Towards an Efficient Synthesis of Taxane Analogs by Dienyne Ring Closing Metathesis

*María José Aldegunde, Luis Castedo, Juan R. Granja**

Departamento de Química Orgánica, Laboratorios del CSIC, Facultad de Química, Universidad de Santiago, 15782 Santiago de Compostela (Spain).

qojuangg@usc.es

SUPPORTING INFORMATION

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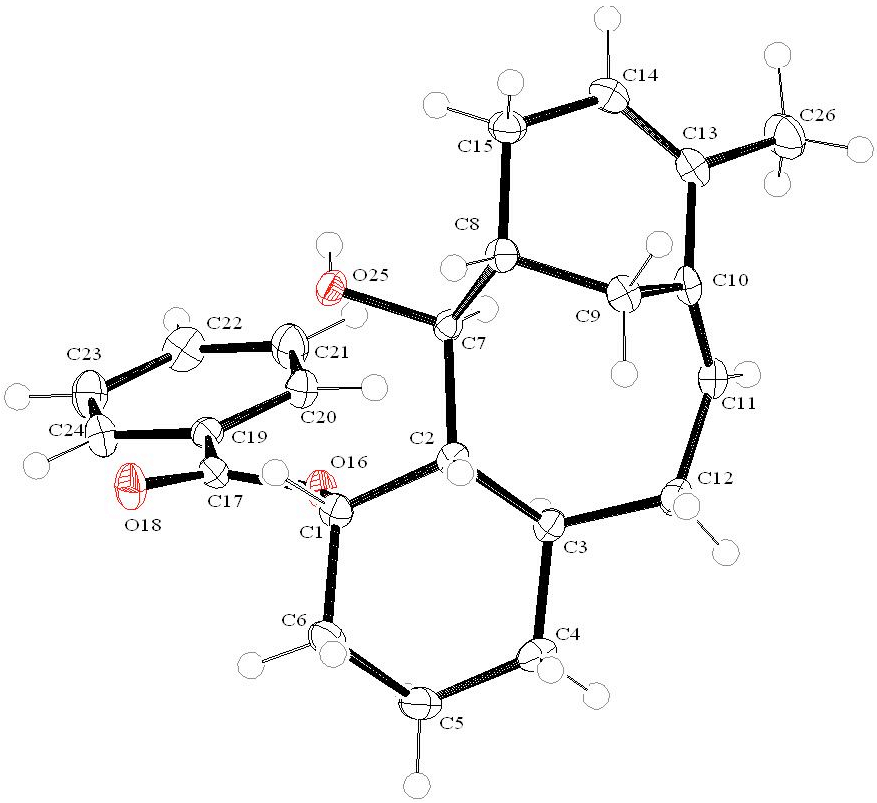


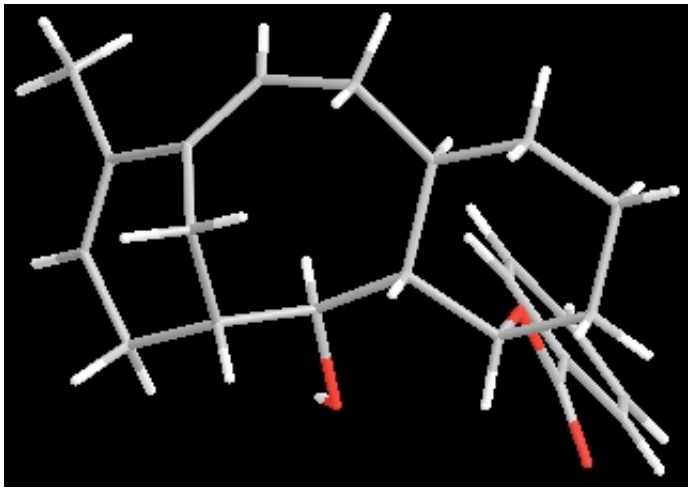


Figure 1SI. X-ray crystallography of an enantiomer of C-4 monobenzoate of diol **15a**$_{4R}$, which allowed establishing unequivocally the trans fusion between B and C ring and also the relative configuration of the stereogenic centers C1, C2, C3, C4 and C10.

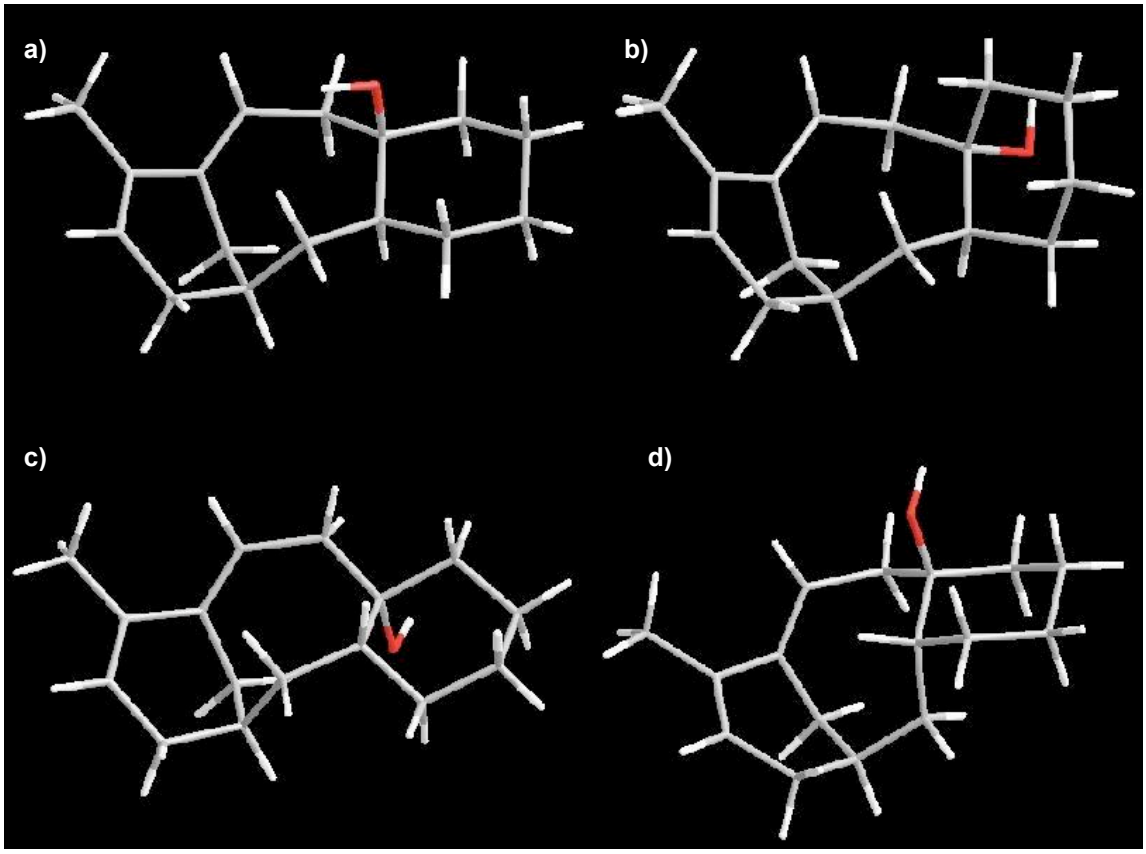


Figure 2SI. Minimized structures of **5a** and **5b** isomers and their corresponding realive energies determined with Gaussian 98W (5.2 version) a) $\mathbf{5a_1}$, 0 kcal/mol; b) $\mathbf{5a_2}$, 6.51 kcal/mol; c) $\mathbf{5b_1}$, 10.40 kcal/mol; d) $\mathbf{5b_2}$, 7.5 kcal/mol

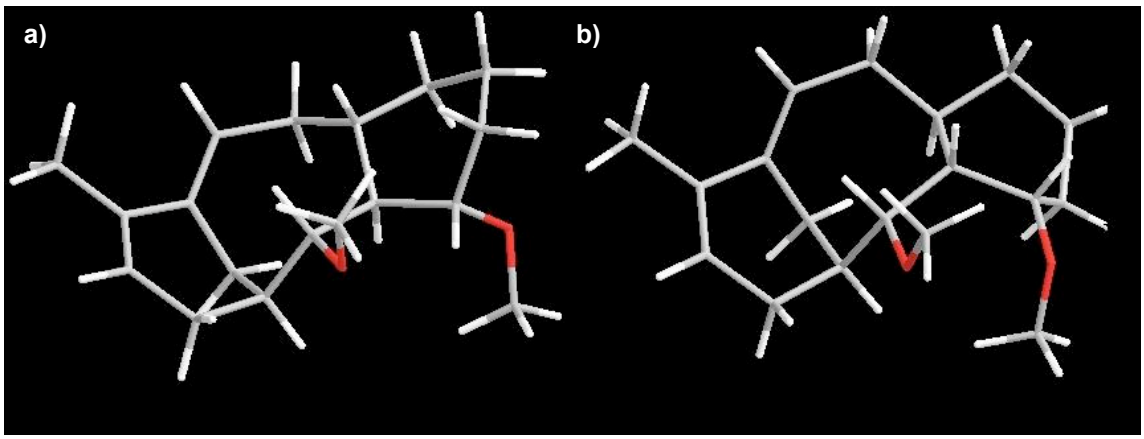
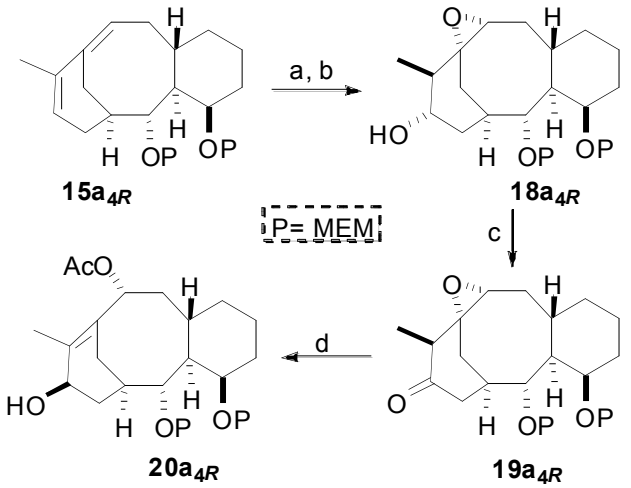


Figure 3SI. Minimized structures of **15a**$_{4S}$ and **15b**$_{4S}$ and their corresponding realive energies determined with Gaussian 98W (5.2 version). a) **15a**$_{4S}$, 0 kcal/mol; b) **15b**$_{4S}$, 20.01 kcal/mol

Scheme 1SI.[a]



[a]Key: (a) MCPBA, CH_2Cl_2, 0 ºC, 93%; (b) i) BH_3.THF, 0 ºC, ii)H_2O_2, NaOH (3M), 95%; (c) i) PDC, CH_2Cl_2, ii) Al_2O_3 (cat), iii) DIEA, DMAP, Ac_2O, 82%; (d) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 ºC, 76%.

General Methods, Instrument Details and Materials

►**General.** All the reagents obtained from commercial suppliers were used without further purification unless otherwise noted. Dichloromethane (DCM) and was dried and distilled over calcium hydride.[1,2] Tetrahydrofurane (THF) was dried and distilled over sodium/benzophenone and toluene from sodium.[1,2] DIEA was dried and distilled over calcium hydride, and then redistilled over nynhidrin.[1,2]. Analytical thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates. Silica gel flash chromatography was performed using E. Merck silica gel (type 60SDS, 230-400 mesh). Preparative thin-layer chromatography was performed on E. Merck silica gel 60 F254 plates (1 mm). Solvent mixtures for chromatography are reported as v/v ratios. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Inova-750 MHz, Bruker AMX-500 MHz or Bruker WM-250 MHz spectrometers. Chemical shifts were reported in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q) or pentuplet (p). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Mercury-300 MHz, Bruker WM-250 MHz or Bruker AMX-500 MHz spectrometers. Carbon resonances were assigned using distortionless enhancement by polarization transfer (DEPT) spectra obtained with phase angles of 135. Fast Atom Bombardement (FAB) mass spectra were recorded on a Micromass Autospec mass spectrometer. Mass Spectrometry of Laser Desorption/Ionization-Time of Flight (MALDI-TOF) was obtained on a Bruker Autoflex mass spectrometer.

► **1H-NMR Assignments**. The signals of the ^{1}H NMR spectra of the peptides in $CDCl_3$ were identified from the corresponding double-quantum-filled 2D COSY (2QF-COSY), TOCSY and/or NOESY and ROESY spectra acquired at concentration and temperature indicated. Mixing times (~250 ms or 400 ms) were not optimized. Spectra were typically acquired using Bruker standard pulse sequences on 500 MHz apparatuses, and were referenced relative to residual proton resonances in $CDCl_3$ (at 7.26 ppm). 1H-NMR spectra also were obtained on a Varian Inova-750 MHz spectometer.

[1] Brown, H. C. "*Organic Synthesis via Boranes"*, Ed. John Wiley & Sons, **1975**

[2] Perrin, D. D.; Armarego, W. I. F. *"Purification of Laboratory Chemicals"*, Ed. Pergamon Press, **1988**

***Synthesis of taxanes* 20a$_{4S}$ *and* 20a$_{4R}$.**

Dyenines 3a. Allyl magnesium bromide (1 M in Et_2O, 0.6 mL, 0.6 mmol) was added to a solution of ketone **8a** (51 mg, 0.20 mmol) at -78 ºC and the resulting solution was stirred for 2 h at the same temperature. The reaction was quenched with NH_4Cl (sat) and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed dried over Na_2SO_4 and concentrated under reduced pressure. The crude was flash chromatographed to yield isomers **3a$_1$** [22 mg, 36%, Rf= 0.4 (10% AcOEt/hexanes), pale yellow oil] and **3a$_2$** [21 mg, 35%, Rf= 0.45 (10% AcOEt/ hexane), pale yellow oil]. **3a$_1$**: **^{1}H-NMR** ($CDCl_3$, 400 MHz, δ): 5.79 (1H, m, H-10), 5.43 (1H, ddd, *J* = 15.3, 6.5, 1.0 Hz, H-13a), 5.31 (1H, m, H-13), 5.11 (2H, m, H-10a), 1.79 (3H, t, *J*= 2.5 Hz, H-18), 0.98 (6H, 2d, *J* = 6.8 Hz, -CH(C$\underline{H_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 100 MHz, δ): 139.9 (CH), 134.0 (CH), 125.5 (CH), 118.3 (CH_2), 77.5 (C), 76.4 (C), 73.1 (C), 45.1 (CH_2), 40.9 (CH), 37.9 (CH_2), 36.8 (CH_2), 35.3 (CH), 31.9 (CH_2), 30.3 (CH), 29.7 (CH_2), 27.3 (CH_2), 25.3 (CH_2), 22.6 (CH_3), 21.7 (CH_2), 3.5 (CH_3). **MS-ESI** (m/z): 325 (M+Na^+, 14), 307 (M+Na^+-H_2O, 71), 282 (M+Na^+-^{i}Pr, 20). **3a$_2$**: **^{1}H-NMR** ($CDCl_3$, 400 MHz, δ): 5.85 (1H, m, H-10), 5.43 (1H, dd, *J*= 15.3, 6.4 Hz, H-13a), 5.31 (1H, ddd, *J*= 14.2, 7.3, 6.4 Hz, H-13), 5.10 (2H, m, H-10a), 1.78 (3H, t, *J*= 2.7 Hz, H-18), 0.97 (6H, d, *J*= 6.8 Hz, -CH(C$\underline{H_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 100 MHz, δ): 139.6 (CH), 134.2 (CH), 125.0 (CH), 118.1 (CH_2), 77.2 (C), 76.3 (C), 73.1 (C), 45.1 (CH_2), 40.7 (CH), 37.8 (CH_2), 36.9 (CH_2), 35.1 (CH), 32.3 (CH_2), 30.3 (CH), 29.7 (CH_2), 27.3 (CH_2), 25.4 (CH_2), 22.7 (CH_3), 21.6 (CH_2), 3.5 (CH_3). **MS-ESI** (m/z): 325 (M+Na^+, 13), 303 (MH^+, 2), 307 (M+Na^+-H_2O, 68), 285 (MH^+-H_2O, 53), 282 (M+Na^+-^{i}Pr, 25).

Dyenines 3b. Dyenines **3b** were prepared from ketone **8b** in the same way as isomers **3a** from **8a, 3b$_1$** [35%, Rf= 0.27 (5% AcOEt/hexanes), pale yellow oil] and **3b$_2$** [35%, Rf= 0.3 (5% AcOEt/hexanes), pale yellow oil]. **3b$_1$**: **^{1}H-NMR** ($CDCl_3$, 400 MHz, δ): 5.80 (1H, m, H-10), 5.43 (1H, dd, *J*= 15.4, 6.3 Hz, H-13a), 5.31 (1H, m, H-13), 5.11 (2H, m, H-10a), 1.78 (3H, t, *J*= 2.5 Hz, H-18), 0.96 (6H, d, *J*= 6.8 Hz, -CH(C$\underline{H_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 100 MHz, δ): 140.0 (CH), 134.0 (CH), 125.6 (CH), 118.3 (CH_2), 77.4 (C), 76.3 (C), 73.1 (C), 45.1 (CH_2), 40.8 (CH), 40.0 (CH_2), 36.8 (CH_2), 35.4 (CH), 31.8 (CH_2), 30.3 (CH), 29.7 (CH_2), 27.3 (CH_2), 25.3 (CH_2), 22.6 (CH_3), 21.7 (CH_2), 3.5 (CH_3). **MS-ESI** (m/z): 325 (M+Na^+, 15), 307 (M+Na^+-H_2O, 55). **3b$_2$**: **^{1}H-NRM** ($CDCl_3$, 400 MHz, δ): 5.8 (1H, m, H-10), 5.43 (1H, dd, *J*= 15.4, 6.4 Hz, H-13a), 5.31 (1H, m, H-13), 5.11 (2H, m, H-10a), 1.78 (3H, t, *J*= 2.6 Hz, H-18), 0.96 (6H, d, *J*= 6.7 Hz, -CH(C$\underline{H_3}$)$_2$). **^{13}C-NRM** ($CDCl_3$, 100 MHz, δ): 139.7 (CH), 134.1 (CH), 125.1 (CH), 118.1 (CH_2), 77.2 (C), 76.2 (C), 73.0 (C), 45.1 (CH_2), 40.8 (CH), 37.8 (CH_2), 36.9 (CH_2), 35.2 (CH), 32.2 (CH_2), 30.3 (CH), 29.7 (CH_2), 27.3 (CH_2), 25.4 (CH_2), 22.6 (CH_3), 21.6 (CH_2), 3.5 (CH_3). **MS-ESI** (m/z): 325 (M+Na^+, 20), 307 (M+Na^+-H_2O, 61).

Compound 5. Second generation Grubbs' catalyst **[Ru]^{G2}** (4 mg, 5 x 10^{-3} mmol) was added to a solution of dyenine **3a$_1$** (15 mg, 0.05 mmol) in benzene (10 mL) and the mixture was stirred at 80 ºC for 2 h, allowed to reach rt and concentrated under reduced pressure. The crude was purified by flash chromatography on aluminium oxide (1% AcOEt/hexanes) to give the tricycle **5** [8 mg, 70%, Rf= 0.4 (10% AcOEt/hexanes), white solid]. **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.67 (1H, t, *J*= 7.3 Hz, H-10), 5.17 (1H, s, H-13), 2.79 (1H, dd, *J*= 11.4, 3.9 Hz, H-15$_a$), 1.79 (3H, d, *J*= 1.7 Hz, H-18). **MS-ESI** (m/z): 255 ($M+Na^+$, 25), 233 (MH^+, 11), 217 (MH^+-CH_4, 14), 215 (MH^+-H_2O, 100). **HRMS**: calculated for $C_{16}H_{24}NaO$: 255.1719; found: 255.1712.

Ketones 8. Ciclohexanone (0.11 mL, 1.10 mmol) was added dropwise to a solution of KHMDS (0.5 M in toluene, 2.2 mL, 1.10 mmol) in DMF (0.5 mL) at -78 ºC. After stirring for 30 min at this temperature, a solution of iodide **7** (160 mg, 0.55 mmol) in DMF (1.5 mL) was added and the final mixture was stirred for another 5 h. The reaction was quenched with NH_4Cl (sat) and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting oil was purified by flash chromatography on silicagel (1% AcOEt/hexanes) to provide isomers **8a** [52 mg, 36%, Rf= 0.5 (10% AcOEt/hexanes), pale yellow oil] and **8b** [53 mg, 37%, Rf= 0.47 (10% AcOEt/hexano), pale yellow oil]. **8a**: **^{1}H-NMR** ($CDCl_3$, 400 MHz, δ): 5.41 (1H, td, *J*= 15.3, 5.9 Hz, H-13a), 5.27 (1H, tdd, *J*= 14.4, 11.5, 7.0 Hz, H-13), 2.55 (1H, m, -$\underline{CH}(CH_3)_2$), 1.77 (3H, dd, *J*= 5.7, 2.6 Hz, H-18), 0.96 (6H, 2d, *J*= 6.8 Hz, -$CH(\underline{CH_3})_2$). **^{13}C-NMR** ($CDCl_3$, 100 MHz, δ): 215.8 (CO), 140.1 (CH), 124.6 (CH), 77.7 (C), 76.5 (C), 52.5 (CH), 39.6 (CH_2), 38.8 (CH_2), 38.3 (CH_2), 37.6 (CH_2), 33.5 (CH), 31.1 (CH), 27.2 (CH_2), 24.5 (CH_2), 23.6 (CH_2), 22.6 (CH_3), 3.5 (CH_3). **MS-ESI** (m/z): 283 ($M+Na^+$, 50), 261 (MH^+, 29), 218 (MH^+-^{i}Pr, 16). **HRMS**: calculated for $C_{18}H_{29}O_1$ (MH^+): 261.2213 ; found: 261.2204. **8b**: **^{1}H-NMR** ($CDCl_3$, 400 MHz, δ): 5.40 (1H, dd, *J*= 15.3, 6.5 Hz, H-13a), 5.27 (1H, dt, *J*= 15.5, 15.2, 8.3 Hz, H-13), 1.76 (3H, dd, *J*= 4.9, 2.4 Hz, H-18), 0.94 (6H, 2d, *J*= 6.8 Hz, -$CH(\underline{CH_3})_2$). **^{13}C-NMR** ($CDCl_3$, 100 MHz, δ): 213.5 (CO), 139.8 (CH), 124.6 (CH), 77.7 (C), 76.5 (C), 48.2 (CH), 41.9 (CH_2), 38.7 (CH_2), 38.3 (CH_2), 36.9 (CH_2), 34.8 (CH), 31.1 (CH), 28.1 (CH_2), 24.8 (CH_2), 23.7 (CH_2), 22.6 (CH_3), 3.5 (CH_3). **MS-ESI** (m/z): 283 ($M+Na^+$, 22), 261 (MH^+, 14), 218 (MH^+-^{i}Pr, 7). **HRMS**: calculated for $C_{18}H_{29}O_1$ (MH^+): 261.2213 ; found: 261.2209.

Ketones 10. In a flamed 50 mL rbf, a suspension of CuBr.DMS (886 mg, 4.3 mmol) and LiCl (182 mg, 4.3 mmol) in THF (12 mL) was prepared and stirred for 10 min until formation of a yellow solution. The mixture was cooled to -78 ºC and AllMgBr (1M in Et_2O, 3.7 mL, 3.7 mmol) was added dropwise. After stirring this solution for 15 min, cyclohex-2-enone (0.18 mL, 1.87 mmol) was added and after another 30 min, a solution of aldehyde **11** (400 mg, 2.24 mmol) in THF (5 mL) was added. The final mixture was stirred at the same temperature for 1.5 h and

the reaction was quenched by adding NH_4Cl (sat) at -78 ºC and then allowed to reach rt. The aqueous layer was extracted with Et_2O and the combined organic extracts were washed dried over Na_2SO_4 and concentrated under reduced pressure. The crude was flash chromatographed on silicagel (6% AcOEt/hexanes) furnishing compounds **10a** [295 mg, 50%, Rf= 0.42 (20% AcOEt/hexanes), colorless oil] and **10b** [293 mg, 50%, Rf= 0.38 (20% AcOEt/hexanes), colorless oil]. **10a**: **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.83 (1H, m, H-10), 5.45 (1H, dd, *J*= 15.6, 6.2 Hz, H-13a), 5.29 (1H, m, H-13), 5.06 (2H, m, H-10a), 3.64 (1H, ddd, *J*= 10.8, 6.3, 3.0 Hz, H-2), 2.79 (1H, d, *J*= 11.0 Hz, -OH), 1.74 (3H, t, *J*= 2.5 Hz, H-18), 0.95 (6H, d, *J*= 6.7 Hz, -CH($\underline{CH_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 63 MHz, δ): 215.9 (CO), 140.0 (CH), 135.1 (CH), 124.2 (CH), 117.6 (CH_2), 77.1 (C), 76.9 (C), 71.3 (CH), 55.9 (CH), 42.6 (CH_2), 41.3 (CH), 41.0 (CH), 37.4 (CH_2), 33.4 (CH_2), 31.0 (CH), 29.6 (CH_2), 26.0 (CH_2), 22.5 (CH_3), 19.4 (CH_2), 3.5 (CH_3). **MS-CI$^+$** (m/z): 317 (MH^+, 16), 299 (MH^+-H_2O, 29), 139 (MH^+-$CH_2OHCH(CH_2C{\equiv}CCH_3)CH_2CH{=}CH^iPr$, 100). **HRMS**: calculated for $C_{21}H_{31}O_2$: 317.248056; found: 317.247537. **10b**: **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.77 (1H, m, H-10), 5.44 (1H, dd, *J*= 15.4, 6.4 Hz, H-13a), 5.26 (1H, m, H-13), 5.04 (1H, m, H-10a), 3.67 (1H, ddd, *J*= 11.1, 8.0, 3.2 Hz, H-2), 2.81 (1H, d, *J*= 11.1 Hz, -OH), 1.77 (3H, t, *J*= 2.5 Hz, H-18), 0.96 (6H, d, *J*= 6.8 Hz, -CH($\underline{CH_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 63 MHz, δ): 216.1 (CO), 140.1 (CH), 135.3 (CH), 124.6 (CH), 117.3 (CH_2), 77.1 (C), 71.8 (CH), 55.8 (CH), 42.7 (CH_2), 41.4 (CH), 41.1 (CH), 37.4 (CH_2), 33.0 (CH_2), 31.0 (CH), 29.8 (CH_2), 26.2 (CH_2), 22.6 (CH_3), 19.4 (CH_2), 3.5 (CH_3). **MS-CI$^+$** (m/z): 317 (MH^+, 14), 299 (MH^+-H_2O, 28).

