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Supporting Information

Predictable Selectivity in Remote C–H Oxidation of Steroids: Analysis of Substrate Binding Mode

Giorgio Olivo[+],* *Giorgio Capocasa*[+], *Barbara Ticconi, Osvaldo Lanzalunga, Stefano Di Stefano,* and Miquel Costas**

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Summary

Instruments and General Methods

GC analyses were carried out on a gas chromatograph equipped with a capillary methyl silicone column (30 m x 0.25 mm x 25 μm) Chrompack CP-Sil 5 CB. GC-MS analyses were performed with a mass detector (EI at 70eV) coupled with a gas chromatograph equipped with a melted silica capillary column (30 m x 0.2 mm x 25 μm) covered with a methyl silicone film (5% phenyl silicone, OV5). NMR spectra were recorded on either a BrukerDPX300 or a BrukerDPX400 spectrometer and were internally referenced to the residual proton solvent signal. Elemental analyses were performed using a CHNS-O EA-1108 elemental analyzer from Fisons. Electrospray ionization mass spectrometry (ESI-MS) experiments were performed on a Bruker Daltonics Esquire 3000 Spectrometer using solutions >1 mM of the analyzed compound. High resolution mass spectra (HRMS) were recorded on a Bruker MicroTOF-Q IITM instrument with an ESI source at Serveis Tècnics of the University of Girona. Samples were introduced into the mass spectrometer ion source by direct infusion through a syringe pump and were externally calibrated using sodium formate. Oxidation products were identified by chromatographic isolation and NMR analysis and/or X-ray crystal structure.

Materials

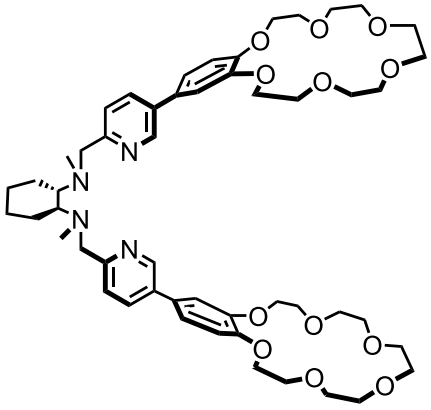
All reagents and solvents were purchased at Sigma Aldrich or Cymit and used at the reagent grade unless otherwise stated. Solvents used for crystallizations were purchased from SDS and Scharlab and were purified and dried by passing through an activated alumina purification system (M-Braun SPS-800). Sigma-Aldrich HPLC-grade acetonitrile was employed for oxidation reactions. $Fe(OTf)_2(CH_3CN)_2$, $Mn(OTf)_2$ and $Zn(OTf)_2$ were prepared according to literature procedures.[1] ^{CR}Pyridine, (^{CR}pdp), (^{CR}pdp)Mn, (^{CR}pdp)Fe were prepared following literature procedures.[2]

Synthesis of ligands and ligand synthons

^{CR}Pyridine chloride,[2] ligand (^{CR}pdp)[2] and ((*S*,*S*)-(^{TMS}PhP)[3] were synthesized as previously described. Symmetric ligands were prepared by general procedure A, while asymmetric ligands were obtained according to general procedure B.

Synthesis of ligands: General Procedure A

An 8 mL vial was charged with ^{CR}pyridine chloride (2.1 molar equivalents), the desired diamine (1 molar equivalent) and NaOH (20 molar equivalents), and then 3 mL of CH_2Cl_2 and 2 mL of distilled water were added. The organic solution turned red after complete dissolution of the reactants, to gradually evolve towards a brownish color. The biphasic mixture was vigorously stirred overnight. After this time, the mixture was diluted with NaOH 1M (5 mL) and then extracted with dichloromethane (10 mL, 4x). The combined organic phases were dried over $MgSO_4$ and the solvent removed by rotatory evaporation, to yield a brown oil. The crude was then purified by column chromatography (SiO_2, CH_2Cl_2:MeOH:NH_4OH 100:8:4) followed by washing with NaOH 1M to afford the pure ligand.

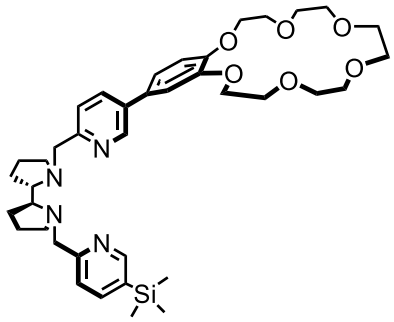


(*S*,*S*)-(^{CR}mcp): ^{CR}pyridine chloride (60 mg, 0.18 μmol, 2.1 molar equivalents) and the desired diamine (10 mg, 0.085 mmol, 1 molar equivalent) were reacted according to general procedure A. After purification, 19 mg of ligand were obtained (25 mg, 0.026 mmol, 51% yield). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.67 (s, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 4H), 6.95 (d, *J* = 8.5 Hz, 2H), 4.21 (q, *J* = 4.6 Hz, 8H), 4.03 – 3.90 (m, 10H), 3.85 (d, *J* = 14.5 Hz, 2H), 3.77 (d, *J* = 5.9 Hz, 8H), 3.75 – 3.70 (m, 8H), 3.69 (s, 8H), 2.70 (d, *J* = 7.0 Hz, 2H), 2.33 (s, 6H), 2.01 (d, *J* = 11.2 Hz, 2H), 1.78 (d, *J* = 7.8 Hz, 2H), 1.31 (s, 2H), 1.19 (d, *J* = 14.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 149.0 146.7, 134.5, 134.3, 131.2, 122.7, 120.0, 114.3, 113.1, 70.8, 70.7, 70.7, 69.6, 69.6, 69.3, 69.1, 64.4, 60.3, 36.7, 25.9, 25.8. HRMS (ESI-QTOF): calctd for $C_{52}H_{72}N_4O_{12}$ 945.5219, found 945.5220.

Synthesis of ligands: General Procedure B

An 8 mL vial was charged with ^{CR}pyridine chloride (1.05 molar equivalents), the desired amine ((*S*,*S*)-(^{TMS}PhP)[3], 1 molar equivalent) and NaOH (15 molar equivalents), and then 3 mL of CH_2Cl_2 and 2 mL of distilled water were added. The organic solution turned red after complete dissolution of the reactants, to gradually evolve towards a brownish color. The biphasic mixture was vigorously stirred overnight. After this

time, the mixture was diluted with NaOH 1M (5 mL) and then extracted with dichloromethane (10 mL, 4x). The combined organic phases were dried over $MgSO_4$ and the solvent removed by rotatory evaporation, to yield a brown oil. The crude was then purified by column chromatography (SiO_2, CH_2Cl_2:MeOH:NH_4OH 100:8:4) followed by washing with NaHOH 1M to afford the pure ligand.



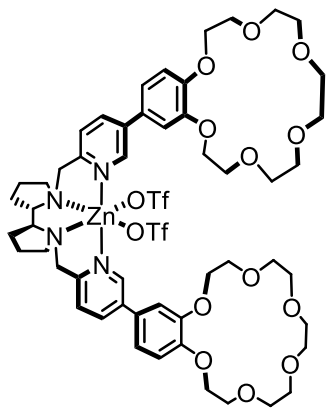
(*S,S*)- (^{TMS,CR}pdp): ^{CR}pyridine chloride (53 mg, 0.12 μmol, 1.05 molar equivalents) and (*S,S*)-^{TMS}PhP[3] (34 mg, 0.11 μmol, 1 molar equivalent) were reacted according to general procedure B. After purification, 19 mg of ligand were obtained (42 mg, 0.052 μmol, 48% yield). ^{1}H-NMR ($CDCl_3$, 300MHz) δ: 8.66 (m, 1H), 8.55 (m, 1H), 7.71 (td, ^{1}J=9 Hz, ^{2}J=3Hz, 2H), 7.40 (dd, ^{1}J=9 Hz, ^{2}J=6Hz, 2H), 7.07 (m, 2H), 6.95 (d, J=6Hz, 1H), 4.20 (m, 6H), 3.94 (m, 4H), 3.76 (m, 4H), 3.73 (m, 4H), 3.69 (s, 4H), 3-52 (dd, ^{1}J=12 Hz, ^{2}J=10Hz, 2H), 3.02 (m, 2H), 2.84 (m, 2H), 2.25 (m, 8H), 0.26 (s, 9H). ^{13}C-NMR δ: 153.0, 149.3, 149.0, 146.9, 141.5, 134.4, 132.5, 131.2, 122.5, 122.1, 120.0, 114.3, 113.1, 70.8, 70.7, 70.5, 69.61, 69.57, 69.3, 69.1, 65.4, 61.0, 60.7, 55.3, 55.2, 26.0, 23.6, -1.3. HRMS (ESI-QTOF): calctd for $C_{39}H_{56}N_4O_6Si$ 705.4042, found 705.4038.

Synthesis of complexes

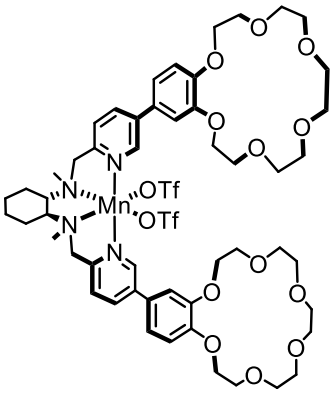
Mn(^{CR}pdp) and Fe(^{CR}pdp) were prepared as previously described.[2]

Synthesis of complexes: General Procedure

Under N_2 atmosphere, solid $Mn(OTf)_2$, $Fe(OTf)_2(CH_3CN)_2$ or $Zn(OTf)_2$ (1 equivalent) was added to a solution of ligand (1 equivalent) in anhydrous THF (0.5-1 mL) . The reaction mixture was left under stirring overnight at room temperature. At this point, diethyl ether (5-6 mL) was added under vigorous stirring. A white precipitate formed, and this was left deposit. The supernatant was removed, and the solid washed with diethyl ether (two times), always under an N_2 atmosphere. The solid was dried, dissolved in CH_2Cl_2, filtered over a plug of Celite® and crystalized under N_2 atmosphere by layering this solution with hexane or by slow evaporation of diethyl ether to obtain, after few days, white or yellow crystals.

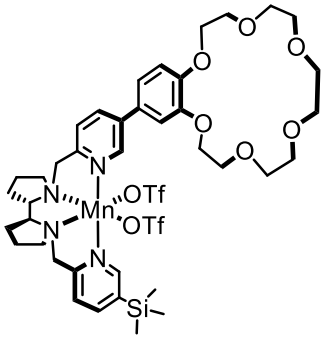


(*R*,*R*)-(^{CR}pdp)Zn: Following general procedure, ligand (*R*,*R*)-(^{CR}pdp) was reacted with $Zn(OTf)_2$. After workup, a crystalline material of the complex was obtained by layering of a CH_2Cl_2 solution of the complex with cyclohexane. ^{1}H NMR (400 MHz, CD_3CN) δ 8.98 (s, 2H), 8.33 (dd, *J* = 8.2, 2.2 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.19 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 1H), 4.26 (s, 2H), 4.21 (s, 2H), 4.13 (s, 2H), 3.79 (s, 5H), 3.62 (d, *J* = 1.9 Hz, 4H), 3.57 (d, *J* = 12.7 Hz, 9H), 3.06 (s, 2H), 2.67 (s, 1H), 2.48 (d, *J* = 7.1 Hz, 2H), 2.03 (s, 2H), 1.78 (s, 2H), 1.41 (s, 2H). ^{13}C NMR δ: 154.3, 150.6, 150.2, 146.0, 139.6, 138.7, 129.4, 126.5, 121.1, 114.0, 112.2, 71.6, 70.2, 69.3, 68.1, 58.9, 54.3, 25.63, 23.7. HRMS (QTOF-MS): calctd for $[Zn(C_{52}H_{70}N_4O_{12})(CF_3SO_3)]^+$ 1155.3796 m/z, found 1155.3799 m/z. Elemental Analysis: calctd for $[Zn(C_{52}H_{70}N_4O_{12})(CF_3SO_3)_2]$ C 46.24%, N 3.99%, H 5.03% found C 46.09%, N 3.94%, H 5.12%. IR: (cm^{-1}) 2865, 1493, 1303, 1238, 1220, 1135, 1031, 633.



(*S*,*S*)-Mn(^{CR}mcp): According to general procedure, solid $Mn(OTf)_2$ (6.7 mg, 19 μmol, 1 equivalent) was added to a THF solution of ligand **(*S*,*S*)-(^{CR}mcp)** (15 mg, 19 μmol, 1 equivalent). After workup, a crystalline material of the complex was obtained by layering of a CH_2Cl_2 solution of the complex with cyclohexane to yield 20 mg of white needles after crystallization (17.5 μmol, 92% yield). Elemental Analysis: calctd for $[Mn(C_{52}H_{72}N_4O_{12})(CF_3SO_3)_2]$ C 46.24%, N 3.99%, H 5.03%, found C 46.40%, N 4.06%, H 4.99%. HRMS (ESI-QTOF): calctd for $[Mn(C_{52}H_{72}N_4O_{12})(CF_3SO_3)]^+$ 1148.4042 m/z, found 1148.4061 m/z. IR: (cm^{-1}) 2867, 1491, 1255, 1214, 1126, 1028, 635.

(*S,S*)-Mn(^{TMS,CR}**pdp)**: According to general procedure, solid $Mn(OTf)_2$ (6.7 mg, 19 μmol, 1 equivalent) was added to a THF solution of ligand **(*S,S*)-(**^{TMS,CR}**pdp)** (15 mg, 19 μmol, 1 equivalent) to yield 20 mg of white needles after crystallization (17.5 μmol, 92% yield). Elemental Analysis for $[Mn(C_{39}H_{56}N_4O_6Si)(CF_3SO_3)_2]$: C 46.54%, H 5.33%, N 5.29%, found C 49.24%, H 5.24%, N 5.22%. HRMS (ESI-QTOF): calctd for $[Mn(C_{39}H_{56}N_4O_6Si)(CF_3SO_3)]^+$ 908.2874 m/z, found 908.2902 m/z. IR: (cm^{-1}) 2868, 1231, 1120, 1033, 981, 845, 637.



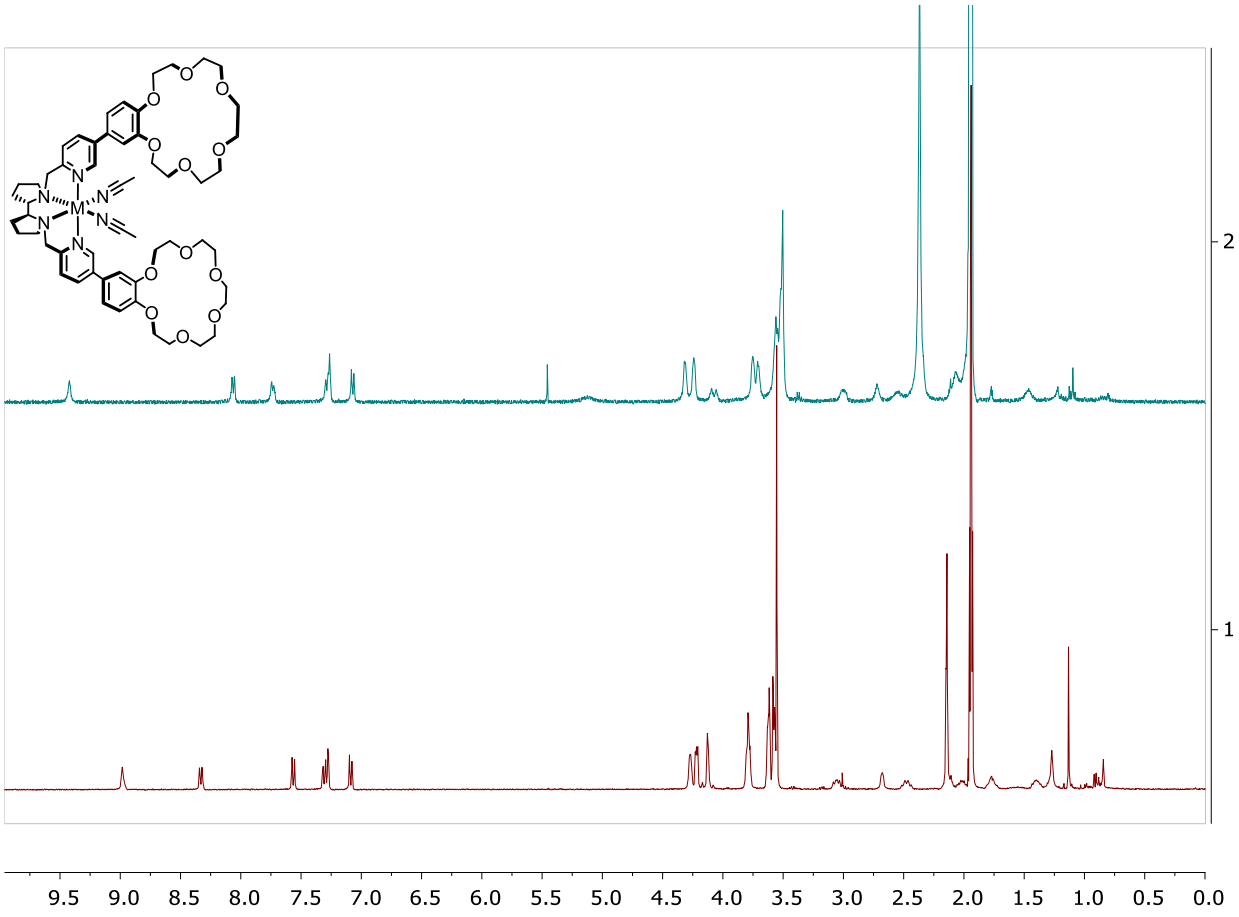


Figure S1. Comparison of ^{1}H-NMR spectra of **(*R*,*R*)-(^{CR}pdp)Zn** (red, bottom) and **(*S*,*S*)-(^{CR}pdp)Fe** (green) recorded at -40°C to maximize the diamagnetic character of the latter.[2] They show the same signal sets, indicating that they adopt the same C2-symmetric *cis*-α configuration in solution.

Crystal structure of (*S*,*S*)-(^{TMS,CR}pdp)Mn

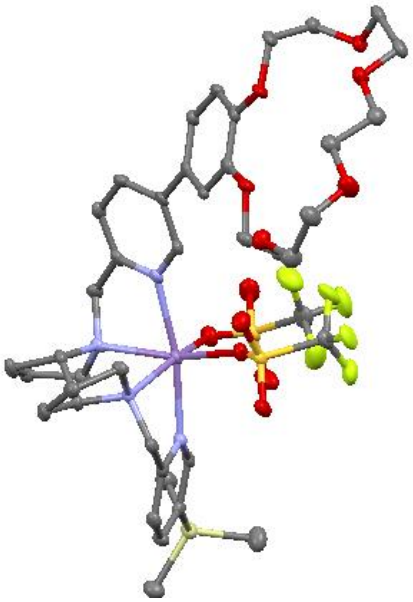


Table S1. Sample and crystal data for (*S*,*S*)-Mn(^{TMS,CR}pdp)

Identification code	TMS	
Chemical formula	$C_{41}H_{56}F_6MnN_4O_{12}S_2Si$	
Formula weight	1058.04 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.050 x 0.150 x 0.200 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21 1	
Unit cell dimensions	a = 14.5956(13) Å	α = 90°
	b = 10.2250(8) Å	β = 109.066(2)°
	c = 16.4449(13) Å	γ = 90°
Volume	2319.6(3) $Å^3$	
Z	2	
Density (calculated)	1.515 g/cm^3	
Absorption coefficient	0.490 mm^{-1}	
F(000)	1102	

Diffractometer	Bruker D8 QUEST ECO
Radiation source	sealed X-ray tube (Mo Kalpha, λ = 0.71073 Å)
Theta range for data collection	2.81 to 24.15°
Index ranges	-16<=h<=16, -11<=k<=11, -18<=l<=18
Reflections collected	70342
Independent reflections	7372 [R(int) = 0.0877]
Coverage of independent reflections	99.6%
Absorption correction	Multi-Scan

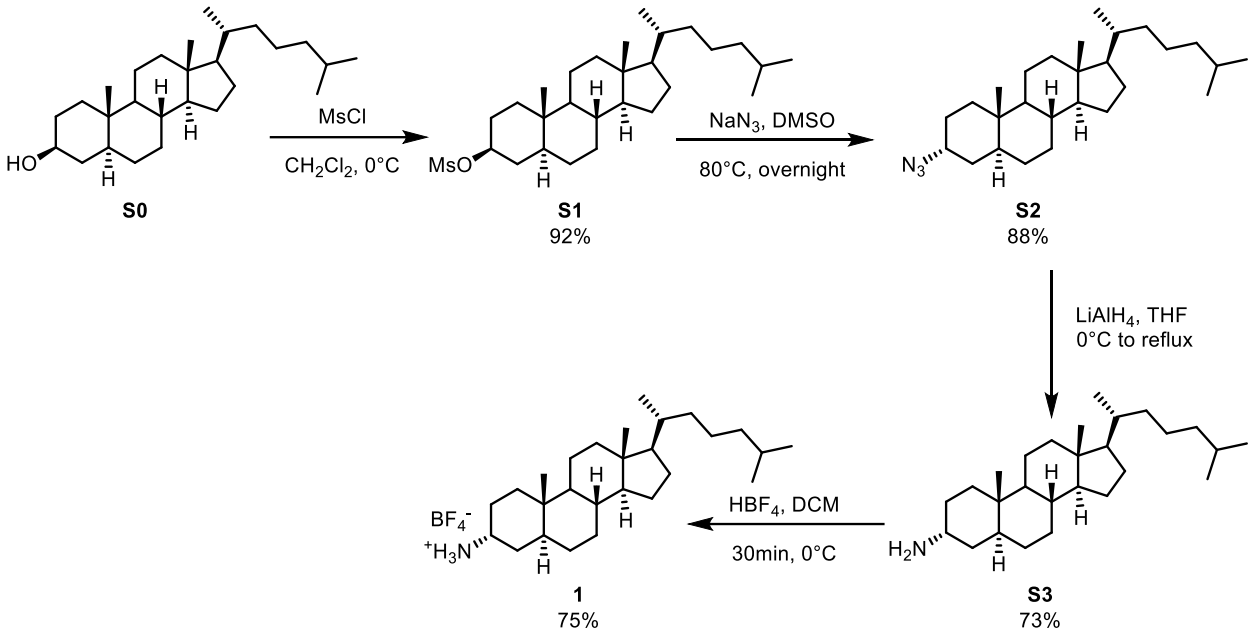
Max. and min. transmission	0.9760 and 0.9080	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	7372 / 1 / 607	
Goodness-of-fit on F^2	1.040	
Final R indices	6705 data; $I>2\sigma(I)$	R1 = 0.0340, wR2 = 0.0695
	all data	R1 = 0.0407, wR2 = 0.0720
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0285P)^2+1.0502P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.019(8)	
Largest diff. peak and hole	0.368 and -0.219 eÅ^{-3}	
R.M.S. deviation from mean	0.049 eÅ^{-3}	

Table S2. List of selected bond lengths (Å) and angles (°) for (*S,S*)-Mn(^{TMS,CR}pdp)

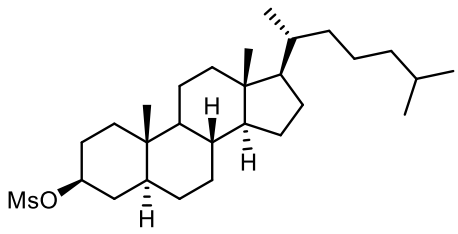
Mn1-O60	2.163(3)	Mn1-O52	2.162(3)
Mn1-N2	2.266(4)	Mn1-N9	2.250(4)
Mn1-N18	2.284(4)	Mn1-N25	2.269(4)
O52-Mn1-O60	100.85(12)	O52-Mn1-N9	161.57(12)
O60-Mn1-N9	93.65(12)	O52-Mn1-N2	92.00(13)
O60-Mn1-N2	98.85(12)	N9-Mn1-N2	74.44(13)
O52-Mn1-N25	92.42(13)	O60-Mn1-N25	89.99(12)
N9-Mn1-N25	98.95(13)	N2-Mn1-N25	169.20(13)

Synthesis of substrates

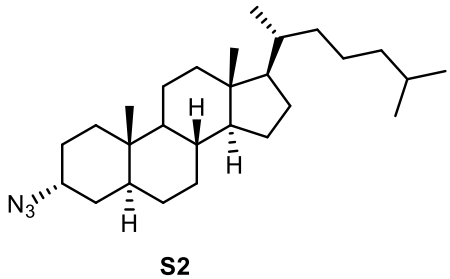
Synthetic scheme for the preparation of 1



Scheme S1. Synthesis of protonated 3α-amino-5α-H-cholestane **1**.

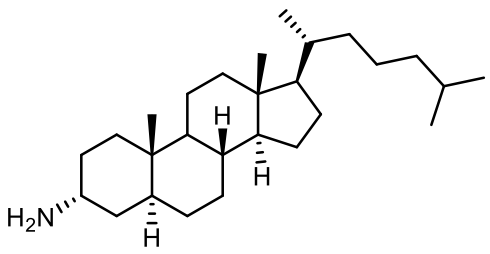


S1: Following a slightly modified literature procedure,[4] commercial alcohol **S0** (5 g, 12.9 mmol) were dissolved in 100 mL of anhydrous CH_2Cl_2. After cooling at 0°C, mesyl chloride (1.2 mL, 15.5 mmol, 1.2 equivalents) were added dropwise and the reaction was left stirring for 15 minutes. After that, ice was added (100 g) and the two phases separated. The aqueous phase was extracted three times with AcOEt (80 mL), the organic phases were collected and dried over $MgSO_4$. The solvent was removed by rotatory evaporation to yield 5.55 g (11.9 mmol, 92% yield) of a white solid, which is pure **S1**, with spectral data in accordance with literature.[4] ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.61 (s, 1H), 2.99 (s, 3H), 1.96 (m, *J* = 12.3 Hz, 2H), 1.85 – 0.94 (m, 27H), 0.93 – 0.78 (m, 13H), 0.64 (s, 4H). ^{13}C NMR δ: 82.3, 56.3, 56.2, 54.0, 44.8, 42.5, 39.9, 39.5, 38.8, 36.8, 36.1, 35.8, 35.4, 35.2, 35.1, 31.9, 28.7, 28.5, 28.2, 28.0, 24.5, 23.8, 22.8, 22.5, 21.2, 18.6, 12.2, 12.0.



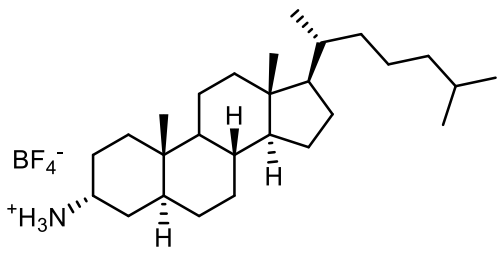
S2: Adapting a literature procedure,[4] mesylate **S1** (500 mg, 1.02 mmol) and NaN_3 (650 mg, 10 mmol, 10 equivalents) were dissolved in 100 mL of DMSO and heated to 80°C overnight. After cooling to room temperature, H_2O (100 mL) was added and the mixture was extracted four times with AcOEt. The organic phase was washed with Brine (200 mL), dried over $MgSO_4$ and the solvent removed by

rotatory evaporation. The white solid was then purified by column chromatography (SiO_2, Hexane) to yield 371 mg (0.90 mmol, 88% yield) of **S2** as a white solid, with spectral data in accordance with literature.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.16 (s, 1H), 1.96 (d, *J* = 12.1 Hz, 1H), 1.84 – 1.58 (m, 3H), 1.58 – 1.28 (m, 13H), 1.27 – 0.93 (m, 14H), 0.87 (dd, *J* = 10.9, 6.5 Hz, 9H), 0.77 (s, 3H), 0.72 (d, *J* = 3.5 Hz, 1H), 0.64 (s, 3H). ^{13}C NMR δ: 56.6, 56.2, 54.5, 45.8, 42.6, 40.0, 39.5, 39.2, 36.3, 36.2, 35.8, 35.5, 32.1, 32.0, 29.2, 28.8, 28.2, 28.0, 24.2, 23.8, 22.8, 2.5, 20.8, 18.6, 12.1, 11.3.



S3

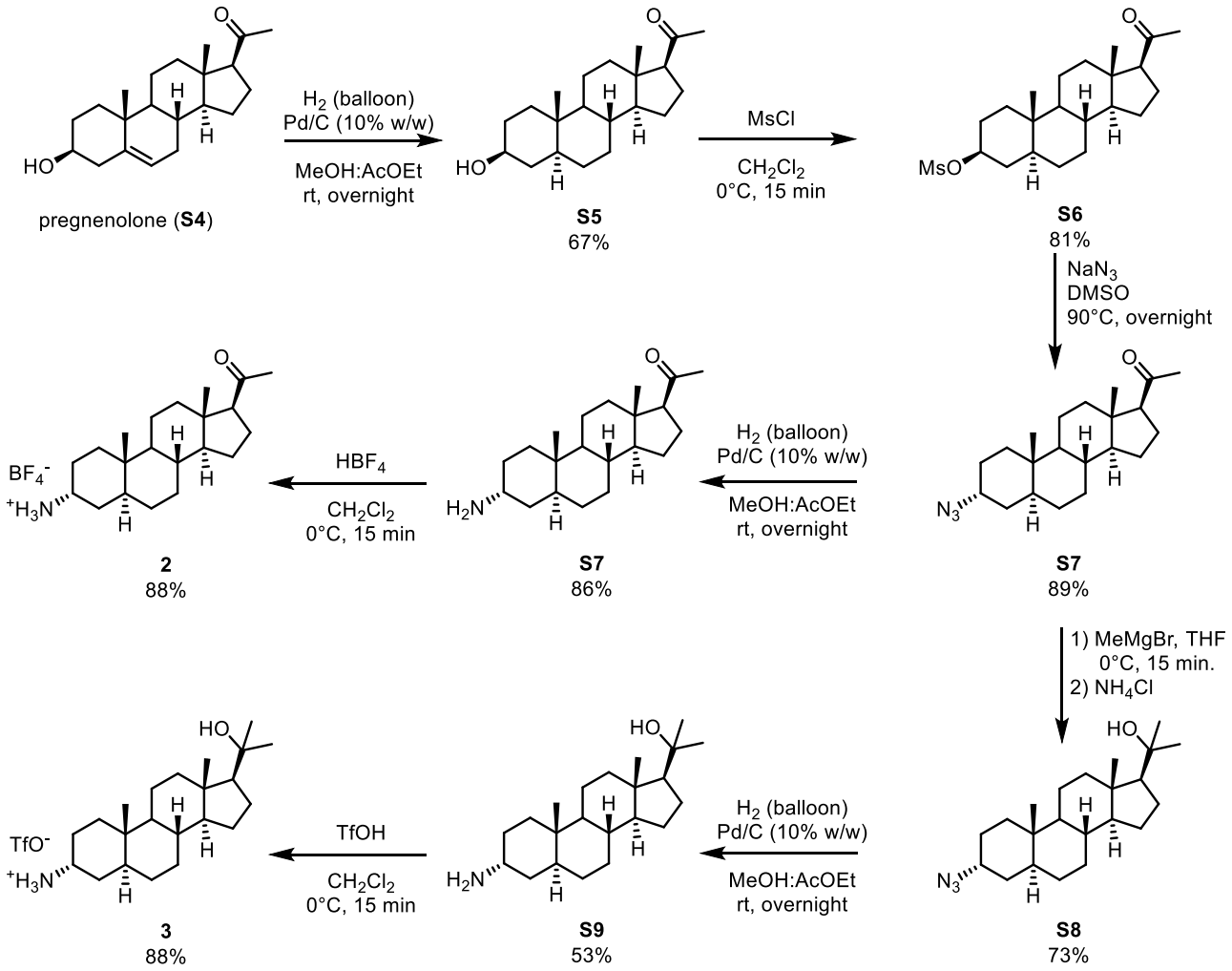
S3: Following a slightly modified literature procedure,[4] $LiAlH_4$ (270 mg, 7.3 mmol, 3 equivalents) was added to an oven-dried, two-necked flask previously filled with N_2. Anhydrous THF (60 mL) were added via syringe. Azide **S2** (1.0 g, 2.42 mmol) was added portion-wise over 15 minutes to the mixture under N_2 at 0°C. The reaction was then slowly heated to reflux (CAREFUL: do not heat too fast to avoid uncontrolled reaction. When the mixture bubbles, the heating was stopped and, after 10 minutes, gently heated up to reflux) and left stirring at that temperature for 16 hours. Then the mixture was cooled down to 0°C, and a 10M solution of NaOH was added dropwise under N_2 until a transparent solution was obtained with white slurry precipitates. At this point water was added (10 mL) dropwise, followed by celite (10 g). The mixture was filtered, and the solvent was then removed by the filtrate by rotatory evaporation. The residue was taken up in a 2M NaOH solution and extracted with CH_2Cl_2 three times. The organic phases were dried over $MgSO_4$, and the solvent removed by rotatory evaporation to yield 684 mg of **S3** (1.77 mmol, 73% yield) with spectral data in accordance with literature.[4] ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.27 (s, 1H), 2.06 (d, *J* = 12.4 Hz, 1H), 1.78 (d, *J* = 38.3 Hz, 3H), 1.69 – 1.52 (m, 6H), 1.50 – 1.39 (m, 6H), 1.38 – 1.02 (m, 15H), 1.01 – 0.93 (m, 9H), 0.87 (s, 3H), 0.82 (s, 1H), 0.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.6, 56.2, 54.5, 45.8, 42.6, 40.0, 39.5, 39.2, 36.3, 36.2, 35.8, 35.5, 32.1, 29.2, 28.8, 28.2, 28.0, 24.2, 23.8, 22.8, 22.5, 20.8, 18.6, 12.1, 11.3.



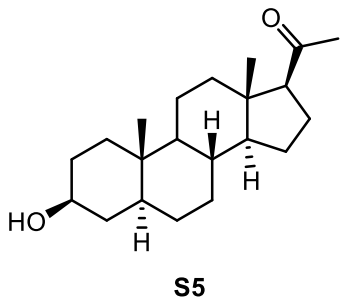
1

1: Adapting literature procedures,[2,5] amine **S3** (500 mg, 1.29 mmol) was dissolved in CH_2Cl_2 (4 mL) at 0°C. A solution of $HBF_4{\cdot}Et_2O$ (1.42 mmol, 1.1 eq.) was added dropwise. After 2-3 minutes a white precipitate formed. The mixture was filtered, and the filtrate was vacuum dried, dissolved in hot CH_3CN and crystallized by slow cooling to yield transparent needles of pure **1** (460 mg, 0.968 mmol, 88% yield). ^{1}H-NMR (400 MHz, CD_3CN) δ: 6.17 (s, 3H), 3.59 (s, 1H), 2.00 (d, *J* = 12.4 Hz, 1H), 1.90 – 1.76 (m, 2H), 1.73 – 1.46 (m, 7H), 1.45 – 0.95 (m, 18H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 6H), 0.81 (s, 3H), 0.75 (s, 1H), 0.68 (s, 3H). ^{13}C NMR (101 MHz, CD_3CN) δ 57.2, 56.9, 54.6, 49.7, 43.1, 40.6, 39.9, 39.5, 36.7, 36.4, 36.3, 35.9, 32.4, 31.9, 30.8, 28.6, 28.4, 24.6, 24.3, 24.2, 22.8, 22.5, 21.2, 18.8, 12.2, 11.4. HRMS: calctd for $C_{27}H_{49}N$-H^+ 388.3938 m/z, found 388.3936 m/z.

Synthetic scheme for the preparation of 2 and 3

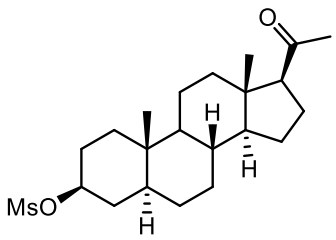


Scheme S2. Synthesis of compounds **2** and **3**.



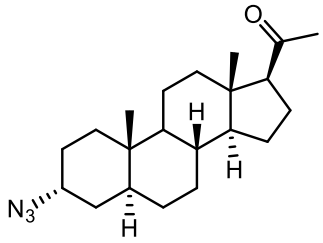
S5

S5: Following a slightly modified literature procedure,[6] commercial pregnenolone **S4** (7 g, 22.1 mmol) was dissolved in 150 mL of an anhydrous MeOH, and AcOEt was added until the substrate was fully dissolved, followed by Pd/C (700 mg, 10% w/w) under N_2. The mixture was evacuated and back-filled with H_2 gas three times before leaving to vigorously stir overnight under an atmosphere of H_2 (balloon). Then the mixture was filtered over celite twice and the solvent was removed by rotatory evaporation. 4.71 g of pure **S5** as a white solid were obtained (14.8 mmol, 67% yield), whose NMR spectrum was in agreement with literature data.[6] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.61(m, 1H), 2.55 (m, 1H), 2.24-2.09 (m, 1H), 2.13 (s, 3H), 2.06-1.98(m, 1H), 1.87-1.78 (m, 1H), 1.78-1.54 (m, 6H), 1.48-1.07 (m, 11H), 1.06-0.85 (m, 2H), 0.82 (s, 3H), 0.77-0.64 (m, 1H) 0.61 (s, 3H).



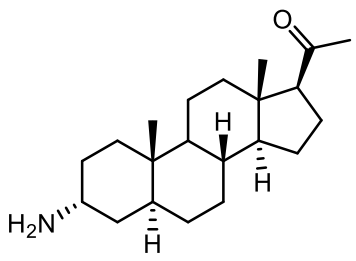
S6

S6: alcohol **S5** (4.71 g, 14.8 mmol) was dissolved in 100 mL of anhydrous CH_2Cl_2. After cooling at 0°C, mesyl chloride (1.4 mL, 17.8 mmol, 1.2 equivalents) were added dropwise and the reaction was left stirring for 15 minutes. After that, ice was added (100 g) and the two phases separated. The aqueous phase was extracted three times with AcOEt (80 mL), the organic phases were collected and dried over $MgSO_4$. The solvent was removed by rotatory evaporation to yield 4.75 g (12.0 mmol, 81% yield) of a white solid (**S1**, which was used without further purification), with spectral data in accordance with literature.[7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (tt, *J* = 10.8, 5.1 Hz, 1H), 2.99 (s, 3H), 2.51 (t, *J* = 8.9 Hz, 1H), 2.10 (m, 4H), 2.00 (d, *J* = 11.8 Hz, 2H), 1.78 (m, 2H), 1.73 – 1.54 (m, 7H), 1.45 – 1.24 (m, 4H + H_2O), 1.23 – 1.12 (m, 3H), 1.04 (s, 1H), 0.93 (s, 1H), 0.82 (s, 3H), 0.72 – 0.66 (m, 1H), 0.60 (s, 3H). ^{13}C NMR δ 209.5, 81.9, 63.7, 56.5, 53.9, 44.8, 44.2, 38.9, 38.8, 36.8, 35.4, 35.3, 35.1, 31.8, 31.5, 28.6, 28.3, 24.3, 22.8, 21.2, 13.4, 12.1.



S7

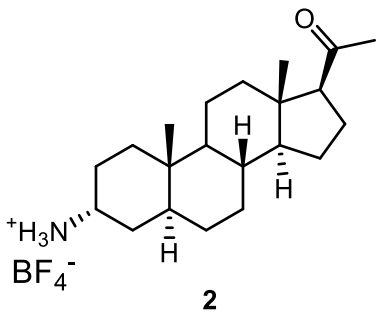
S7: Mesylate **S6** (0.500 mg, 1.26 mmol) and NaN_3 (790 mg, 10 mmol, 10 equivalents) were dissolved in 100 mL of DMSO and heated to 80°C overnight. After cooling to room temperature, H_2O (100 mL) was added and the mixture was extracted four times with AcOEt. The organic phase was washed with Brine (200 mL), dried over $MgSO_4$ and the solvent removed by rotatory evaporation. The white solid was then purified by crystallization from hot AcOEt to yield 385 mg (1.12 mmol, 89% yield) of **S2** as a white solid, with spectral data in accordance to literature.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (m, 1H), 2.55 (m, 1H), 2.19 (m, 1H), 2.13 (m, 3H), 2.01 (m, 1H), 1.66 (m, 6H), 1.44 (m, 6H), 1.22 (m, 6H), 0.98 (m, 1H), 0.80 (s, 3H), 0.80 (m, 1H), 0.61 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.7, 63.8, 58.1, 56.7, 54.0, 44.2, 40.0, 39.0, 3.92, 35.4, 32.9, 32.5, 31.8, 31.6, 28.2, 25.6, 24.4, 22.8, 20.8, 13.5, 11.6.



S8

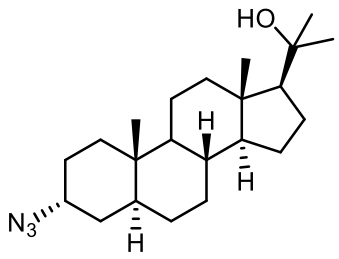
S8: Azide **S7** (1 g, 2.9 mmol) was loaded into a 250 mL round bottom flask together with a stir-bar. The flask was evacuated and back-filled with N_2 (3x) 50 mL of anhydrous and degassed MeOH and 20 mL of degassed EtOAc were added to fully dissolve the solid. 46 mg of Pd/C (10% w/w) were added in the reaction mixture under N_2 and then the flask was evacuated and back-filled with H_2 (3x). A hydrogen-filled balloon was connected to the flask and the reaction was stirred overnight. The mixture was vacuum-filtered over celite, and the solvent was removed by the filtrate to yield amine **S8** as a white solid (790 mg, 2.5 mmol, 86% yield) with spectral data in accordance with literature.[7] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.53 (d, *J* = 9.0 Hz, 1H),

2.10 (s, 3H), 1.99 (t, *J* = 7.5 Hz, 1H), 1.76 – 1.58 (m, 5H), 1.53 (d, *J* = 16.7 Hz, 1H), 1.40 (d, *J* = 16.5 Hz, 6H), 1.27 (s, 2H), 1.17 (d, *J* = 11.1 Hz, 5H), 0.77 (s, 3H), 0.59 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.7, 63.8, 56.8, 54.3, 45.7, 44.3, 39.1, 36.4, 36.2, 35.5, 32.1, 32.0, 31.5, 29.1, 28.6, 24.4, 22.8, 20.8, 13.4, 11.3.



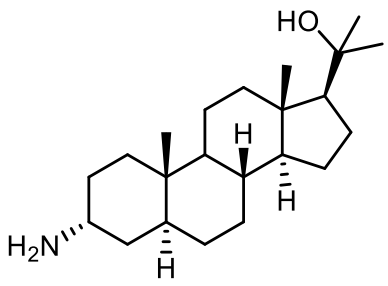
2

2: Amine **S8** (500 mg, 1.58 mmol) was dissolved in CH_2Cl_2 (4 mL) at 0°C. A solution of $HBF_4 \cdot Et_2O$ (1.73 mmol, 1.1 equivalents) was added dropwise. After 2-3 minutes a white precipitate formed. The mixture was filtered, and the filtrate was vacuum dried, dissolved in hot CH_3CN and crystallized by slow cooling to yield transparent needles of pure **1** (560 g, 1.39 mmol, 88% yield). ^{1}H-NMR (400 MHz, CD_3CN) δ: 6.37 – 5.95 (m, 3H), 3.60 (s, 1H), 2.58 (t, *J* = 9.0 Hz, 1H), 2.06 (s, 5H), 1.92 – 1.81 (m, 1H), 1.76 – 1.55 (m, 7H), 1.48 – 1.37 (m, 3H), 1.36 – 1.11 (m, 8H), 1.02 – 0.88 (m, 1H), 0.81 (s, 4H), 0.58 (s, 3H). ^{13}C-NMR (400 MHz, CD_3CN) δ: 209.6, 63.9, 6.13, 54.5, 49.7, 44.4, 39.5, 39.3, 36.4, 35.9, 32.3, 31.9, 31.4, 30.8, 28.3, 24.7, 24.3, 23.1, 21.2, 13.4, 11.4. HRMS: calctd for $C_{21}H_{36}NO\text{-}H^+$ 318.2791 m/z, found 318.2795 m/z



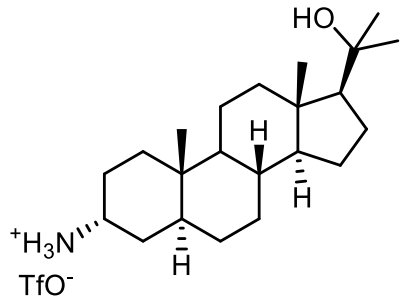
S9

S9: 670 mg of azide **S7** (1.95 mmol) were dissolved in 10 mL of THF. The reaction vessel was put in an ice bath and 2.8 mL of a 1M solution of MeMgBr (4.36 eq) were slowly added while stirring the mixture. Upon completing the addition, the reaction vessel was left for 30' in the ice bath. 10 mL of a saturated solution of NH_4Cl were added slowly to the reaction mixture; the THF was evaporated and the resulting slurry was extracted thrice with ethyl acetate. The combined organic layers were washed with water, brine and dried over $MgSO_4$. After distillation of the solvent, the crude was purified by flash column chromatography (SiO_2; Hex: AcOEt 2: 1) to afford 512 mg of product (73% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 1H), 2.05 (d, *J* = 12.2 Hz, 1H), 1.66 (m, 6H), 1.42 (m, 7H), 1.30 (s, 3H), 1.28 – 1.19 (m, 4H), 1.18 (s, 3H), 1.14 (m, 1H), 1.11 – 0.84 (m, 4H), 0.81 (s, 3H), 0.79 (s, 3H), 0.76 – 0.68 (m, 1H). ^{13}C NMR δ: 73.5, 60.2, 58.2, 56.6, 54.1, 43.0, 40.3, 40.0, 35.9, 34.8, 32.8, 32.5, 31.7, 31.0, 30.0, 28.3, 25.6, 23.7, 23.1, 20.6, 13.6, 11.6. HRMS: calctd for $C_{22}H_{37}N_3O\text{-}Na^+$ 382.2829 m/z, found 382.2823 m/z.



S10

S10: Following a slightly modified literature procedure, azide **S9** (512 mg, 0.90 mmol) was loaded into a 250 mL round bottom flask together with a stir-bar. The flask was evacuated and back-filled with N_2 (3x) 50 mL of anhydrous and degassed MeOH and 20 mL of degassed AcOEt were added to fully dissolve the solid. 46 mg of Pd/C (10% w/w) were added in the reaction mixture under N_2 and then the flask was evacuated and back-filled with H_2 (3x). A hydrogen-filled balloon was connected to the flask and the reaction was stirred overnight. The mixture was vacuum-filtered over a bed of celite and the filtrate was concentrated and purified by column chromatography (DCM → DCM + 9% MeOH + 4% concentrated ammonia solution). The amine was dissolved in dichloromethane, washed with NaOH 1M and the organic phase was dried over $MgSO_4$ to afford 250 mg of pure amine (53% yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.19 (br, 1H), 2.06 (m, 1H), 1.81-1.59 (m, 5H), 1.59-1.35 (m, 8H), 1.31 (s, 3H), 1.29-1.13 (m, 10H), 1.13-1.85 (m, 4H), 1.85-0.77 (m, 6H), 0.77-0.61 (m, 1H). ^{13}C NMR δ: 73.8, 60.5, 57.0, 54.7, 46.0, 43.3, 40.7, 39.4, 36.6, 36.6, 35.2, 32.4, 32.2, 31.3, 30.3, 29.4, 29.0, 24.0, 23.4, 20.9, 13.9, 11.6. HRMS: calctd for $C_{22}H_{39}NO$-H^+ 334.3104 m/z, found 334.3102 m/z.



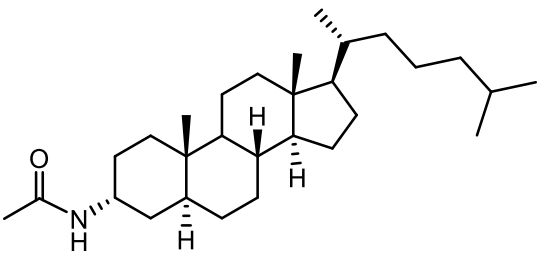
3

3: 142 mg of amine **S10** were suspended in 2 mL of DCM. Enough MeOH was added to fully dissolve the substrate. The reaction vessel was put in an ice-bath. 1.05 equivalents of TfOH from a freshly-made DCM stock solution (about 200 µL) were slowly added to the dissolved amine while stirring. After 20 minutes, the solvent was vacuum-distilled and the resulting solid was washed several times with Et_2O. The solid was dried and suspended in a small quantity of acetonitrile. Just enough MeOH was added to fully dissolve the residue. After filtration on celite, a layer of Et_2O was carefully added on top of the solution. After 12h, a white solid crystallized as transparent needle. The precipitate was washed with Et_2O and the supernatant was concentrated, re-dissolved and re-crystallized as described above a second time. In total, 95 mg of pure TfOH salt were recovered (53% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 3.52 (m, 1H), 2.13 (m, 1H), 1.96 (m, 1H), 1.71 (m, 7H), 1.56 (m, 1H), 1.41 (m, 3H), 1.28 (m, 1H), 1.20 (s, 3H), 1.06 (m, 3H), 0.89(s, 3H), 0.85 (s, 3H). ^{13}C-NMR: δ 74.4, 62.2, 58.3, 55.6, 44.4, 41.8, 40.7, 37.4, 36.5, 33.2, 33.0, 32.4, 31.3, 30.2, 29.6, 25.7, 25.0, 24.5, 22.0, 14.4, 11.9. HRMS: calctd for $C_{22}H_{39}NO$-H^+ 334.3104 m/z, found 334.3101 m/z.

Synthesis of acetylated amines

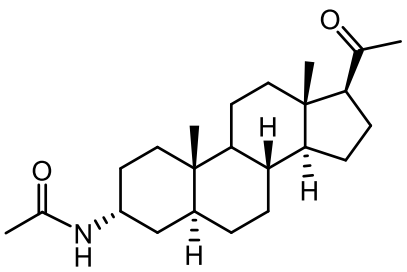
General acetylation procedure

Amine (0.2 mmol) was dissolved in CH_3CN at 0°C. Ac_2O (0.5 mL) and Et_3N (0.2 mL) were added and the mixture was then stirred for 45 minutes. The reaction was quenched by addition of ice. H_2O and CH_2Cl_2 were added, the organic phase was separated, washed with H_2SO_4 1M, $NaHCO_3$ (sat.) and H_2O and finally dried over $MgSO_4$. The solvent was removed by rotatory evaporation to yield the corresponding pure acetamide quantitatively (92-98% yield).



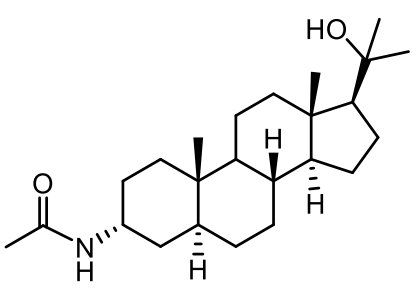
S11

S11: 96% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.73 (s, 1H), 4.19 – 4.04 (m, 1H), 1.99 (s, 4H), 1.87 – 1.77 (m, 1H), 1.71 – 1.44 (m, 8H + *H_2O*), 1.34 (d, *J* = 16.8 Hz, 5H), 1.29 – 1.03 (m, 11H), 0.98 (d, *J* = 9.7 Hz, 3H), 0.93 – 0.82 (m, 10H), 0.80 (s, 3H), 0.73 – 0.66 (m, 1H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.10, 56.61, 56.31, 54.60, 44.76, 42.59, 41.07, 40.03, 39.50, 36.17, 36.05, 35.79, 35.42, 33.25, 32.82, 32.00, 28.49, 28.22, 28.00, 25.98, 24.15, 23.85, 23.77, 22.81, 22.55, 20.78, 18.66, 12.07, 11.44. HRMS: calctd for $C_{29}H_{51}NO$-Na^+ 452.3863 m/z, found 452.3859 m/z.



S12

S12: 94% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 4.13 (s, 1H), 2.51 (t, *J* = 9.0 Hz, 1H), 2.16 (d, *J* = 10.9 Hz, 1H), 2.11 (s, 3H), 1.99 (s, 4H), 1.64 (dt, *J* = 29.5, 15.2 Hz, 8H), 1.42 (d, *J* = 3.1 Hz, 1H), 1.32 (d, *J* = 22.1 Hz, 2H), 1.23 – 1.10 (m, 5H), 1.01 (t, *J* = 10.7 Hz, 1H), 0.97 – 0.83 (m, 2H), 0.80 (s, 3H), 0.75 (s, 1H), 0.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6, 169.1, 63.8, 56.8, 54.5, 44.7, 44.2, 41.1, 39.1, 36.1, 35.4, 33.3, 32.8, 31.9, 31.5, 28.3, 25.9, 24.3, 23.8, 22.8, 20.8, 13.5, 11.4. HRMS: calctd for $C_{25}H_{37}NO_2$-Na^+ 406.2716 m/z, found 406.2712 m/z.



S13

S13: 93% yield. ^{1}H-NMR (400 MHz, Chloroform-*d*) δ 5.68 (s, 1H), 4.13 (s, 1H), 2.11 – 2.04 (m, 1H), 1.99 (s, 3H), 1.76 – 1.60 (m, 6H), 1.54 – 1.32 (m, 6H), 1.30 (s, 3H), 1.21 (d, *J* = 4.3 Hz, 2H), 1.19 (s, 3H), 1.12 (dd, *J* = 19.6, 10.7 Hz, 3H), 1.00 (d, *J* = 3.5 Hz, 2H), 0.93 – 0.86 (m, 1H), 0.81 (d, *J* = 4.8 Hz, 6H), 0.69 (td, *J* = 11.8, 11.2, 3.9 Hz, 1H). ^{13}C NMR δ 169.1, 73.5, 60.3, 56.7, 54.5, 44.7, 43.0, 41.1, 40.3, 36.1, 34.8, 33.2, 32.8, 31.9, 31.0, 30.1, 28.4, 26.0, 23.8, 23.7, 23.1, 20.6, 13.7, 11.4. HRMS: calctd for $C_{24}H_{41}NO_2$-Na^+ 398.3030 m/z, found 398.3031 m/z.

Binding studies

Binding of 1 to (*R*,*R*)-(^{CR}pdp)Zn

NMR spectra

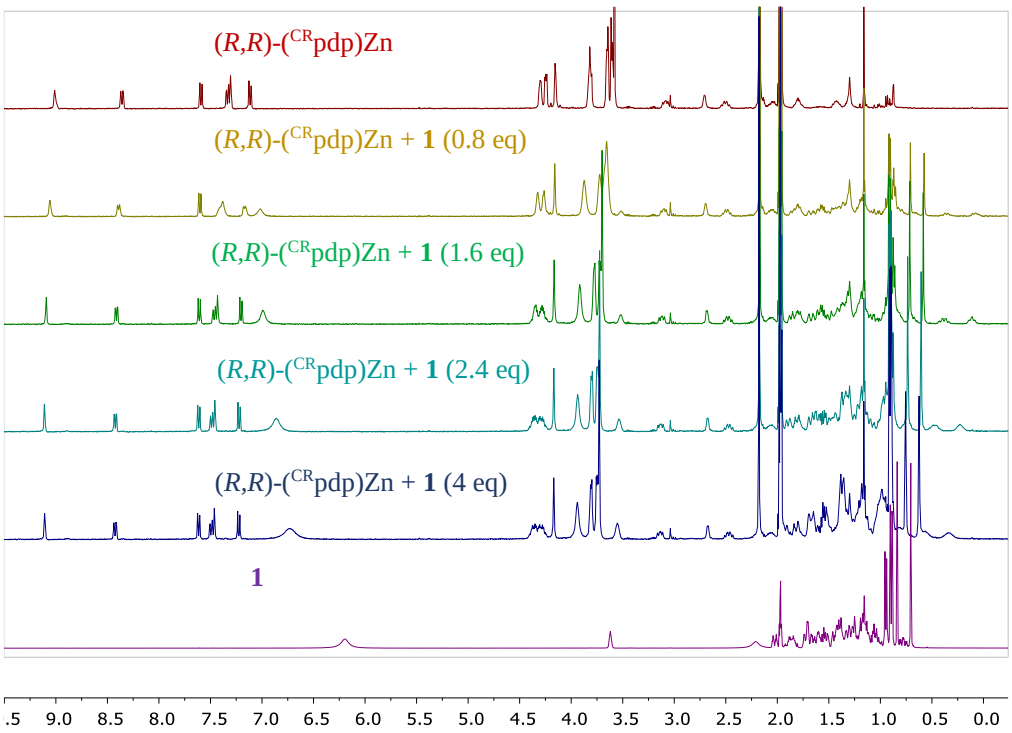
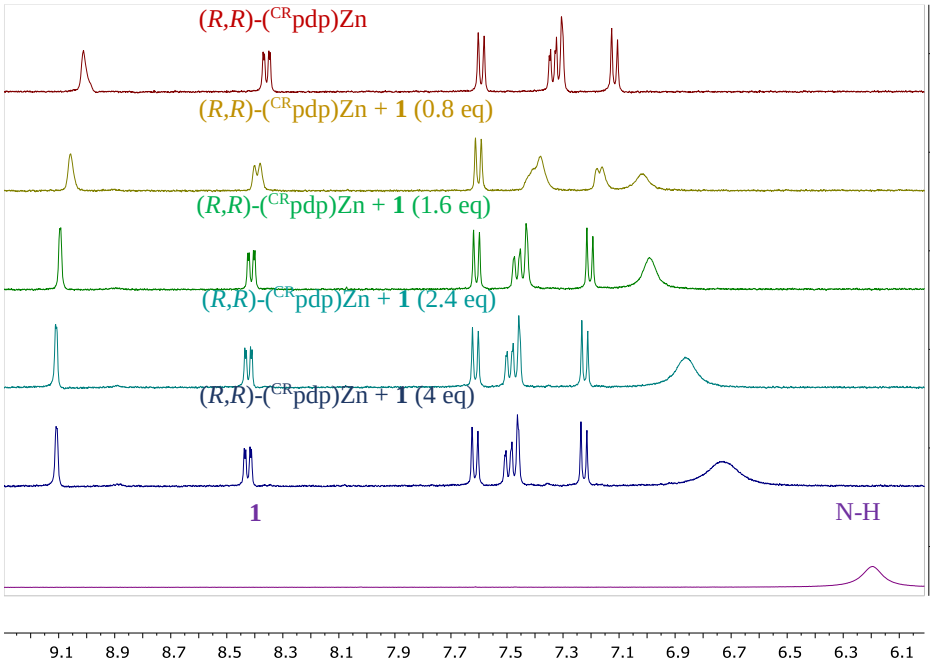


Figure S2. NMR monitoring of the binding of 1 to (*R*,*R*)-(^{CR}pdp)Zn. Variation of the ^{1}H-NMR spectrum of (*R*,*R*)-(^{CR}pdp)Zn (red spectrum, top) upon addition of **1**. Note in particular the appearance of signals below 0.5 ppm. Spectrum of pure **1** (purple spectrum, bottom) is reported for the sake of comparison.

