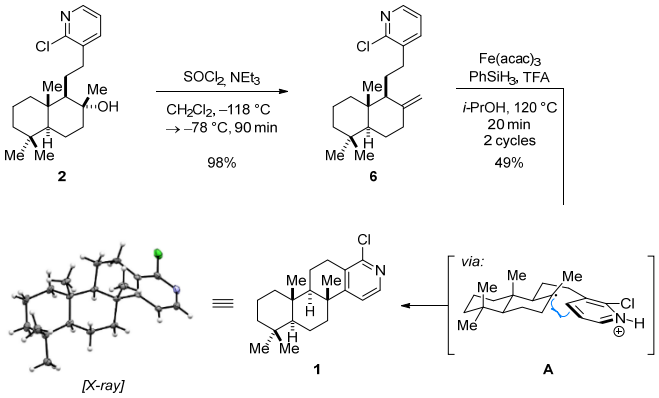
Reduction of (+)-sclareolide with $LiAlH_4$ and in-situ benzylation was followed by a Wittig-type fragmentation of the intermediate 2-methyl benzyl ether (not shown) to give alkene **3** in multigram quantities.[11] Iodide **4** was prepared from pyridine **5** on gram scale in 91% yield using a Sandmeyer reaction.[12, 13] The coupling of **3** and **4** required intensive optimization. Using standard coupling conditions, e.g. $Pd(dppf)Cl_2$ as catalyst, only 46% yield of the desired product could be isolated. In addition, significant β-hydride elimination, as well as homocoupling of the iodide **4** was observed. Gratifyingly, using Buchwald's precatalyst XPhos Pd G2,[14] no β-hydride elimination products and only trace amounts of homocoupling products were detected. Under these conditions, the coupling product **2** was isolated in 73% yield on gram scale.

While contemplating the use of *N*-phthalimidoyl oxalates for radical generation, we quickly recognized the incompatibility of the acidic reaction conditions of the Minisci reaction and the acid-labile nature of the radical precursor.[15] Instead, we opted for a hydrogen atom transfer (HAT) initiated radical generation from an exocyclic alkene (Scheme 3). Hence, alkene **6** was synthesized in excellent yield and selectivity by low-temperature elimination of tertiary alcohol **2** using $SOCl_2$ (exo:endo > 15:1 by ^1H NMR of the crude reaction mixture).

Next, we evaluated several reported conditions for hydrogen atom transfer-initiated Minisci reaction with alkene **6**.[16-18] Although recent interest in the Minisci reaction has led to the development of diverse conditions for its initiation, applications in the context of complex molecule synthesis remain limited.[19, 20] To our dismay, using $Fe(acac)_3$, $PhSiH_3$ with either TFA or $BF_3{\cdot}OET_2$ we only observed the decomposition of the starting material at either 23 °C or 60 °C. Remarkably, performing the reaction in a pressure tube at elevated temperatures (120 °C) led to product formation along with substantial amounts of unreacted starting material. While increasing the initial amounts of $Fe(acac)_3$ or $PhSiH_3$ also resulted in the decomposition of starting material, we observed that the renewed addition of $Fe(acac)_3$, $PhSiH_3$ and TFA after brief heating to 120 °C gave full conversion.



Scheme 2. Synthesis of alcohol **2** by a *B*-alkyl Suzuki reaction; THF = tetrahydrofuran, TBAI = tetrabutylammonium iodide, DMF = *N*,*N*-dimethylformamide, $(9\text{-BBN})_2$ = 9-borabicyclo[3.3.1]nonane dimer.

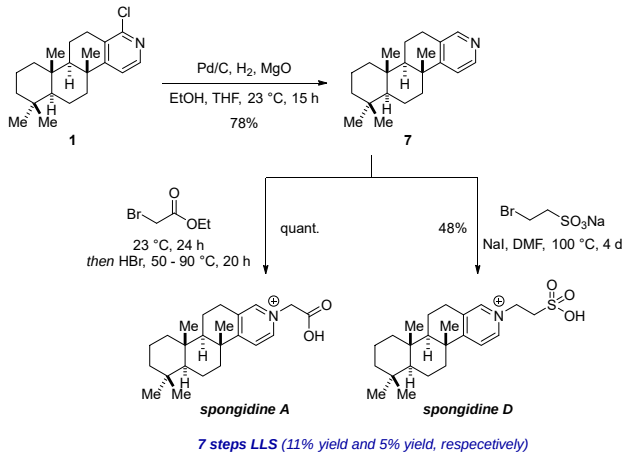


Scheme 3. Synthesis of chloropyridine **1** by an intramolecular Minisci reaction; TFA = trifluoroacetic acid.

Under the optimized conditions, we were able to isolate chloropyridine **1** in 49% yield (see Table 1 in the Supporting Information for details). The radical addition is highly diastereoselective as only a single diastereomer was detected. The (*R*)-configuration of the newly formed quaternary center can be rationalized by the orientation of the chloropyridine moiety away from the sterically shielding methyl group at C10 and was proven via X-ray crystallography.[21] Interestingly, we did not detect any dehalogenated or hydrogenated side products under the optimized reaction conditions. Mechanistically, we hypothesize that the hydrogen atom transfer of a [Fe]-H species onto the alkene generates the tertiary radical **A**, which attacks the electron-poor chloropyridine moiety in the C16 position. The necessity for the forcing reaction conditions is presumably a reflection of the high kinetic barrier for addition to the chloropyridine. Further oxidation and proton loss of the resulting radical cation yields chloropyridine **1** (see Scheme SI1 in the Supporting Information for details).[17, 18, 22, 23]

With chloropyridine **1** in hand, we began to study the hydrogenolysis of the carbon-chlorine bond (Scheme 4). Under a variety of conditions, we either observed no conversion (Pd/C, H_2 using either $NaHCO_3$/NaOAc or TFA as an additive) or decomposition of starting material (Zn/AcOH). Interestingly, sparging the reaction solvent and Pd/C with H_2 before the addition of substrate leads to the formation of pyridine **7** in 78% yield. This finding might be rationalized by the poisoning effect of pyridine on catalytically active palladium species.[24]

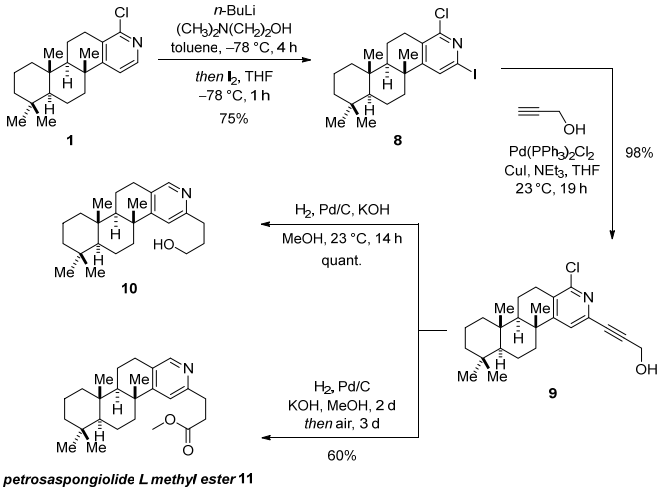
Initially, we tried to reproduce Basabe's procedure to alkylate pyridine **7** with either bromoacetic acid or sodium 2-bromoethanesulfonate.[7] During our investigation, we encountered problems handling the small solvent volume employed (2.0 M, using 0.01 mL bromobenzene or DMF, respectively), which resulted in a low conversion of starting material in our hands.



Scheme 4. Completion of the synthesis of spongidine A and spongidine D.

Therefore, we opted for a procedure consisting of alkylation with bromoacetic acid ethyl ester and subsequent ester hydrolysis. The reaction of pyridine **7** with bromoacetic acid ethyl ester occurred smoothly after 24 h at 23 °C (Scheme 4). Subsequently, we cleaved the corresponding ethyl ester with hydrogen bromide at elevated temperature (50-90 °C, 20 h) to yield spongidine A in quantitative yield.[25] Spongidine D was synthesized in 48% yield through alkylation of **7** with sodium 2-bromoethanesulfonate and sodium iodide in DMF (0.055 M) at 100 °C for 4 d. The obtained analytical data matched the published data.[1, 6, 7]

In order to synthesize petrosaspongiolide L, we were faced with the challenge of selectively functionalizing the C16-H bond in either chloropyridine **1** or pyridine **7**. From the outset, we were concerned that a second Minisci reaction might be inhibited by the reduced electrophilicity of the dialkylated pyridine. Indeed, attempts to utilize a Minisci reaction led only to the decomposition of the starting material (AIBN, $(SiMe_3)_3SiH$, $Br(CH_2)_2COOBn$).[22, 26] Despite the failure of our Minisci approach multiple methods for selective C-H functionalization of pyridines at the C-2 position have been developed in recent years. We started our investigation with a rhodium-catalyzed alkylation using various esters of acrylic acid. However, we were unable to detect the alkylated products using either **1** or **7** directly or the corresponding pyridine *N*-oxides (formed *in situ* using DMDO).[27, 28] Afterward, we investigated the phosphonium salt formation of pyridines (Tf_2O, PPh_3, CH_2Cl_2, −78 °C), in hopes of subsequently displacing the resulting phosphonium leaving group with a carbon nucleophile. Unfortunately, neither a change of base (DBU or NEt_3) nor the addition of PPh_3 or base at 23 °C led to the formation of the desired phosphonium salt and only complex mixtures were obtained.[29] Gratifyingly, the selective lithiation of chloropyridine **1** with *n*-BuLi and 2-dimethylaminoethanol at -78 °C generated an aryllithium species that could be trapped with I_2 to give chloroiodopyridine **8** in 31% yield along with 52% unreacted starting material (Scheme 5).[30-32] We were able to increase the yield of this transformation to 75% yield by extending the lithiation time from 2 h to 4 h.



Scheme 5. Functionalization of the pyridine ring and synthesis of petrosaspongiolide L methyl ester **11**.

Subsequently, we used a Sonogashira reaction to couple chloroiodopyridine **8** and propargyl alcohol to provide alkyne **9** in 98% yield.[33]

Next, the simultaneous hydrogenation of the alkyne and the hydrogenolysis of the carbon-chlorine bond was investigated. The previously established conditions for the hydrogenolysis of chloropyridine **1** using MgO and Pd/C proved unsuccessful and led to no conversion of starting alkyne **9**, even when applying 30 bar of hydrogen pressure. However, changing the base from MgO to KOH[34] and using over-stoichiometric amounts of Pd/C led to the formation of alcohol **10** in quantitative yield.

We then investigated a variety of oxidizing agents to synthesize the carboxylic acid from alcohol **10**. To our dismay, the oxidation of alcohol **10** to either the corresponding aldehyde (using Dess–Martin periodinane, SO_3·pyridine, NCS/SMe_2) or carboxylic acid (using $RuCl_3/H_5IO_6$, PDC, PCC, TEMPO/PIDA, Pt/O_2, TPAP/NMO) was unsuccessful under a variety of conditions, yielding only complex mixtures. Fortunately, after the global hydrogenolysis of **9**, a Heyns oxidation with atmospheric oxygen generated petrosaspongiolide L methyl ester **11** in 60% yield.[35] Lastly, we attempted the hydrolysis of the methyl ester to furnish petrosaspongiolide L. While we were able to convert the methyl ester to the acid (using LiOH) and confirm its generation via high-resolution mass spectrometry, we were unable to isolate petrosaspongiolide L due to decomposition upon attempted isolation.

In conclusion, we have accomplished an efficient entry into the spongidine alkaloids. Our approach utilizes a radical disconnection and late-stage C-H functionalization to increase step efficiency.[36, 37] The tetracyclic ring system of the spongian terpene alkaloids was formed in a single step using a rare example of an intramolecular hydrogen atom transfer-initiated Minisci reaction. This synthetic strategy enabled the short synthesis of spongidine A and D in only 7 steps from (+)-sclareolide in 11% and 5% yield, respectively (previously 2% and

1% yield over 23 steps)[7]. Furthermore, we identified and synthesized chloropyridine **1** as a platform intermediate that might be valuable in the synthesis of other spongian terpene alkaloids and showcased this approach in the synthesis of petrosaspongiolide L methyl ester.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

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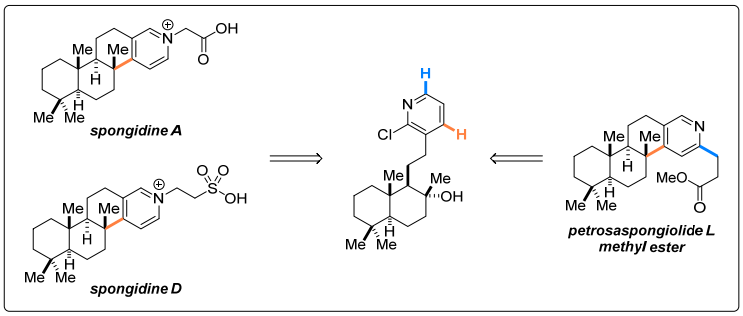
TOC Graphic


spongidine A
spongidine D
petrosaspongiolide L
methyl ester

Supporting Information

Synthesis of spongidine A, D and petrosaspongiolide L methyl ester using pyridine C-H functionalization

Florian Bartels, Manuela Weber and Mathias Christmann*

Table of Contents

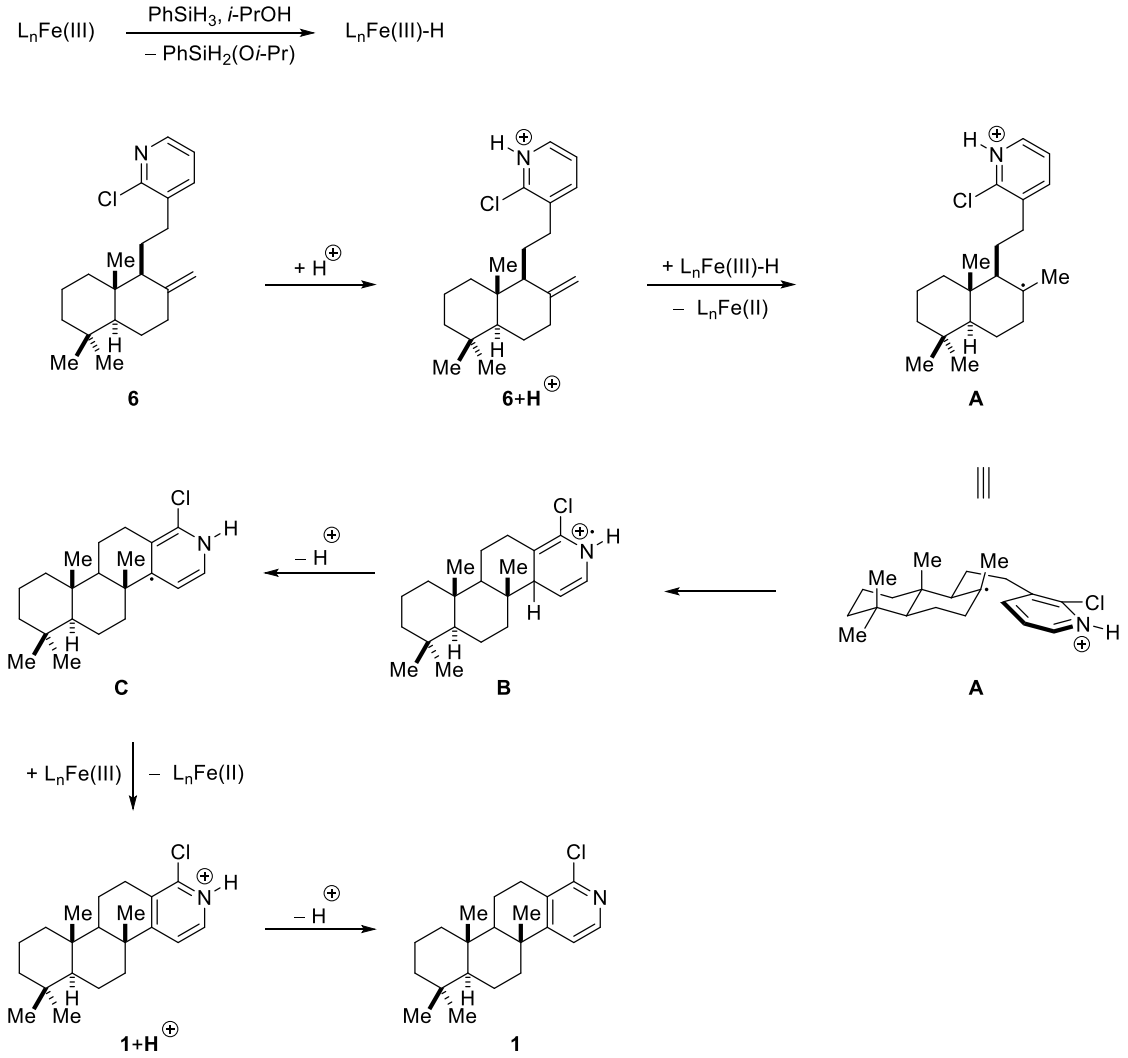
1. General Methods 3
2. Scheme SI1: Proposed Mechanism of the intramolecular Minisci Reaction 4
3. Table 1: Optimization Study for the Synthesis of Chloropyridine **1** 5
4. Synthesis of Compounds 6
5. NMR-Spectra 25
6. Crystallographic Data 39
7. Previous Synthesis of Spongidine A and Spongidine D 40
8. References 42

1. General Methods

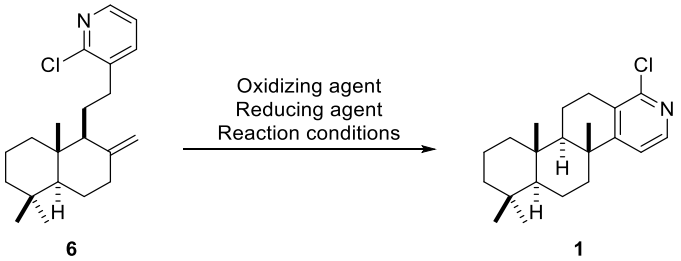
All reactions sensitive to moisture and air were carried out using heat-gun dried (630 °C) glassware under an argon atmosphere. Dry solvents (CH_2Cl_2, Et_2O, THF, Toluene) were purified by Solvent Purification System M-BRAUN Glovebox Technology SPS-800. Dry DMF was obtained from Acros Organics 99.8%, extra dry over molecular sieves. Dry pyridine was obtained from Sigma Aldrich, anhydrous, 99.8%. Solvents for column chromatography were used after short path distillation using a rotary evaporator. Commercial reagents were used as received unless otherwise stated. Reactions were carried out under magnetic stirring with Teflon coated stirring bars and were monitored by TLC analysis on 0.20 mm silica gel plates (Macherey-Nagel G/UV254). Visualization was performed by UV irradiation (254 nm) or staining of TLC plates with an acidic vanillin solution (1 g vanillin, 20 mL conc. acetic acid, 10 mL conc. sulfuric acid, 170 mL methanol) or $KMnO_4$ solution (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.2 mL 10% NaOH, 200 mL H_2O) and heat. Column chromatography was carried out on silica gel 60 M (0.04–0.063 mm) from Macherey-Nagel. Reverse phase HPLC was carried out on Gemini-NX 5µ C18, 4.6×250 mm. Concentration under reduced pressure was performed by rotary evaporation at 40 °C.

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker (ECP 400, AC 500, AV 700) or JEOL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to $CDCl_3$ (^{1}H: 7.26 ppm; ^{13}C: 77.16 ppm) and CD_3OD (^{1}H: 3.31 ppm; ^{13}C: 49.00 ppm). Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sext = sextet, m = multiplet, $_{br}$ = broad, and combinations thereof), coupling constant and integration. Integrals are in accordance with assignments; coupling constants are given in Hz. For detailed peak assignments, 2D spectra were recorded when necessary (COSY, DEPT, HMQC, HMBC, TOCSY, GOESY). IR spectra were measured on a JASCO FT/IR–4100 instrument equipped with an ATR unit. High-resolution ESI analyses were performed on a Varian Inc. Ionspec QFT-7. Optical rotation measurements were performed on a P-2000 polarimeter from Jasco in a 10 cm optical-path length cell with the frequency of the Na*D* line measured at the temperature and concentration (in g/100 mL) indicated. Melting points were measured with a Stuart melting point apparatus SMP30 and are uncorrected.