Alcohols 13a: METHOD A. DIBAL (1 M, 1.5 mL, 1.5 mmol) was added dropwise to a solution of ketone **10a** (215 mg, 0.68 mmol) in CH_2Cl_2 (17 mL) at -78 ºC. The mixture was stirred at this temperature for 3 h and the reaction was then quenched with NH_4Cl (sat, 10 mL) and let to reach rt. HCl (1 M, 3 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography on silicagel (8-12% AcOEt/hexanes) to provide diols **13a$_{4R}$** [52 mg, 24%, Rf= 0.4 (20% AcOEt/hexanes), colorless oil] and **13a$_{4S}$** [112 mg, 52%, Rf= 0.3 (20% AcOEt/hexano), colorless oil]. **13a$_{4R}$**: **^{1}H-NMR** ($CDCl_3$, 400 MHz, δ): 5.84 (1H, m, H-10), 5.51 (1H, dd, *J*= 15.4, 6.5 Hz, H-13a), 5.37 (1H, m, H-13), 5.01 (2H, m, H-10a), 4.31 (1 H, brs, H-2), 3.91 (1H, m, H-4), 3.06 (2H, s, -OH), 2.51 (1H, m, -$\underline{CH}(CH_3)_2$), 1.77 (3H, t, *J*= 2.5 Hz, H-18), 0.97 (6H, d, *J*= 6.8 Hz, -CH($\underline{CH_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 100 MHz, δ): 140.2 (CH), 136.8 (CH), 125.1 (CH), 116.1 (CH_2), 77.1 (C), 76.3 (C), 73.4 (CH), 68.1 (CH), 44.5 (CH), 40.2 (CH), 37.2 (CH_2), 33.4 (CH_2), 31.7 (CH), 31.6 (CH_2), 31.1 (CH), 29.7 (CH_2), 22.5 (CH_3), 19.8 (CH_2), 19.2 (CH_2), 3.4 (CH_3). **MS-ESI** (m/z): 341 ($M+Na^+$, 100), 301 (MH^+-H_2O, 44), 283 (MH^+-H_2O x 2, 37). **HRMS**: calculated for $C_{21}H_{34}NaO_2$: 341.2451, found: 341.2454. **13a$_{4S}$**: **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.80 (1H,

m, H-10), 5.46 (1H, dd, *J*= 15.5, 6.1 Hz, H-13a), 5.30 (1H, m, H-13), 4.99 (2H, m, H-10a), 4.07 (1H, brs, H-2), 3.71 (1H, m, H-4), 2.96 (1H, s, -OH), 2.71 (1H, s, -OH), 1.78 (3H, t, *J*= 2.5 Hz, H-18), 0.96 (6H, d, *J*= 6.7 Hz, -CH($\underline{CH_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ): 140.3 (CH), 137.0 (CH), 124.9 (CH), 116.1 (CH_2), 78.3 (C), 77.5 (C), 75.9 (CH), 71.8 (CH), 51.0 (CH), 44.7 (CH), 40.2 (CH), 38.2 (CH_2), 35.3 (CH_2), 31.1 (CH), 30.8 (CH_2), 29.7 (CH_2), 23.5 (CH_2), 22.5 (CH_3), 18.1 (CH_2), 3.5 (CH_3). **MS-ESI** (m/z): 341 ($M+Na^+$, 100), 301 (MH^+-H_2O, 42), 283 (MH^+-H_2O x 2, 15). **HRMS**: calculated for $C_{21}H_{34}NaO_2$: 341.2451, found: 341.2452.

METHOD B. $NaBH_4$ (40 mg, mmol) was added to a solution of ketone **10a** (170 mg, 0.53 mmol) in MeOH (10 mL) at 0 ºC. The mixture was stirred at this temperature for 2 h and then quenched with with NH_4Cl (sat). The aqueous layer was extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was flash chromatographed on silicagel (4% AcOEt/hexanes) furnishing compounds **13a$_{4R}$** [129 mg, 77%] and **13a$_{4S}$** [21 mg, 12%].

Alcohols 13b$_{4R}$ and 13b$_{4S}$. These alcohols were prepared from ketone **10b** in the same way as alcohols **13a** from **10a**; **13b$_{4R}$** [51%, Rf= 0.3 (20% AcOEt/hexanes), colorless oil] and **13b$_{4S}$** [24%, Rf= 0.4 (20% AcOEt/hexanes), colorless oil]. **13b$_{4R}$**: **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.73 (1H, m, H-10), 5.50 (1H, dd, *J*= 15.4, 6.1 Hz, H-13a), 5.35 (1H, m, H-13), 4.99 (2H, m, H-10a), 3.88 (1H, dd, *J*= 4.7, 2.6 Hz, H-2), 3.73 (1H, m, H-4), 1.79 (3H, t, *J*= 2.5 Hz, H-18), 0.97 (6H, d, *J*= 6.7 Hz, -CH($\underline{CH_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ): 139.9 (CH), 137.2 (CH), 125.2 (CH), 116.1 (CH_2), 78.2 (C), 77.1 (C), 74.2 (CH), 71.7 (CH), 51.2 (CH), 44.4 (CH), 40.8 (CH), 38.1 (CH_2), 35.1 (CH_2), 34.0 (CH_2), 31.5 (CH_2), 31.0 (CH), 29.7 (CH_2), 22.5 (CH_3), 20.1 (CH_2), 3.4 (CH_3). **MS-ESI**(m/e, I): 341 ($M+Na^+$, 82), 301 (MH^+-H_2O, 33). **HRMS**: calculated for $C_{21}H_{34}NaO_2$: 341.2451, found: 341.2452. **13b$_{4SL}$**: **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.81 (1H, m, H-10), 5.45 (1H, dd, *J*= 15.4, 6.4 Hz, H-13a), 5.28 (1H, m, H-13), 4.99 (2H, m, H-10a), 4.31 (1H, brs, H-2), 3.88 (1H, m, H-4), 3.10 (2H, m, -OH), 1.79 (3H, t, *J*= 2.5 Hz, H-18), 0.97 (6H, d, *J*= 6.7 Hz, -CH($\underline{CH_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ): 140.3 (CH), 136.7 (CH), 123.5 (CH), 116.3 (CH_2), 77.3 (C), 73.0 (CH), 67.9 (CH), 44.4 (CH), 40.5 (CH), 37.3 (CH_2), 33.5 (CH_2), 32.6 (CH_2), 31.7 (CH), 31.1 (CH), 29.7 (CH_2), 22.5 (CH_3), 19.8 (CH_2), 19.5 (CH_2), 3.5 (CH_3). **MS-ESI**(m/z): 341 ($M+Na^+$, 100), 301 (MH^+-H_2O, 49), 283 (MH^+-H_2O x 2, 62). **HRMS**: calculated for $C_{21}H_{34}NaO_2$: 341.2451, found: 341.2453.

Compound 14a$_{4S}$. DIEA (1.1 mL, 6.48 mmol) and ClMEM (0.49 mL, 4.32 mmol) were added to a solution of diol **13a$_{4S}$** (115 mg, 0.36 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was stirred at rt for 12 h. The reaction mixture was poured into NH_4Cl (sat) and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give an oil that was purified by flash chromatography on silicagel (7% AcOEt/hexanes) providing the diprotected compound **14a$_{4S}$** [96%, Rf= 0.4 (20%

AcOEt/hexanes), yellow oil]. **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.76 (1H, m, H-10), 5.41 (1H, dd, *J*= 15.7, 6.1 Hz, H-13a), 5.25 (1H, m, H-13), 4.98 (2H, m, H-10a), 5.01-4.68 (4H, m, -OCH_2O- x 2), 3.84-3.51 (10H, m, H-2, H-4, -O$\underline{CH_2CH_2}$OMe x 2), 3.37 (6H, s, -OMe x 2), 1.76 (3H, t, *J*= 2.4 Hz, H-18), 0.94 (6H, d, *J*= 8.9 Hz, -CH($\underline{CH_3}$)$_2$). **^{13}C-NMR** ($CDCl_3$, 63 MHz, δ): 139.6 (CH), 137.1 (CH), 124.6 8CH), 115.9 (CH_2), 97.7 (CH_2), 94.9 (CH_2), 80.7 (CH), 77.5 (CH), 76.8 (C), 77.2 (C), 71.8 (CH_2), 71.7 (CH_2), 67.6 (CH_2), 66.8 (CH_2), 58.9 (CH_3), 47.7 (CH), 42.02 (CH), 38.8 (CH_2), 37.2 (CH), 32.8 (CH_2), 31.1 (CH_2), 31.0 (CH), 22.6 (CH_2), 22.5 (CH_3), 18.8 (CH_2), 3.4 (CH_3). **MS-ESI** (m/z): 517 (M+Na^+, 100). **HRMS**: calculated for $C_{29}H_{50}O_6$: 517.3500; found: 517.3494.

Compound 14a$_{4R}$. This compound was prepared from diol **13a$_{4R}$** in the same way as **14a$_{4S}$** from **13a$_{4S}$**; **14a$_{4R}$** [85%, Rf= 0.4 (20% AcOEt/hexanes), yellow oil]. **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.84 (1 H, m), 5.43 (1H, dd, *J*= 15.3, 6.3 Hz, H-13a), 5.27 (1H, m, H-13), 5.00 (2H, m, H-10a), 4.91-4.58 (4H, m, -OCH_2O- x 2), 4.01 (1H, d, *J*= 3.9 Hz, H-2), 3.86 (1H, dd, *J*= 5.5, 3.3 Hz, H-4), 3.67 (8H, m, -O$\underline{CH_2CH_2}$OMe x 2), 3.39 (6H, s, -OMe x 2), 1.76 (3H, t, *J*= 2.2 Hz, H-18), 0.96 (6H, d, *J*= 6.8 Hz, -CH($\underline{CH_3}$)$_2$). **MS-ESI** (m/z): 517 (M+Na^+, 100).

Compound 14b$_{4S}$. This compound was prepared from diol **13b$_{4S}$** in the same way as **14a$_{4S}$** from **13a$_{4S}$**; **14a$_{4S}$** [85%, Rf= 0.4 (20% AcOEt/hexanes), yellow oil]. **^{1}H-NMR** ($CDCl_3$, 250 MHz, δ): 5.81 (1H, m, H-10), 5.45 (1H, dd, *J*= 15.3, 6.3 Hz, H-13a), 5.28 (1H, m, H-13), 5.02 (2H, m, H-10a), 4.95-4.61 (4H, m, -OCH_2O- x 2), 4.25 (1H, s, H-2), 4.00 (1H, d, *J*= 7.2 Hz, H-4), 3.93-3.48 (8H, m, -O$\underline{CH_2CH_2}$OMe x 2), 3.38 (6H, s, -OMe x 2), 1.78 (3H, t, *J* = 2.4 Hz, H-18), 0.96 (6H, d, *J*= 6.7 Hz, -CH($\underline{CH_3}$)$_2$). **MS-ESI** (m/z): 517 (M+Na^+, 100).

Compound 14b$_{4R}$. This compound was prepared from diol **13b$_{4R}$** in the same way as **14a$_{4S}$** from **13a$_{4S}$**; **14b$_{4R}$** [93%, Rf= 0.4 (20% AcOEt/hexanes), yellow oil]. **^{1}H-NRM** ($CDCl_3$, 300 MHz, δ): 5.73 (1H, dt, *J*= 16.9, 7.7 Hz, H-10), 5.43 (1H, dd, *J*= 15.3, 6.4 Hz, H-13a), 5.27 (1H, m, H-13), 4.98 (2H, m, H-10), 4.87-4.61 (4H, m, -OCH_2O- x 2), 3.88-3.46 (10H, m, H-2, H-4, -O$\underline{CH_2CH_2}$OMe x 2), 3.35 (6H, s, -OMe x 2), 1.74 (3H, dd, *J*= 4.2, 2.3 Hz, H-18), 0.93 (6H, 2d, *J*= 6.7 Hz, -CH($\underline{CH_3}$)$_2$). **MS-ESI** (m/z): 517 (M+Na^+, 100).

Compound 15a$_{4S}$. This compound was prepared from dyenine **14a$_{4S}$** in the same way as **5** from **3a$_1$**; **15a$_{4S}$** [71%, Rf= 0.2 (25% AcOEt/hexanes), white solid]. **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 5.58 (1H, t, *J*= 8.1 Hz, H-10), 5.17 (1H, s, H-13), 4.91 (1H, d, *J*= 7.1 Hz, -OCH_2O-), 4.71 (1H, d, *J*= 7.1 Hz, -OCH_2O-), 4.67 (1H, d, *J*= 6.6 Hz, -OCH_2O-), 4.61 (1H, d, *J*= 6.6 Hz, -OCH_2O-), 3.85 (1H, ddd, *J*= 9.8, 4.8, 3.3 Hz, -O$\underline{CH_2CH_2}$OMe), 3.71 (2H, dtd, *J*= 15.6, 11.0, 4.6 Hz, -O$\underline{CH_2CH_2}$OMe), 3.65 (1H, dd, *J*= 10.5, 3.7 Hz, H-2), 3.55 (5H, m, -O$\underline{CH_2CH_2}$OMe), 3.48 (1H, dd, *J*= 11.7, 4.8 Hz, H-4), 3.38 (3H, s, -OMe), 3.37 (3H, s, -OMe), 2.98 (1H, dd, *J*= 12.0, 4.0 Hz, H-15$_a$), 2.14 (2H, s, H-14), 1.96 (1H, dd, *J*= 7.6, 2.7 Hz, H-1), 1.76 (3H, d, *J*= 1.6 Hz, H-

18), 1.70 (1H, ddd, *J*= 13.9, 10.2, 3.7 Hz, H-3), 1.46 (1H, m, H-8). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 140.9 (C), 136.7 (C), 121.6 (CH), 121.2 (CH), 98.2 (CH_2), 96.1 (CH_2), 84.1 (CH), 78.9 (CH), 71.9 (CH_2), 68.2 (CH_2), 66.9 (CH_2), 59.0 (CH_3), 52.5 (CH), 44.2 (CH), 40.4 (CH), 36.9 (CH_2), 34.6 (CH_2), 33.9 (CH_2), 29.8 (CH_2), 28.4 (CH_2), 22.7 (CH_2), 18.6 (CH_3). **MS-ESI** (m/z): 463 ($M+K^+$, 17), 447 ($M+Na^+$, 100). **HRMS**: calculated for $C_{24}H_{40}NaO_6$: 447.2717, found: 447.2716.

Compound 15a$_{4R}$. This compound was prepared from dyenine **14a$_{4S}$** in the same way as **5** from **3a$_1$**; **15a$_{4R}$** [69%, Rf= 0.2 (25% AcOEt/hexanes), white solid]. **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 5.61 (1H, t, *J*= 7.8 Hz, H-10), 5.21 (1H, s, H-10), 4.94 (1H, d, *J*= 6.0 Hz, -OCH_2O-), 4.80 (2H, c, *J*= 3.9 Hz, -OCH_2O-), 4.58 (1H, d, *J*= 6.1 Hz, -OCH_2O-), 4.26 (1H, s, H-4), 3.79 (1H, ddd, *J*= 11.1, 5.1, 3.6 Hz, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.73 (2H, m, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.65 (1H, ddd, *J*= 11.1, 6.4, 3.9 Hz, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.58 (1H, dd, *J*= 9.7, 6.8 Hz, H-2), 3.53 (4H, m, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.36 (3H, s, -OMe), 3.35 (3H, s, -OMe), 2.94 (1H, ddd, *J*= 11.9, 4.2, 1.5 Hz, H-15$_a$), 1.97 (1H, m, H-1), 1.88 (1H, m, H-8), 1.76 (3H, d, *J*= 1.6 Hz), 1.53 (1H, ddd, *J*= 10.5, 6.6, 1.8 Hz, H-3). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 140.3 (C), 136.8 (C), 121.9 (CH), 120.3 (CH), 100.1 (CH_2), 94.2 (CH_2), 84.9 (CH), 71.8 (CH_2), 68.7 (CH_2), 68.3 (CH_2), 65.4 (CH), 59.0 (CH_3), 53.0 (CH), 42.8 (CH), 38.4 (CH), 36.1 (CH_2), 35.9 (CH_2), 32.6 (CH_2), 29.2 (CH_2), 28.8 (CH_2), 19.9 (CH_2), 18.4 (CH_3). **MS-ESI** (m/z): 447 ($M+Na^+$, 100). **HRMS**: calculated for $C_{24}H_{40}NaO_6$: 447.2717, found: 447.2716.

Epoxide 17a$_{4S}$. MCPBA (10 mg, 0.055 mmol) was added to a solution of **15a$_{4S}$** (20 mg, 0.050 mmol) in CH_2Cl_2 (2 mL) at 0 ºC and the mixture was stirred at this temperature for 1h. The reaction was quenched with NaOH (10%) and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were dried over over Na_2SO_4 and concentrated under reduced pressure to give an oil that after purification by flash chromatography on silicagel (2% AcOEt/hexano) furnished compound **17a$_{4S}$** [19 mg, 93%, Rf= 0.5 (50% AcOEt/hexano)]. **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 5.49 (1H, s, H-13), 4.91 (1H, d, *J*= 7.2 Hz, -OCH_2O-), 4.71 (2H, dd, *J*= 6.9, 5.5 Hz, -OCH_2O-), 4.63 (1H, d, *J*= 6.8 Hz, -OCH_2O-), 3.90-3.72 (2H, m, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.68 (2H, m, -$OCH_2O$-, H-2), 3.65-3.49 (6H, m, -OCH_2O-, H-4), 3.38 (3H, s, -OMe), 3.37 (3H, s, -OMe), 2.81 (1H, dd, *J*= 9.5, 5.1 Hz, H-10), 2.10 (1H, d, *J*= 11.0 Hz, H-1), 2.01 (1H, dd, *J*= 12.9, 1.5 Hz, H-15$_a$), 1.78 (1H, dd, *J*= 12.9, 2.6 Hz, H-15$_b$), 1.60 (1H, m, H-8), 1.47 (3H, d, *J*= 1.3 Hz, H-18), 1.38 (1H, dt, *J*= 10.1, 3.0 Hz, H-3). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 135.7 (C), 124.9 (CH), 97.8 (CH_2), 95.9 (CH_2), 82.6 (CH), 78.5 (CH), 71.9 (CH_2), 68.3 (CH_2), 66.9 (CH_2), 61.0 (C), 59.1 (CH_3), 58.0 (CH), 51.8 (CH), 40.7 (CH), 39.8 (CH_2), 39.0 (CH), 34.5 (CH_2), 33.5 (CH_2), 28.9 (CH_2), 28.2 (CH_2), 22.8 (CH_2), 15.9 (CH_3). **MS-IQ$^+$** (m/z): 441 (MH^+, 2), 423 (MH^+-H_2O, 10), 335 (MH^+-HOMEM, 14).

Epoxialcohol 18a$_{4S}$. BH_3.THF (1 M in THF, 167 μL, 0.167 mmol) was added to a solution of epoxide **17a$_{4S}$** (20 mg, 0.083 mmol) in THF (3.1 mL) at 0 ºC. After stirring for 1.5 h at this temperature, NaOH (3 M, 0.3 mL) and H_2O_2 (30%, 0.15 mL) were added and the resulting mixture was stirred for 2 h at 0 ºC and then allowed to reach rt. The reaction mixture was diluted Et_2O with and poured over NaOH (3 M). The aqueous layer was extracted with Et_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography on silicagel (90% AcOEt/hexanes) to yield compound as a single **18a$_{4S}$** diastereomer [36 mg, 96%, Rf= 0.2 (100% AcOEt), white solid]. **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 4.82 (1H, d, *J*= 7.3 Hz, -O$\underline{CH_2}$O-), 4.75 (1H, d, *J*= 7.4 Hz, -O$\underline{CH_2}$O-), 4.71 (1H, d, *J*= 7.5 Hz, -O$\underline{CH_2}$O-), 4.69 (1H, d, *J*= 7.3 Hz, -O$\underline{CH_2}$O-), 4.10 (1H, ddd, *J*= 10.7, 7.4, 2.2 Hz, -O$\underline{CH_2CH_2}$OMe), 3.89 (1H, dt, *J*= 10.8, 4.8 Hz, H-13), 3.79 (1H, td, *J*= 10.7, 4.2 Hz, -O$\underline{CH_2CH_2}$OMe), 3.65 (1H, dd, *J*= 5.9, 2.6 Hz, H-2), 3.63-3.55 (3H, m, -O$\underline{CH_2CH_2}$OMe), 3.52 (2H, t, *J*= 4.6 Hz, -O$\underline{CH_2CH_2}$OMe), 3.42 (1H, ddd, *J*= 11.0, 4.1, 2.3 Hz, -O$\underline{CH_2CH_2}$OMe), 3.38 (3H, s, -OMe), 3.36 (3H, s, -OMe), 3.31 (1H, m, H-4), 3.15 (1H, brs, -OH), 2.88 (1H, dd, *J*= 9.1, 5.5 Hz, H-10), 2.32 (1H, m, H-14$_a$), 2.04 (1H, m, H-1), 1.92 (1H, cd, *J*= 13.3, 6.6 Hz, H-12), 1.81 (2H, m, H-15), 1.46 (1H, m, H-8), 1.42 (1H, d, *J*= 3.5 Hz, H-3), 0.85 (3H, d, *J*= 6.7 Hz, H-18). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 97.4 (CH_2), 95.8 (CH_2), 83.6 (CH), 78.4 (CH), 72.4 (CH_2), 71.8 (CH_2), 70.6 (CH), 68.7 (CH_2), 67.0 (CH_2), 61.8 (C), 59.1 (CH_3), 59.0 (CH_3), 54.7 (CH), 51.0 (CH), 44.4 (CH), 41.3 (CH), 40.7 (CH_2), 39.6 (CH), 37.1 (CH_2), 34.6 (CH_2), 33.4 (CH_2), 32.6 (CH_2), 22.8 (CH_2), 9.9 (CH_3). **MS-ESI** (m/z): 497 (M+K^+, 11), 481 (M+Na^+, 100). **HRMS**: calculated for $C_{24}H_{42}NaO_8$: 481.2772; found: 481.2759.

Epoxialcohol 18a$_{4R}$. This compound was prepared from epoxide **17a$_{4S}$** in the same way as **18a$_{4S}$** from epoxide **17a$_{4S}$**; **18a$_{4R}$** [95%, Rf= 0.2 (100% AcOEt), white solid]. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 4.86 (1H, d, *J*= 8.0 Hz, -O$\underline{CH_2}$O-), 4.71 (2H, s, -O$\underline{CH_2}$O-), 4.61 (1H, d, *J*= 7.9 Hz, -O$\underline{CH_2}$O-), 4.15 (1H, ddd, *J*= 10.7, 8.9, 1.9 Hz, H-13), 4.00 (1H, s, H-2), 3.95-3.44 (9H, m, H-4, -O$\underline{CH_2CH_2}$OMe x 2), 3.38 (6H, s, -OMe x 2), 2.89 (1H, dd, *J*= 9.0, 5.2 Hz, H-10), 2.45 (1H, d, *J*= 12.4 Hz, H-14$_a$), 1.97 (1H, dd, *J*= 10.4, 6.7 Hz, H-12), 0.88 (3H, d, *J*= 6.6 Hz, H-18). **^{13}C-NMR** ($CDCl_3$, 75 MHz, δ): 100.6(CH_2), 96.5 (CH_2), 84.3 (CH), 75.3 (CH), 72.6 (CH_2), 71.8 (CH_2), 71.1 (CH), 68.6 (CH_2), 68.0 (CH_2), 61.8 (C), 59.0 (CH_3), 58.8 (CH_3), 54.6 (CH), 51.6 (CH), 44.5 (CH), 40.6 (CH), 40.3 (CH_2), 37.7 (CH2), 36.0 (CH_2), 35.1 (CH), 31.6 (CH_2), 30.3 (CH_2), 19.5 (CH_2), 9.9 (CH_3). **MS-ESI** (m/z): 481 (M+Na^+, 100).