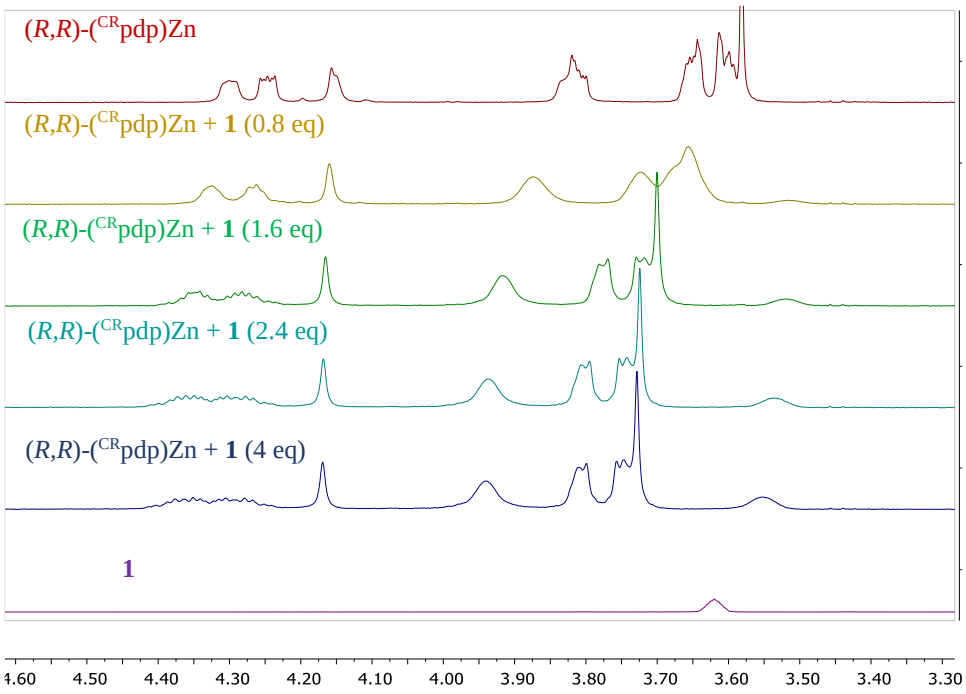
Zoom in of selected regions are reported in the following page

Enlargement of the aromatic region



Upon binding, both the ligand signals and, more significantly, the N-H signals, are shifted downfield.

Enlargement of the crown ether region



Note the downfield shift of the signals of the crown ether (-OCH_2CH_2O-) upon binding.

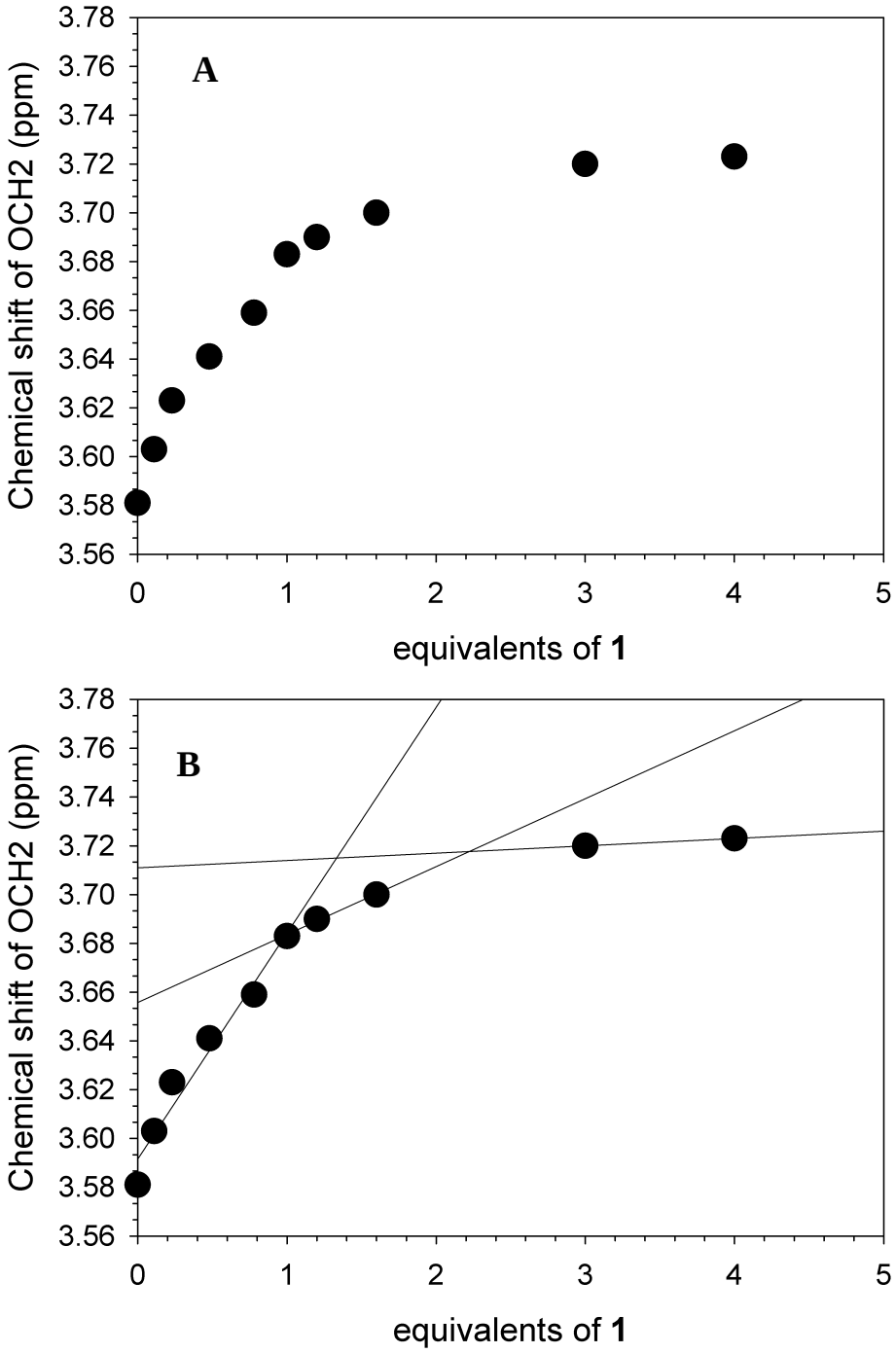


Figure S3. Binding curve. (A) Titration of 2 mM (*R*,*R*)-(^{CR}pdp)Zn with **1** (CD_3CN, 25°C). (B) Rough analysis that suggests a 2:1 stoichiometry for the binding in the presence of excess **1**. The figure was obtained after extrapolation of lines for the points below 1 eq, between 1 and 2 equivalents and above 2 equivalents of **1**. The intercepts at 1:1 and ≈1:2 ratios qualitatively support the overall stoichiometry.

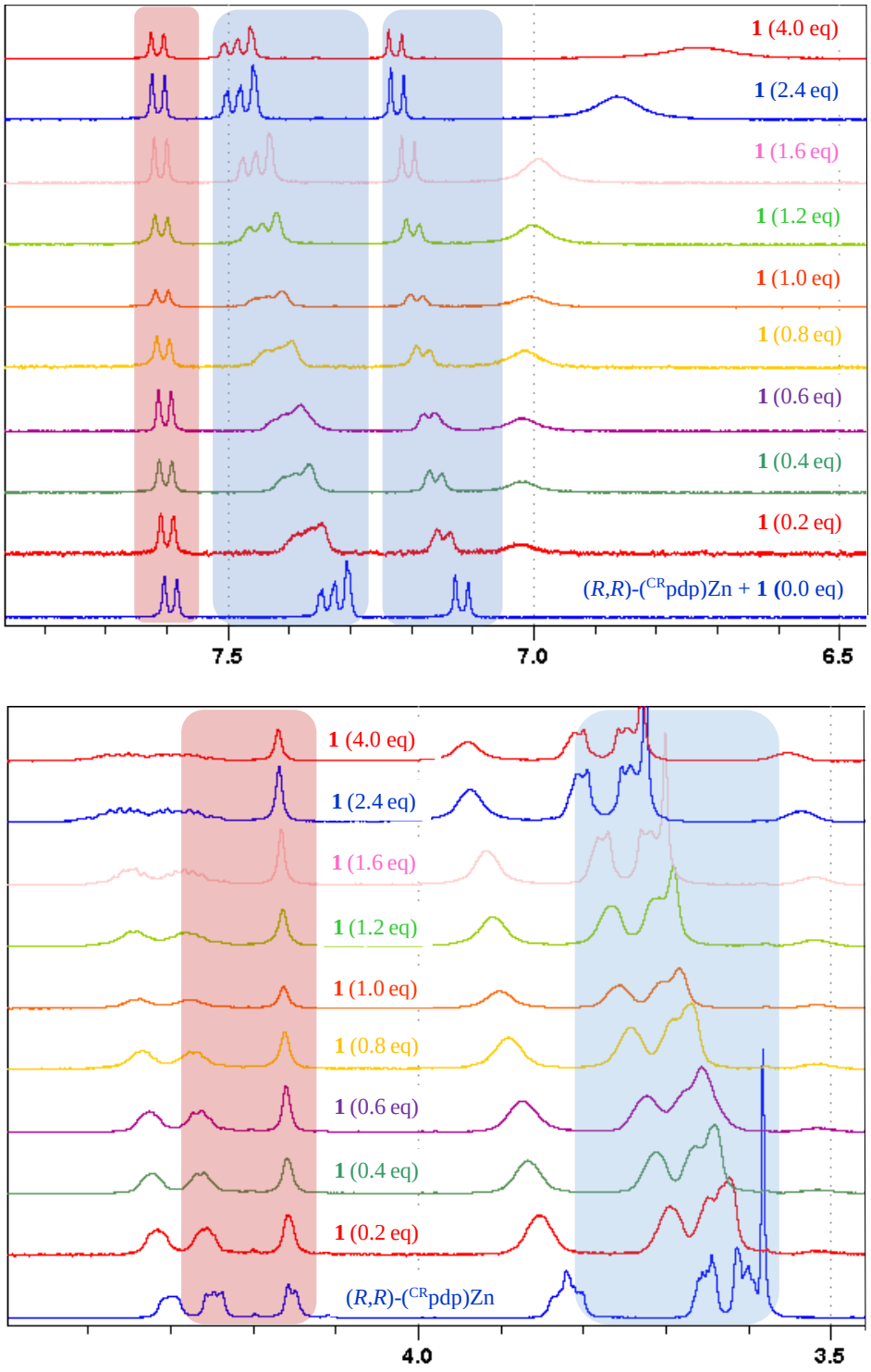


Figure S4. Determination of the stoichiometry of the binding of 1 to (*R,R*)-(^{CR}pdp)Zn by analysis of the variation of the benzocrown ether signals. Note the loss and subsequent recovery of definition of the benzocrown signals (in the blue rectangles), consistent with an initial C2 symmetry of the free host (red, bottom spectrum), loss of this symmetry when exchanging 1:1 adducts with lower symmetry are formed (middle spectra) and recovery of the C2 symmetry and of definition as 2:1equivalence is approached (purple, top spectrum). Note also the loss of significant broadening for the signals of other moieties of the ligand, less affected by the binding of **1**. Enlargement of the aromatic (top) and aliphatic regions (bottom) are shown.

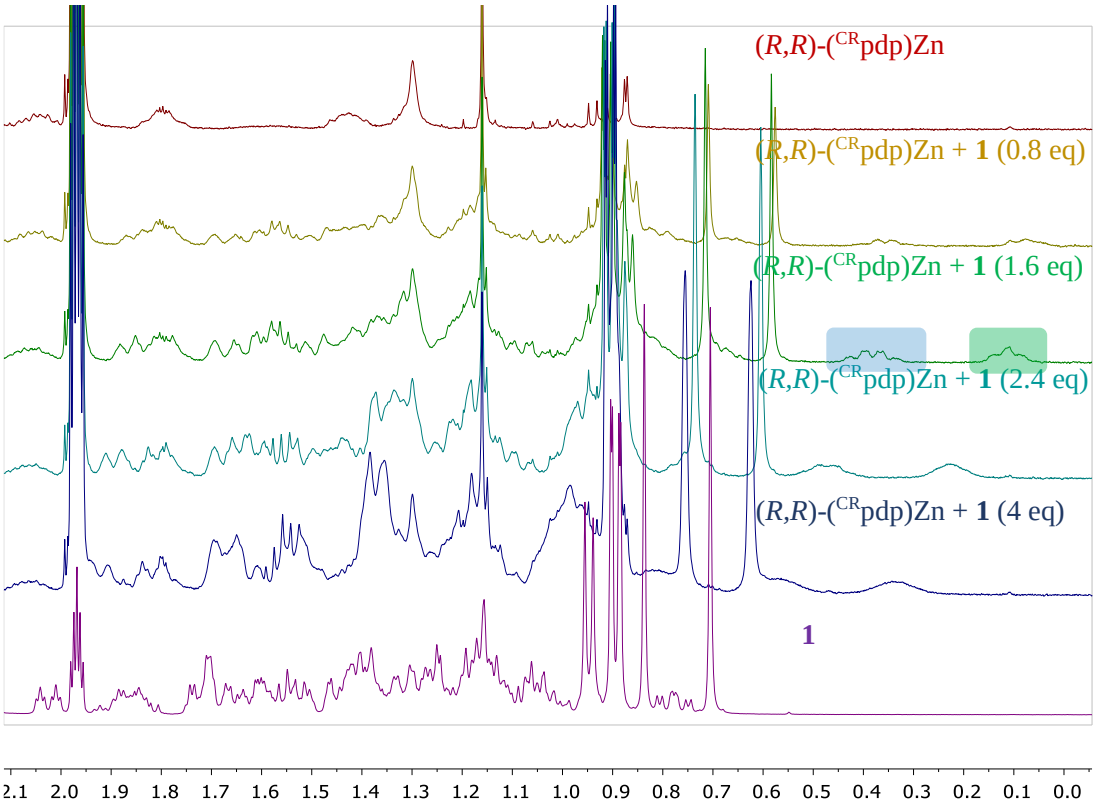
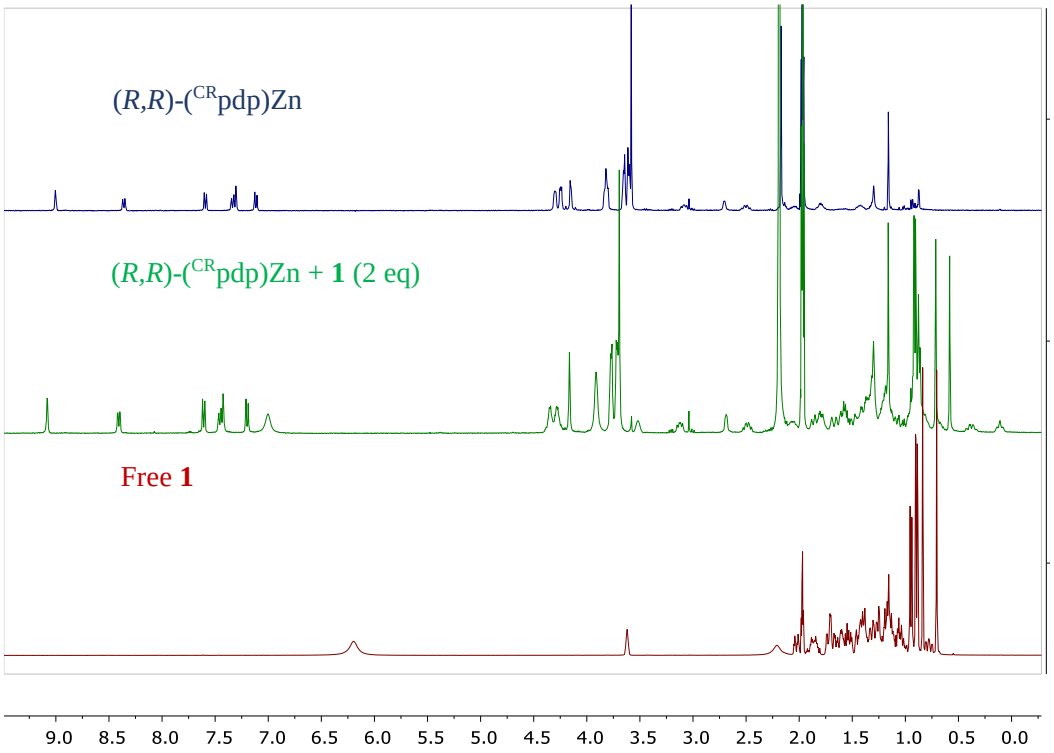


Figure S5. Guest exchange after the equivalence. Titration of 2 mM (*R*,*R*)-(^{CR}pdp)Zn with **1** (CD_3CN, 25°C), aromatic region. Note the upfield shift of the signals of **1** upon binding, which is not homogeneous for every signal. Note also that the high downfield shift of C_9-H (highlighted in green) and $C_{7\alpha}$-H (highlighted in blue) signals, as well as the general upfield shift, is eroded after the equivalence, indicating a rapid exchange process between bound and unbound **1** that occurs on NMR timescale.

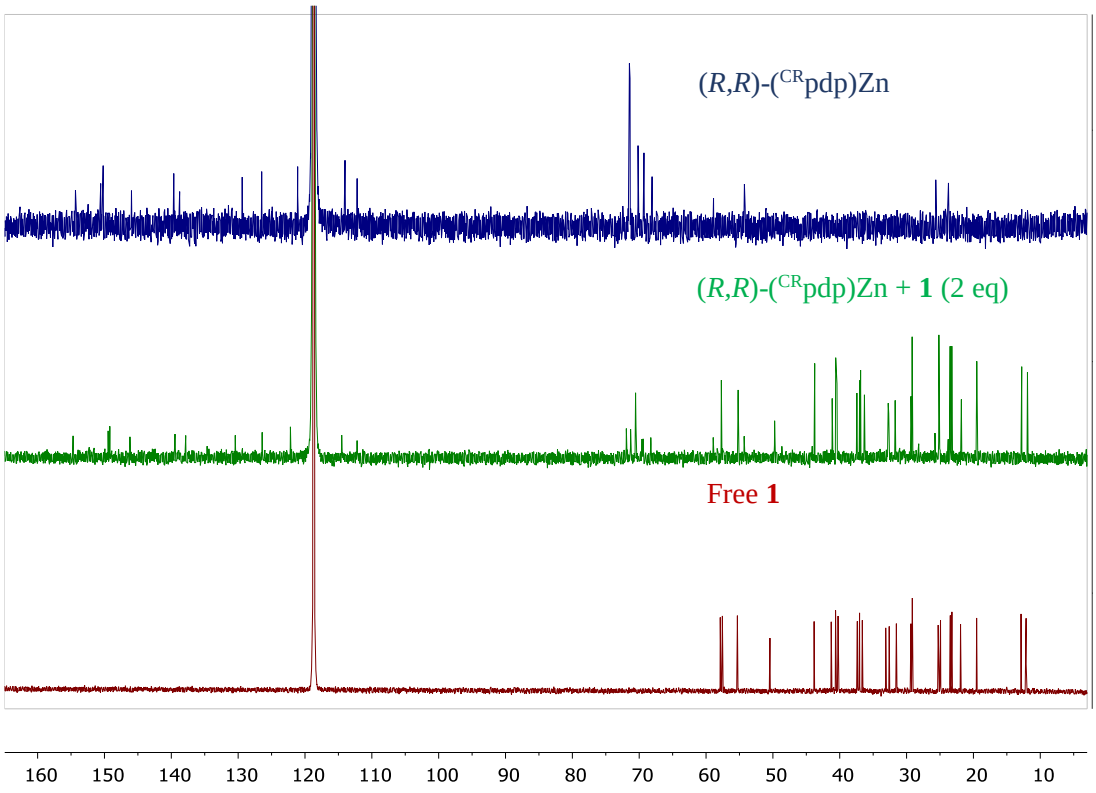
Selected ^{1}H NMR and ^{13}C NMR spectra are reported in the following pages.

*Comparison of NMR spectra of **1**, (R,R)-(^{CR}pdp)Zn and **1**$_2$·(R,R)-(^{CR}pdp)Zn*

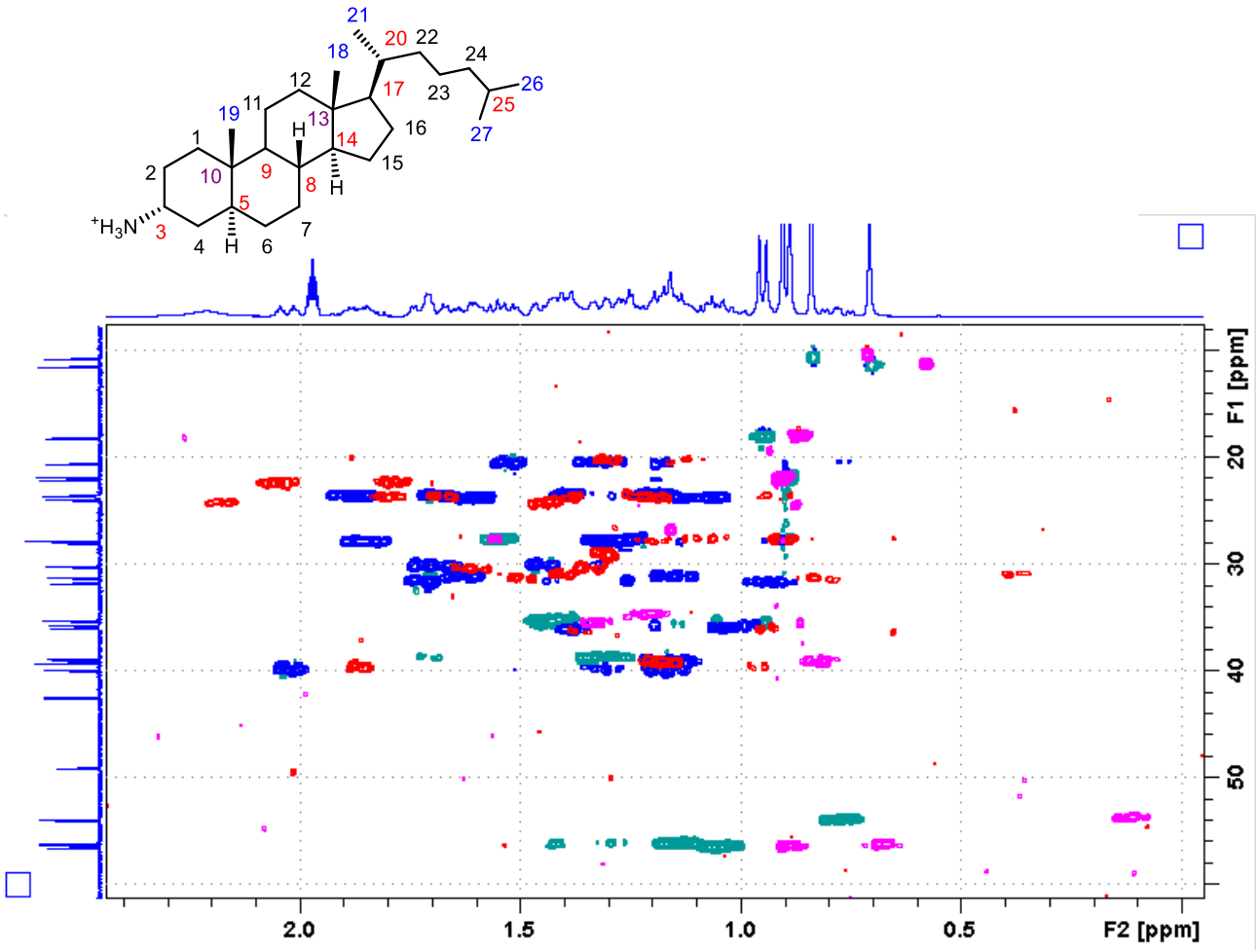
^{1}H-NMR spectra



^{13}C-NMR spectra



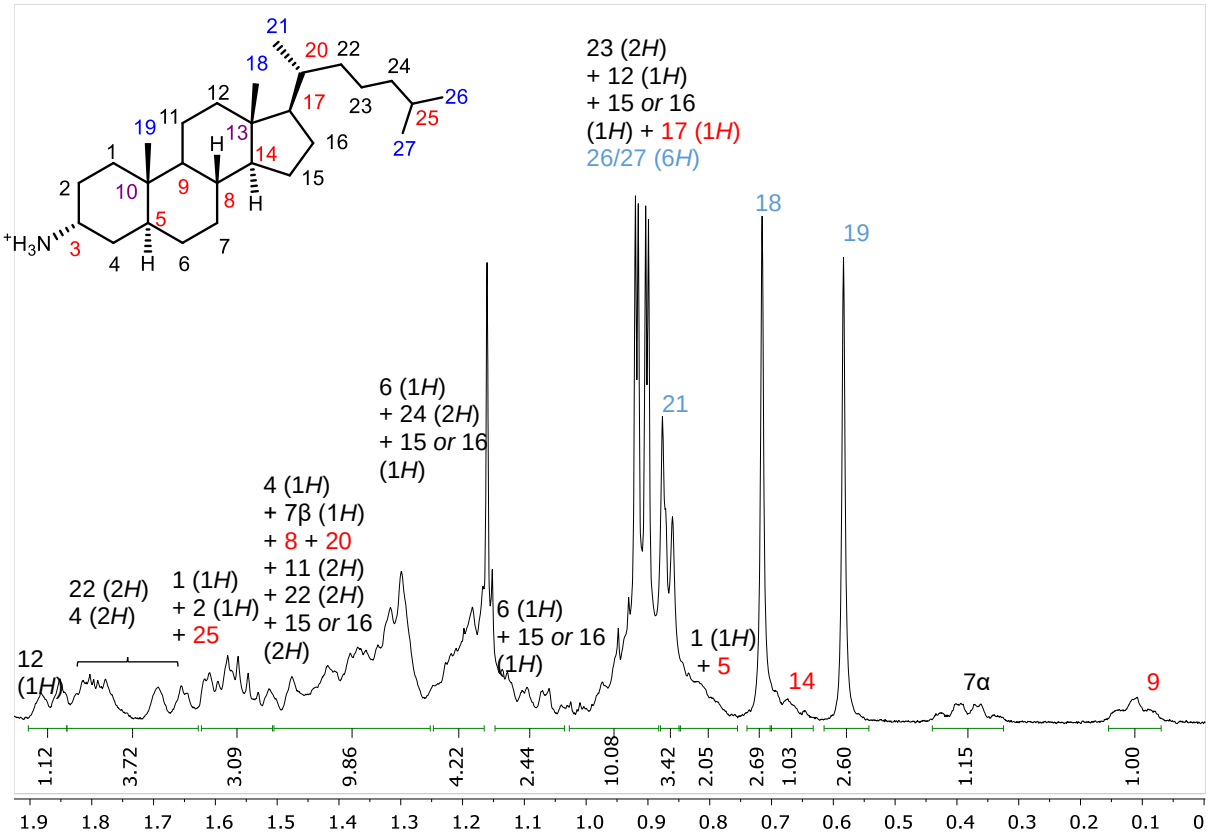
HSQC spectra



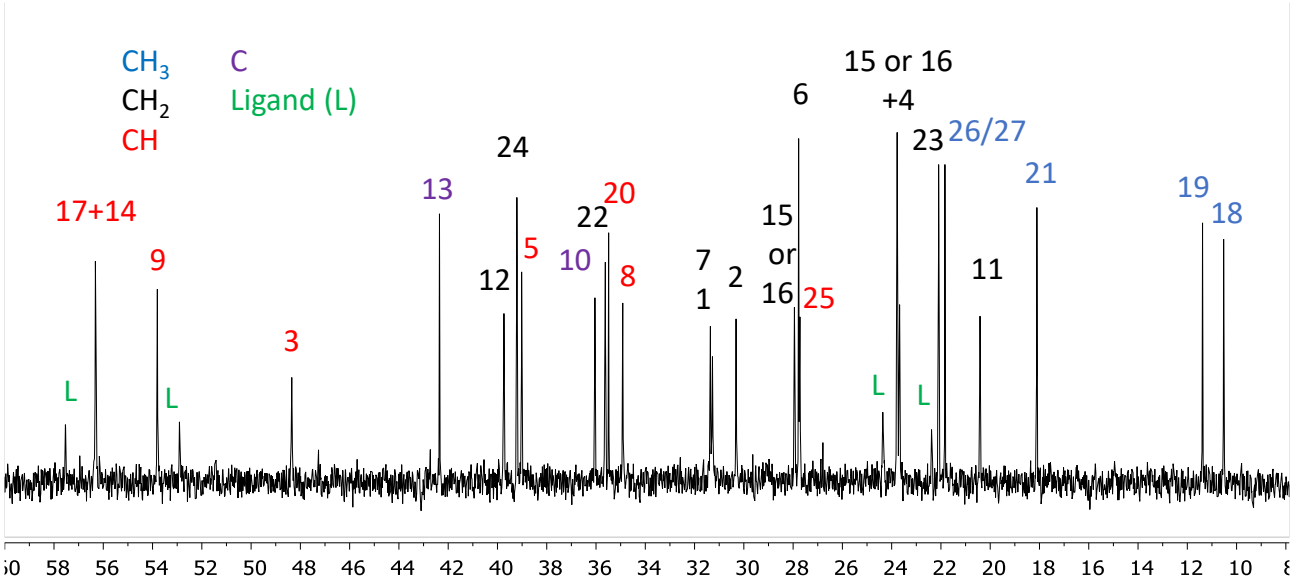
Blue signals refer to CH_2 of free **1**. Green signals refer to C*H* and CH_3 of free **1**. Red signals refer to CH_2 of **1**$_2$·(*R*,*R*)-(^{CR}pdp)Zn. Pink signals refer to C*H* and CH_3 of **1**$_2$·(*R*,*R*)-(^{CR}pdp)Zn.

Assignment of NMR signals of ***1***$_2$*·(R,R)-(*^{CR}*pdp)Zn*

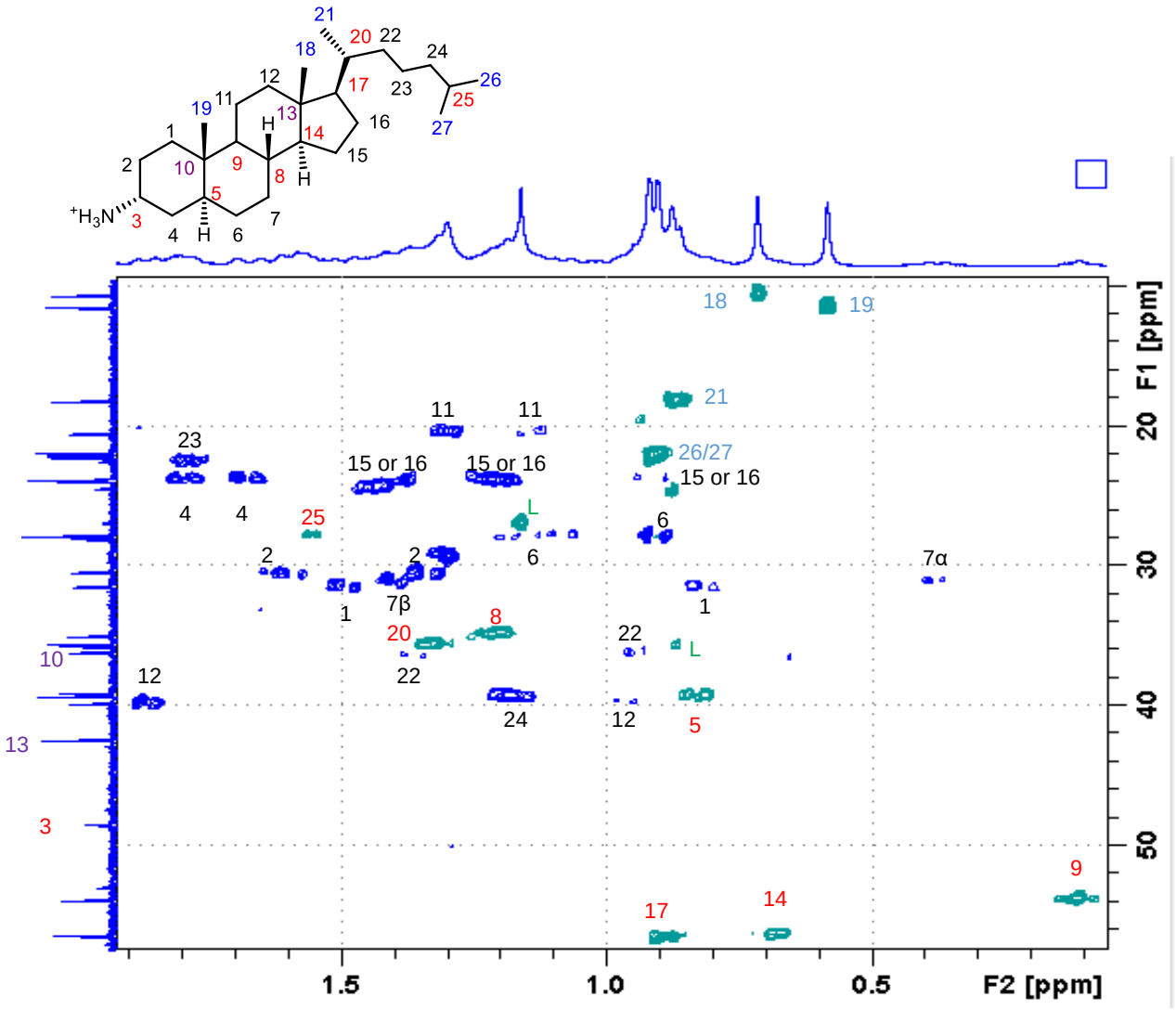
^{1}H-NMR spectra



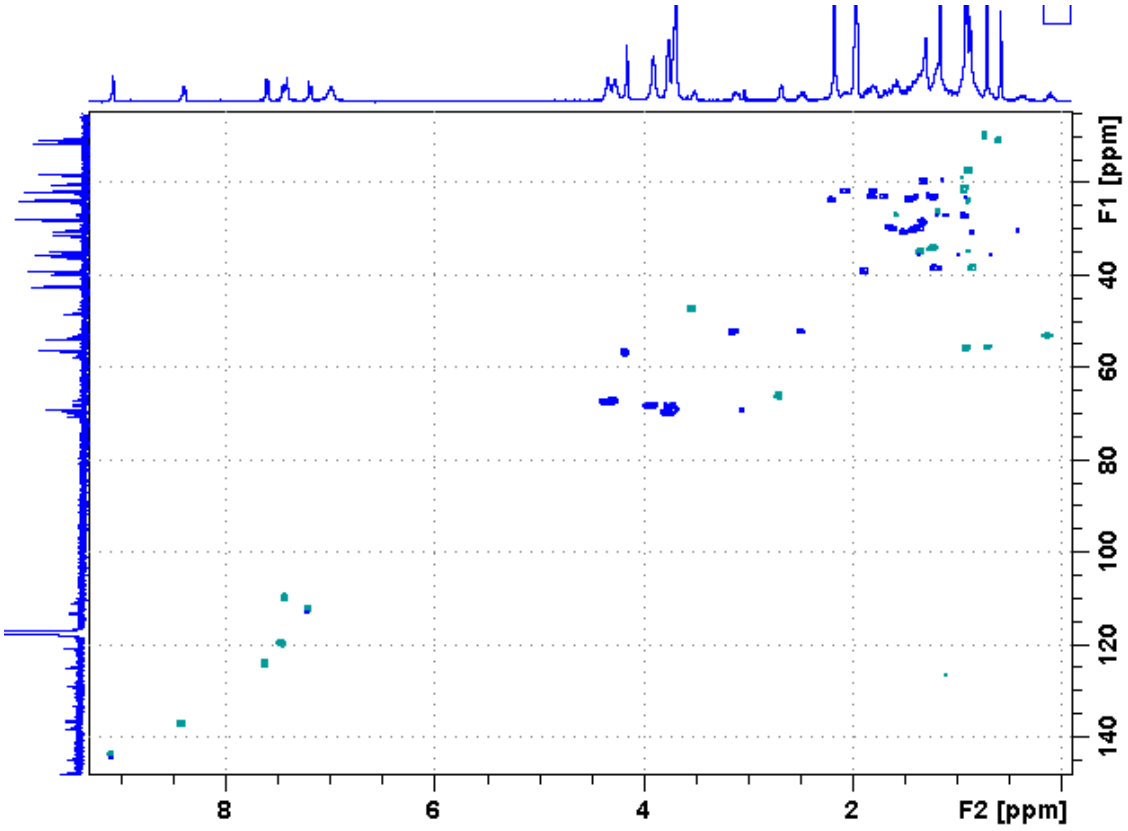
^{13}C-NMR spectrum



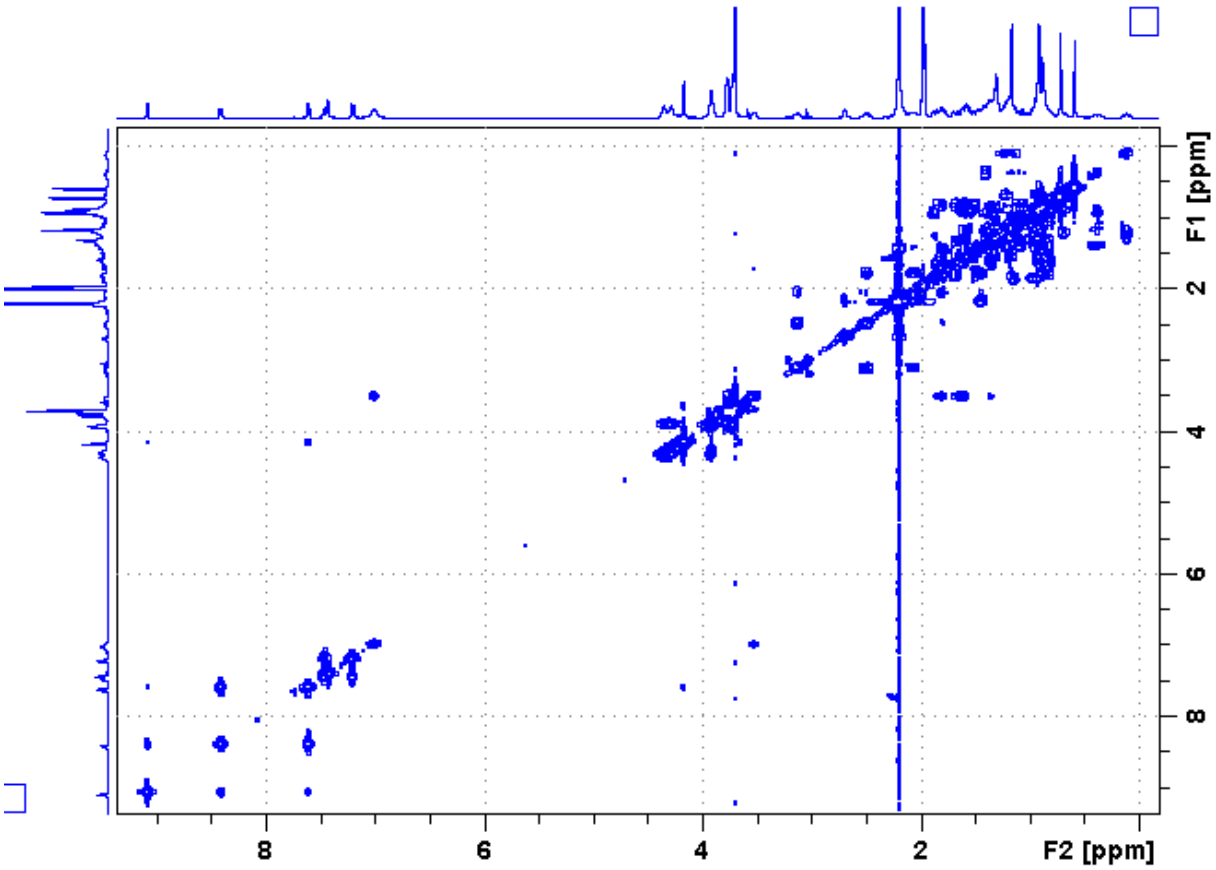
HSQC spectrum (and signal assignment) of $\mathbf{1}_2$·(*R*,*R*)-(^{CR}pdp)Zn



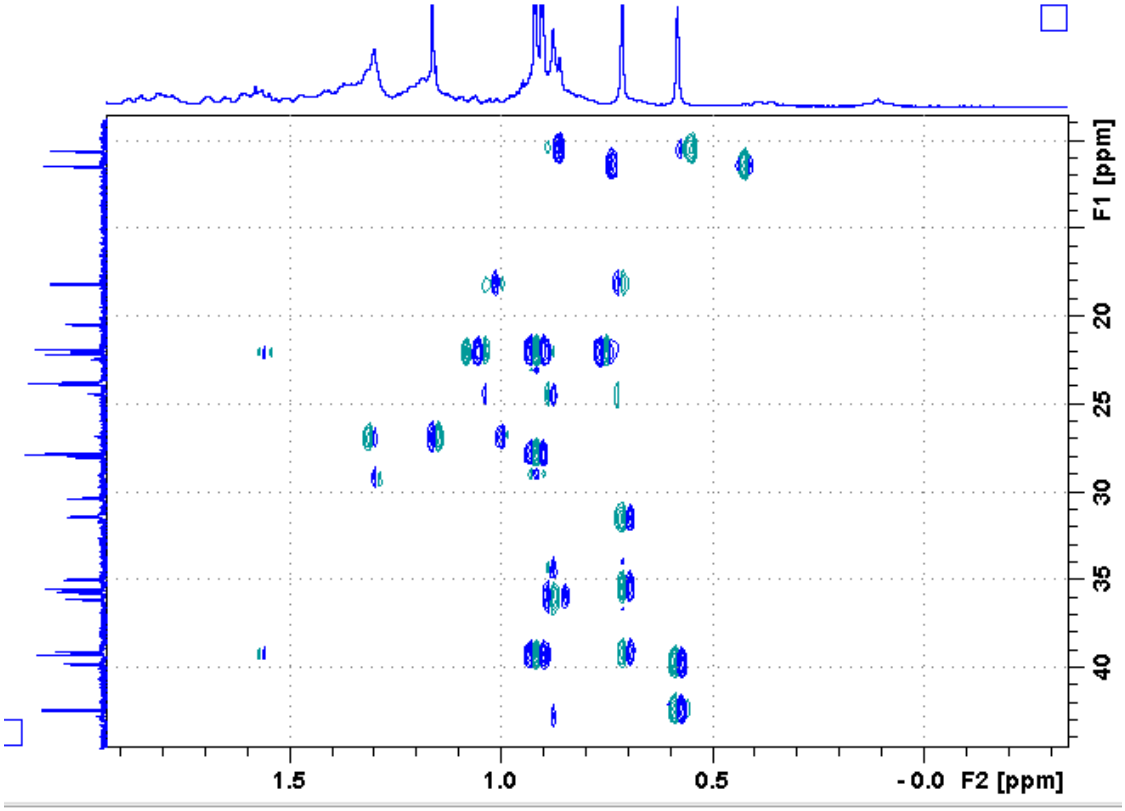
Signals were assigned after analysis of HSQC, HMBC, TOCSY, NOESY and COSY spectra (reported in the following pages). Signals marked with L are from the ligand backbone of the complex.



Full HSQC spectrum of $\mathbf{1}_2$·(*R*,*R*)-(^{CR}pdp)Zn



COSY spectrum of $\mathbf{1}_2$·(*R*,*R*)-(^{CR}pdp)Zn.



HMBC spectrum of $\mathbf{1}_2$·(*R*,*R*)-(^{CR}pdp)Zn (enlargement of aliphatic region).

*Shift of the signals of **1** upon binding*

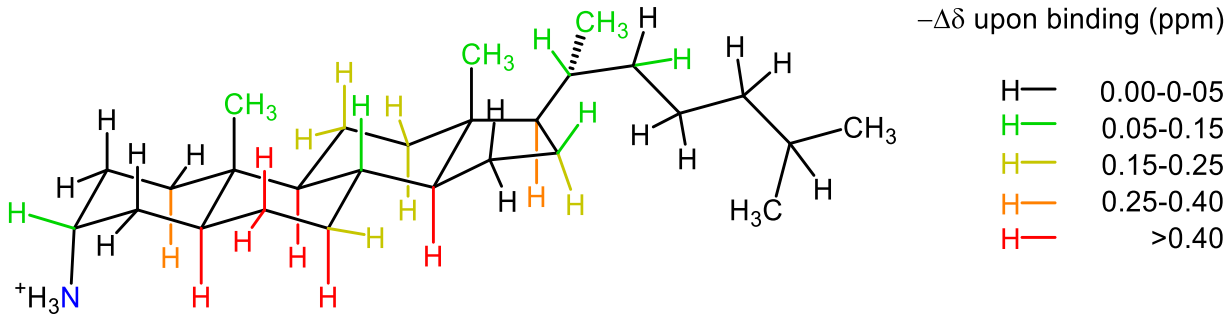


Figure S6. Graphical depiction of all C-H shifts of 1 upon binding.

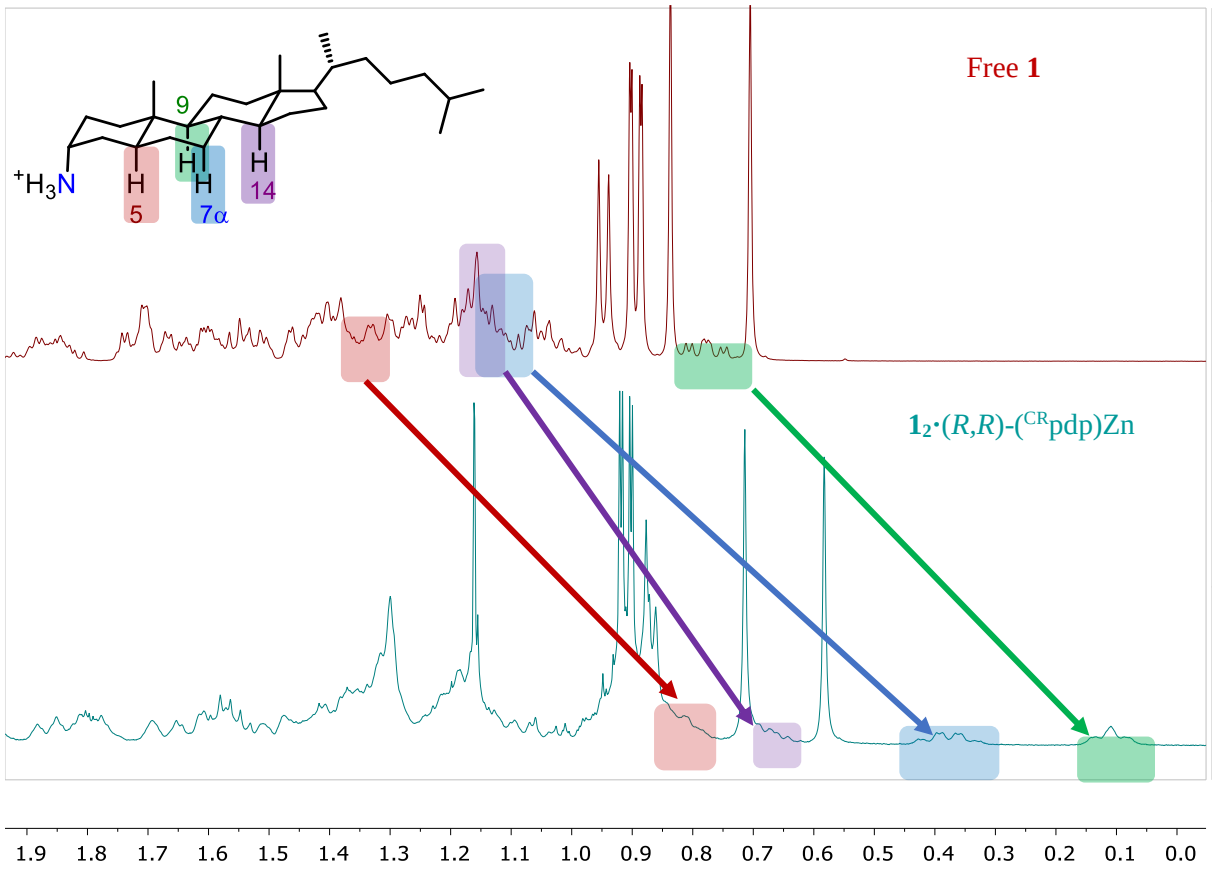


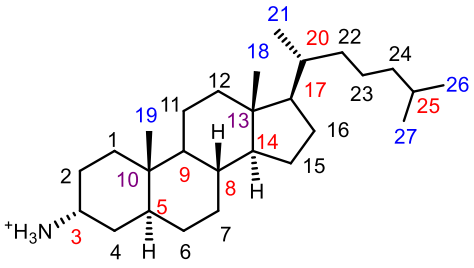
Figure S7: ^{1}H-NMR spectra with the most significant shifts experienced by 1 upon binding.

Table S3: Shift of ^{1}H chemical shift of 1 upon binding

Signal	Free **1**	Bound **1**	Δδ upon binding	Δδ (on the same CH_2, α vs β face)
*Steroid Core: Ring A: median shift -0.11 (*α -0.12, β -0.12)				
C_1-H_2	1.62	1.50	-0.12	+0.20
	1.15	0.83	-0.32	
C_2-H_2	1.85	1.62	0.23	+0.27
	1.32	1.36	+0.04	
C_3-H	3.62	3.51	-0.11	-
C_4-H_2	1.86	1.88	+0.02	+0.27
	1.40	1.69	+0.29	
C_5-H	1.31	0.82	-0.49	-
*Steroid Core: Ring B: median shift -0.46 (*α -0.59, β -0.33*)*				
C_6-H_2	1.70	1.13	-0.57	-0.02
	1.45	0.90	-0.55	
C_7-H_2	1.73	1.49	-0.24	+0.33
	0.94	0.37	-0.57	
C_8-H	1.39	1.21	-0.18	-
C_9-H	0.77	0.11	-0.66	-
*Steroid Core: Ring C: median shift -0.25 (*α -0.29, β -0.19*)*				
C_{11}-H_2	1.52	1.30	-0.22	-0.12
	1.32	1.14	-0.18	
C_{12}-H_2	2.02	1.86	-0.16	+0.15
	1.18	0.96	-0.22	
C_{14}-H	1.14	0.67	-0.47	-
*Steroid Core: Ring D: median shift -0.06 (*α -0.10, β -0.01*)*				
C_{15}-H_2	1.33	1.38	+ 0.05	+0.06
	1.24	1.24	-0	
C_{16}-H_2	1.60	1.43	-0.07	+0.03
	1.06	0.92	-0.14	
C_{17}-H	1.06	0.89	-0.17	-

		Methyls -0.11		
C_{18}-H_3	0.68	0.56	-0.12	-
C_{19}-H_3	0.80	0.69	-0.11	-
		Lateral chain: median shift -0.03		
C_{20}-H	1.44	1.34	-0.10	-
C_{21}-H_3	0.92	0.84	-0.08	-
C_{22}-H_2	1.38 1.00	1.36 0.94	-0.02 -0.06	+0.04
C_{23}-H_2	1.70	1.69	-0.01	0
C_{24}-H_2	1.18	1.18	0	0
C_{25}-H	1.54	1.55	+0.01	-
$C_{26/27}$-H_3	0.89	0.90	+0.01	-

Chemical shifts have been obtained by analysis of the HSQC spectra.



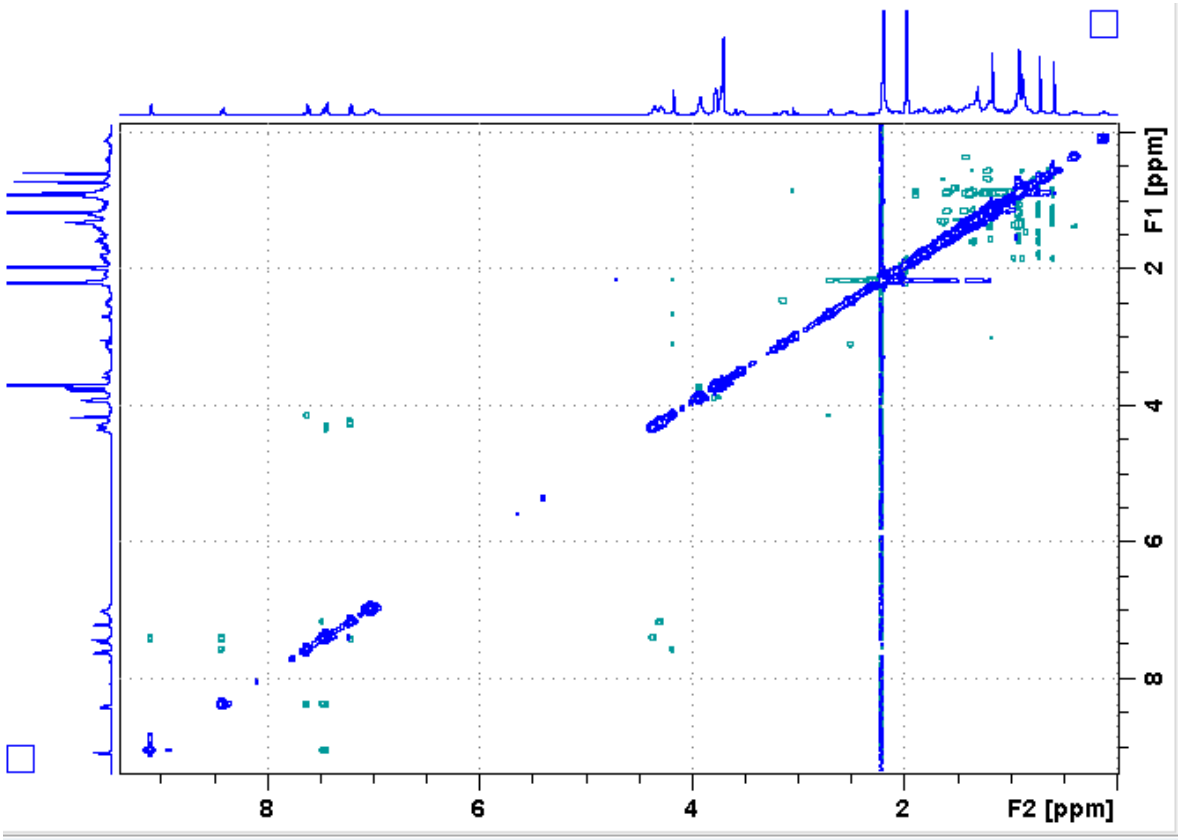
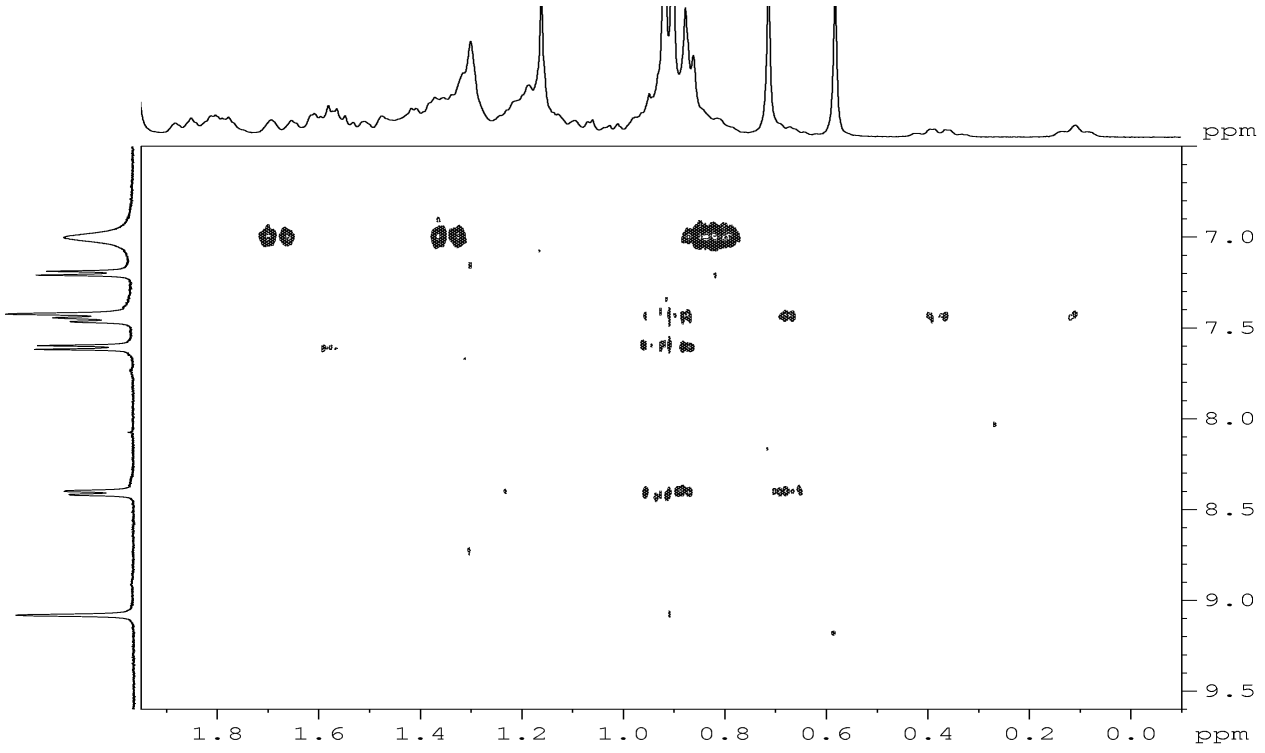


Figure S8: NOESY spectrum of 1_2·(*R*,*R*)-(^{CR}pdp)Zn.



Intermolecular NOESY correlation. NOESY spectrum of **1_2**·(*R*,*R*)-(^{CR}pdp)Zn (enlargement of aromatic-steroid correlations; assignment and key correlations in Figure 3C).

*Displacement of **1** with Ba(OTf)$_2$ from **1$_2$**·(R,R)-(CRpdp)Zn*

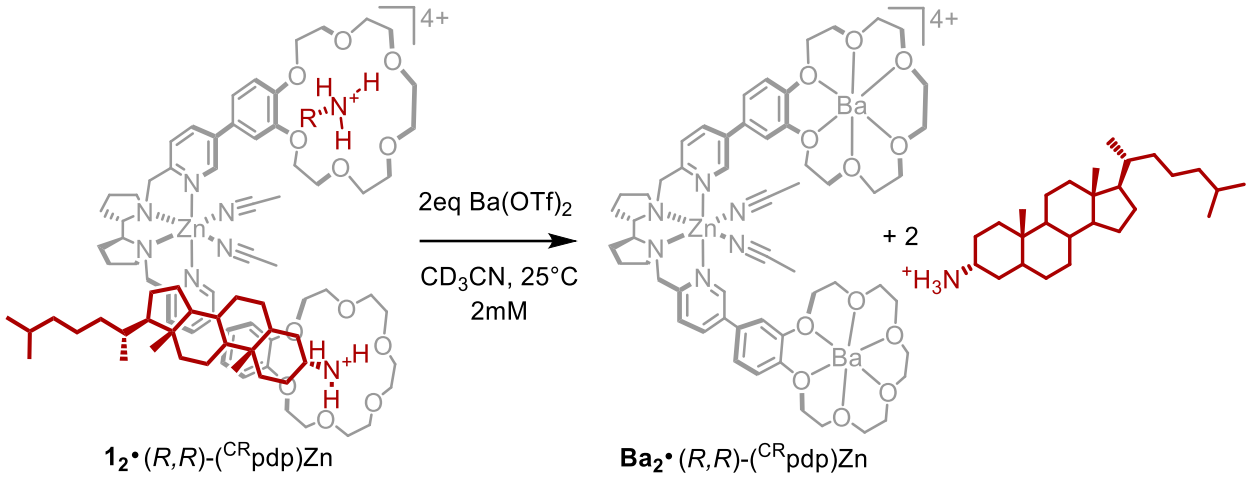


Figure S9: Reaction Scheme.