2. Scheme SI1: Proposed Mechanism of the intramolecular Minisci Reaction



3. Table 1: Optimization Study for the Synthesis of Chloropyridine **1**

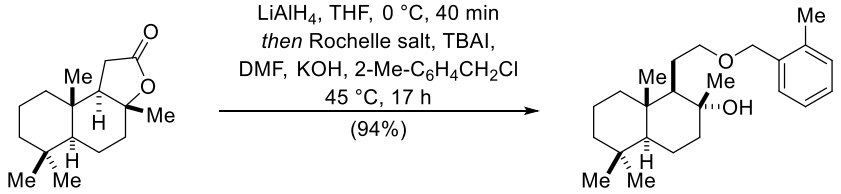


6 **1**

Entry	Oxidizing agent	Reducing agent	Reaction conditions	Observation/ Yield
1	$Fe(acac)_3$ (50 mol%)	$PhSiH_3$ (2.5 eq.)	(*t*-BuO)$_2$ (3.0 eq.), TFA (2.0 eq.), EtOH, 60 °C, 16 h	Decomposition
2	$Fe(acac)_3$ (2.0 eq.)	$PhSiH_3$ (2.2 eq.)	TFA (2.0 eq.), EtOH, 60 °C, 16 h	Decomposition
3	$Fe(acac)_3$ (1.0 eq.)	$PhSiH_3$ (2.5 eq.)	(*t*-BuO)$_2$ (3.0 eq.), TFA (2.0 eq.), 2-Propanol, 23 °C, 16 h	Decomposition
4	$Fe(acac)_3$ (1.0 eq.)	$PhSiH_3$ (2.5 eq.)	TFA (1.0 eq.), 2-Propanol, 23 °C, 16 h	Decomposition
5	$Fe(acac)_3$ (1.0 eq.)	$PhSiH_3$ (1.0 eq.)	$BF_3{\cdot}Et_2O$ (2.0 eq.), THF/MeOH (4:1), 60 °C, 16 h	Decomposition
6	$Fe(acac)_3$ (3.0 eq.)	$PhSiH_3$ (3.0 eq.)	$BF_3{\cdot}Et_2O$ (2.0 eq.), THF/MeOH (5:1), 150 °C, 30 min	Decomposition
7	2 x $Fe(dibm)_3$ (1.0 eq.)	2 x $PhSiH_3$ (2.5 eq.)	TFA (1.0 eq.), 2-Propanol, 120 °C, 15 min, *then* TFA (1.0 Eq.), 120 °C, 15 min	37%
8	2 x $Fe(acac)_3$ (1.0 eq.)	$PhSiH_2$(O*i*-Pr) (2.5 eq. + 20 eq.)	TFA (1.0 eq.), 2-Propanol, 120 °C, 20 min, *then* TFA (1.0 eq.), 120 °C, 4.5 h	19%
9	2 x $Fe(acac)_3$ (1.0 eq.)	2 x $PhSiH_3$ (2.5 eq.)	TFA (1.3 eq.), 2-Propanol, 120 °C, 10 min, *then* TFA (1.3 eq.), 120 °C, 20 min	49%

4. Synthesis of Compounds

Ether **S1**



(+)-sclareolide $C_{16}H_{26}O_2$ (250.38)

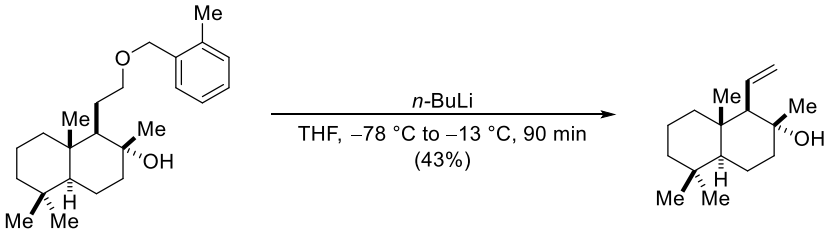
S1 $C_{24}H_{38}O_2$ (358.56)

To $LiAlH_4$ (535 mg, 14.1 mmol, 0.70 eq.) in THF (5 mL) at 0 °C was added a solution of (+)-sclareolide (5.04 g, 20.1 mmol, 1.0 eq.) in THF (25 mL) over 5 min. After 30 min at the same temperature Rochelle salt (6.84 g, 24.2 mmol, 1.2 eq.), DMF (80 mL), tetrabutylammonium iodide (751 mg, 2.03 mmol, 10 mol%), freshly ground KOH (4.51 g, 80.5 mmol, 4.0 eq.) and 2-Me-$C_6H_4CH_2Cl$ (10.5 mL, 60.4 mmol, 3.0 eq.) were added successively, and the reaction mixture was heated to 45 °C for 17 h. Water was added, and the mixture was diluted with EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed repeatedly with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc 10:1) to afford ether **S1** (6.78 g, 18.9 mmol, 94%) as a colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.30 – 7.28 (m, 1H), 7.22 – 7.14 (m, 3H), 4.58 – 4.48 (m, 2H), 3.64 (ddd, *J* = 8.7, 5.4, 4.1 Hz, 1H), 3.38 (ddd, *J* = 10.1, 8.7, 4.5 Hz, 1H), 3.24 (s_{br}, 1H), 2.34 (s, 3H), 1.90 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.77 (ddt, *J* = 15.3, 10.2, 5.2 Hz, 1H), 1.68 – 1.53 (m, 4H), 1.46 – 1.34 (m, 3H), 1.30 – 1.20 (m, 2H), 1.18 – 1.10 (m, 4H), 0.93 – 0.82 (m, 5H), 0.79 (s, 6H).

The spectral data matched the previously obtained data.[1]

Alkene **3**



S1

$C_{24}H_{38}O_2$
(358.56)

3

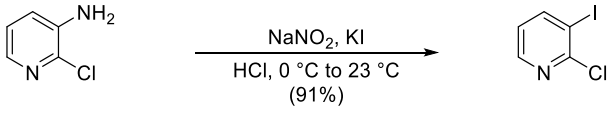
$C_{16}H_{28}O$
(236.39)

To a solution of ether **S1** (7.67 g, 21.4 mmol, 1.0 eq.) in THF (170 mL) at −78 °C was added a solution of *n*-BuLi (34.2 mL, 2.5 M in hexane, 85.6 mmol, 4.0 eq.). After 10 min at that temperature, the reaction mixture was warmed to −13 °C (change of cooling baths) and stirred for 90 min. Water was added, and the reaction mixture was diluted with EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc 1:0 to 15:1 to 10:1) to afford alkene **3** (2.19 g, 9.24 mmol, 43%) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 5.82 (dt, *J* = 16.8, 10.2 Hz, 1H), 5.26 (dd, *J* = 10.2, 2.5 Hz, 1H), 5.15 (dd, *J* = 16.9, 2.4 Hz, 1H), 1.94 (s_{br}, 1H), 1.90 (dt, *J* = 12.6, 3.3 Hz, 1H), 1.75 (d, *J* = 10.2 Hz, 1H), 1.71 – 1.64 (m, 1H), 1.56 (tt, *J* = 14.4, 3.7 Hz, 1H), 1.51 – 1.36 (m, 4H), 1.38 – 1.23 (m, 1H), 1.19 (s, 3H), 1.14 (td, *J* = 13.5, 12.8, 4.3 Hz, 1H), 0.93 – 0.89 (m, 4H), 0.89 – 0.85 (m, 4H), 0.81 (s, 3H).

The spectral data matched the previously obtained data.[1]

Iodide **4**



5
$C_5H_5ClN_2$
(128.56)

4
C_5H_3ClIN
(239.44)

3-Amino-2-chloropyridine **5** (5.00 g, 38.9 mmol, 1.0 eq.) was added to HCl (6 M, aq., 40.2 mL) at 0 °C. $NaNO_2$ (4.29 g, 62.2 mmol, 1.6 eq.) in H_2O (20.0 mL) was added dropwise to the reaction mixture over 5 min followed by the dropwise addition of KI (15.5 g, 93.3 mmol, 2.4 eq.) in H_2O (20.0 mL). The reaction mixture was stirred for 5 min at 0 °C and 50 min at 23 °C. NaOH (5 M, aq., 77.8 mL) and EtOAc were added. The phases were separated, and the aqueous phase was extracted with EtOAc (2x). The combined organic extracts were washed consecutively with a saturated aqueous solution of $Na_2S_2O_3$ and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc 15:1 to 10:1) to afford the title compound (8.33 g, 35.2 mmol, 91%) as a white solid.

R_f = 0.64 (*n*-pentane/EtOAc, 5:1).

^{1}H-NMR (700 MHz, $CDCl_3$): δ [ppm] = 8.35 (dd, *J* = 4.7, 1.8 Hz, 1H), 8.13 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.94 (dd, *J* = 7.8, 4.7 Hz, 1H).

^{13}C-NMR (176 MHz, $CDCl_3$): δ [ppm] = 154.6, 149.0, 148.9, 123.3, 95.0.

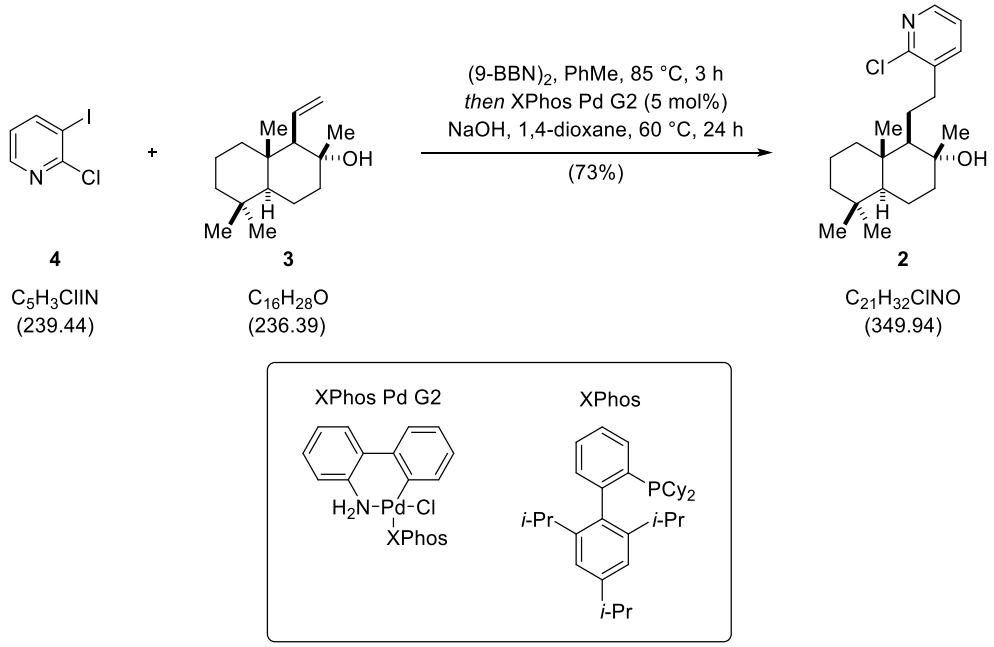
IR (ν/cm^{-1}, ATR) = 3044, 2954, 2919, 2851, 1733, 1550, 1462, 1382, 1136, 1006.

HRMS (ESI): *m/z* calculated for $C_5H_4ClIN^+$ $[M+H]^+$: 239.9072, found 239.9069.

Mp: 93 - 94 °C.

The spectral data matched the previously obtained data.[2, 3]

Alcohol **2**



Alkene **3** (1.30 g, 5.50 mmol, 1.6 eq.) and 9-BBN dimer (1.68 g, 13.8 mmol, 3.9 eq.) were mixed and heated to 60 °C for 20 min. The reaction mixture was heated to 85 °C for 70 min. Subsequently, toluene (degassed by sparging with Ar for 20 min, 3.0 mL) was added, and heating was continued at 85 °C for 70 min. After cooling to 60 °C NaOH (degassed by sparging with Ar for 20 min, 7.10 mL, 3 M, 21.3 mmol, 6.0 eq.) was added, and the mixture was stirred for 10 min. Afterward, 1,4-dioxane (degassed by sparging with Ar for 20 min, 15.0 ml), iodide **4** (850 mg, 3.55 mmol, 1.0 eq.) and XPhos Pd G2 (140 mg, 177 µmol, 5 mol%) were added sequentially. The flask was rinsed with 1,4-dioxane (degassed by sparging with Ar for 20 min, 3.0 ml) and stirred at that temperature for 24 h. The reaction mixture was cooled to 23 °C and water and EtOAc were added. The organic phase was separated, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc 4:1 to 1:1) to afford the title compound (902 mg, 2.58 mmol, 73%) as a white solid.

$\mathbf{R}_f$ = 0.28 (*n*-pentane/EtOAc, 3:1).

$[\alpha]_D^{27}$ = +31.9 (*c* = 0.48, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.19 (dd, *J* = 4.7, 1.9 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.9 Hz, 1H), 7.13 (dd, *J* = 7.5, 4.7 Hz, 1H), 2.85 (ddd, *J* = 13.6, 11.6, 5.5 Hz, 1H), 2.75 (ddd, *J* = 13.6, 11.6, 5.5 Hz, 1H), 1.86 (dt, *J* = 12.3, 3.2 Hz, 1H), 1.78 – 1.73 (m, 1H), 1.70 – 1.51 (m, 4H), 1.45 – 1.34 (m, 4H), 1.29 – 1.23 (m, 1H), 1.21 – 1.08 (m, 5H), 1.00 – 0.91 (m, 2H), 0.85 (s, 3H), 0.76 (s, 6H).

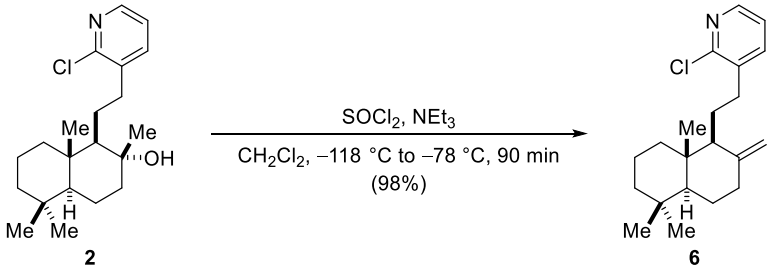
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = .151.2, 147.1, 139.0, 137.4, 122.7, 74.4, 61.6, 56.2, 44.7, 42.0, 39.7, 39.2, 36.6, 33.5, 33.3, 25.7, 24.2, 21.6, 20.6, 18.6, 15.5.

IR (ν/cm^{-1}, ATR) = 3411, 2926, 2866, 2235, 1565, 1455, 1407, 1387, 1079, 800.

HRMS (ESI): *m/z* calculated for $C_{21}H_{33}ClNO^{+}$ $[M+H]^{+}$: 350.2245, found 350.2256.

Mp: 112 - 114 °C.

Alkene **6**



A solution of alcohol **2** (168 mg, 480 μmol, 1.0 eq.) and NEt_3 (dried by distillation over CaH_2, 0.67 mL, 0.49 g, 4.80 mmol, 10.0 eq.) in CH_2Cl_2 (16.0 mL) was cooled to −118 °C (ethanol, N_2(l)) and $SOCl_2$ (0.10 mL, 0.17 g, 1.44 mmol, 3.0 eq.) in CH_2Cl_2 (4.0 mL) was added dropwise over the wall of the flask over 10 min. The reaction mixture was allowed to warm to −78 °C (ethanol, dry ice) over 90 min. Methanol (0.5 mL) was added, and the reaction mixture was warmed to 23 °C. A saturated aqueous solution of $NaHCO_3$ and CH_2Cl_2 was added successively. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2x). The combined organic extracts were washed with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc 1:0 to 40:1 to 25:1 to 10:1) to afford the title compound (157 mg, 472 μmol, 98%) as a colorless liquid, which slowly crystallized.

$\mathbf{R_f}$ = 0.61 (*n*-pentane/$CHCl_3$, 2:1).

$[\alpha]_D^{27}$ = +45.0 (*c* = 0.42, $CHCl_3$).

^{1}H-NMR (700 MHz, $CDCl_3$): δ [ppm] = 8.26 – 8.22 (m, 1H), 7.52 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.17 (dd, *J* = 7.4, 4.7 Hz, 1H), 4.91 (s, 1H), 4.68 (s, 1H), 2.92 – 2.85 (m, 1H), 2.56 – 2.49 (m, 1H), 2.45 – 2.41 (m, 1H), 2.00 (td, *J* = 13.1, 5.3 Hz, 1H), 1.88 – 1.83 (m, 1H), 1.77 – 1.70 (m, 2H), 1.67 – 1.62 (m, 2H), 1.57 – 1.52 (m, 1H), 1.50 – 1.45 (m, 1H), 1.41 – 1.36 (m, 1H), 1.36 – 1.30 (m, 1H), 1.16 (td, *J* = 13.4, 4.1 Hz, 1H), 1.08 (dd, *J* = 12.6, 2.7 Hz, 1H), 0.97 (td, *J* = 12.9, 4.0 Hz, 1H), 0.87 (s, 3H), 0.80 (s, 3H), 0.68 (s, 3H).

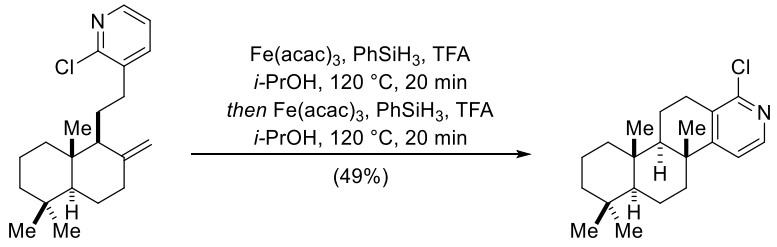
^{13}C-NMR (176 MHz, $CDCl_3$): δ [ppm] = 151.4, 148.5, 147.2, 139.0, 137.5, 122.7, 106.6, 56.7, 55.7, 42.3, 39.9, 39.1, 38.5, 33.8 (2C), 32.5, 24.6, 23.7, 21.9, 19.5, 14.6.

IR (ν/cm^{-1}, ATR) = 2927, 2846, 2364, 1644, 1563, 1456, 1408, 1197, 1074, 890.

HRMS (ESI): *m/z* calculated for $C_{21}H_{31}ClN^+$ $[M+H]^+$: 332.2140, found 332.2135.

Mp: 72 - 74 °C.

Chloropyridine **1**



6

$C_{21}H_{30}ClN$
(331.92)

1

$C_{21}H_{30}ClN$
(331.92)

To a solution of $Fe(acac)_3$ (15.4 mg, 43.6 μmol, 1.0 eq.), alkene **6** (14.2 mg, 42.8 μmol, 1.0 eq.) and TFA (4.28 μL, 6.34 mg, 55.6 μmol, 1.3 eq.) in *i*-PrOH (degassed by sparging with Ar for 20 min, 4.0 mL) was added $PhSiH_3$ (13.6 μL, 11.9 mg, 107 μmol, 2.5 eq.) and heated in a pressure tube to 120 °C for 10 min. After cooling to 0 °C $Fe(acac)_3$ (15.4 mg, 43.6 μmol, 1.0 eq.), TFA (4.28 μL, 6.34 mg, 55.6 μmol, 1.3 eq.) and $PhSiH_3$ (13.6 μL, 11.9 mg, 107 μmol, 2.5 eq.) were added sequentially and the reaction was heated to 120 °C for 20 min. After cooling to 23 °C the mixture was concentrated under reduced pressure, and the residue was purified by preparative thin-layer chromatography (SiO_2, *n*-pentane/EtOAc 70:1 and 11:1) to afford the title compound (7.0 mg, 21.1 μmol, 49%) as a colorless solid. Crystals suitable for X-ray crystallography were obtained after the evaporation of a $MeCN/CH_2Cl_2$ mixture.

$\mathbf{R}_f$ = 0.18 (toluene/$CHCl_3$, 1:1).

$[\alpha]_D^{27}$ = −26.7 (*c* = 0.48, $CHCl_3$).