Compound 19a$_{4S}$. PDC (41 mg, 0.11 mmol) and 4 Å molecular sieves (5 mg) were added to a solution of **18a$_{4S}$** (25 mg, 0.055 mmol) in CH_2Cl_2 (1.9 mL). The suspension was stirred for 4 h and filtered through a short pad of celite, washing the solids with Et_2O. The ethereous solution was concentrated under reduced pressure and the resulting residue was redisolved in CH_2Cl_2 (1.4

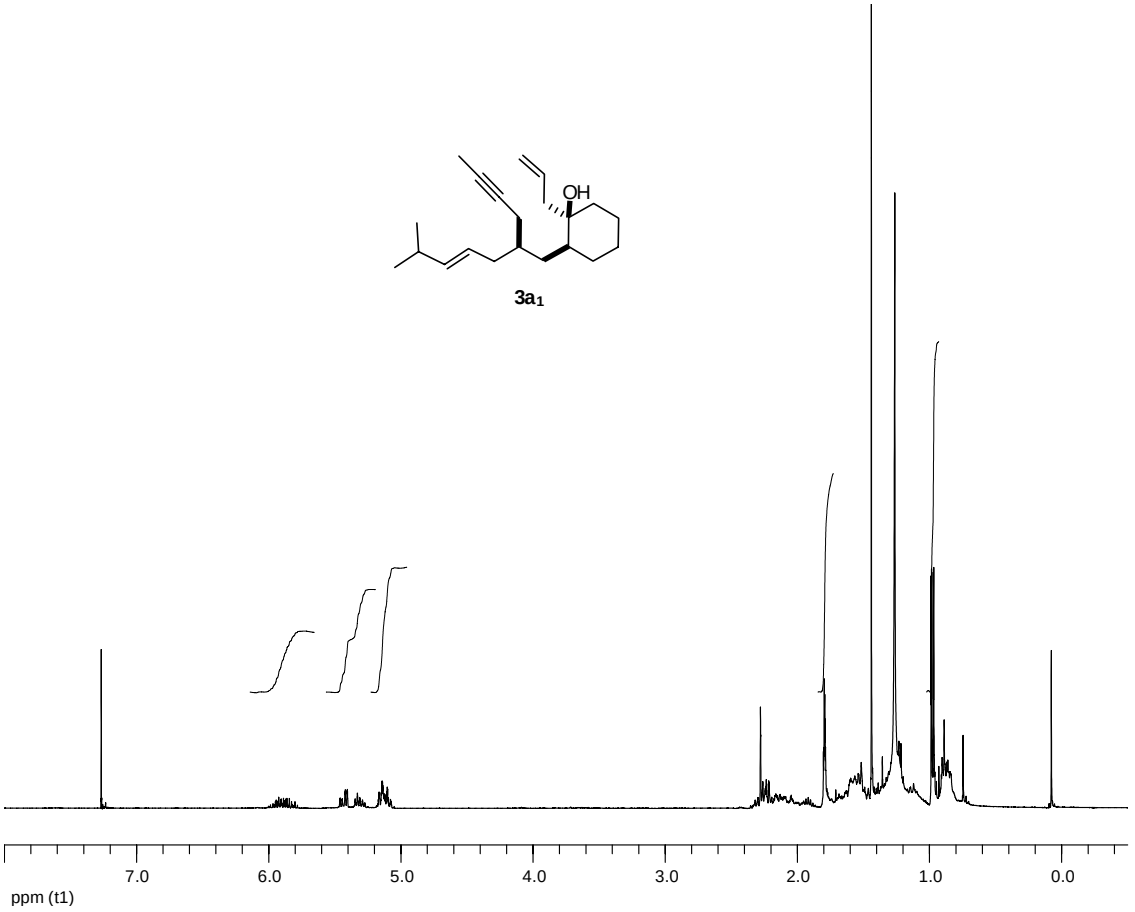
mL) and treated with aluminium oxide (1 mg). After 1 h, DIEA (19 μL, 0.11 mmol), DMAP (1 mg, 0.011 mmol) y Ac_2O (10 μL, 0.11 mmol) were added and the final solution was stirred overnight. The reaction was quenched with $NaHCO_3$ (sat) and the aqueous layer was extracted with Et_2O. The organic extracts were washed with $NaHCO_3$ (sat), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was flash cromatographed on silicagel (90% AcOEt/hexanes) to yield the ketone **19a$_{4S}$** [88%, Rf= 0.4 (100% AcOEt), white solid]. **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 5.75 (1H, dd, *J*= 8.2, 3.6 Hz, H-10), 4.81 (1H, d, *J*= 7.1 Hz, -O$\underline{CH_2}$O-), 4.73 (1H, d, *J*= 7.1 Hz, -O$\underline{CH_2}$O-), 4.69 (1H, d, *J*= 6.9 Hz, -O$\underline{CH_2}$O-), 4.62 (1H, d, *J*= 6.9 Hz, -O$\underline{CH_2}$O-), 3.80 (1H, td, *J*= 10.7, 4.4 Hz, -O$\underline{CH_2CH_2}$OMe), 3.73 (1H, m, -O$\underline{CH_2CH_2}$OMe), 3.68 (1H, m, H-2), 3.63 (2H, ddd, *J*= 10.6, 7.6, 4.3 Hz, -O$\underline{CH_2CH_2}$OMe), 3.55 (2H, t, *J*= 4.7 Hz, -O$\underline{CH_2CH_2}$OMe), 3.50 (2H, m, -O$\underline{CH_2CH_2}$OMe), 3.43 (1H, m, H-4), 3.39 (3H, s, -OMe), 3.36 (3H, s, -OMe), 2.88 (1H, td, *J*= 14.1, 3.4 Hz, H-15$_a$), 2.59 (1H, dd, *J*= 18.0, 2.7 Hz, H-14$_a$), 2.51 (1H, d, *J*= 5.3 Hz, H-1), 2.46 (1H, m, H-14$_b$), 2.10 (3H, s, -$COCH_3$), 1.99 (1H, m, H-8), 1.94 (1H, m, H-3), 1.82 (3H, d, *J*= 1.8 Hz, H-18). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 199.3 (CO), 170.0 (CO), 153.7 (C), 132.1 (C), 96.8 (CH_2), 95.6 (CH_2), 80.9 (CH), 78.2 (CH), 72.6 (CH), 71.8 (CH_2), 71.7 (CH_2), 67.8 (CH_2), 67.2 (CH_2), 59.0 (CH_3), 50.0 (CH), 41.7 (CH_2), 40.1 (CH), 39.3 (CH), 35.3 (CH_2), 32.6 (CH_2), 29.7 (CH_2), 23.4 (CH_2), 21.1 (CH_3), 11.7 (CH_3). **MS-ESI** (m/z): 521 ($M+Na^+$, 34), 499 (MH^+, 100). **HRMS**: calculated for $C_{26}H_{43}O_9$: 499.2907; found: 499.2893.

Compound 19a$_{4R}$. This compound was prepared from **18a$_{4R}$** in the same way as **19a$_{4S}$** from **18a$_{4S}$**; **19a$_{4R}$** [82%, Rf= 0.4 (100% AcOEt), white solid]. **^{1}H-NMR** ($CDCl_3$, 300 MHz, δ): 5.62 (1H, dd, *J*= 9.6, 5.4 Hz, H-10), 4.66 (4H, m, -O$\underline{CH_2}$O-), 3.81 (1H, s, H-2), 3.78-3.44 (9H, m, H-4, -O$\underline{CH_2CH_2}$OMe x 2), 3.38 (3H, s, -OMe), 3.37 (3H, s, -OMe), 2.76 (1H, td, *J*= 4.0, 2.2 Hz, H-15$_a$), 2.48(3H, m, H-14, H-1), 2.07 (3H, s, $COCH_3$), 1.86 (3H, d, *J*= 1.6 Hz, H-18). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 198.5 (CO), 170.3 (CO), 152.0 (C), 132.7 (C), 95.6 (CH_2), 95.3 (CH_2), 85.1 (CH), 79.7 (CH), 73.6 (CH), 71.7 (CH_2), 67.6 (CH_2), 67.4 (CH_2), 59.1 (CH_3), 59.0 (CH_3), 53.8 (CH), 40.7 (CH_2), 40.0 (CH), 37.1 (CH_2), 35.3 (CH_2), 32.6 (CH), 31.0 (CH_2), 24.6 (CH_2), 21.8 (CH_2), 21.1 (CH_3), 12.0 (CH_3). **MS-ESI** (m/z): 521 ($M+Na^+$, 23), 499 (MH^+, 100).

Compound 20a$_{4S}$. A solution of ketone **19a$_{4S}$** (12 mg, 0.024 mmol) in MeOH (1 mL) at 0 ºC was treated with $CeCl_3.7H_2O$ (10 mg, 0.026 mmol) and $NaBH_4$ (1 mg, 0.026 mmol) and stirred for 30 min at this temperature. The reaction was quenched with NH_4Cl (sat) and extracted with Et_2O. The organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel (90% AcOEt/hexanes) to provide the allylic alcohol **20a$_{4S}$** [9 mg, 75%, Rf= 0.3 (100% AcOEt), white solid]. **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 5.49 (1H, dd, *J*= 11.3, 5.8 Hz, H-10), 4.77 (1H, d, *J*= 7.2 Hz, -O$\underline{CH_2}$O-), 4.73 (1H, d, *J*= 7.0 Hz, -O$\underline{CH_2}$O-), 4.64 (1H, d, *J*= 6.8 Hz, -O$\underline{CH_2}$O-), 4.61 (1H, d, *J*= 7.2 Hz, -O$\underline{CH_2}$O-),

4.28 (1H, d, *J*= 6.4 Hz, H-2), 4.22 (1H, dd, *J*= 10.7, 5.0 Hz, H-13), 3.73 (1H, cd, *J*= 9.5, 4.6, 4.4 Hz, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.68 (2H, m, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.61 (1H, ddd, *J*= 10.8, 5.4, 3.9 Hz, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.55-3.46 (4H, m, -O$\underline{CH_2}\underline{CH_2}$OMe), 3.35 (3H, s, -OMe), 3.34 (3H, s, -OMe), 3.18 (1H, ddd, *J*= 14.9, 8.4, 3.2 Hz, H-4), 2.68 (1H, d, *J*= 14.6 Hz, H-15_a), 2.54 (1H, m, H-1), 2.16 (1H, m, H-9_a) 2.05 (1H, m, H-14_a), 1.98 (3H, s, $COCH_3$), 1.85 (3H, s, H-18), 1.51 (1H, m, H-3), 1.47 (1H, m, H-15_b), 1.43 (1H, m, H-8). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 170.7 (CO), 139.9 (C), 129.2 (C), 94.4 (CH_2), 94.0 (CH_2), 78.9 (CH), 75.5 (CH), 72.5 (CH), 71.9 (CH_2), 71.8 (CH_2), 70.0 (CH), 67.4 (CH_2), 66.9 (CH_2), 59.1 (CH_3), 59.0 (CH_3), 55.3 (CH), 36.5 (CH_2), 35.8 (CH), 35.7 (CH_2), 34.6 (CH), 33.6 (CH_2), 33.1 (CH_2), 24.3 (CH_2), 21.9 (CH_2), 21.4 (CH_3), 11.5 (CH_3). **MS-ESI** (m/e, I): 523 (M+Na^+, 100), 481 (M+Na^+-Ac, 20), 463 (M+Na^+-AcOH, 6). **HRMS**: calculated for $C_{26}H_{44}NaO_9$: 523.2878, found: 523.2867.

Compound 20a$_{4R}$. This compound was prepared from **19a$_{4R}$** in the same way as **20a$_{4S}$** from **19a$_{4S}$**; **20a$_{4R}$** [76%, Rf= 0.3 (100% AcOEt), white solid]. **^{1}H-NMR** ($CDCl_3$, 500 MHz, δ): 5.57 (1H, dd, *J*= 11.0, 5.6 Hz, H-10), 4.75-4.61 (4H, m, -O$\underline{CH_2}$O- x 2), 4.19 (1H, dd, *J*= 10.5, 5.9 Hz, H-13), 3.79-3.51 (10H, m, -O$\underline{CH_2}\underline{CH_2}$OMe x 2, H-2, H-4), 3.38 (3H, s, -OMe), 3.38 (3H, s, -OMe), 2.64 (1H, d, *J*= 14.6 Hz, H-15_a), 2.43 (1H, td, *J*= 14.4, 7.1 Hz, H-1), 2.01 (3H, s, $COCH_3$), 1.90 (3H, s, H-18). **^{13}C-NMR** ($CDCl_3$, 125 MHz, δ): 170.7 (CO), 140.0 (C), 128.3 (CO), 94.8 (CH_2), 94.7 (CH_2), 84.9 (CH), 78.4 (CH), 72.4 (CH), 71.9 (CH_2), 71.8 (CH_2), 70.1 (CH), 67.7 (CH_2), 67.0 (CH_2), 59.0 (CH_3), 55.1 (CH), 37.4 (CH_2), 37.3 (CH_2), 35.0 (CH), 32.7 (CH_2), 31.2 (CH), 30.2 (CH_2), 22.2 (CH_2), 21.4 (CH_3), 20.5 (CH_2), 11.6 (CH_3). **MS-ESI** (m/z): 523 (M+Na^+, 100).



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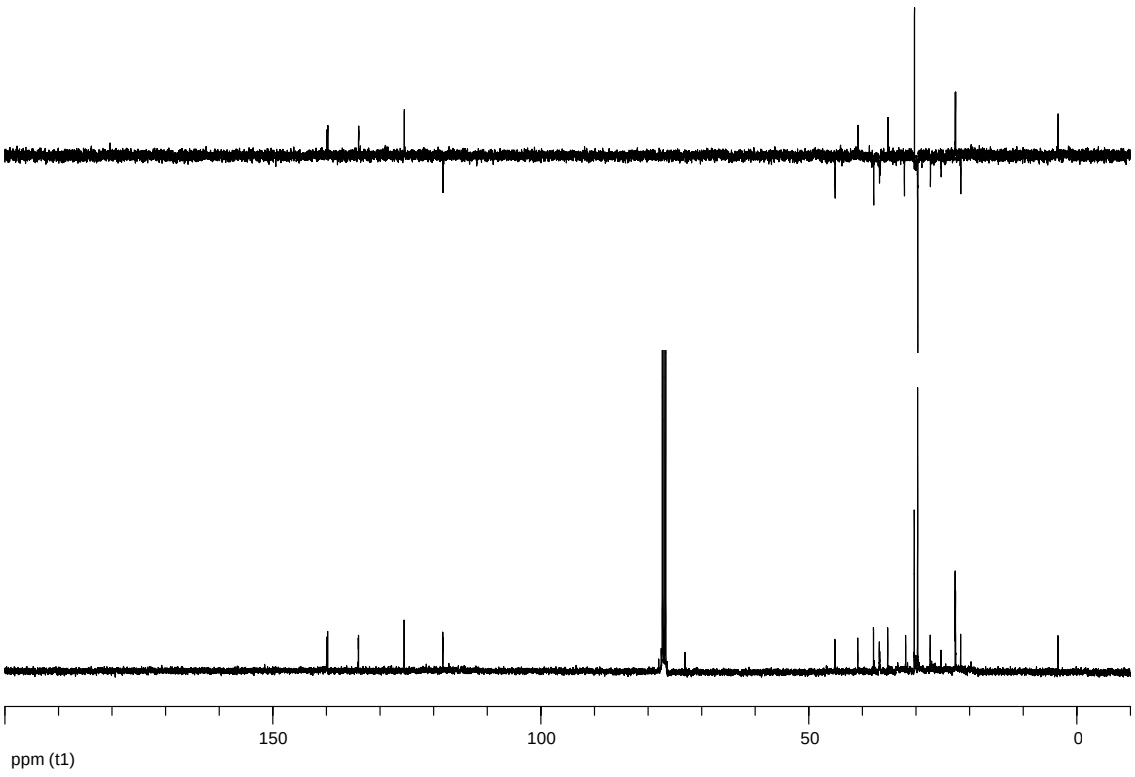

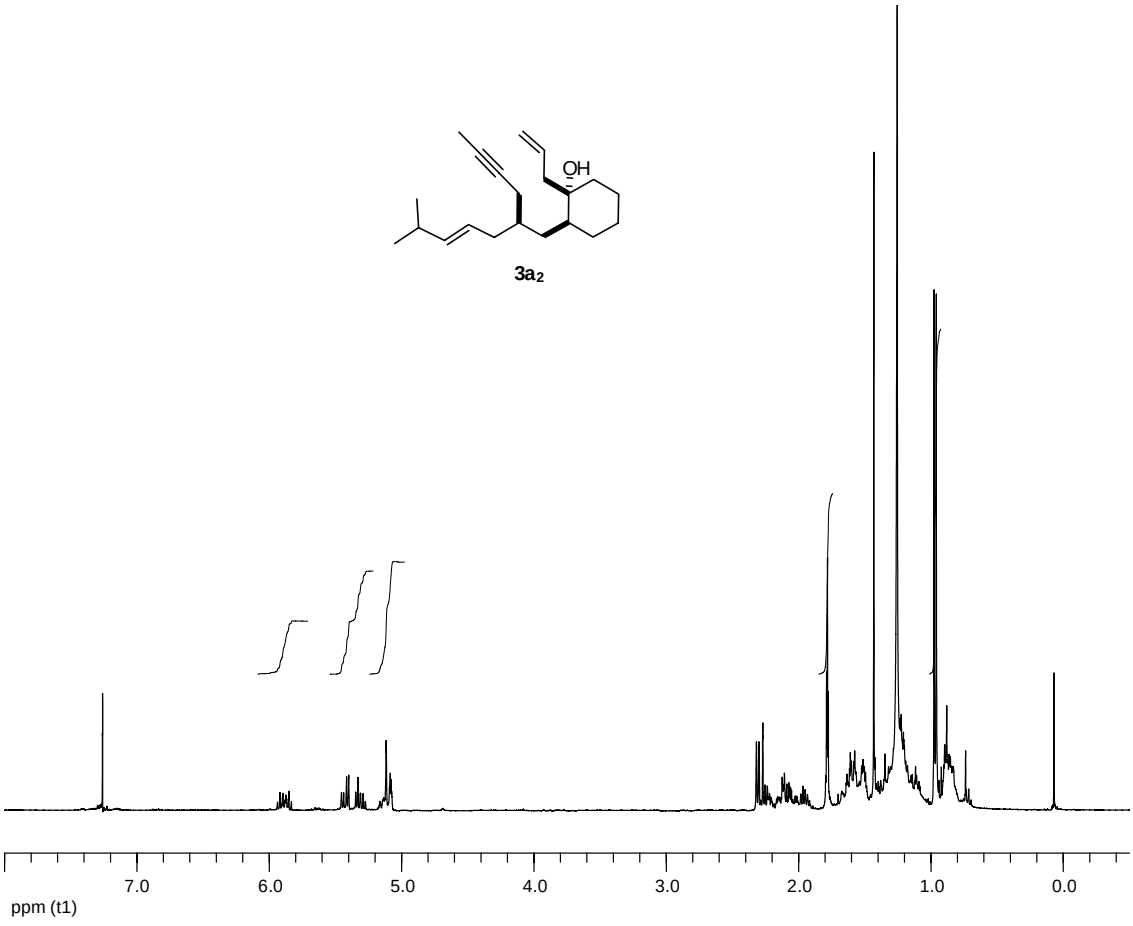

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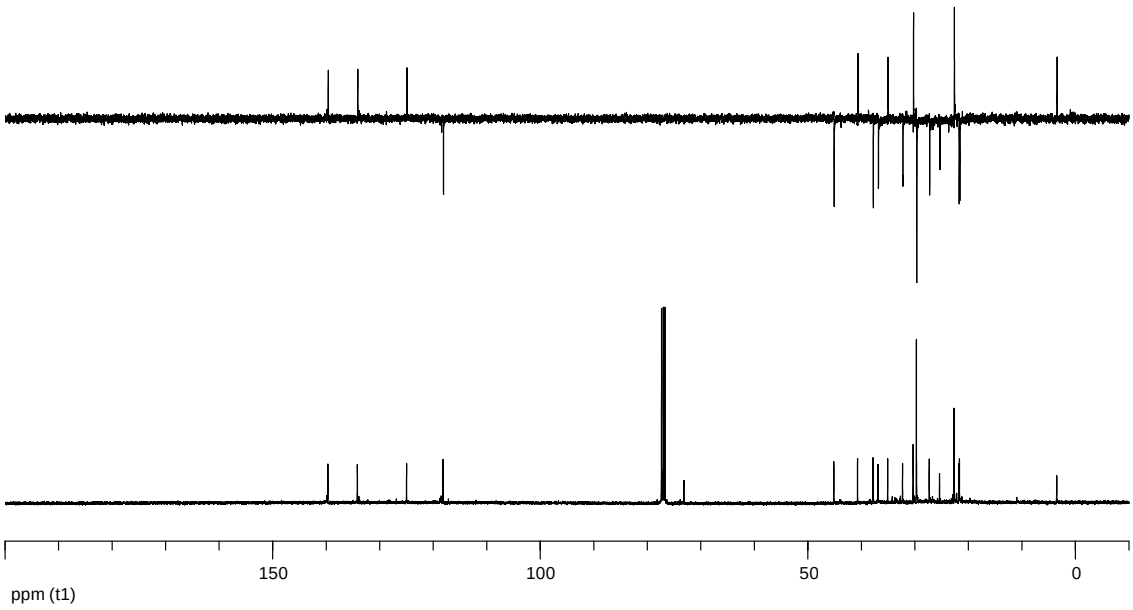