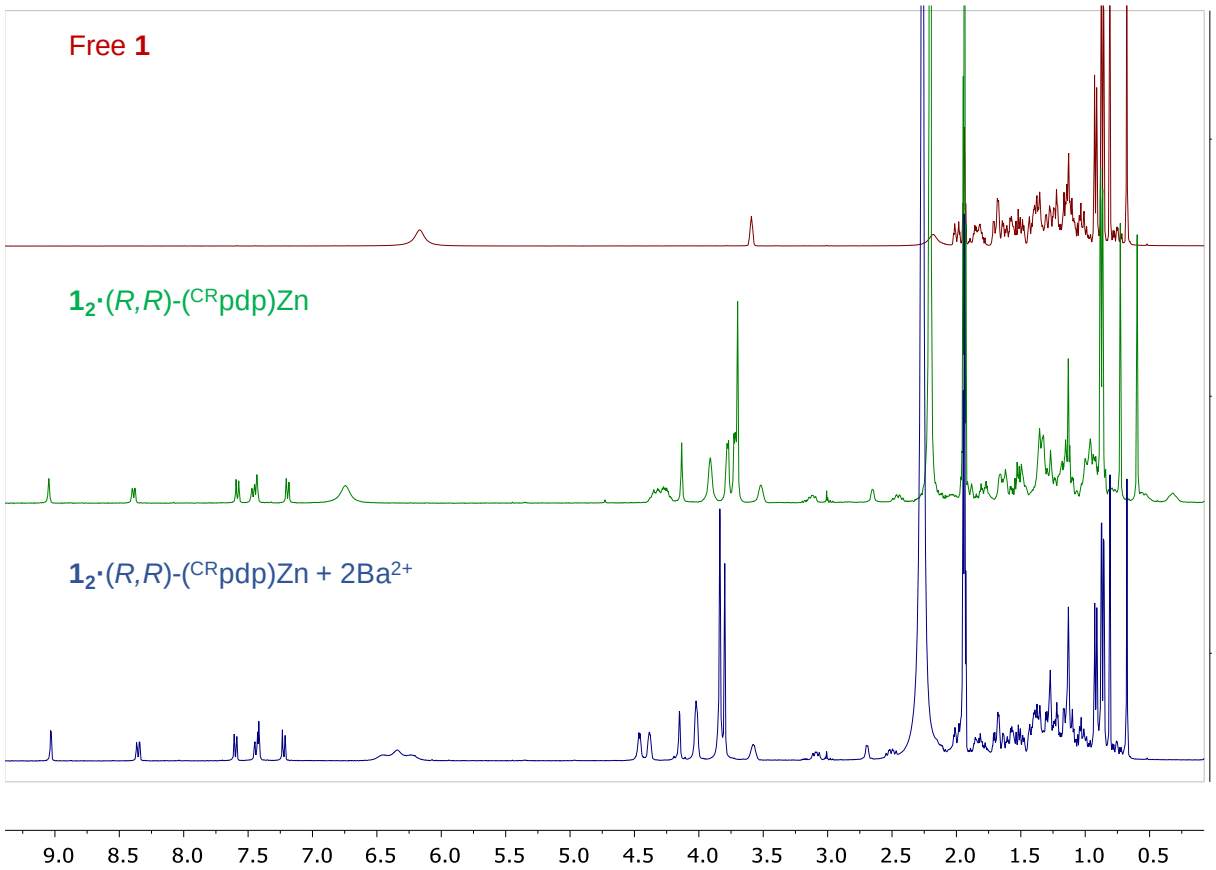
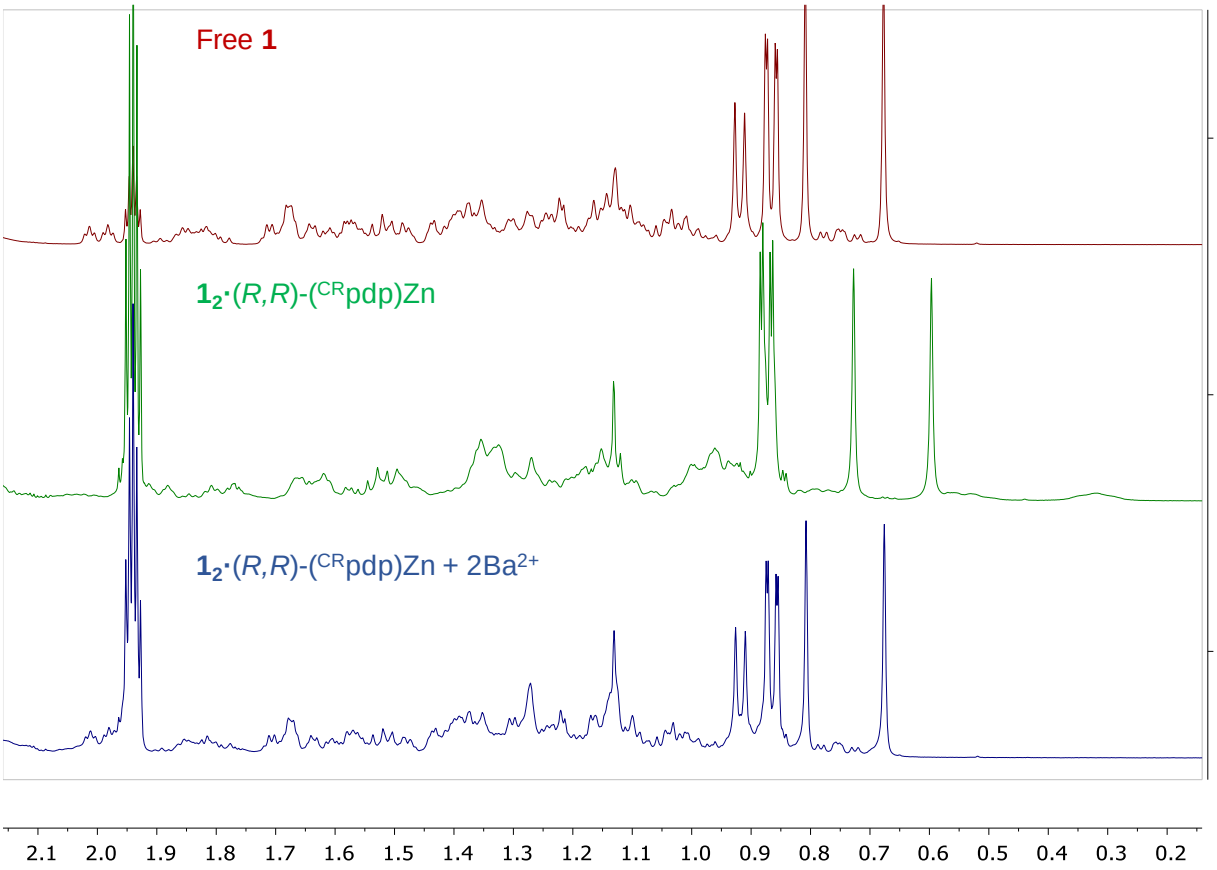
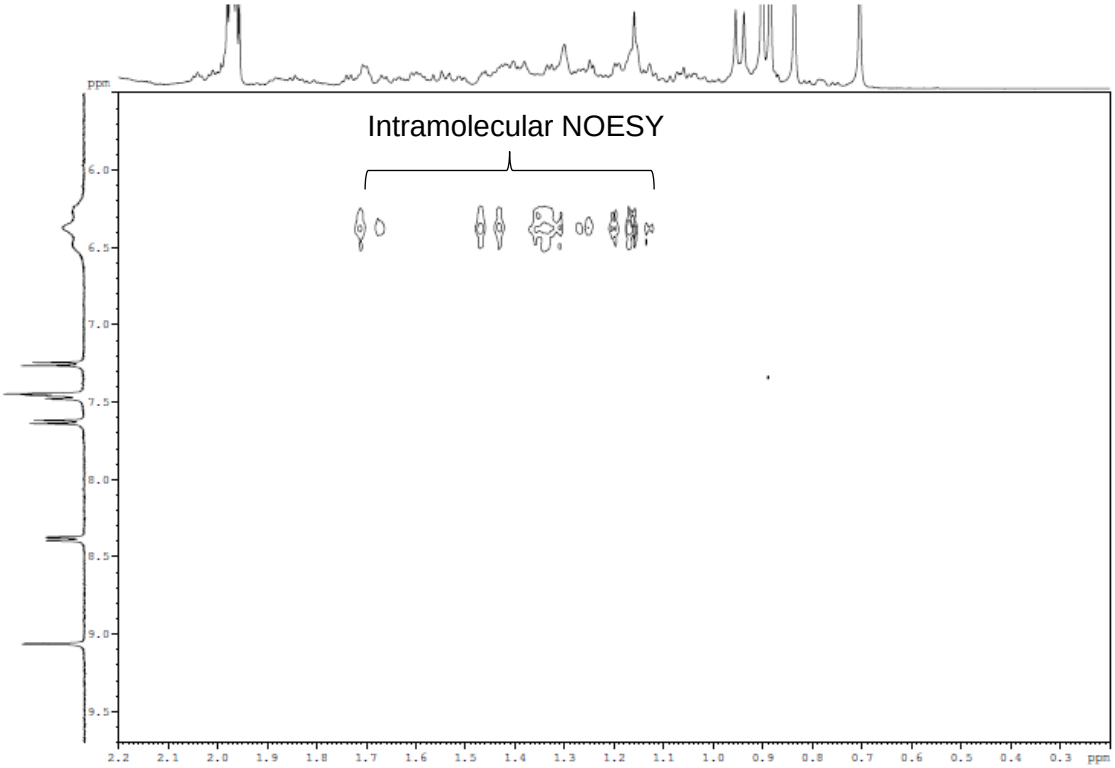


Figure S10: ^{1}H-NMR spectra of 1, 1$_2$·(*R*,*R*)-(CRpdp)Zn and Ba$_2$·(*R*,*R*)-(CRpdp)Zn + 2 eq of 1.

An enlargement of the aliphatic regions is displayed in the following page.



Enlargement of the aliphatic region.



(Lack of) intermolecular NOESY correlation between **1** and Ba_2·(*R*,*R*)-(CRpdp)Zn.

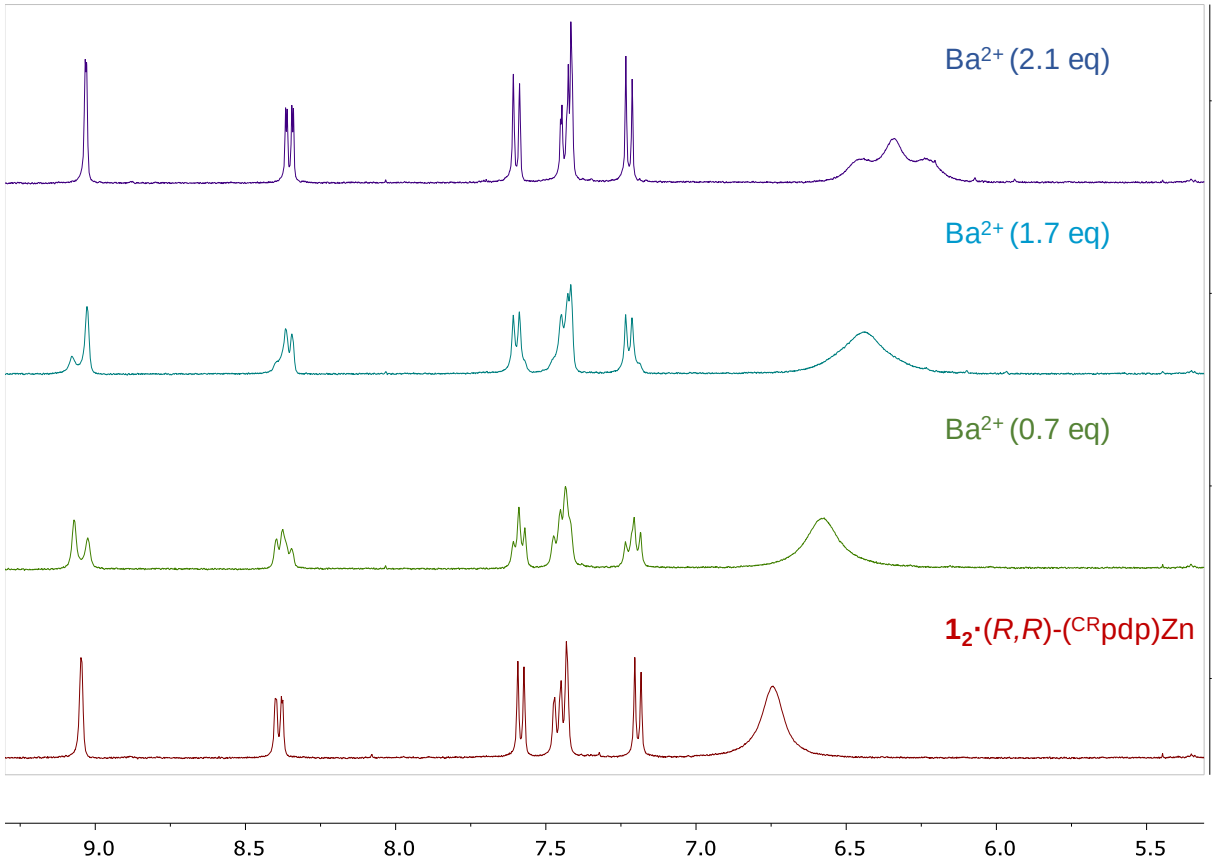


Figure S11: NMR monitoring of the displacement of 1 from 1_2·(*R*,*R*)-(^{CR}pdp)Zn.

Note the appearance of two set of signals (i.e. for the pyridine Cα-H at 9.1 ppm) that correspond to **1_2**·(*R*,*R*)-(^{CR}pdp)Zn (right) and to Ba_2·(*R*,*R*)-(^{CR}pdp)Zn (left) upon addition of substoichiometric amounts of $Ba(OTf)_2$ (with respect to the crown ethers). The presence of two set of signals implies that the Ba^{2+} guest in Ba_2·(*R*,*R*)-(^{CR}pdp)Zn does not undergo exchange with **1** (or that the exchange is slower than NMR timescale) in line with a higher affinity[2] of 18-benzocrown-6 ethers for Ba^{2+} vs the ammonium R-NH_3^+.

Docking of crystal structures

A rough predictive docking model was obtained by simple juxtaposition of the crystal structures of (*S*,*S*)-(^{CR}pdp)Fe[2] (only the *O*-atom of the triflate anion displayed) and an amide derivative of **1**[4] (devoid of the acyl moiety). To keep the model as simple as possible, the *N*-atom of the amide derivative of **1** was manually placed roughly at the center of the crown ether (with Hyperchem 8.0), without any computed geometry optimization or computed docking. The resulting structure is displayed below.

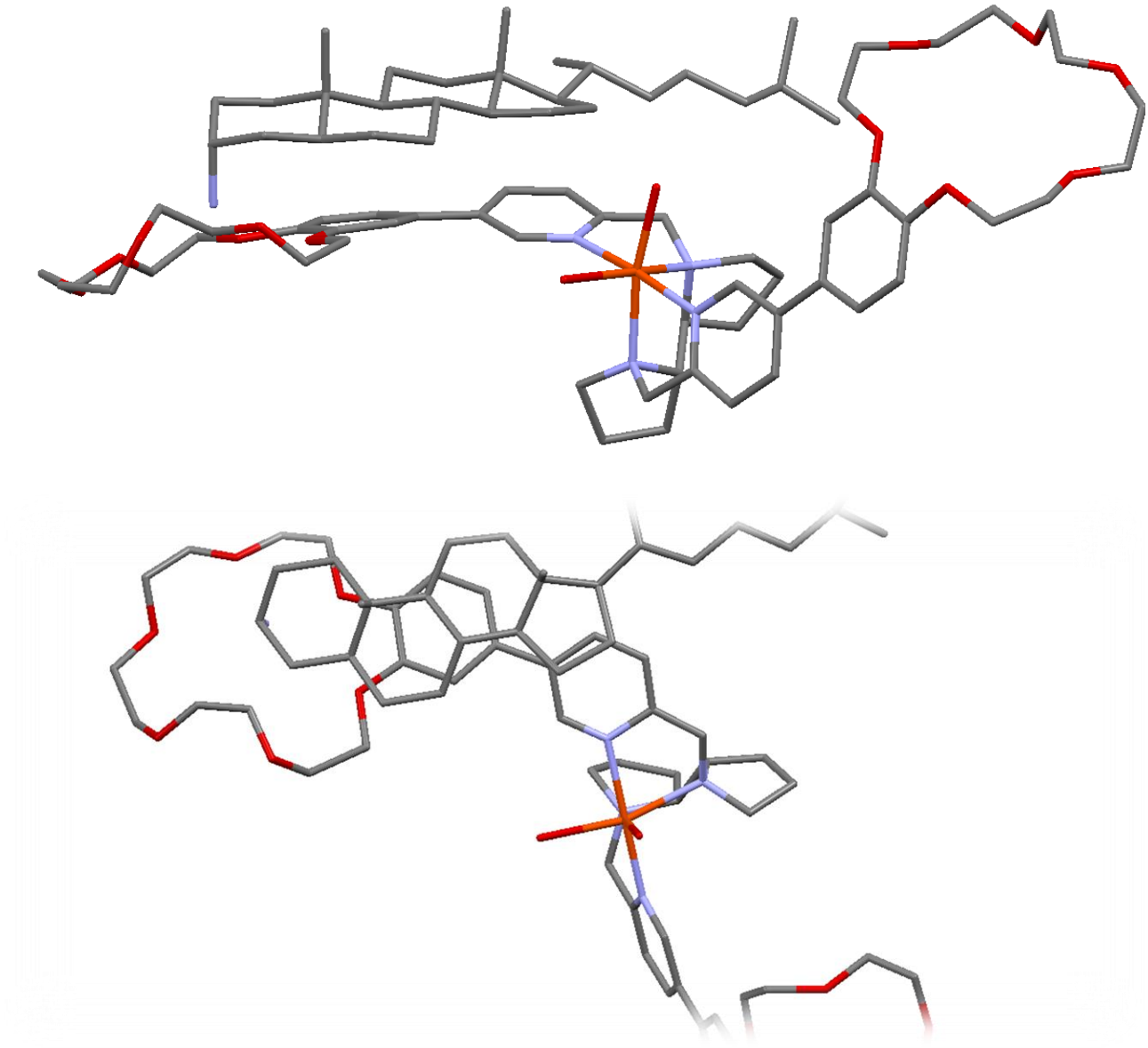


Figure S12: Non-computed docking of the crystal structures of (*S*,*S*)-(^{CR}pdp)Fe[2] and an amide derivative of **1**. [4]Front and top view of the adduct.

*Binding of **2** to (R,R)-(CRpdp)Zn*

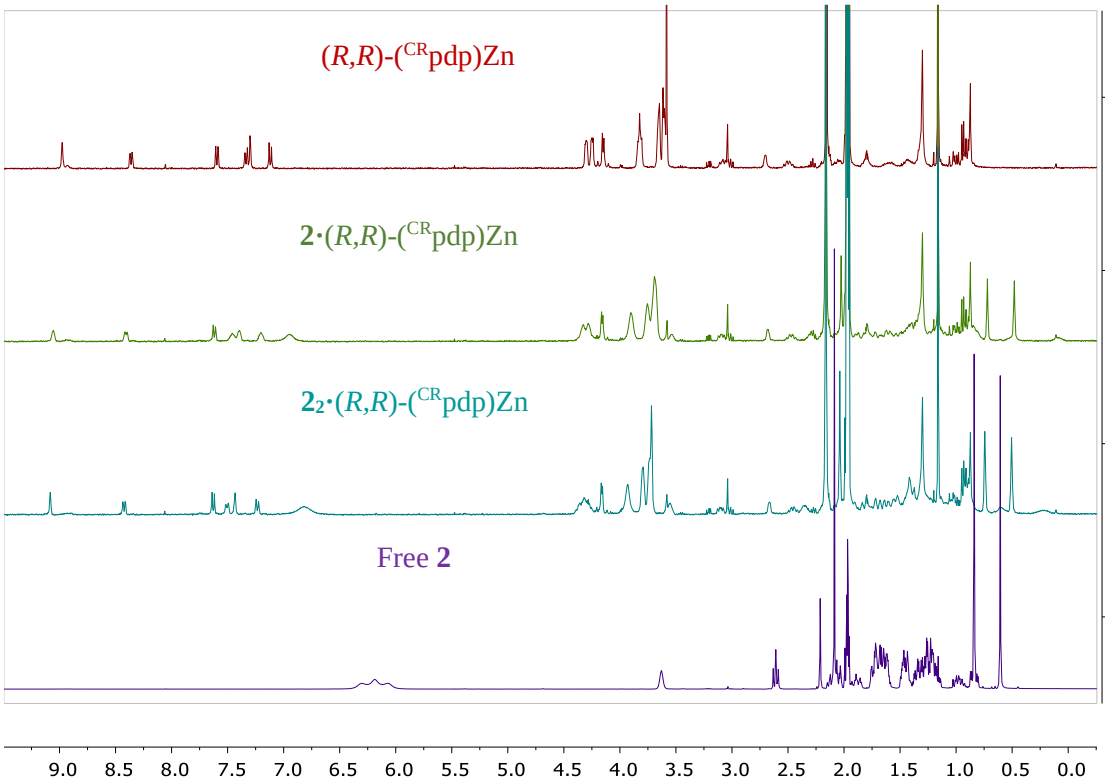
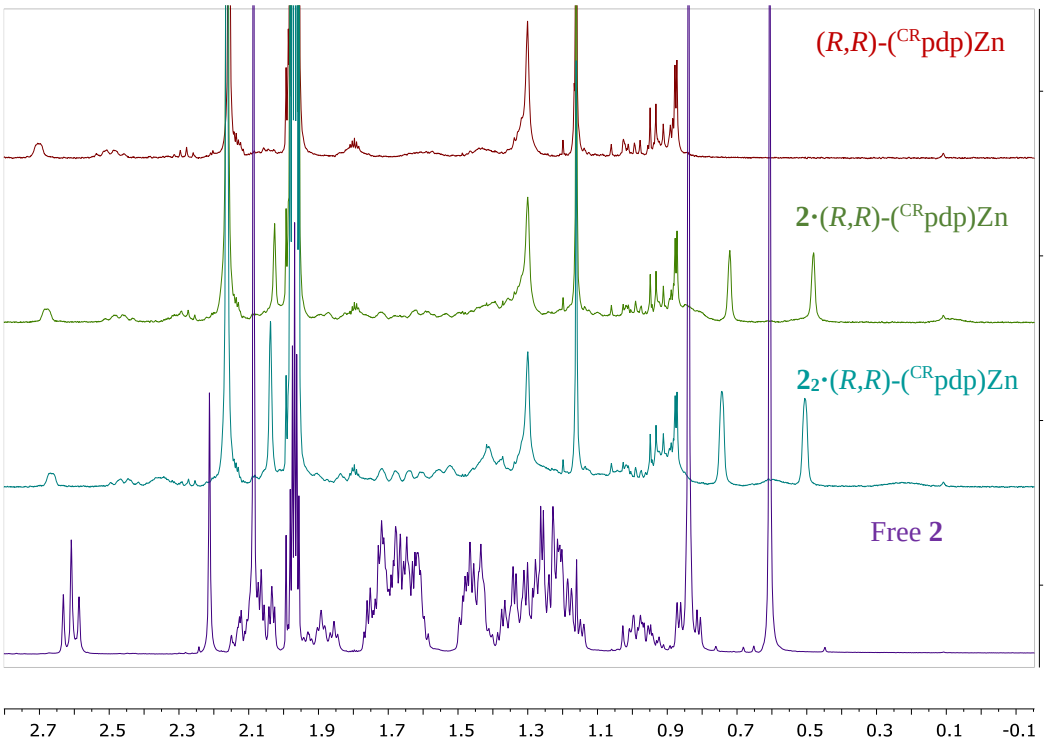
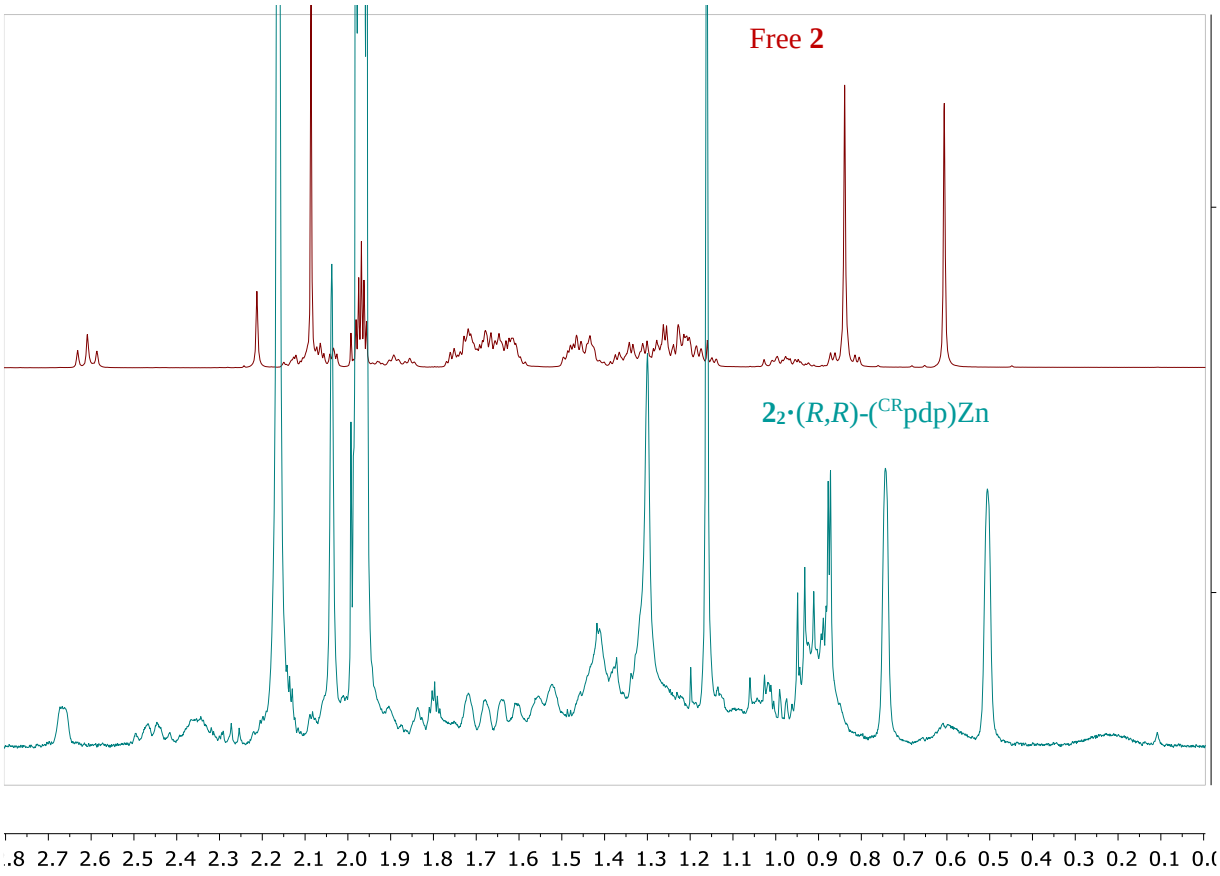


Figure S13: ^{1}H-NMR monitoring of the binding of 2 to (*R*,*R*)-(CRpdp)Zn.

Enlargement of the aliphatic region and comparison between free and bound **2** are displayed below.



Enlargement of the aliphatic region.



Comparison between free and bound **2**.

*Binding of **3** to (R,R)-(CRpdp)Zn*

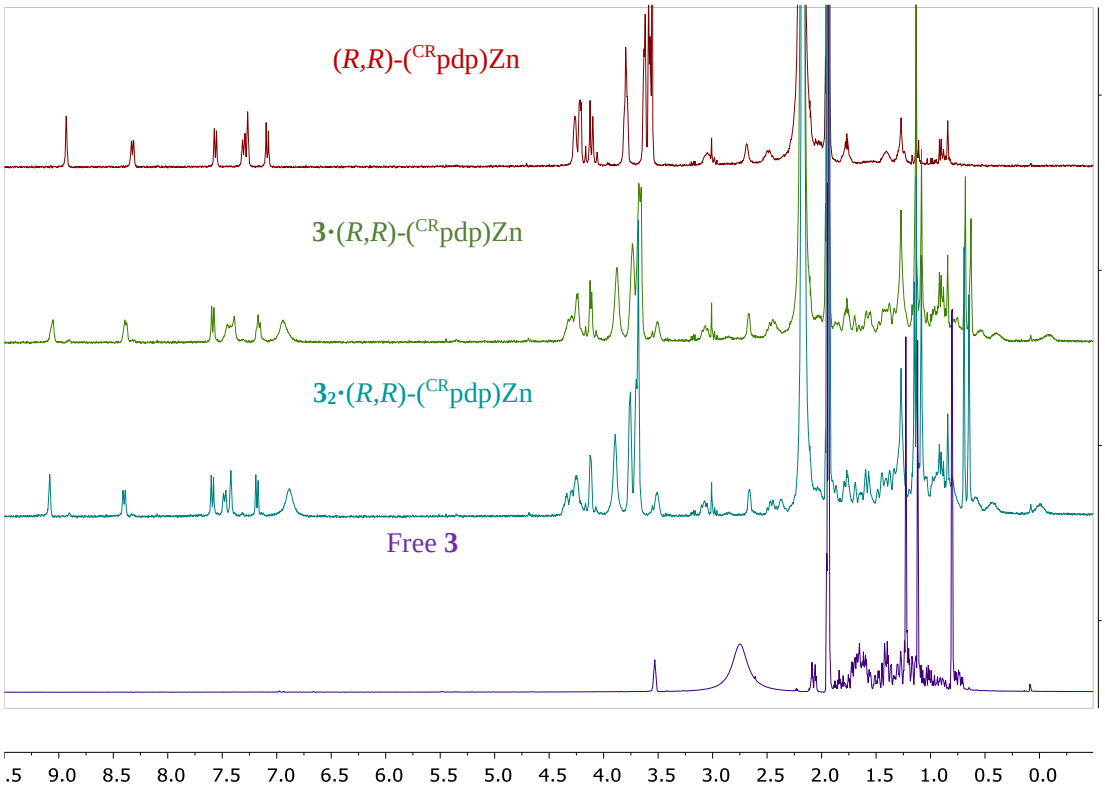
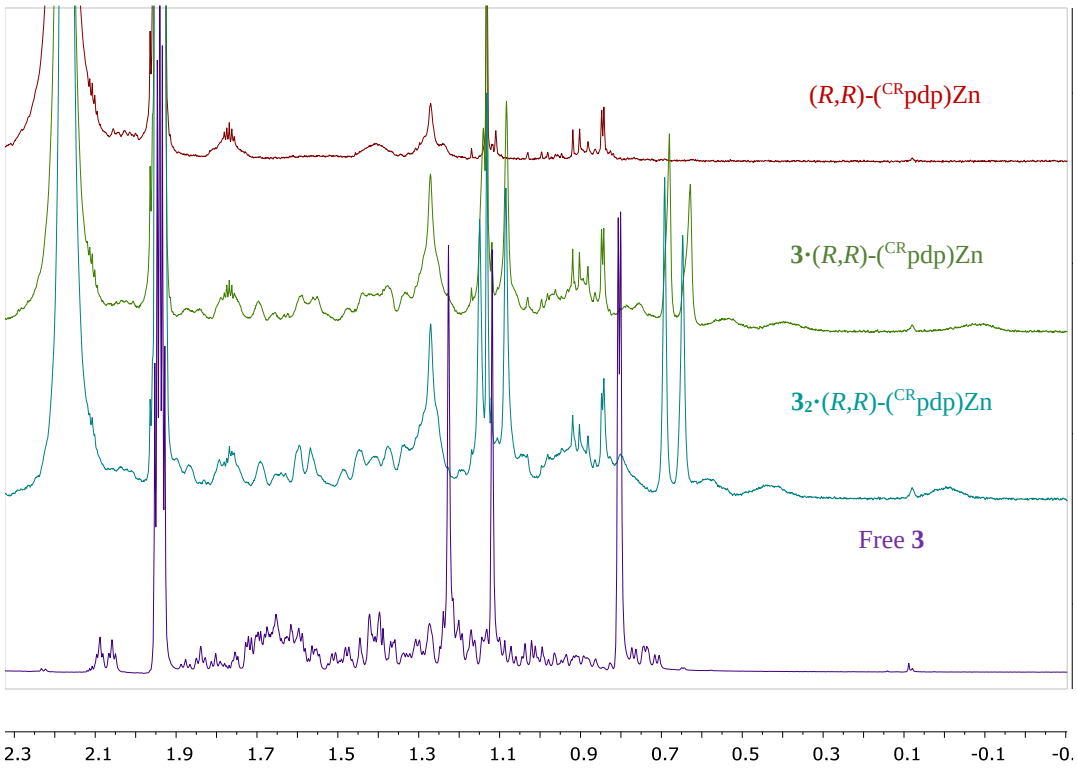
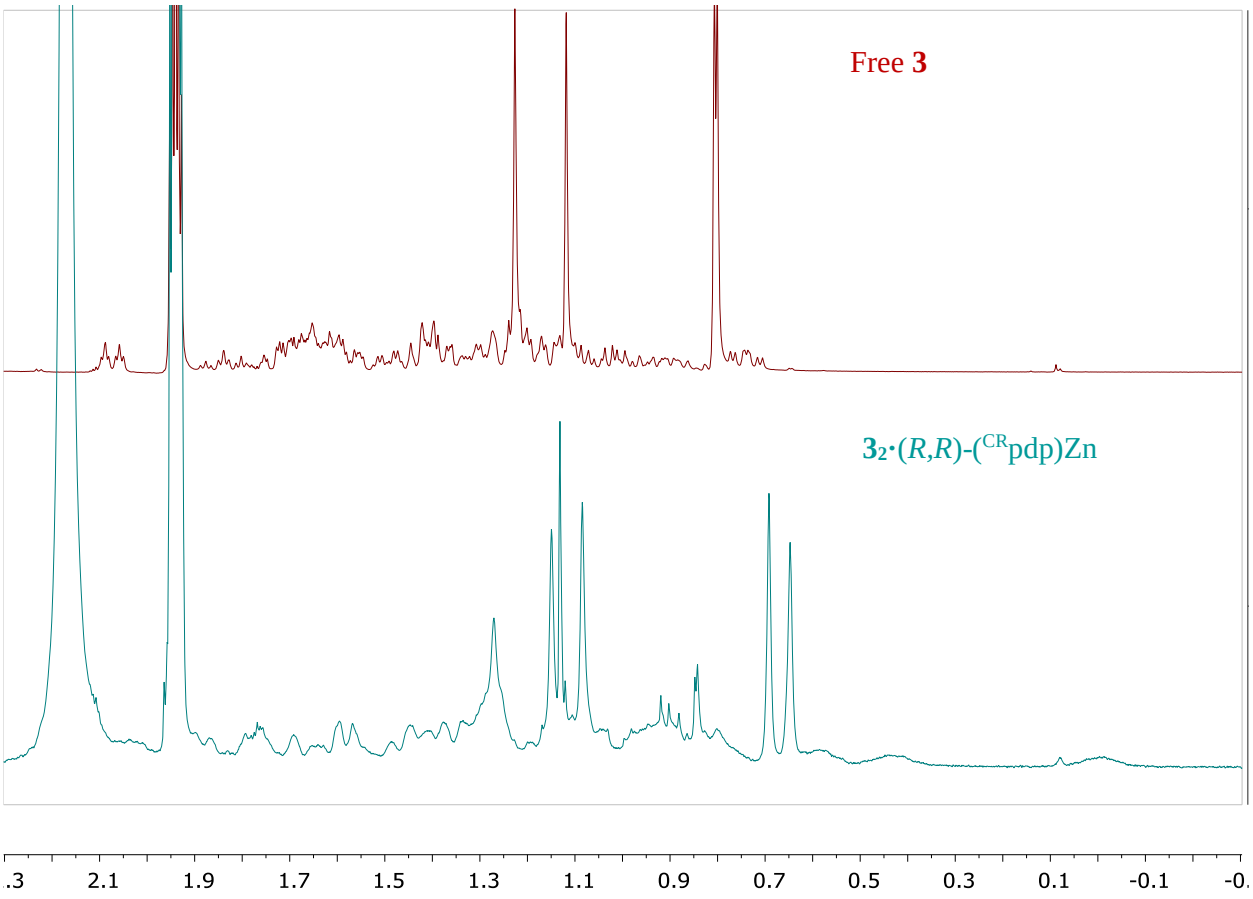


Figure S14: ^{1}H-NMR monitoring of the binding of 3 to (*R,R*)-(CRpdp)Zn.

Enlargement of the aliphatic region and comparison between free and bound **3** are displayed below.



Enlargement of the aliphatic region.



Comparison between free and bound **3**.

Oxidation reactions

General Oxidation procedure

Catalytic reactions: Mn (0.37 μmol, 1 mol%) or Fe catalyst (1.85 μmol, 5 mol%), substrate (37 μmol, 1 equivalent) and AcOH (46 μL, 814 μmol, 22 equivalents for Mn catalysts or 23 μL, 412 μmol, 11 equivalents for Fe catalysts) were dissolved in 1.8 mL of CH_3CN (HPLC grade, Sigma Aldrich) inside an 8-mL vial equipped with a magnetic stir bar at 0°C (ice-bath). A ~0.8 M solution of H_2O_2 in CH_3CN (92 μmol, 2.5 molar equivalents) diluted from commercially available H_2O_2 water solution (50% w/w, Sigma Aldrich) was slowly delivered over 30 minutes by syringe pump. *Stoichiometric reactions:* Mn or Fe (0.37 μmol, 1 equivalent), substrate (0.72 μmol, 2 equivalent) and AcOH (8 μmol, 22 equivalents for Mn catalysts or 4 μmol, 11 equivalents for Fe catalysts) were dissolved in 400 μL of CH_3CN (HPLC grade, Sigma Aldrich) inside an 8-mL vial equipped with a magnetic stir bar at 0°C (ice-bath). A ~0.1 M solution of H_2O_2 in CH_3CN (1.8 μmol, 2.5 molar equivalents) diluted from commercially available H_2O_2 water solution (50% w/w, Sigma Aldrich) was slowly delivered over 30 minutes by syringe pump. *Workup:* After the reaction, 0.5 equivalents (18.5 μmol) of internal standard (biphenyl) were added. The mixture was then treated with triethyl amine (200 μL) and acetic anhydride (300 μL) at 0°C for 50 minutes. After this time, water (2 mL) was added and the mixture was stirred for additional 10 minutes. This solution was extracted with dichloromethane (3 mL) and the organic phase was washed with H_2SO_4 2 M (4 mL), a saturated $NaHCO_3$ aqueous solution (4 mL) and water (4 mL), dried over $MgSO_4$ and analyzed by GC. *Large scale oxidations:* Oxidation procedure and workup were carried out as described above, but the amounts were scaled accordingly. After acetylation workup, the products were purified by column chromatography separation (SiO_2, AcOEt:Hex 1:1, MeOH 1-5%).

*Oxidation of **1***

Table S4: Oxidation of 1 under stoichiometric conditions.[a]

Entry	catalyst	Conv./Tot. yield [b] (%)	**1a** (%)	**1b**[c] (%)	**1c** (%)	Sel. for **1a**[d] (%) *undirected*	Sel. for **1b** or **1c**[d] (%) *Recognition-driven*
1	(*S*,*S*)-(pdp)Mn	60/22	6	4	3	27	18 (**1b**)
2	(*R*,*R*)-(pdp)Mn	51/22	8	5	3	36	23 (**1b**)
3	(*S*,*S*)-(pdp)Fe	85/27	6	7	5	22	26 (**1b**)
4	(*R*,*R*)-(pdp)Fe	75/35	9	4	4	26	11 (**1b**)
5	(*S*,*S*)-(^{TIPS}pdp)Mn	75/35	10	4	3	29	11 (**1b**)
6	(*R*,*R*)-(^{TIPS}pdp)Fe	75/21	5	4	3	24	19 (**1b**)
7[e]	(*S*,*S*)-(^{CR}pdp)Mn	30/22[e]	-	5	3	-	23 (**1b**)
8[e]	(*R*,*R*)-(^{CR}pdp)Mn	33/25[e]	-	3	2	-	12 (**1b**)
9[e]	(*S*,*S*)^{CR,TMS}pdp-Mn	53/36[e]	-	7	6	-	19 (**1b**)
10	(*S*,*S*)-(^{CR}pdp)Fe	8/5	-	1.5	3	-	60 (**1c**)
11	(*R*,*R*)-(^{CR}pdp)Fe	37/23	-	5	11	-	48 (**1c**)

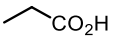
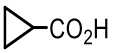
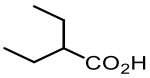
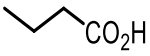
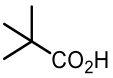
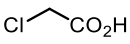
[a]Reaction Conditions: cat 1 eq (0.1 μmol, 2 mM), **1** 2 eq (0.2 μmol), AcOH 22 eq (or 11 eq with Fe catalysts), H_2O_2 2.5 eq. Workup as described above. GC yields referred to biphenyl as internal standard. All reactions have been carried out in duplicate (error ± 5%). [b]Total yield obtained by the sum of all product peaks detected (including few non-identified products). [c]In non-directed oxidations, the peak for **1b** contains another ketone product that is not detected in recognition-driven oxidations by GC-MS analysis. [d]Defined as (main product/tot. yield). [e]14-16% of olefinic products (deriving from elimination in the GC injector of secondary acetylated alcohols) are detected.

Table S5: Oxidation of 1 under catalytic conditions.[a]

Entry	catalyst	Conv./Tot. yield[a] (%)	**1a** (%)	**1b** (%)	**1c** (%)	Sel. for **1a**[d] (%) *undirected*	Sel. for **1b**or **1c**[d] (%) *Recognition-driven*
1	(*S*,*S*)-(pdp)Mn	26/23	12	7	4	52	30 (**1b**)
2	(*R*,*R*)-(pdp)Mn	61/31	14	9	6	45	29 (**1b**)
3	(*S*,*S*)-(pdp)Fe	56/28	12	8	8	42	29 (**1b**)
4	(*R*,*R*)-(pdp)Fe	63/27	12	7	8	44	30 (**1c**)
5	(*S*,*S*)-(^{TIPS}pdp)Mn	62/35	21	8	4	60	23 (**1b**)
6	(*R*,*R*)-(^{TIPS}pdp)Fe	34/32	14	9	7	44	28 (**1b**)
7[b]	(*S*,*S*)-(^{CR}pdp)Mn	16/15	tr.	13[c]	2	-	87 (**1b**)
8[d]	(*R*,*R*)-(^{CR}pdp)Mn	32/21[e]	tr.	10[c]	11	-	52 (**1c**)
9[d]	(*S*,*S*)^{CR}mcp-Mn	40/16	tr.	10[c]	3	-	62 (**1b**)
10[d]	(*S*,*S*)^{CR,TMS}pdp-Mn	45/15	<1	8	3	-	53 (**1b**)
11	(*S*,*S*)-(^{CR}pdp)Fe	27/18	tr.	6	6	-	33 (**1c**)
12	(*R*,*R*)-(^{CR}pdp)Fe	28/17	tr.	3	14	-	82 (**1c**)
13	"	61/43	tr.	6	37	-	86 (**1c**)
14	"	82/48.	tr.	6	41	-	85 (**1c**)

[a]Reaction Conditions: cat 1 mol% (0.1 μmol, 2 mM, or 5mol% for Fe catalysts), **1** 1 eq (10 μmol), AcOH 22 eq (or 11 eq with Fe catalysts), H_2O_2 2.5 eq. Workup, yields, total yield and selectivity calculated as described in the footnote a of Table S4. [b]Reaction run with propanoic acid instead of acetic acid and at -40°C. [c]C_{16} alcohol is the main product in **1b** according to GC-MS analysis. [d]Significant amounts (5-10%) of olefinic products (according to GC-MS analysis) have been detected, and are likely formed by elimination of acetylated secondary alcohols.

Table S6: Optimization of the oxidation of 1 with (*S,S*)-(^{CR}pdp)Mn.[a]

Entry	Carboxylic acid	Temp.	Conv./Tot. yield[a] (%)	**1a** (%)	**1b**[b] (%)	**1c** (%)	**1b** Sel.[a] (%)
1[c]	AcOH	0°C	47/22	tr.	11	3	50
2[c,d]	"	"	37/20	tr.	10	3	50
3[c,e]	"	"	76/25	tr.	11	3	44
4[c,f]	"	"	26/26	2	10	2	39
5		"	28/14	tr.	11	3	78
6	"	"	28/15	tr.	10	2	67
7[d]	"	"	24/15	tr.	12	3	80
8[e]	"	-40°C	16/15	tr.	13	2	87
9		"	21/13	tr.	9	2	69
10		"	15/14	tr.	11	2	79
11[c]		"	34/19	tr.	11	3	58
12[c]		"	44/20	1	9	3	45
13		"	10/6	tr.	3	0.5	50

[a]Reaction Conditions, workup, yields, total yield and selectivity calculated as described in the footnote a of Table S5. [b]C_{16} alcohol is the main product in **1b** according to GC-MS analysis. [c]Significant amounts (5-10%) of olefinic products (according to GC-MS analysis) have been detected, and are likely formed by elimination of acetylated secondary alcohols. [d]cat 3mol%. [e]cat 5mol%. [f]TFE solvent.

Table S7: Oxidation of 2.[a]

Entry	catalyst	Conv./Tot. yield[a] (%)	**2b** (%)	**2c**[b] (%)	Sel. for **2c**[b] (%) *undirected*	Sel. for **2b**[a] (%) *Recognition-driven*
1	(*S*,*S*)-(pdp)Mn	50/16	0.5	5	31	3
2[c]	(*S*,*S*)-(pdp)Fe	90/29	tr.	6	21	-
2[c]	(*R*,*R*)-(pdp)Fe	28/18	tr.	4	22	-
3	(*S*,*S*)-(^{CR}pdp)Mn	59/33	18	5	15	54
4[c]	"	65/27	16	6	22	59
5[d]	"	52/44	25 (23)[e]	6	14	57
6	(*R*,*R*)-(^{CR}pdp)Mn	45/30	17	9	30	57
7[c]	(*S*,*S*)-(^{CR}pdp)Fe	80/14	1	7	50	7
8[c]	(*R*,*R*)-(^{CR}pdp)Fe	23/18	2	10	55	11

[a]Reaction Conditions as described in the footnote a of Table S5 and in general oxidation procedure. **2b** is detected as an olefin (likely the α,β unsaturated ketone) in GC analysis, likely due to elimination of the acetylated alcohol in the GC injector. [b]**2c** is a ketone product, likely at C_{15} position. However, its low yield prevented isolation and reliable characterization. [c]cat 10mol%, H_2O_2 3.5 eq. [d]propanoic acid instead of acetic acid. [e]isolated yield (in mixture with other oxidation products, 60% purity).

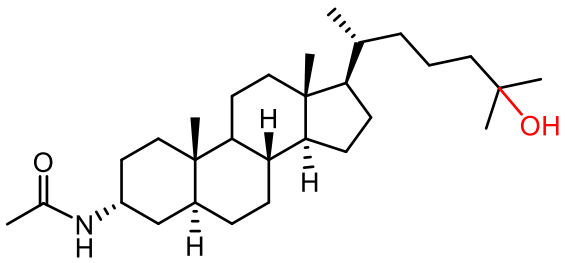
Table S8: Oxidation of 3.[a]

Entry	catalyst	Conv./Tot. yield[a] (%)	**3c** (%)	**3c** sel. (%)
1	(*S*,*S*)-(pdp)Mn	35/22[b]	1	5
2[c]	(*R*,*R*)-(pdp)Fe	79/25[d]	5	20
3	(*S*,*S*)-(^{CR}pdp)Mn	31/14[b]	1	7
4[c]	(*R*,*R*)-(^{CR}pdp)Fe	75/40[b]	28	70

[a]Reaction conditions as described in the footnote a of Table S5 and in general oxidation procedure. [b]combined yield of 5 oxidation products. [c]cat 10mol%, H_2O_2 3.5 eq. [d]combined yield of 8 oxidation products.

Oxidation products

Oxidation products have been isolated after performing the oxidation reaction according to General Oxidation Protocol on 1 mmol scale with the appropriate catalyst specified below. After acylation and extractions, the products were isolated by column chromatography purification (SiO_2, AcOEt:Hex 1:2, 1-8% MeOH) to yield compounds of purity between 50 and 90%. When possible, purity of the oxidation products was enhanced by crystallization from hot CH_3CN.



1a

1a: **1** (1 mmol) was oxidized with (*S*,*S*)-(pdp)Mn. After workup and column chromatography, 0.18 mmol (18% yield) of 1a were isolated (purity 72%, analyzed by GC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (s, 1H), 4.13 (s, 1H), 2.21 (d, *J* = 9.6 Hz, 2H), 2.01 (s, 3H), 1.81 (ddt, *J* = 14.6, 9.4, 5.4 Hz, 1H), 1.73 – 1.53 (m, 13H), 1.37 (s, 8H), 1.23 (d, *J* = 15.7 Hz, 10H), 1.10 (s, 11H), 0.93 (s, 3H), 0.90 – 0.84 (m, 3H), 0.80 (s, 3H), 0.65 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.2, 56.6, 56.2, 54.6, 49.7, 44.9, 44.3, 42.6, 41.1, 40.9, 40.0, 36.4, 36.0, 35.8, 35.7, 35.4, 35.1, 33.2, 32.7, 32.0, 30.5, 29.7, 29.4, 29.2, 28.5, 28.2, 25.9, 20.8, 18.6, 18.2, 12.1, 11.4. HRMS: calctd for $C_{29}H_{51}NO_2$-Na^+ 468.3812 m/z, found 468.3804 m/z.

Crystal structure of 1a

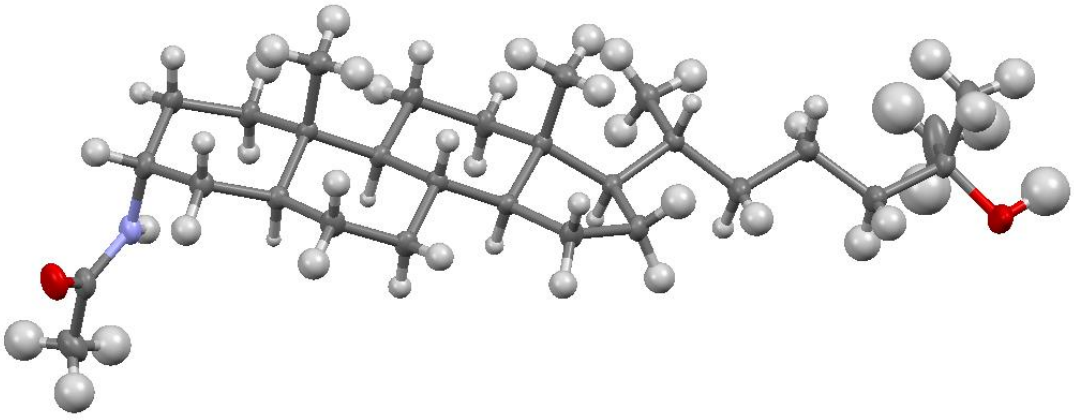
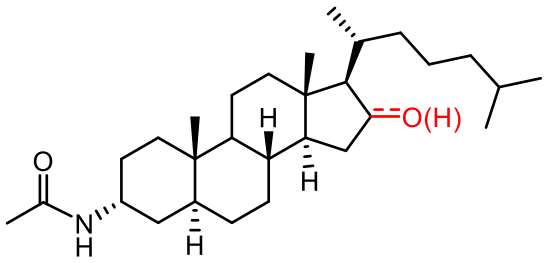


Table S9. Sample and crystal data for **1a**

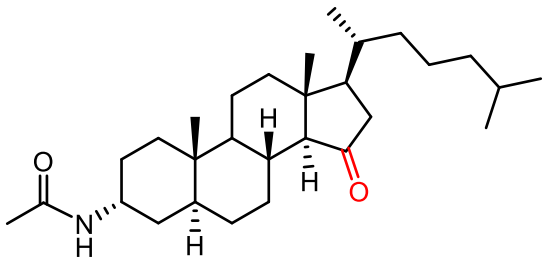
Identification code	e25_OH	
Chemical formula	$C_{29}H_{51}NO_2$	
Formula weight	445.70 g/mol	
Temperature	100(2) K	
Wavelength	0.71076 Å	
Crystal size	0.100 x 0.320 x 0.400 mm	
Crystal habit	colorless block	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.7007(6) Å	α = 90°
	b = 17.0410(10) Å	β = 90°
	c = 20.4277(15) Å	γ = 90°
Volume	2680.7(3) $Å^3$	
Z	4	
Density (calculated)	1.104 g/cm^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	992	

Diffractometer	'Bruker D8 QUEST ECO' three-circle diffractometer	
Radiation source	Ceramic x-ray tube (Mo Kα, λ = 0.71076 Å)	
Theta range for data collection	3.22 to 27.50°	
Index ranges	-9<=h<=10, -17<=k<=22, -26<=l<=26	
Reflections collected	30696	
Independent reflections	6099 [R(int) = 0.0481]	
Coverage of independent reflections	99.2%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9930 and 0.9740	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	6099 / 0 / 435	
Goodness-of-fit on F^2	1.084	
Final R indices	5331 data; I>2σ(I)	R1 = 0.0470, wR2 = 0.1179
	all data	R1 = 0.0575, wR2 = 0.1242
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0601P)^2+0.7839P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	0.1(4)	
Largest diff. peak and hole	0.269 and -0.188 $eÅ^{-3}$	
R.M.S. deviation from mean	0.043 $eÅ^{-3}$	



1b

1b: **1** (1 mmol) was oxidized with (*S*,*S*)-(pdp)Mn (1%). After workup and column chromatography, 0.07 mmol (7% yield) of **1c** were isolated in an inseparable 2:1 mixture with **1c** (purity 55%, analyzed by GC). In some oxidation reactions, mainly the ones catalyzed by (*S*,*S*)-(^{CR}pdp)Mn complexes, the GC peak of **1b** was found to contain an alcohol product also by GC-MS analysis. Since the isolation and purification of this alcohol product demonstrated to be not viable via oxidation and chromatographic separation, this compound was identified as a secondary alcohol on C_{16} by comparison of its GC retention time with that of C_{15} and C_{16} alcohols obtained via $NaBH_4$ reduction of isolated C_{15} and C_{16} ketones, **1b** and **1c** respectively. The corresponding GC chromatograms are displayed in the GC section (*vide infra*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.11 (s, 1H), 2.19 (dd, *J* = 18.1, 7.6 Hz, 1H), 2.09 (s, 1H), 1.99 (s, 4H), 1.82 – 1.48 (m, 14H), 1.30 (s, 8H), 1.16 (d, *J* = 20.6 Hz, 9H), 0.99 (s, 4H), 0.87 (s, 7H), 0.84 (d, *J* = 7.7 Hz, 4H), 0.81 (s, 3H), 0.74 (s, 1H), 0.65 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.8, 216.0, 169.1, 68.2, 65.9, 54.4, 54.2, 51.6, 50.9, 44.7, 43.3, 41.0, 39.2, 39.1, 38.9, 36.2, 35.9, 34.2, 33.0, 32.8, 32.7, 32.0, 31.3, 29.7, 28.2, 28.0, 25.9, 25.0, 23.8, 22.7, 22.6, 20.3, 18.7, 13.9, 11.4. HRMS: calctd for $C_{29}H_{49}NO_2$-Na^+ 466.3656 m/z, found 466.3662 m/z.



1c

1c: **1** (1 mmol) was oxidized with (*R*,*R*)-(^{CR}pdp)Fe (3x5%). After workup, column chromatography and crystallization from hot CH_3CN, 0.37 mmol (37% yield) of **1c** were isolated (purity 88%, analyzed by GC). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 5.71 (s, 1H), 4.10 (s, 1H), 2.67 (d, *J* = 13.3 Hz, 1H), 2.43 (dd, *J* = 18.4, 8.3 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.98 (s, 3H), 1.83 – 1.74 (m, 1H), 1.73 – 1.63 (m, 4H), 1.53 (t, *J* = 14.5 Hz, 6H), 1.41 – 1.26 (m, 6H), 1.23 – 1.01 (m, 8H), 0.98 (d, *J* = 6.2 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 7H), 0.80 (s, 3H), 0.74 (s, 3H), 0.68 (d, *J* = 14.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.1, 169.1, 65.9, 54.1, 51.6, 44.7, 42.3, 42.0, 41.1, 39.9, 39.3, 36.1, 36.0, 35.3, 33.1, 32.6, 31.8, 30.6, 28.0, 27.9, 23.7, 22.7, 22.5, 20.3, 19.0, 13.0, 11.3. HRMS: calctd for $C_{29}H_{49}NO_2$-Na^+ 466.3656 m/z, found 466.3660 m/z.