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.11 (d, *J* = 5.2 Hz, 1H), 7.09 (d, *J* = 5.4 Hz, 1H), 3.01 – 2.89 (m, 1H), 2.66 (ddd, *J* = 18.6, 11.5, 7.8 Hz, 1H), 2.37 – 2.27 (m, 1H), 1.91 (s, 1H), 1.84 – 1.78 (m, 1H), 1.75 – 1.70 (m, 1H), 1.68 – 1.60 (m, 2H), 1.59 – 1.50 (m, 1H), 1.48 – 1.43 (m, 2H), 1.42 – 1.38 (m, 1H), 1.22 – 1.19 (m, 1H), 1.18 (s, 3H), 1.16 – 1.08 (m, 1H), 0.92 (s, 3H), 0.88 – 0.86 (m, 4H), 0.86 – 0.84 (m, 4H).

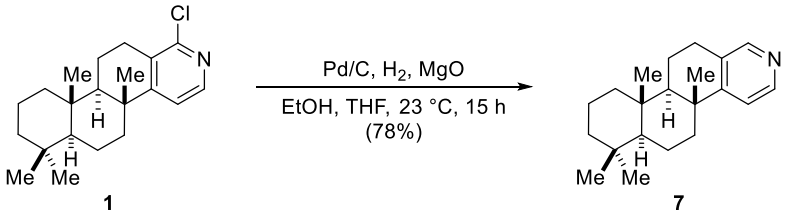
^{13}C-NMR (126 MHz, $CDCl_3$): δ [ppm] = 162.3, 152.0, 146.5, 129.9, 119.1, 56.2, 53.9, 42.1, 40.1, 39.8, 38.6, 37.8, 33.4 (2C), 28.6, 25.7, 21.5, 19.0, 18.6, 17.3, 16.4.

IR (ν/cm^{-1}, ATR) = 2925, 2852, 1726, 1578, 1542, 1460, 1386, 1324, 1105, 835.

HRMS (ESI): *m/z* calculated for $C_{21}H_{31}ClN^+$ $[M+H]^+$: 332.2140, found 332.2151.

Mp: 153 - 156 °C.

Pyridine **7**



A suspension of Pd/C (10 wt%, 12.1 mg, 11.3 μmol, 0.4 eq.) and MgO (10.3 mg, 255 μmol, 9.0 eq.) in EtOH (1 mL) was purged with H_2 (balloon) for 2 min. Then a solution of chloropyridine **1** (9.4 mg, 28.3 μmol, 1.0 eq.) in THF/EtOH (1:1, 4 mL) was added, and purging was continued for 2 min. The reaction mixture was stirred at 23 °C for 15 h under an H_2 (balloon) atmosphere. The suspension was filtered through a short silica pad with EtOAc/$CHCl_3$ (1:1) as the eluent. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc/NEt_3 150:45:2) to afford the title compound (6.6 mg, 22.2 μmol, 78%) as a colorless solid.

$\mathbf{R_f}$ = 0.41 (*n*-pentane/EtOAc, 1:1).

$[\alpha]_D^{23}$ = −62.6 (*c* = 0.07, $CHCl_3$) [Lit[4]: $[\alpha]_D^{22}$ = −76.0 (*c* = 0.27, $CHCl_3$)].

^{1}H-NMR (700 MHz, $CDCl_3$): δ [ppm] = 8.29 (d, *J* = 5.3 Hz, 1H), 8.26 (s, 1H), 7.10 (d, *J* = 5.3 Hz, 1H), 2.93 (dd, *J* = 17.3, 6.4 Hz, 1H), 2.77 (ddd, *J* = 17.8, 11.6, 7.4 Hz, 1H), 2.34 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.91 (ddt, *J* = 11.7, 7.7, 2.0 Hz, 1H), 1.83 – 1.78 (m, 1H), 1.76 – 1.71 (m, 1H), 1.70 – 1.61 (m, 2H), 1.59 – 1.51 (m, 1H), 1.50 – 1.42 (m, 2H), 1.42 – 1.37 (m, 1H), 1.28 – 1.21 (m, 1H), 1.18 (s, 3H), 1.17 – 1.12 (m, 1H), 0.93 (s, 3H), 0.90 – 0.83 (m, 8H).

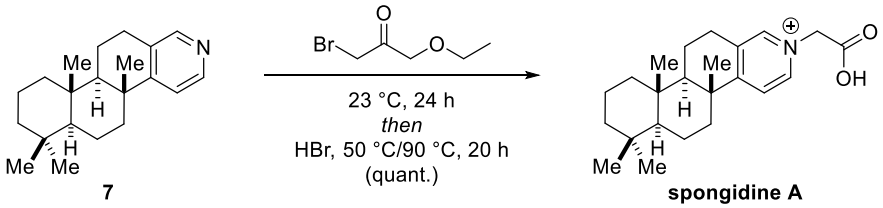
^{13}C-NMR (176 MHz, $CDCl_3$): δ [ppm] = 158.8, 150.5, 147.1, 130.8, 119.4, 56.4, 54.7, 42.2, 39.9, 39.8, 38.1, 37.9, 33.5, 33.4, 27.8, 25.8, 21.6, 19.0, 18.7, 17.6, 16.5.

IR (ν/cm^{-1}, ATR) = 2952, 2924, 2855, 2360, 2034, 1740, 1697, 1462, 1079, 830.

HRMS (ESI): *m/z* calculated for $C_{21}H_{32}N^+$ $[M+H]^+$: 298.2530, found 298.2530.

Mp: 104 - 106 °C.

Spongidine A



Ethyl bromoacetate (0.359 mL, 0.539 g, 3.23 mol, 600 eq.) was added to pyridine **7** (1.6 mg, 5.4 μmol, 1.0 eq.) and stirred for 24 h at 23 °C. The reaction mixture was concentrated under reduced pressure. HBr (1.0 mL) was added and the reaction mixture heated to 60 °C for 2 h in a sand bath. HBr (1.0 mL) was added and the reaction mixture heated to 90 °C for 2 h and 16 h at 50 °C in a sand bath. The reaction mixture was concentrated under reduced pressure to afford the title compound (2.4 mg, 6.7 μmol, quant.) as brown solid.

R_f = 0.11 (CH_2Cl_2/MeOH, 9:1).

$[\alpha]_D^{25}$ = −32.5 (*c* = 0.21, MeOH) [Lit[5]: **$[\alpha]_D$** = −16.2 (*c* = 0.010, MeOH), Lit[4]: **$[\alpha]_D^{22}$** = −41.3 (*c* = 0.15, MeOH)].

^{1}H-NMR (500 MHz, MeOH-d_4): δ [ppm] = 8.62 (s, 1H), 8.58 (d, *J* = 6.6 Hz, 1H), 7.99 (d, *J* = 6.6 Hz, 1H), 5.40 (s, 2H), 3.16 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.99 (ddd, *J* = 18.4, 11.3, 7.6 Hz, 1H), 2.53 (dt, *J* = 12.5, 3.3 Hz, 1H), 2.08 – 2.03 (m, 1H), 1.89 – 1.66 (m, 5H), 1.59 (td, *J* = 12.8, 4.0 Hz, 1H), 1.52 – 1.47 (m, 1H), 1.45 – 1.41 (m, 1H), 1.39 – 1.36 (m, 1H), 1.32 (s, 3H), 1.21 (td, *J* = 13.6, 4.2 Hz, 1H), 1.03 (s, 3H), 0.99 – 0.95 (m, 2H), 0.91 (s, 3H), 0.91 (s, 3H).

Note: RCOO*H* was not assigned.

^{13}C-NMR (176 MHz, MeOH-d_4): δ [ppm] = 171.7, 168.6, 146.7, 143.7, 138.2, 125.1, 60.8, 57.2, 54.5, 43.0, 41.0, 40.7, 40.1, 39.1, 34.3, 33.7, 28.5, 25.6, 21.8, 19.8, 19.5, 17.7, 16.9.

IR (ν/cm^{-1}, ATR) = 3385, 2924, 2852, 1739, 1642, 1506, 1458, 1366, 1217, 1076.

HRMS (ESI): *m/z* calculated for $C_{23}H_{34}NO_2^+$ $[M]^+$: 356.2584, found 356.2586.

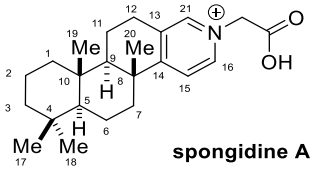


Table 2: NMR comparison of natural spongidine A with synthetic material.

No.	natural[5]		synthetic	
	^{1}H-NMR[a]	^{13}C-NMR[b]	^{1}H-NMR[c]	^{13}C-NMR[d]
1	0.99	40.6	0.98 m	40.7
	1.88		1.86 m[e]	
2	1.54	19.6	1.51 m	19.8
	1.77		1.75 m[e]	
3	1.23	43.2	1.21 td (13.6, 4.2)	43.0
	1.45		1.44 m	
4	/	34.3	/	34.3
5	0.99	57.3	0.98 m	57.2
6	1.70	19.4	1.70 m[e]	19.5
	1.83		1.84 m[e]	
7	1.58	40.4	1.59 td (12.8, 4.0)	40.1
	2.53 dd (12.4, 3.0)		2.53 dt (12.5, 3.3)	
8	/	40.5	/	41.0
9	1.36	54.7	1.35 m	54.5
10	/	40.0	/	39.1
11	1.80	18.0	1.81 m	17.7
	2.05 m		2.05 m	
12	2.97 m	28.5	2.99 ddd (18.4, 11.3, 7.6)	28.5
	3.15 dd (18.0, 6.2)		3.16 dd (16.8, 6.8)	
13	/	137.7	/	138.2
14	/	170.2	/	171.7
15	7.90 d (6.3)	124.7	7.99 d (6.6)	125.1
16	8.49 d (6.3)	143.3	8.58 d (6.6)	143.7
17	0.93 s	33.8	0.91 s	33.7
18	0.93 s	21.9	0.91 s	21.8
19	1.04 s	16.8	1.03 s	16.9
20	1.32 s	25.6	1.32 s	25.6
21	8.53 s	146.3	8.62 s	146.7
$-CH_2$*COOH*	/	170.5	/	168.6
$-$*CH_2*COOH	5.07 s	63.9	5.40 s	60.8

All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet. All spectra are measured in MeOD and are referenced to the residual solvent peak. [a] Recorded at 500 MHz. [b] Recorded at 125 MHz. [c] Recorded at 700 MHz. [d] Recorded at 176 MHz. [e] Signal overlapping.

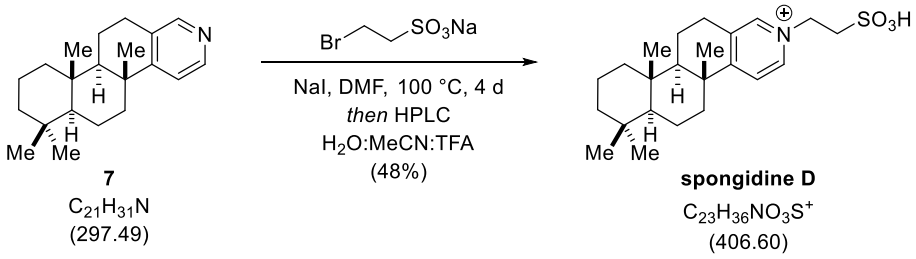
Comment on the comparison between the published NMR-data of the natural sample and the synthetic material: We observed a discrepancy, especially in the pyridinium ion moiety and the acetic acid substituent. We believe the unreported counterion of the pyridinium ion might cause the observed differences. The NMR-shift of the synthetic material obtained by Basabe and coworkers, which presumably has a bromide counterion to the pyridinium, is in good agreement with our material (only ^{13}C data available, Table 3).[6]

Table 3: NMR comparison of synthetic spongidine A (Basabe and coworkers) with synthetic material from this work.

No.	Basabe and coworkers[6] ^{13}C-NMR[a]	This work ^{13}C-NMR[b]
1	40.7	40.7
2	19.8	19.8
3	43.0	43.0
4	34.2	34.3
5	57.2	57.2
6	19.5	19.5
7	40.1	40.1
8	41.0	41.0
9	54.8	54.5
10	39.1	39.1
11	17.7	17.7
12	28.5	28.5
13	138.1	138.2
14	171.6	171.7
15	125.1	125.1
16	143.7	143.7
17	21.8	33.7
18	33.7	21.8
19	16.9	16.9
20	25.6	25.6
21	146.7	146.7
$-CH_2$*COOH*	168.7	168.6
$-$*CH*$_2$COOH	60.9	60.8

All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. All spectra are measured in MeOD and are referenced to the residual solvent peak. [a] Recorded at 100 MHz. [b] Recorded at 176 MHz.

Spongidine D



To a solution of pyridine **7** (3.3 mg, 11 μmol, 1.0 eq.) in DMF (0.2 mL) was added NaI (38 mg, 0.26 mmol, 23 eq.) and sodium 2-bromoethanesulfonate (18 mg, 83 μmol, 7.5 eq.) and stirred at 100 °C in a sand bath for 24 h. Sodium 2-bromoethanesulfonate (18 mg, 83 μmol, 7.5 eq.) was added, and the reaction mixture was stirred at 100 °C in a sand bath for 3 d. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with MeCN and filtered. The filtrate was concentrated and purified by reverse phase HPLC (MeCN:H_2O 70:30 + 0.1% TFA, flowrate: 0.7 mL/min) to afford the title compound (2.3 mg, 5.4 μmol, 48%) as colorless solid.

R_f = 0.36 (CH_2Cl_2/MeOH, 9:1).

$[\alpha]_D^{23}$ = −17.8 (*c* = 0.23, MeOH) [Lit[5]: **$[\alpha]_D$** = −6 (*c* = 0.016, MeOH), Lit[4]: **$[\alpha]_D^{22}$** = −10.1 (*c* = 0.02, MeOH)].

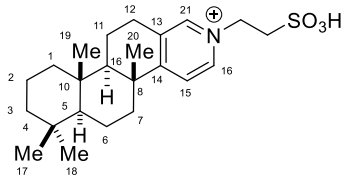
^{1}H-NMR (500 MHz, MeOH-d_4): δ [ppm] = 8.65 (s, 1H), 8.62 (d, *J* = 6.6 Hz, 1H), 7.88 (d, *J* = 6.6 Hz, 1H), 4.80 – 4.77 (m, 2H), 3.40 (t, *J* = 6.2 Hz, 2H), 3.18 – 3.10 (m, 1H), 2.96 (ddd, *J* = 18.4, 10.9, 8.0 Hz, 1H), 2.52 – 2.47 (m, 1H), 2.07 – 1.99 (m, 1H), 1.89 – 1.63 (m, 5H), 1.60 – 1.40 (m, 3H), 1.37 – 1.32 (m, 1H), 1.29 (s, 3H), 1.20 (td, *J* = 13.6, 4.1 Hz, 1H), 1.01 (s, 3H), 0.96 (d, *J* = 12.7 Hz, 2H), 0.91 (s, 3H), 0.90 (s, 3H).

Note: RSO_3H is not assigned.

^{13}C-NMR (176 MHz, MeOH-d_4): δ [ppm] = 170.9, 146.0, 142.8, 137.9, 124.9, 58.0, 57.2, 54.5, 51.5, 43.0, 40.8 (2C), 40.1, 39.1, 34.2, 33.7, 28.4, 25.5, 21.8, 19.8, 19.5, 17.8, 16.8.

IR (ν/cm^{-1}, ATR) = 3357, 2923, 2849, 1680, 1641, 1457, 1385, 1202, 1122, 1025, 976.

HRMS (ESI): *m/z* calculated for $C_{23}H_{36}NO_3S^+$ $[M]^+$: 406.2411, found 406.2414.



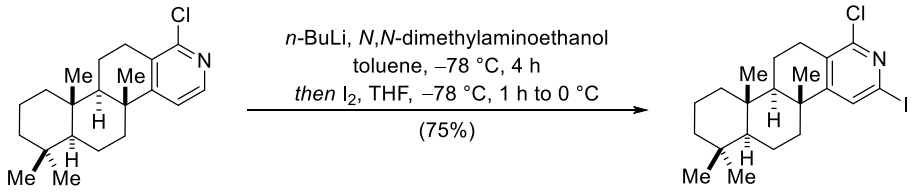
spongidine D

Table 4: NMR comparison of natural spongidine D with synthetic material.

	natural[5]		synthetic	
No.	^{1}H-NMR[a]	^{13}C-NMR[b]	^{1}H-NMR[c]	^{13}C-NMR[d]
1	0.97 1.88	40.8	0.96 d (12.7) 1.87 m[e]	40.8
2	not reported not reported	19.9	1.50 m 1.85 m[e]	19.5
3	1.22 1.46	43.2	1.20 td (13.6, 4.1) 1.45 m	43.0
4	/	34.6	/	34.2
5	0.95	57.3	0.95 d (12.7)	57.2
6	1.70 1.88	19.6	1.70 m[e] 1.85 m[e]	19.8
7	1.58 2.50 dd (12.4, 3.0)	39.7	1.56 m 2.50 m	40.1
8	/	40.2	/	40.8
9	1.35	54.6	1.34 m	54.5
10	/	39.2	/	39.1
11	1.79 2.06 m	16.9	1.80 m 2.03 m	17.8
12	2.98 m 3.25 dd (18.0, 6.2)	28.5	2.96 ddd (18.4, 10.9, 8.0) 3.14 m	28.4
13	/	137.8	/	137.9
14	/	171.0	/	170.9
15	7.93 d (6.3)	124.9	7.88 d (6.6)	124.9
16	8.65 d (6.3)	142.8	8.62 d (6.6)	142.8
17	0.93 s	33.8	0.90 s	33.7
18	0.93 s	21.3	0.91 s	21.8
19	1.04 s	16.9	1.01 s	16.8
20	1.32 s	25.6	1.29 s	25.5
21	8.68 s	146.1	8.65 s	146.0
$-CH_2CH_2SO_3H$	4.88 t (6.2)	57.5	4.85 m	58.0
$-CH_2CH_2SO_3H$	3.43 t (6.2)	51.1	3.40 t (6.2)	51.5

All chemical shifts are reported in ppm. Coupling constants are in parentheses and are reported in Hz. m = centered multiplet. All spectra are measured in MeOD and are referenced to the residual solvent peak. [a] Recorded at 500 MHz. [b] Recorded at 125 MHz. [c] Recorded at 700 MHz. [d] Recorded at 176 MHz. [e] Signal overlapping.

Chloroiodopyridine **8**



1

$C_{21}H_{30}ClN$
(331.93)

8

$C_{21}H_{29}ClIN$
(457.82)

To a solution of *N*,*N*-dimethylaminoethanol (freshly distilled over KOH, 92.9 µL, 82.3 mg, 923 µmol, 8.0 eq.) in toluene (1.0 mL) at −78 °C was added *n*-BuLi (2.5 M, 739 µL, 1.85 mmol, 16.0 eq.) dropwise. After 15 min, a solution of chloropyridine **1** (38.3 mg, 115 µmol, 1.0 eq.) in toluene (2.0 mL) was added dropwise over 5 min. After 4 h a solution of I_2 (264 mg, 1.04 mmol, 9.0 eq.) in THF (1.3 mL) was added dropwise. The reaction temperature was maintained at −78 °C for 1 h. Then the reaction mixture was stirred for 40 min at 0 °C (change of cooling baths). Water (3 mL) and EtOAc were added, and the phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc 1:0 to 40:1 to 25:1 to 15:1) to afford the title compound (39.6 mg, 86.5 µmol, 75%) as a slightly yellow solid.

$\mathbf{R_f}$ = 0.29 (*n*-pentane/EtOAc, 50:1).

$[\alpha]_D^{20}$ = −57.8 (*c* = 3.96, $CHCl_3$).

^{1}H-NMR (700 MHz, $CDCl_3$): δ [ppm] = 7.49 (s, 1H), 2.88 (dd, *J* = 18.4, 6.5 Hz, 1H), 2.58 (ddd, *J* = 18.8, 11.5, 7.8 Hz, 1H), 2.28 – 2.22 (m, 1H), 1.95 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.82 – 1.76 (m, 1H), 1.75 – 1.71 (m, 1H), 1.69 – 1.56 (m, 2H), 1.56 – 1.48 (m, 1H), 1.48 – 1.43 (m, 2H), 1.42 – 1.37 (m, 1H), 1.18 (s, 3H), 1.16 – 1.12 (m, 2H), 0.91 (s, 3H), 0.87 (s, 3H), 0.85 – 0.82 (m, 5H).