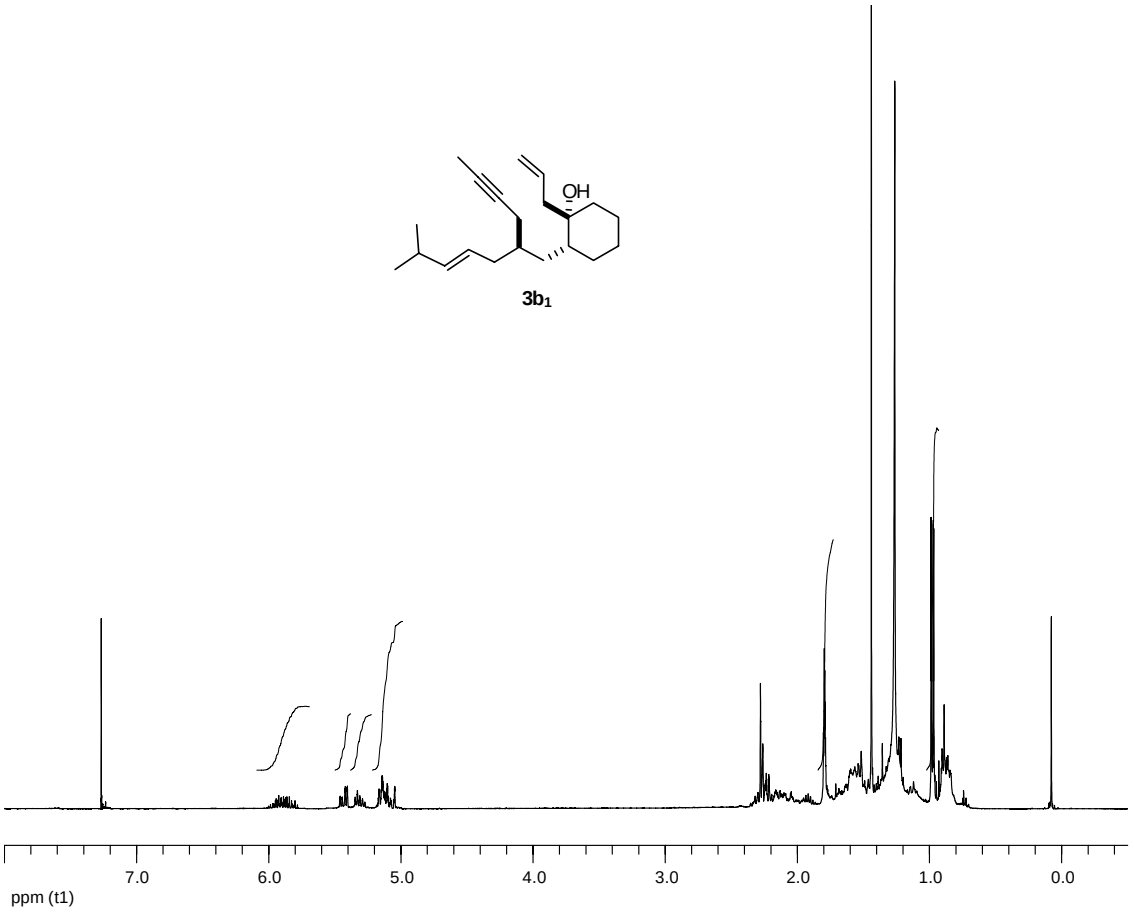

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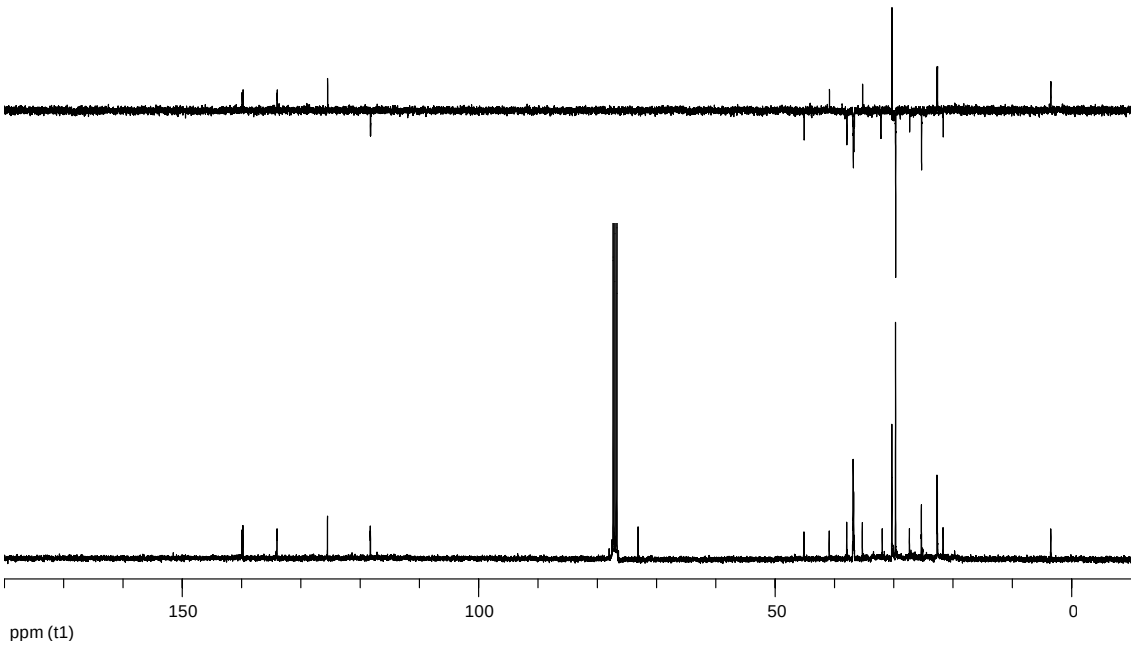
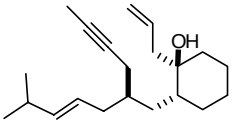
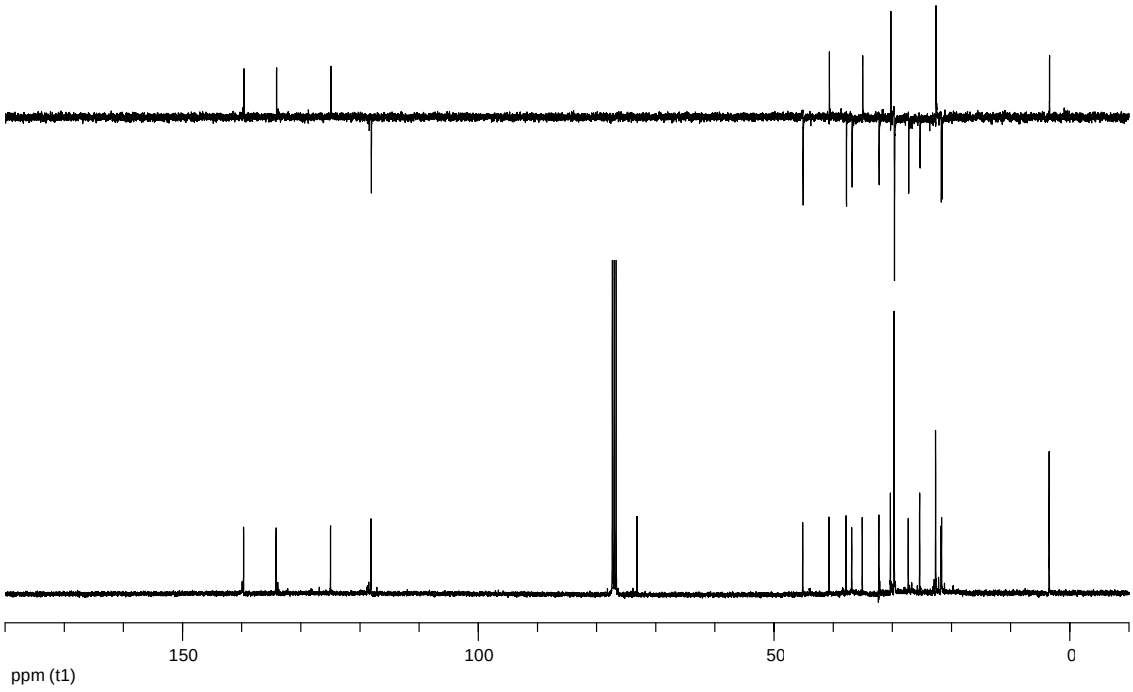
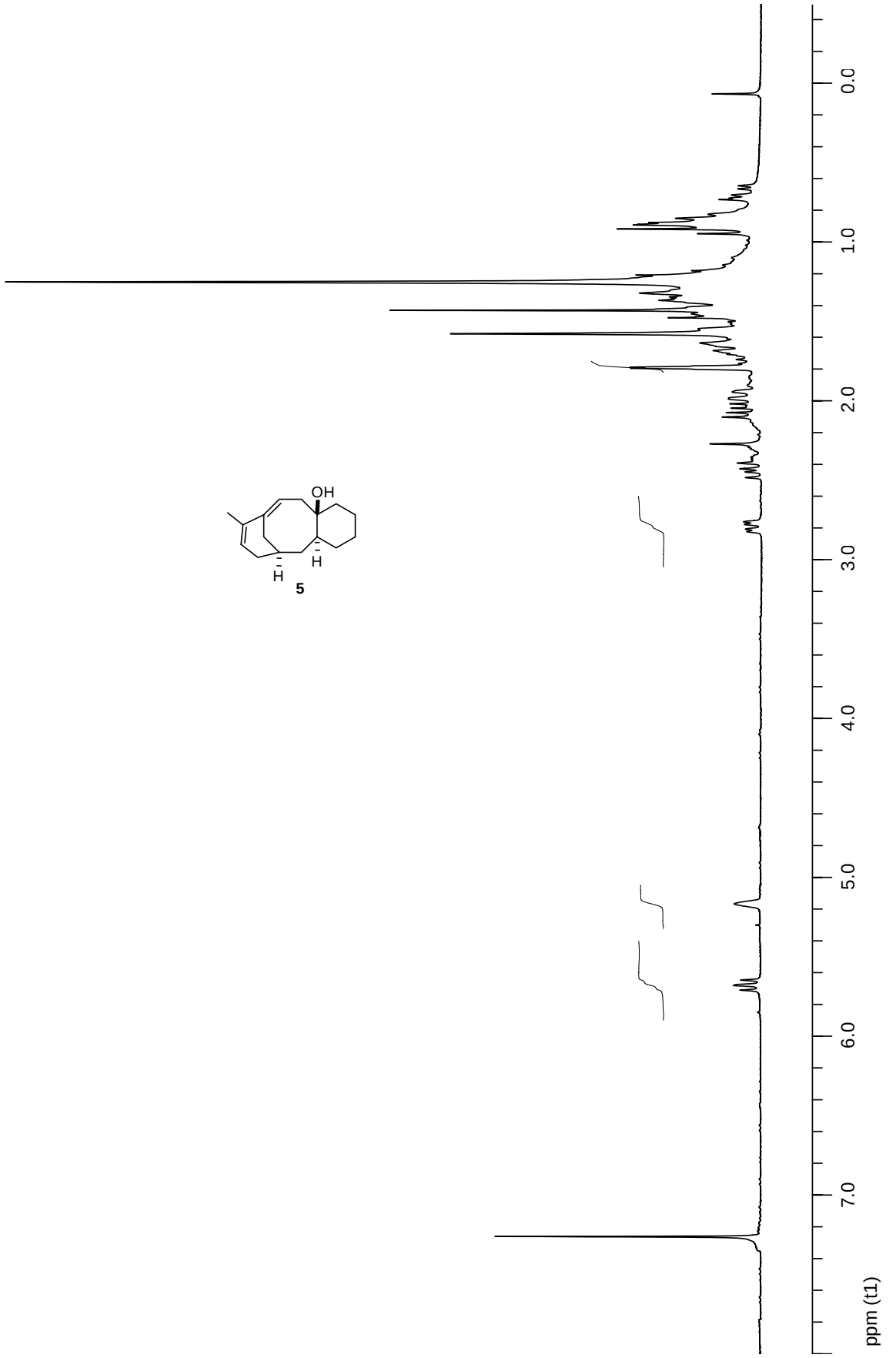




3b$_2$

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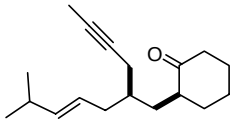
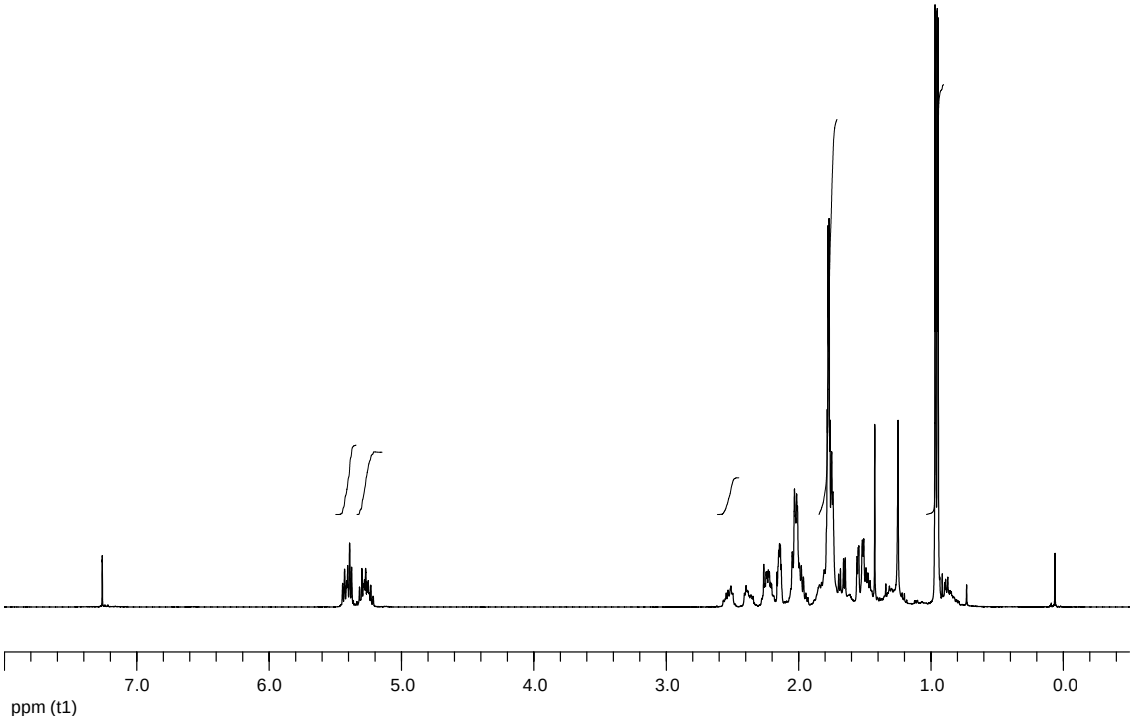
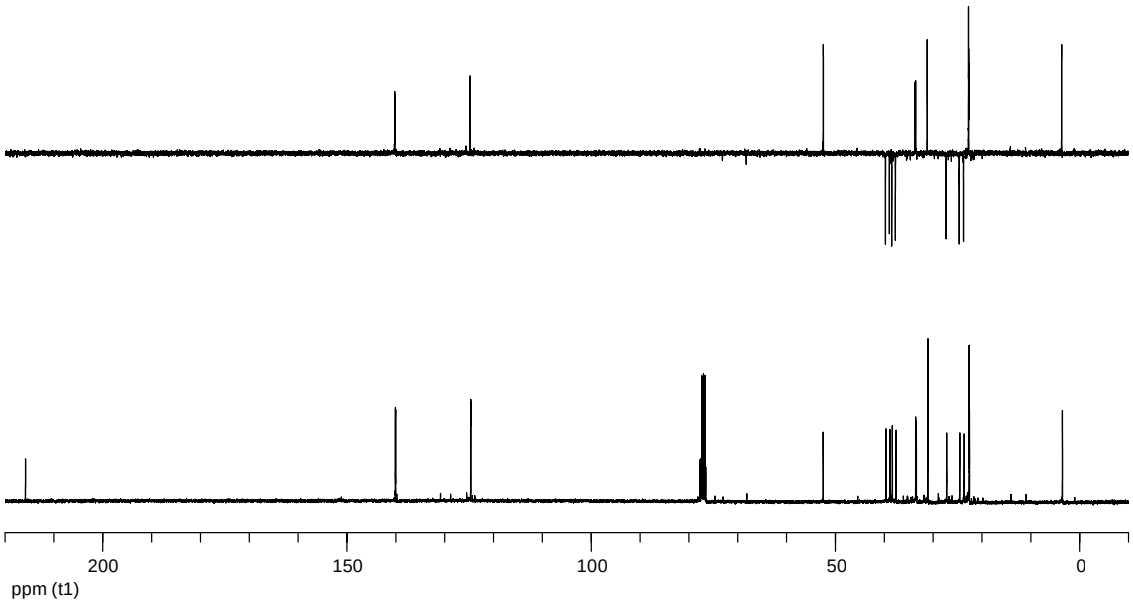
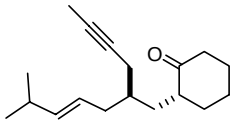


8a







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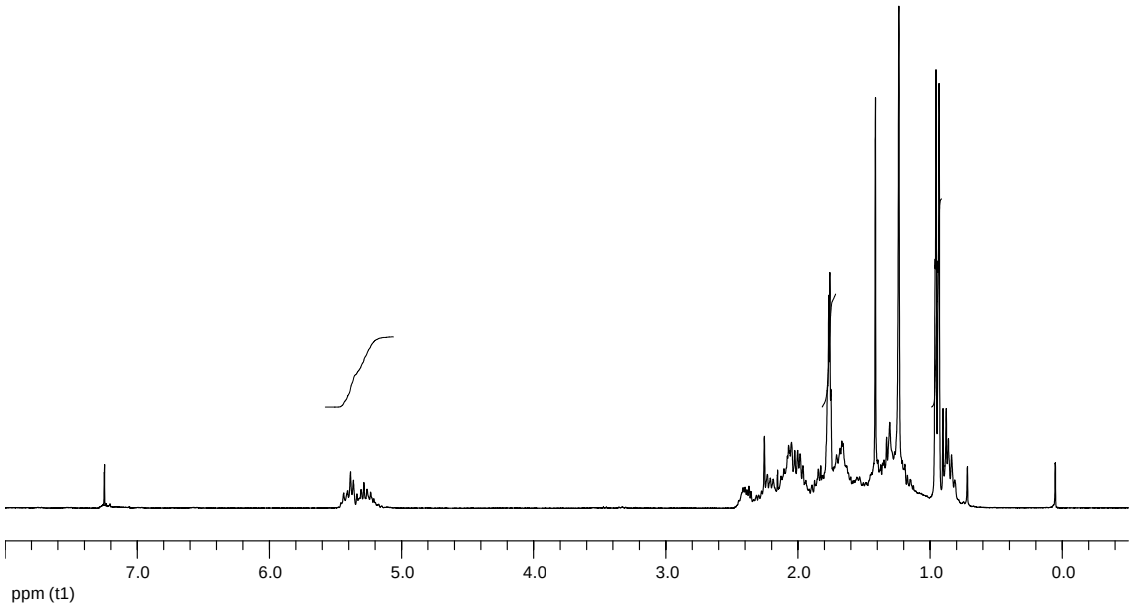

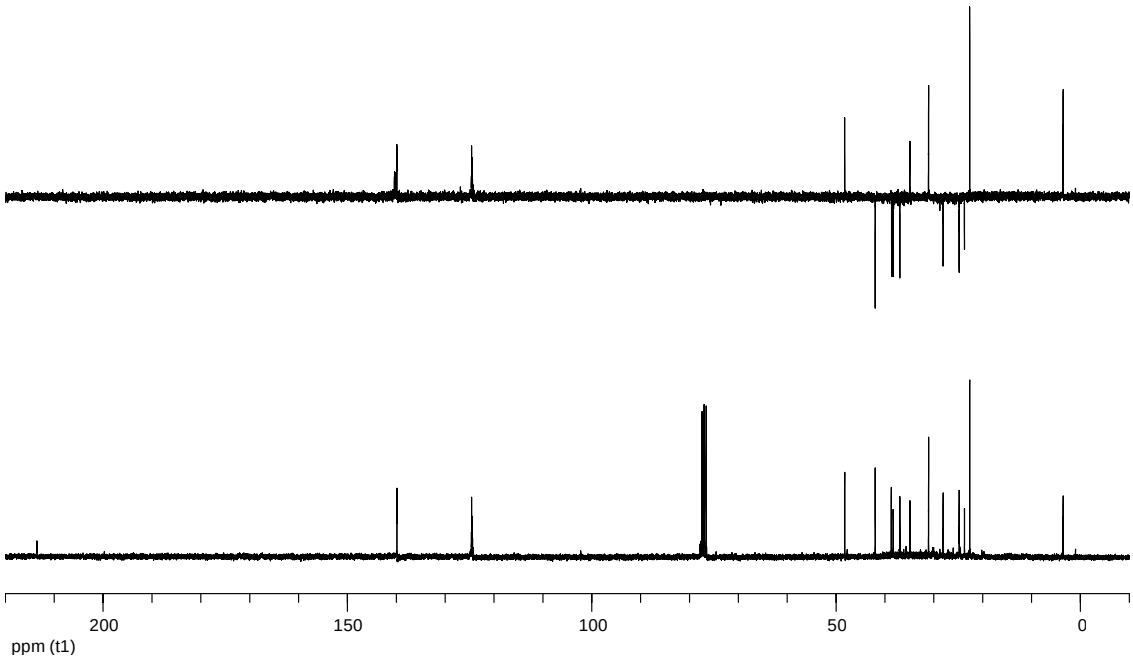

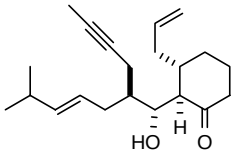

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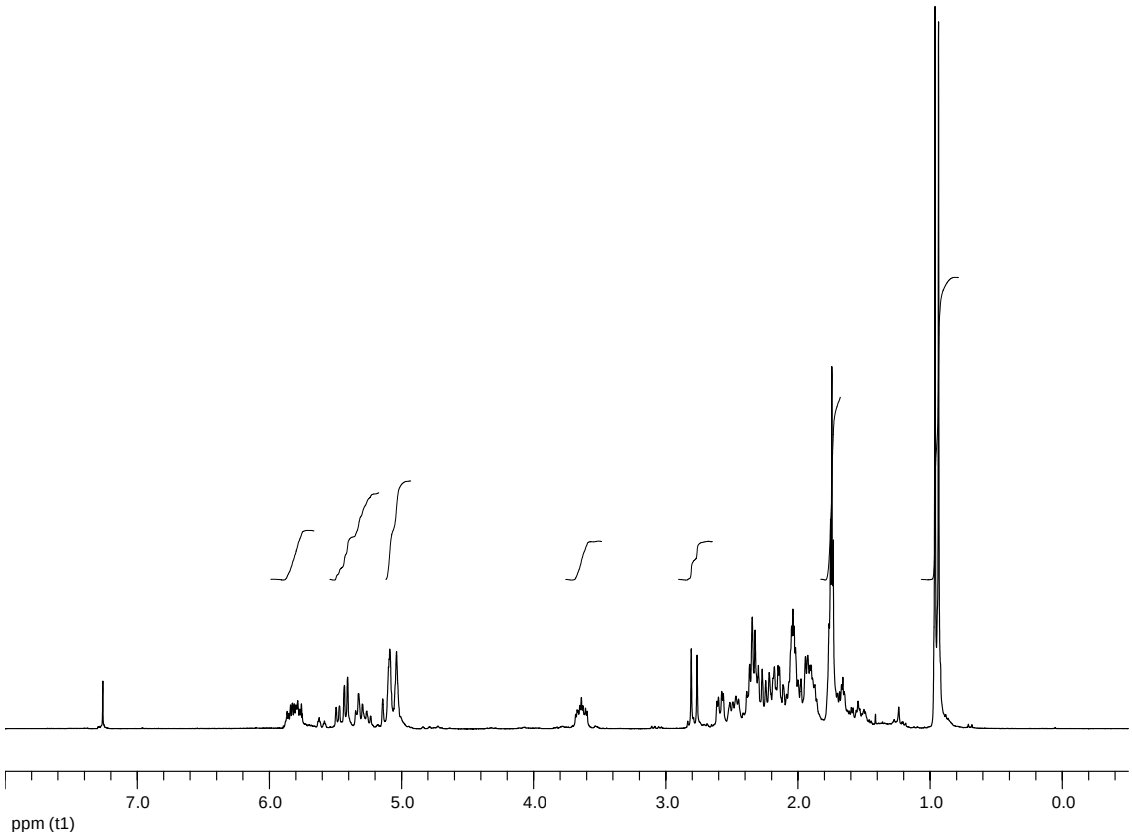

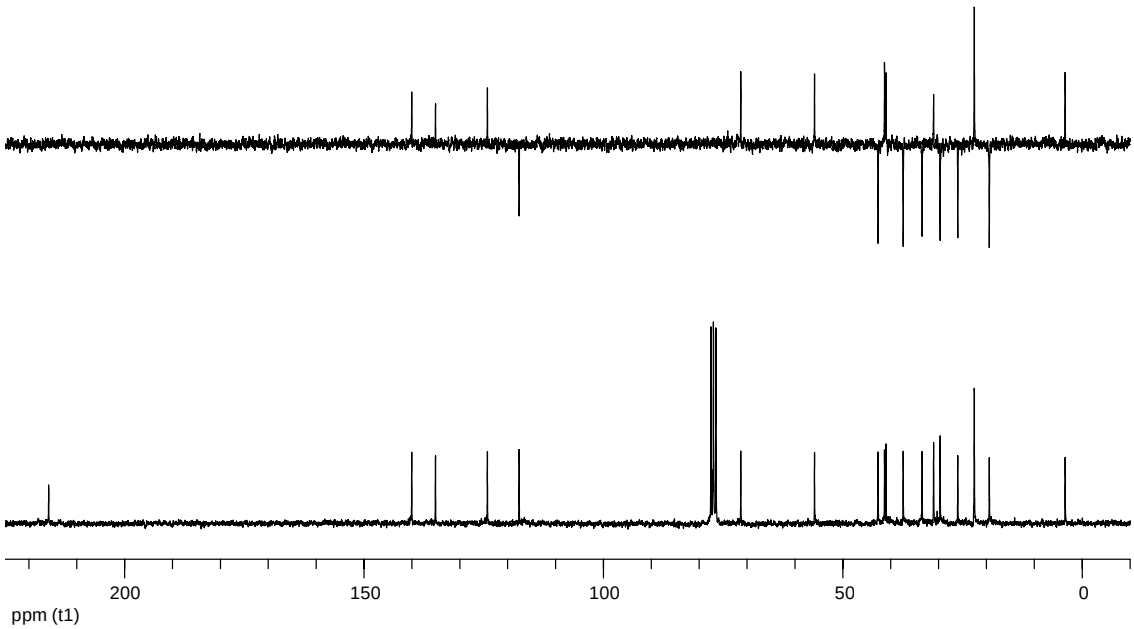

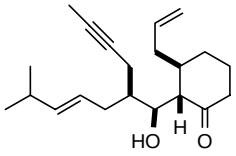

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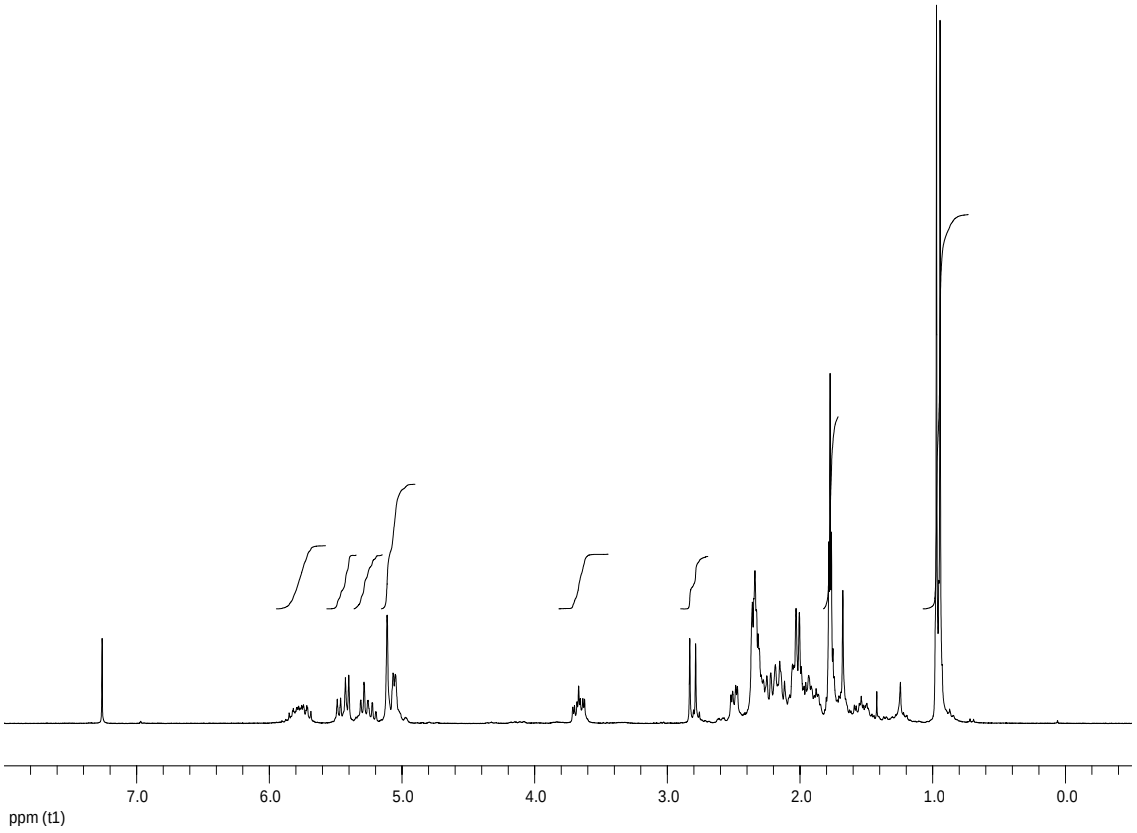
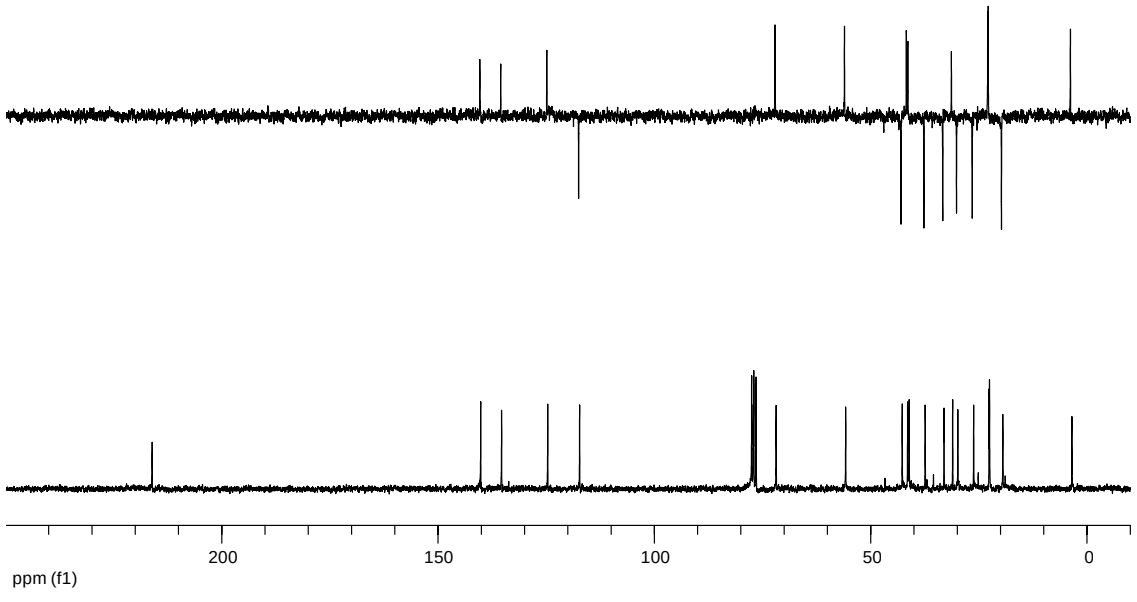
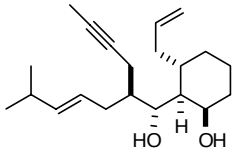
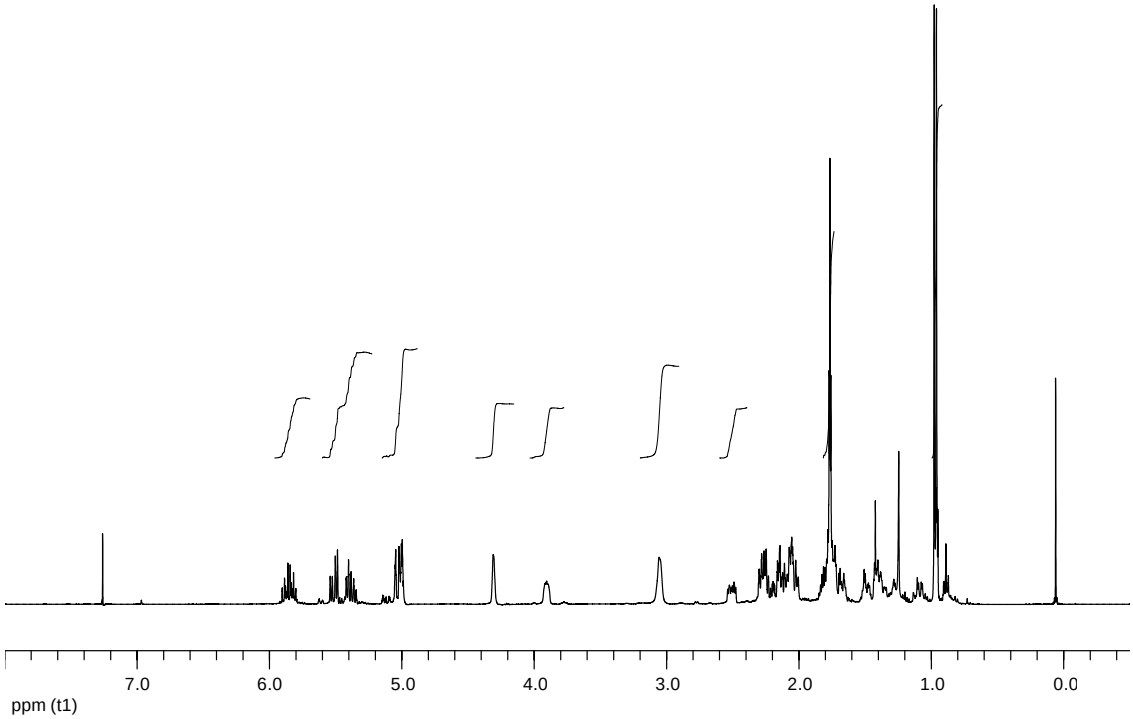
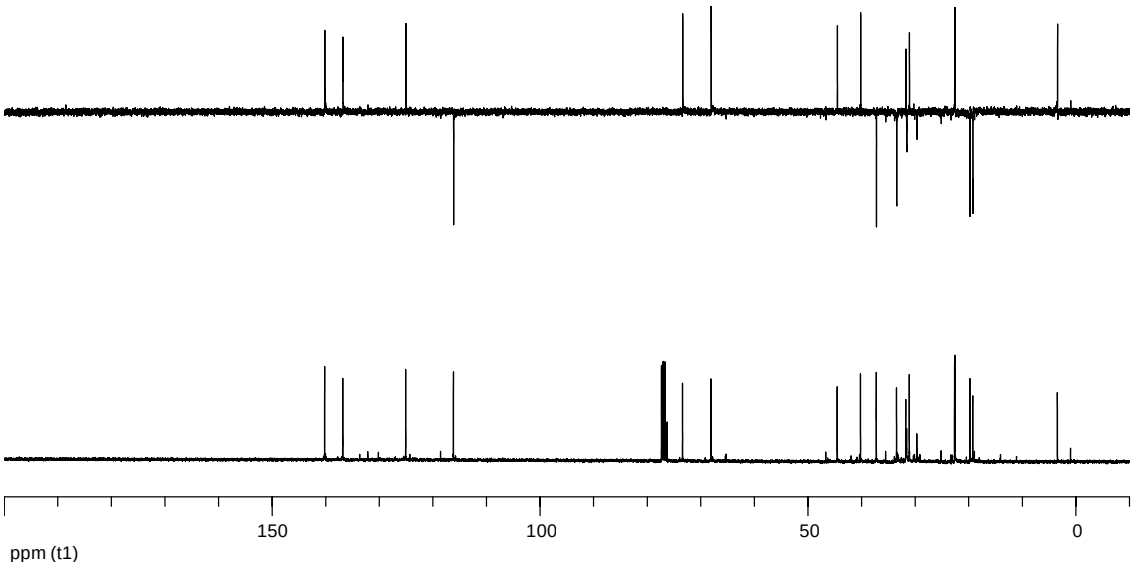