Crystal structure of 1c

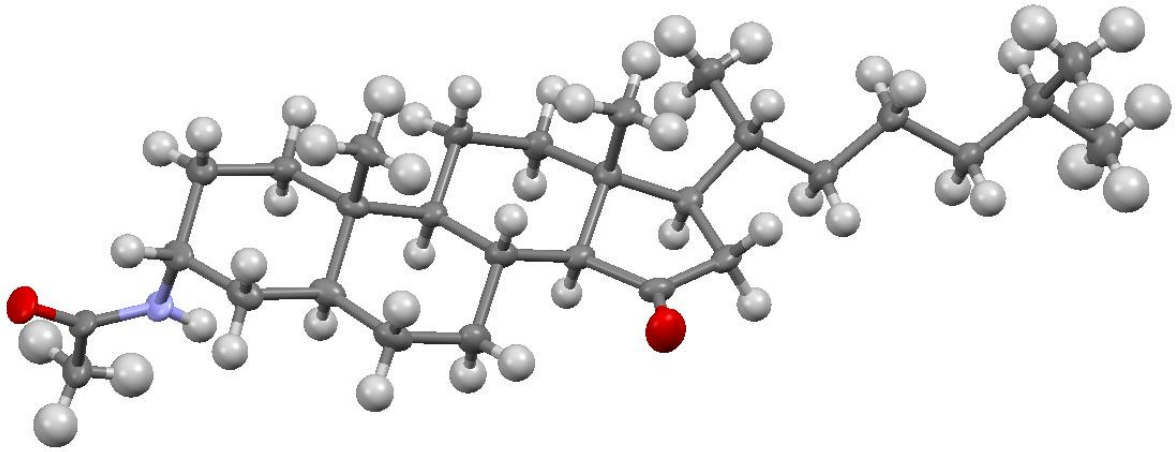
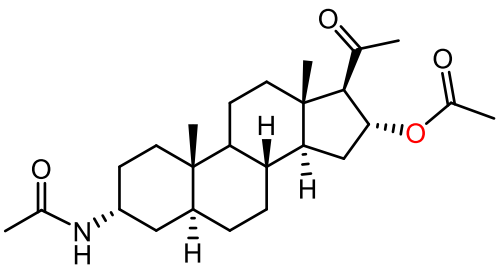


Table S10. Sample and crystal data for **1c**

Identification code	K15	
Chemical formula	$C_{29}H_{49}NO_2$	
Formula weight	443.69 g/mol	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal size	0.060 x 0.100 x 0.400 mm	
Crystal habit	colorless needle	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.7908(11) Å	α = 90°
	b = 21.665(3) Å	β = 90°
	c = 28.185(3) Å	γ = 90°
Volume	5367.9(11) $Å^3$	
Z	8	
Density (calculated)	1.098 g/cm^3	

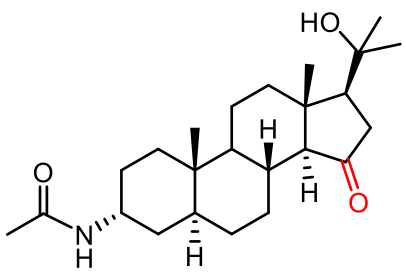
Absorption coefficient	0.067 mm^{-1}
F(000)	1968

Diffractometer	three-circle diffractometer	
Radiation source	Ceramic x-ray tube (Mo Kα, λ = 0.71076 Å)	
Theta range for data collection	2.36 to 24.18°	
Index ranges	-10<=h<=10, -24<=k<=24, -32<=l<=32	
Reflections collected	59129	
Independent reflections	8552 [R(int) = 0.0827]	
Coverage of independent reflections	99.5%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9960 and 0.9740	
Structure solution technique	direct methods	
Structure solution program	SHELXT 2014/5 (Sheldrick, 2014)	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2017/1 (Sheldrick, 2017)	
Function minimized	$\Sigma\ w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	8552 / 0 / 589	
Goodness-of-fit on F^2	1.078	
Final R indices	7212 data; I>2σ(I)	R1 = 0.0642, wR2 = 0.1551
	all data	R1 = 0.0779, wR2 = 0.1620
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0725P)^2+3.8755P]$ where $P=(F_o^2+2F_c^2)/3$	
Absolute structure parameter	-0.9(7)	
Largest diff. peak and hole	0.798 and -0.349 $eÅ^{-3}$	
R.M.S. deviation from mean	0.050 $eÅ^{-3}$	



2b

2b: **2**(1 mmol) was oxidized with (*S*,*S*)-(^{CR}pdp)Mn (10%). After workup and column chromatography, 0.23 mmol (23% yield) of **2b** were isolated (purity 60%, analyzed by GC). GC analysis of 2b leads to an eliminated product after loss of AcOH likely at the GC injector, since NMR analysis revealed no trace of olefinic products both in the crude mixture and in the isolated product mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 5.48 (t, *J* = 7.4 Hz, 1H), 4.12 (s, 2H), 2.65 (d, *J* = 6.4 Hz, 1H), 2.00 (d, *J* = 3.0 Hz, 6H), 1.79 (d, *J* = 4.8 Hz, 1H), 1.71 – 1.51 (m, 15H), 1.37 (d, *J* = 14.3 Hz, 4H), 1.25 (s, 6H), 1.13 – 0.89 (m, 7H), 0.80 (d, *J* = 7.5 Hz, 4H), 0.64 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5, 170.6, 169.1, 75.8, 70.2, 54.4, 54.3, 44.7, 44.7, 41.0, 39.0, 36.1, 34.8, 33.4, 33.2, 32.7, 31.9, 31.8, 31.5, 29.7, 28.2, 25.9, 25.9, 23.8, 21.2, 20.4, 14.6, 11.4. HRMS: calctd for $C_{25}H_{39}NO_4$-Na^+ 440.2771 m/z, found 440.2771 m/z.

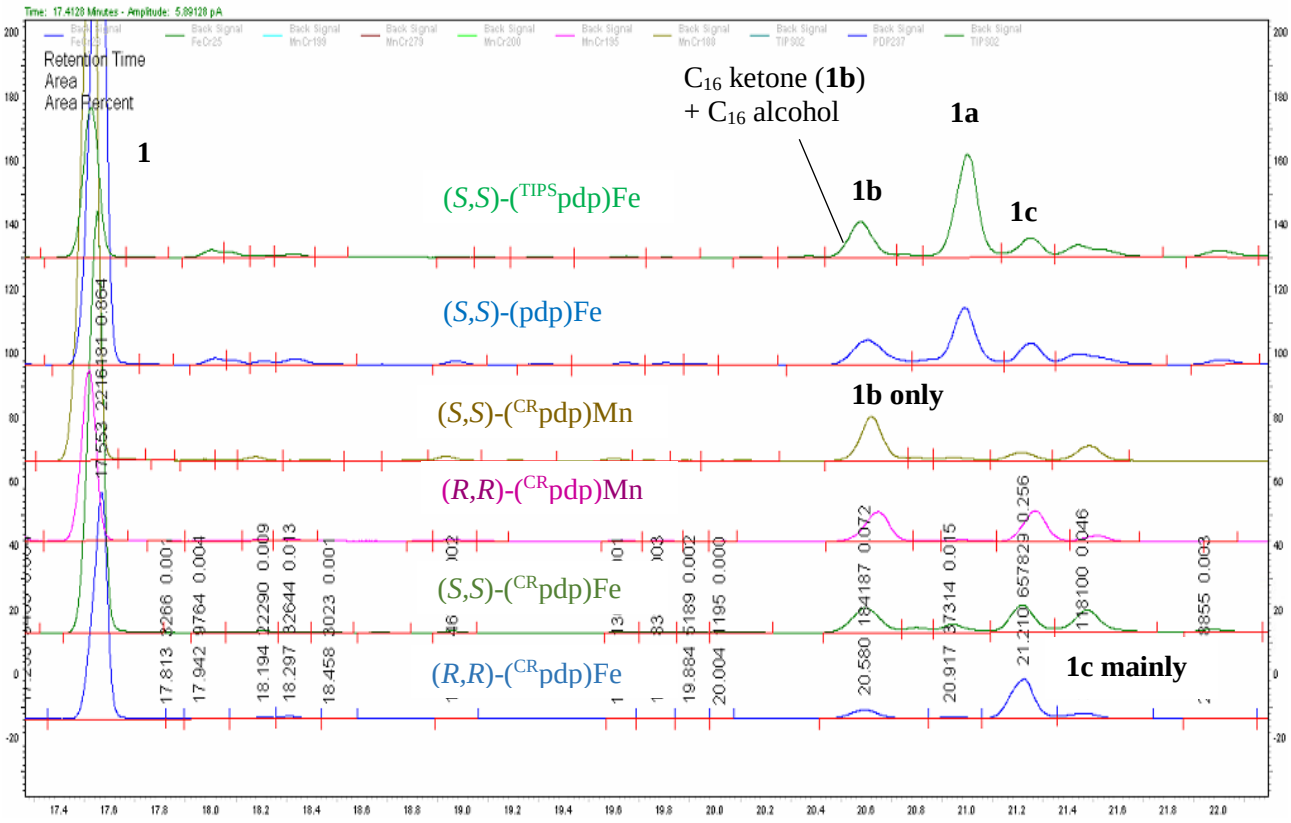


3c

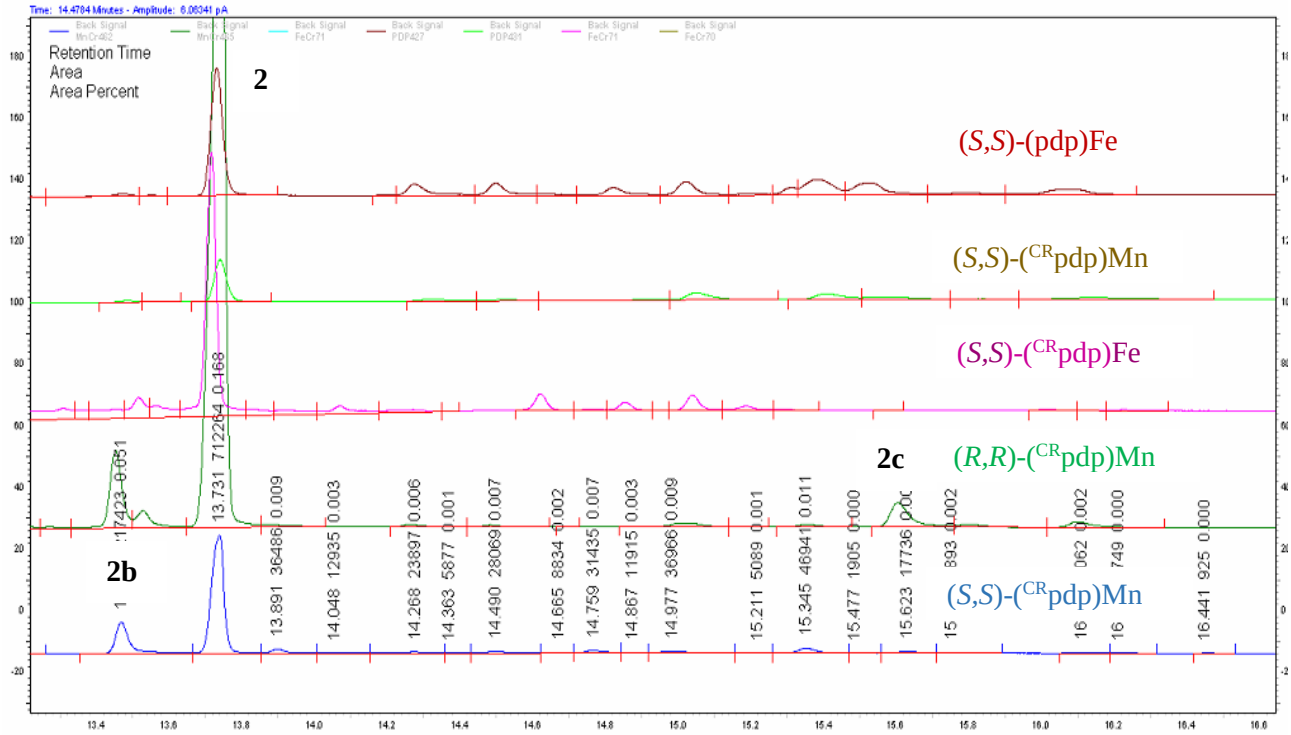
3c: **3** (1 mmol) was oxidized with (*R*,*R*)-(^{CR}pdp)Fe (3x5%). After workup and column chromatography, 0.27 mmol (27% yield) of **3c** were isolated (purity >95%, analyzed by GC). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (s, 1H), 4.12 (s, 1H), 2.77 – 2.62 (m, 1H), 2.32 (s, 1H), 2.23 (d, *J* = 12.3 Hz, 1H), 1.99 (s, 3H), 1.87 (s, 1H), 1.76 (d, *J* = 7.6 Hz, 1H), 1.69 (s, 1H), 1.66 (d, *J* = 7.7 Hz, 3H), 1.62 – 1.51 (m, 5H), 1.49 (d, *J* = 4.6 Hz, 1H), 1.39 (s, 3H), 1.30 (d, *J* = 8.7 Hz, 3H), 1.24 (d, *J* = 6.6 Hz, 6H), 1.18 (d, *J* = 5.8 Hz, 1H), 1.07 – 1.00 (m, 1H), 0.90 (s, 3H), 0.85 (d, *J* = 4.9 Hz, 1H), 0.81 (s, 3H), 0.70 (s, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 169.1, 72.7, 66.0, 55.5, 54.1, 44.7, 43.0, 41.1, 40.2, 37.4, 36.2, 33.1, 32.6, 31.5, 31.4, 30.6, 30.4, 28.0, 25.9, 23.8, 20.2, 14.4, 11.4. HRMS: calctd for $C_{24}H_{39}NO_3$-Na^+ 412.2822 m/z, found 412.2825 m/z.

GC chromatograms of oxidation reactions

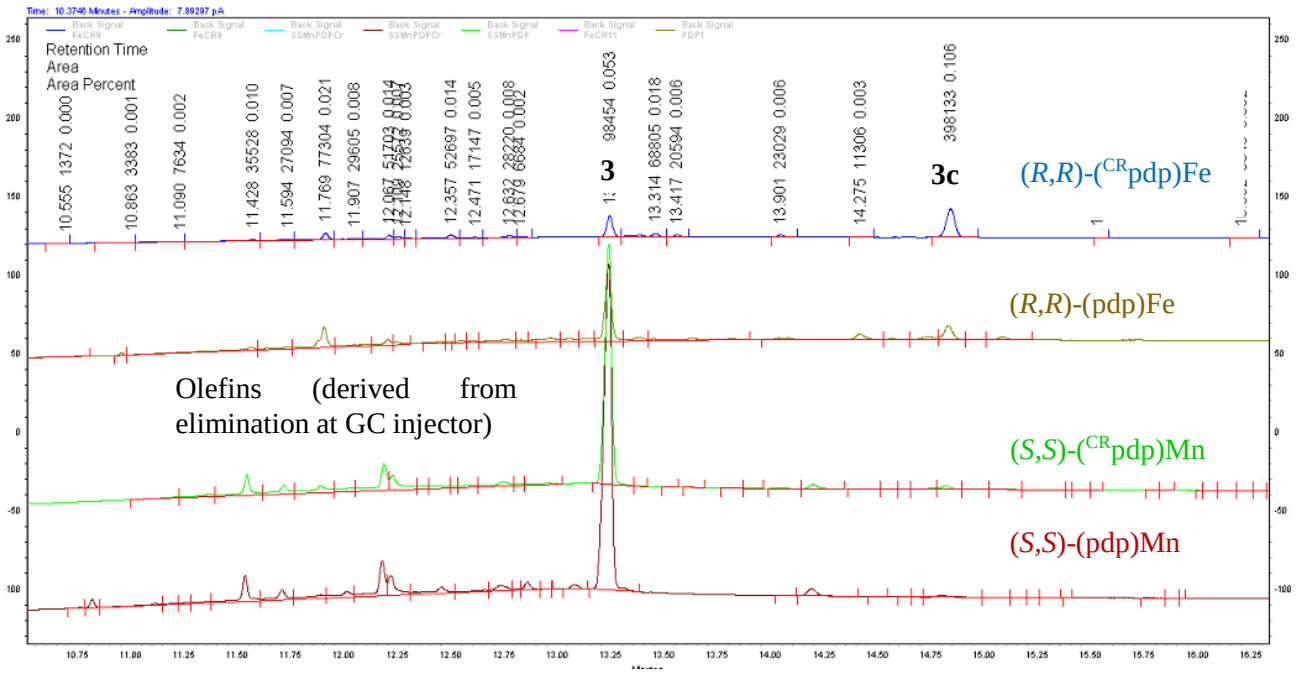
*Oxidation of **1***



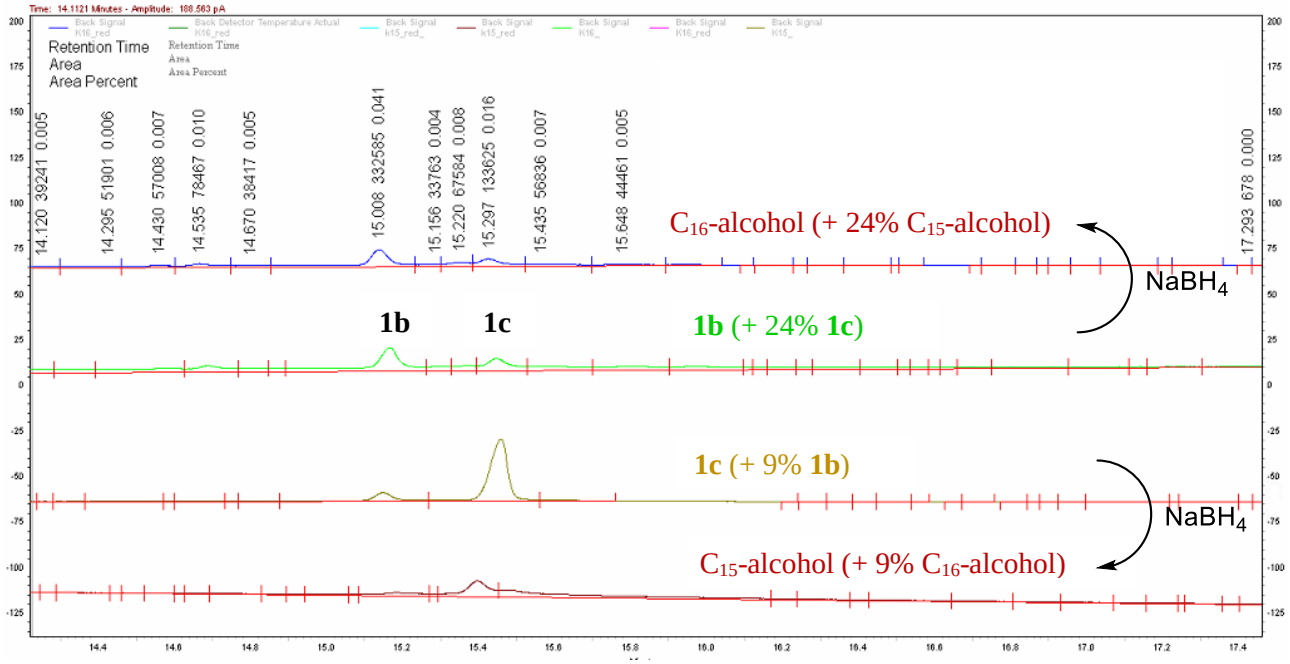
*Oxidation of **2***

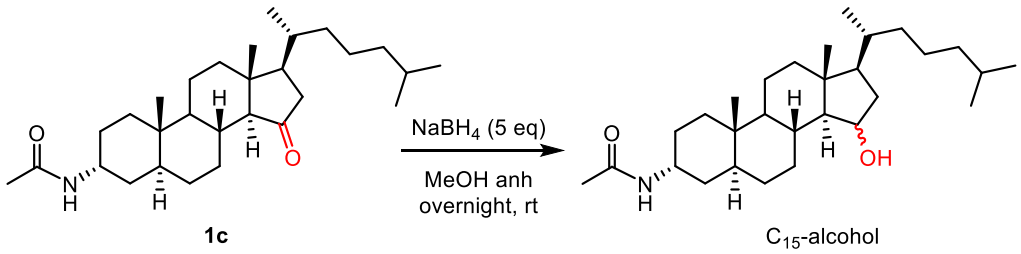


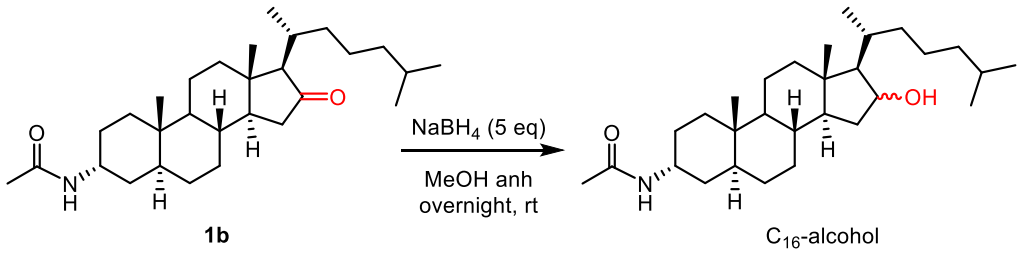
*Oxidation of **3***



Identification of GC retention time of C_{16} alcohol (detected in the oxidation of **1**)





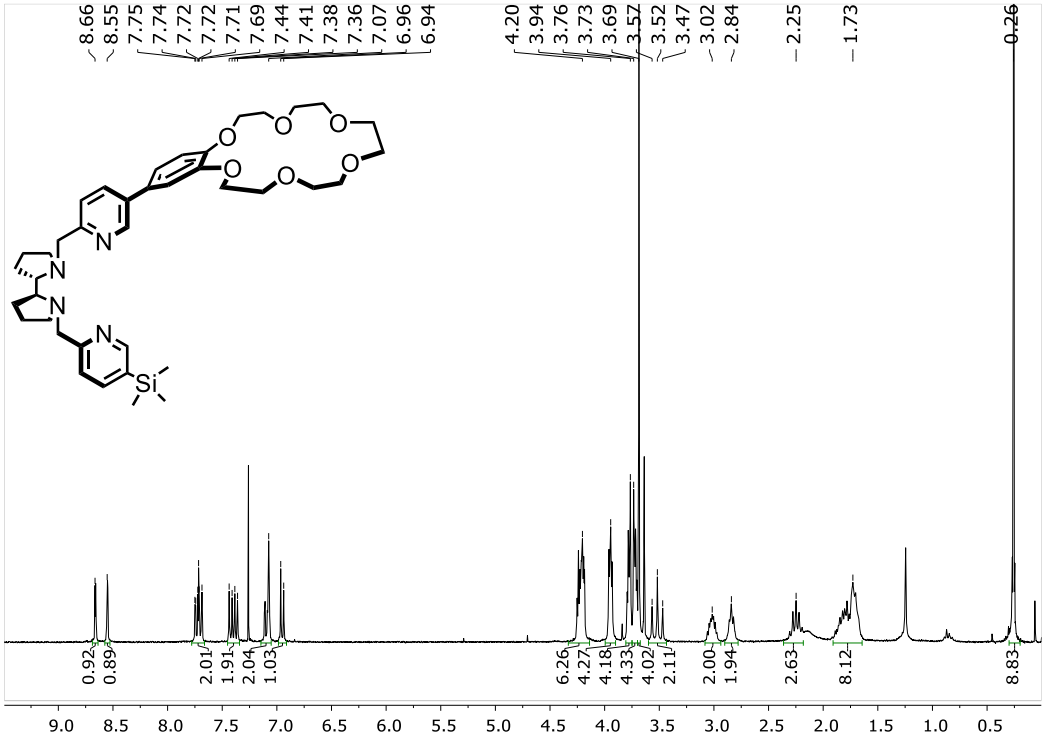


Isolation of the alcohol on C_{16} was not possible. Therefore, isolated ketones **1b** and **1c** (purity 55 and 88%, respectively) were treated with $NaBH_4$ (5 eq, MeOH anh, rt, overnight, extraction workup) and analyzed by GC. Completion of the reaction was ensured by GC-MS analysis. C_{16} alcohol resulted to have the same retention time as **1b**, therefore their combined yield is reported in Table 1. GC-MS analysis revealed that this C_{16} alcohol is the main product only in the oxidation of **1** promoted by catalysts (*S*,*S*)-(^{CR}pdp)Mn, (*S*,*S*)-(^{CR}mcp)Mn and (*S*,*S*)-(^{CR,TMS}pdp)Mn.

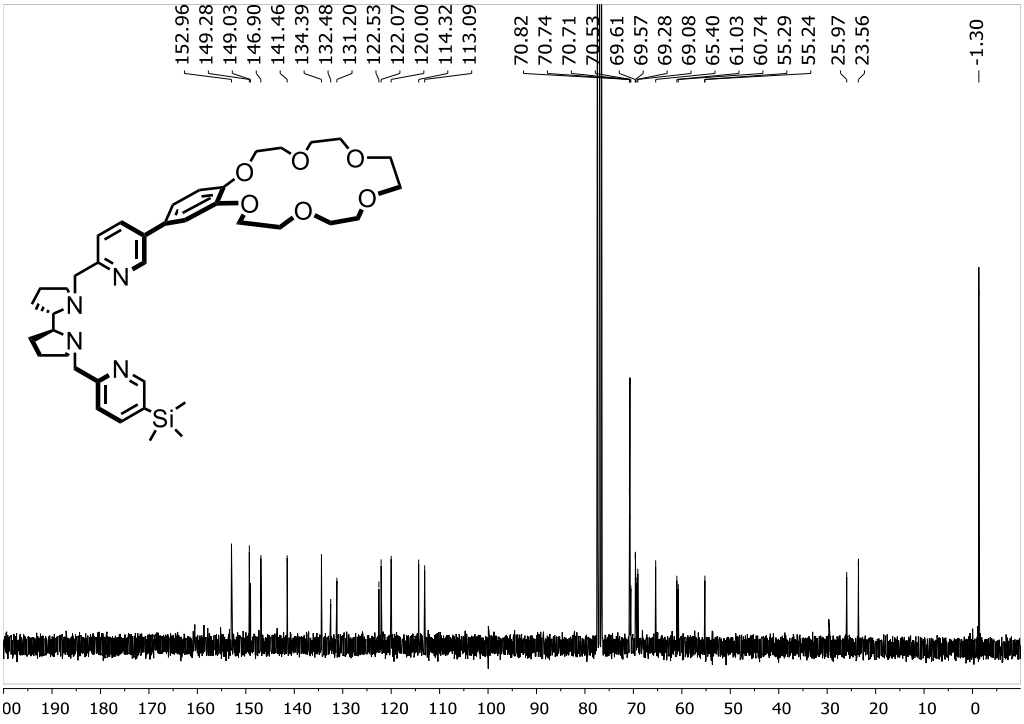
NMR spectra

Ligands and ligand synthons

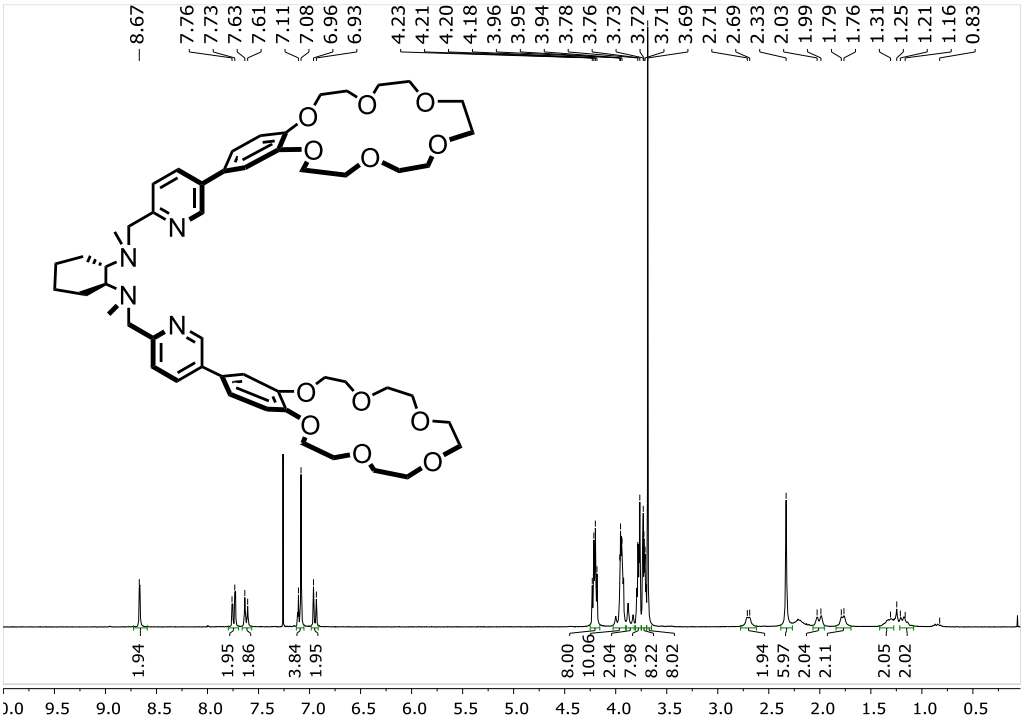
^{1}H NMR spectrum of (*S*,*S*)-(^{CR,TMS}pdp)



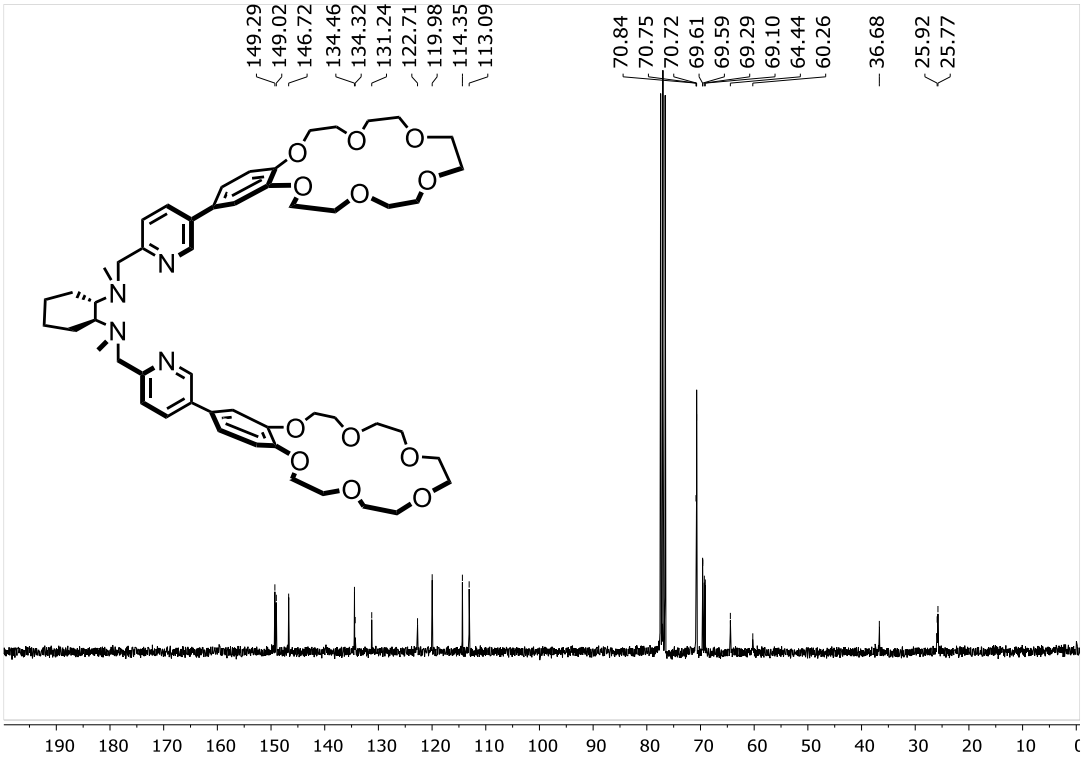
^{13}C NMR spectrum of (*S*,*S*)-(^{CR,TMS}pdp)



^{1}H NMR spectrum of (*S*,*S*)-(^{CR}mcp)

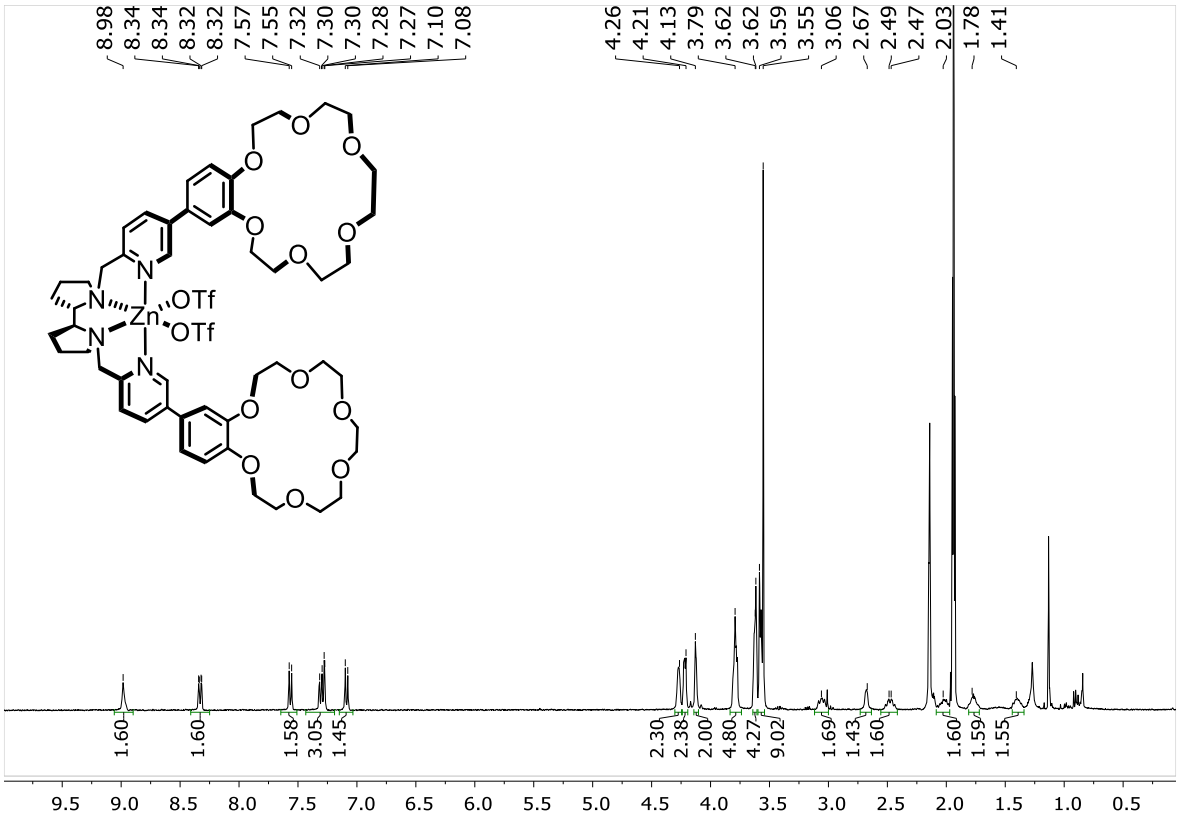


^{13}C NMR spectrum of (*S*,*S*)-(^{CR}mcp)

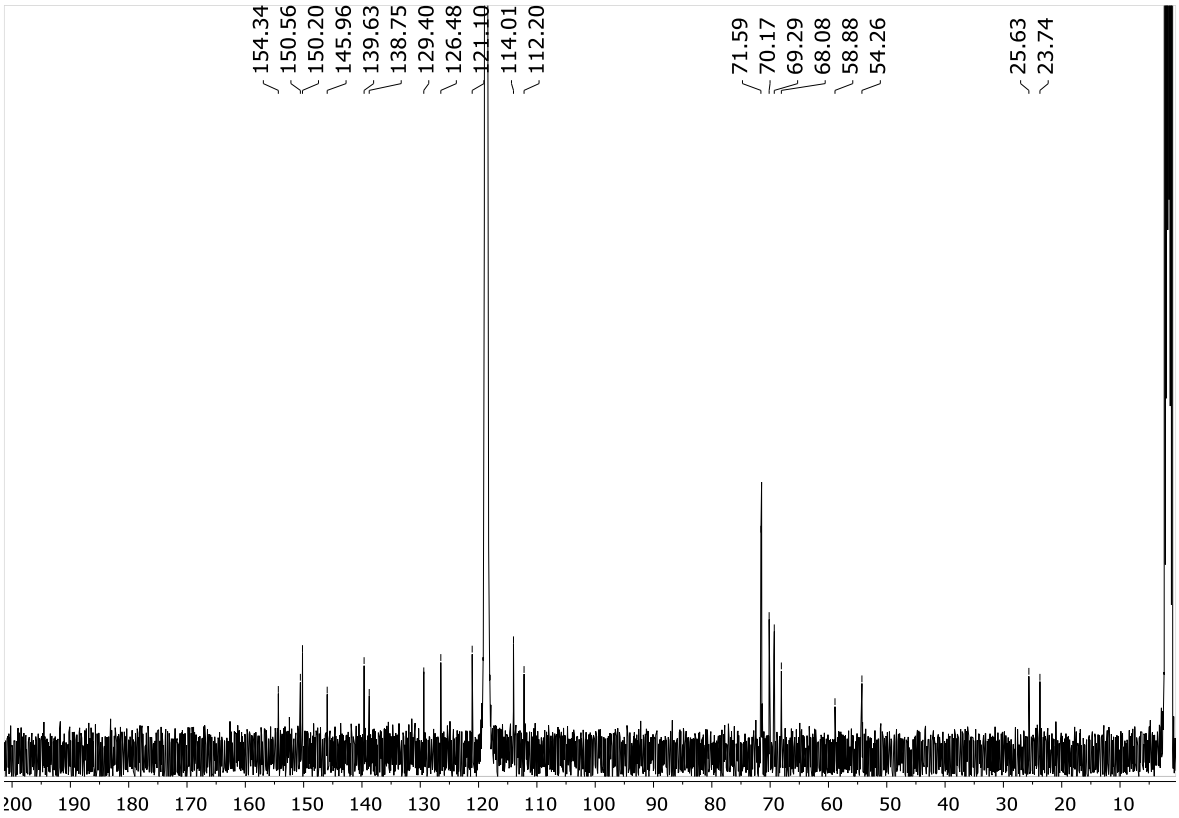


Complexes

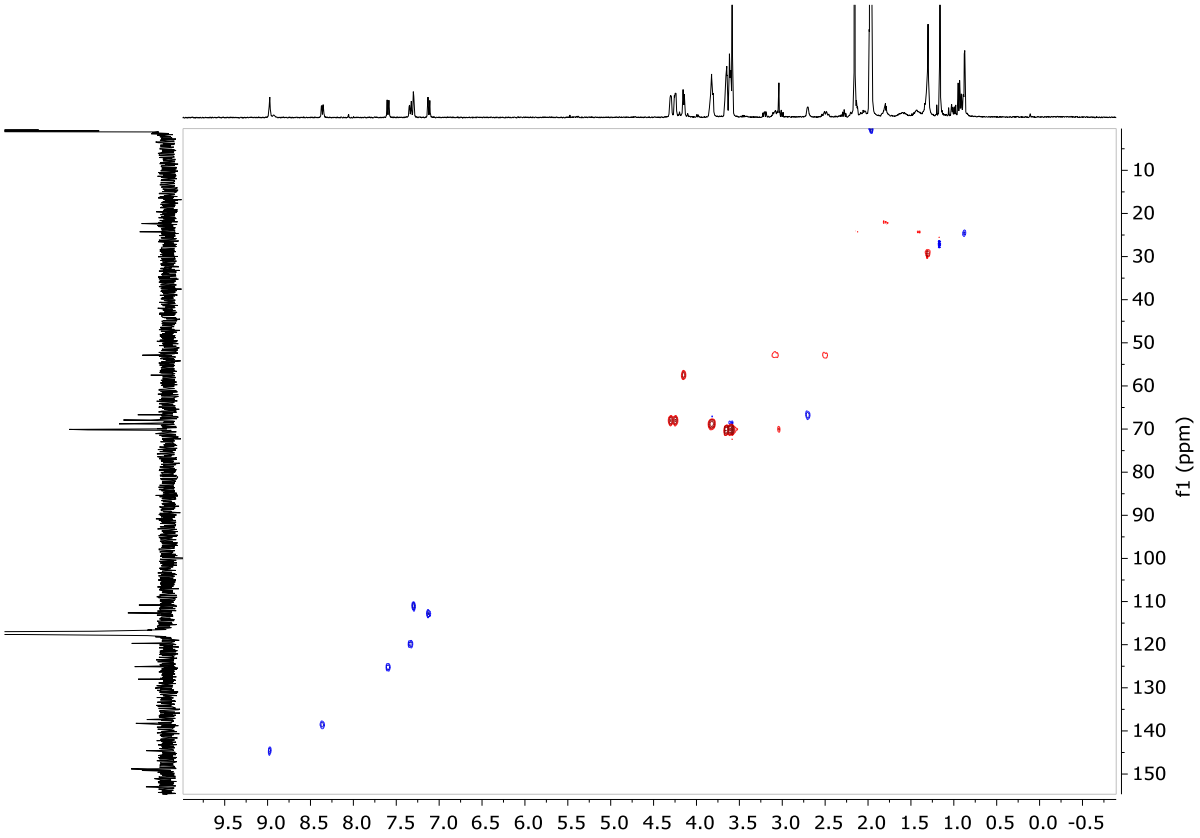
^{1}H NMR spectrum of (*R*,*R*)-(^{CR}pdp)Zn



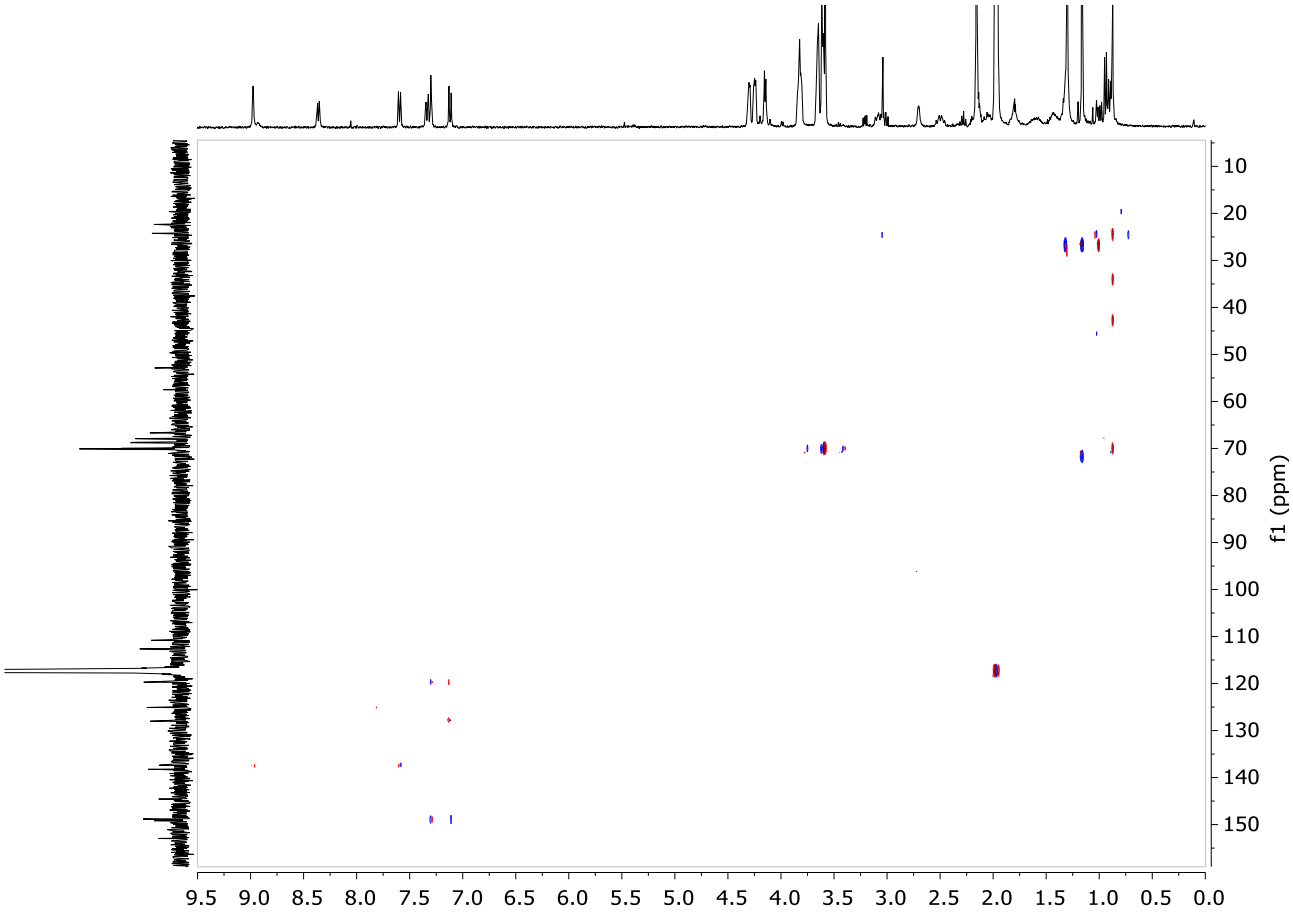
^{13}C NMR spectrum of (*R*,*R*)-(^{CR}pdp)Zn