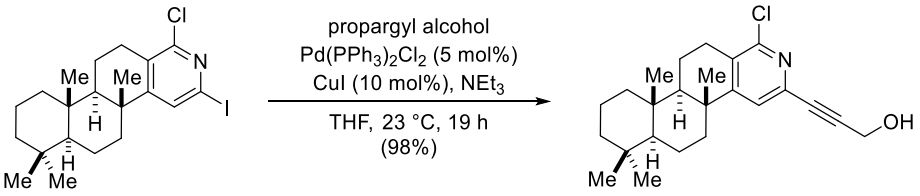
^{13}C-NMR (176 MHz, $CDCl_3$): δ [ppm] = 164.0, 150.9, 130.4, 129.8, 111.4, 56.1, 53.6, 42.0, 40.0, 39.8, 38.7, 37.8, 33.4 (2C), 28.2, 25.7, 21.6, 19.0, 18.6, 17.1, 16.4.

IR (ν/cm^{-1}, ATR) = 2925, 2848, 2362, 2094, 1728, 1551, 1525, 1458, 1384, 1096, 1023.

HRMS (ESI): *m/z* calculated for $C_{21}H_{29}ClINNa^+$ $[M+Na]^+$: 480.0925, found 480.0949.

Mp: 93 - 95 °C.

Alkyne **9**



8

$C_{21}H_{29}ClIN$
(457.82)

9

$C_{24}H_{32}ClNO$
(385.98)

To a suspension of CuI (1.6 mg, 8.37 µmol, 10 mol%) and $Pd(PPh_3)Cl_2$ (2.9 mg, 4.18 µmol, 5 mol%) in THF (0.5 mL) was added NEt_3 (69.6 µL, 50.8 mg, 502 µmol, 6.0 eq.) and propargyl alcohol (14.5 µL, 14.1 mg, 251 µmol, 3.0 eq.) sequentially. A solution of chloroiodopyridine **8** (38.3 mg, 83.7 µmol, 1.0 eq.) in THF (3.0 mL) was added, and the reaction flask was stirred at 23 °C for 19 h in the dark. The reaction mixture was directly purified by flash column chromatography (SiO_2, *n*-pentane/EtOAc 10:1 to 5:1 to 2:1) to afford the title compound (31.6 mg, 81.9 µmol, 98%) as a slightly brown solid.

R_f = 0.74 (*n*-pentane/EtOAc, 1:1).

$[\alpha]_D^{20}$ = −45.2 (*c* = 0.48, $CHCl_3$).

^{1}H-NMR (700 MHz, $CDCl_3$): δ [ppm] = 7.25 (s, 1H), 4.49 (s, 2H), 2.94 (dd, *J* = 18.6, 6.2 Hz, 1H), 2.64 (ddd, *J* = 18.8, 11.4, 7.7 Hz, 1H), 2.28 (d, *J* = 12.1 Hz, 1H), 2.23 – 2.12 (s_{br}, 1H), 1.95 (dd, *J* = 13.5, 7.5 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.75 – 1.69 (m, 1H), 1.67 – 1.57 (m, 2H), 1.57 – 1.48 (m, 1H), 1.48 – 1.42 (m, 2H), 1.42 – 1.35 (m, 1H), 1.16 (s, 3H), 1.16 – 1.10 (m, 2H), 0.91 (s, 3H), 0.88 – 0.81 (m, 8H).

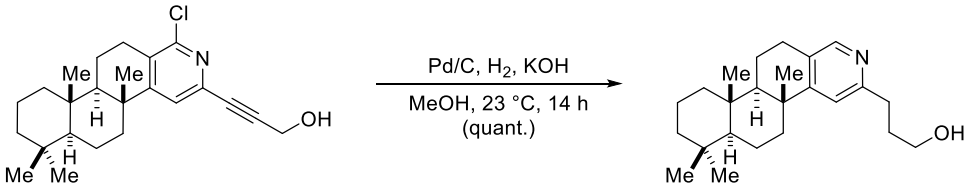
^{13}C-NMR (176 MHz, $CDCl_3$): δ [ppm] = 162.5, 151.7, 139.2, 130.4, 122.7, 87.3, 84.3, 56.1, 53.7, 51.6, 42.0, 40.0, 39.8, 38.6, 37.7, 33.4 (2C), 28.7, 25.6, 21.5, 19.0, 18.6, 17.2, 16.3.

IR (ν/cm^{-1}, ATR) = 3377, 2924, 2853, 1732, 1577, 1528, 1458, 1437, 1379, 1047.

HRMS (ESI): *m/z* calculated for $C_{24}H_{32}ClNONa^+$ $[M+Na]^+$: 408.2064, found 408.2080.

Mp: 167 - 168 °C (Decomposition).

Alcohol **10**



9

$C_{24}H_{32}ClNO$
(385.98)

10

$C_{24}H_{37}NO$
(355.57)

A suspension of Pd/C (10 wt%, 39.7 mg, 37.3 μmol, 4.8 eq.) and KOH (3.9 mg, 70.0 μmol, 9.0 eq.) in MeOH (2 mL) was purged with H_2 (balloon) for 2 min. A solution of alkyne **9** (3.0 mg, 7.8 μmol, 1.0 eq.) in MeOH (4 mL) was added, and purging was continued for 2 min. The reaction mixture was stirred at 23 °C for 16 h under an H_2 (balloon) atmosphere. The suspension was filtered through a Celite® pad with $CHCl_3$ as the eluent. The mixture was concentrated under reduced pressure to obtain the title compound (3.0 mg, 8.4 μmol, quant.) as a colorless solid.

R_f = 0.48 (CH_2Cl_2/MeOH, 9:1).

$[\alpha]_D^{22}$ = −44.0 (*c* = 0.30, $CHCl_3$).

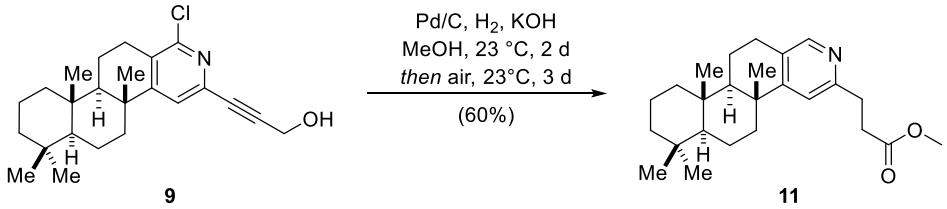
^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.14 (s, 1H), 6.99 (s, 1H), 3.71 (t, *J* = 5.7 Hz, 2H), 2.92 – 2.86 (m, 3H), 2.72 (ddd, *J* = 17.7, 11.4, 7.4 Hz, 1H), 2.37 – 2.27 (m, 1H), 1.99 – 1.85 (m, 3H), 1.84 – 1.76 (m, 1H), 1.76 – 1.68 (m, 1H), 1.68 – 1.58 (m, 2H), 1.57 – 1.51 (m, 1H), 1.50 – 1.36 (m, 3H), 1.24 – 1.19 (m, 1H), 1.17 (s, 3H), 1.15 – 1.11 (m, 2H), 0.92 (s, 3H), 0.88 – 0.81 (m, 8H).

^{13}C-NMR (176 MHz, $CDCl_3$): δ [ppm] = 159.8, 158.2, 149.2, 128.3, 118.6, 62.9, 56.4, 54.7, 42.2, 39.9 (2C), 38.2, 37.9, 35.7, 33.5, 33.4, 31.7, 27.5, 25.8, 21.6, 19.0, 18.7, 17.6, 16.5.

IR (ν/cm^{-1}, ATR) = 3289, 2923, 2855, 2362, 1736, 1600, 1547, 1381, 1196, 1072.

HRMS (ESI): *m/z* calculated for $C_{24}H_{38}NO^+$ $[M+H]^+$: 356.2948, found 356.2964.

Petrosaspongiolide L methyl ester **11**



9

$C_{24}H_{32}ClNO$
(385.98)

11

$C_{25}H_{37}NO_2$
(383.58)

A suspension of Pd/C (10 wt%, 81.6 mg, 76.7 μmol, 2.0 eq.) and KOH (10.8 mg, 192 μmol, 5.0 eq.) in MeOH (3 mL) was purged with H_2 (balloon) for 2 min. A solution of alkyne **9** (14.8 mg, 38.3 μmol, 1.0 eq.) in MeOH (5 mL) was added, and purging was continued for 2 min. After 23 h Pd/C (10 wt%, 122 mg, 115 μmol, 3.0 eq.) and KOH (12.9 mg, 230 μmol, 6.0 eq.) were added, and the reaction mixture was purged with H_2 (balloon). After stirring under an H_2 atmosphere for 16 h Pd/C (10 wt%, 122 mg, 115 μmol, 3.0 eq.) and KOH (19.4 mg, 345 μmol, 9.0 eq.) were added, and the reaction mixture was purged with H_2 (balloon). After 16 h the H_2 atmosphere was exchanged, and air was slowly introduced. After 3 d the suspension was filtered through a Celite® pad with $CHCl_3$. The mixture was concentrated under reduced pressure and purified by preparative TLC (SiO_2, *n*-pentane/EtOAc 11:4) to afford the title compound (8.8 mg, 22.9 μmol, 60%) as a colorless solid.

R_f = 0.72 (EtOAc).

$[\alpha]_D^{22}$ = −43.5 (*c* = 0.62, $CHCl_3$).

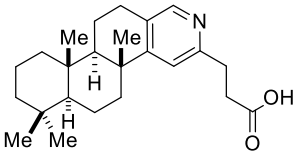
^{1}H-NMR (700 MHz, $CDCl_3$): δ [ppm] = 8.17 (s, 1H), 7.01 (s, 1H), 3.66 (s, 3H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.89 (dd, *J* = 17.0, 6.3 Hz, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.74 – 2.68 (m, 1H), 2.38 – 2.30 (m, 1H), 1.89 (dd, *J* = 13.4, 7.5 Hz, 1H), 1.82 – 1.77 (m, 1H), 1.75 – 1.71 (m, 1H), 1.69 – 1.59 (m, 2H), 1.58 – 1.50 (m, 1H), 1.48 – 1.43 (m, 2H), 1.42 – 1.37 (m, 1H), 1.23 – 1.18 (m, 1H), 1.17 (s, 3H), 1.15 – 1.12 (m, 1H), 0.93 (s, 3H), 0.88 – 0.83 (m, 8H).

^{13}C-NMR (176 MHz, $CDCl_3$): δ [ppm] = 173.8, 159.8, 156.7, 149.6, 128.7, 118.6, 56.4, 54.7, 51.8, 42.2, 39.9 (2C), 38.2, 37.9, 33.9, 33.5, 33.4, 32.8, 27.5, 25.8, 21.6, 19.0, 18.7, 17.6, 16.5.

IR (ν/cm^{-1}, ATR) = 2925, 2851, 2363, 1739, 1598, 1550, 1441, 1371, 1250, 911.

HRMS (ESI): *m/z* calculated for $C_{25}H_{38}NO_2^+$ $[M+H]^+$: 384.2897, found 384.2900.

Petrosaspongiolide L

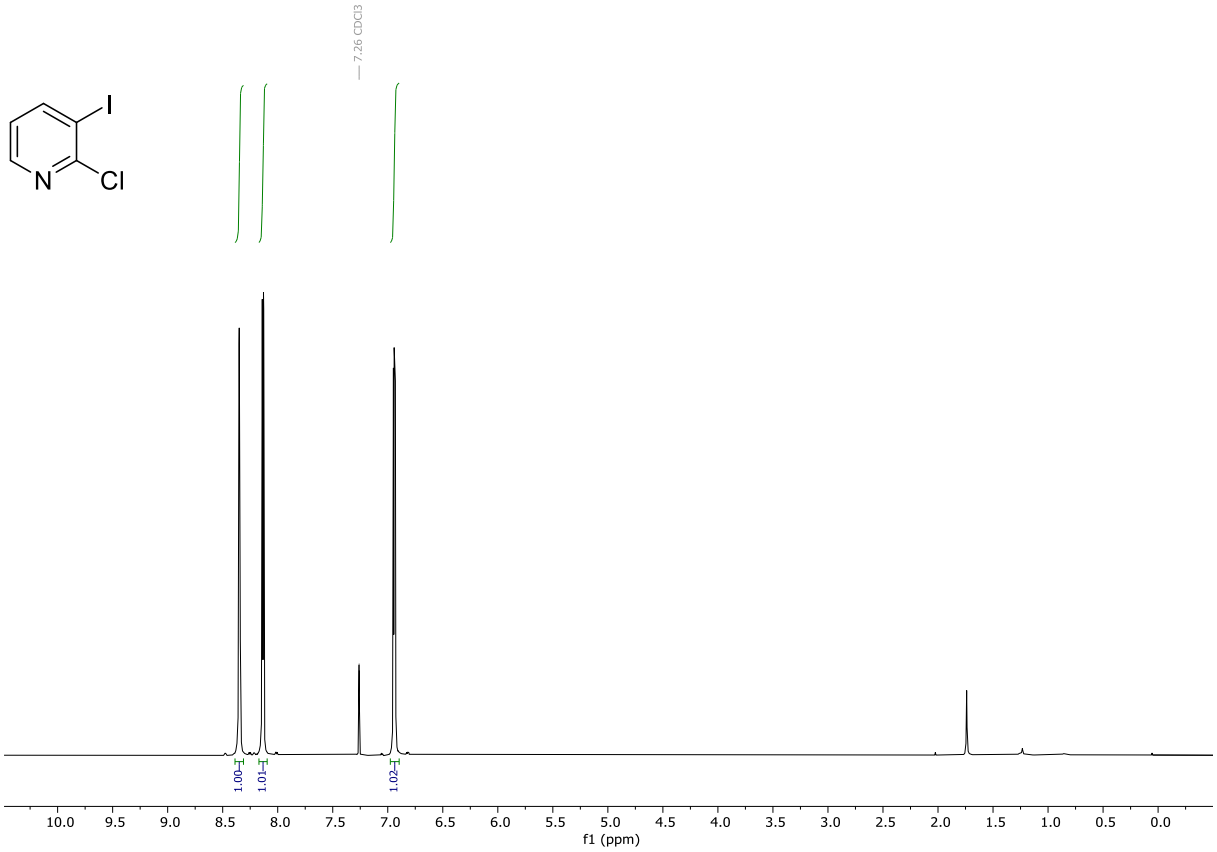


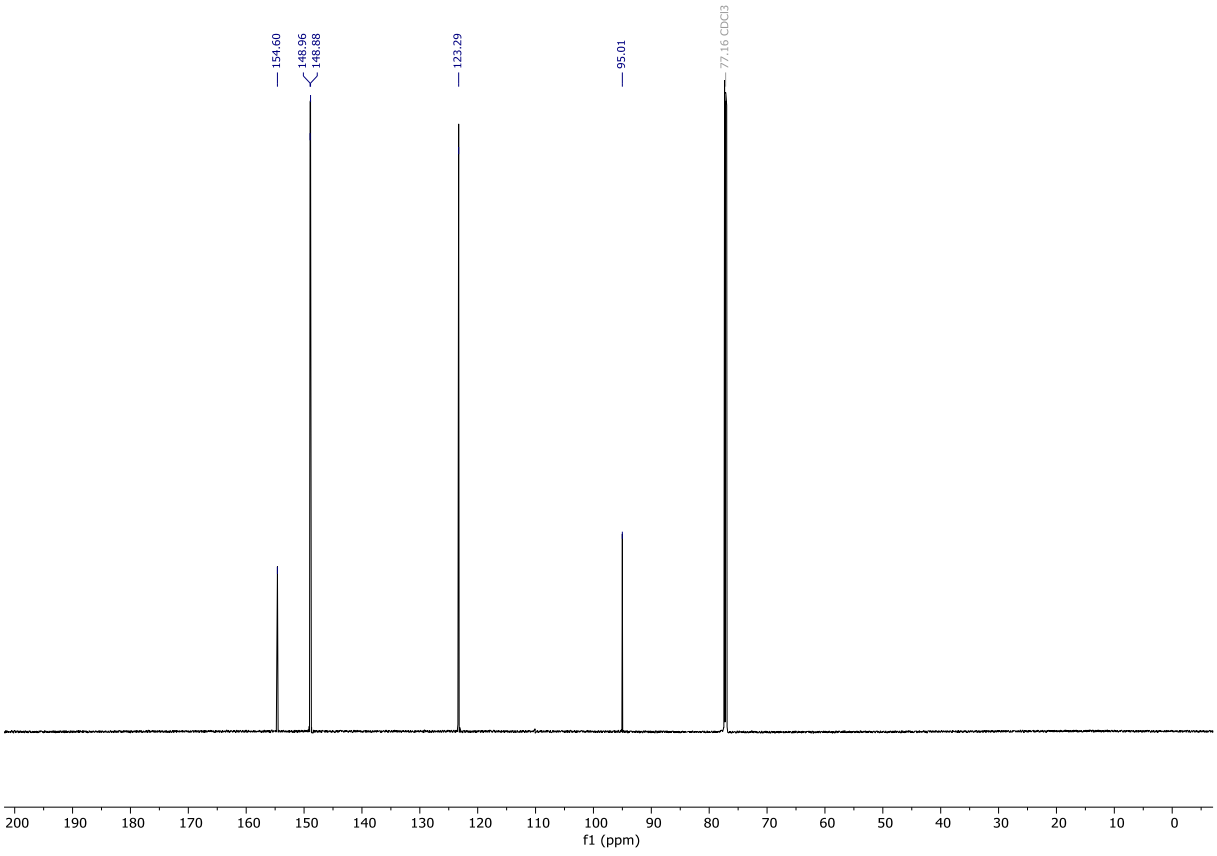
Petrosaspongiolide L

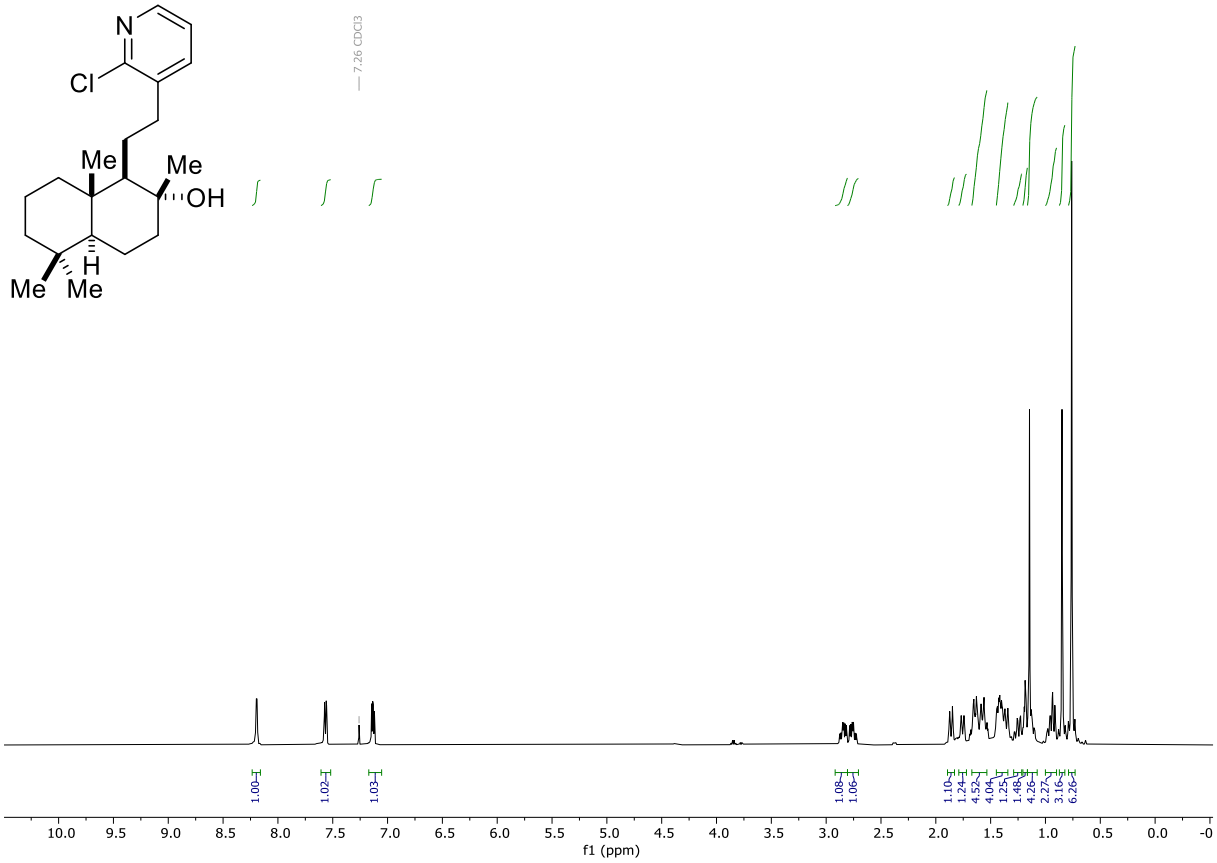
$C_{24}H_{35}NO_2$
(369.55)

HRMS (ESI): *m/z* calculated for $C_{24}H_{35}NO_2$ $[M+H]^+$: 370.2741, found 370.2759.