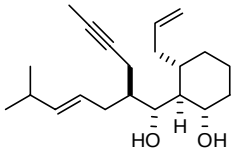




13a$_{4R}$







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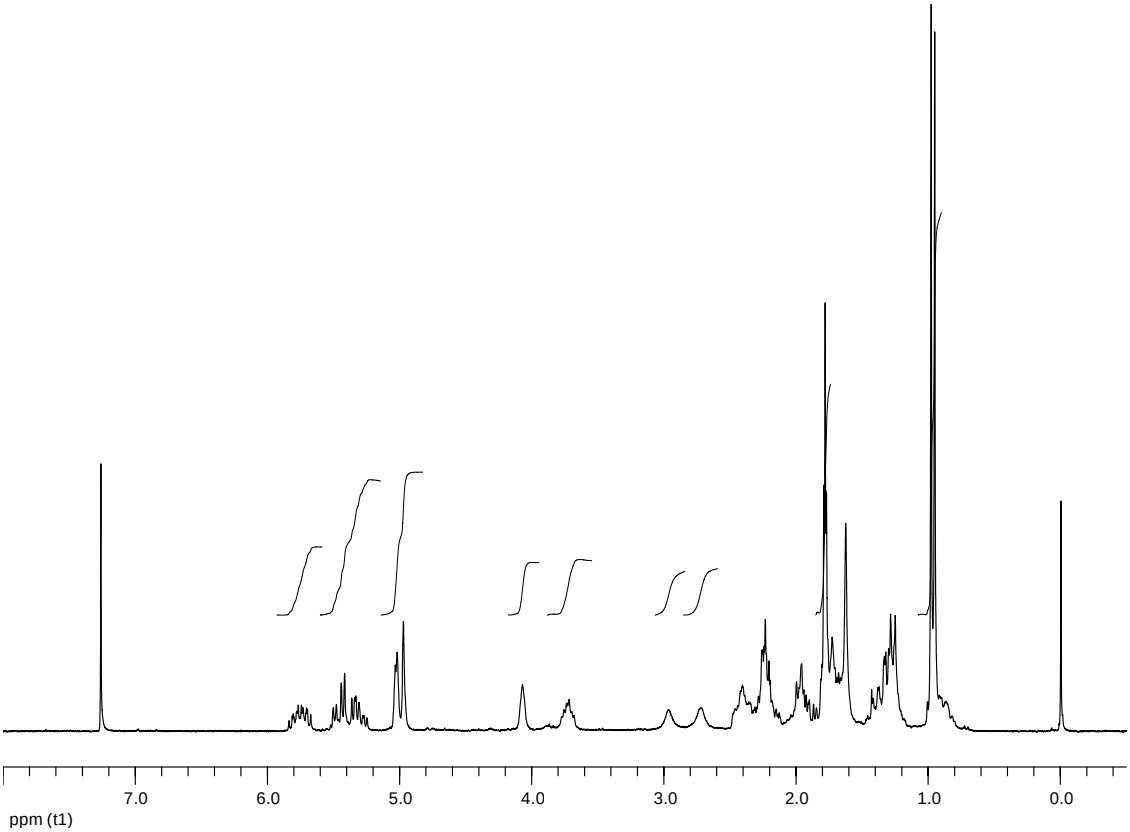
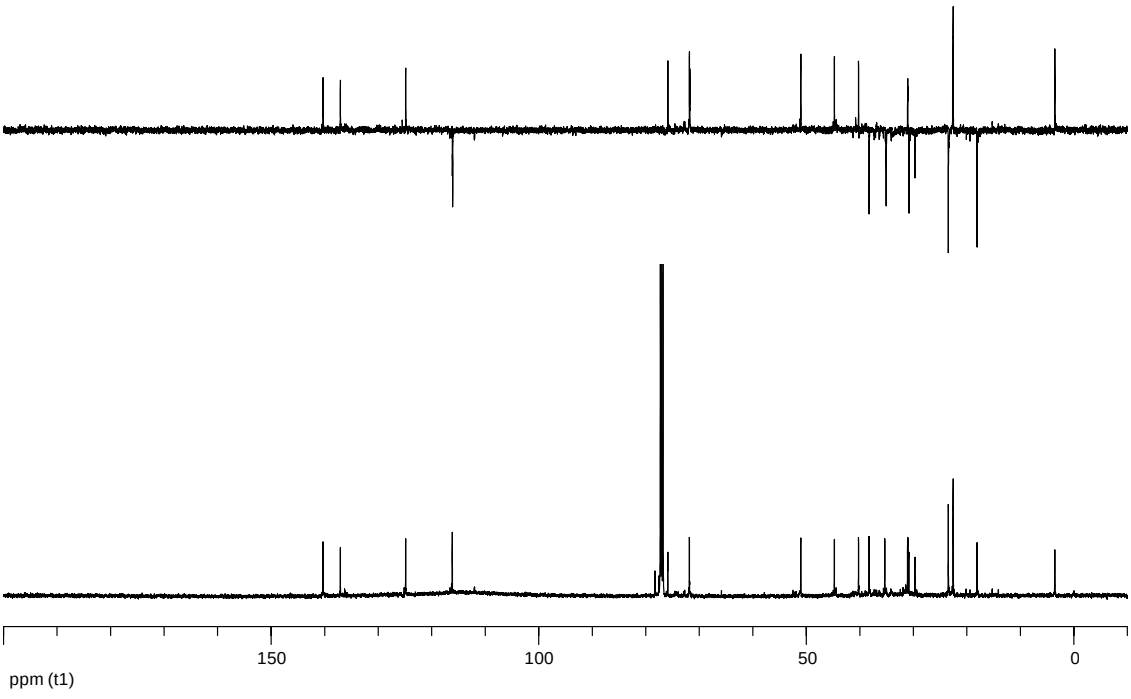
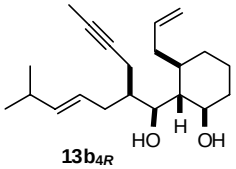
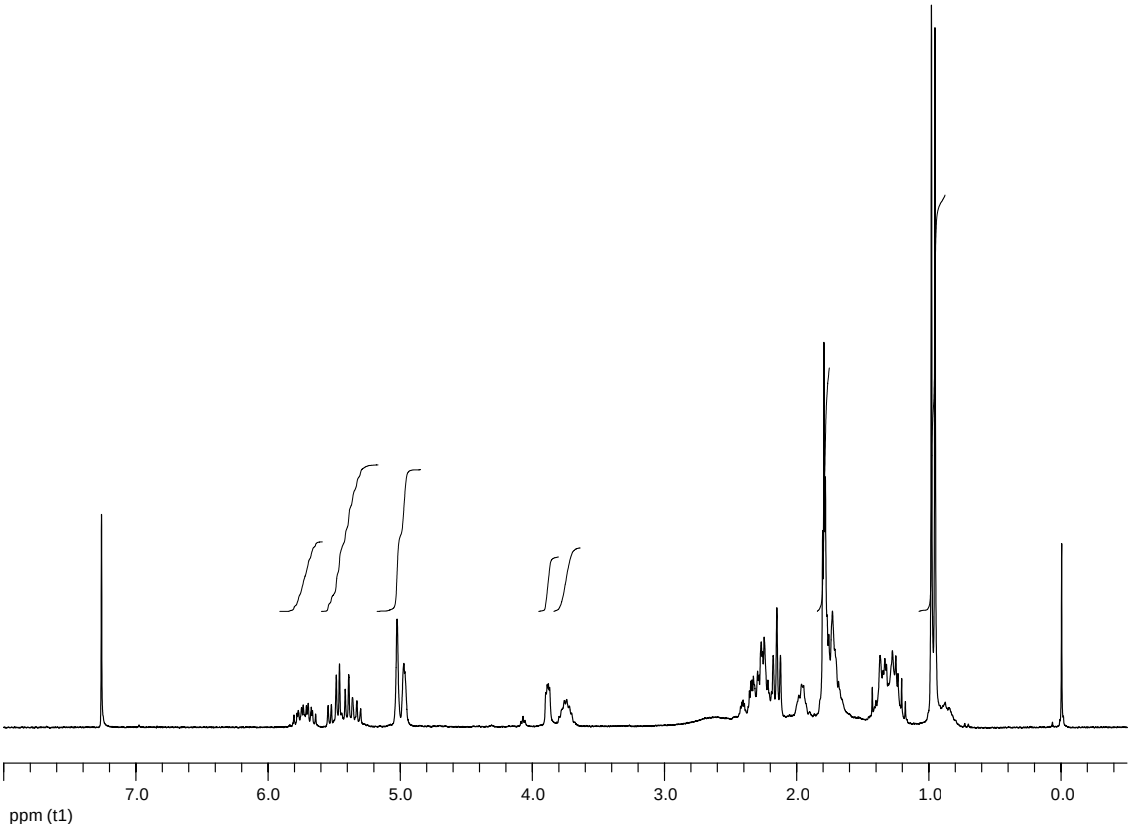
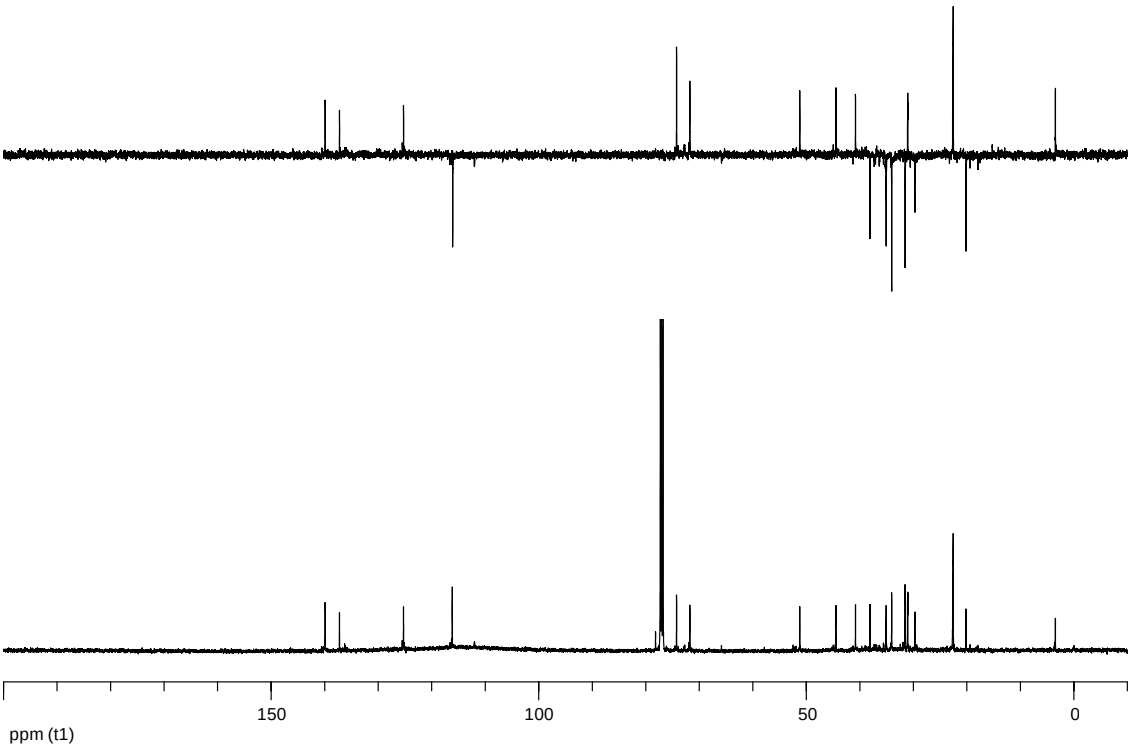