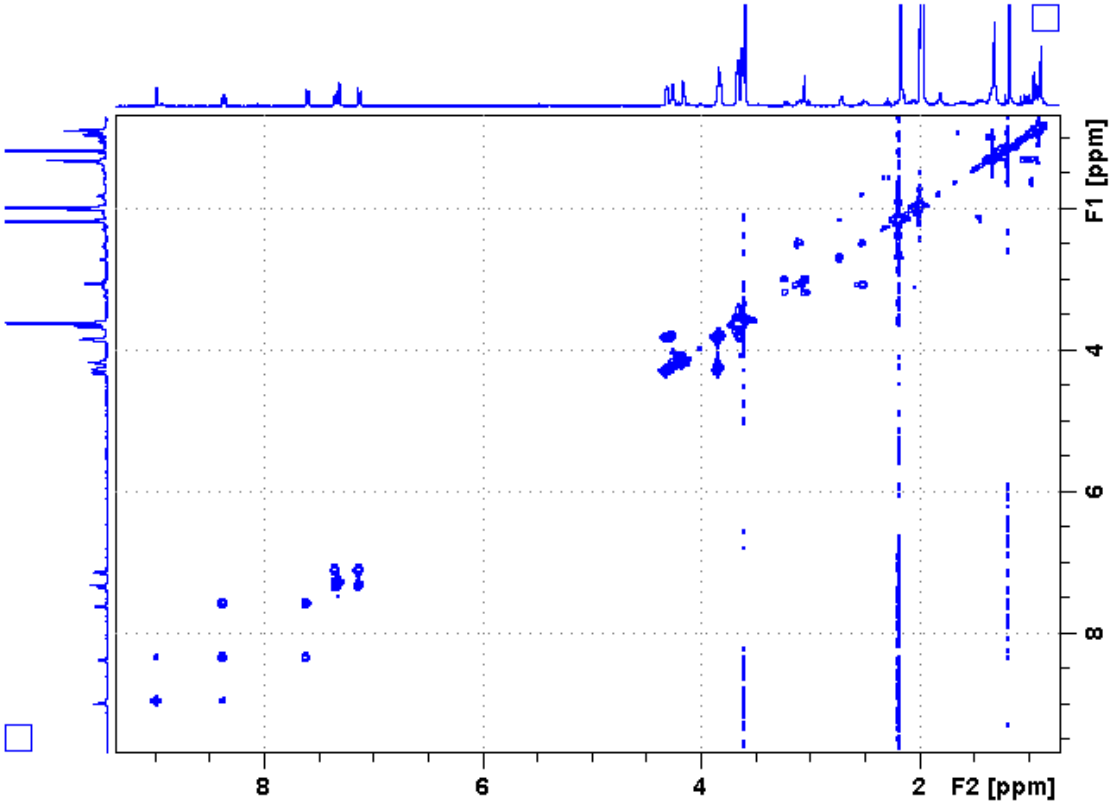
HSQC of (*R*,*R*)-(^{CR}pdp)Zn



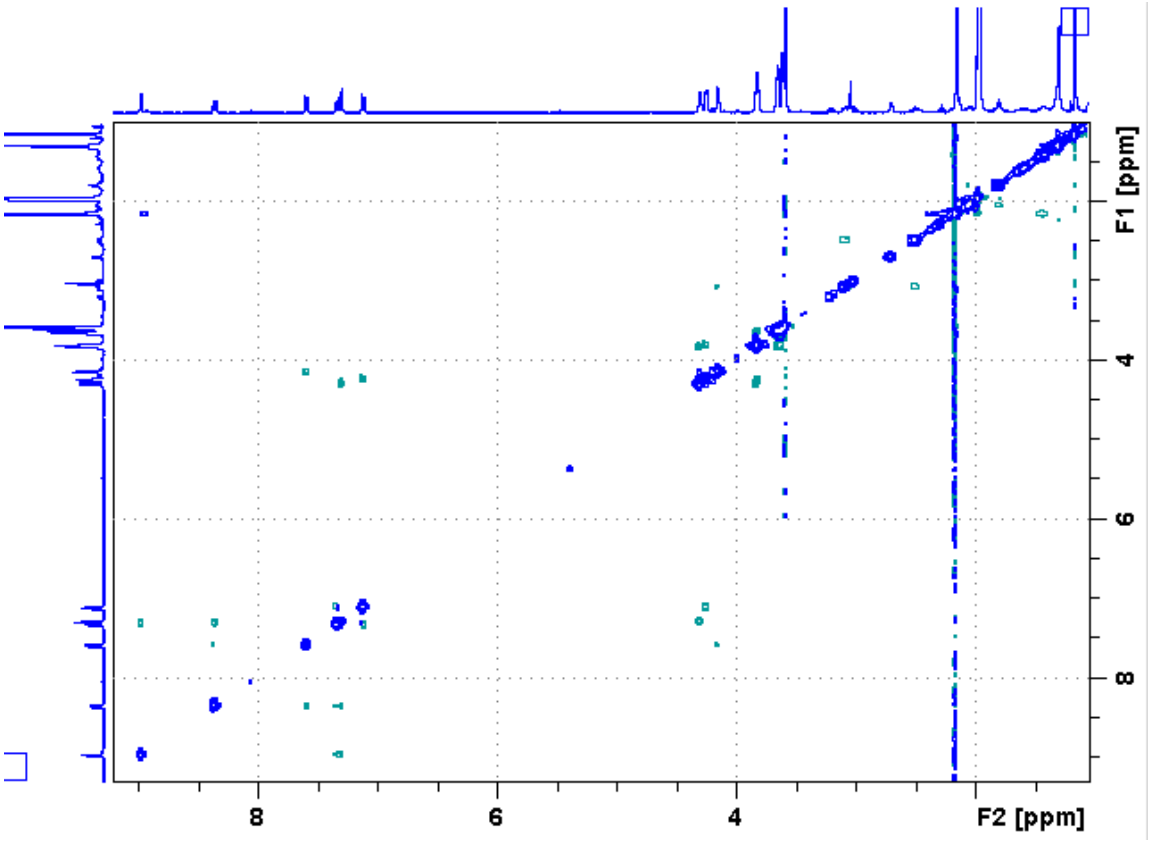
HMBC of (*R*,*R*)-(^{CR}pdp)Zn



COSY of (*R*,*R*)-(^{CR}pdp)Zn

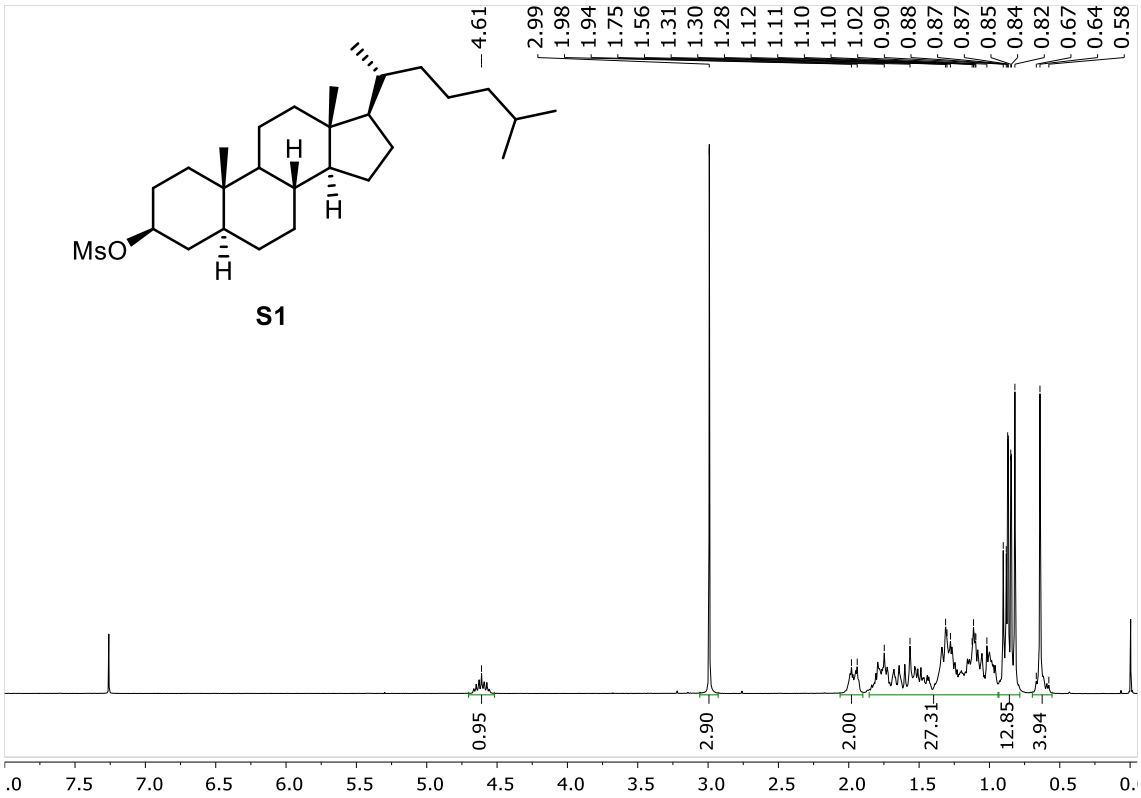


NOESY of (*R*,*R*)-(^{CR}pdp)Zn

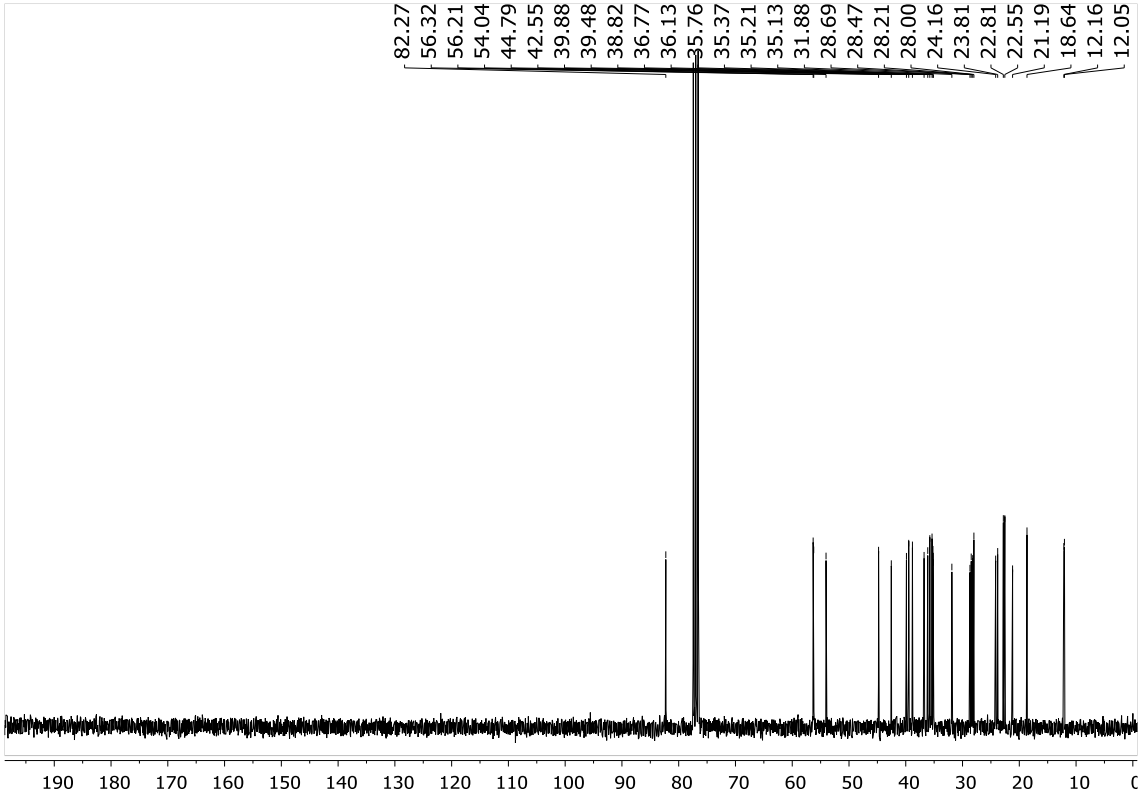


Substrates

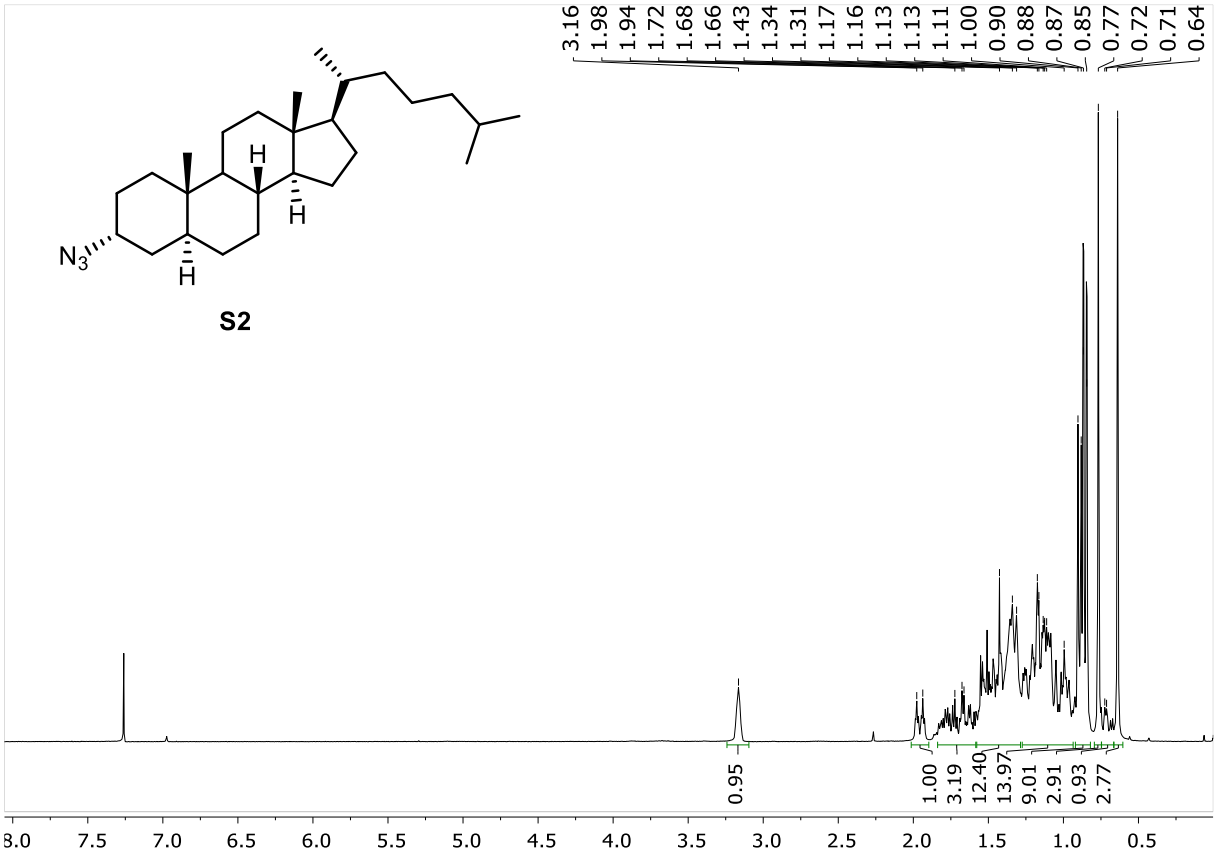
^{1}H-NMR spectrum of **S1**



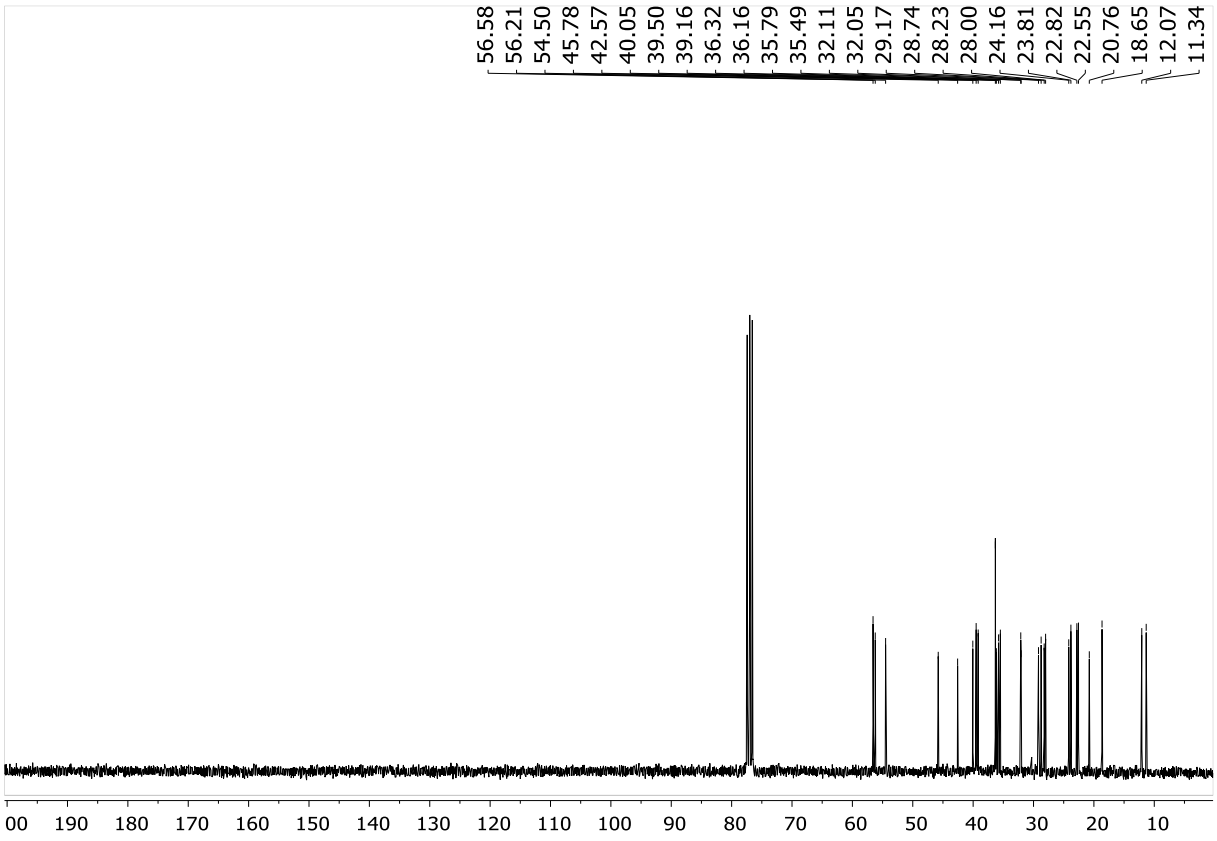
^{13}C-NMR spectrum of **S1**



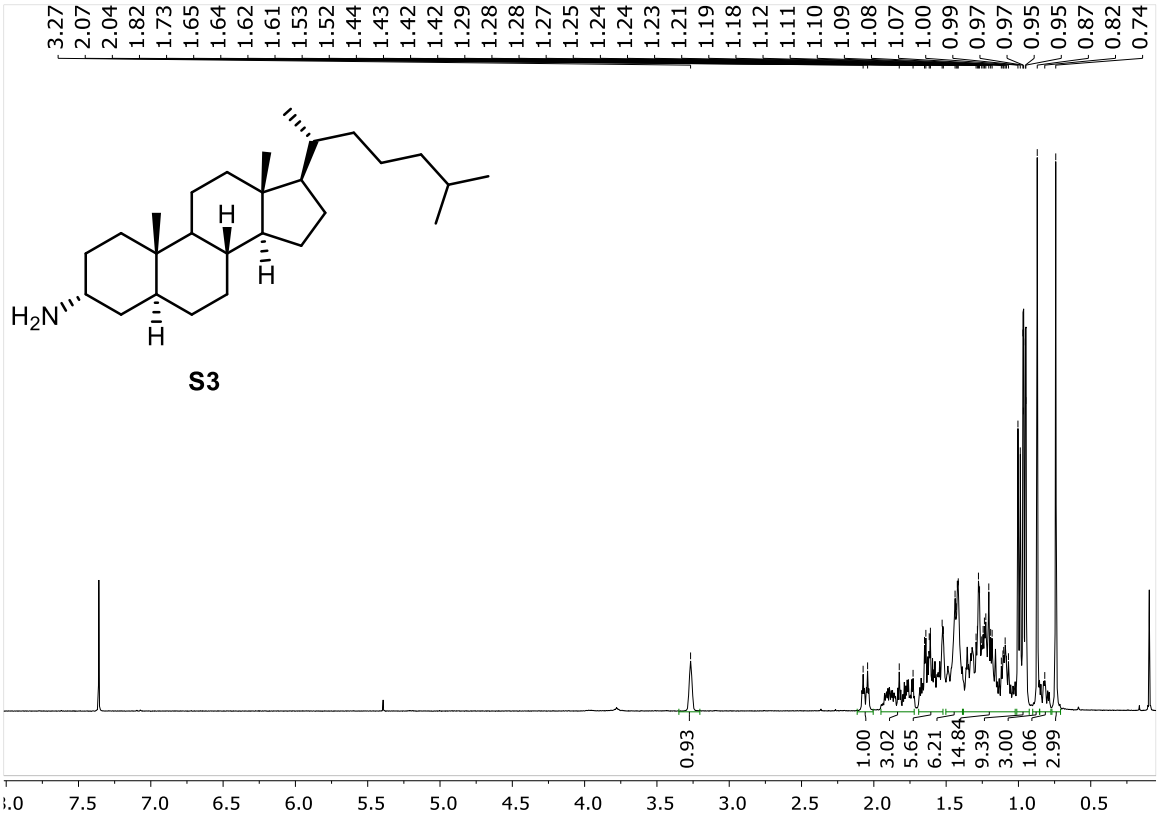
^{1}H-NMR spectrum of **S2**



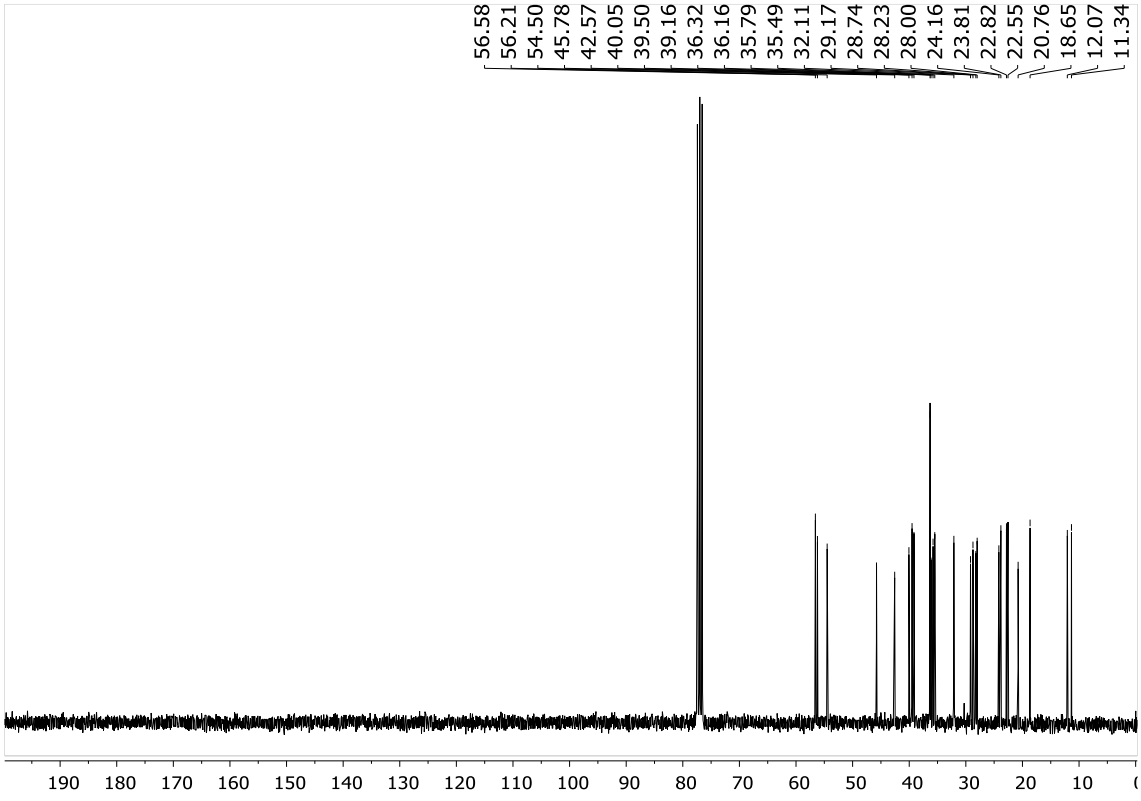
^{13}C-NMR spectrum of **S2**



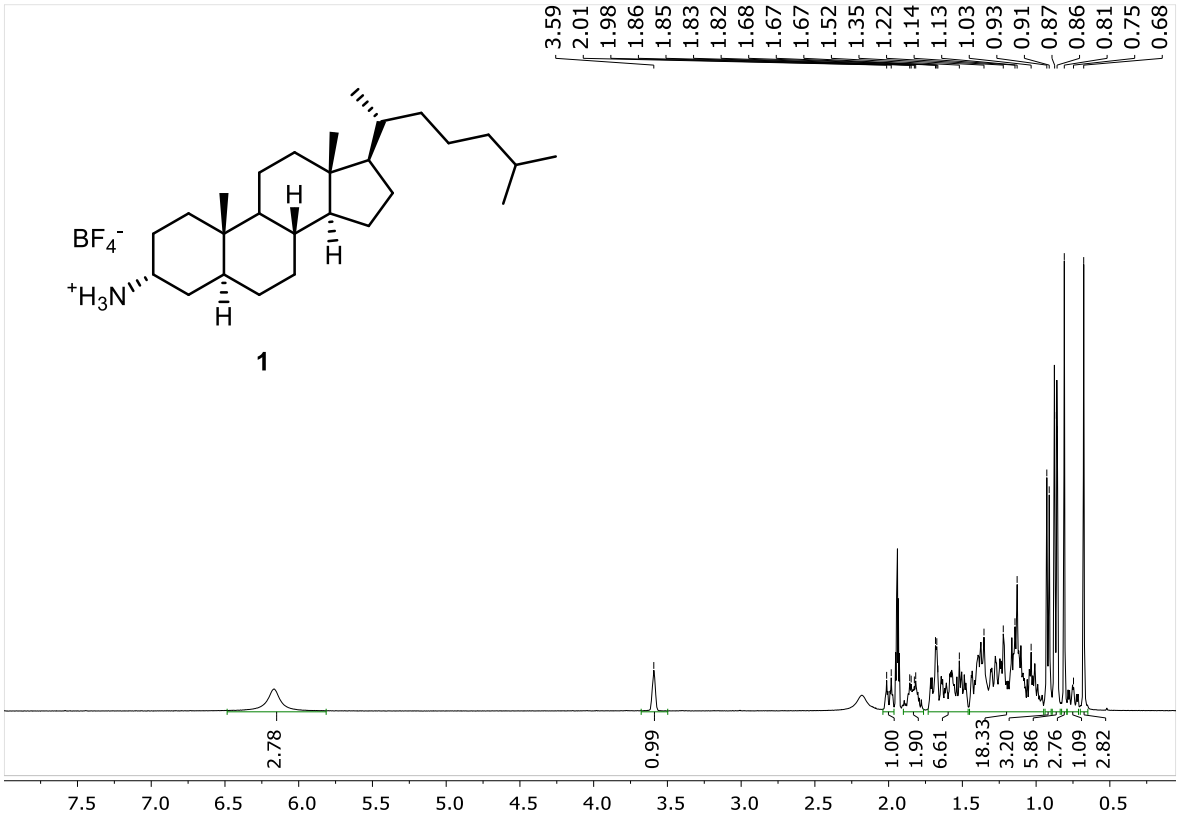
^{1}H-NMR spectrum of **S3**



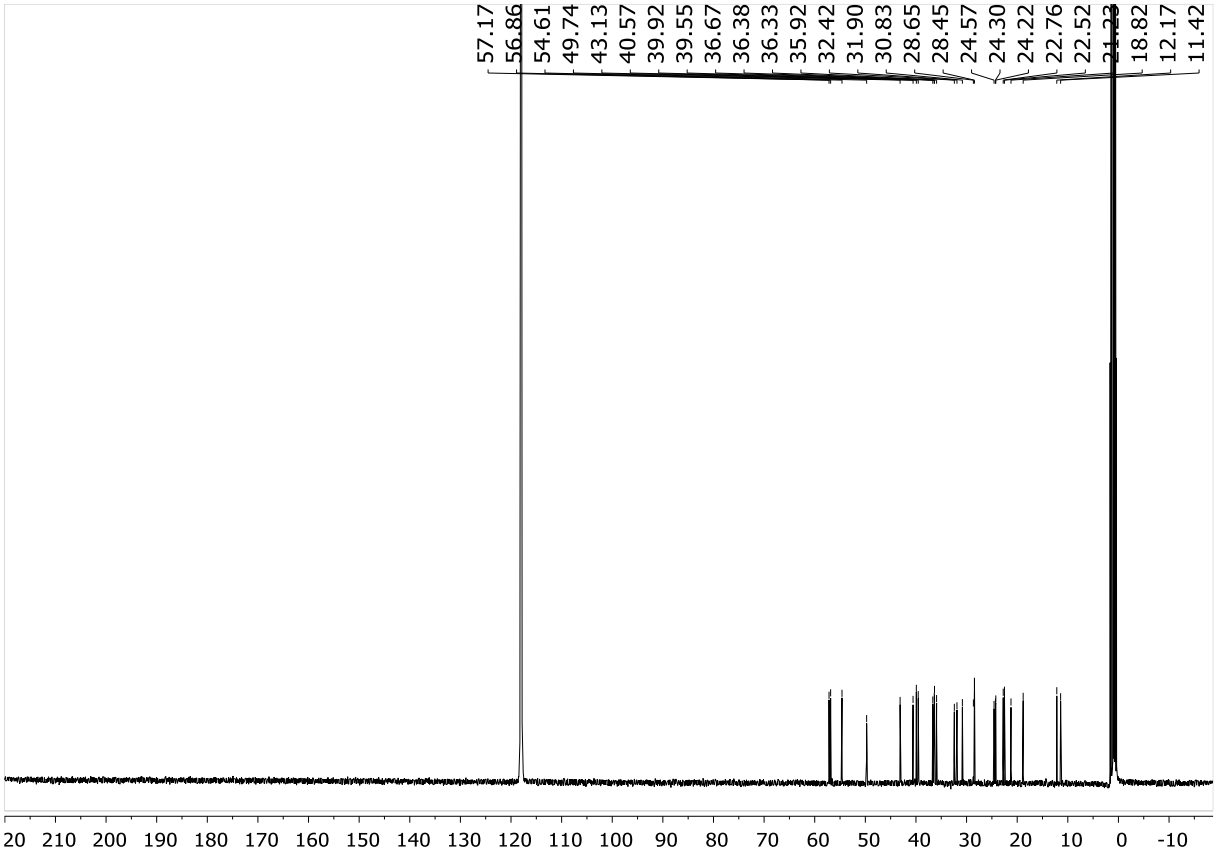
^{13}C-NMR spectrum of **S3**



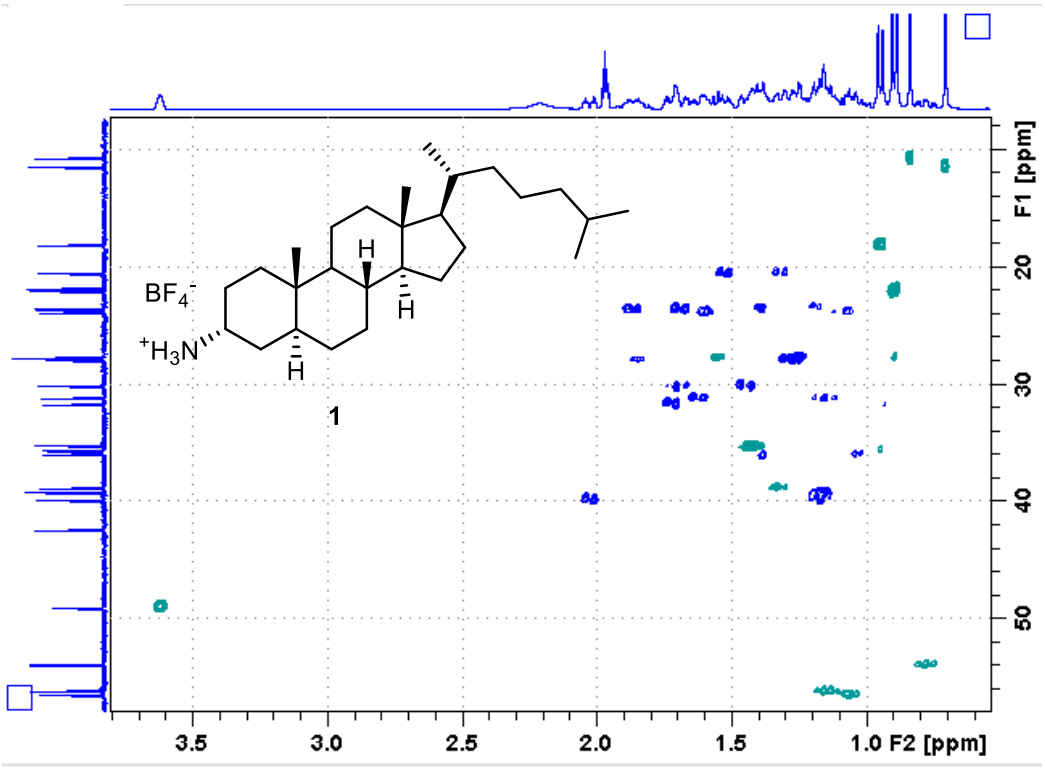
^{1}H-NMR spectrum of **1**



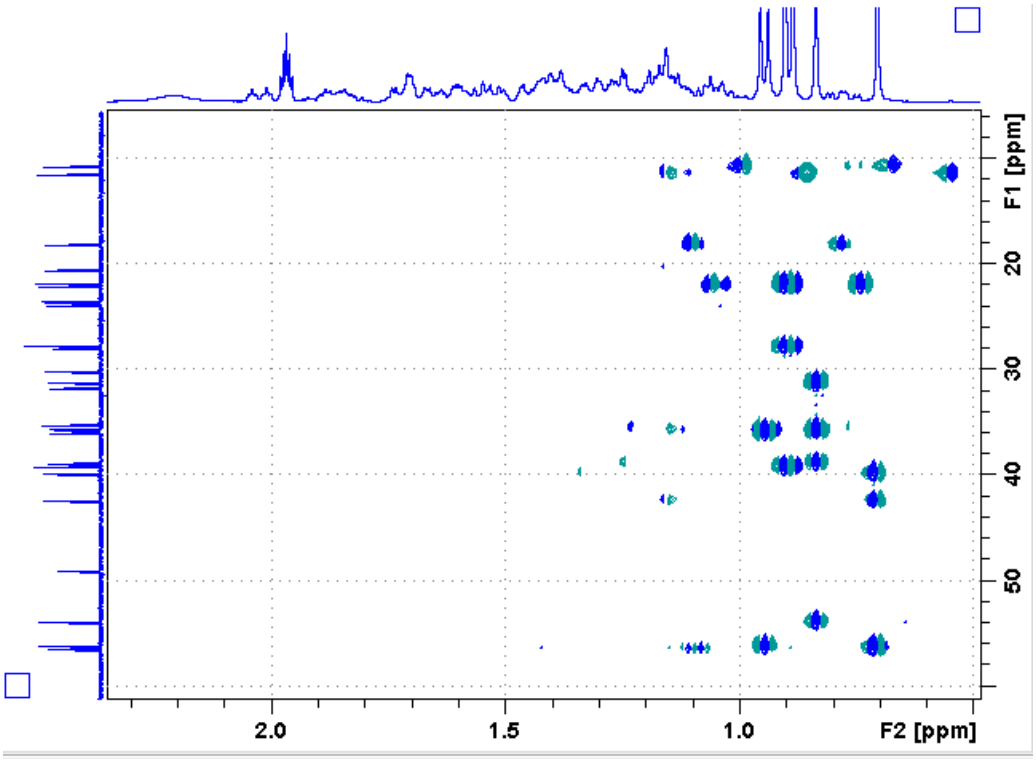
^{13}C-NMR spectrum of **1**



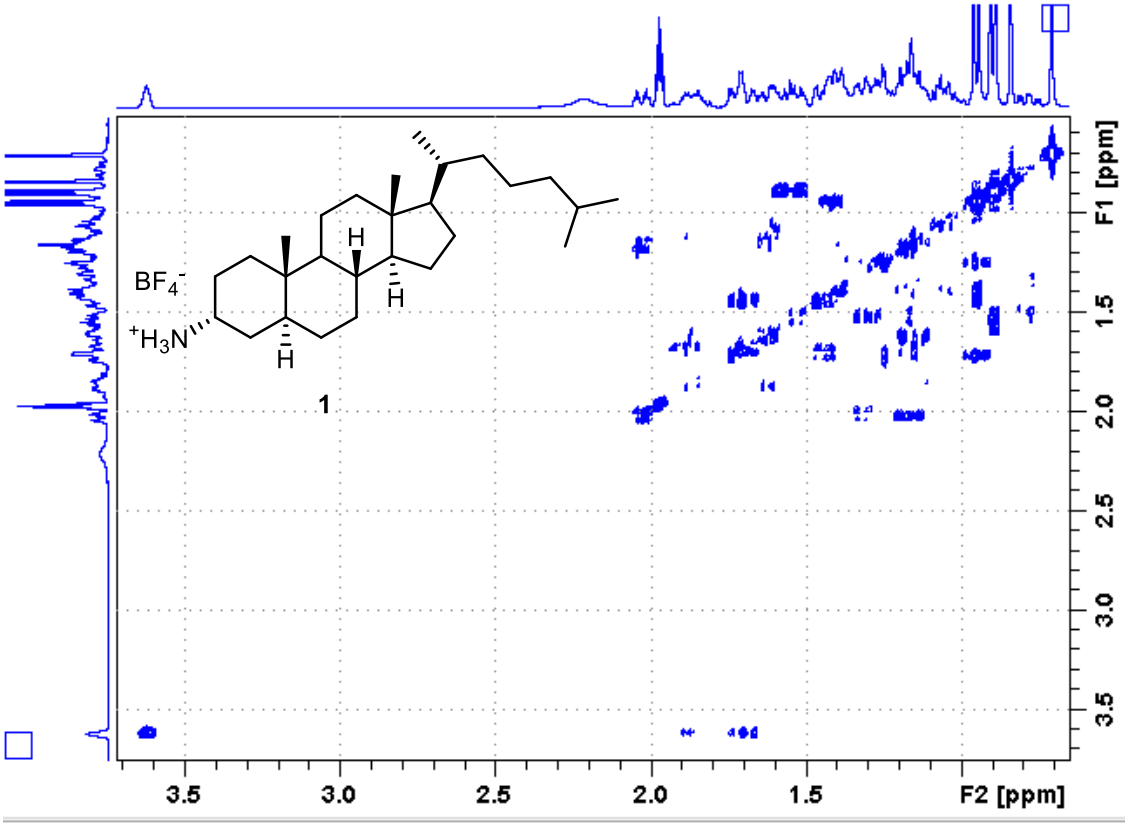
HSQC*ed* of **1**



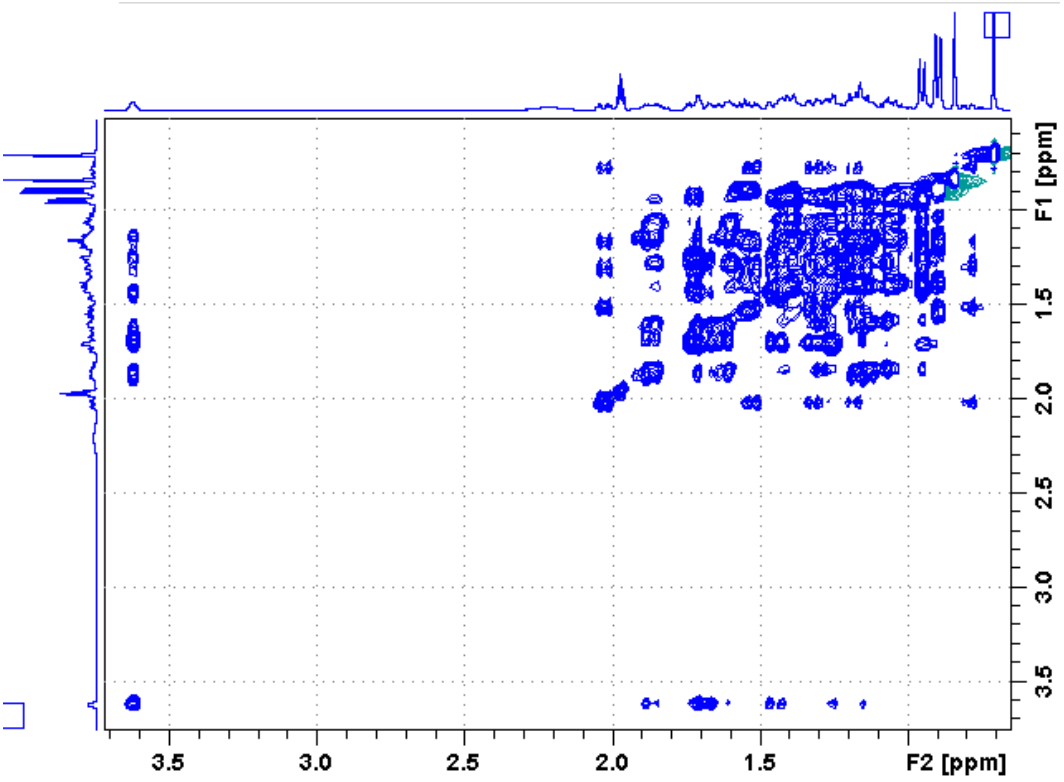
HMBC of **1**



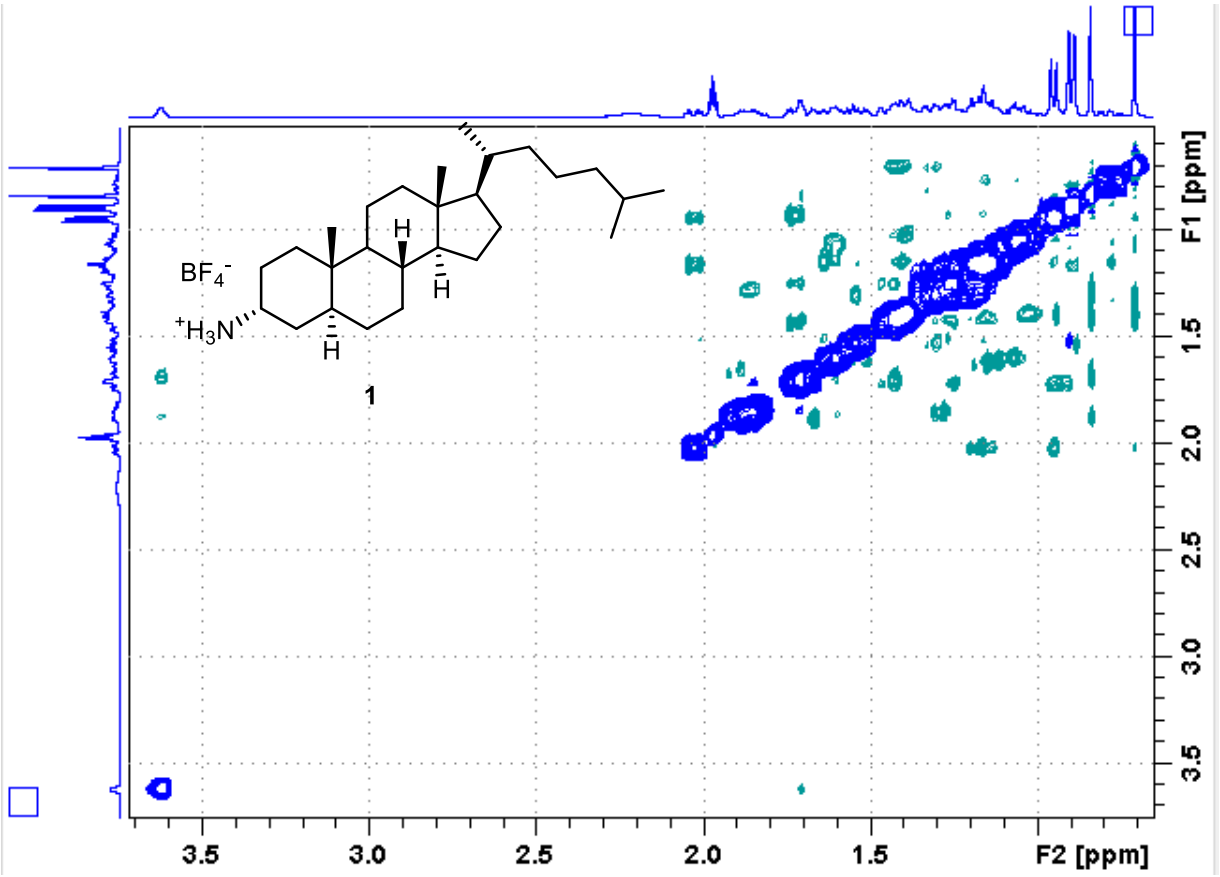
COSY of **1**



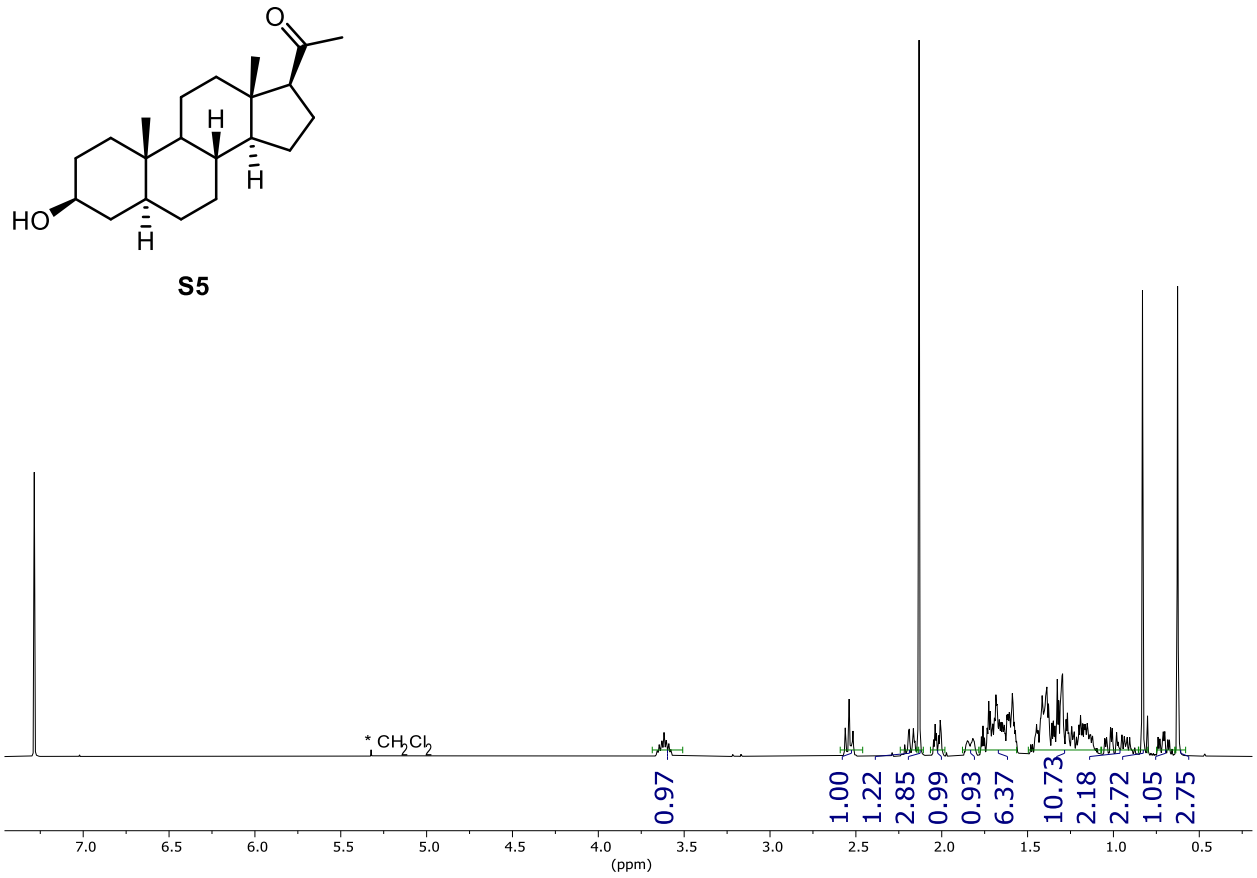
TOCSY of **1**



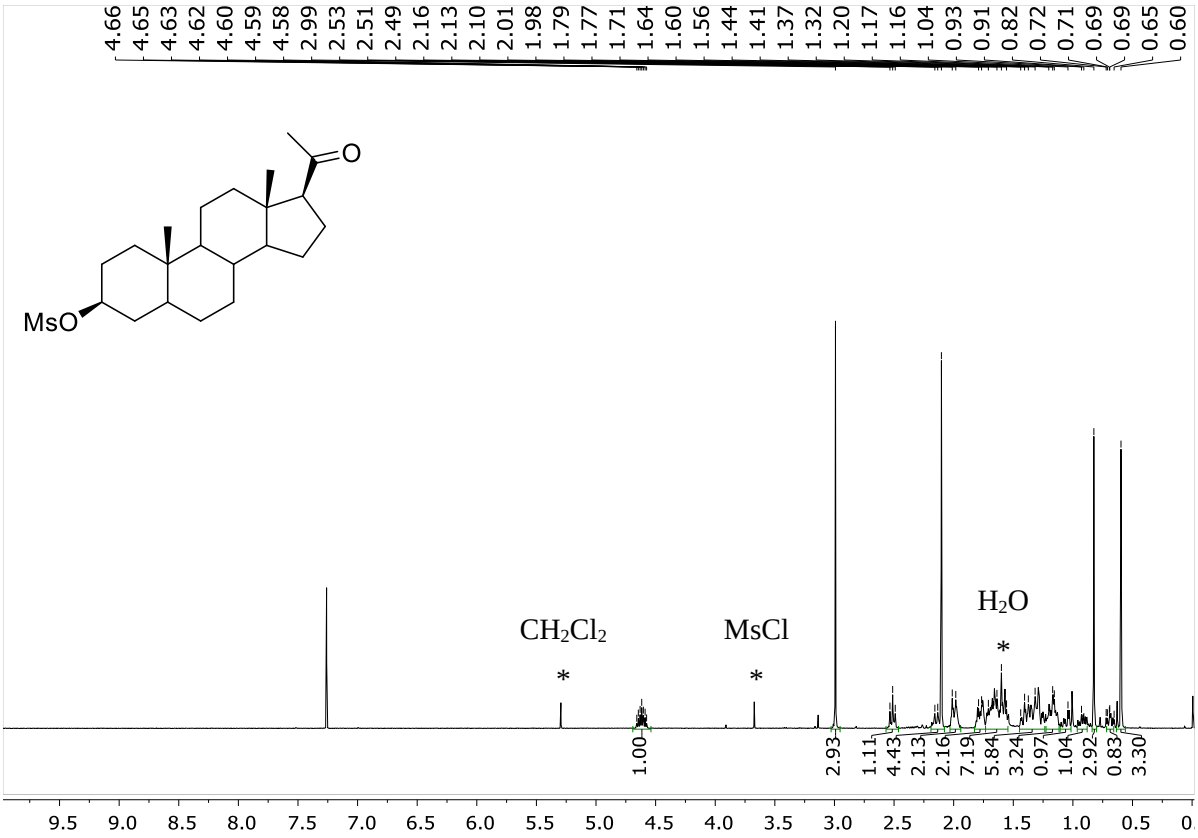
NOESY of **1**



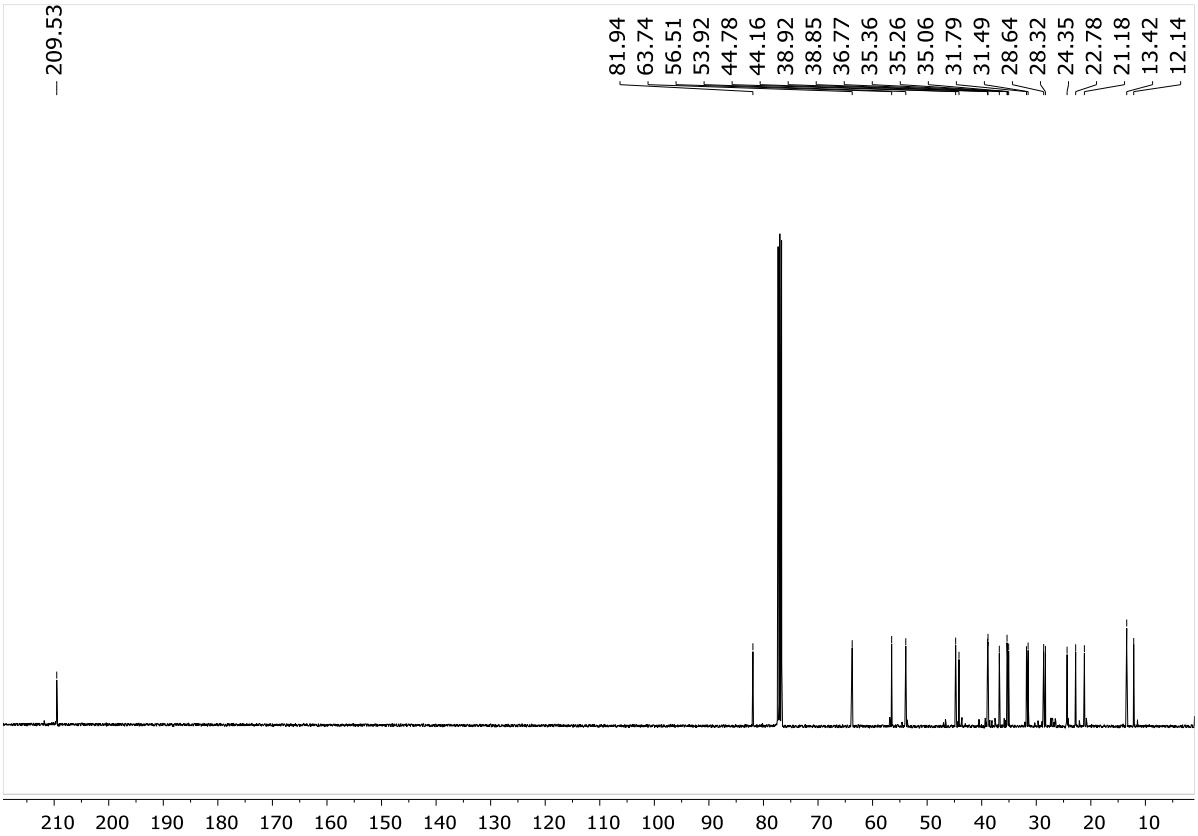
^{1}H-NMR spectrum of **S5**



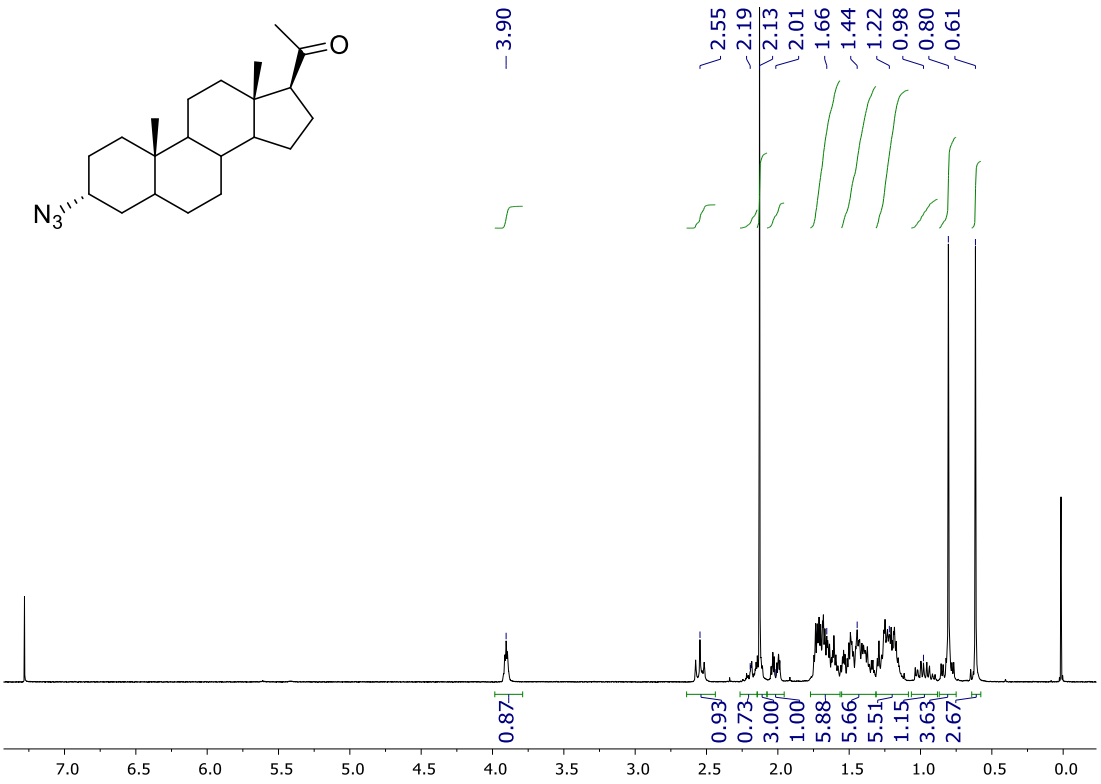
^{1}H-NMR spectrum of **S6**



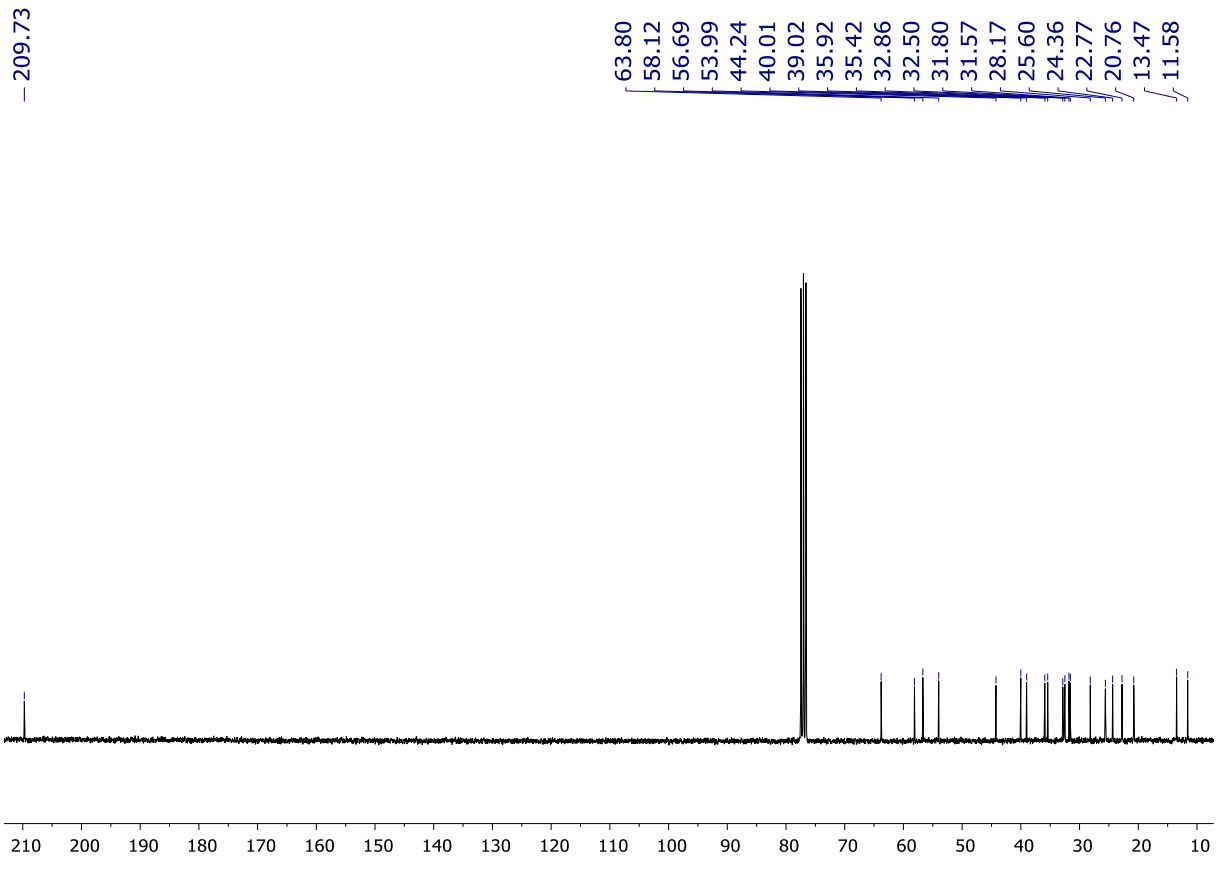
^{13}C-NMR spectrum of **S6**



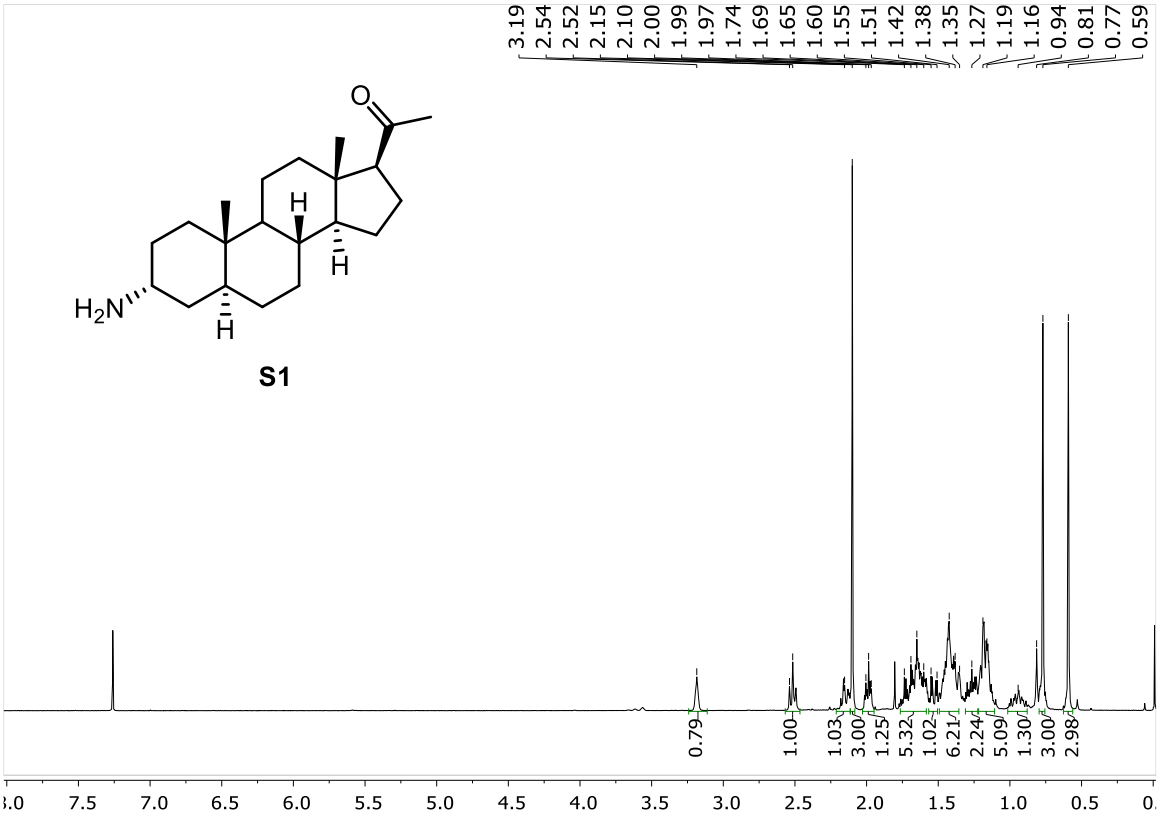
^{1}H-NMR spectrum of **S7**



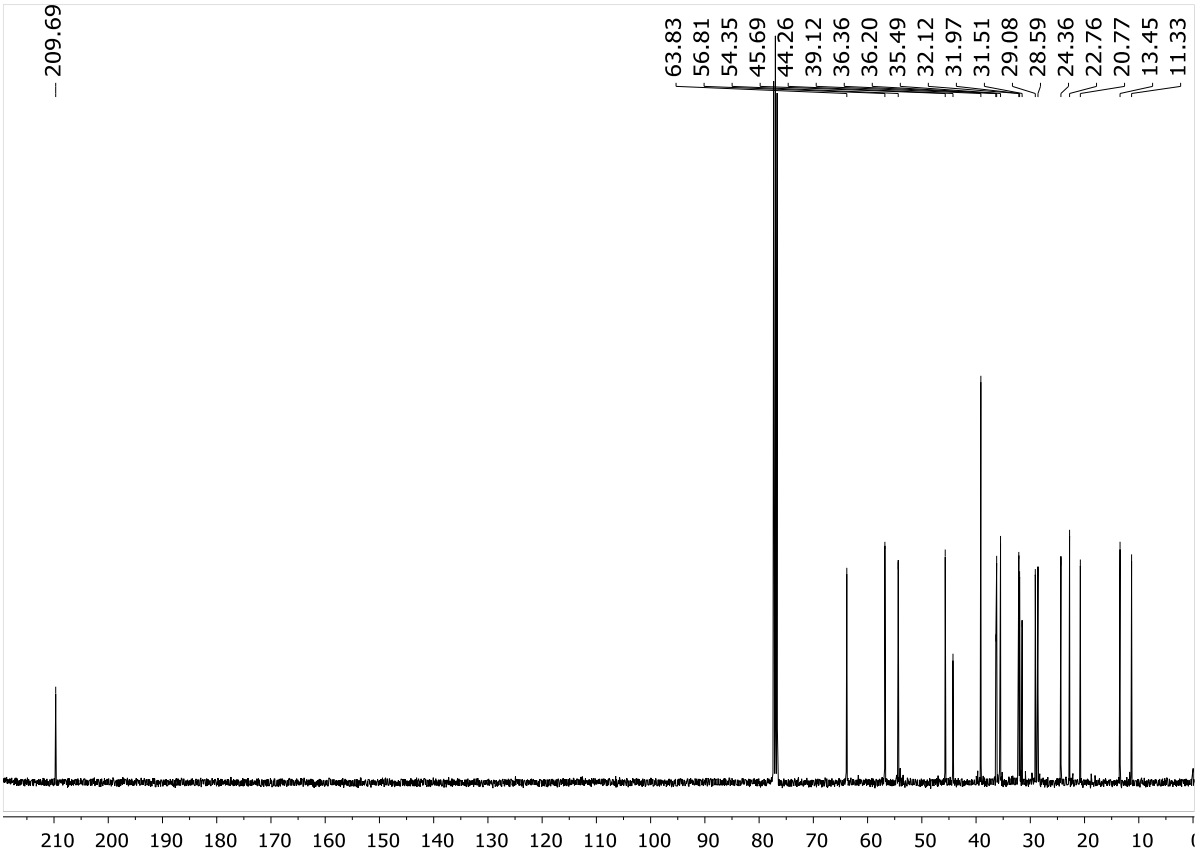
^{13}C-NMR spectrum of **S7**



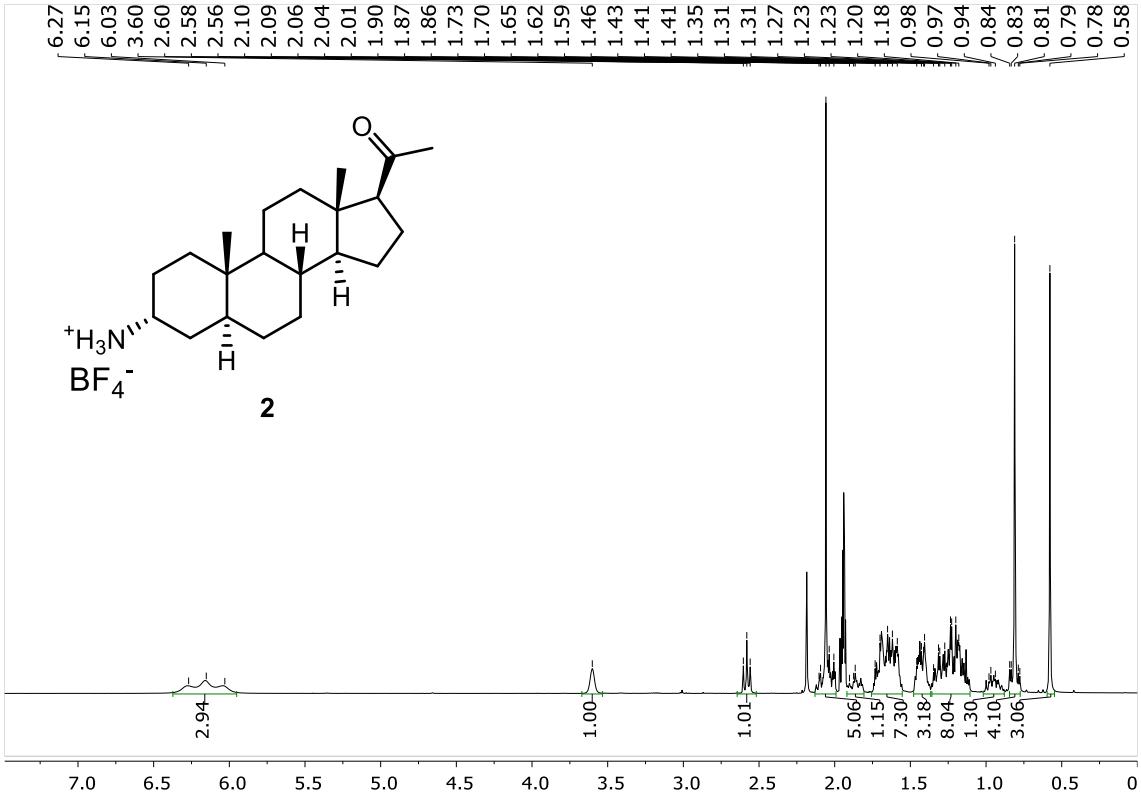
^{1}H-NMR spectrum of **S8**



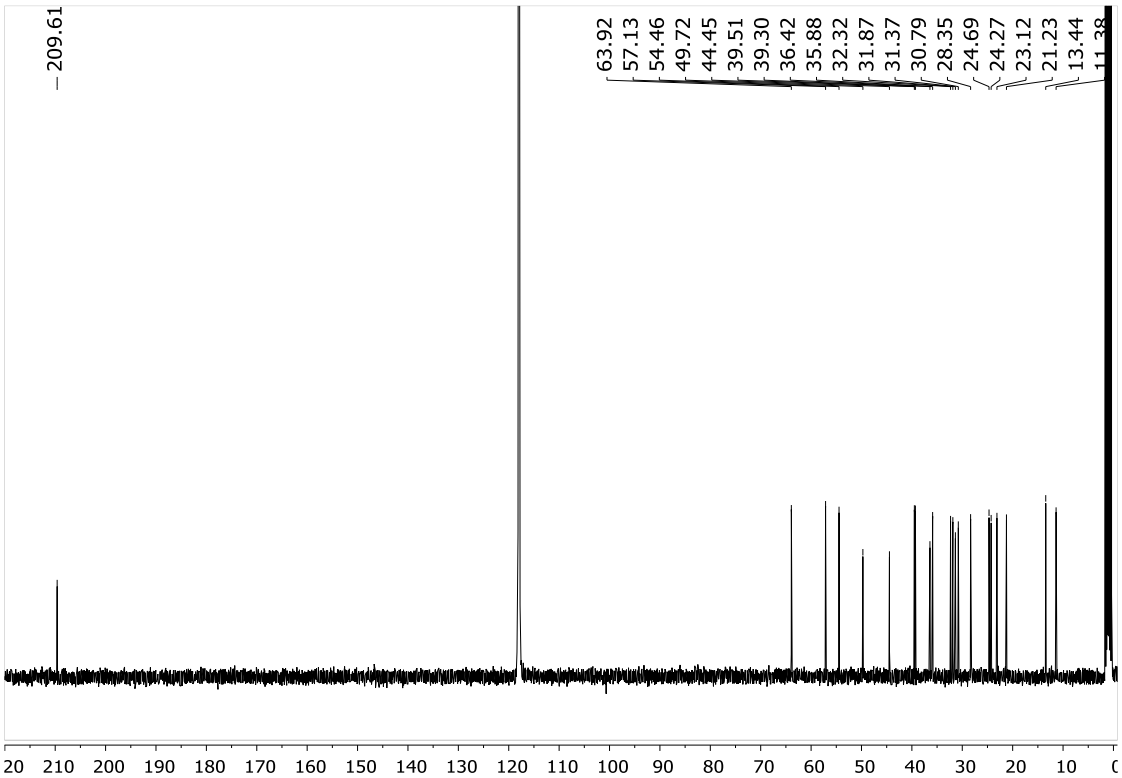
^{13}C-NMR spectrum of **S8**