5. NMR-Spectra






N
Cl
Me
Me
OH
H
Me
Me
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1.00
1.02
1.03
1.08
1.06
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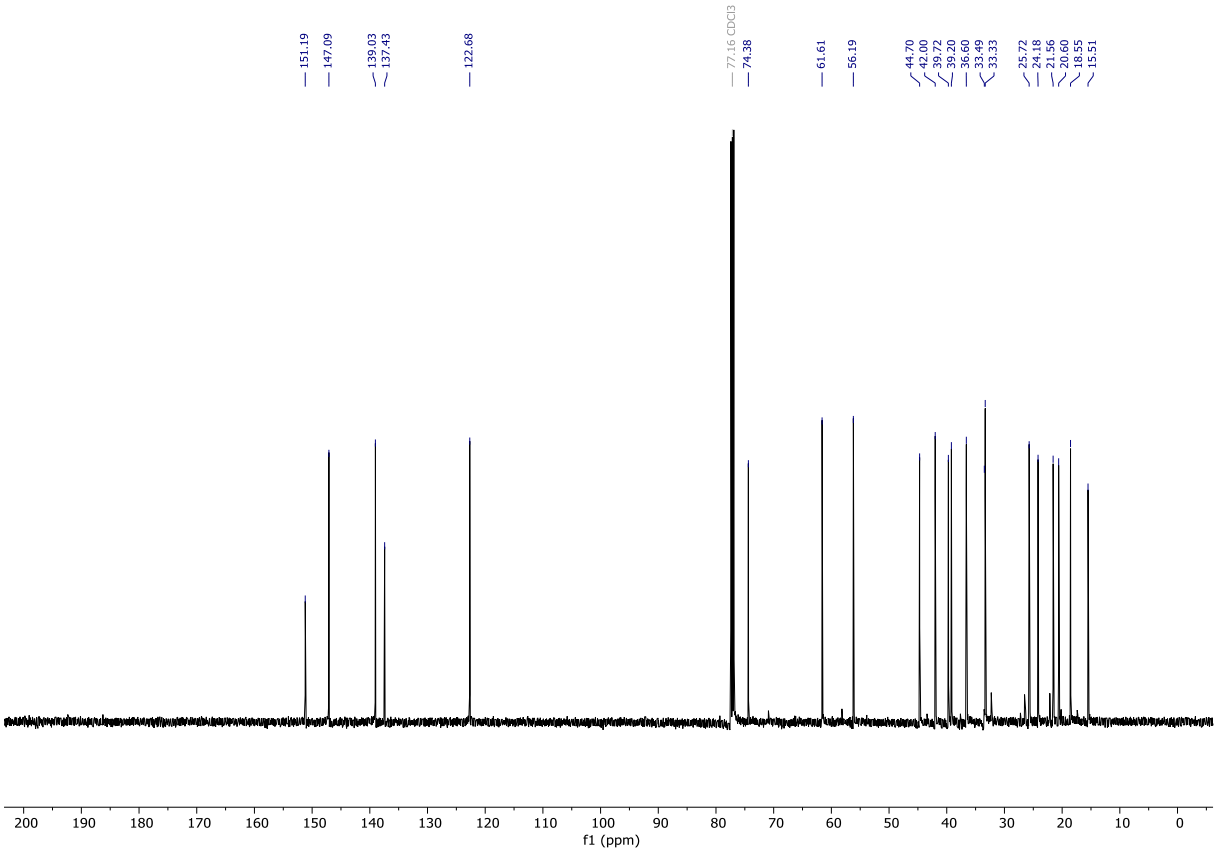
1.24
4.52
4.04
1.25
1.48
4.26
2.27
3.16
6.26
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)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39.20
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33.49
33.33
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21.56
20.60
18.55
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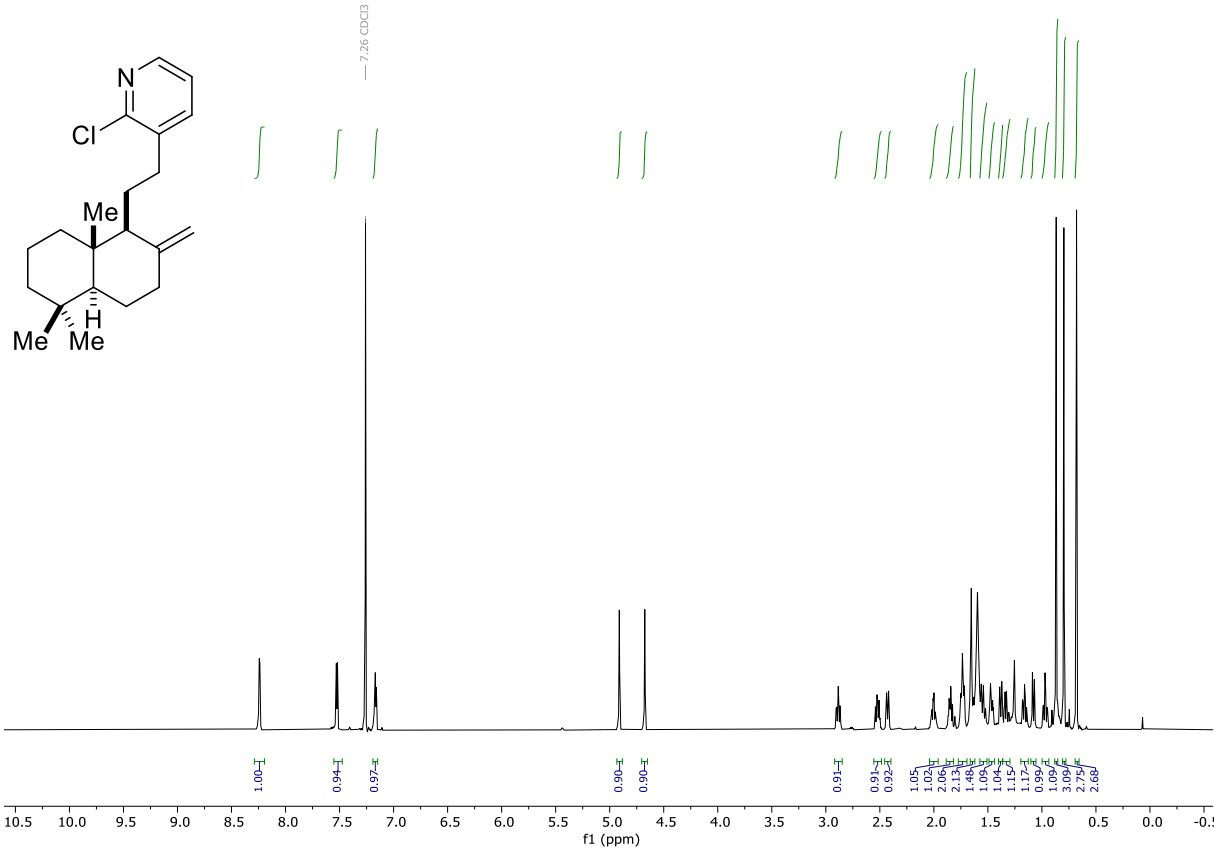
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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Me
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Me
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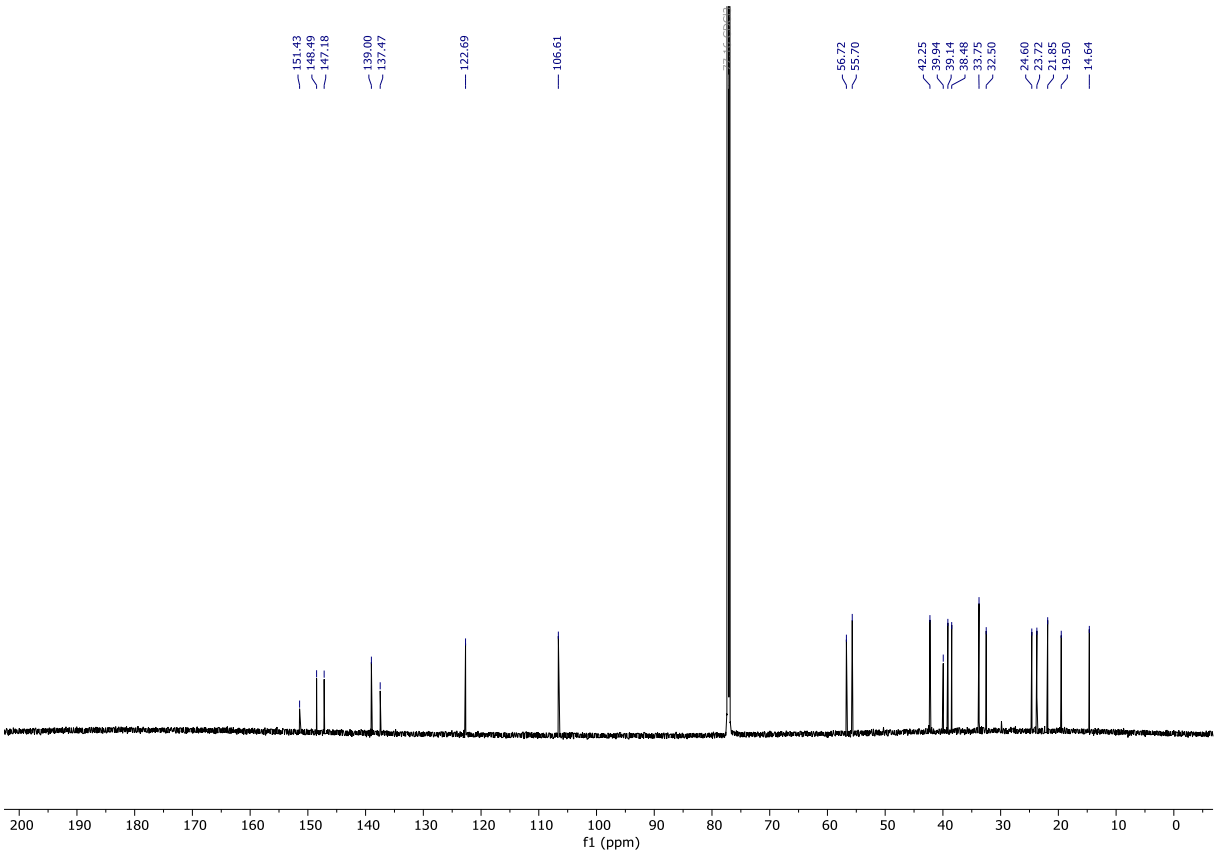
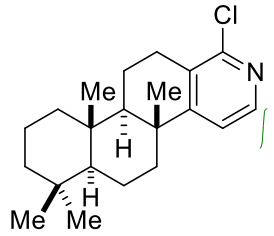
0.92
1.05
1.02
2.06
2.13
1.48
1.09
1.04
1.15
1.17
0.99
1.09
3.09
2.75
2.68
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


151.43
148.49
147.18
139.00
137.47
122.69
106.61
56.72
55.70
42.25
39.94
39.14
38.48
33.75
32.50
24.60
23.72
21.85
19.50
14.64
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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N
Me
Me
H
H
Me
Me

7.26 CDCl3
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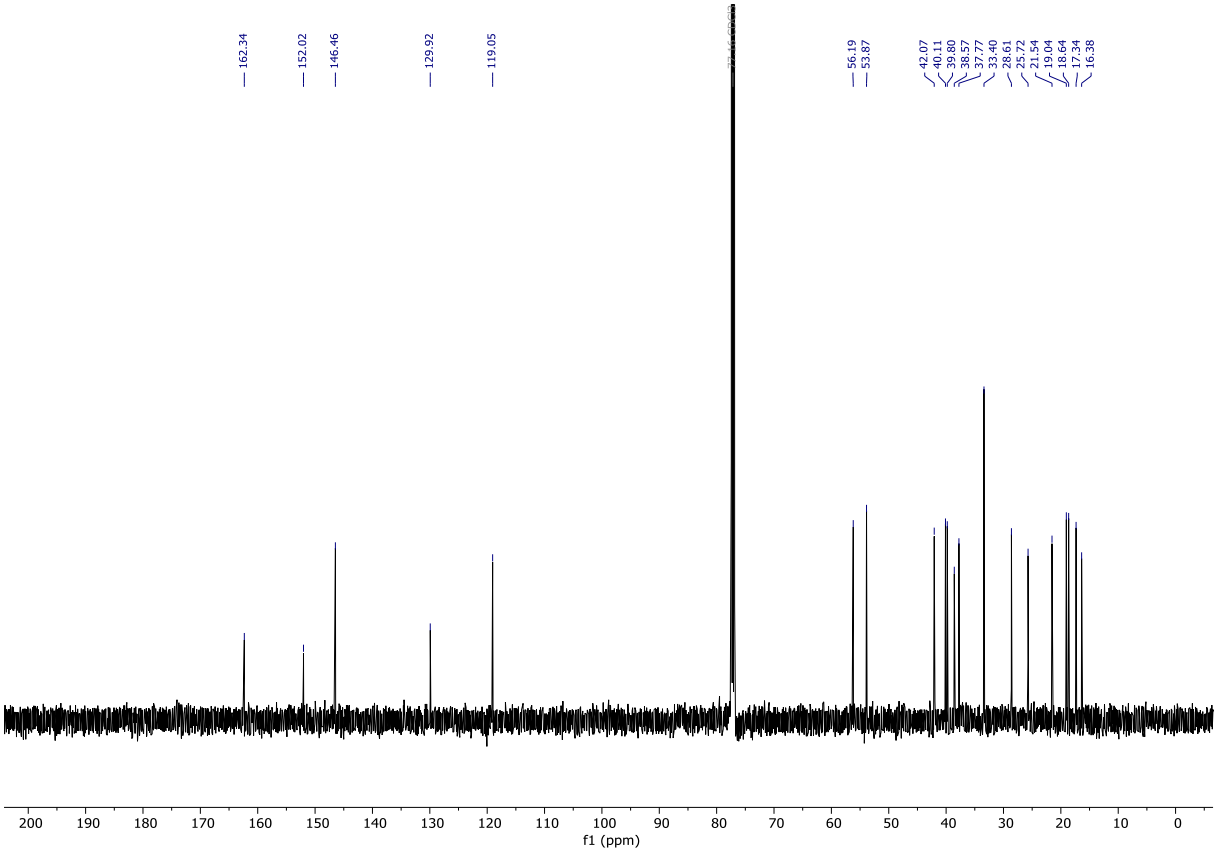
1.05
1.06
1.05
1.10
1.06
1.08
1.19
2.43
1.23
1.99
1.46
0.82
2.94
1.24
3.04
3.61
3.99
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


162.34
152.02
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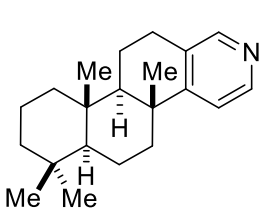
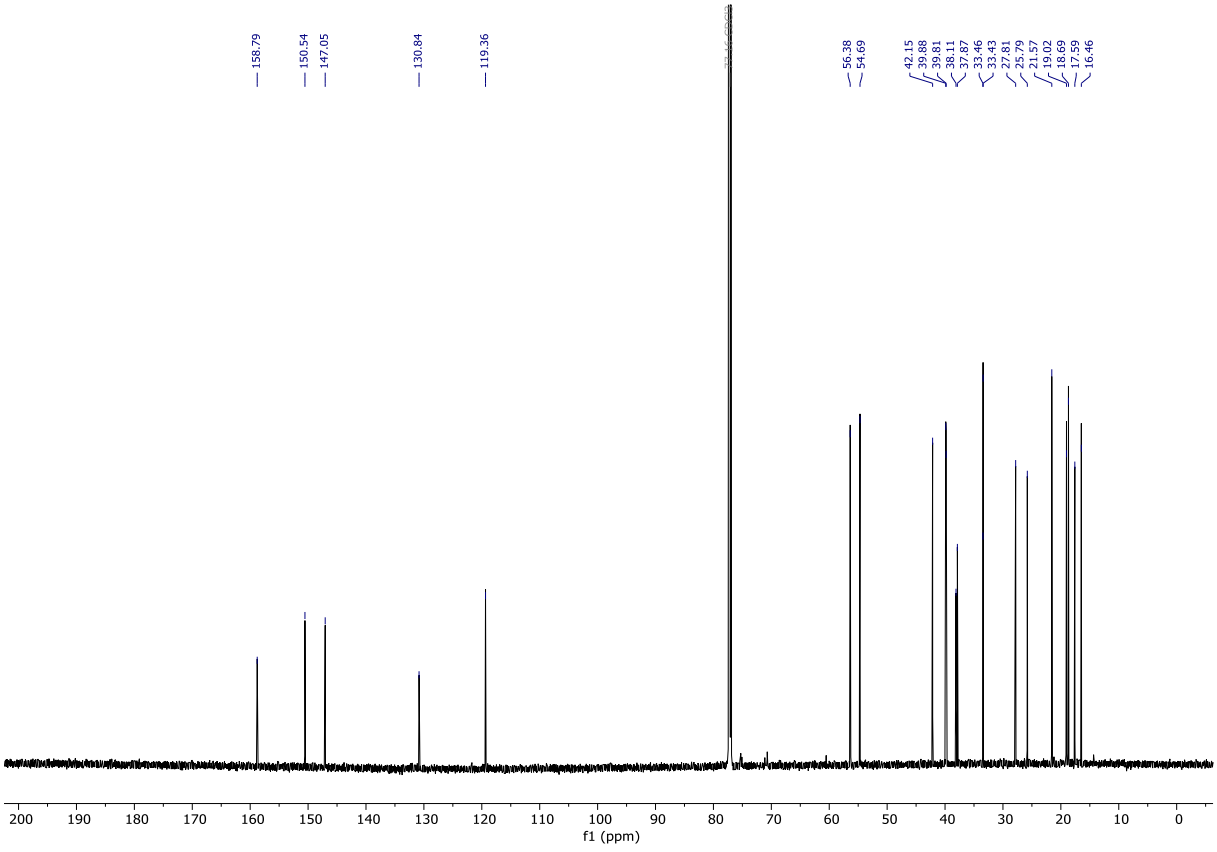
129.92
119.05
56.19
53.87
42.07
40.11
39.80
38.57
37.77
33.40
28.61
25.72
21.54
19.04
18.64
17.34
16.38
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
N
H
H
Me
Me