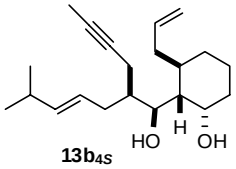




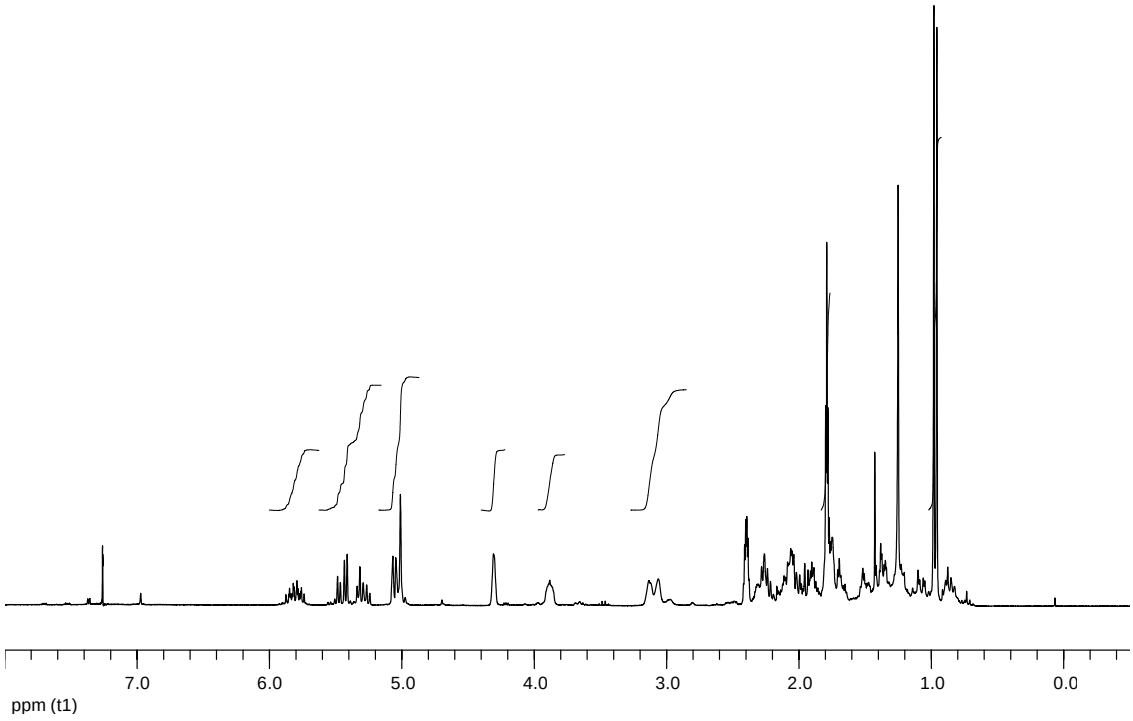
13b$_{4R}$

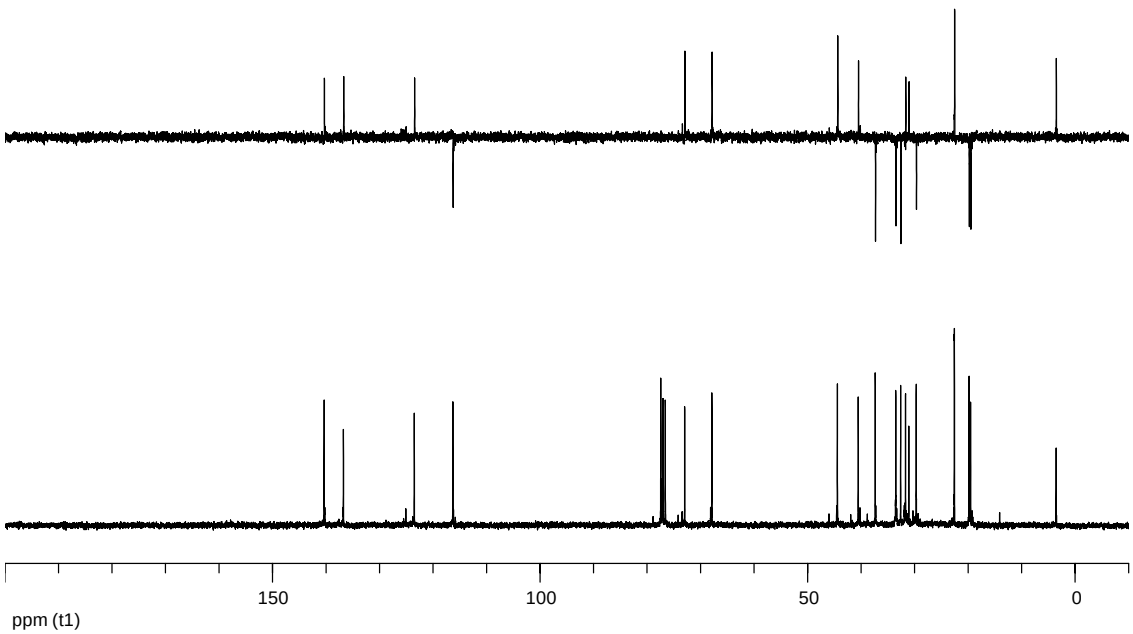


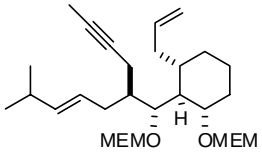




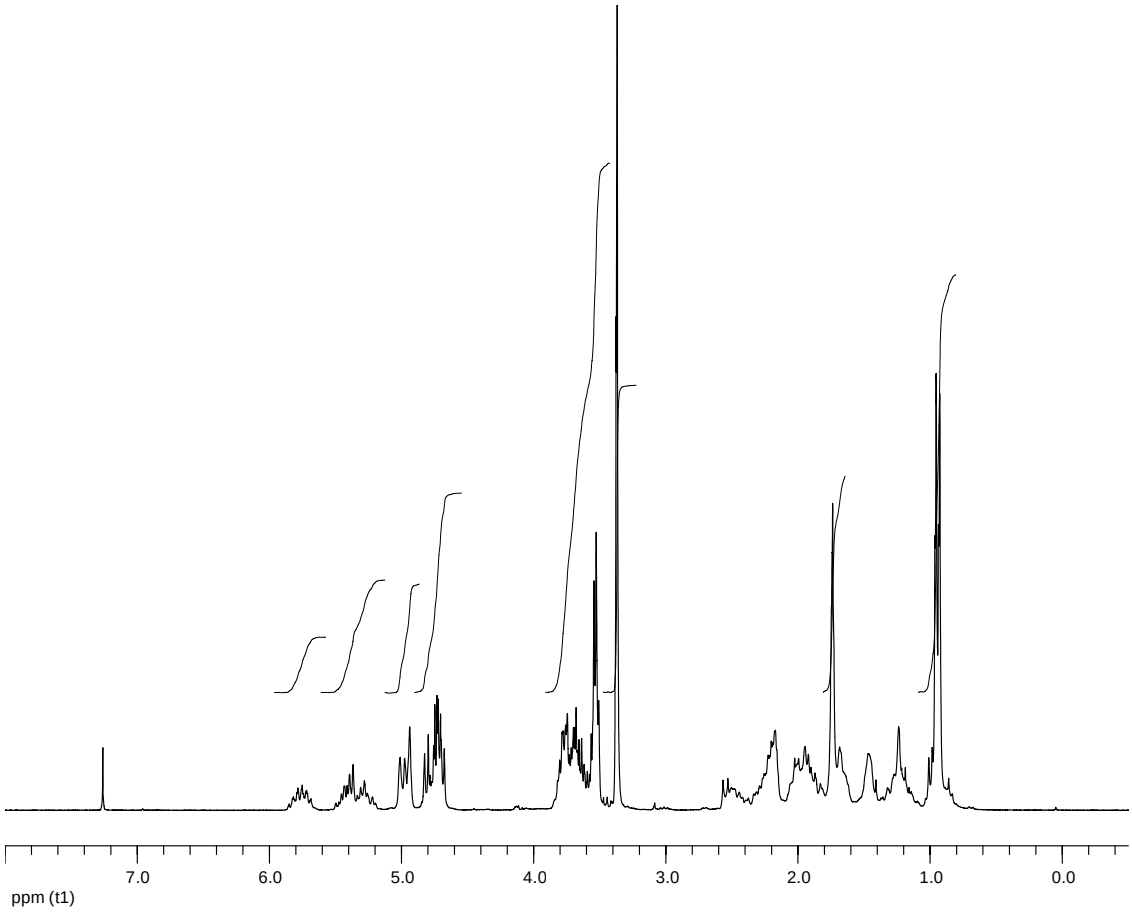
13b$_{4S}$

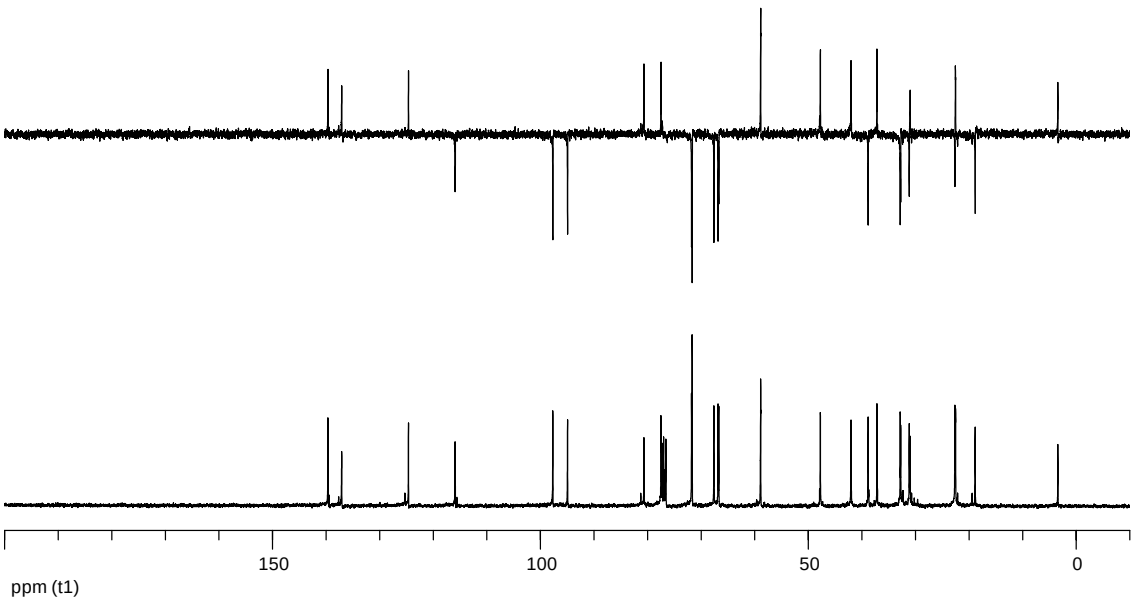


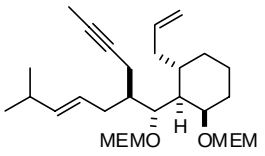




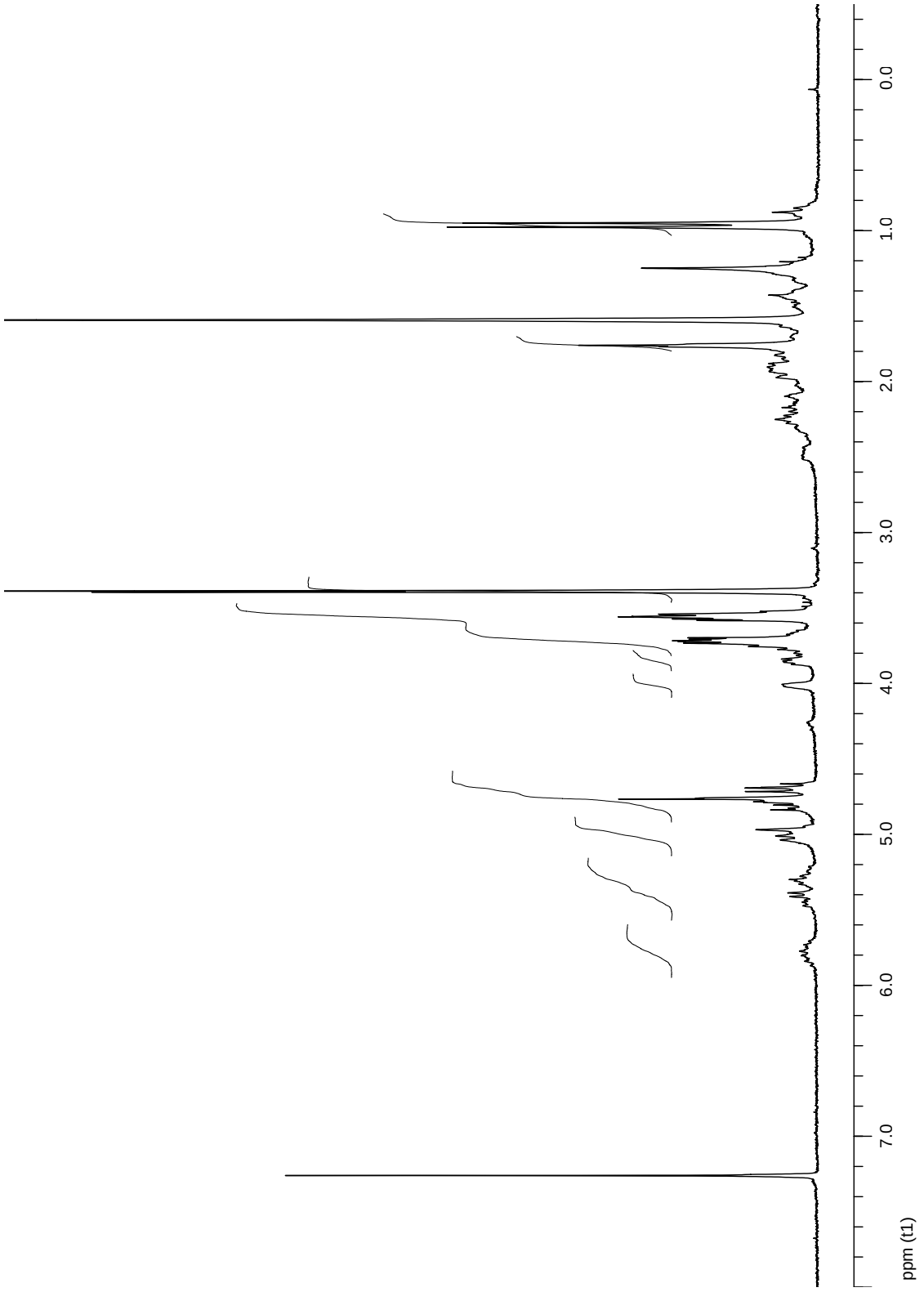
14a$_{4S}$

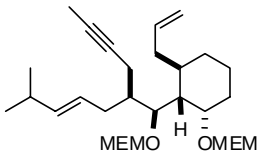




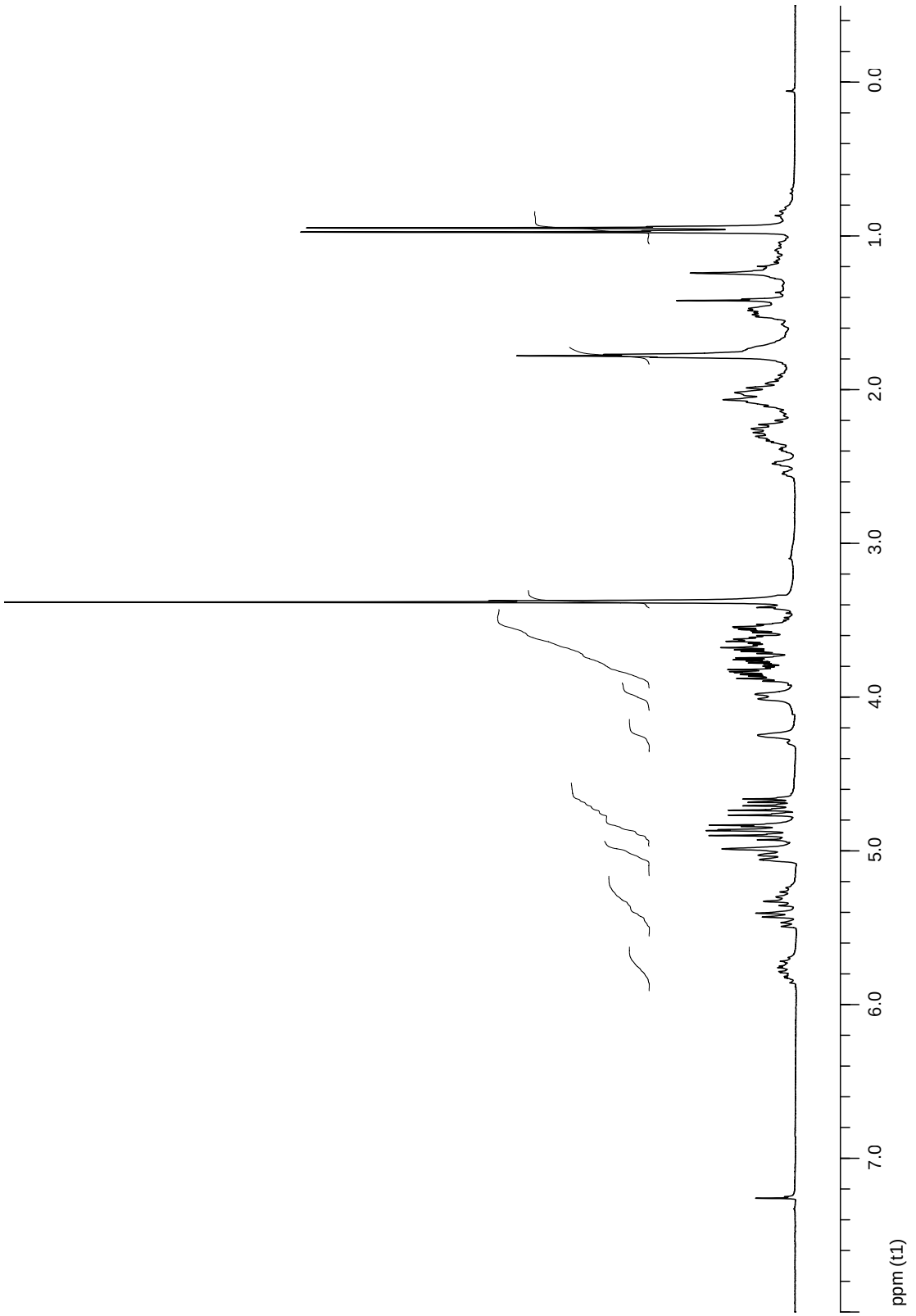


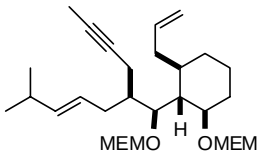
14a$_{4R}$



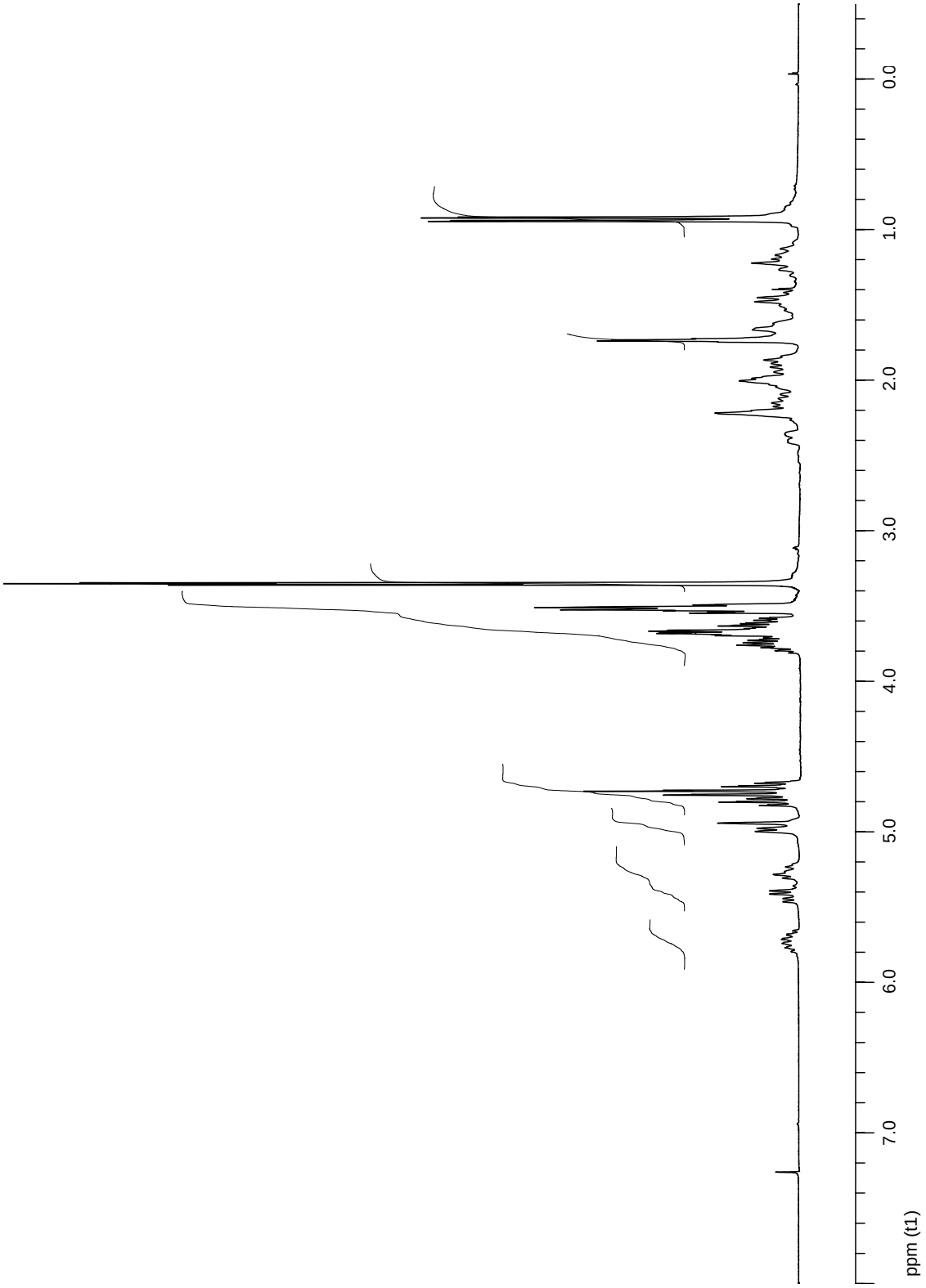


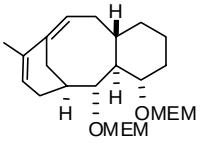
14b$_{4S}$



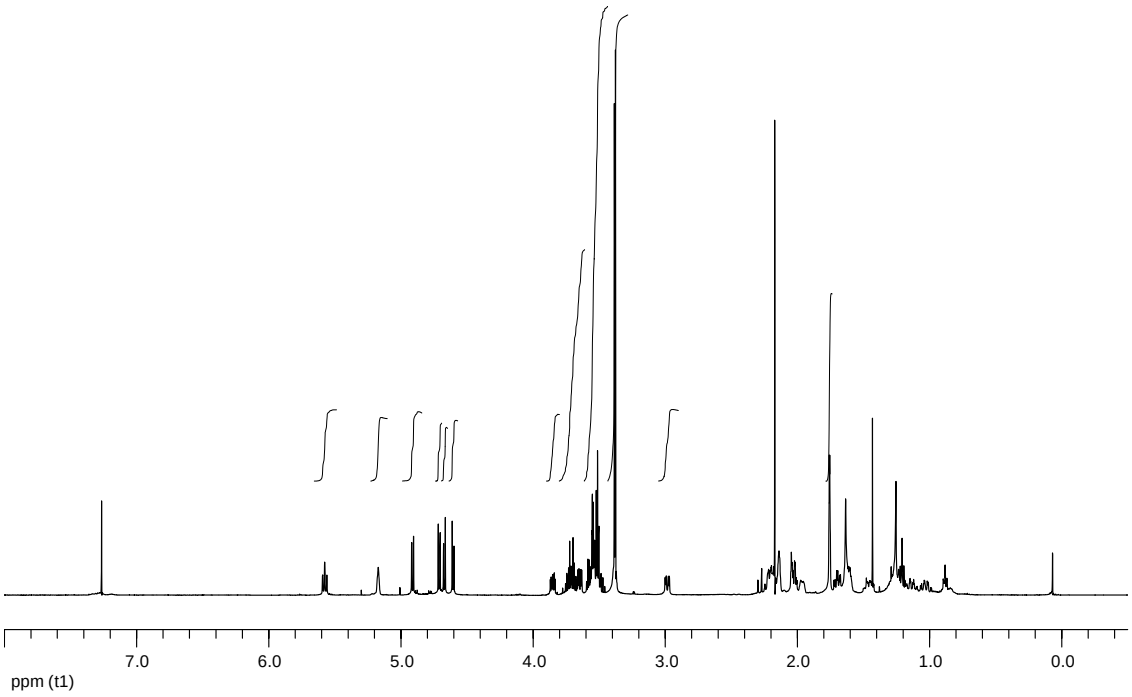


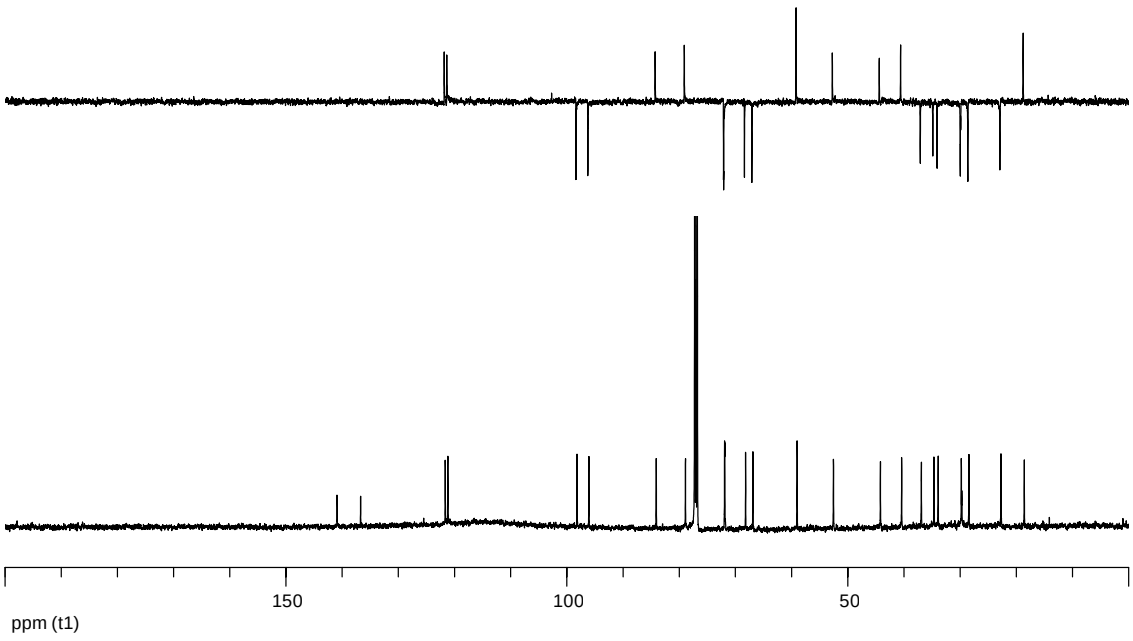
14b$_{4R}$



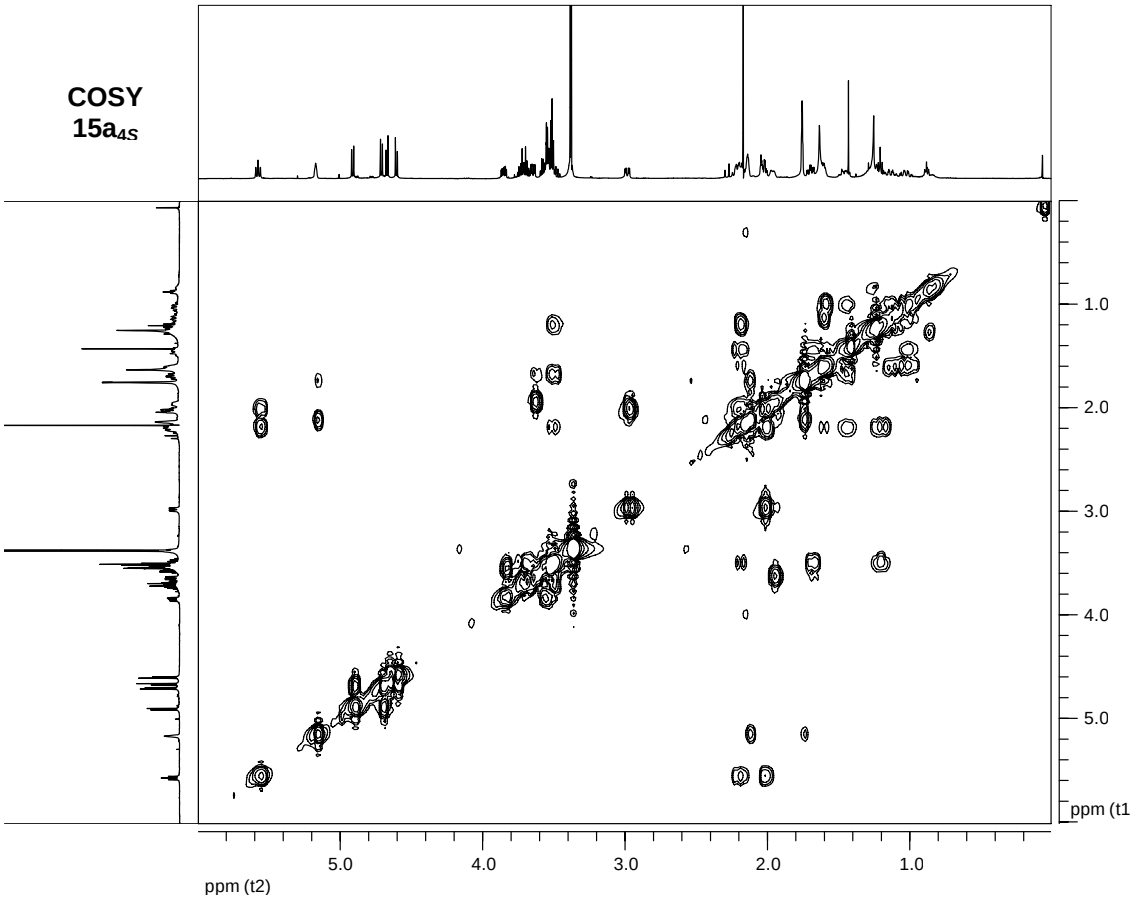


15a$_{4S}$

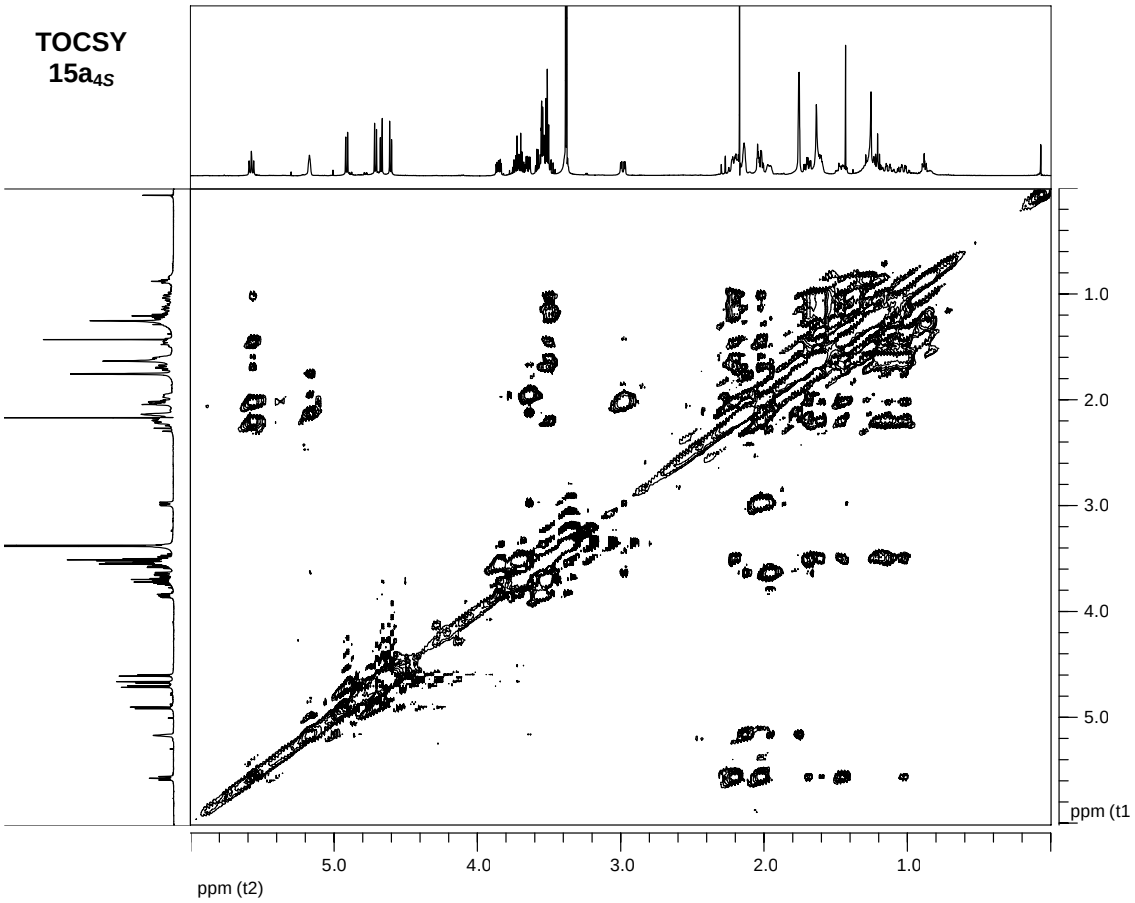




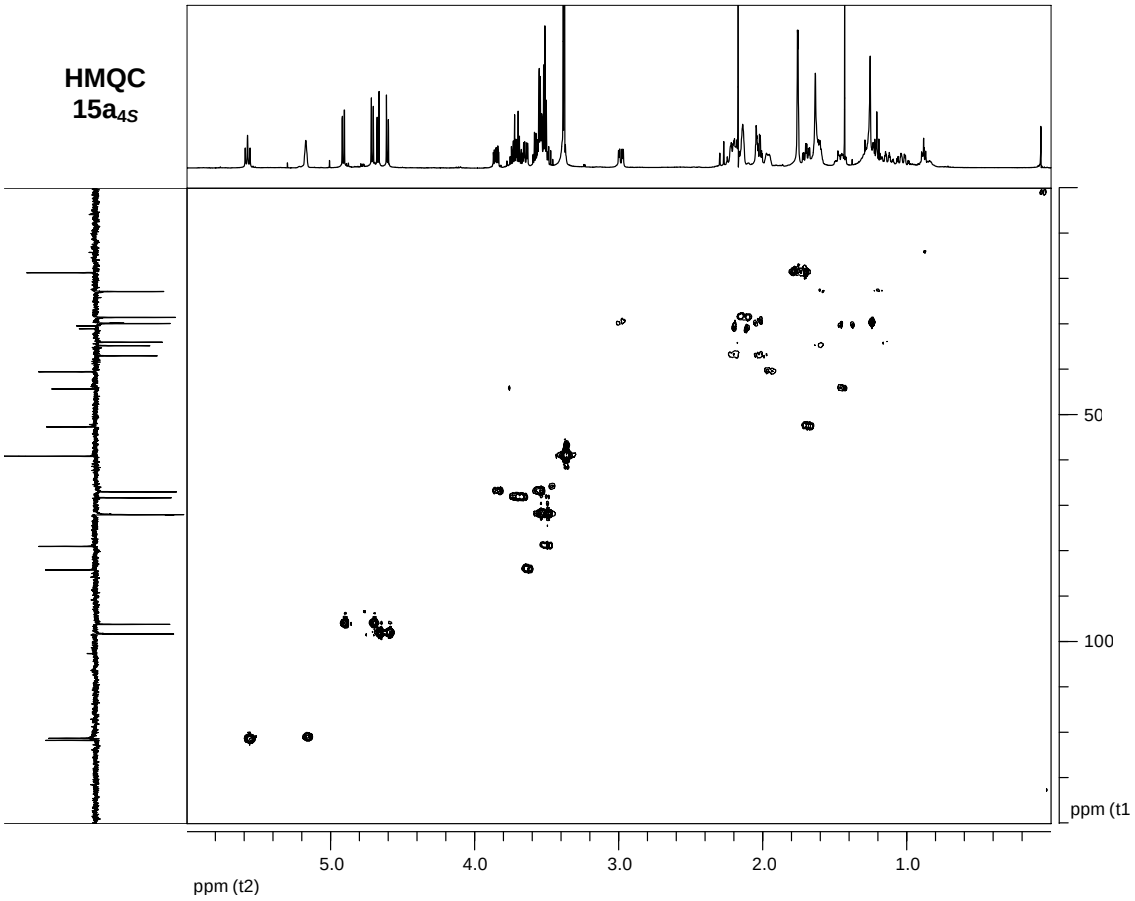