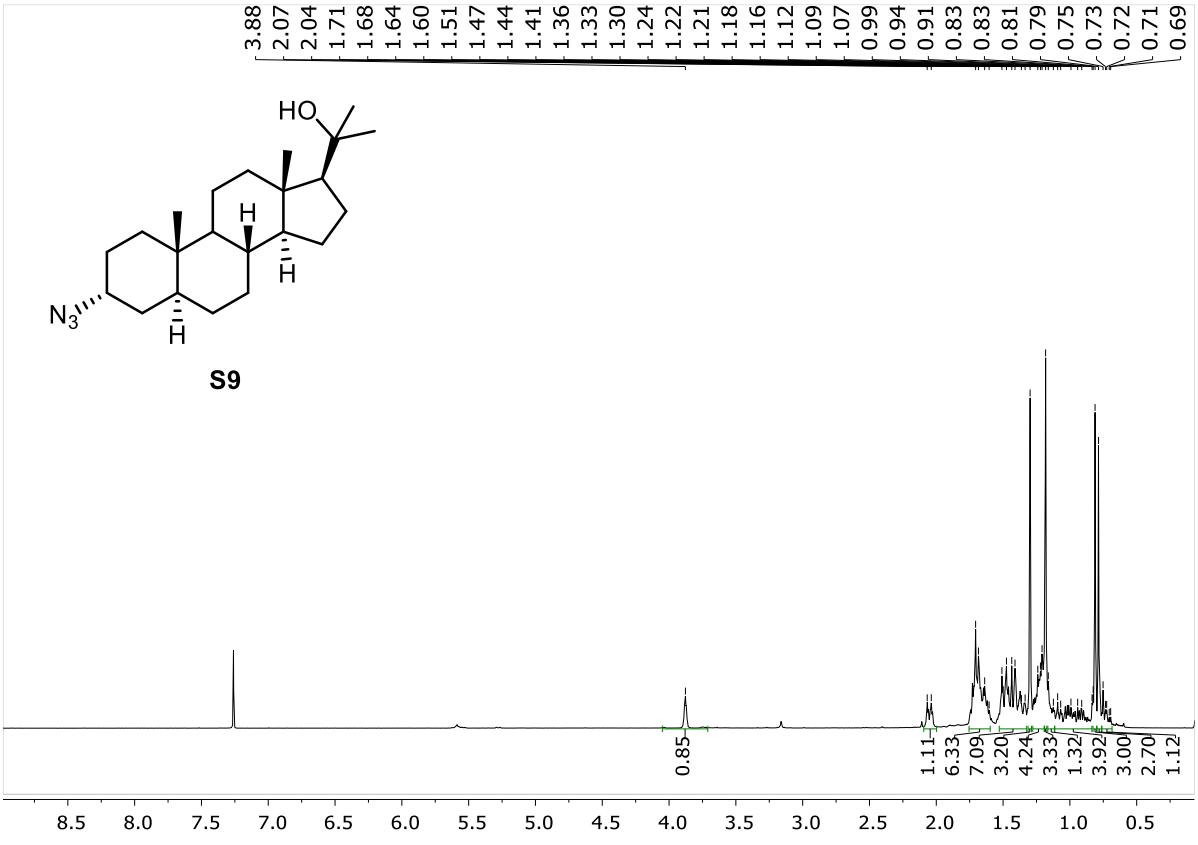
^{1}H-NMR spectrum of **2**



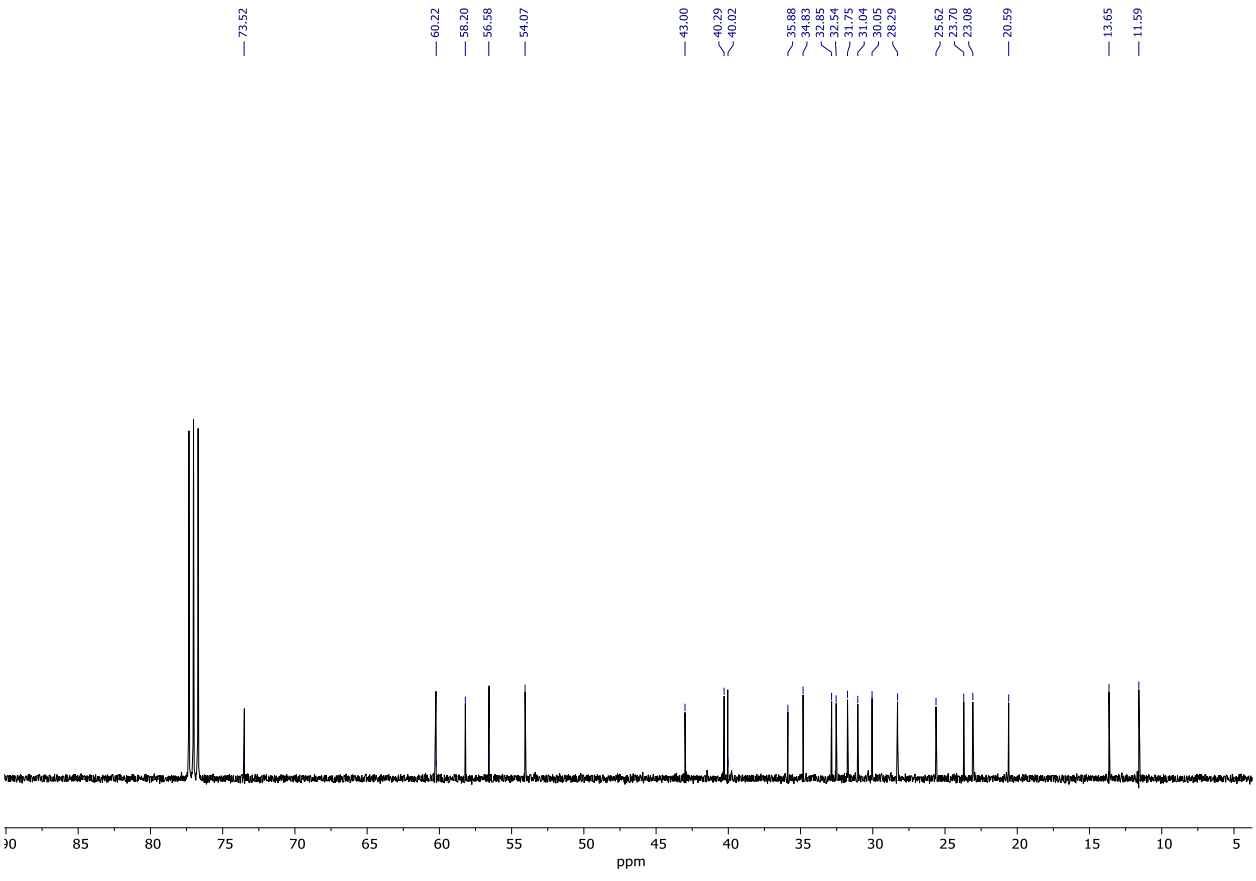
^{13}C-NMR spectrum of **2**



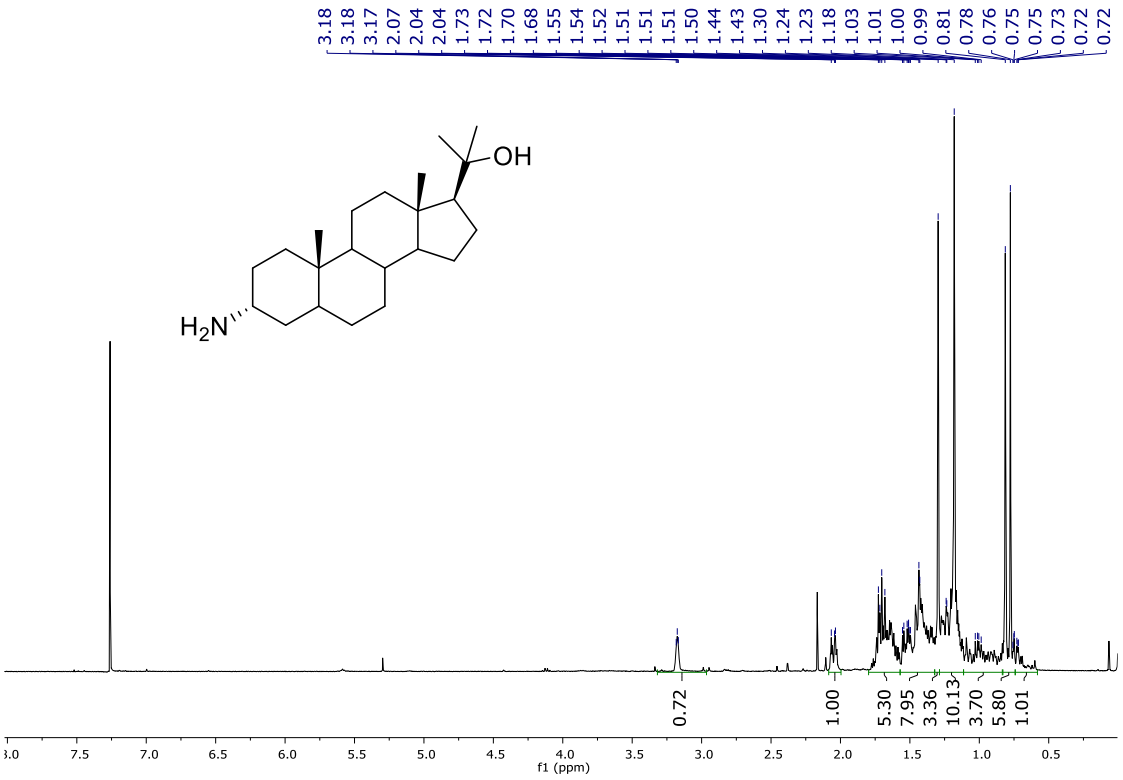
^{1}H-NMR spectrum of **S9**



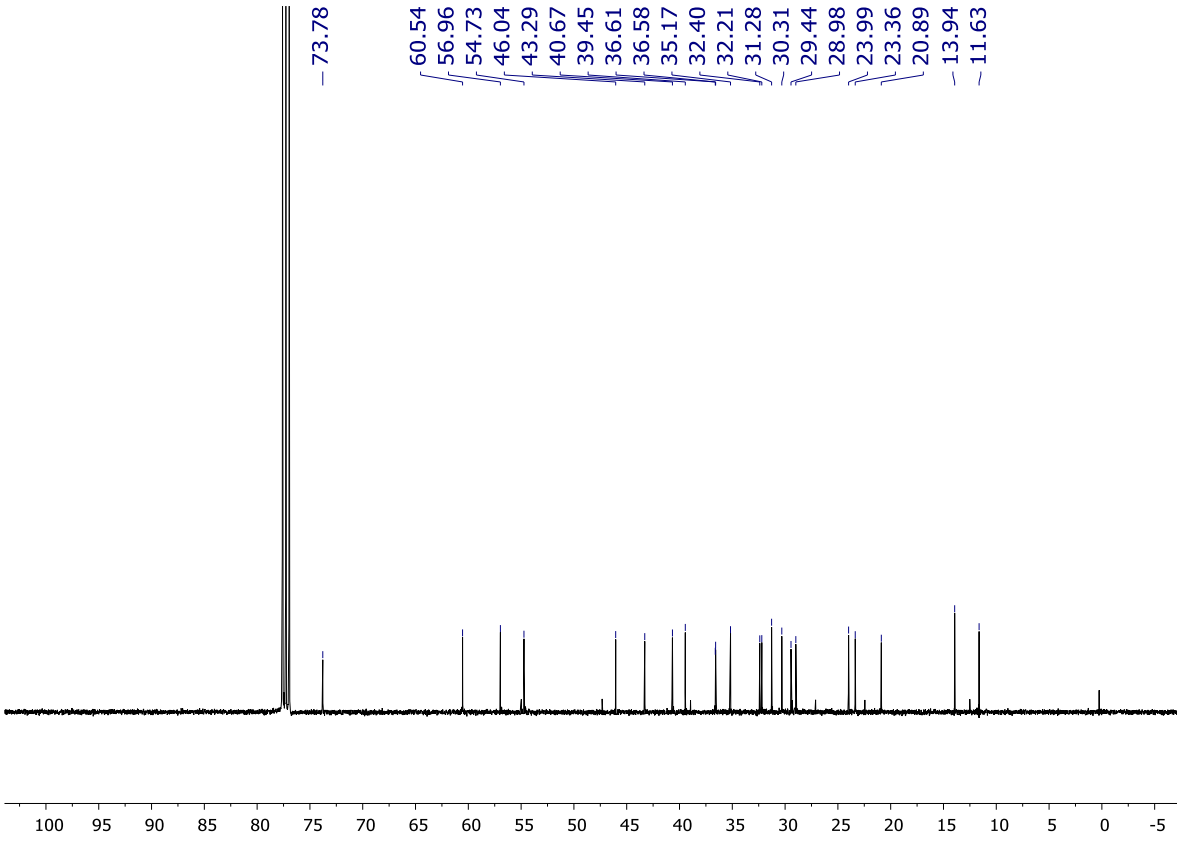
^{13}C-NMR spectrum of **S9**

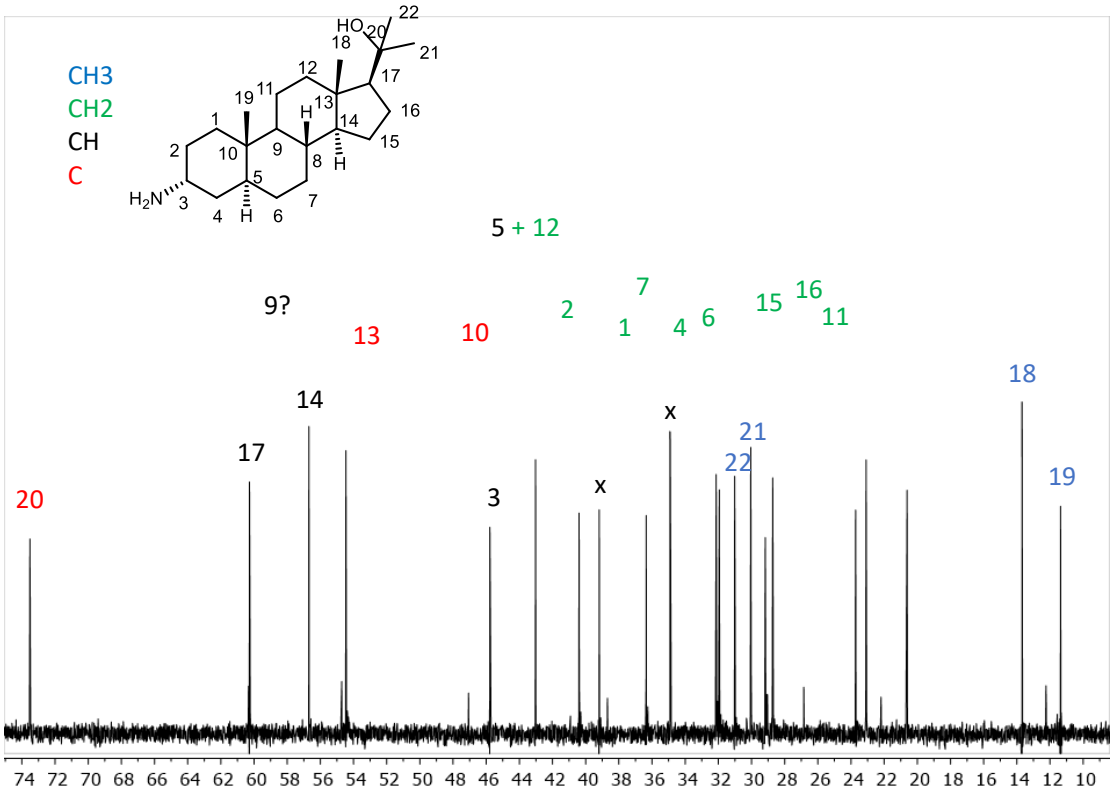


^{1}H-NMR spectrum of **S10**



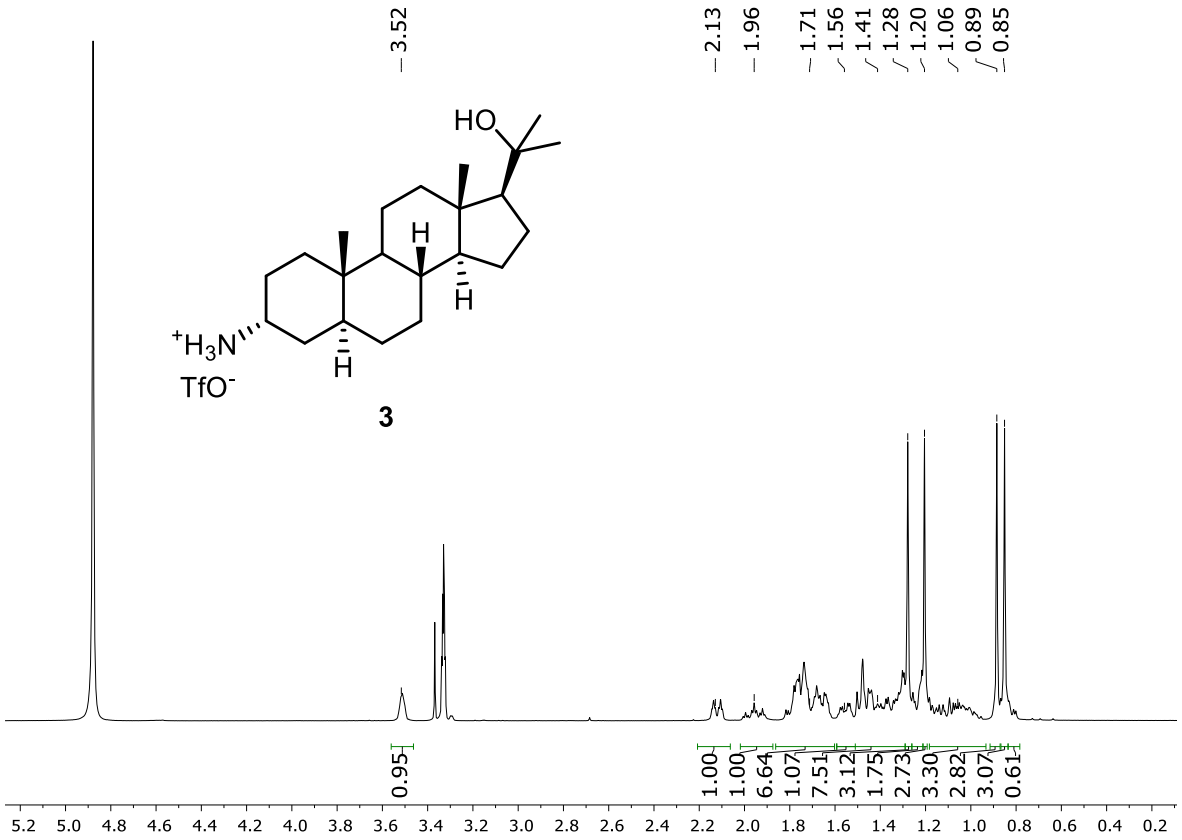
^{13}C-NMR spectrum of **S10**



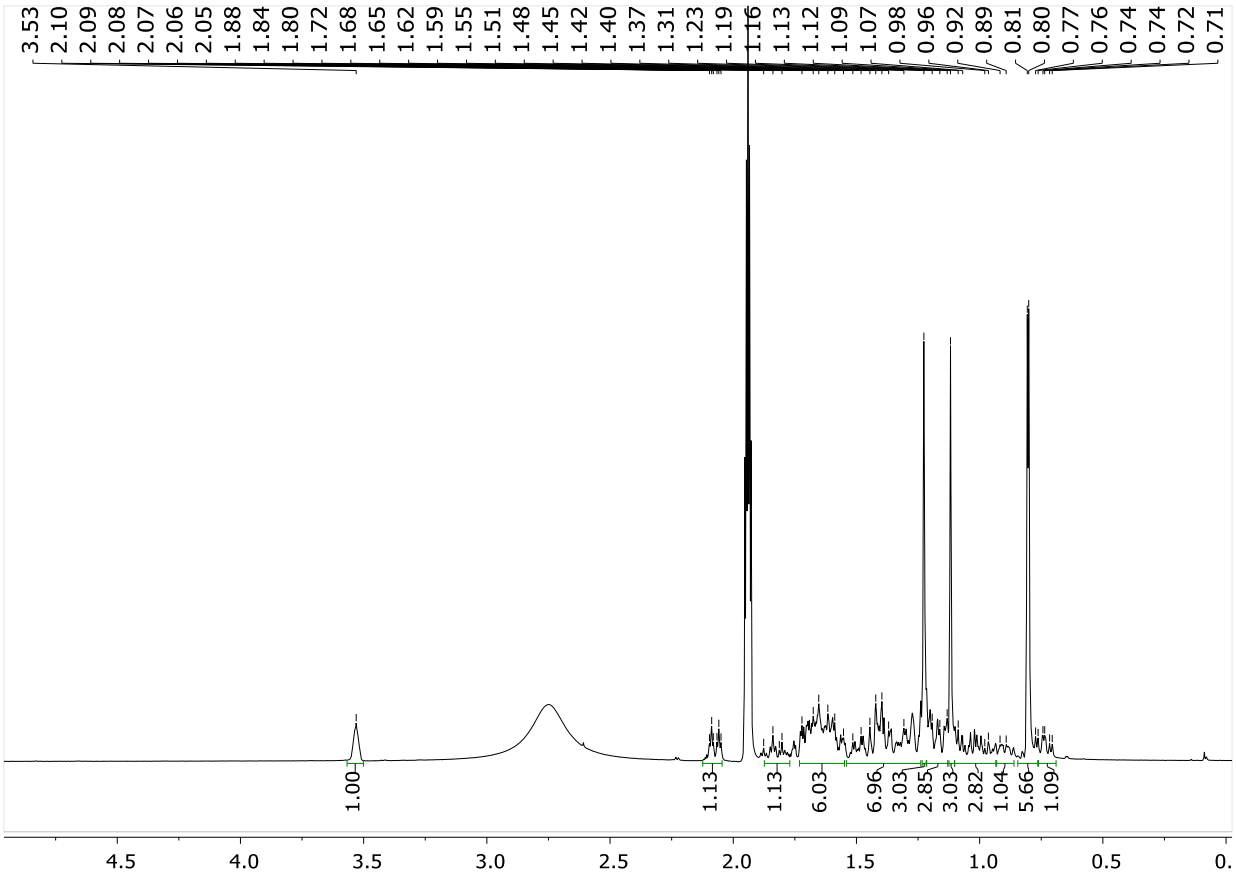


Assignment of the ^{13}C-NMR carbon signals of **S10**.

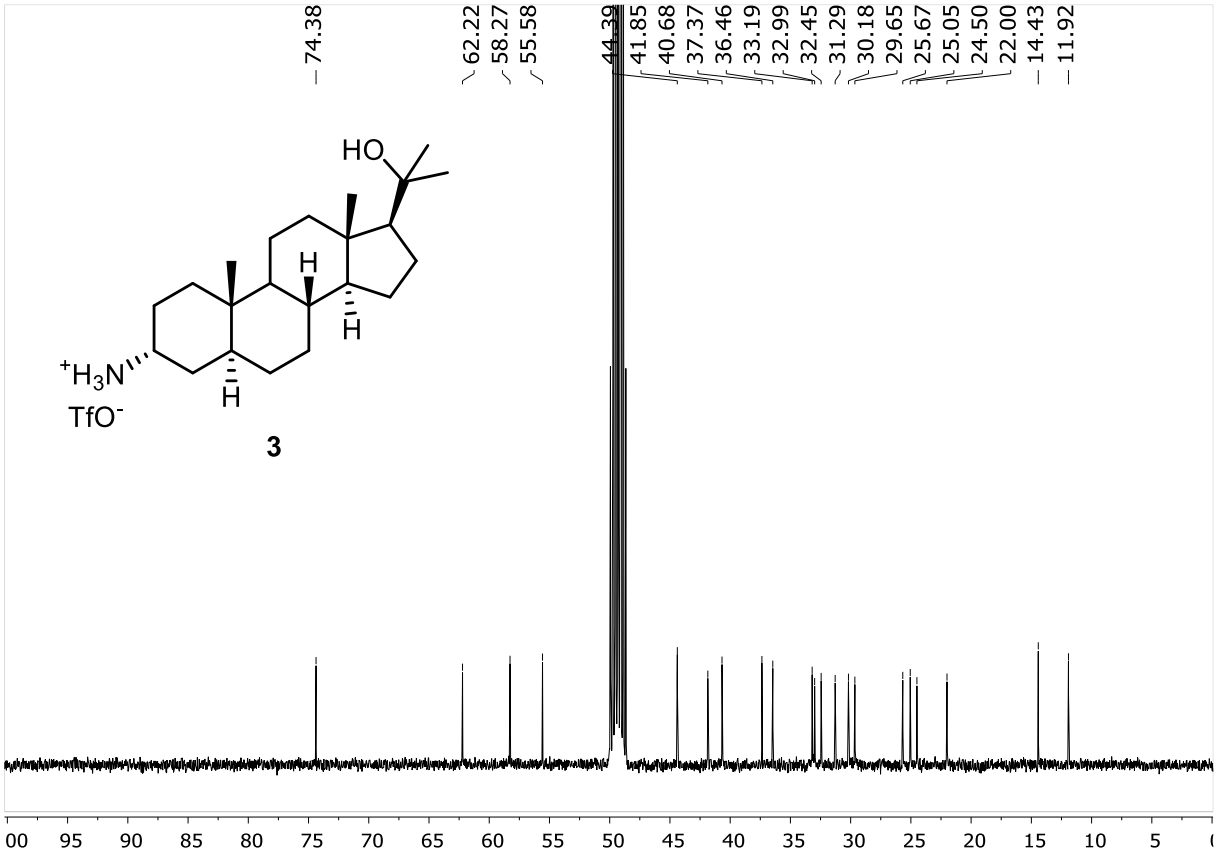
^{1}H-NMR spectrum of **3** (CD_3OD)



^{1}H-NMR spectrum of **3** (CD_3CN)

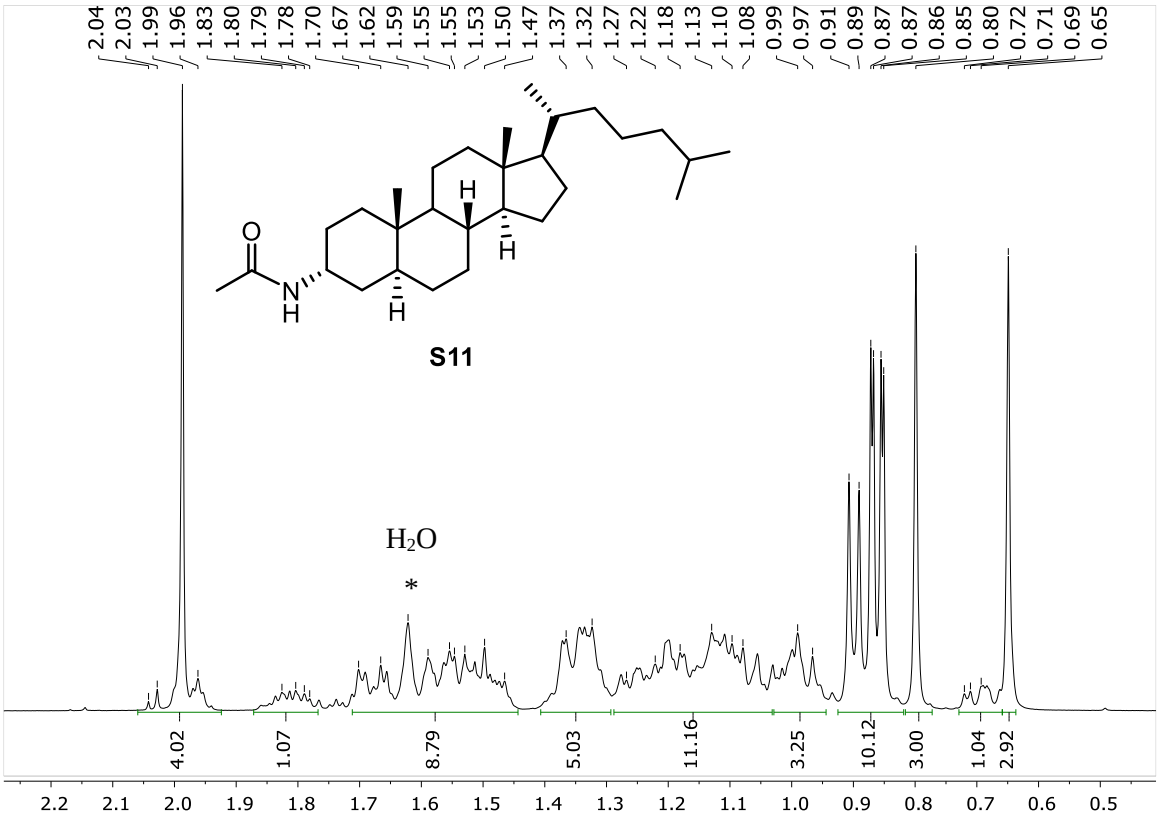


^{13}C-NMR spectrum of **3** (CD_3OD)

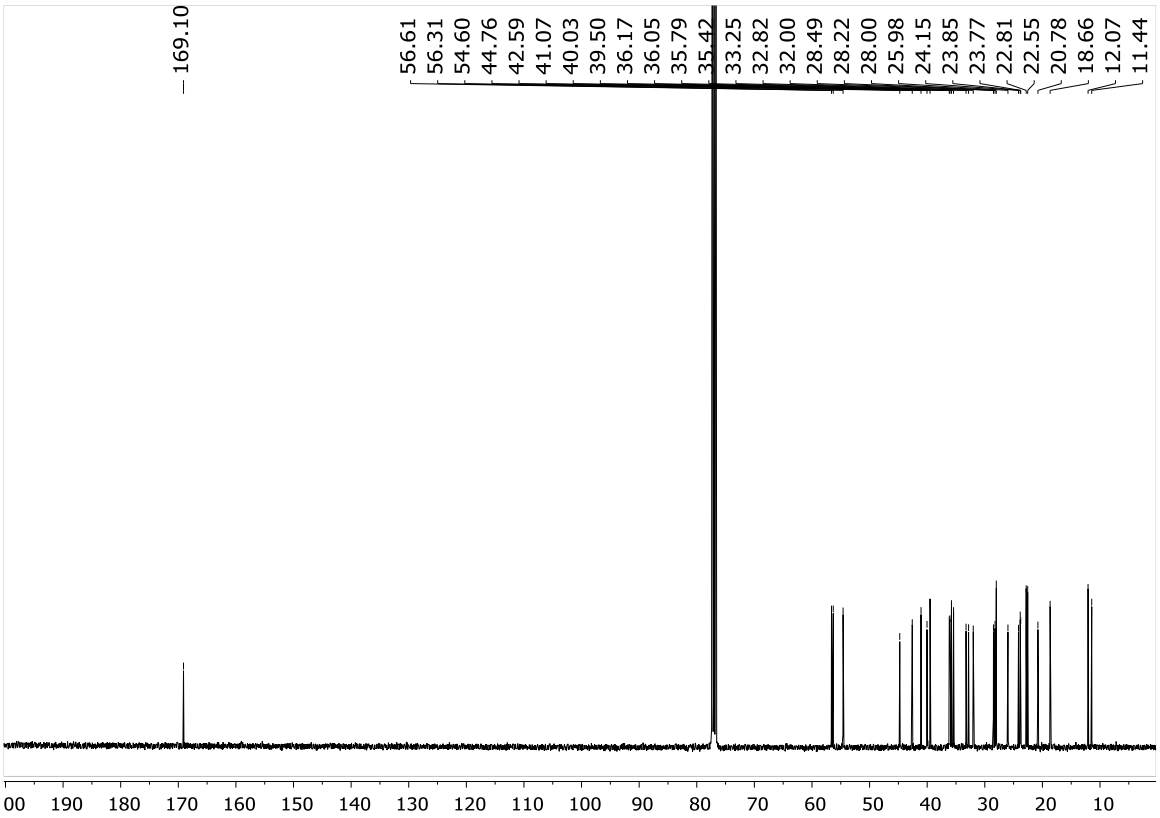


Synthesis of acetylated amines

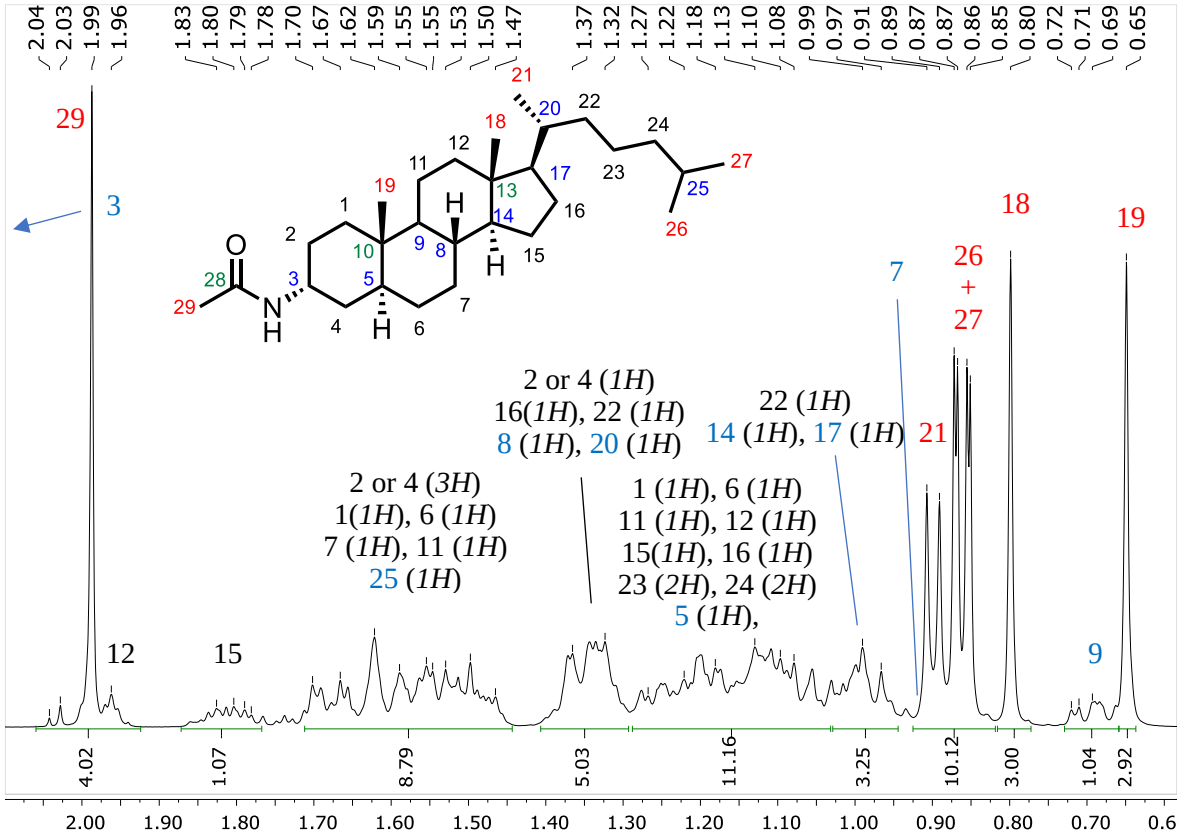
^{1}H-NMR spectrum of **S11**



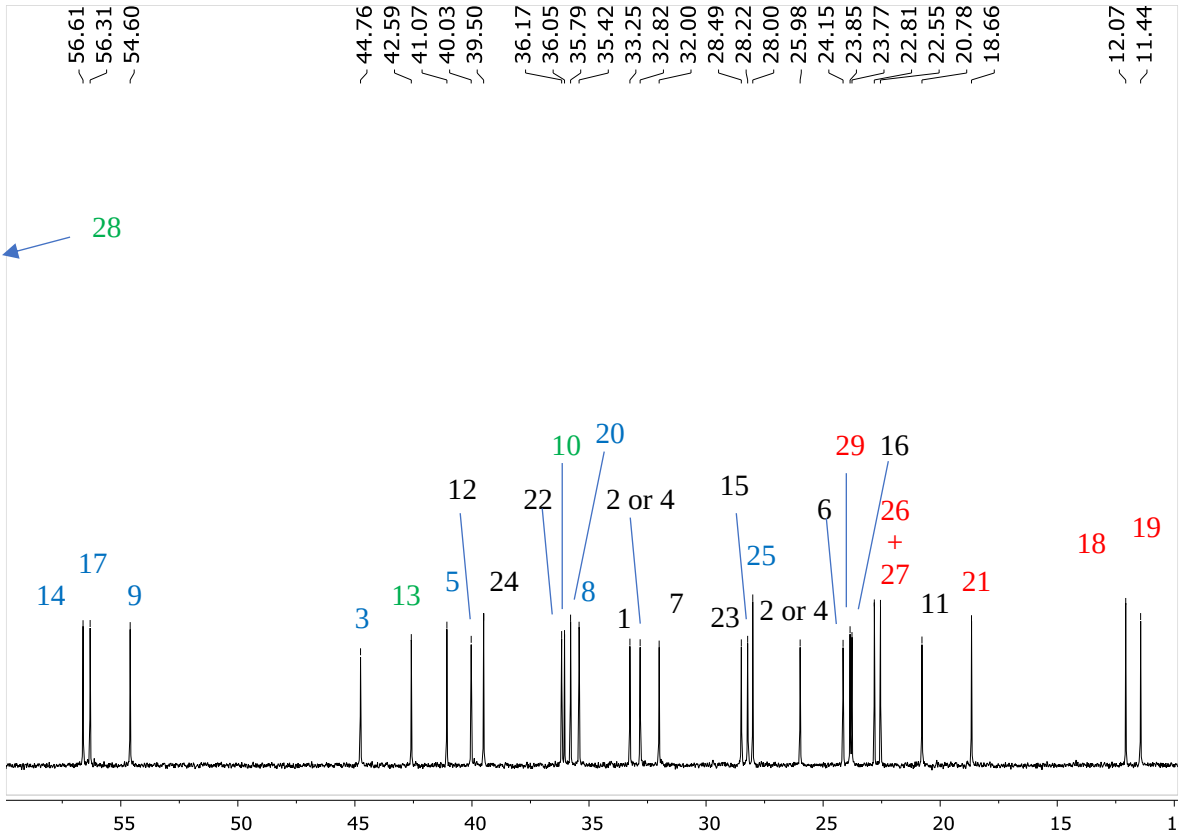
^{13}C-NMR spectrum of **S11**



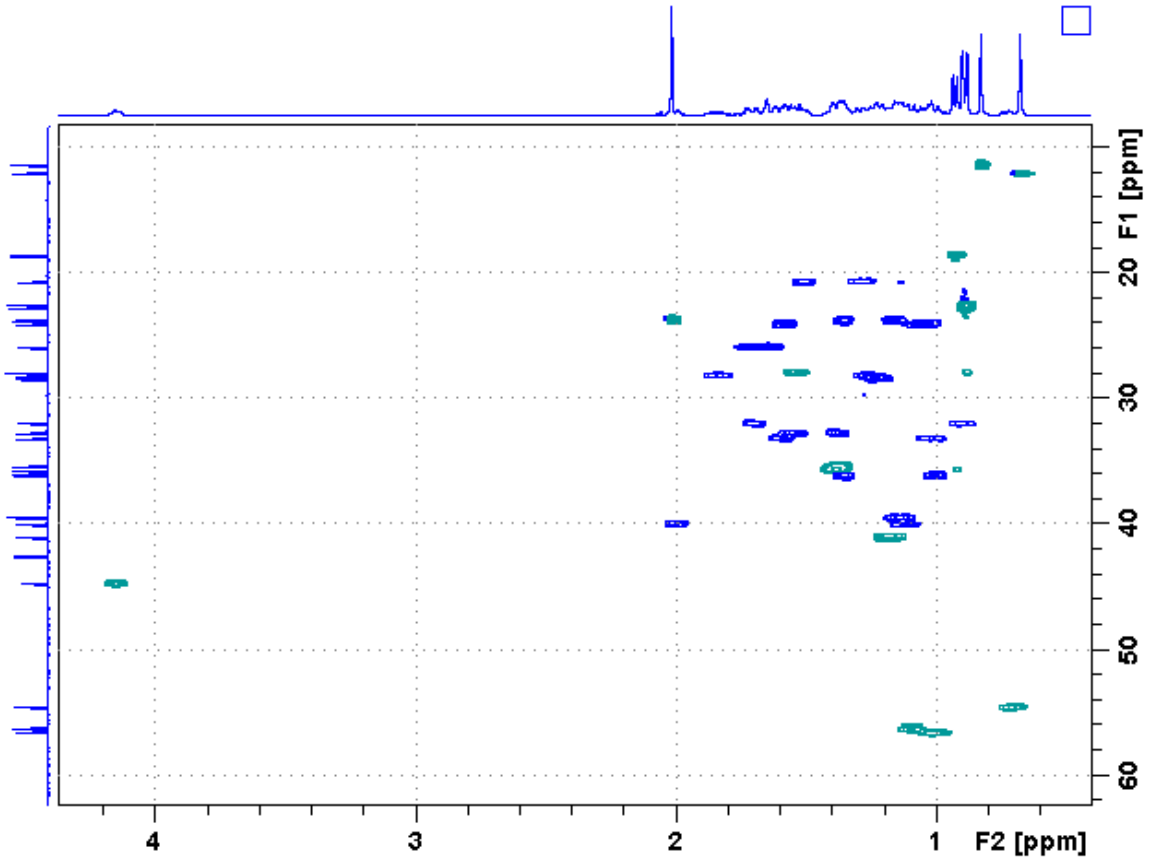
Assignment of signals of **S11** (^{1}H-NMR)



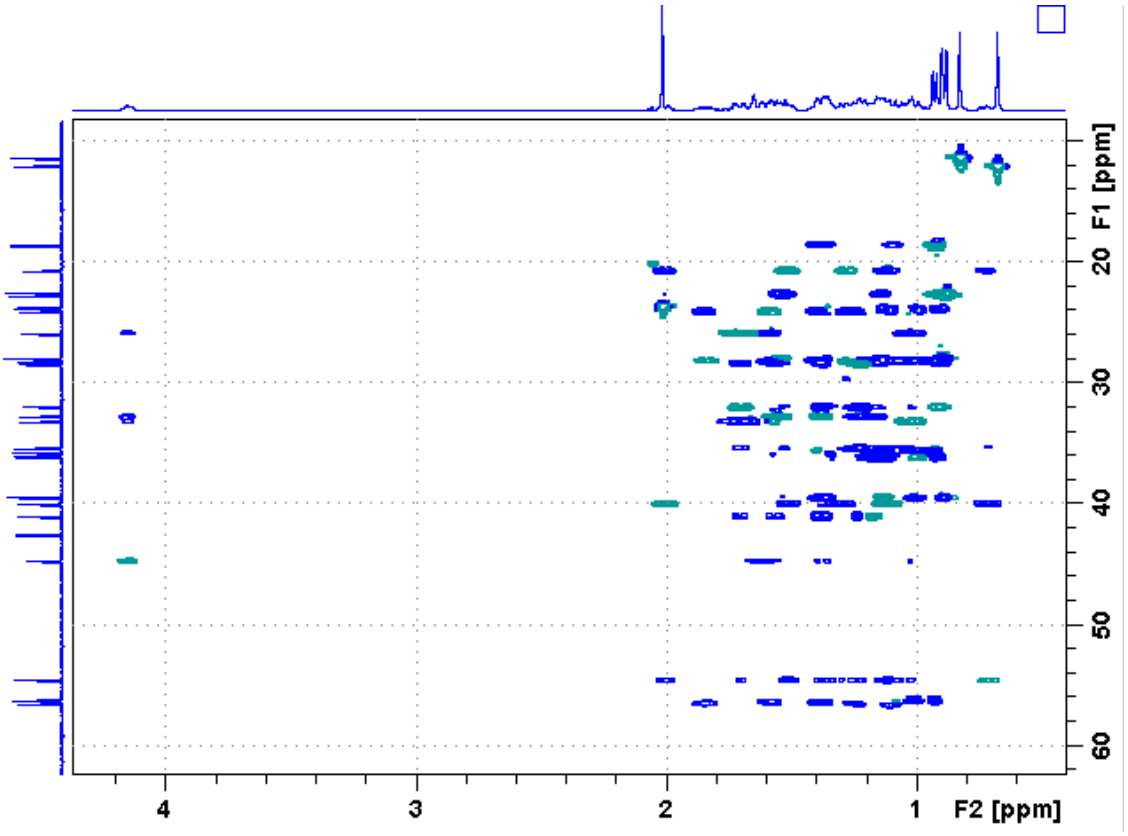
(^{13}C-NMR)



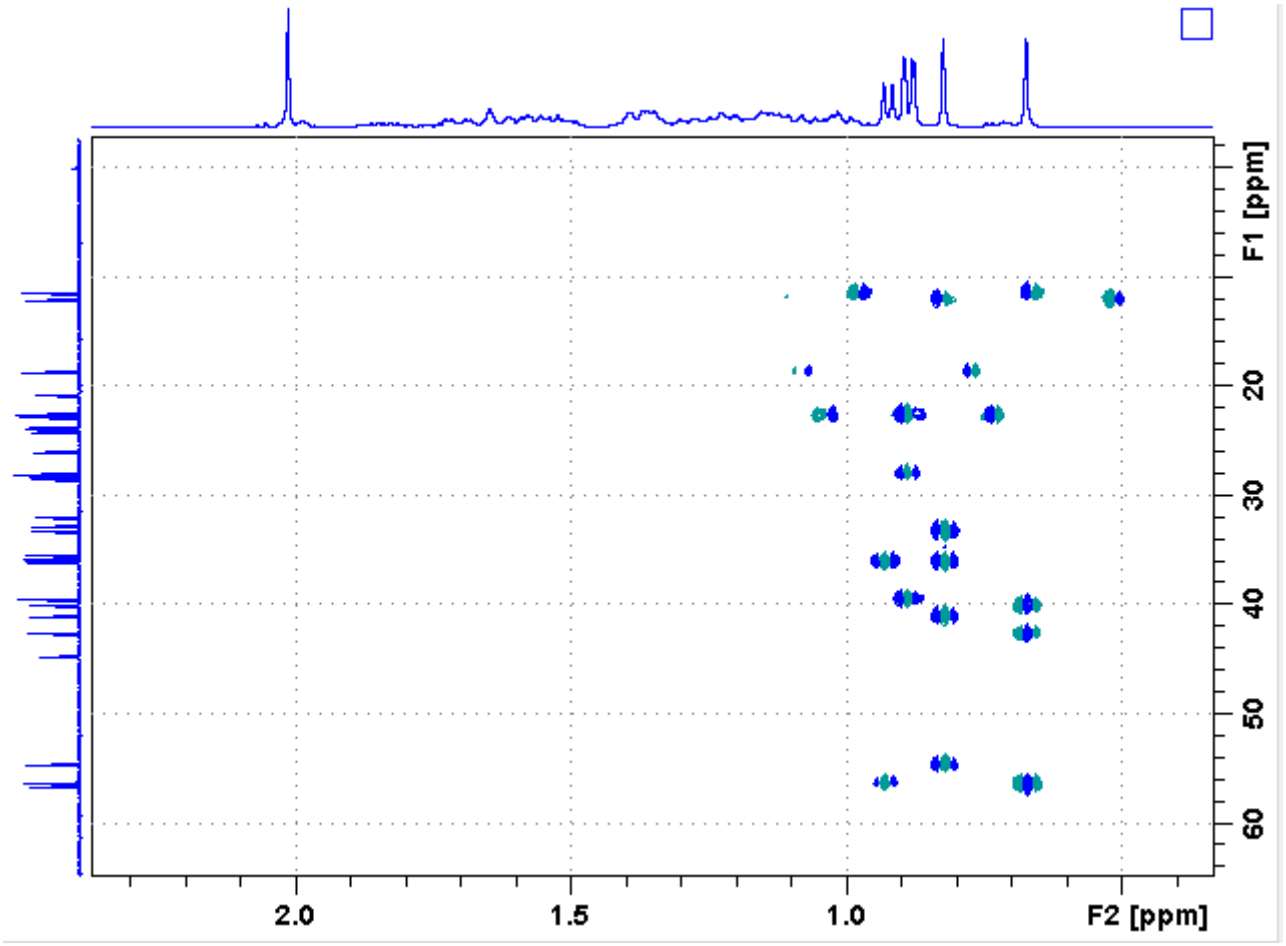
HSQC*ed* of **S11**



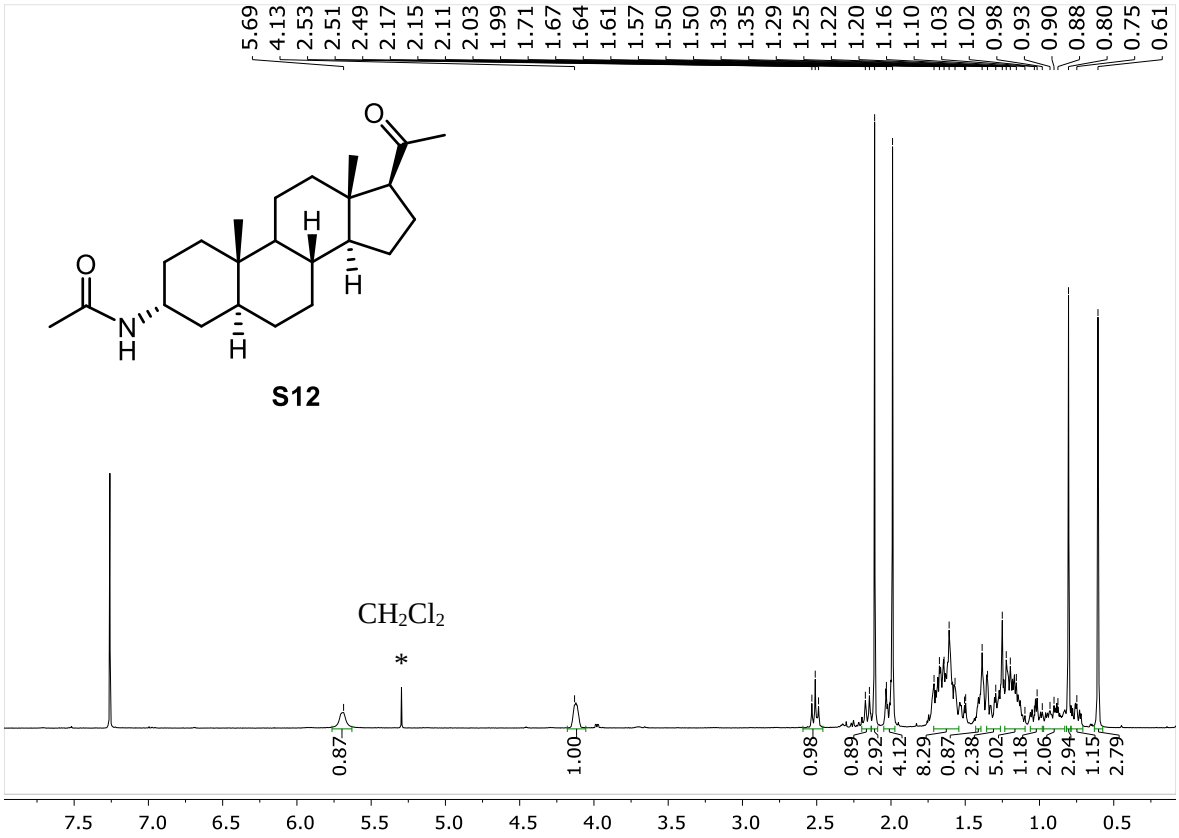
HSQC-TCOSY of **S11**



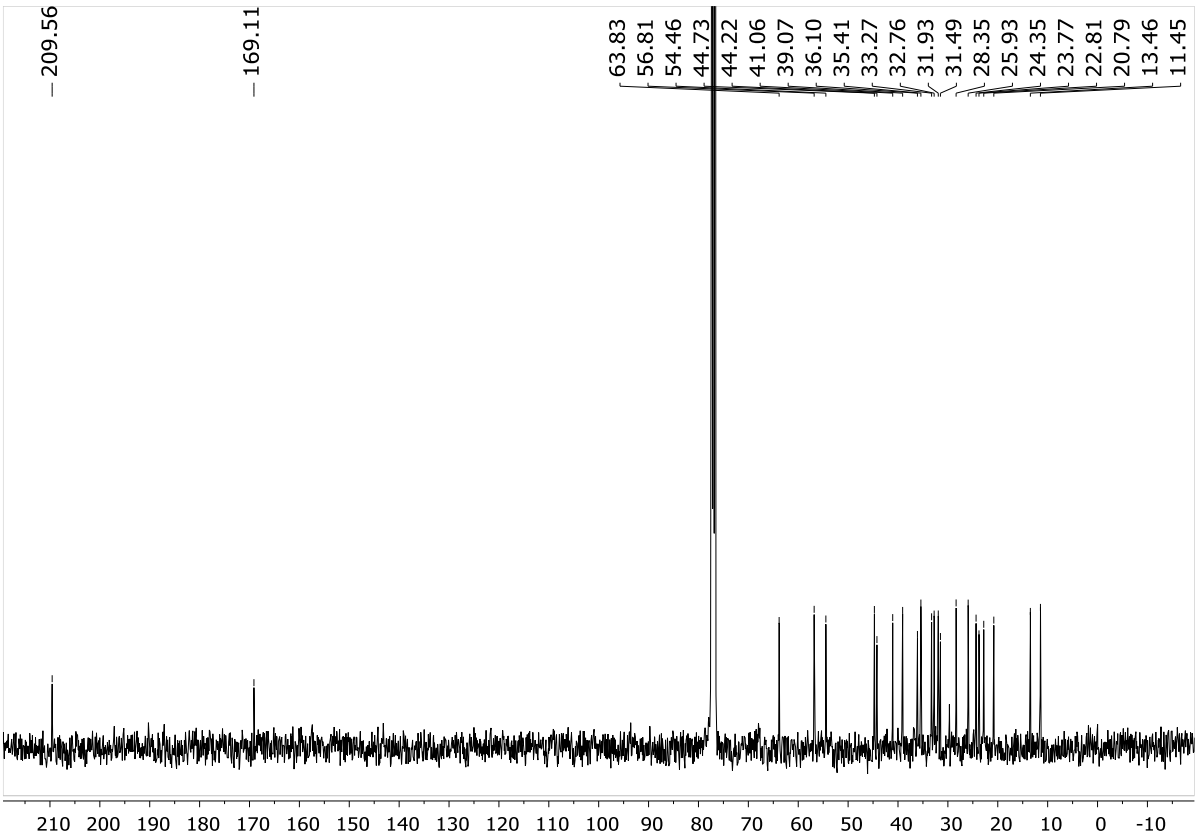
HMBC of **S11**



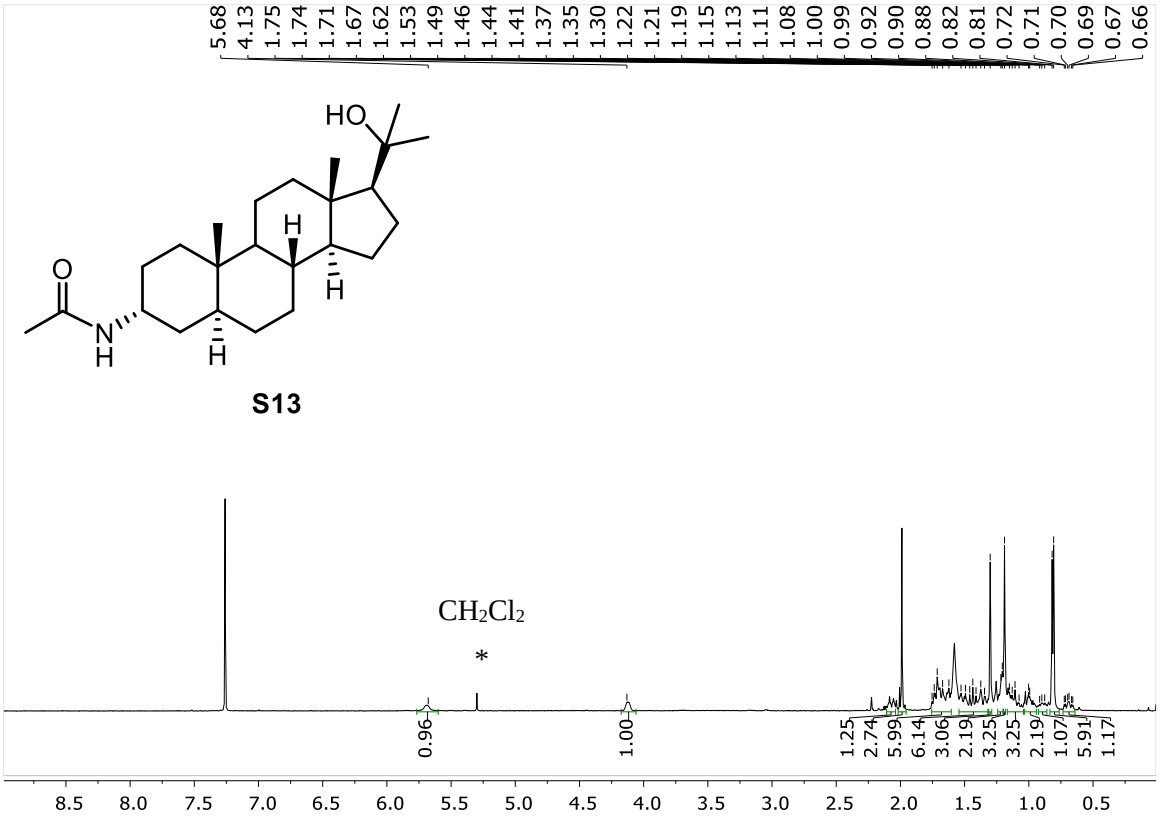
^{1}H-NMR spectrum of **S12**



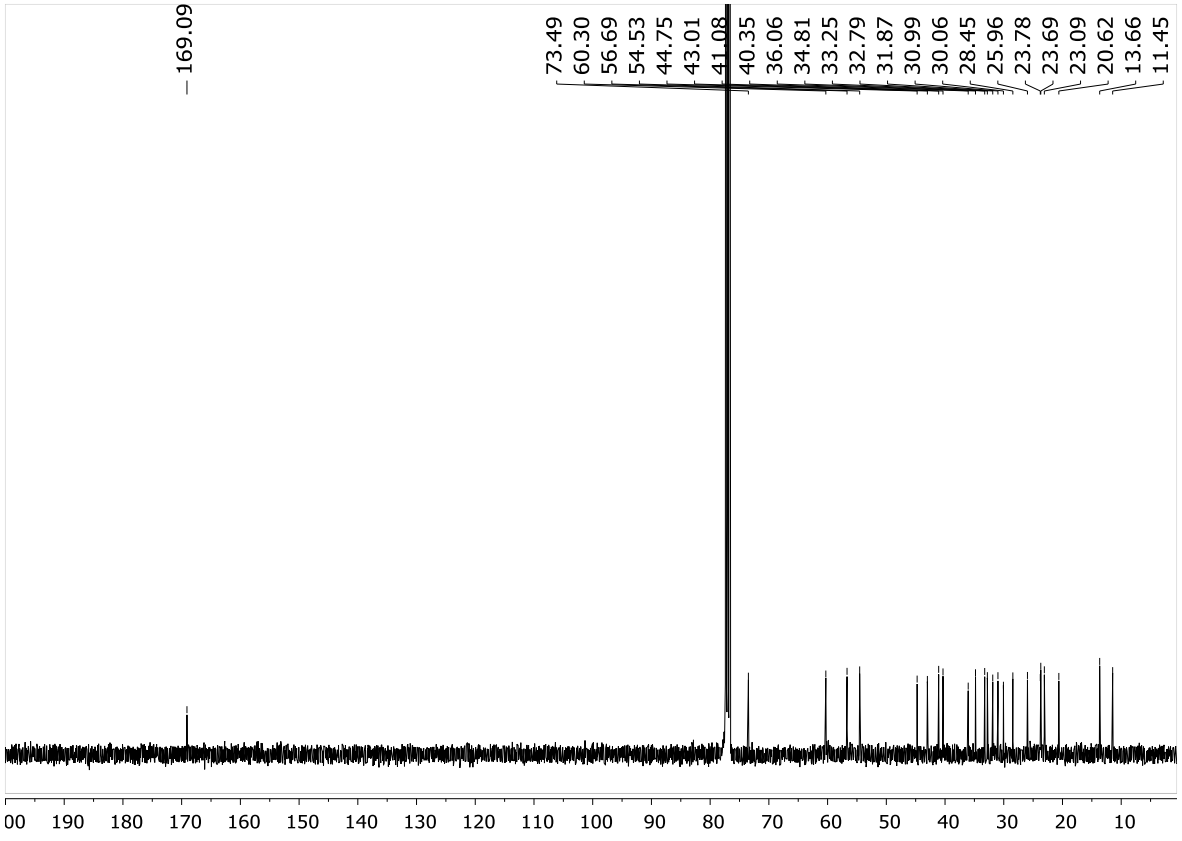
^{13}C-NMR spectrum of **S12**



^{1}H-NMR spectrum of **S13**

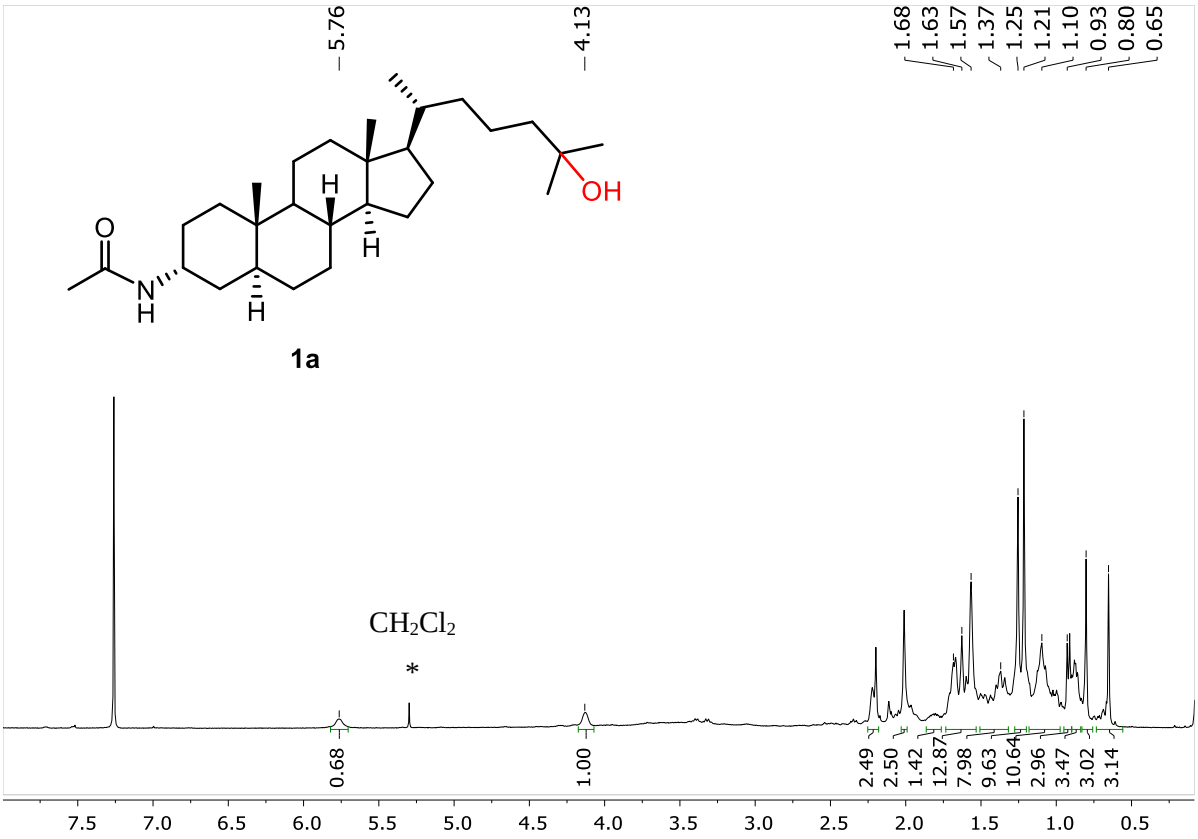


^{13}C-NMR spectrum of **S13**

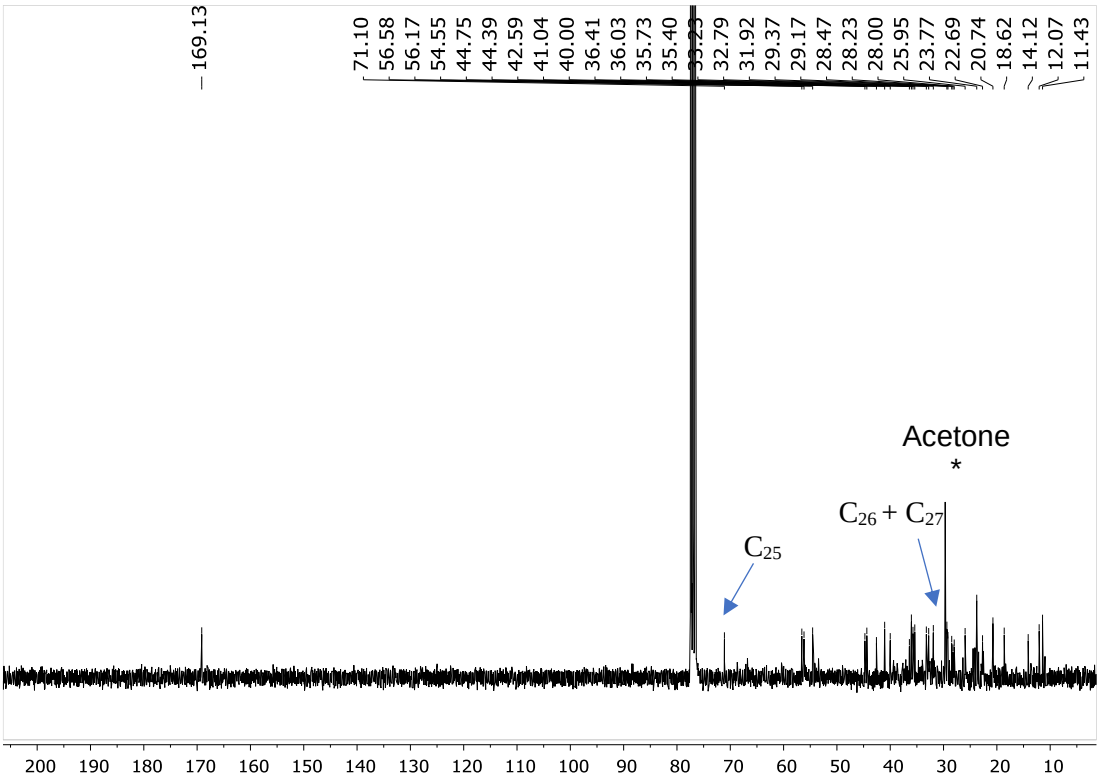


Oxidation products

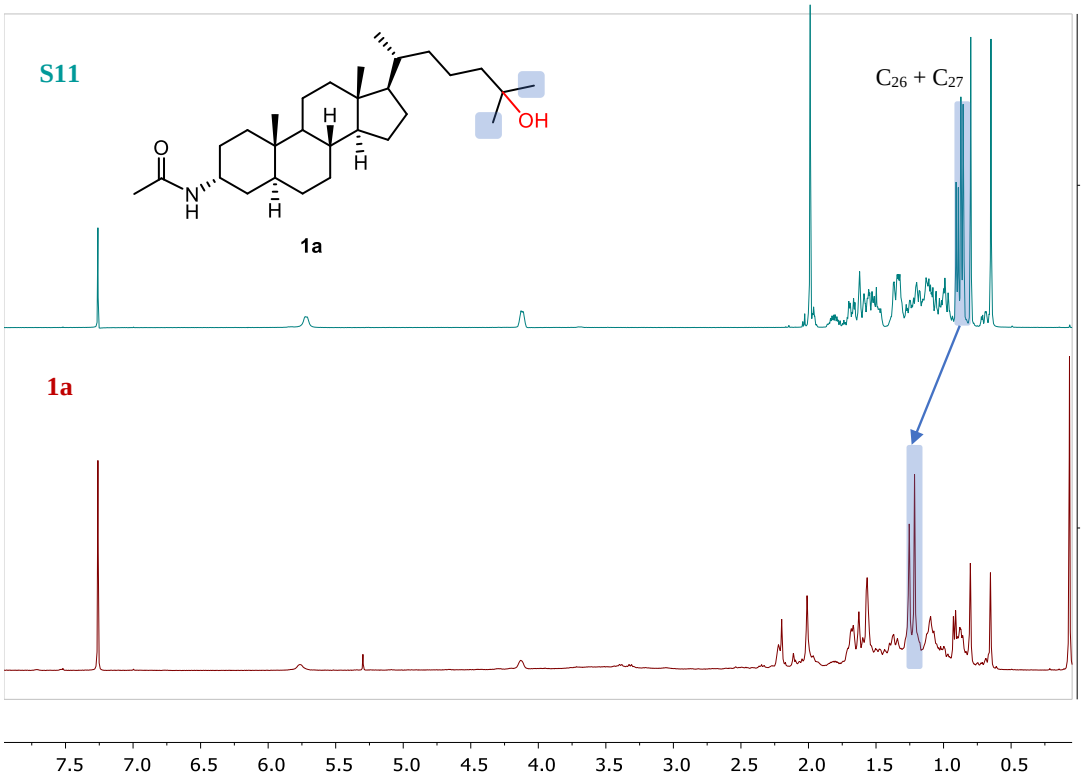
^{1}H-NMR spectrum of **1a** (purity 72% by GC analysis)