7.26 CDCl3
1.07
0.95
1.00
1.03
1.03
1.06
1.09
1.14
1.12
2.23
1.18
2.17
1.12
1.49
3.02
1.30
3.14
8.71
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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150.54
147.05
130.84
119.36
56.38
54.69
42.15
39.88
39.61
38.11
37.67
33.46
33.43
27.81
25.79
21.57
19.02
18.69
17.39
16.46
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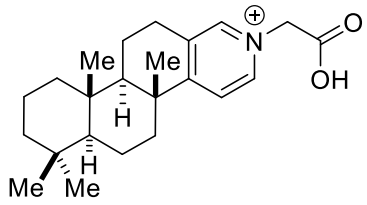
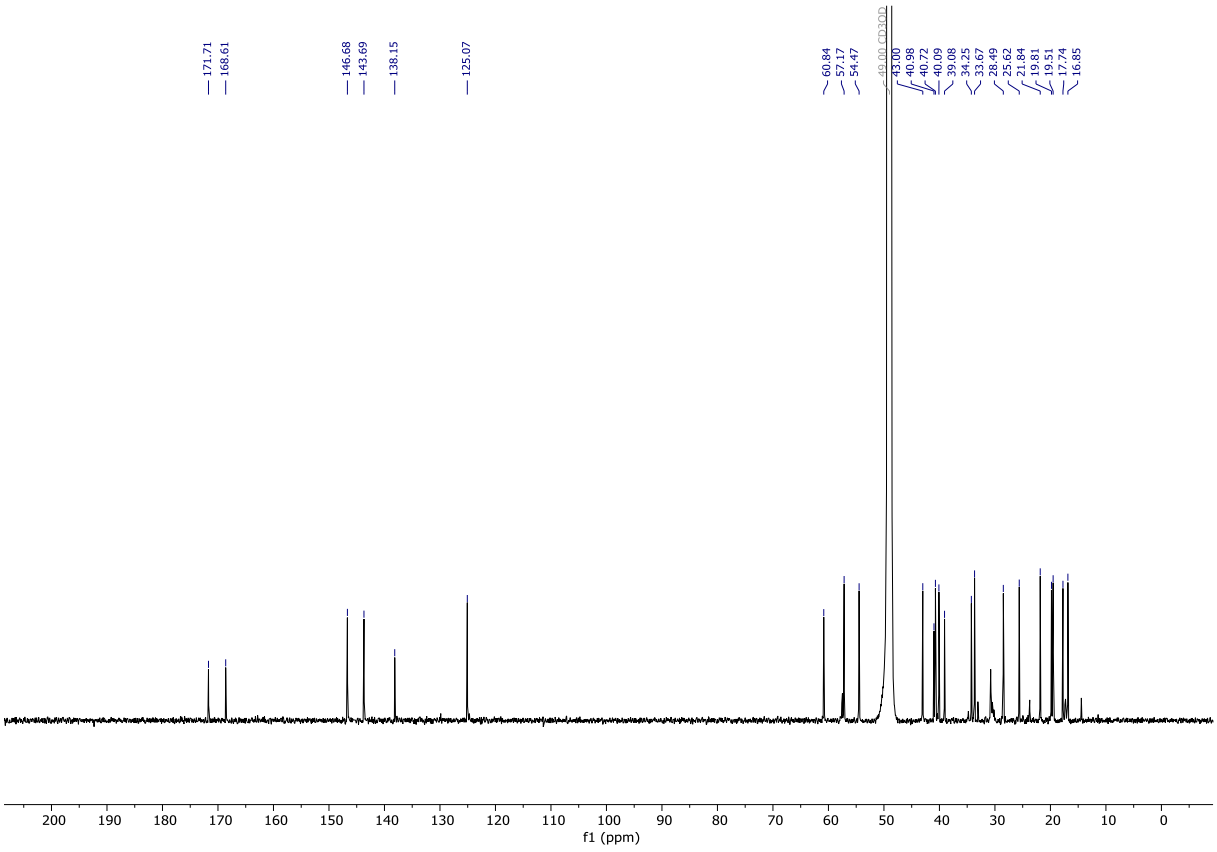
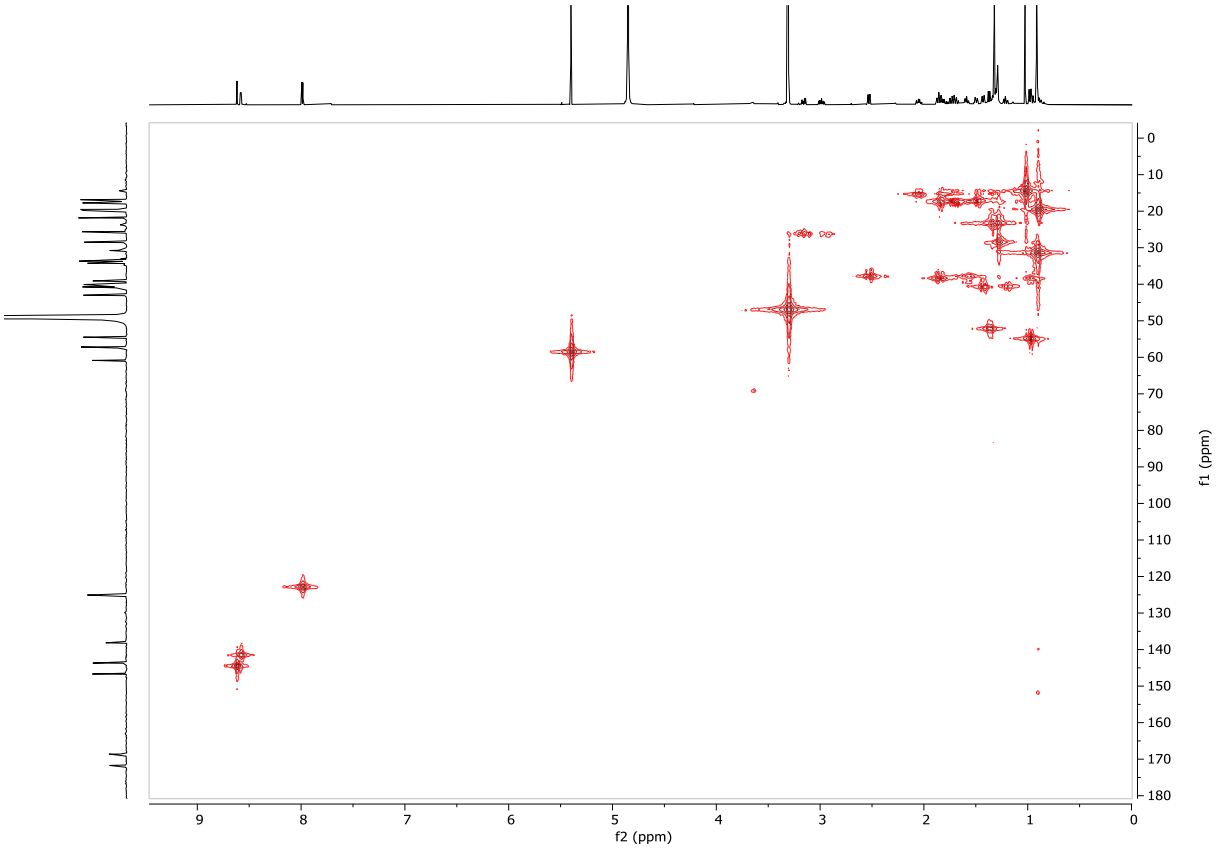
f1 (ppm)


Me
Me
H
H
Me
Me
N
O
OH

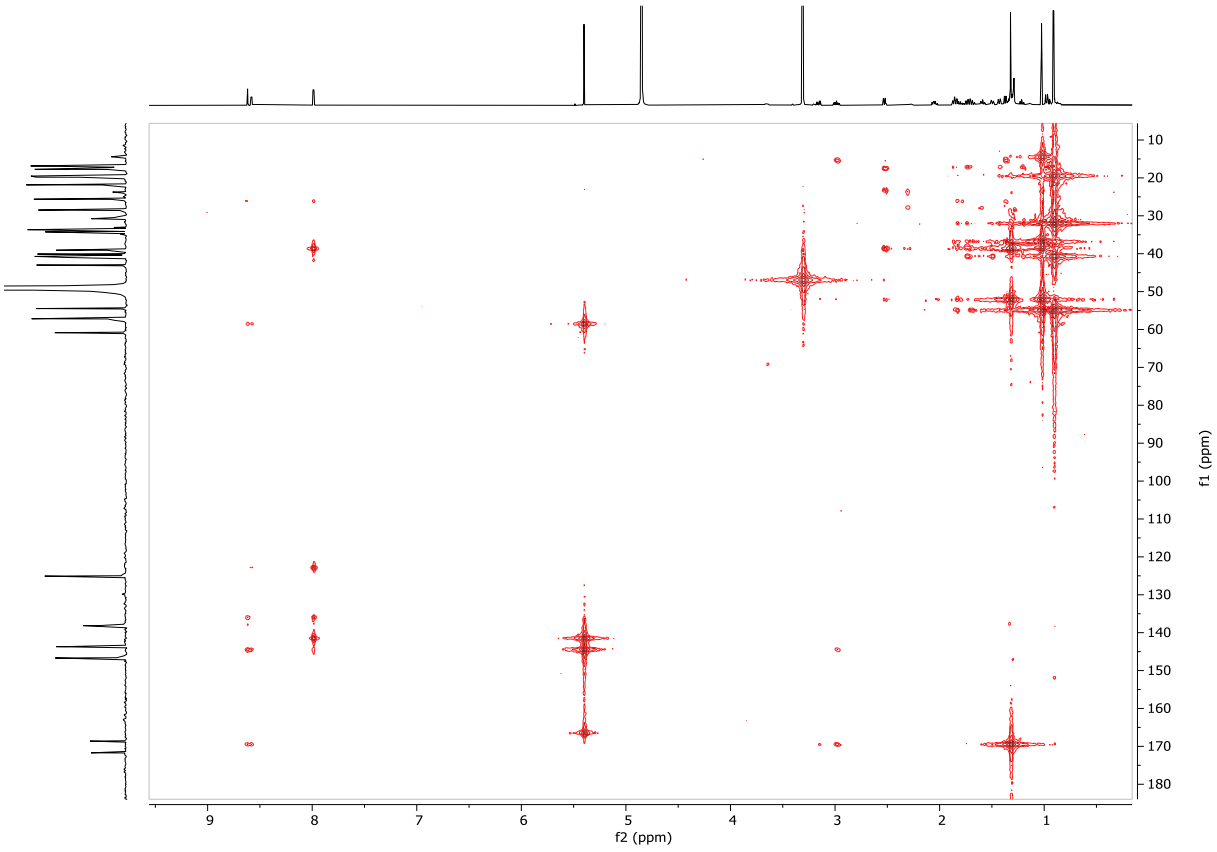
0.94
0.95
0.93
1.96
1.10
1.06
1.08
1.28
6.49
1.76
1.25
1.28
1.29
3.11
1.28
2.96
1.93
5.98
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

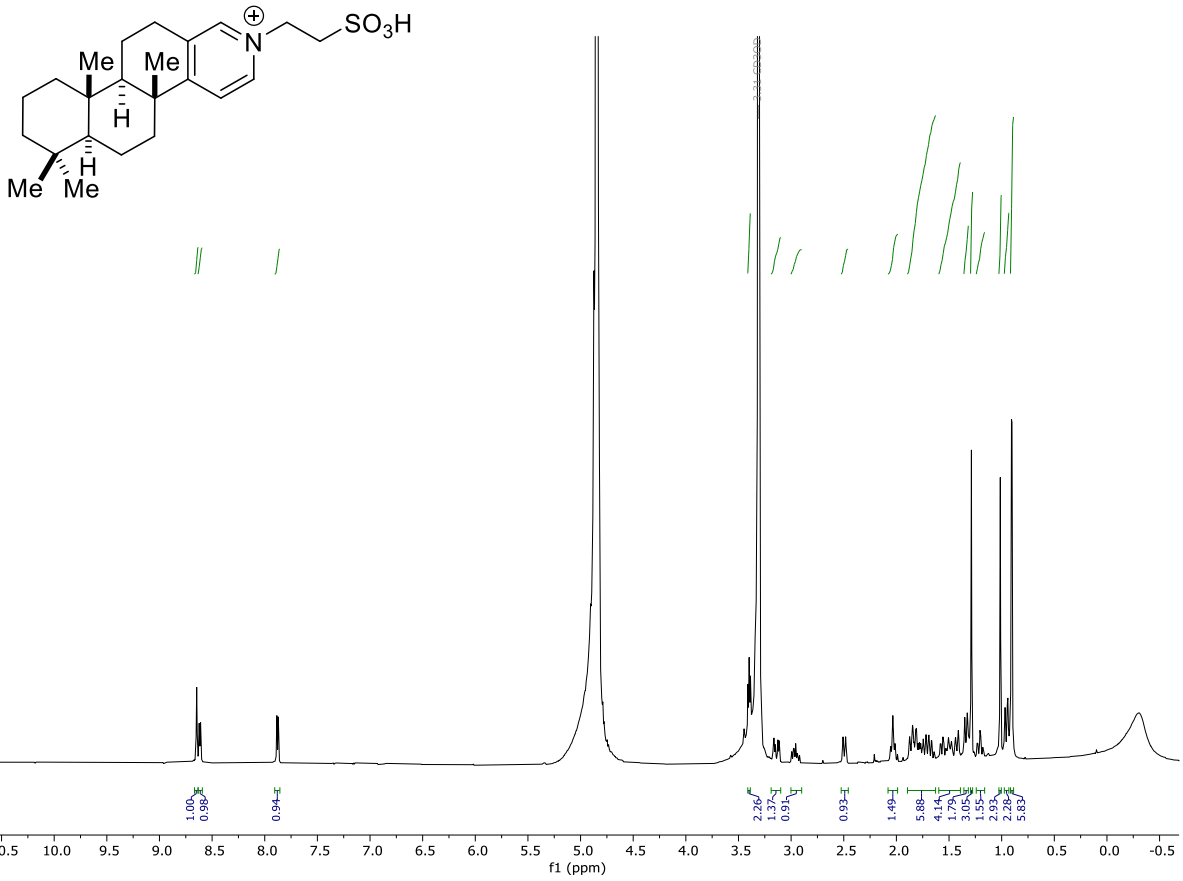

171.71
168.61
146.68
143.69
138.15
125.07
60.84
57.17
54.47
49.00 CD3OD
43.00
40.98
40.72
40.09
39.08
34.25
33.67
28.49
25.62
21.84
19.81
19.51
17.74
16.85
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

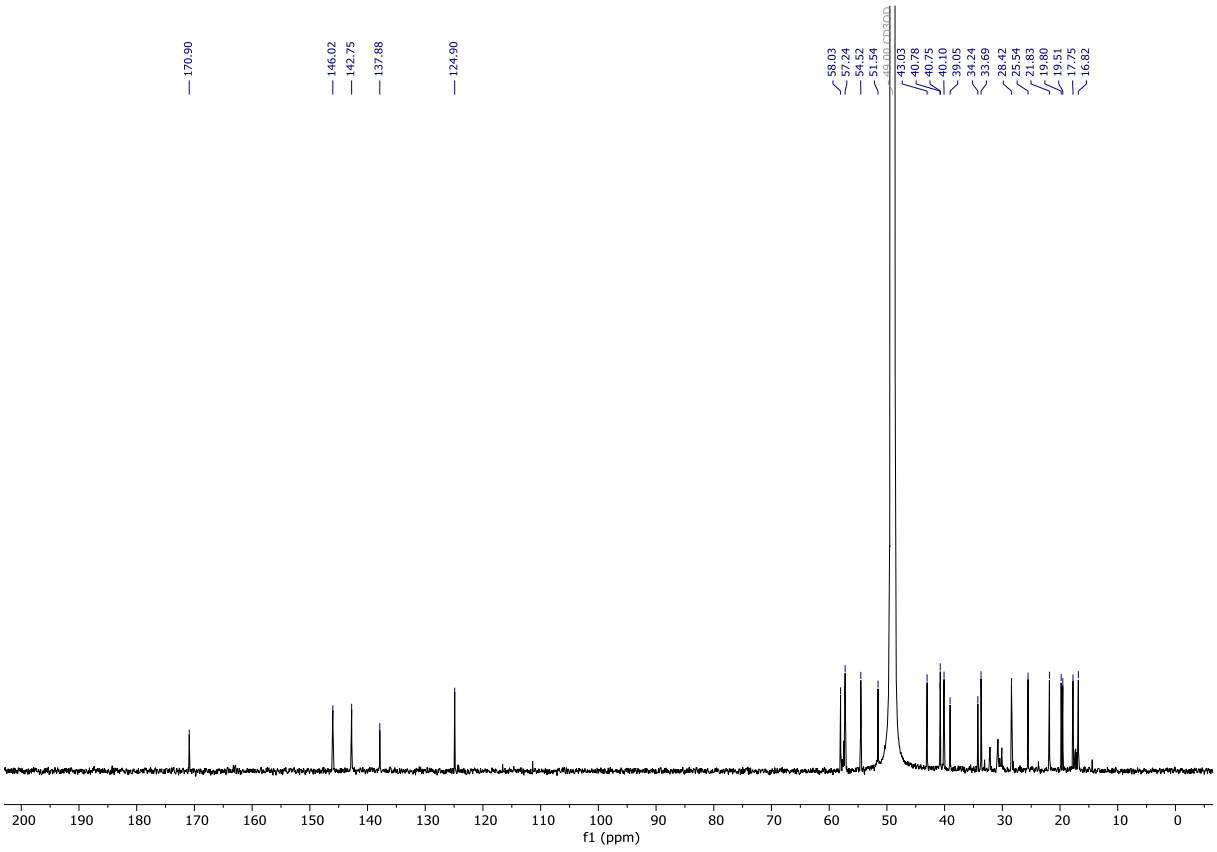
HMQC of spongidine A



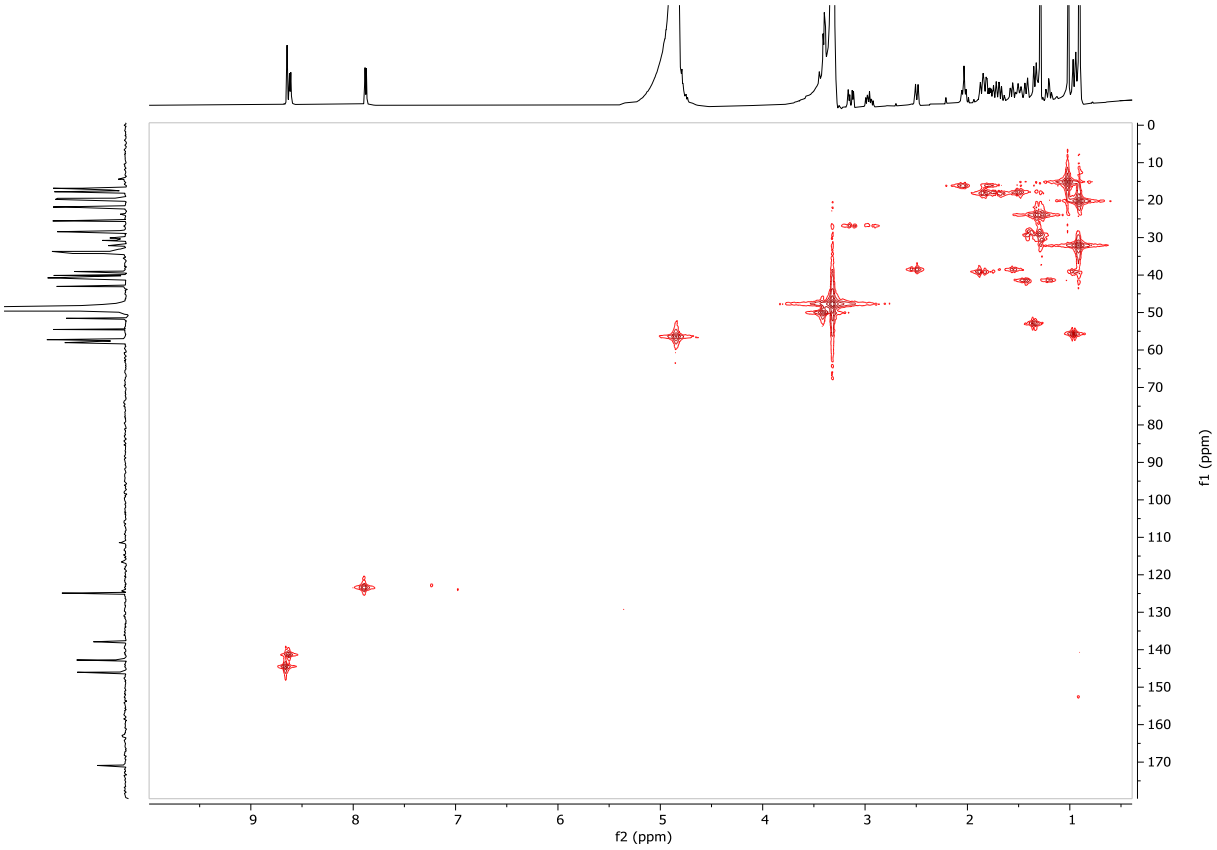
HMBC of spongidine D



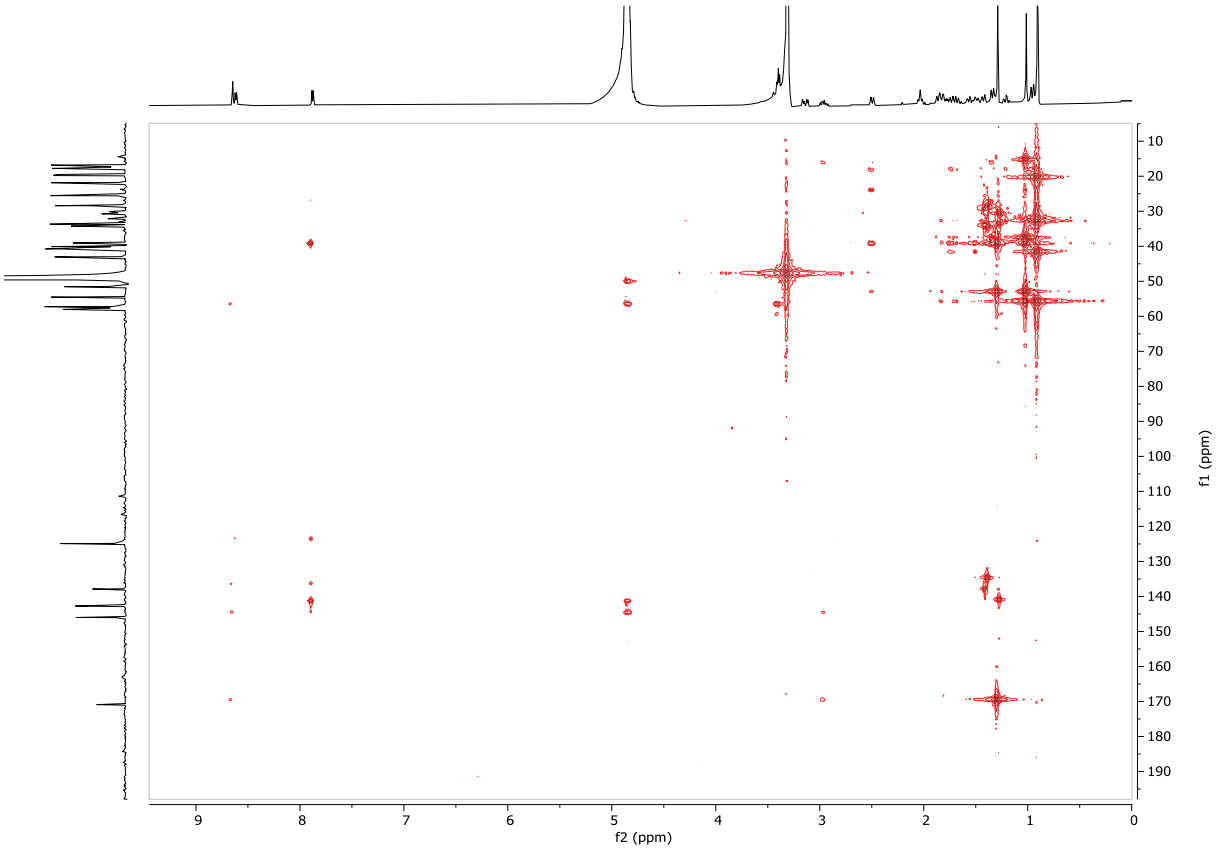

SO3H
N
Me
Me
H
H
Me
Me
1.00
0.98
0.94
2.26
1.37
0.91
0.93
1.49
5.88
4.14
1.79
3.05
1.55
2.93
2.28
5.83
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