COSY
15a$_{4S}$



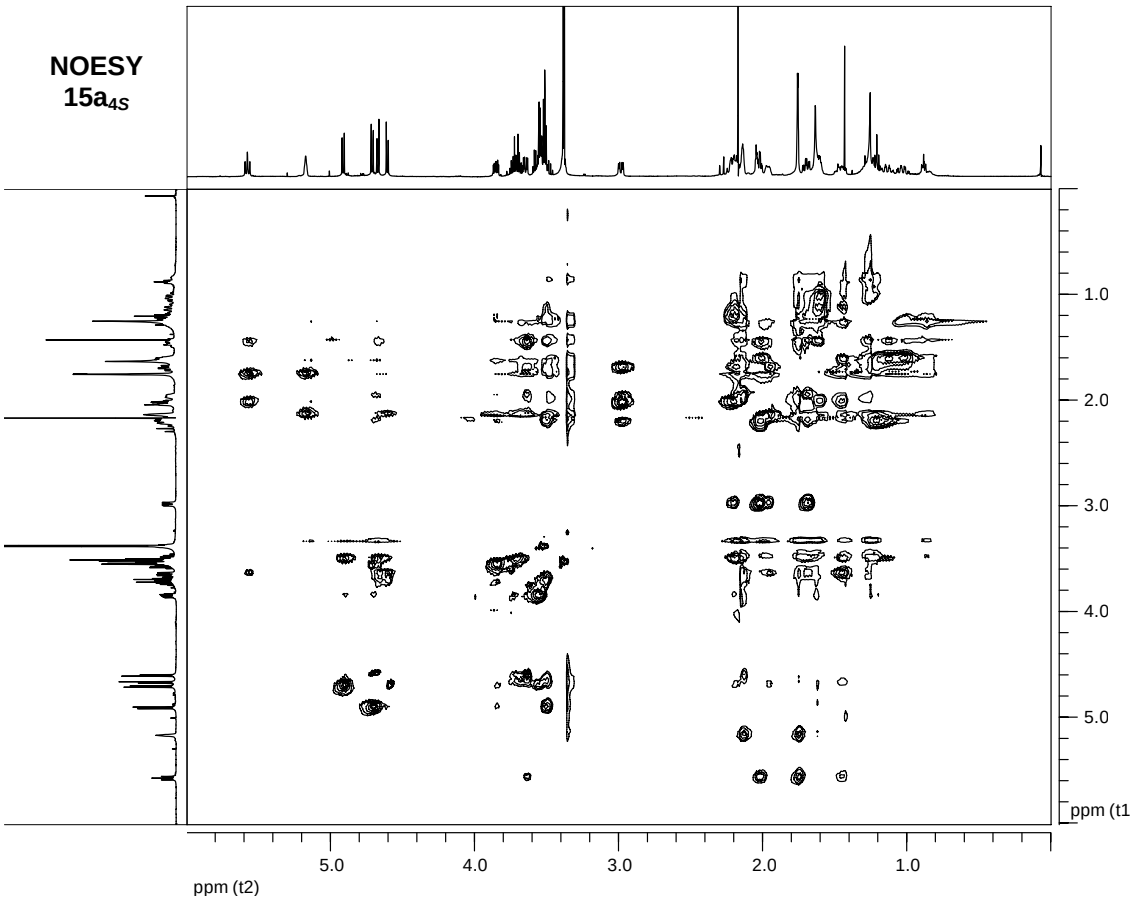
TOCSY
15a$_{4S}$

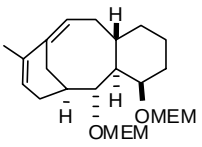


HMQC
15a$_{4S}$

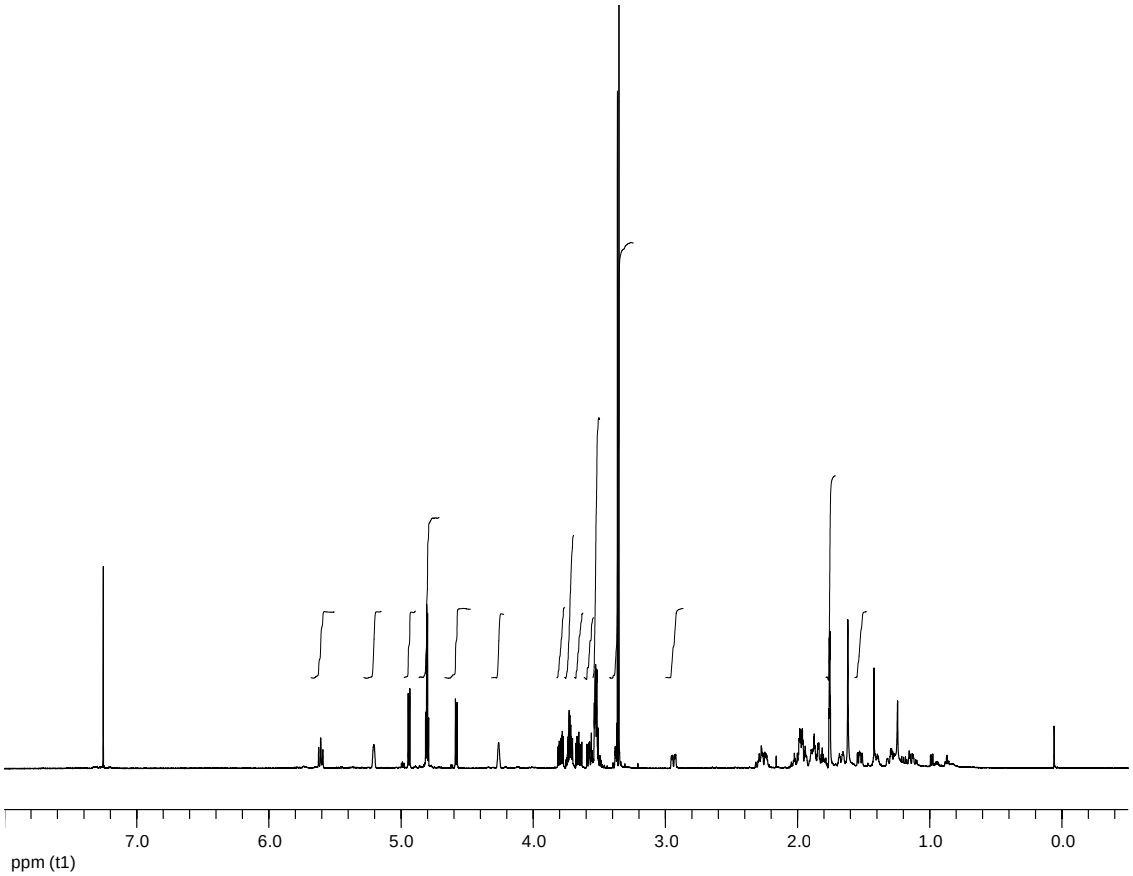


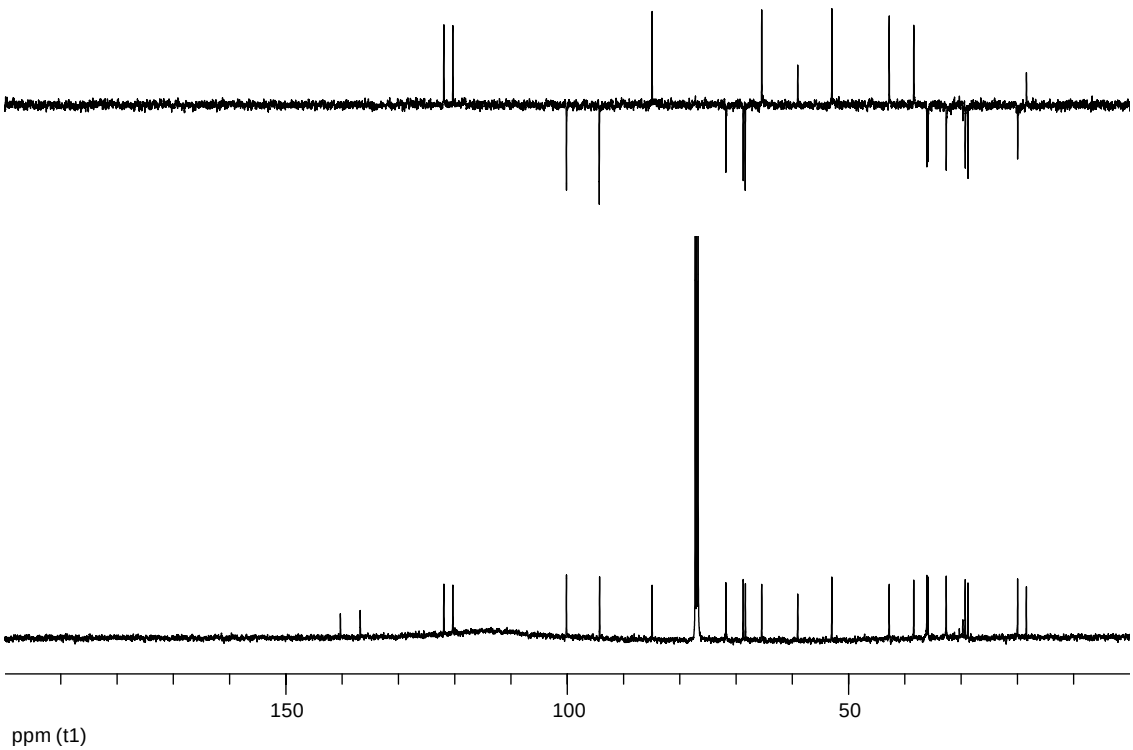
NOESY
15a$_{4S}$



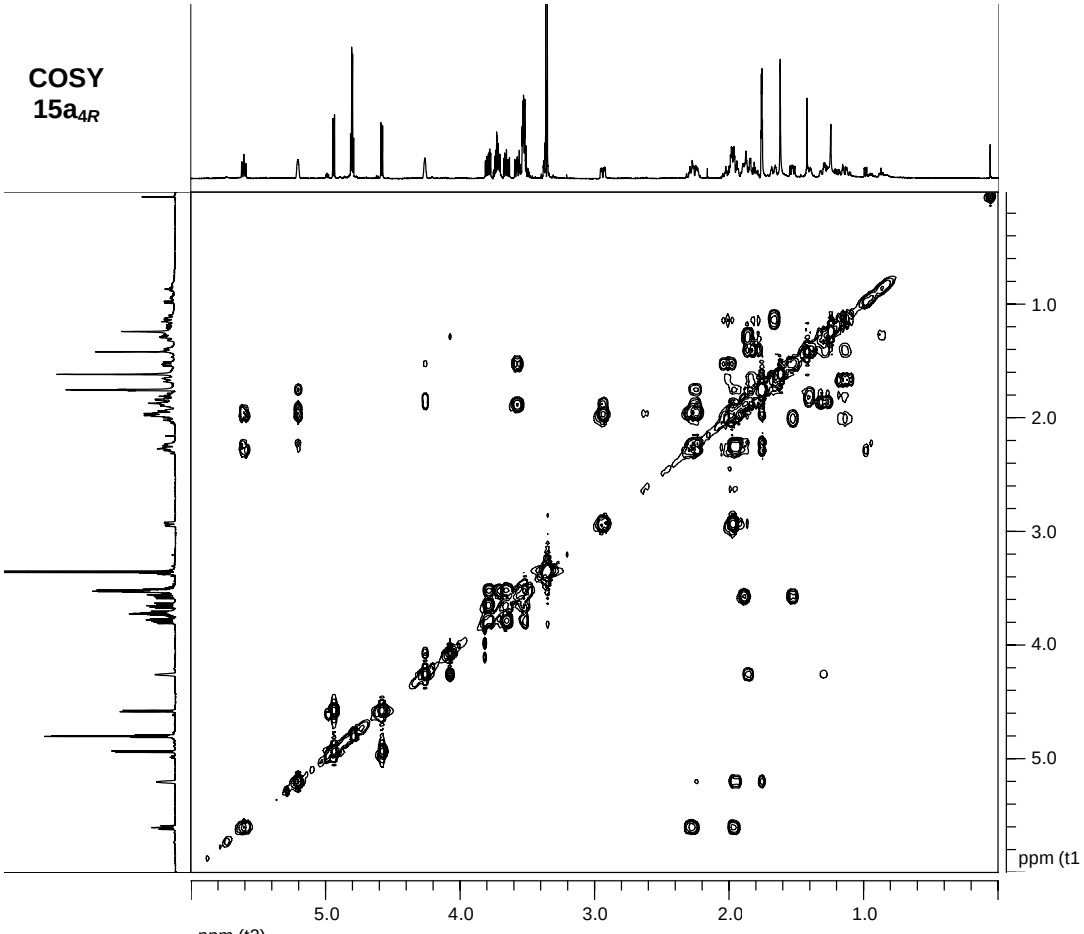


15a$_{4R}$

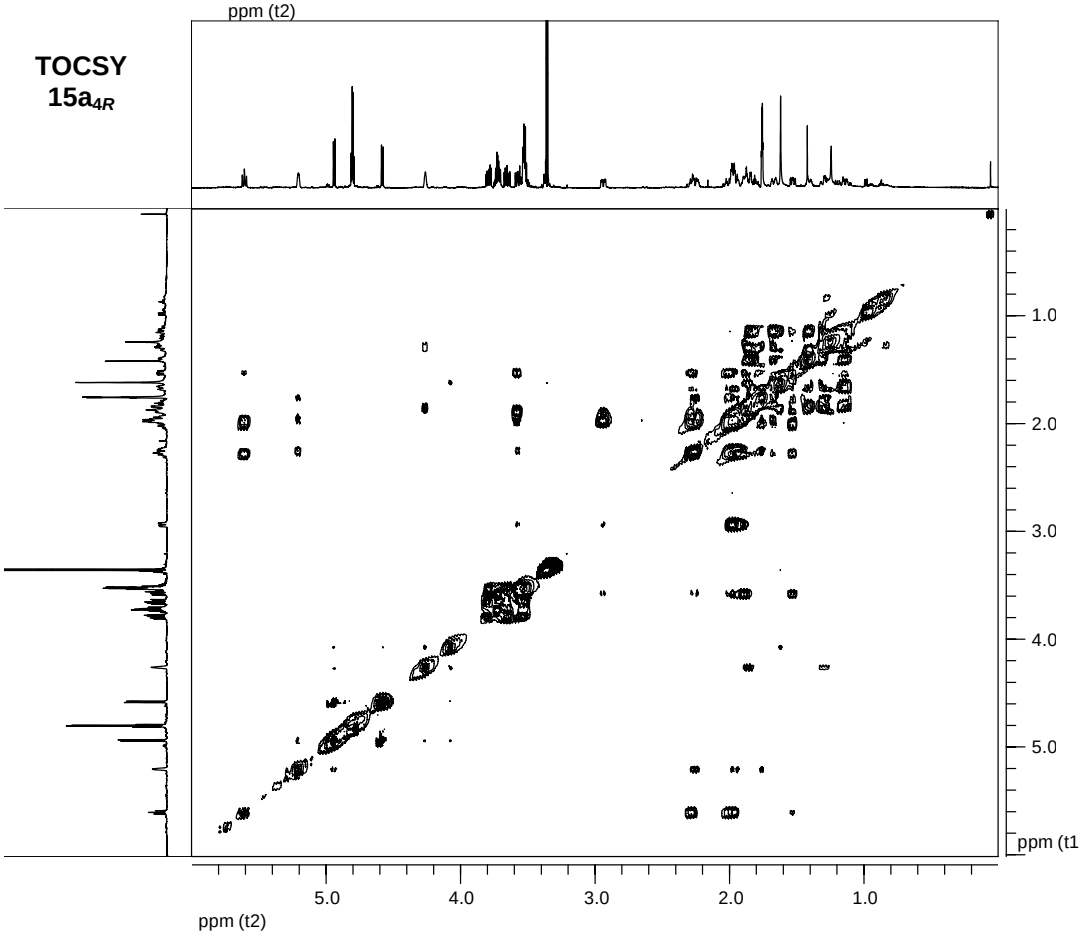


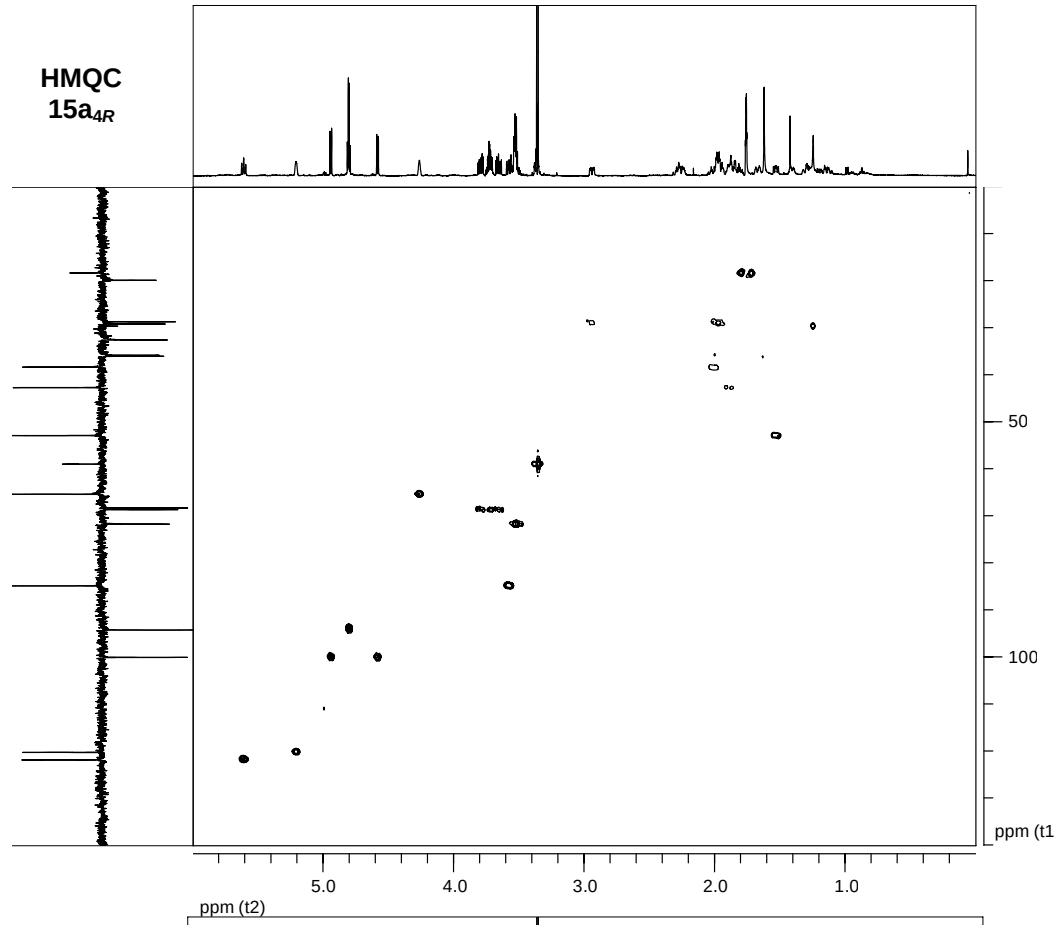


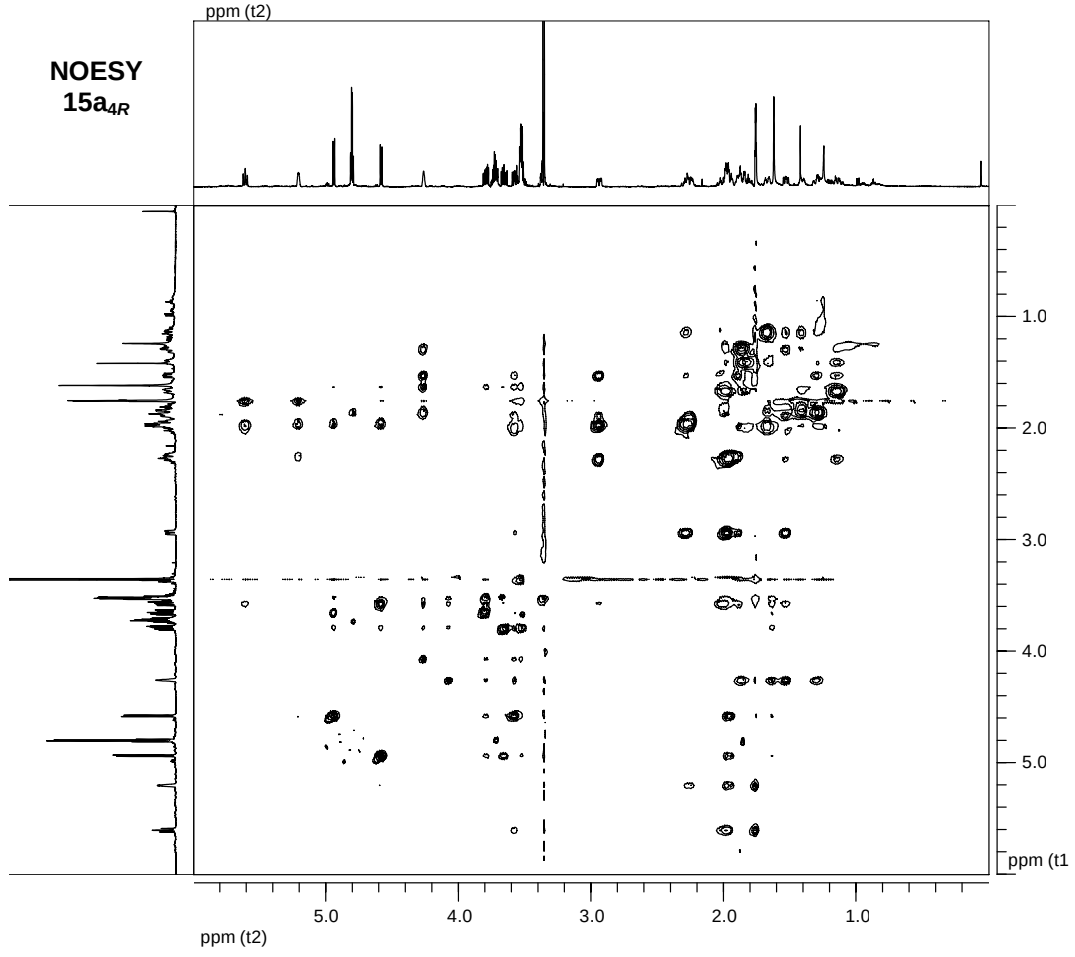
COSY
15a*4R*



TOCSY
15a*4R*




HMQC
15a4R
50
100
ppm (t1
5.0
4.0
3.0
2.0
1.0
ppm (t2)


NOESY
15a4R
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2.0
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4.0
5.0
ppm (t1
5.0
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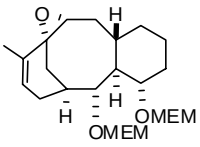
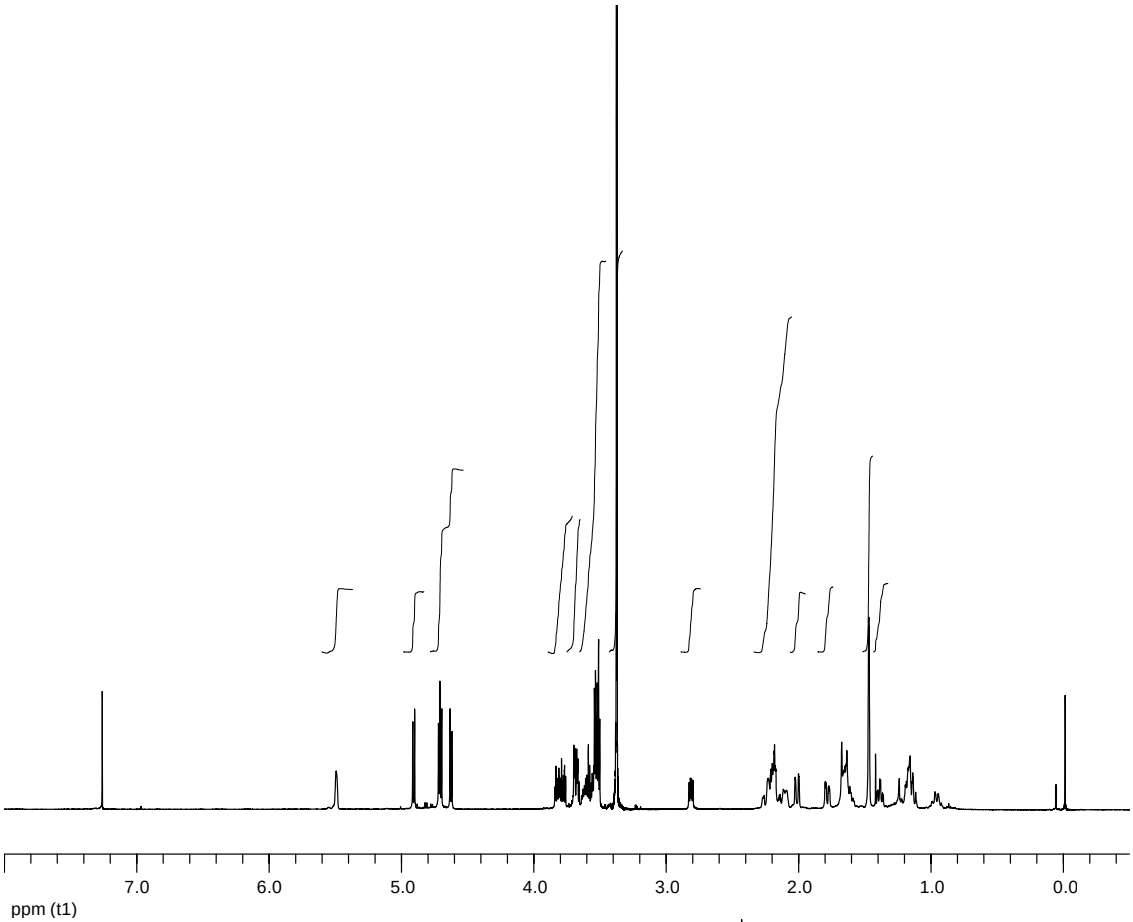
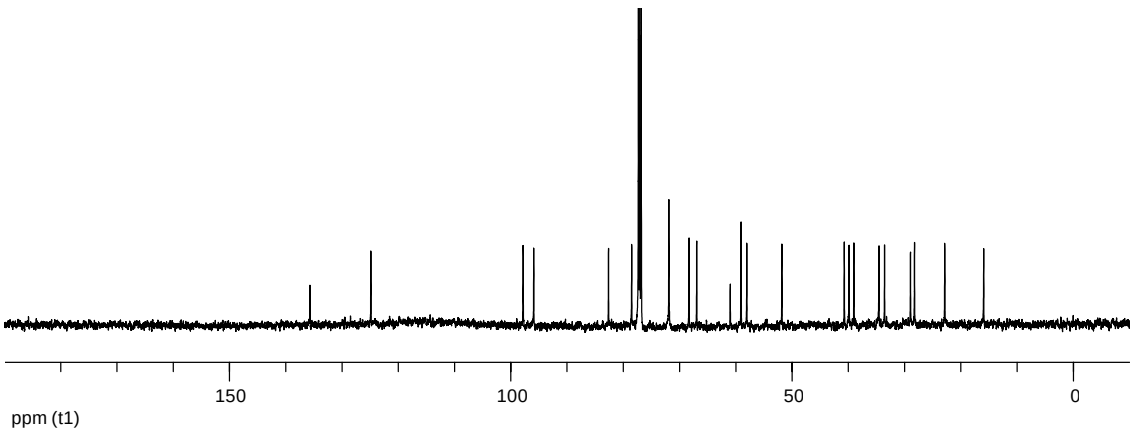
3.0
2.0
1.0
ppm (t2)