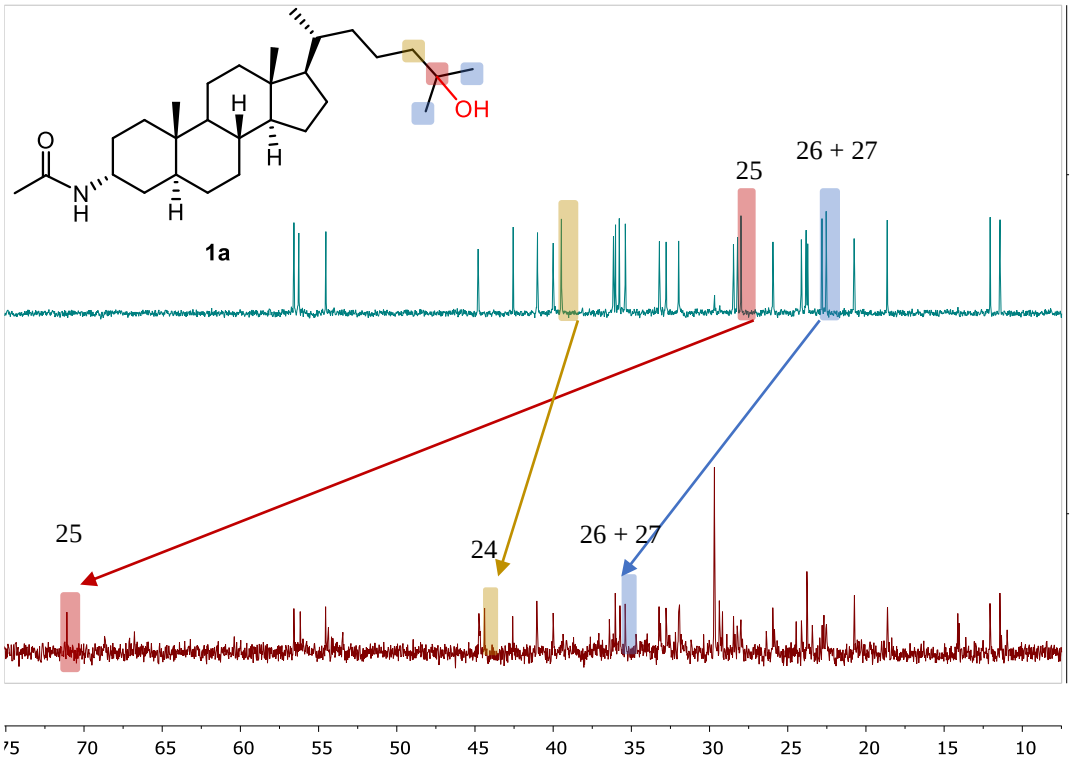
^{13}C-NMR spectrum of **1a**



Comparison of ^{1}H and ^{13}C NMR spectra of **1a** and **S11**

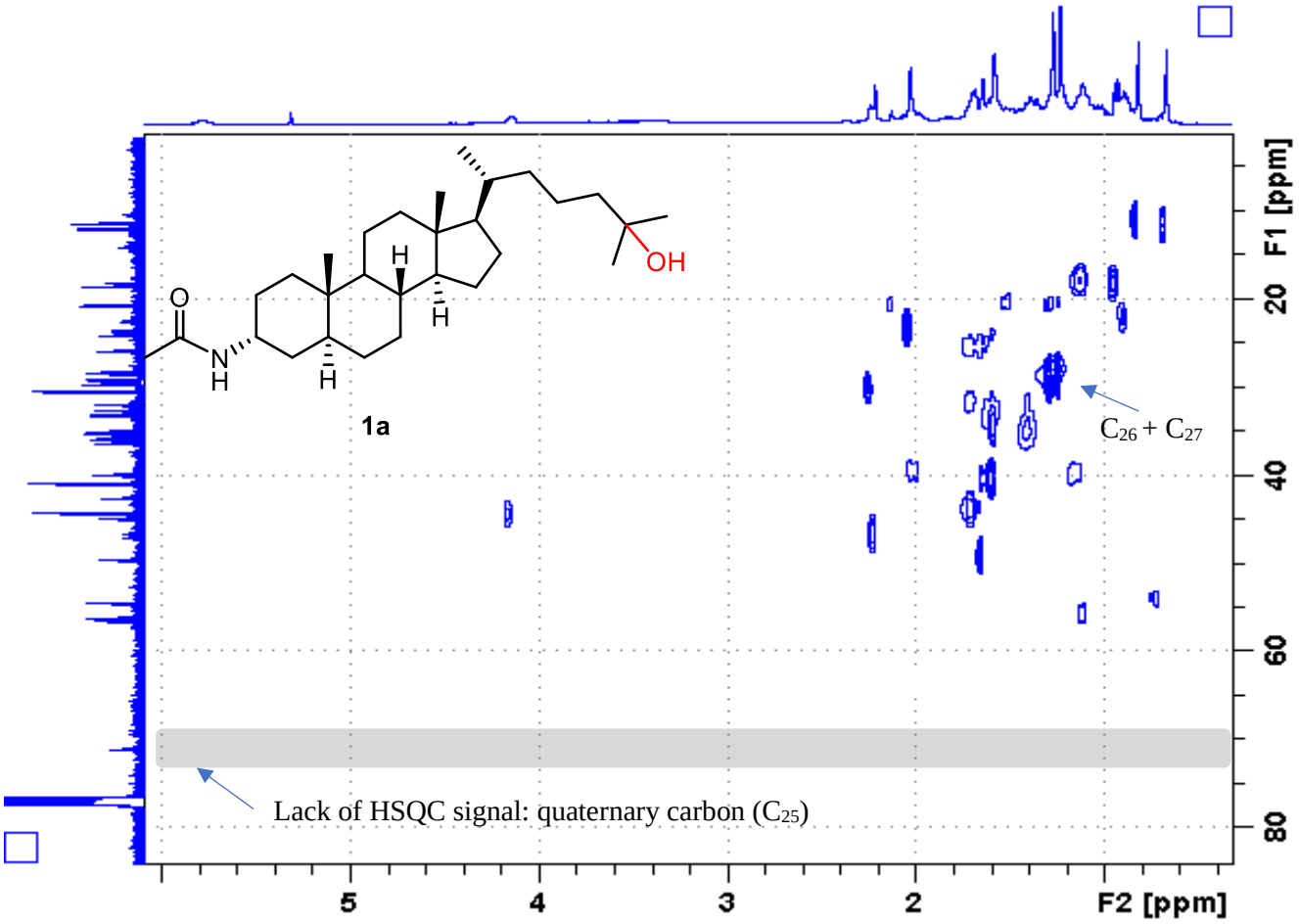


Stacking of ^{1}H-NMR spectra. Note the shifts of the signals of methyls C_{26} and C_{27} in the oxidation product.

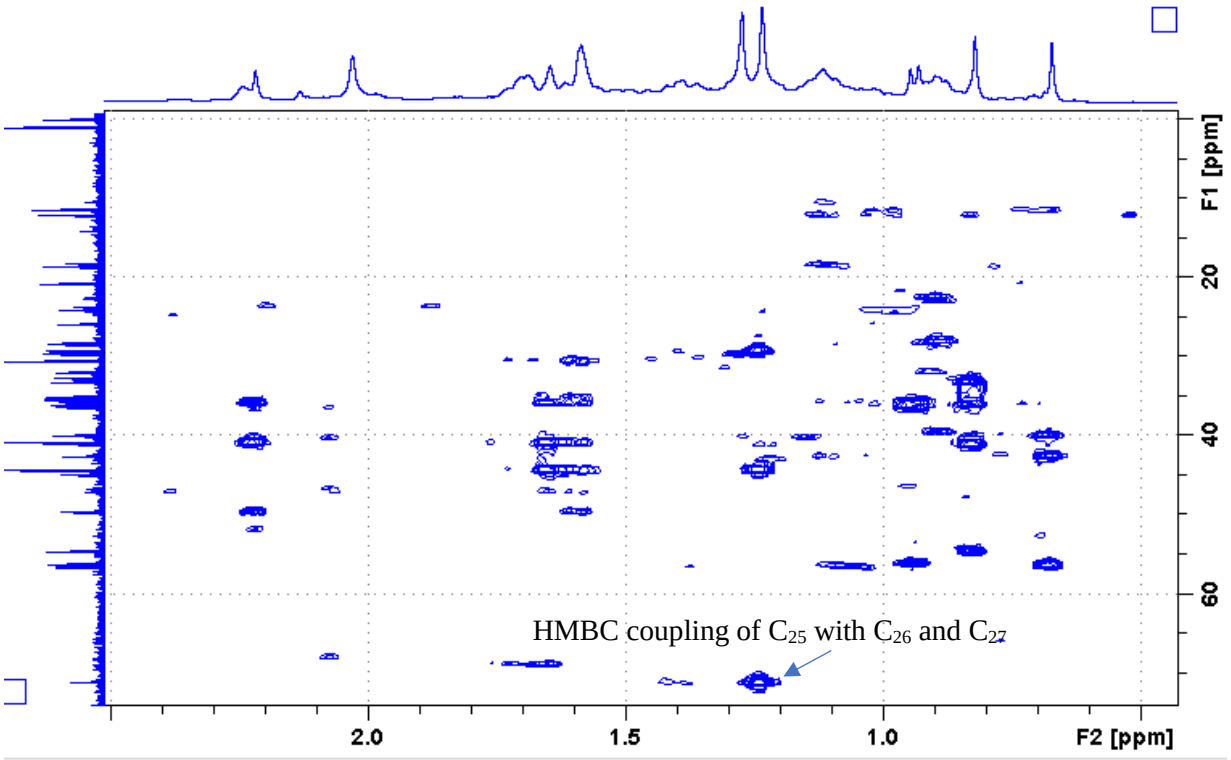


Stacking of ^{1}H-NMR spectra. Note that the most significant shifts from **S11** to **1a** correspond to C_{26} and C_{27}, C_{25} and C_{24}.

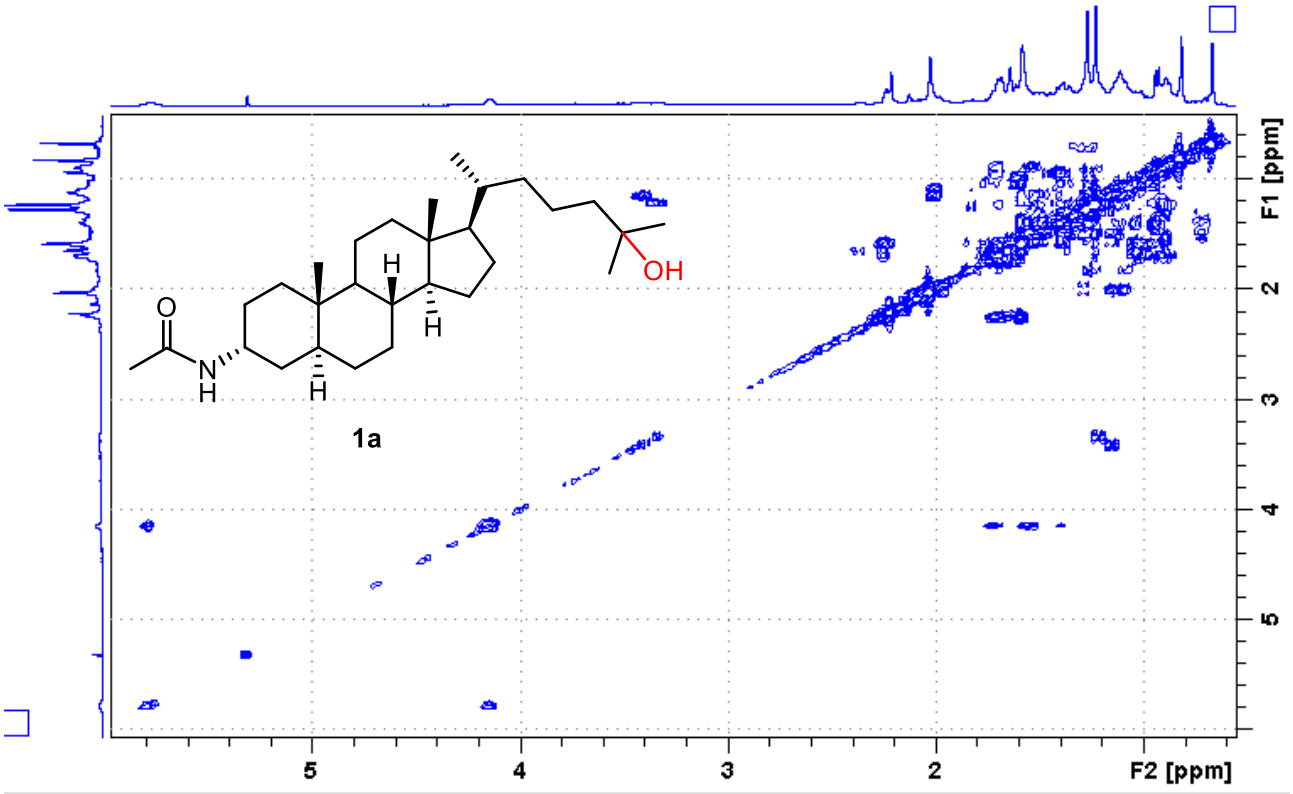
HSQC of **1a**



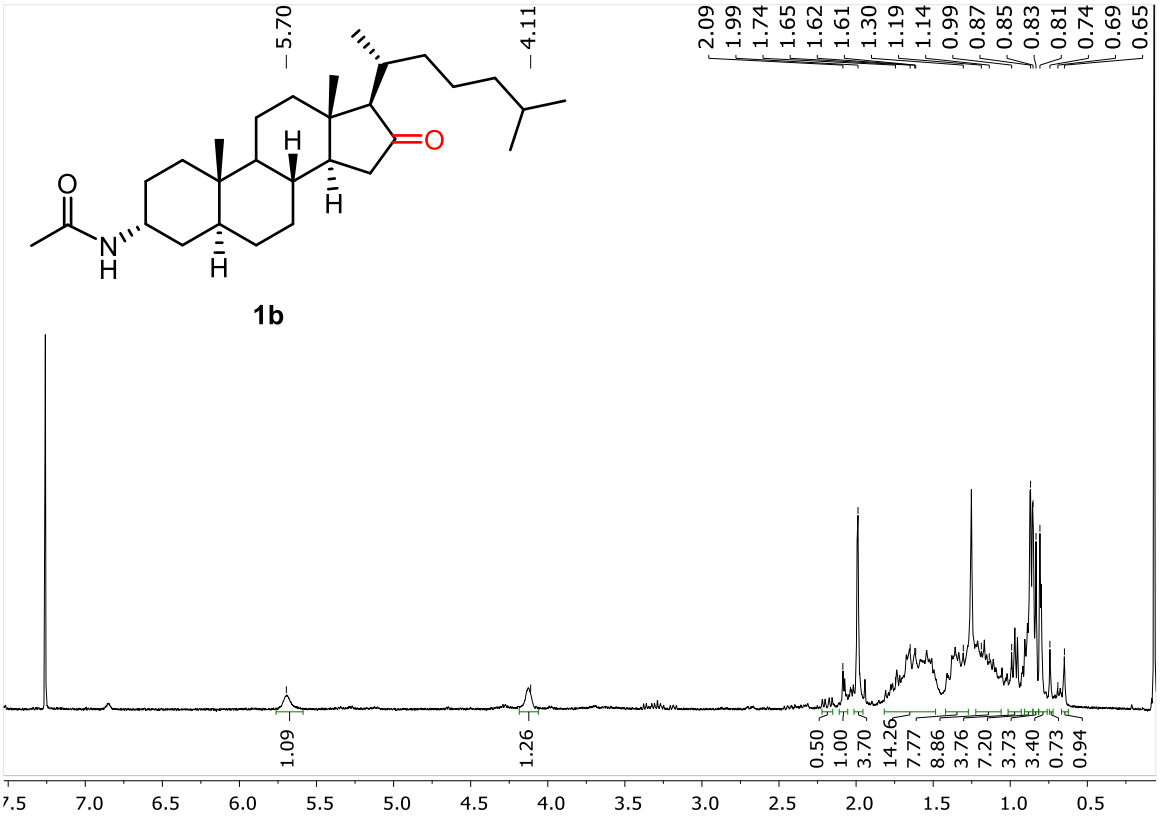
HMBC of **1a**



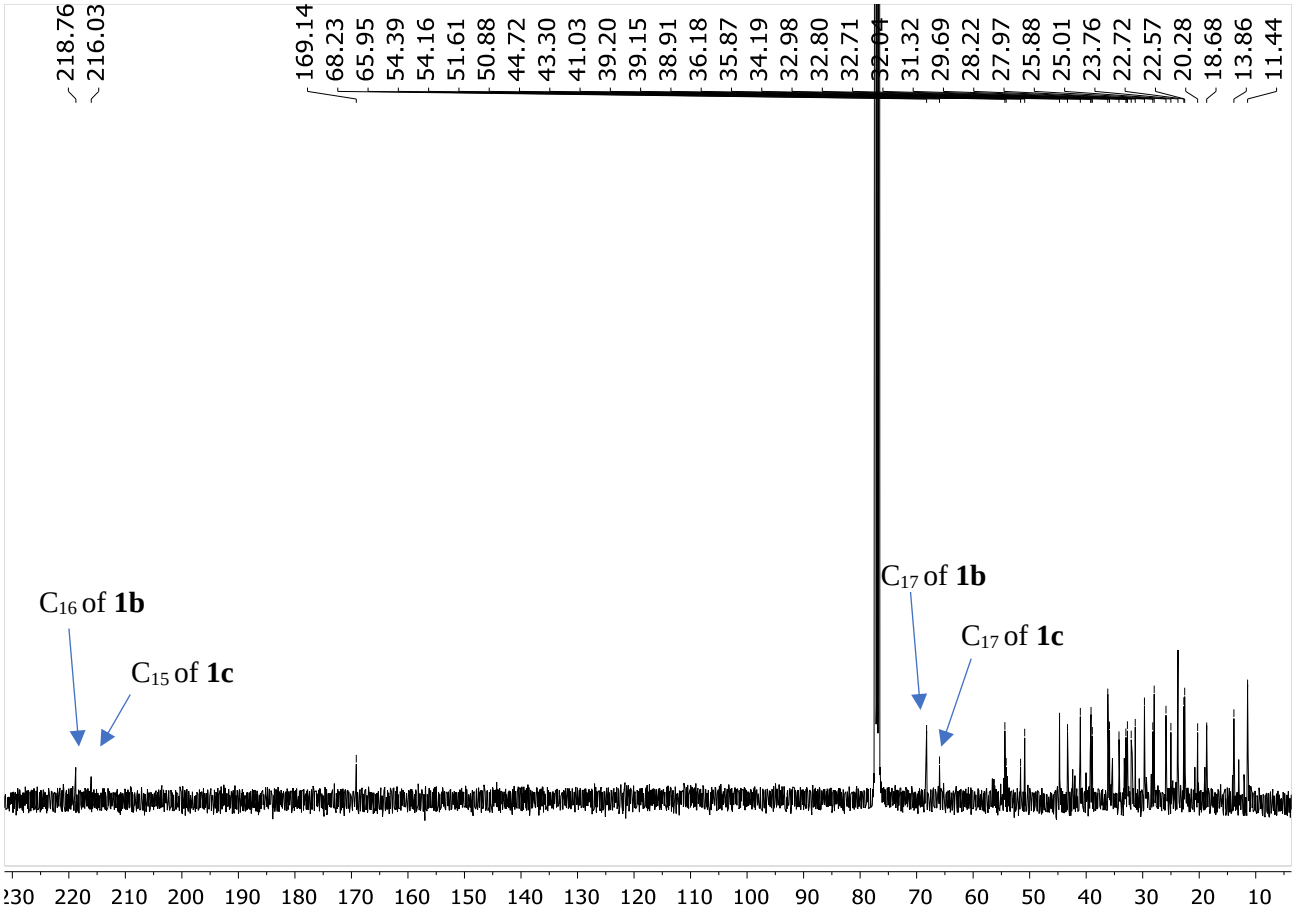
COSY of **1a**



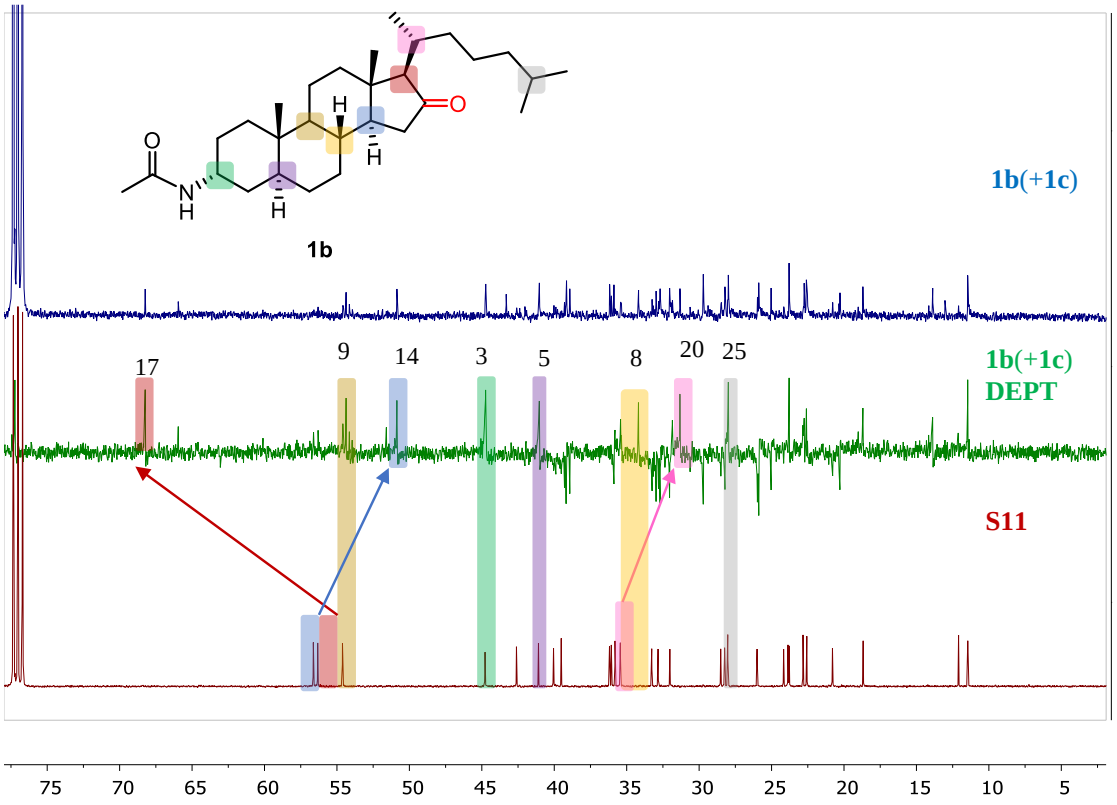
^{1}H-NMR spectrum of **1b** (2:1 mixture with **1c** and residues of **S11**)



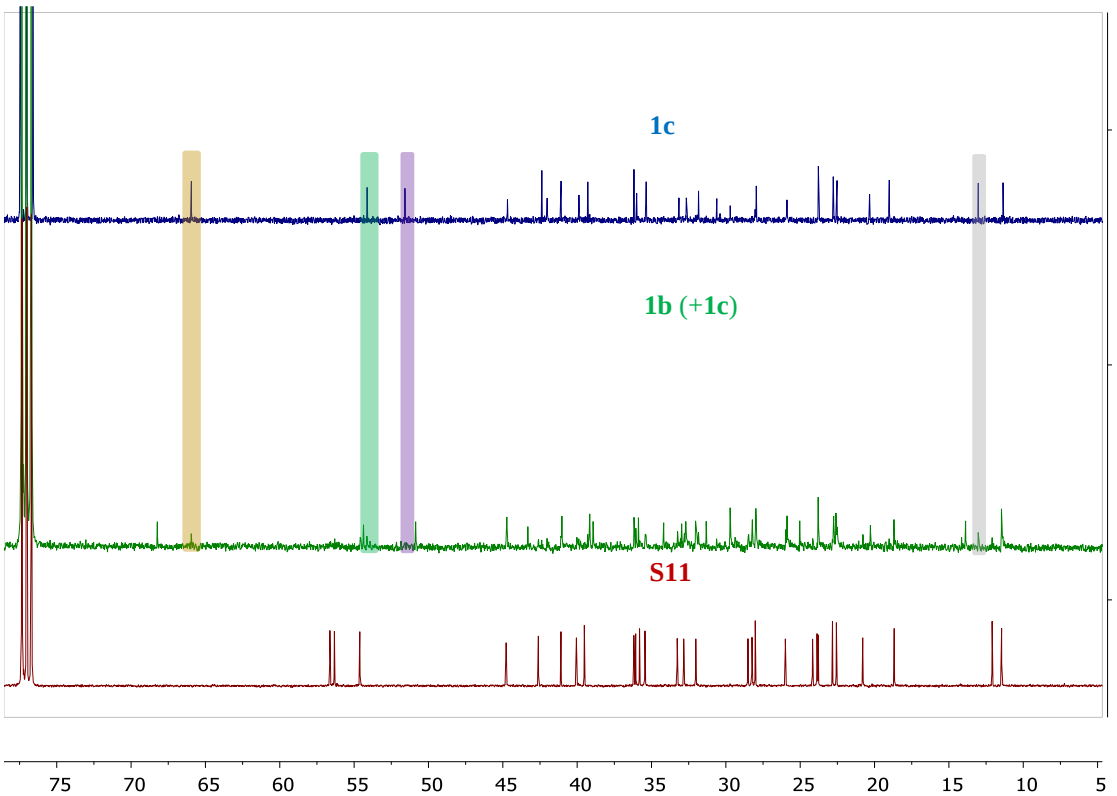
^{13}C-NMR spectrum of **1b**



Comparison of ^{1}H and ^{13}C NMR spectra of **1b**, DEPT of **1b**, **S11** and **1c**

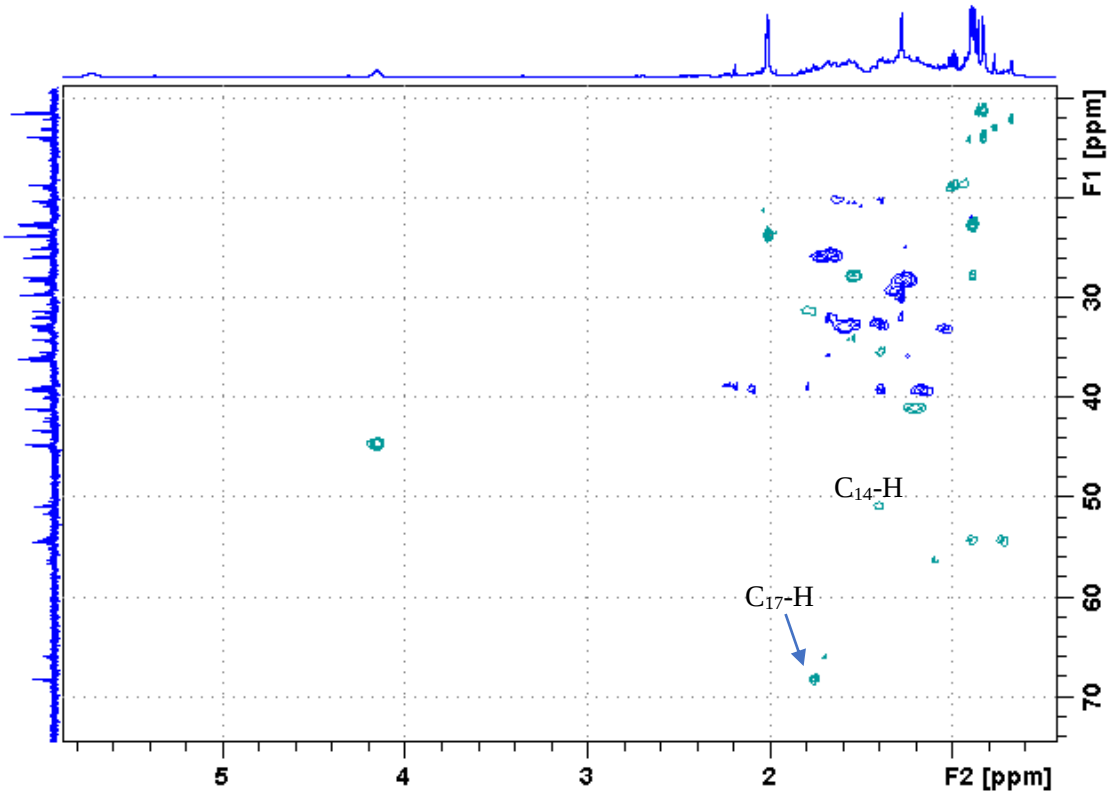


Stacking of ^{13}C-NMR spectra of **1b**, its DEPT 145° and **S11**. Note that the only tertiary C-H bonds (evidenced by DEPT and colored) experiencing significant shifts compared to **S11** are close to ring D (C_{17}, C_{14} and C_{20}).



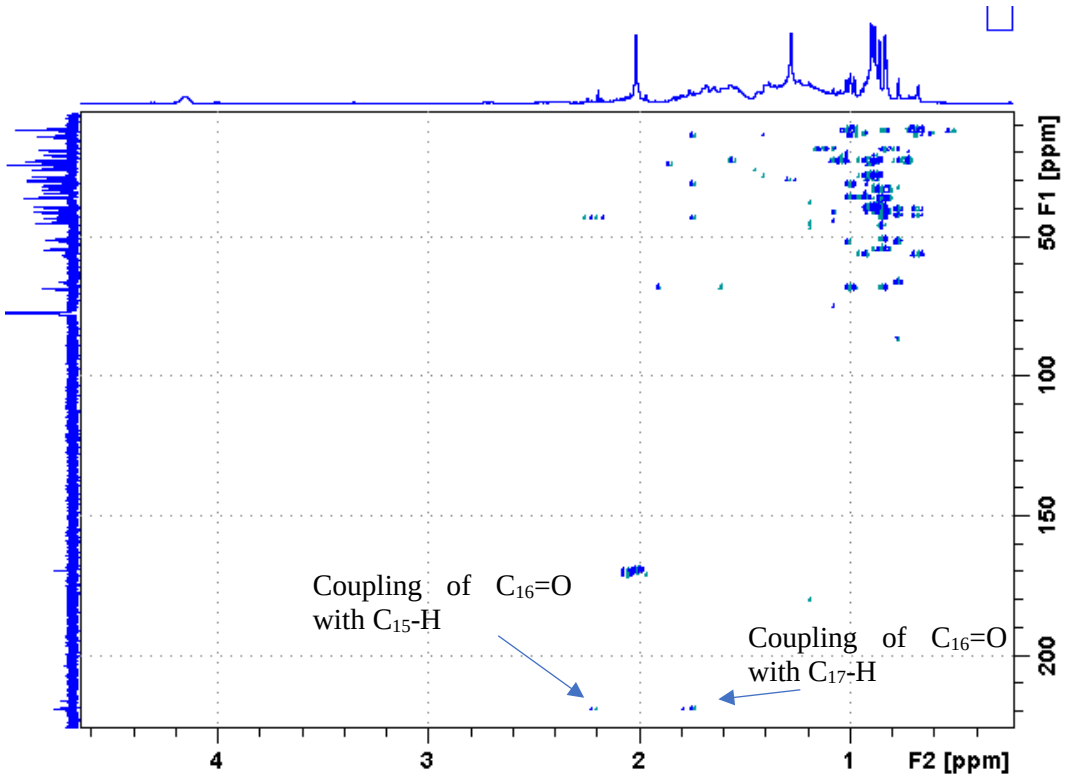
Comparison of the ^{13}C signals of the mixture of **1b**:**1c** with those of **S11** and **1c**. Note that the minor component of the mixture has the same signals of **1c**.

HSQC of **1b**

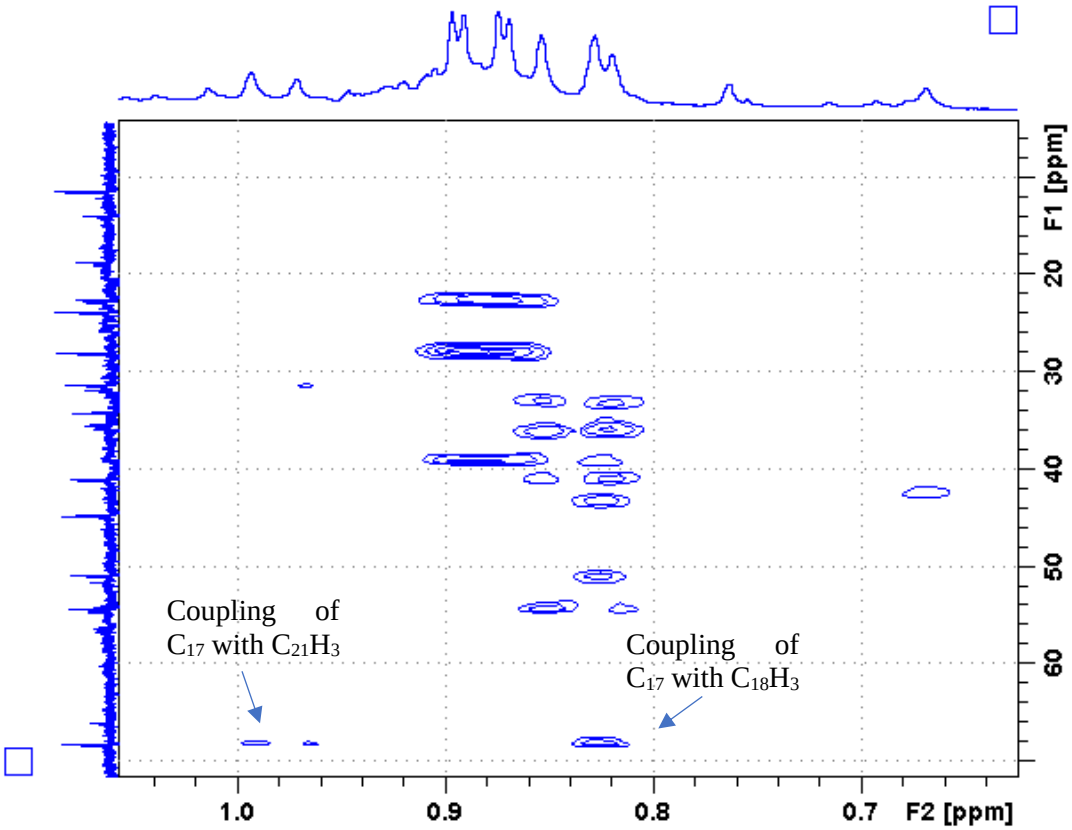


Note that the signal at 68 ppm corresponds to a C-H (C_{17}-H).

HMBC of **1b**

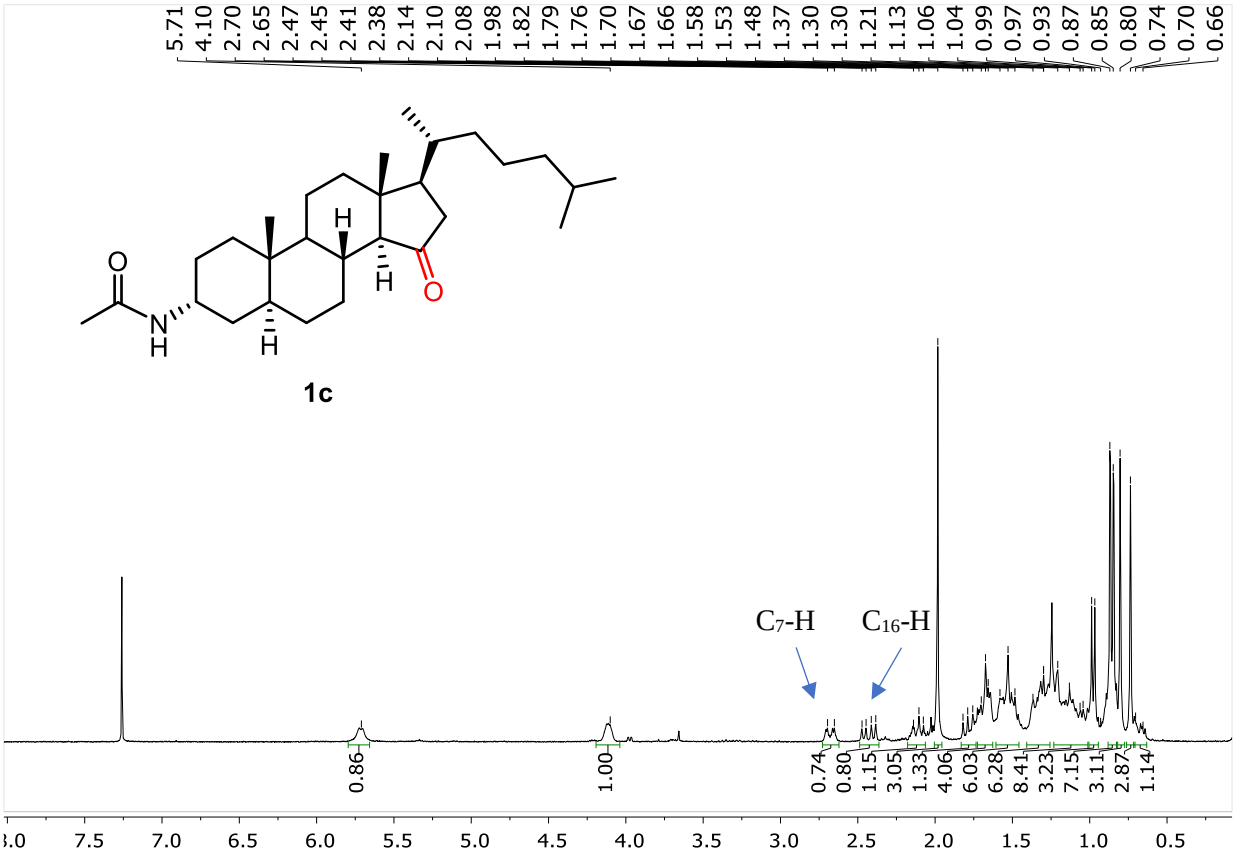


Enlargement of the HMBC spectrum of **1b** (coupling with methyls).

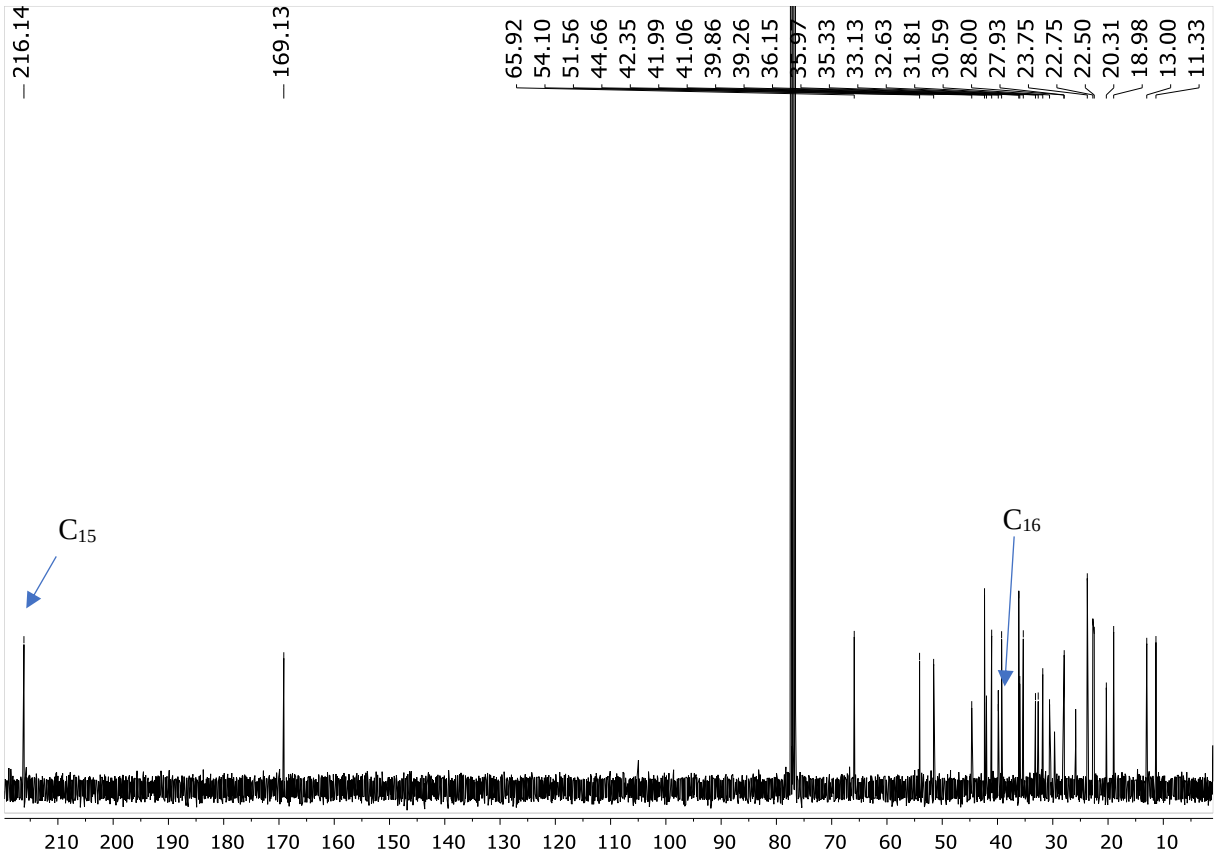


Note the coupling of the signal at 68 ppm with both $C_{18}H_3$ and $C_{21}H_3$, that unequivocally assign it to C_{17}-H.

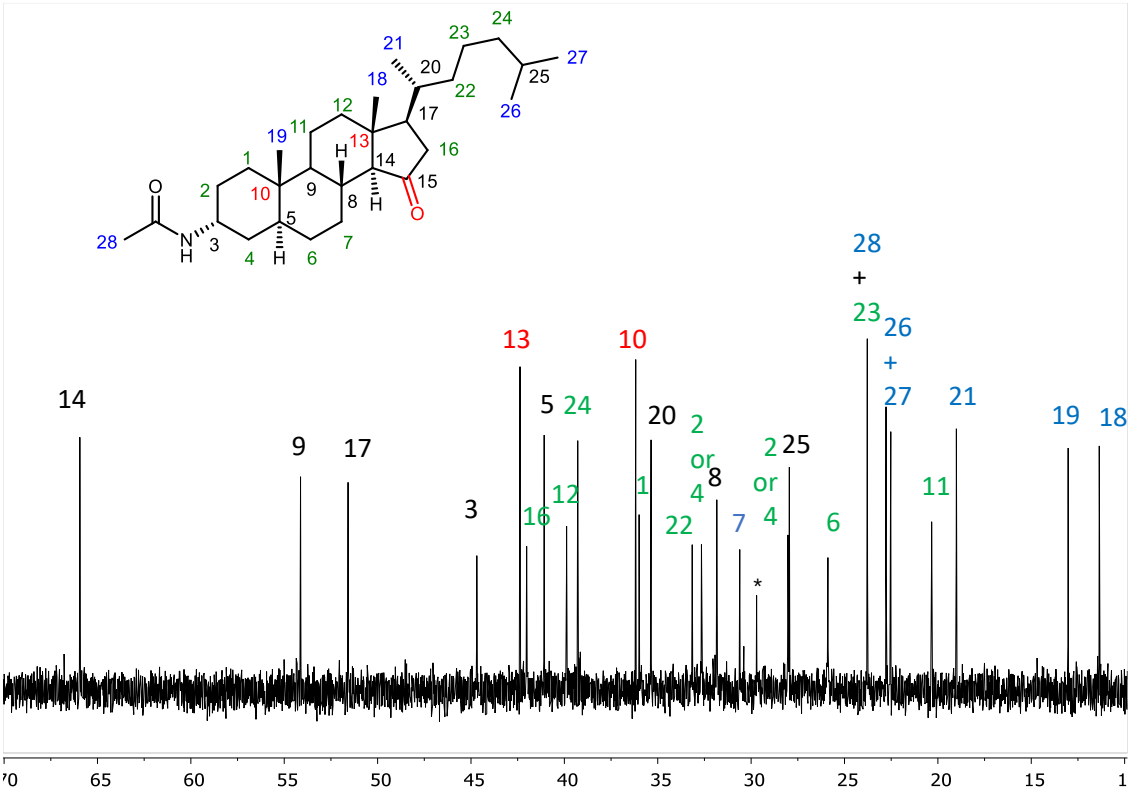
^{1}H-NMR spectrum of **1c**



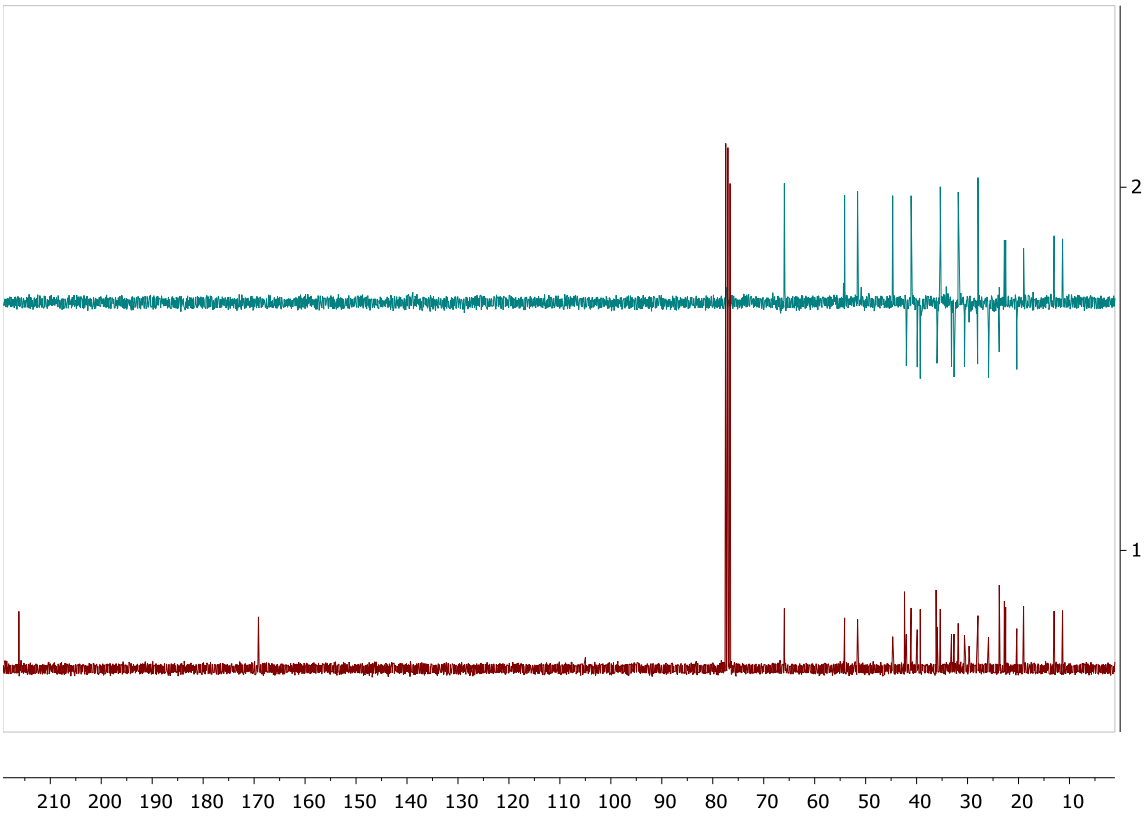
^{13}C-NMR spectrum of **1c**



Assignment of the ^{13}C-NMR signals of **1c** (purity 88% analyzed by GC)

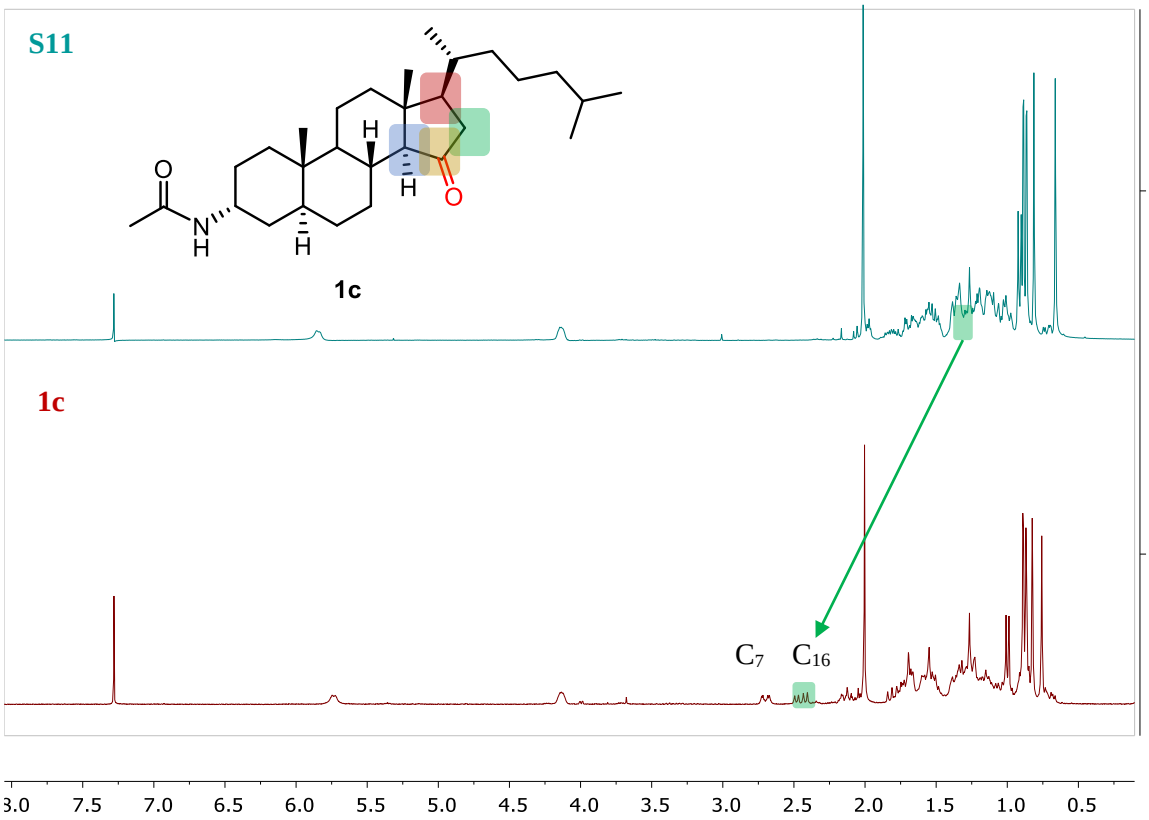


The peak marked with an asterisk is acetone. Assignment made on the basis of HSQC, HMBC, COSY and TOCSY analysis.