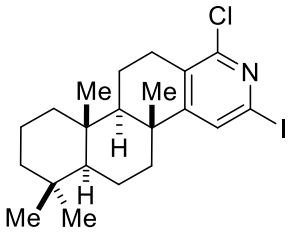

170.90
146.02
142.75
137.88
124.90
58.03
57.24
54.52
51.54
43.03
40.78
40.75
40.10
39.05
34.24
33.69
28.42
25.54
21.83
19.80
19.51
17.75
16.82
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HMQC of spongidine D

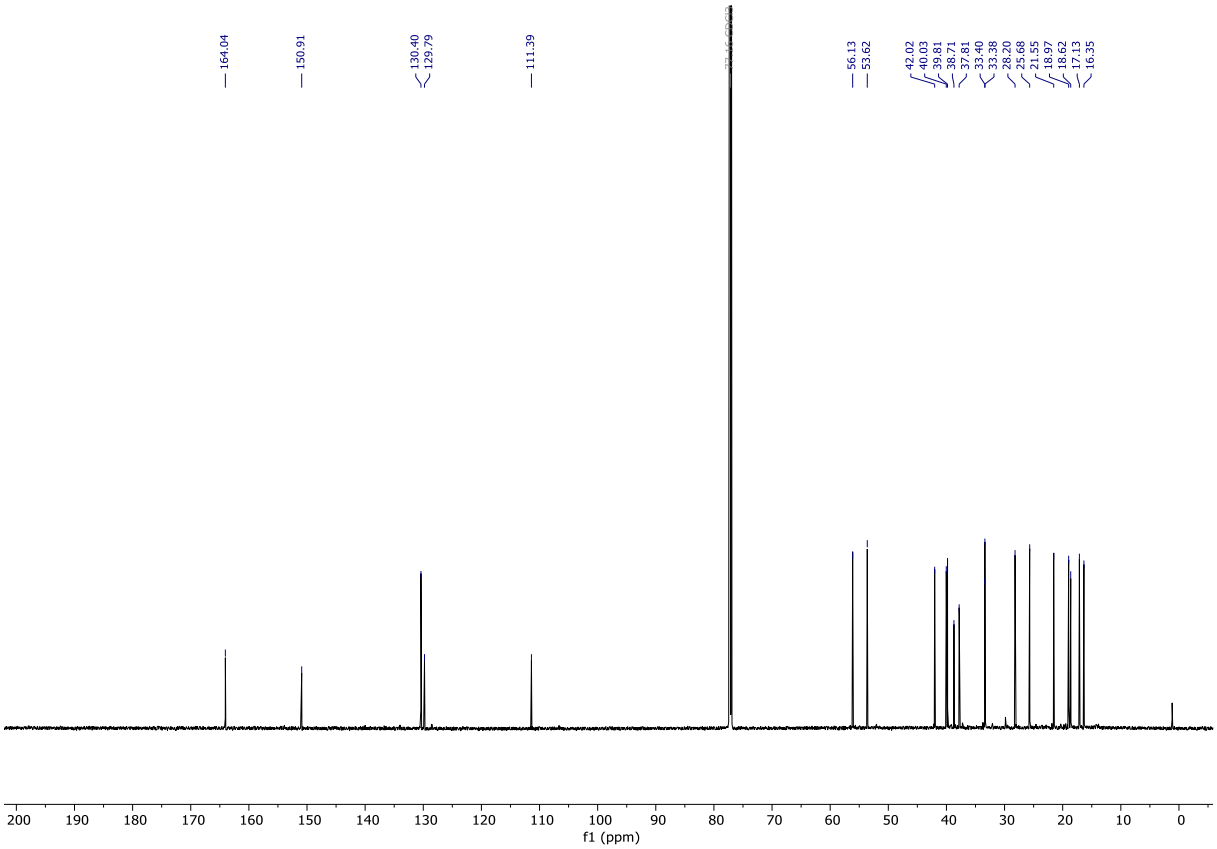


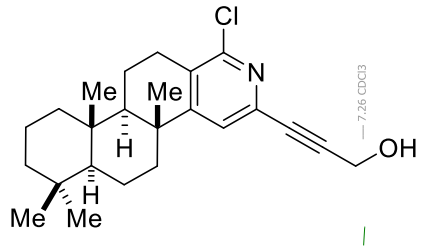
HMBC of spongidine D



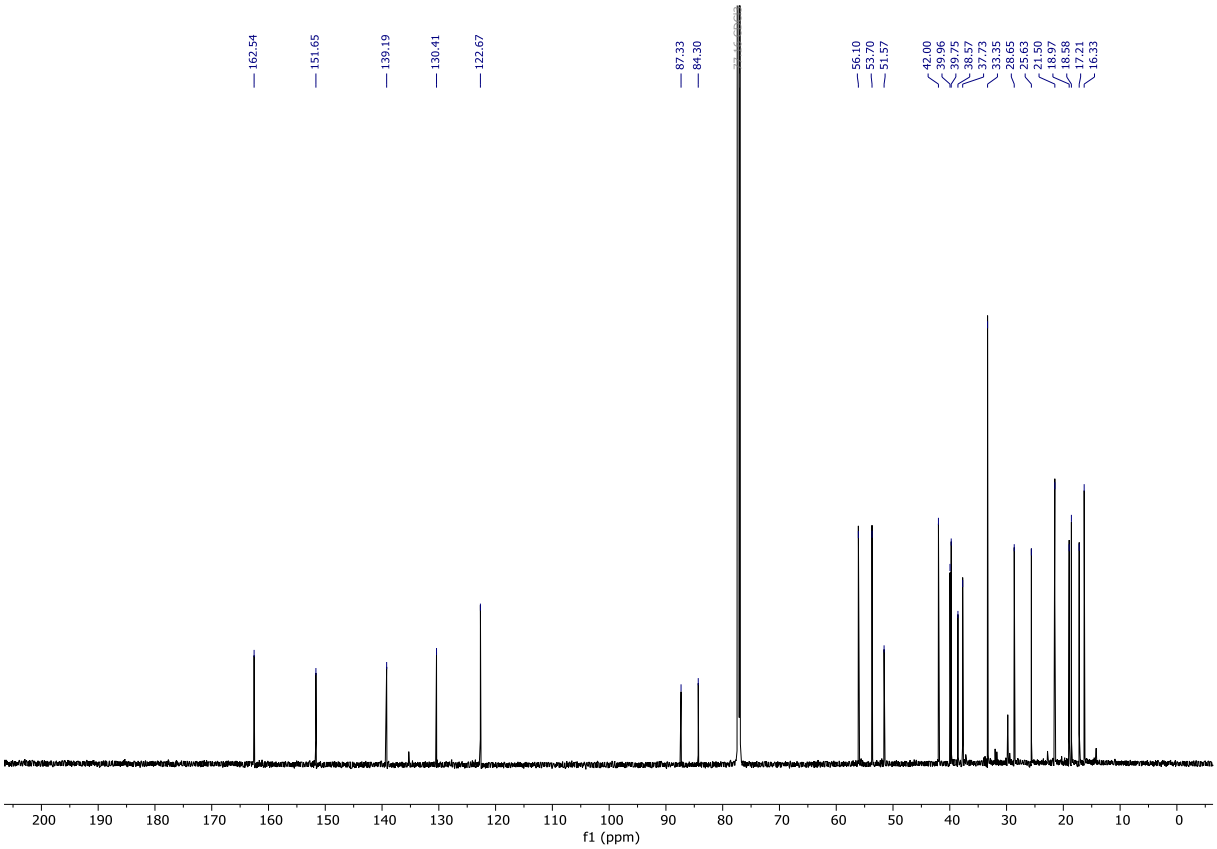

Cl
N
I
Me
Me
H
H
Me
Me

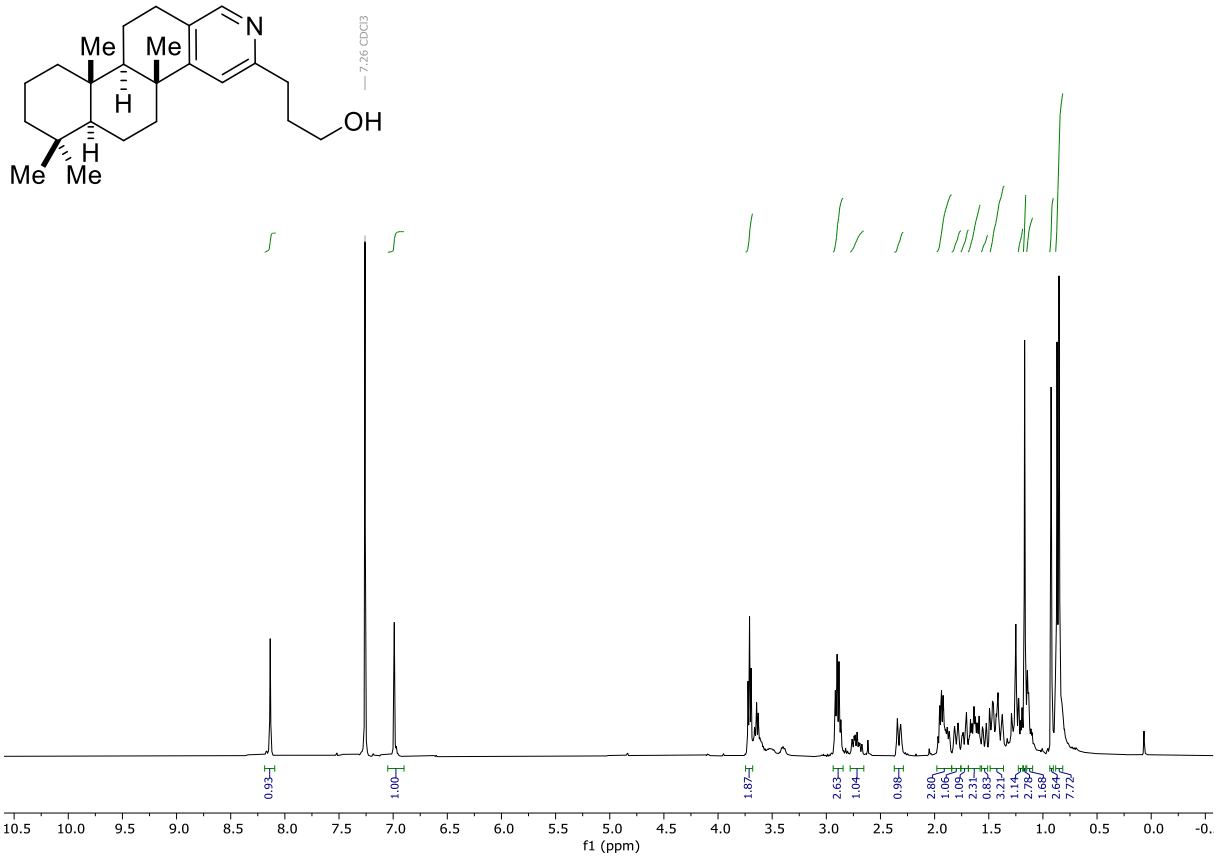
7.26 CDCl3
1.00
0.96
0.96
1.00
0.99
0.97
0.97
2.42
1.10
2.10
1.18
2.85
2.37
2.99
3.09
5.30
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.
f1 (ppm)

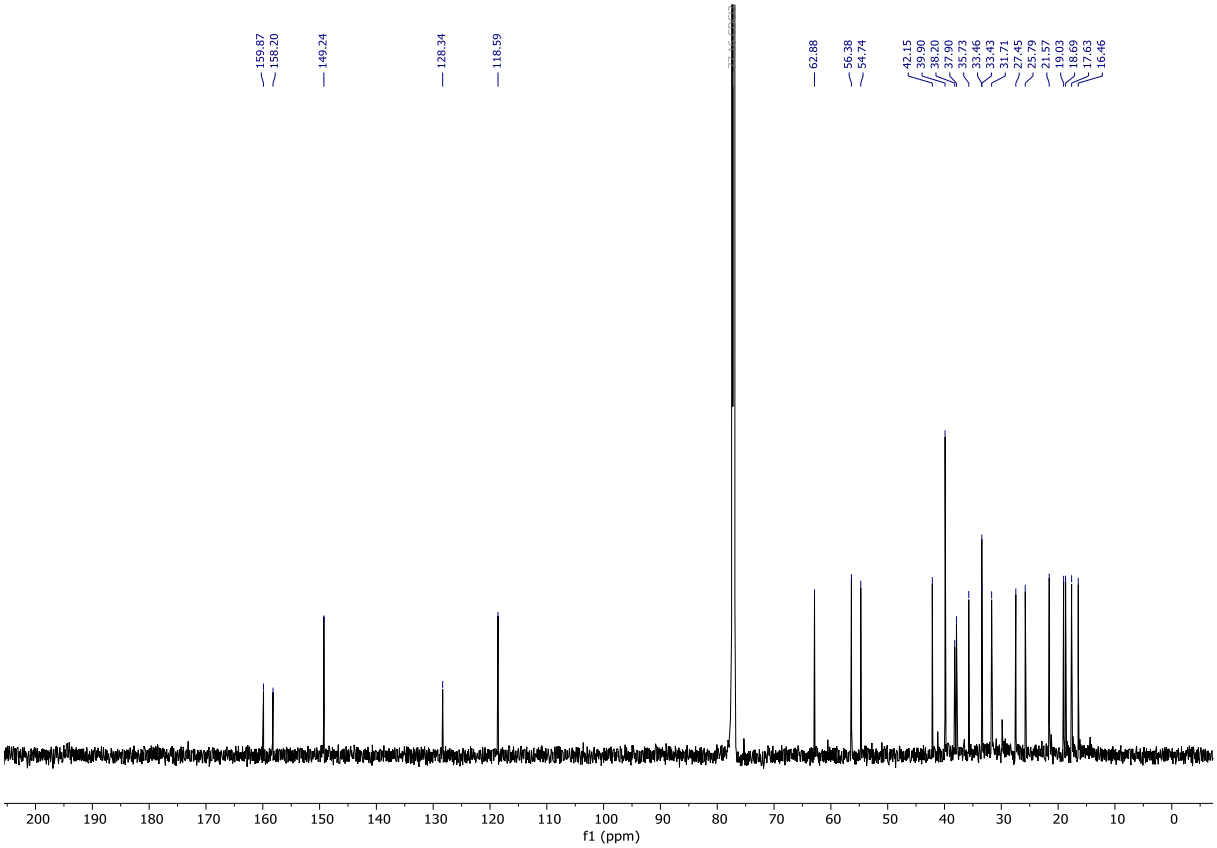

164.04
150.91
130.40
129.79
111.39
56.13
53.62
42.02
40.03
39.81
38.71
37.81
33.40
33.38
28.20
25.68
21.55
18.97
18.62
17.13
16.35
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

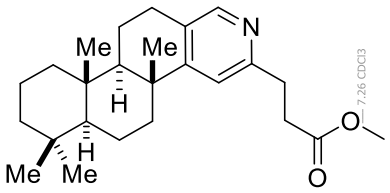

Cl
N
Me
Me
H
OH
H
Me
Me

7.26 CDCl3
1.00
2.00
0.97
0.97
1.12
0.84
1.07
1.03
1.05
2.32
1.23
1.90
1.48
2.83
2.36
2.91
8.33
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

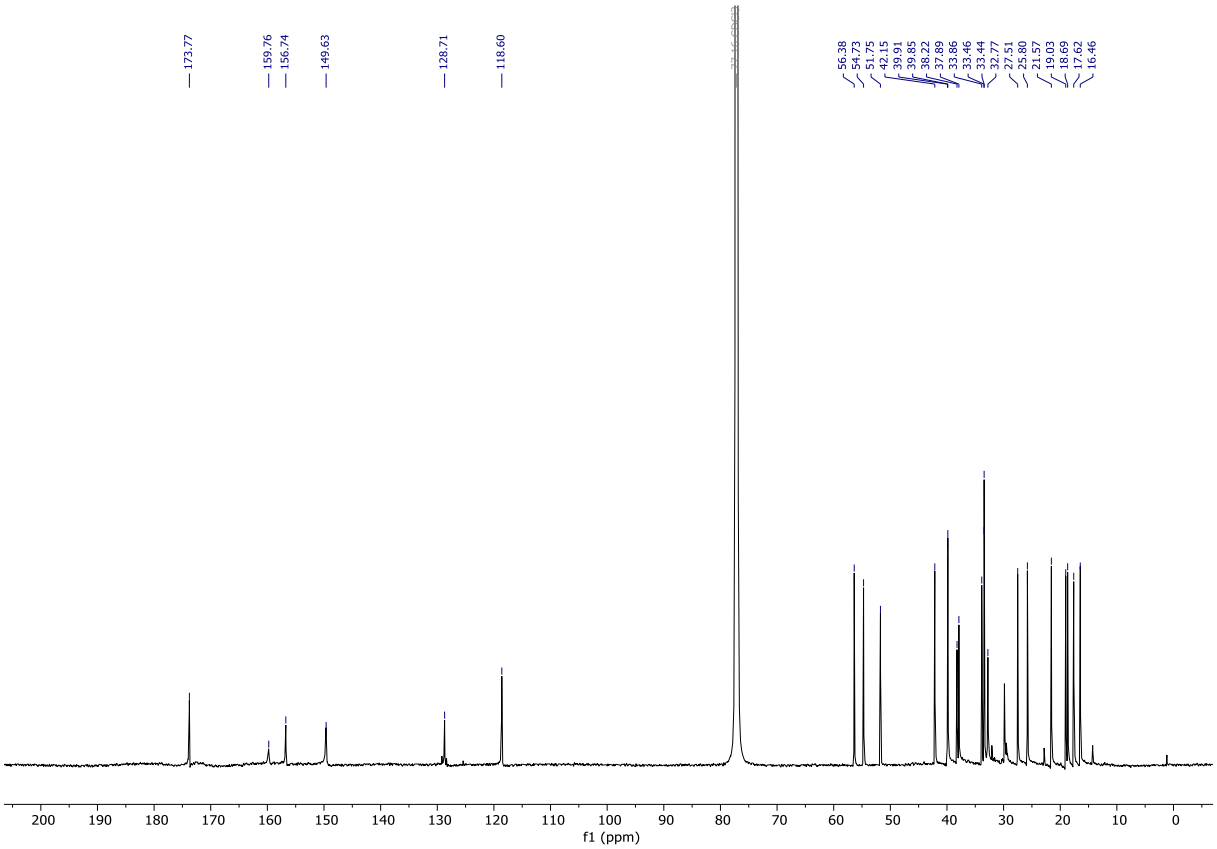

162.54
151.65
139.19
130.41
122.67
87.33
84.30
77.16 CDCl3
56.10
53.70
51.57
42.00
39.96
39.75
38.57
37.73
33.35
28.65
25.63
21.50
18.97
18.58
17.21
16.33
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
Me
H
N
OH
H
Me
Me
7.26 CDCl3
0.93
1.00
1.87
2.63
1.04
0.98
2.80
1.06
1.09
2.31
0.83
3.21
1.14
2.78
1.68
2.64
7.72
f1 (ppm)


159.87
158.20
149.24
128.34
118.59
62.88
56.38
54.74
42.15
39.90
39.20
37.90
35.73
33.46
33.43
31.71
27.45
25.79
21.57
19.03
18.69
17.63
16.46
f1 (ppm)


Me
Me
N
H
H
Me
Me
O
O

7.26 CDCl3
1.00
1.00
3.13
2.11
1.18
1.90
0.90
1.26
1.36
1.37
1.39
2.39
1.36
2.39
1.29
1.36
2.88
1.01
3.25
8.43
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


173.77
159.76
156.74
149.63
128.71
118.60
77.16 CDCl3
56.38
54.73
51.75
42.15
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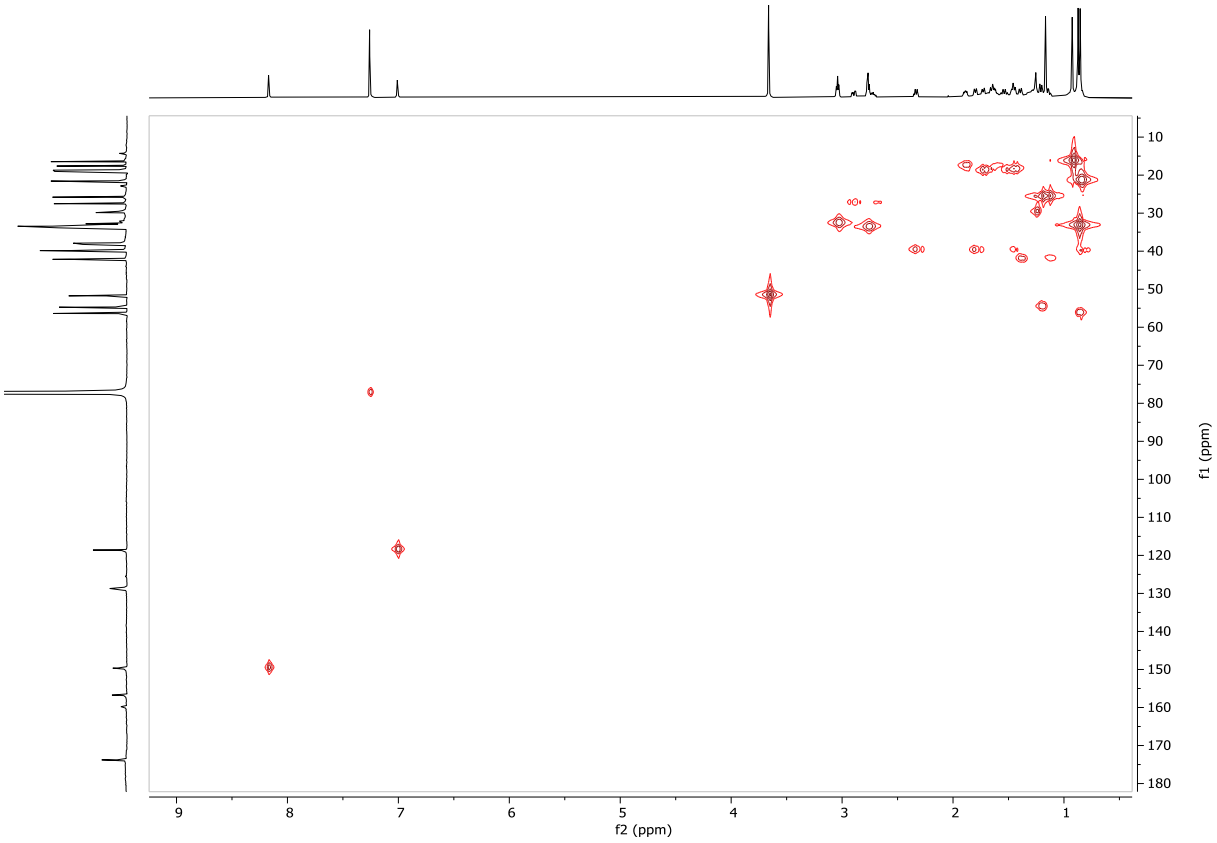
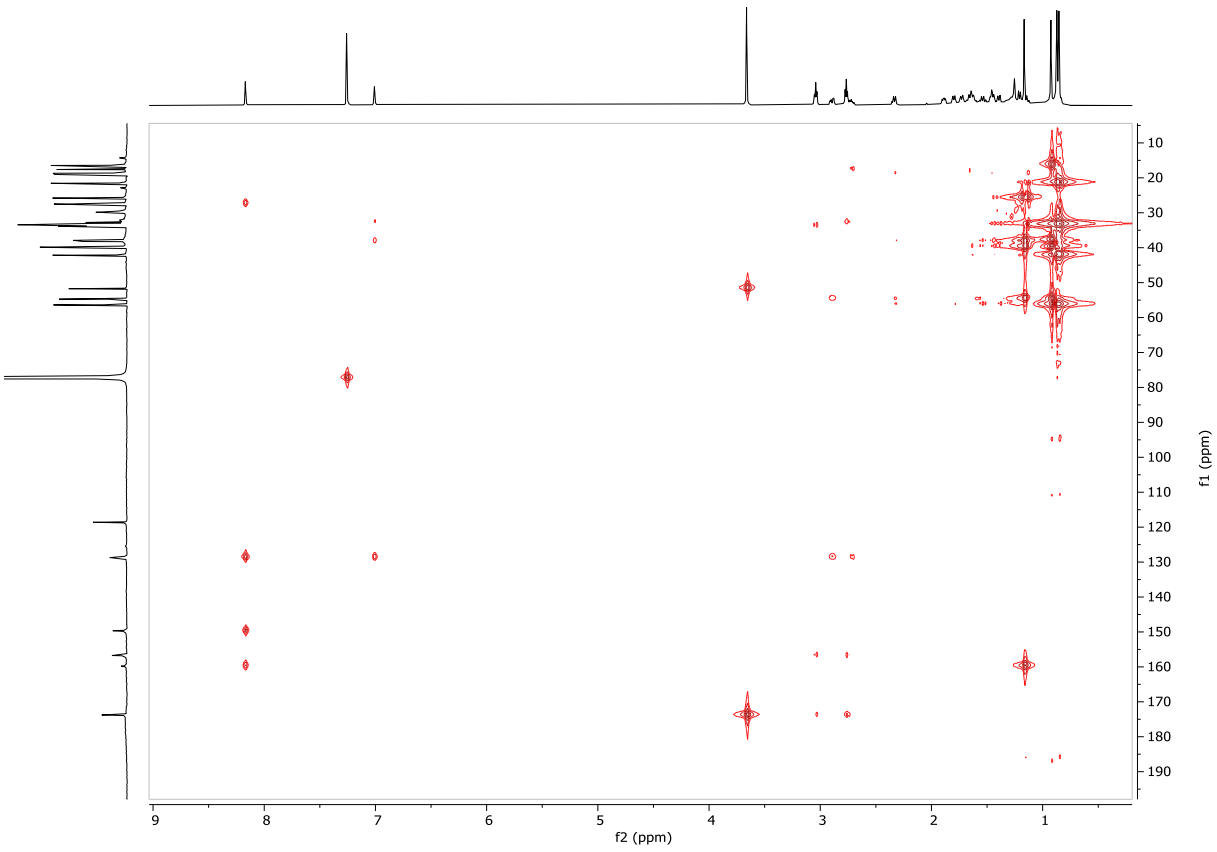
39.85
38.22
37.89
33.86
33.46
33.44
32.77
27.51
25.80
21.57
19.03
18.69
17.62
16.46
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HMQC of petrosaspongiolide L methyl ester

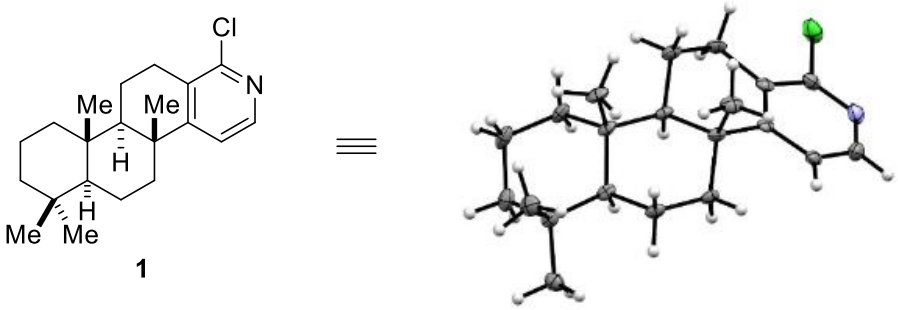


HMBC of petrosaspongiolide L methyl ester



6. Crystallographic Data

Chloropyridine **1**

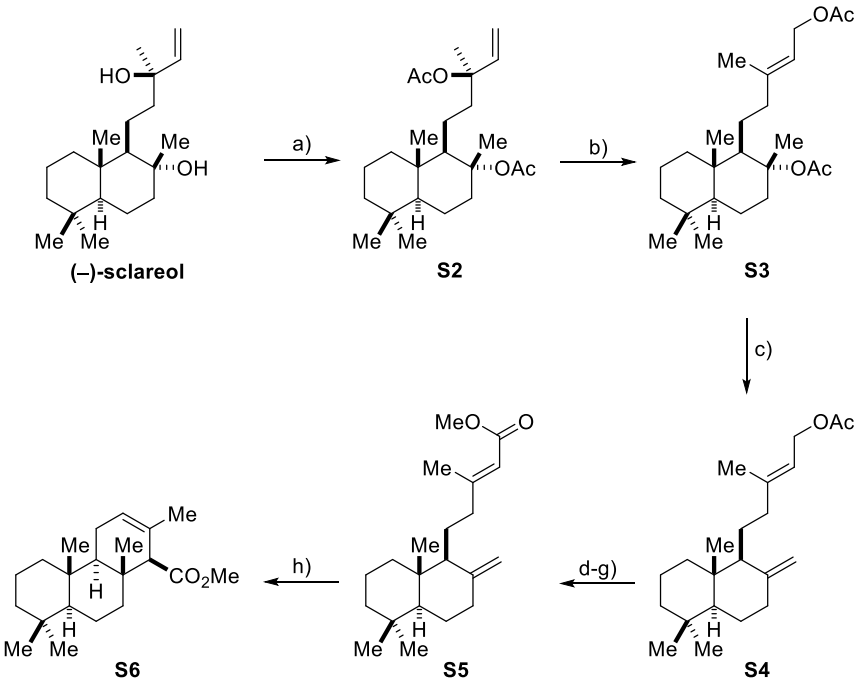


1

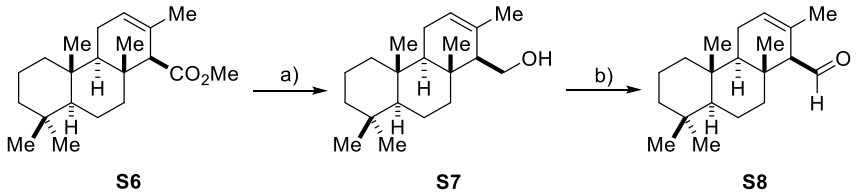
CCDC 1859575 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

7. Previous Synthesis of Spongidine A and Spongidine D

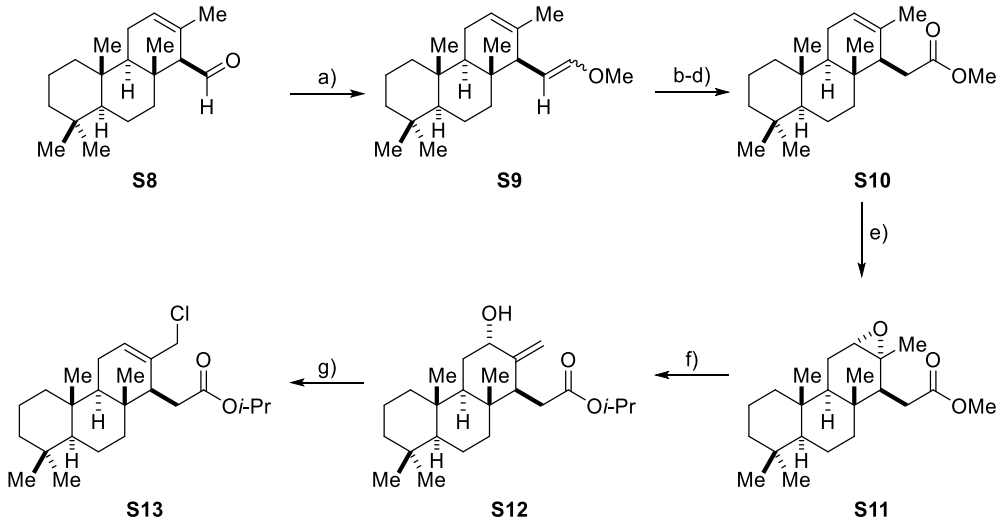
The synthesis of spongidine A and spongidine D by Basabe and coworkers was achieved in 2% and 1% yield over 23 steps in the longest linear sequence, respectively. The synthetic effort was published in 3 publications (schemes SI2 to SI5, shown below for clarity).[4, 7, 8] Additionally, the synthesis was published in the dissertation of Araceli Blanco Martín.[6]



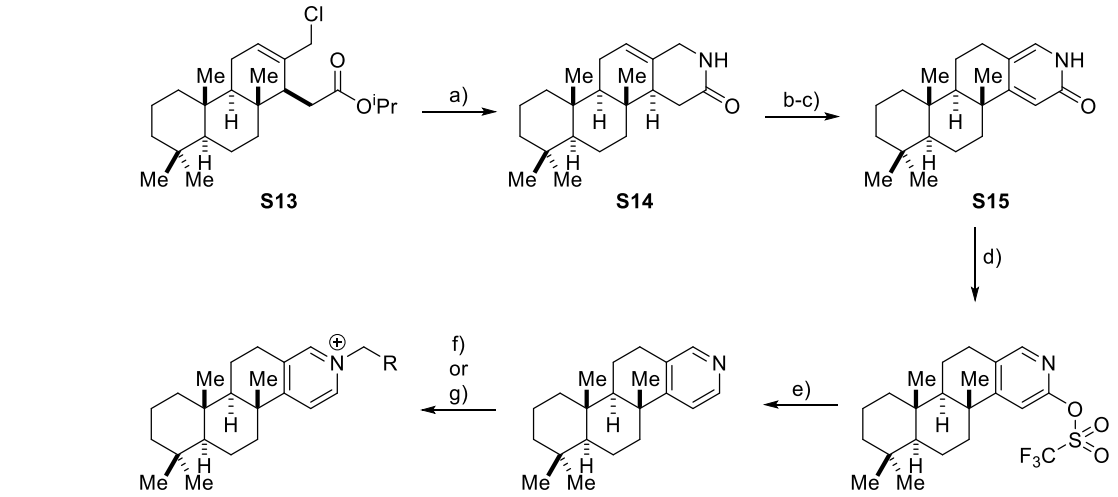
Scheme SI2. Synthesis of ester **S6**, according to *Basabe* and co-workers.[7] Reaction conditions: a) AcCl, CH_2Cl_2, *N*,*N*-Dimethylanilin, rt, 12 h, quant.; b) $PdCl_2(MeCN)_2$, THF, rt, 1 h, 92%; c) SiO_2, hexane, 100 °C, 1 h, 88%; d) K_2CO_3, MeOH, rt, 6 h, quant.; e) MnO_2, CH_2Cl_2, rt, 8 h, 85%; f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, rt, 12 h; g) $TMSCHN_2$, C_6H_6/MeOH (1:1), rt, 10 min, 89% over 2 steps; h) HCOOH, 65 °C, 1.5 h, 89%.



Scheme SI3. Synthesis of aldehyde **S8,** according to *Basabe* and co-workers.[8] Reaction conditions: a) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 60%; b) TPAP, NMO, CH_2Cl_2, MS 4 Å, rt, 1 h, 98%.



Scheme SI4. Synthesis of allyl chloride **S13**, according to *Basabe* and co-workers.[4] Reaction conditions: a) $MeOCH_2PPh_3Cl$, THF, NaHMDS, −78 °C, 1 h, 80%; b) *p*-TsOH, acetone, RT, 2 h, 99%; c) $NaClO_2$, *t*-BuOH, 2-methyl-2-butene, NaH_2PO_4, rt, 3 h; d) $TMSCHN_2$, C_6H_6/MeOH 1:1, 0 °C, 10 min, 85% over 2 steps; e) *m*-CPBA, CH_2Cl_2, 0 °C to rt, 2 h, 98%; f) Al(*i*-PrO)$_3$, toluene, 150 °C, 16 h, 50%; g) $SOCl_2$, Et_2O, 0 °C to rt, 3 h, 89%.



Scheme SI5. Synthesis of spongidine A and spongidine D, according to *Basabe* and co-workers.[4] Reaction conditions: a) NH_4OH, EtOH, 50 °C, 7 h, 73%; b) HI, C_6H_6, 80 °C, 5 h, 99%; c) LDA, THF, O_2 (air), −78 °C to 45 °C, 5 h, 91%; d) Tf_2O, CH_2Cl_2, pyridine, −78 °C to RT, 2 h, 66%; e) $Pd(OAc)_2$, dppf, NEt_3, $NH_4(HCO_2)$, DMF, 60 °C, 3 h, 67%; f) $BrCH_2COOH$, C_6H_5Br, 85 °C, 24 h, 56%; g) $BrCH_2CH_2SO_3Na$, DMF, 100 °C, 15 h, 49%.

8. References

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2. J. T. Kuethe, A. Wong and I. W. Davies, *J. Org. Chem.*, 2004, **69**, 7752-7754.
3. T. Sakamoto, Y. Kondo and H. Yamanaka, *Chem. Pharm. Bull.*, 1985, **33**, 4764-4768.
4. P. Basabe, A. Blanco, I. S. Marcos, D. Díez, O. Bodero, M. Martín and J. G. Urones, *Tetrahedron*, 2011, **67**, 3649-3658.
5. S. De Marino, M. Iorizzi, F. Zollo, C. Debitus, J.-L. Menou, L. F. Ospina, M. J. Alcaraz and M. Payá, *J. Nat. Prod.*, 2000, **63**, 322-326.
6. A. Blanco-Martín, Dissertation, University of Salamanca, 2011.
7. J. G. Urones, I. S. Marcos, P. Basabe, A. Gomez, A. Estrella and A. M. Lithgow, *Nat. Prod. Lett.*, 1994, **5**, 217-220.
8. P. Basabe, S. Delgado, I. S. Marcos, D. Diez, A. Diego, M. De Román and J. G. Urones, *J. Org. Chem.*, 2005, **70**, 9480-9485.