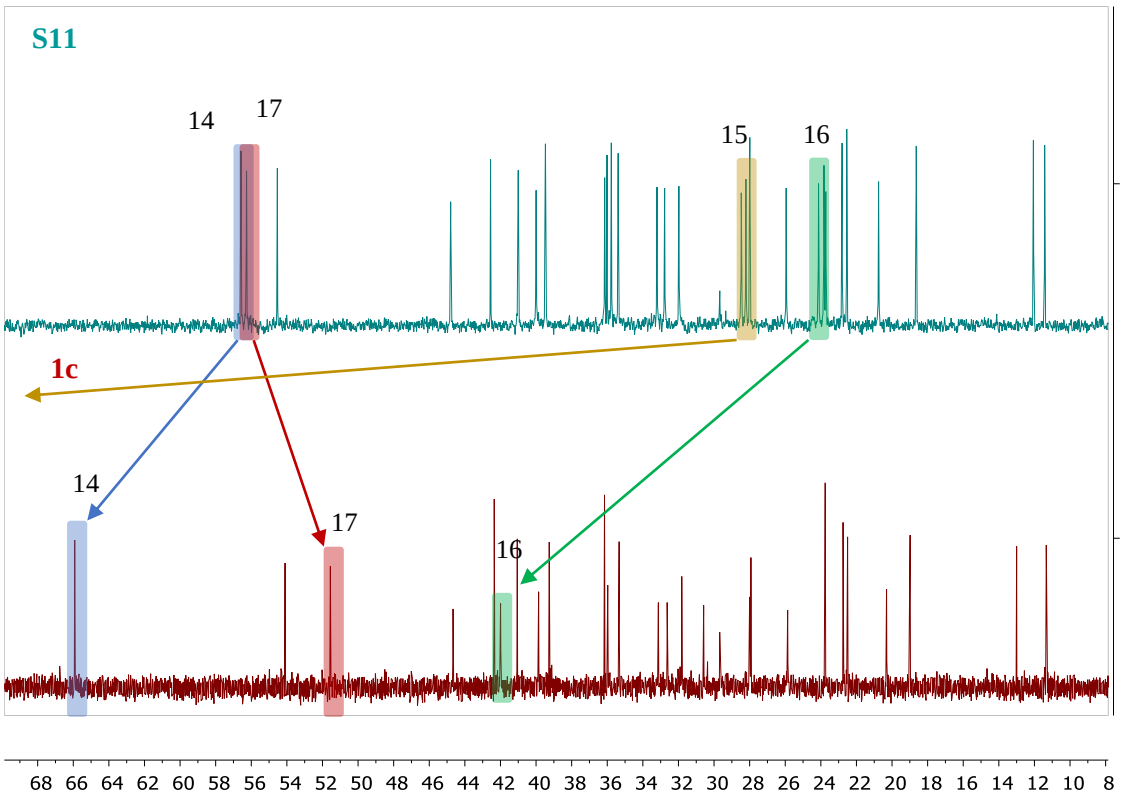


Stacking of the ^{13}C-NMR spectrum (red, bottom) of **1c** with its DEPT-135 spectrum.

Comparison of ^{1}H and ^{13}C NMR spectra of **1c** and **S11**

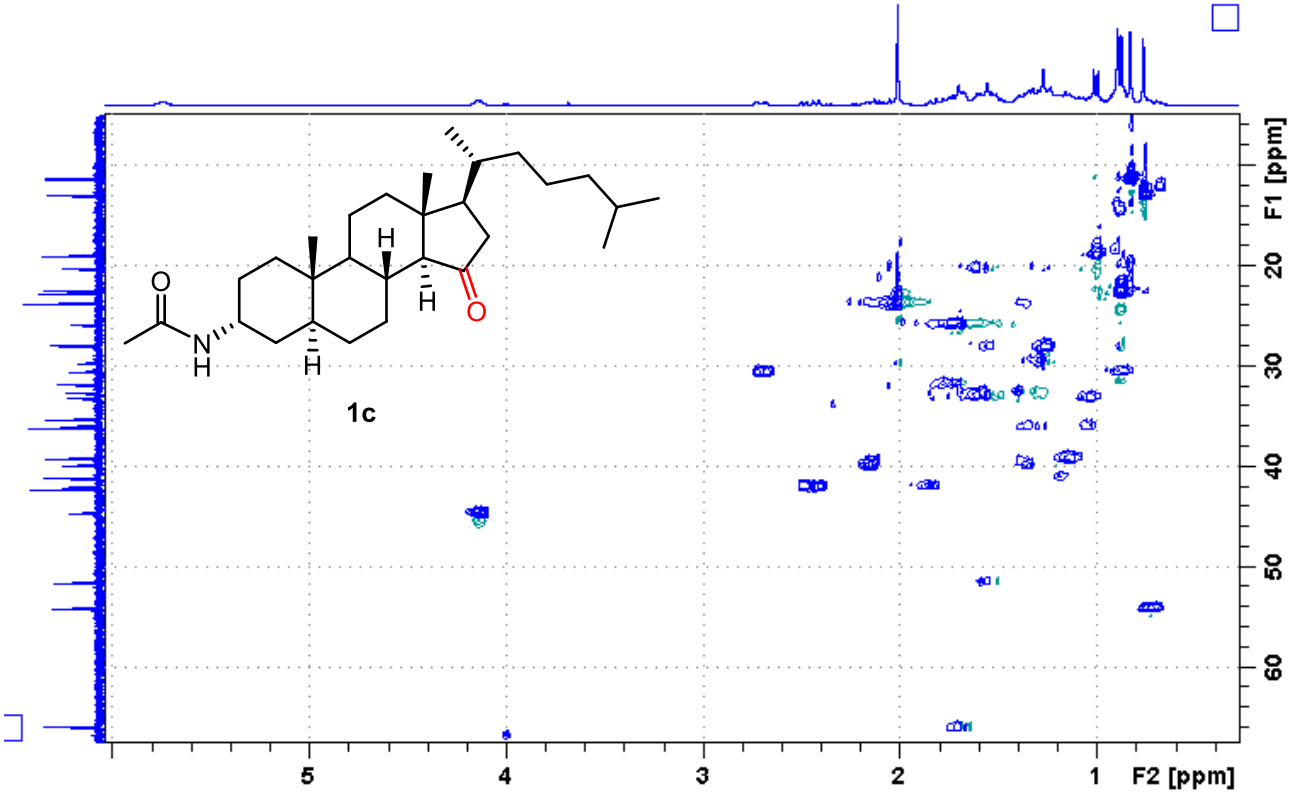


Stacking of ^{1}H-NMR spectra. Note the appearance of new signals in the 2.2-3 ppm region, assigned to C_7-H(β) and C_{16}-H.

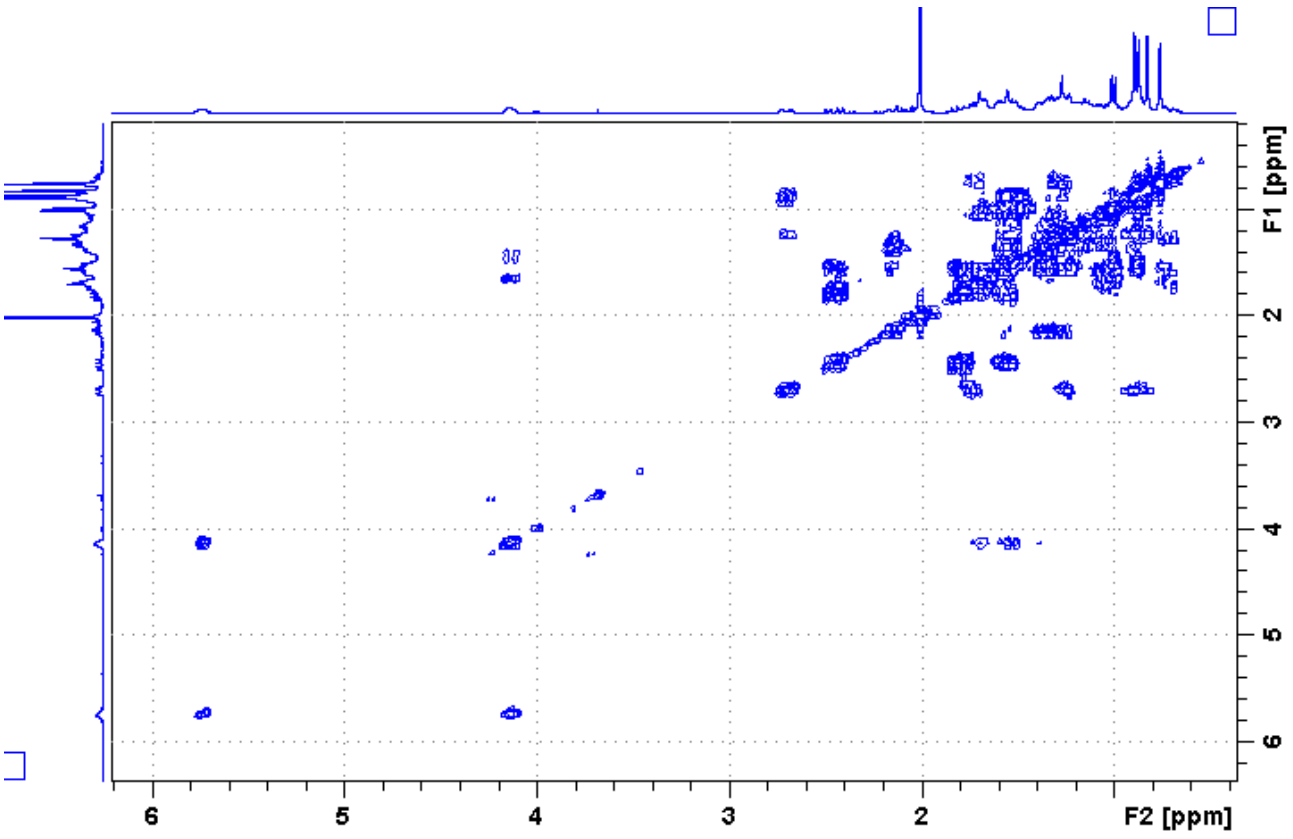


Stacking of the ^{13}C-NMR spectra. Note the shifts of the signals on the D-ring.

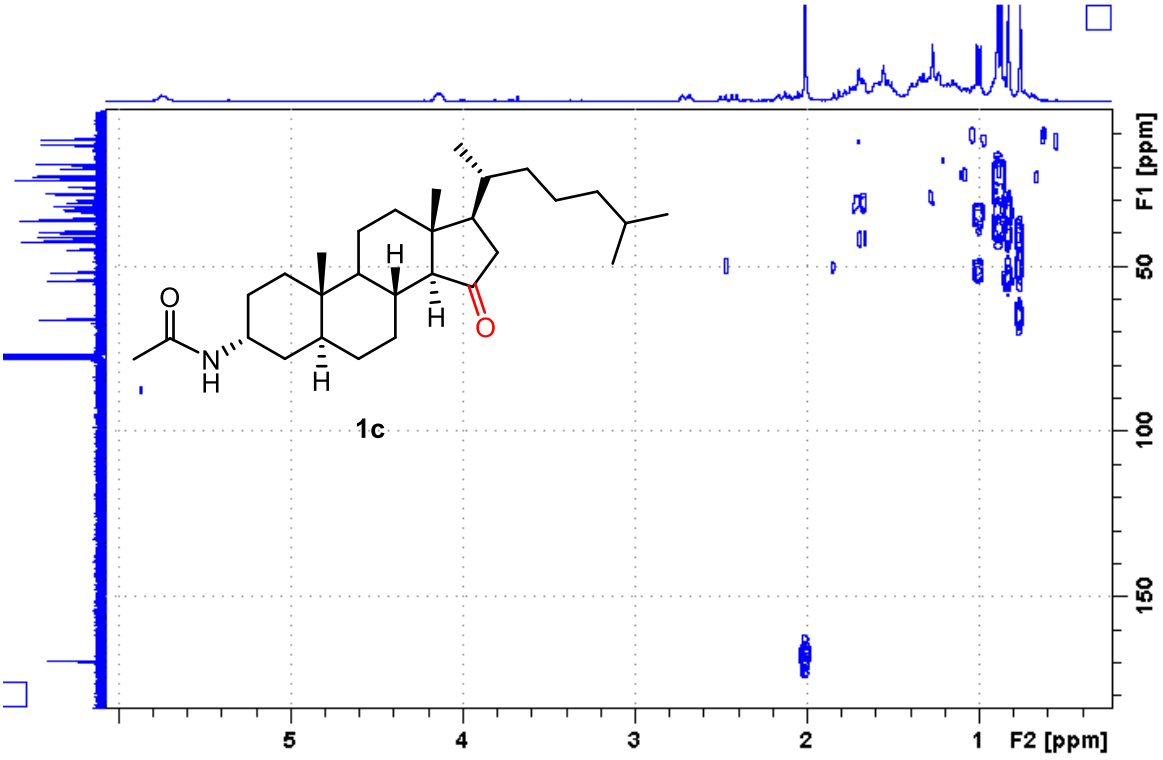
HSQC of **1c**



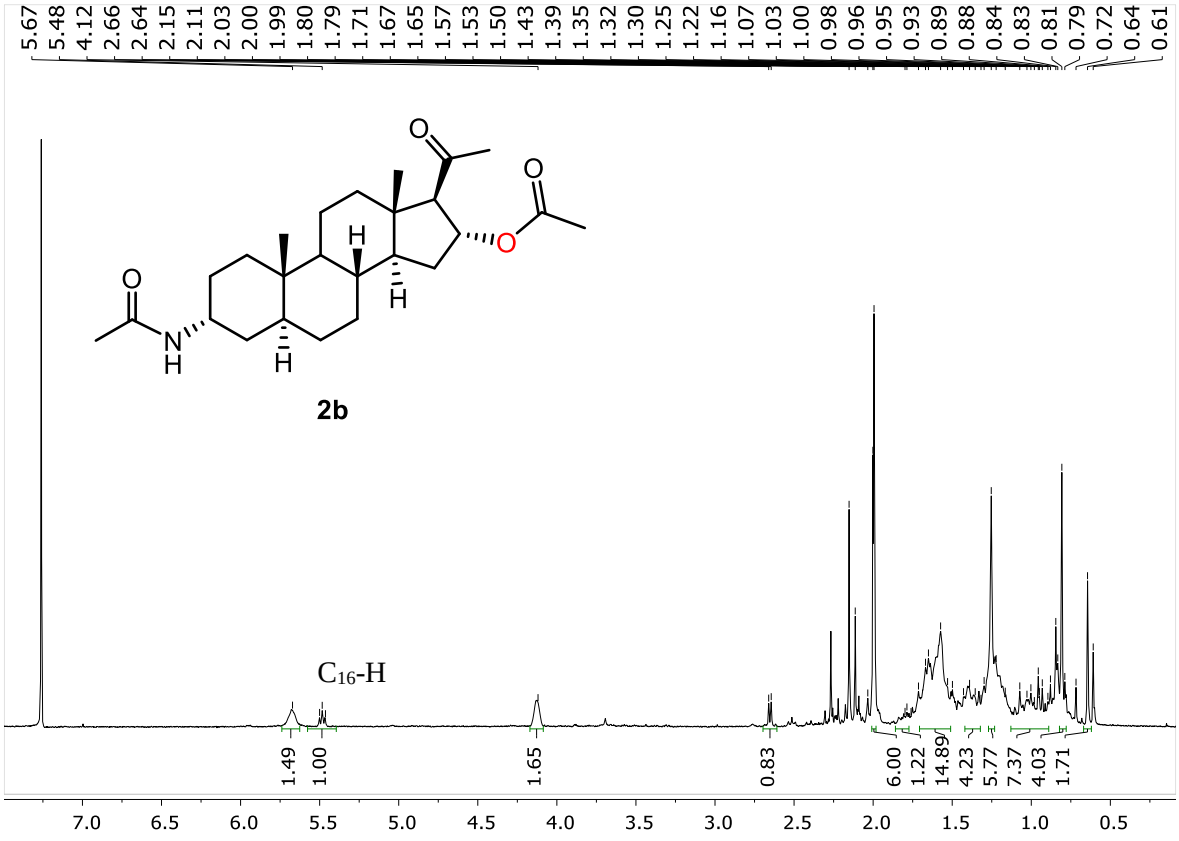
COSY of **1c**



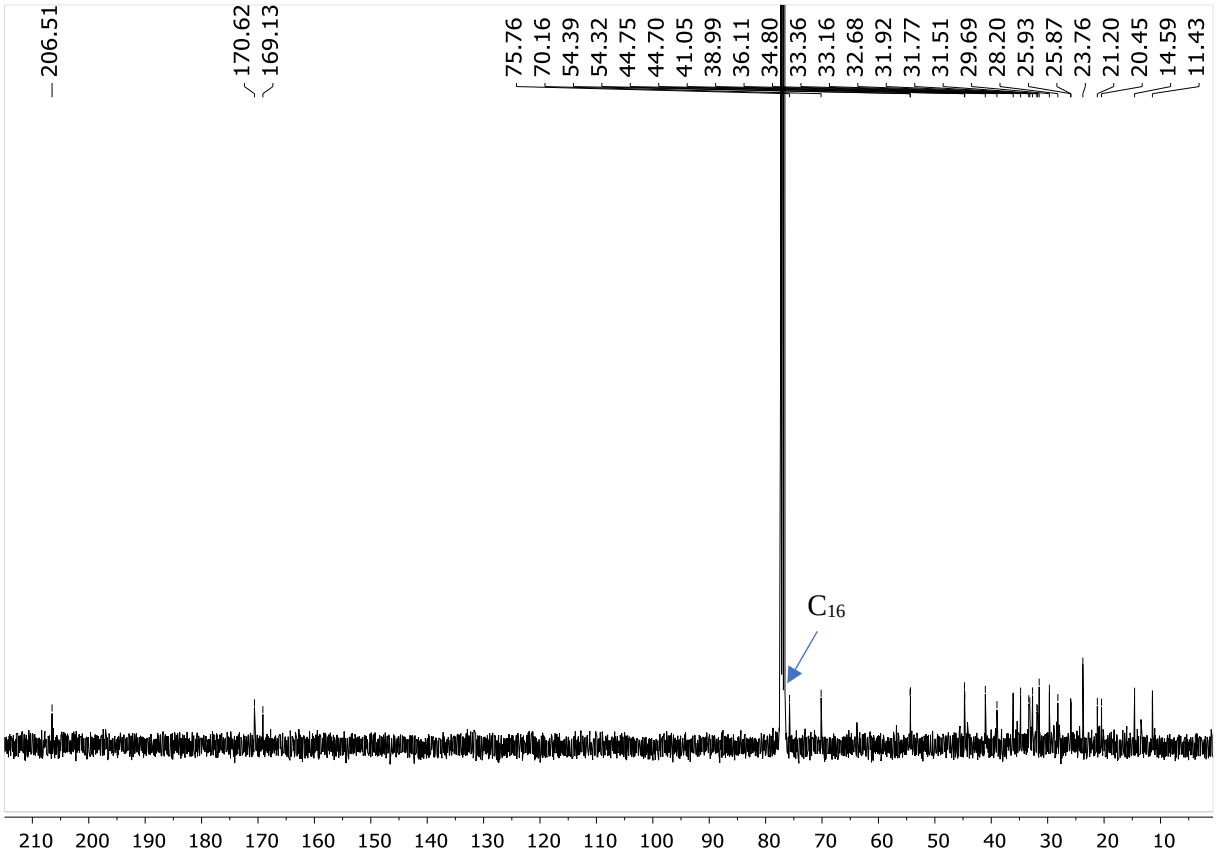
HMBC of **1c**



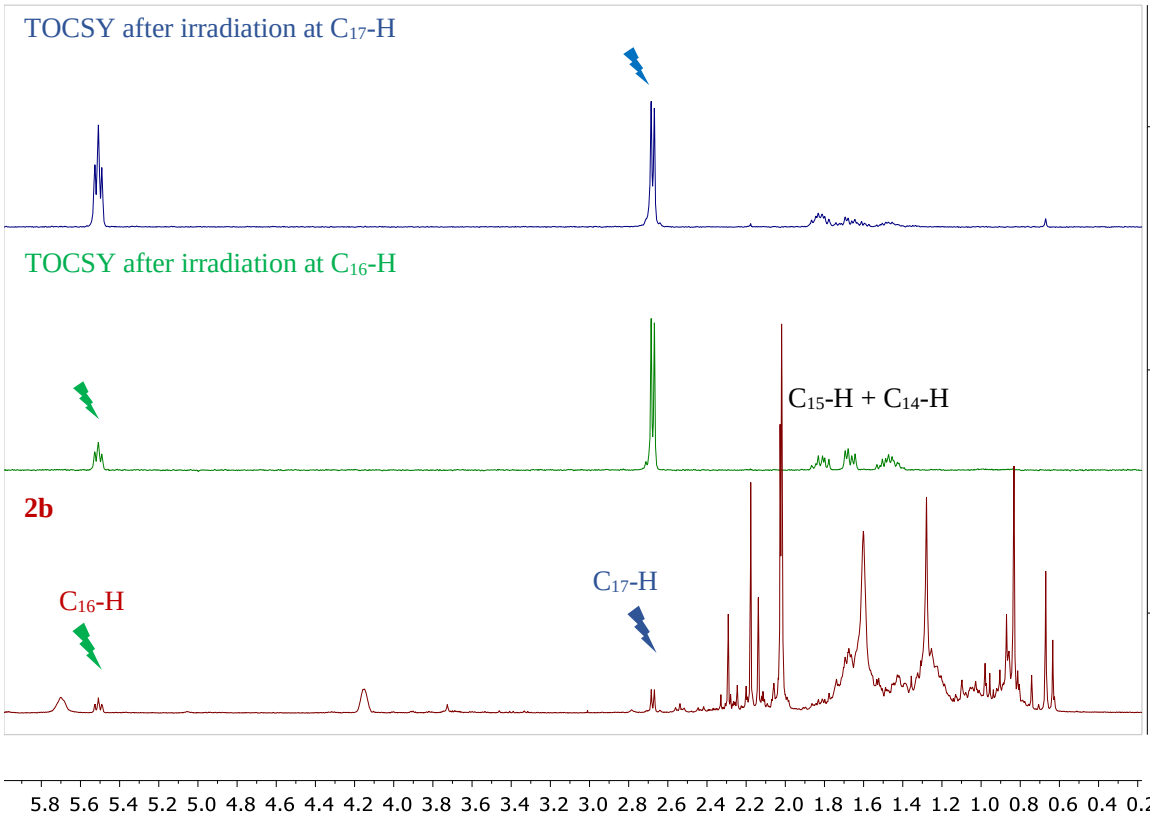
^{1}H-NMR spectrum of **2b**



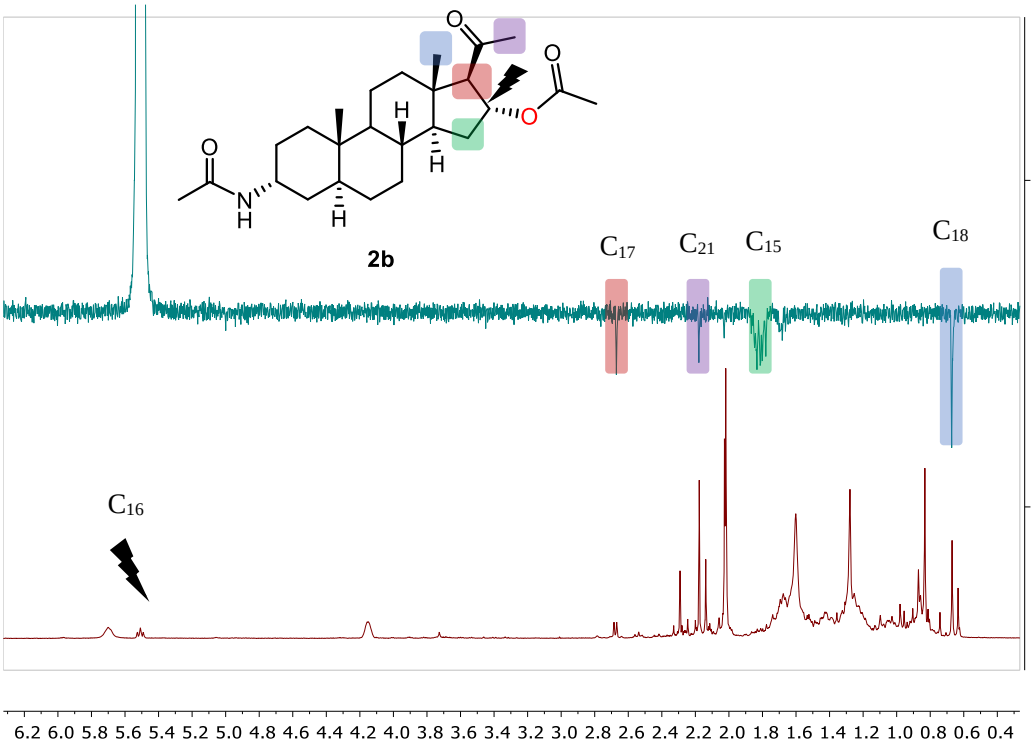
^{13}C-NMR spectrum of **2b**



Spectra obtained after selective irradiation of key signals in **2b**

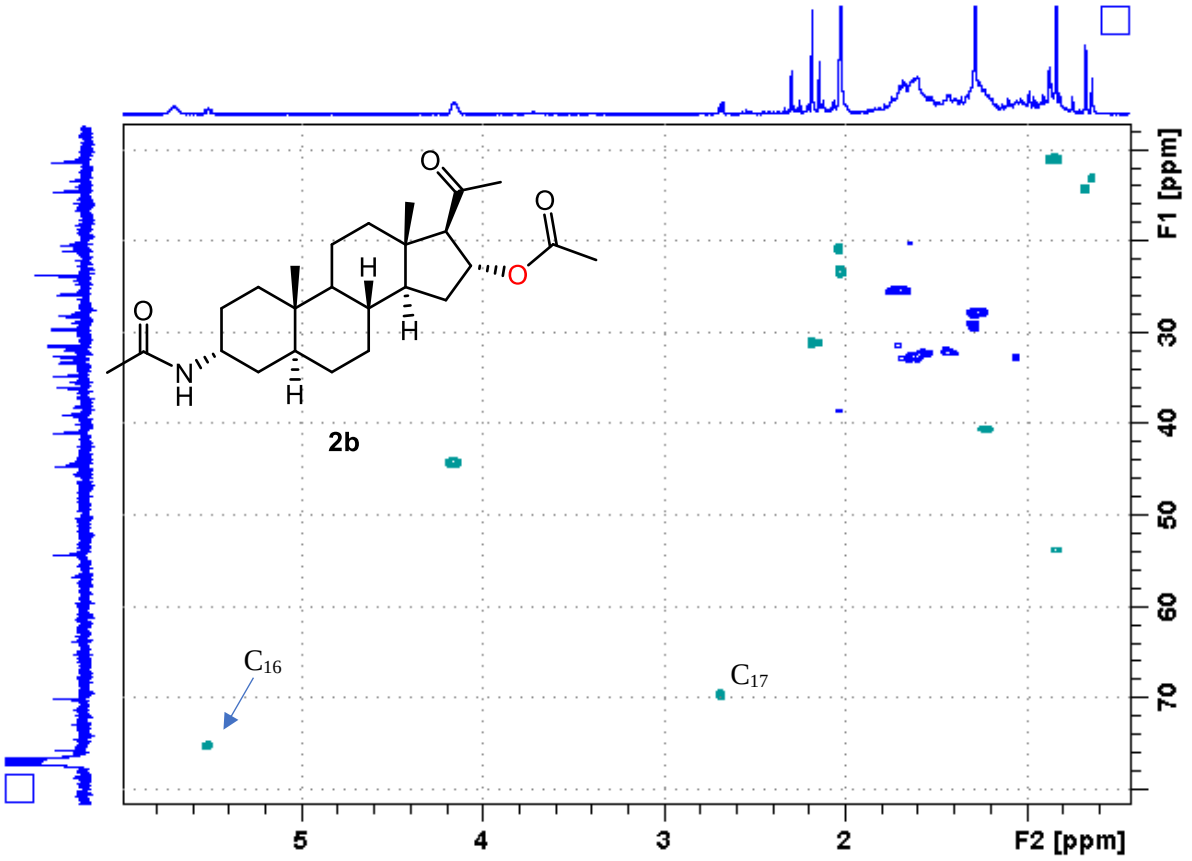


Selective TOCSY spectra. ^{1}H-NMR spectrum of **2b** (red, bottom) with its selective TOCSY spectrum obtained after irradiation at 5.50 ppm (C16-H signal; green spectrum, middle) and at 2.67 (C17-H signal, blue top).

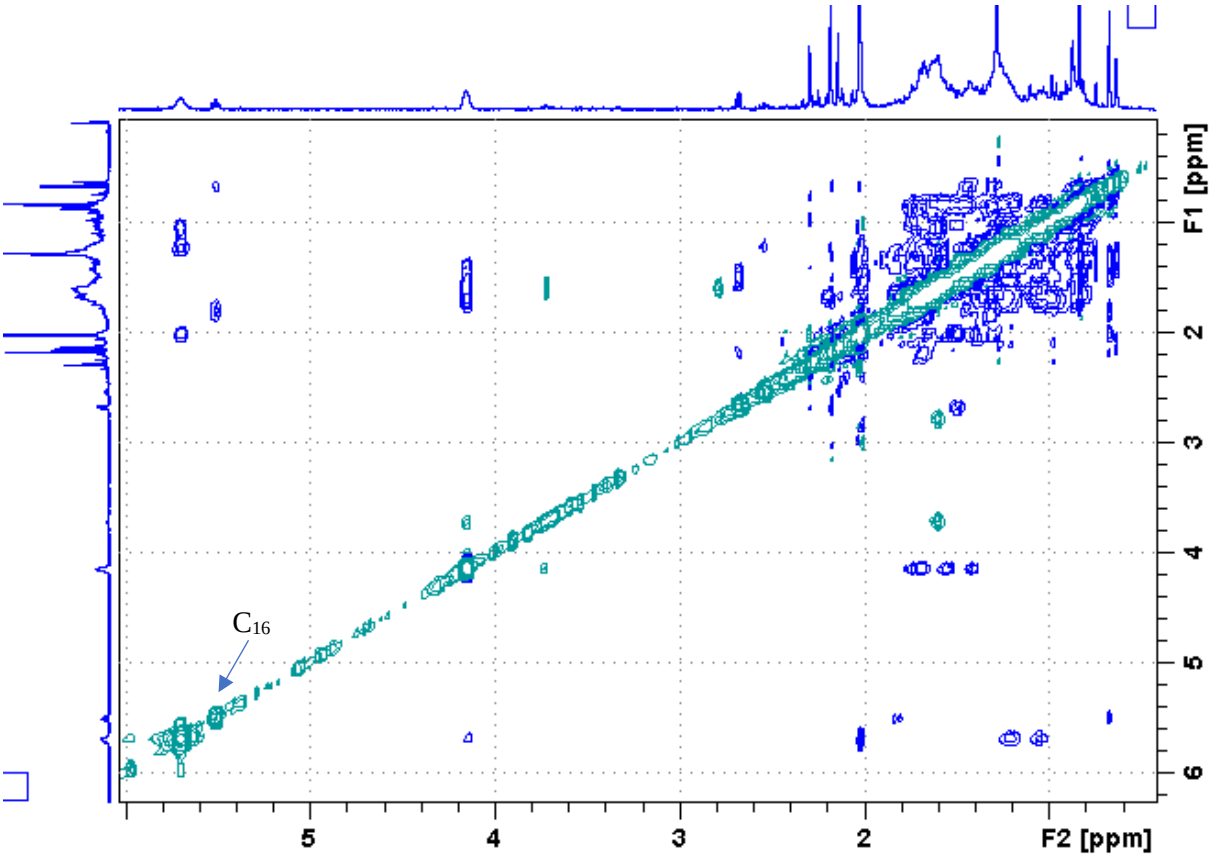


Selective NOESY spectrum (green, top) obtained after irradiation at 5.48 ppm (C16-H) in comparison with the ^{1}H-NMR spectrum of **2b** (red, bottom) with its NOESY correlations.

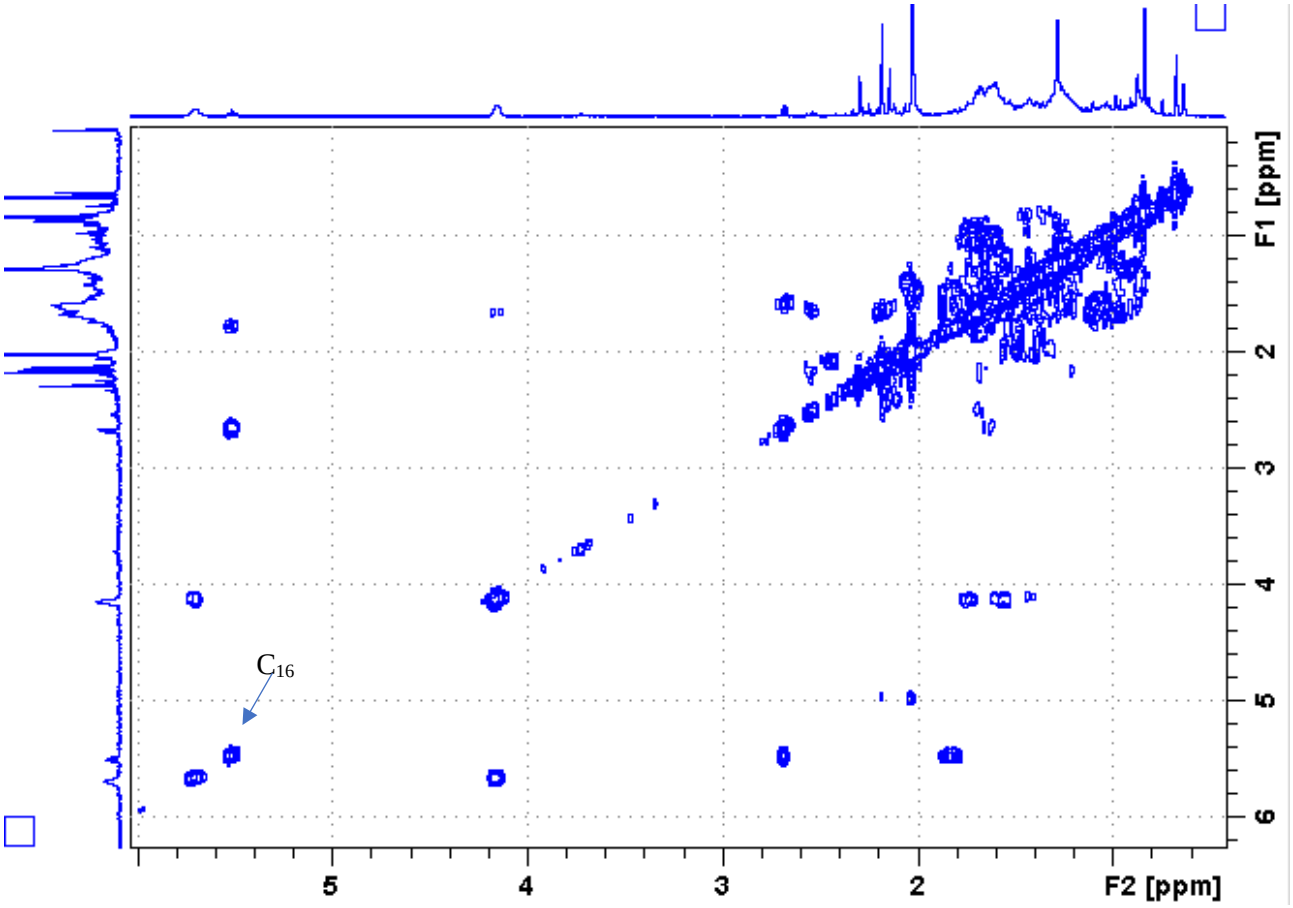
HSQC*ed* of **2b**



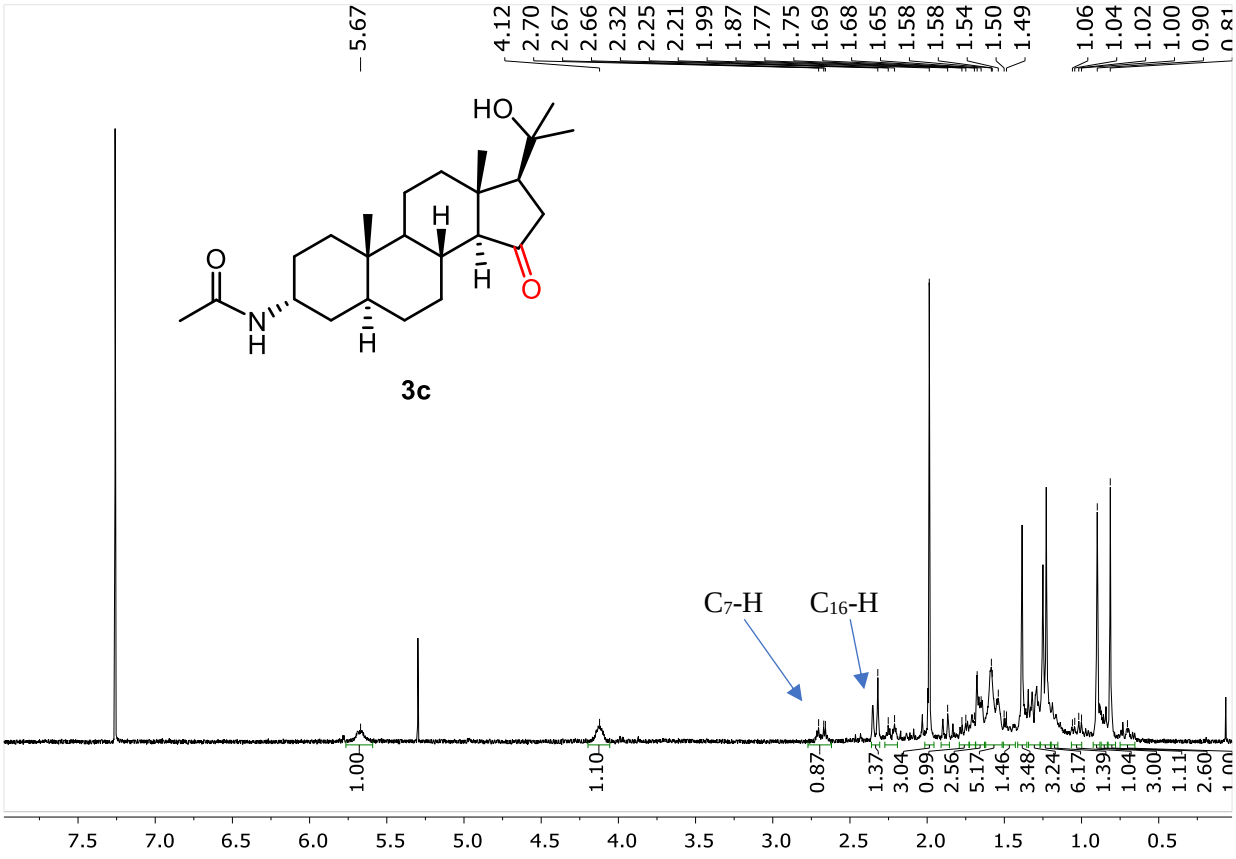
NOESY of **2b**



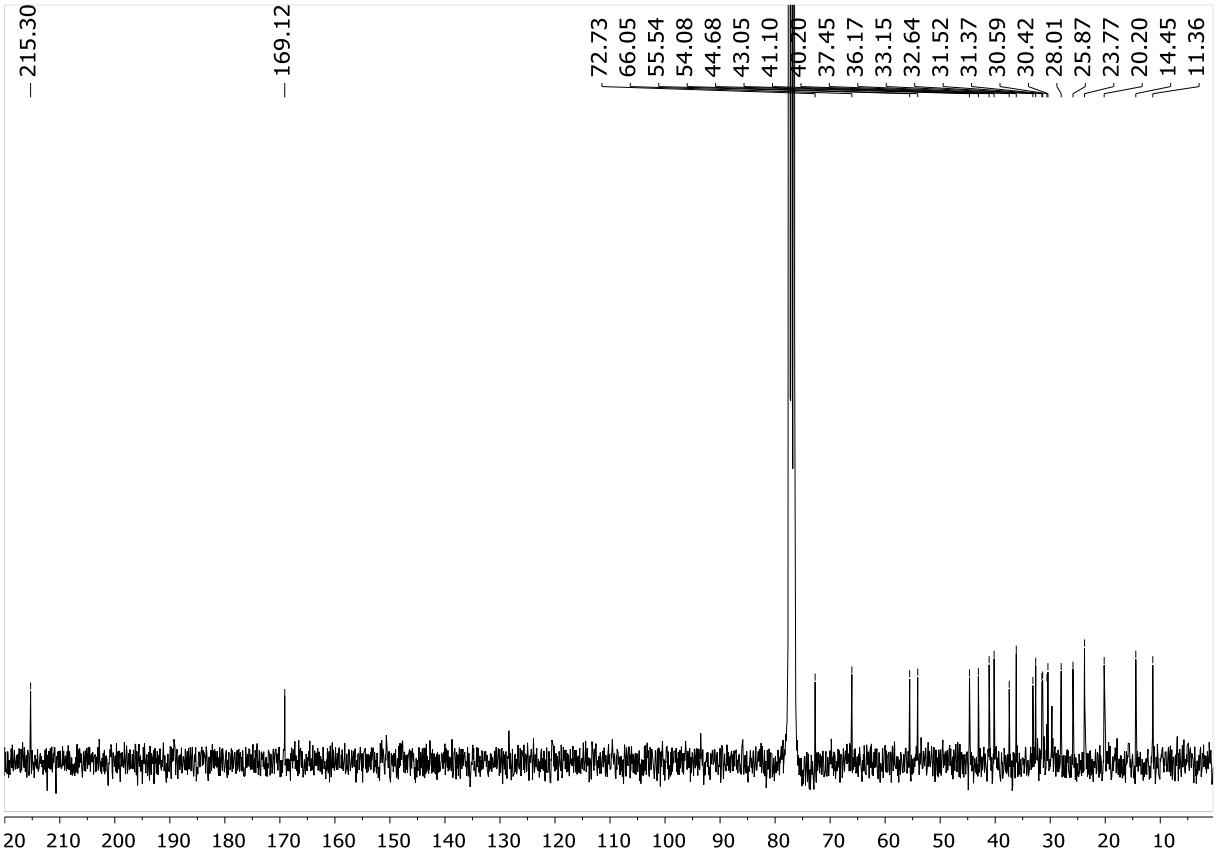
COSY of **2b**



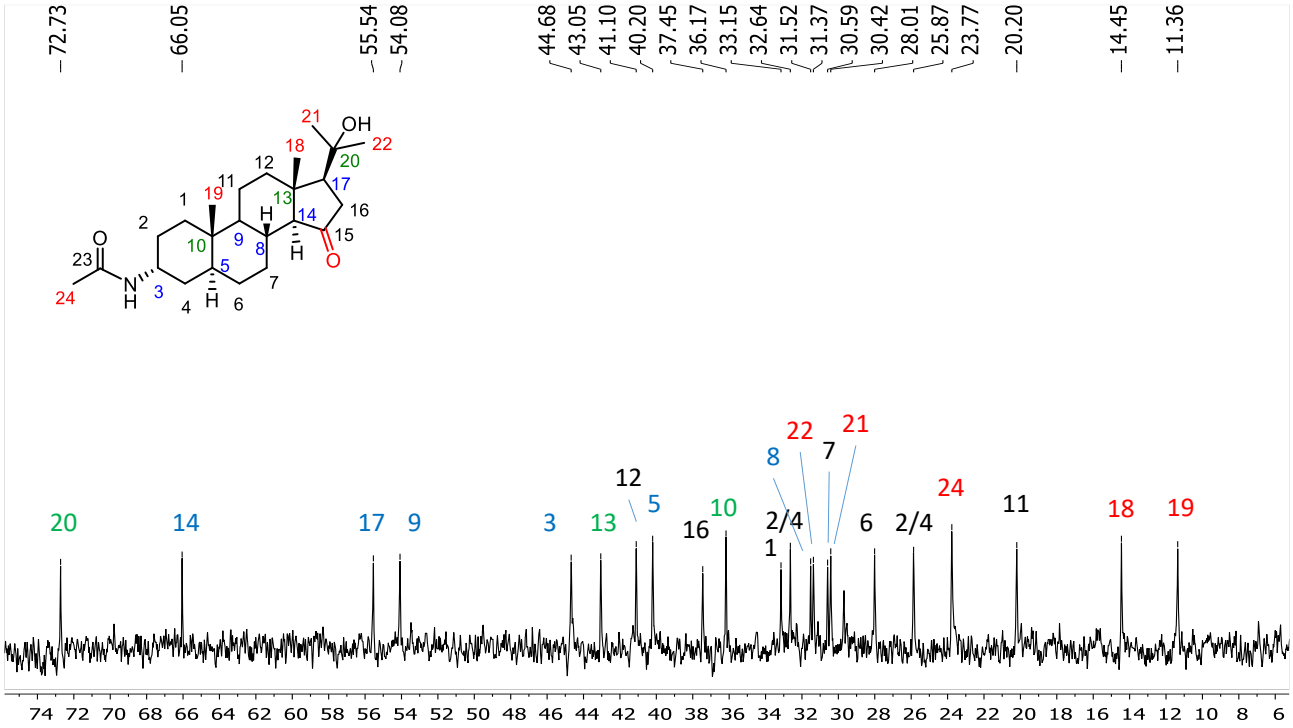
^{1}H-NMR spectrum of **3c**



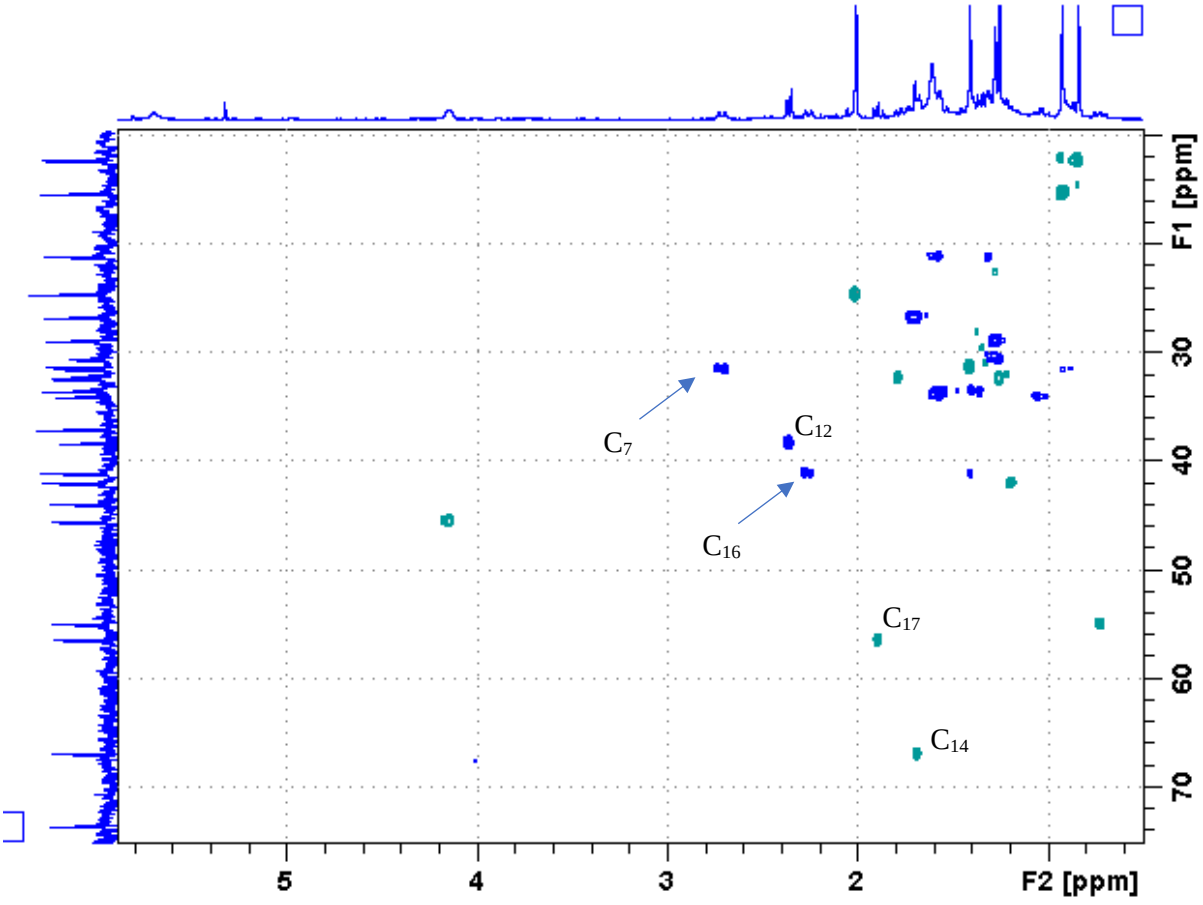
^{13}C-NMR spectrum of **3c**



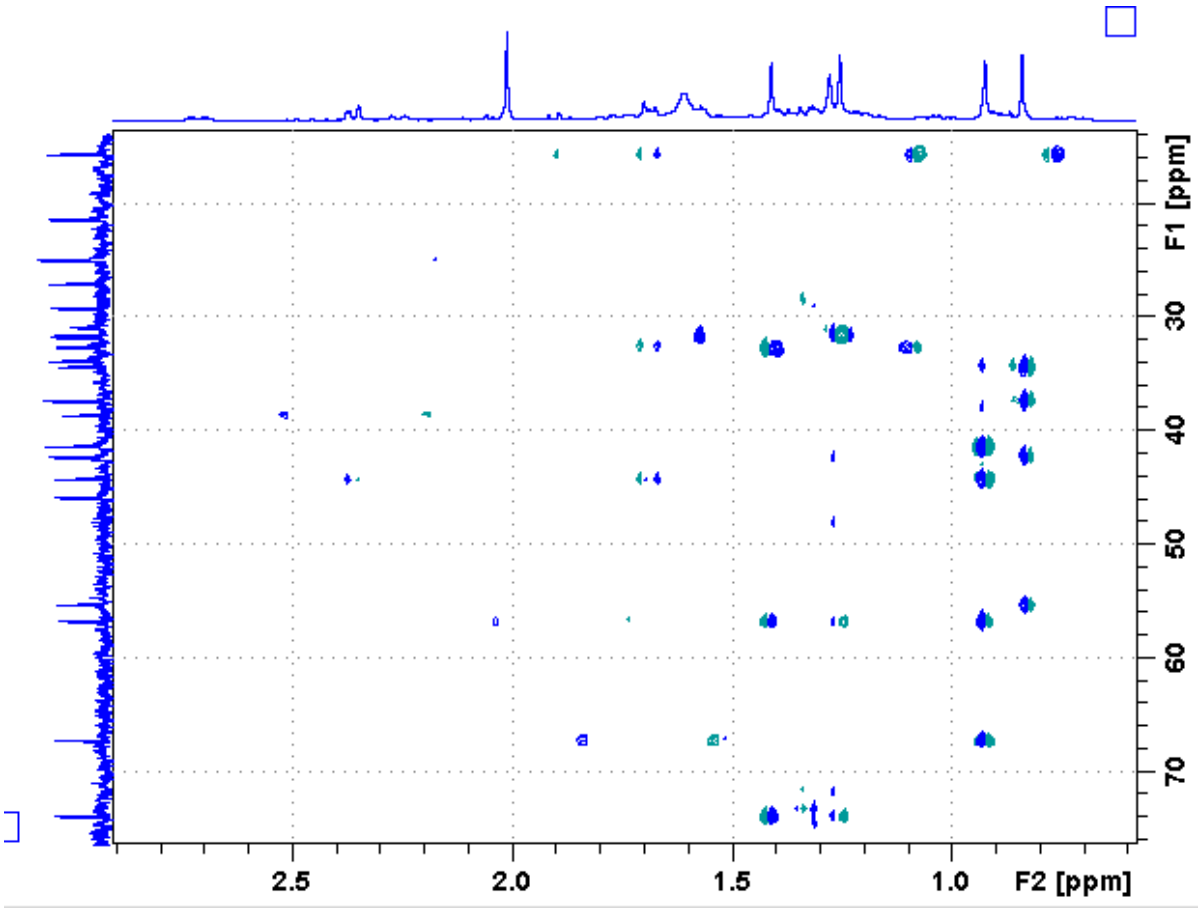
Assignment of the ^{13}C-NMR signals of **3c**



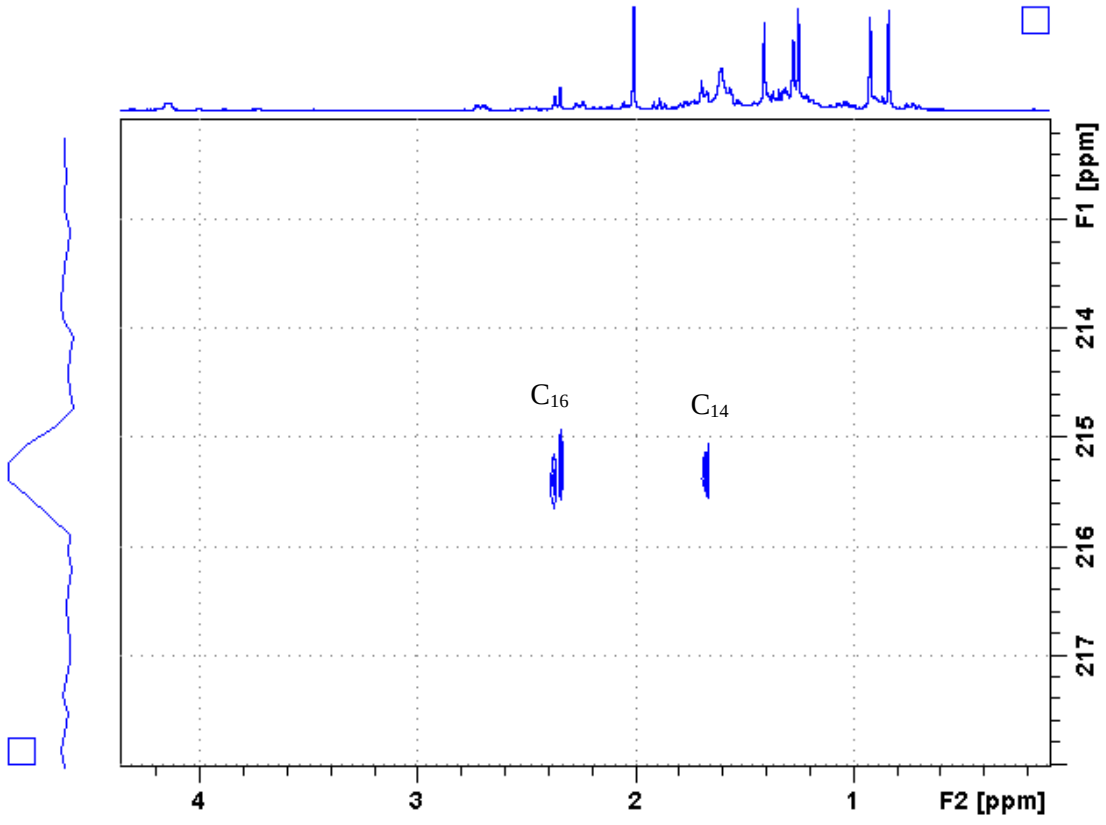
HSQC*ed* of **3c**



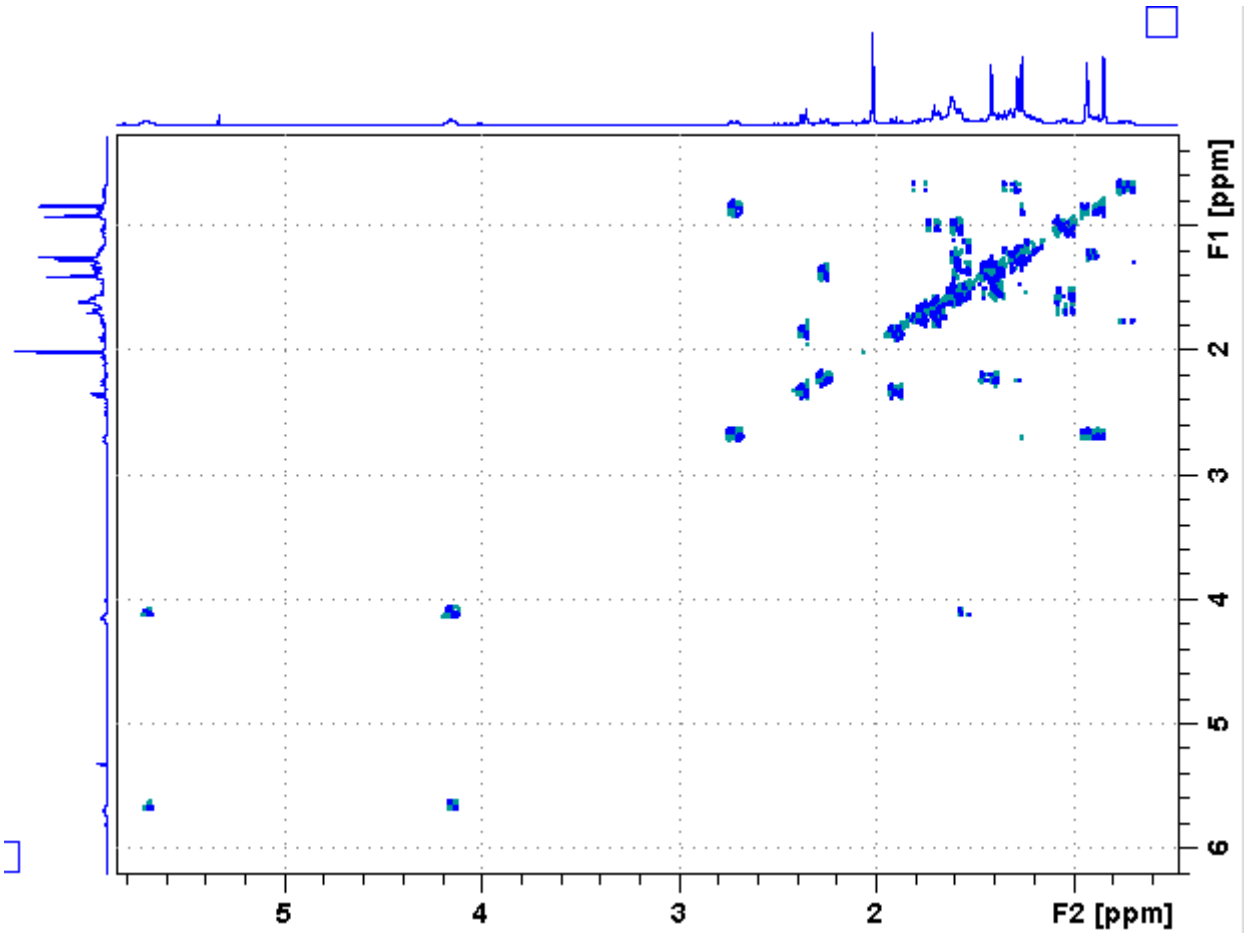
HMBC of **3c**



Selective HMBC of **3c** after irradiation at 215 ppm



COSY of **3c**



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