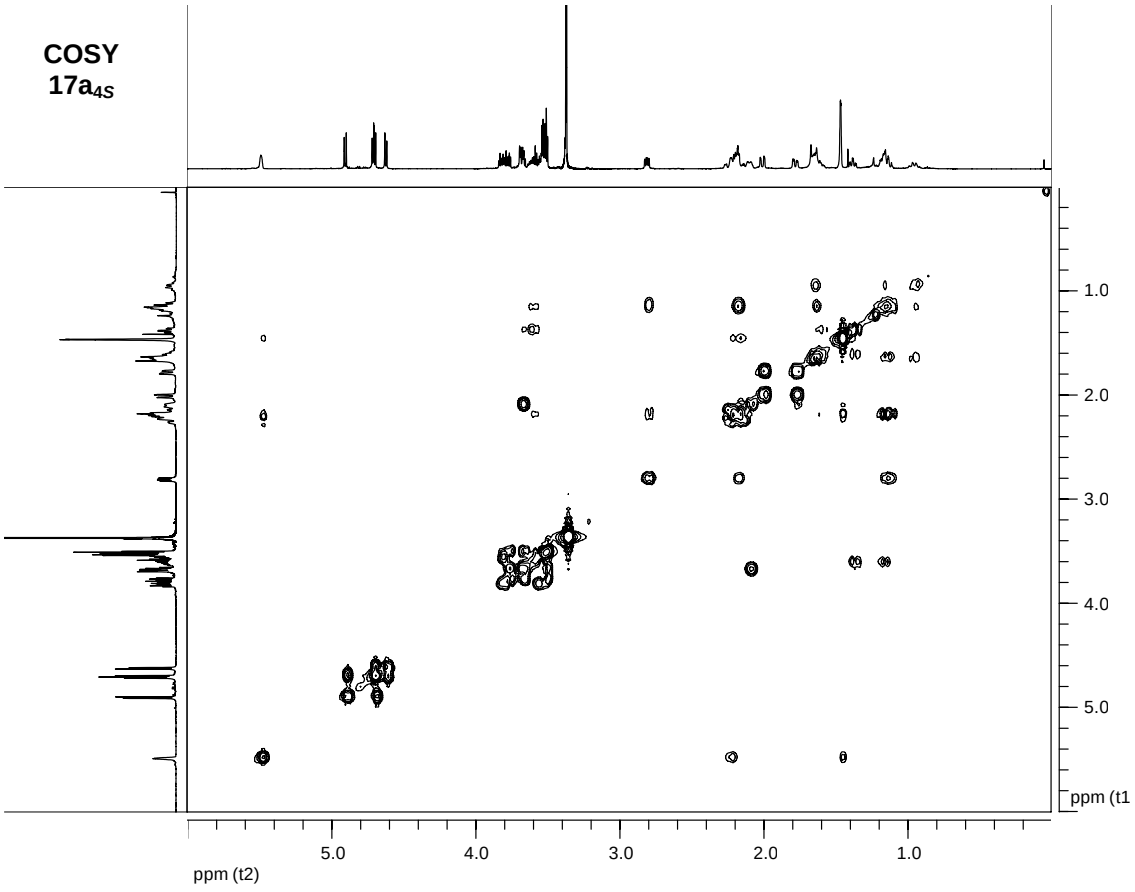


17a$_{4S}$

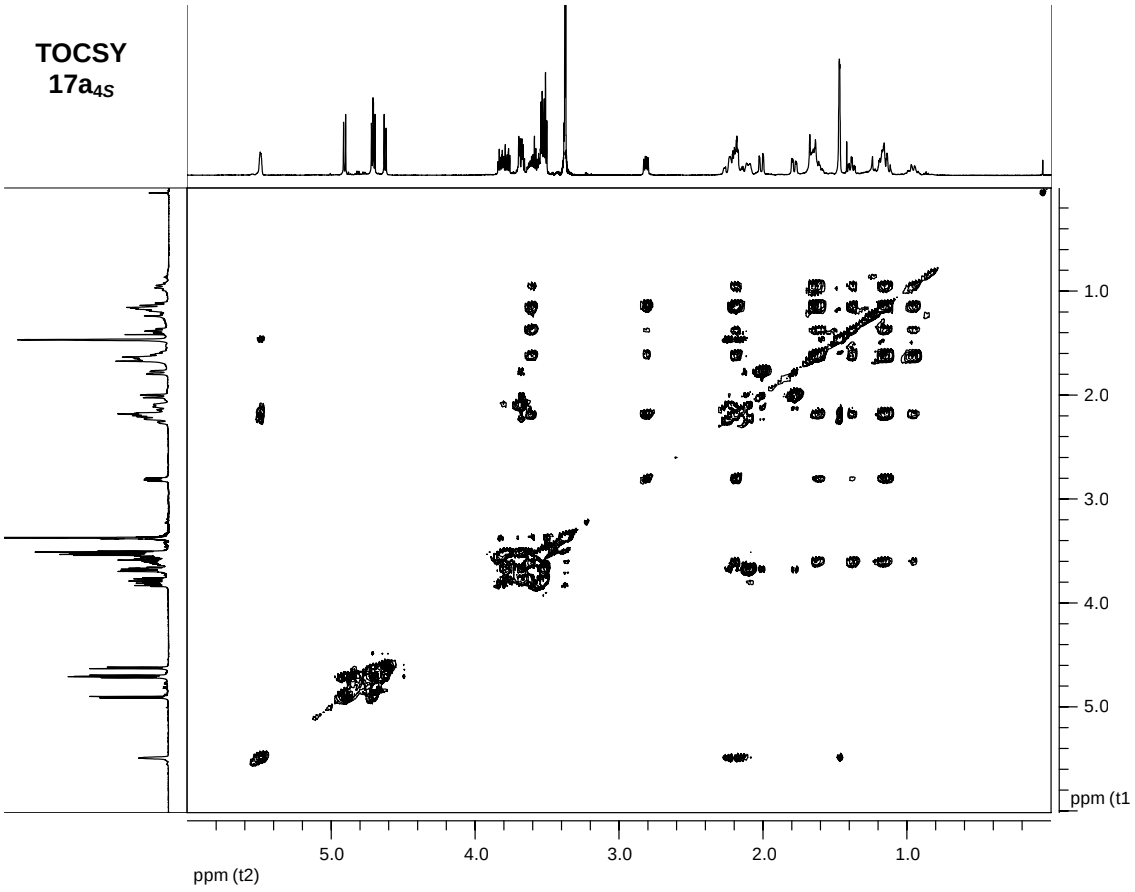




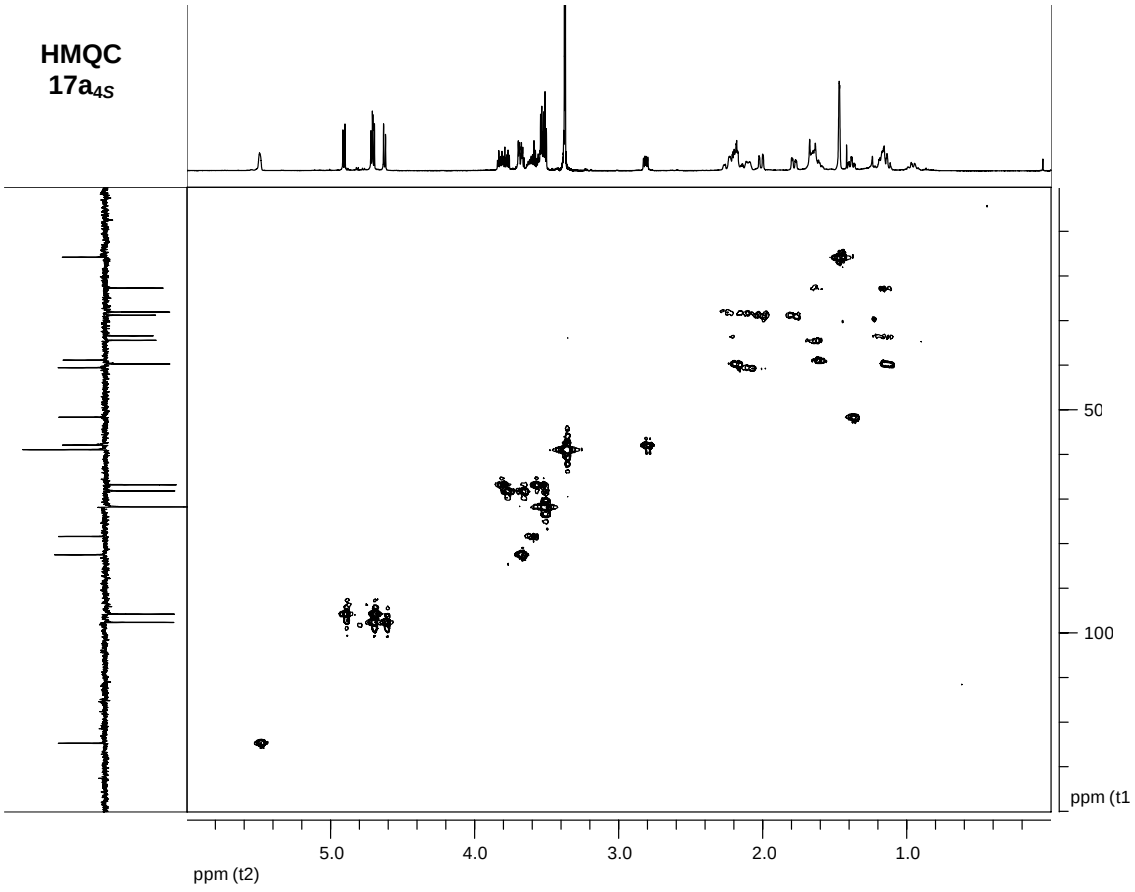
COSY
17a$_{4S}$



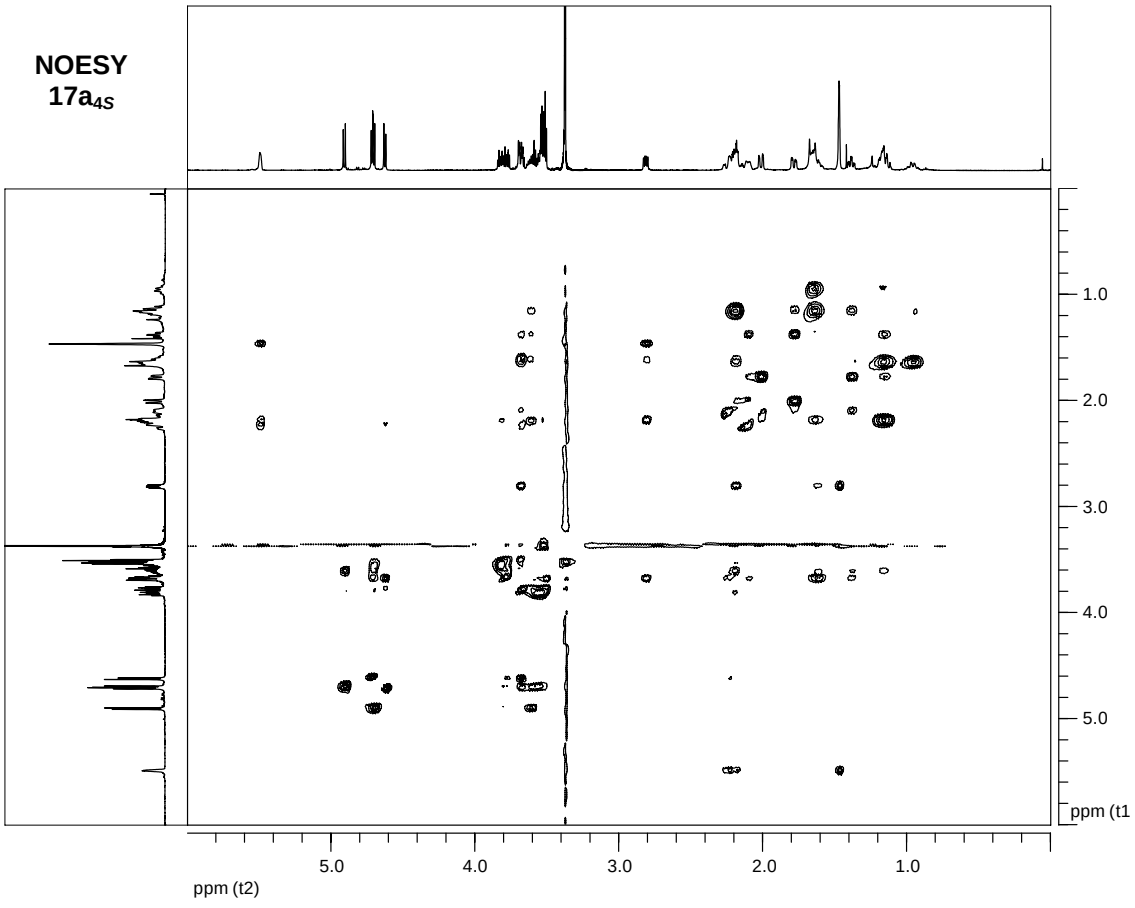
TOCSY
17a$_{4S}$

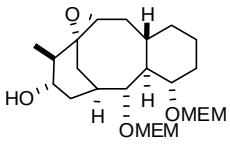


HMQC
17a$_{4S}$

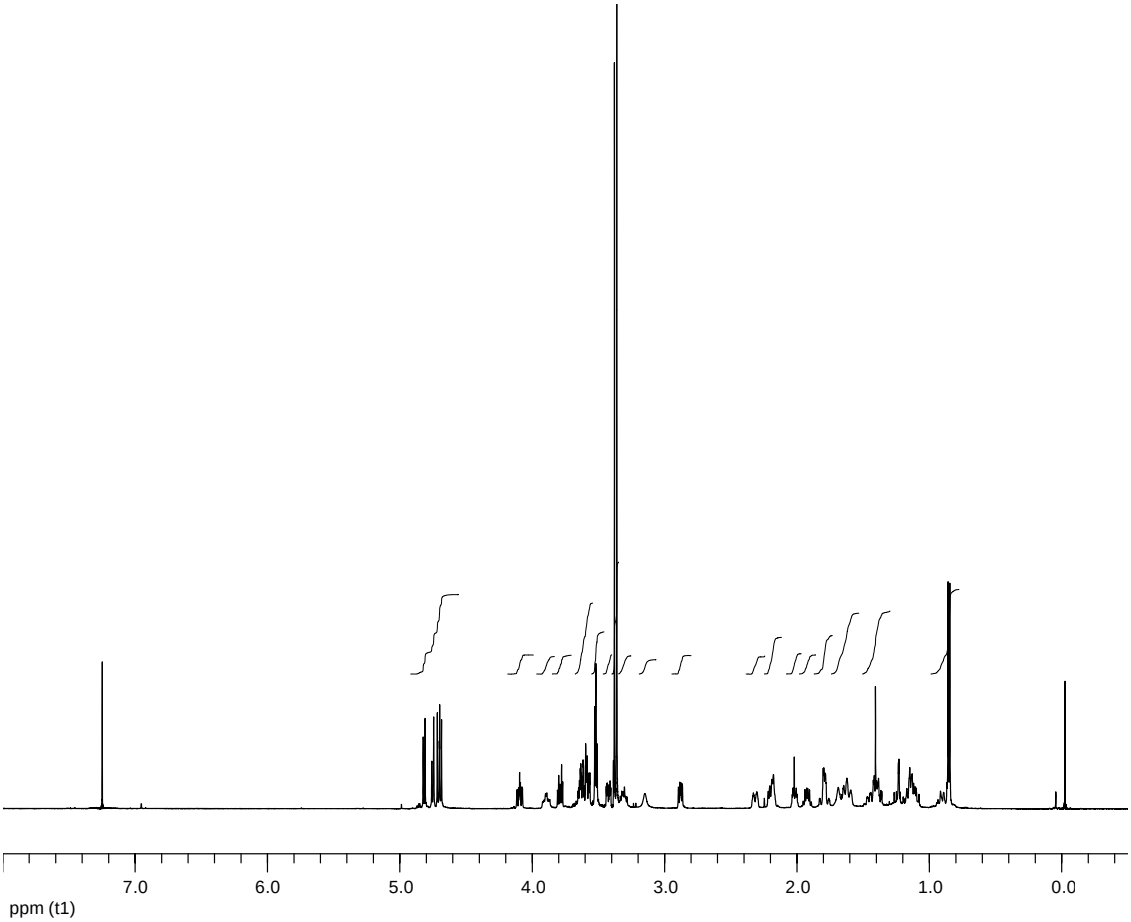


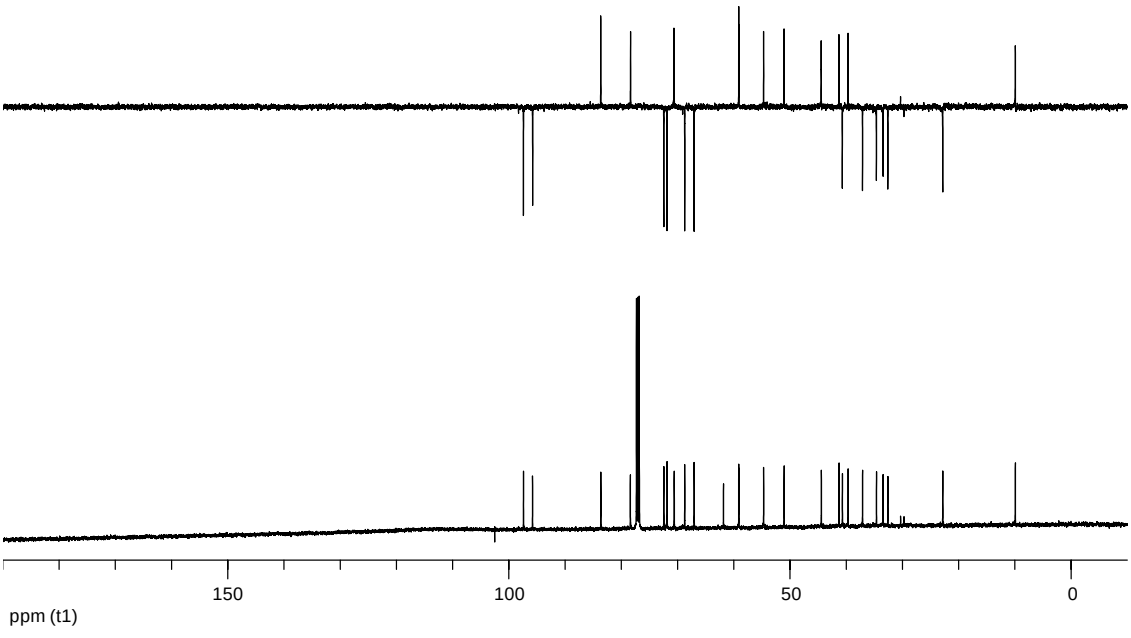
NOESY
17a$_{4S}$



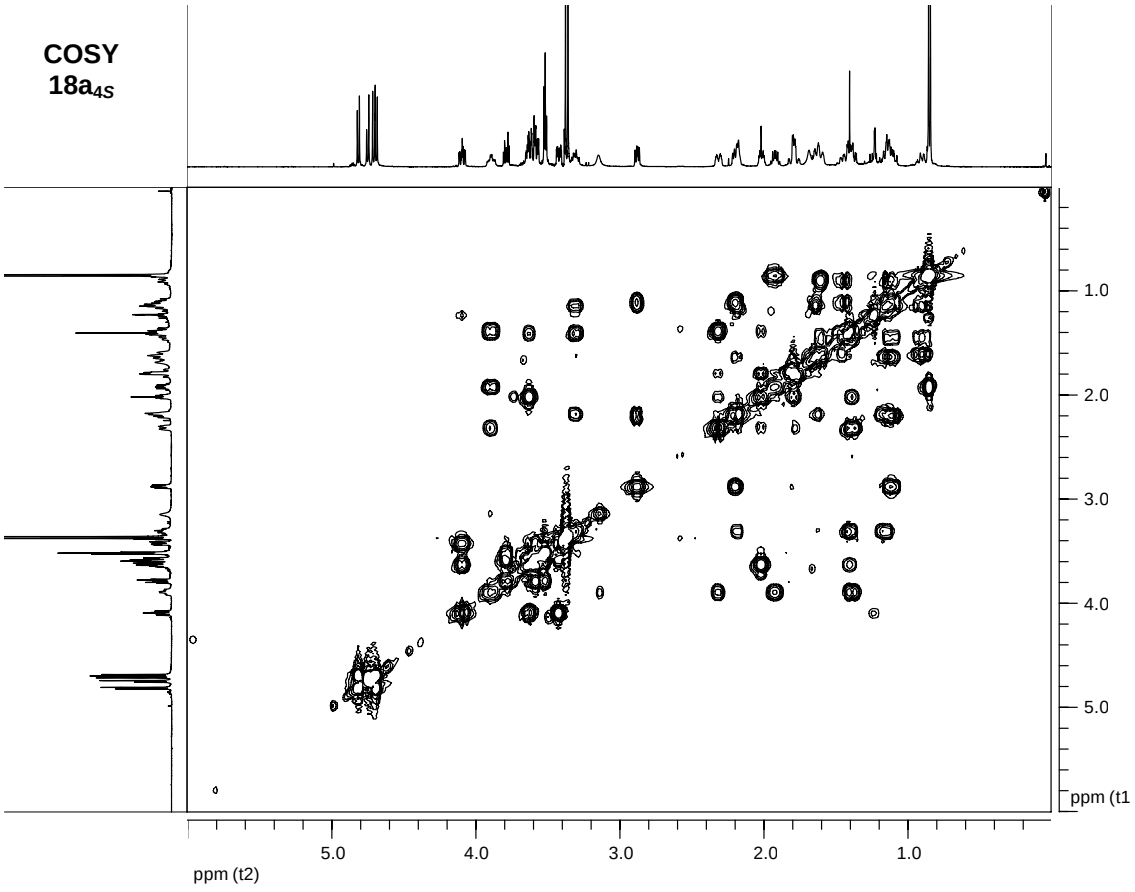


18a$_{4S}$

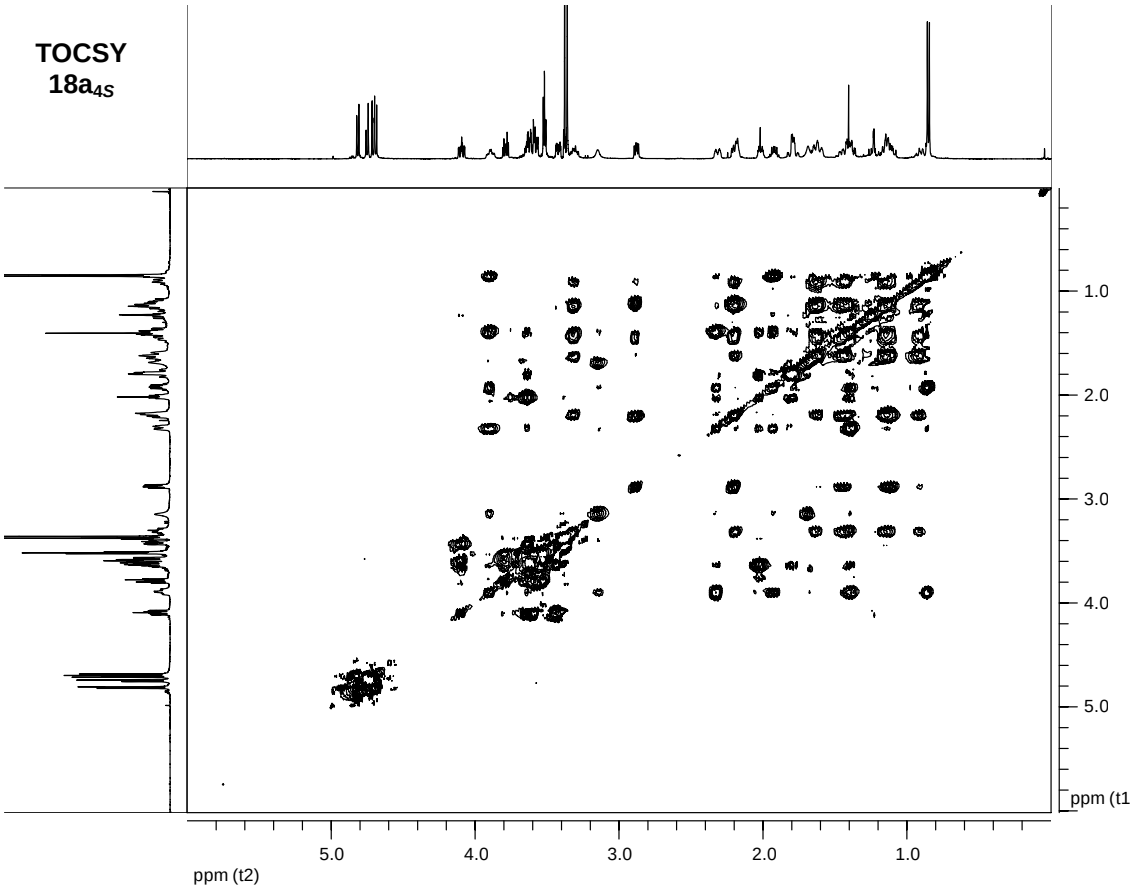




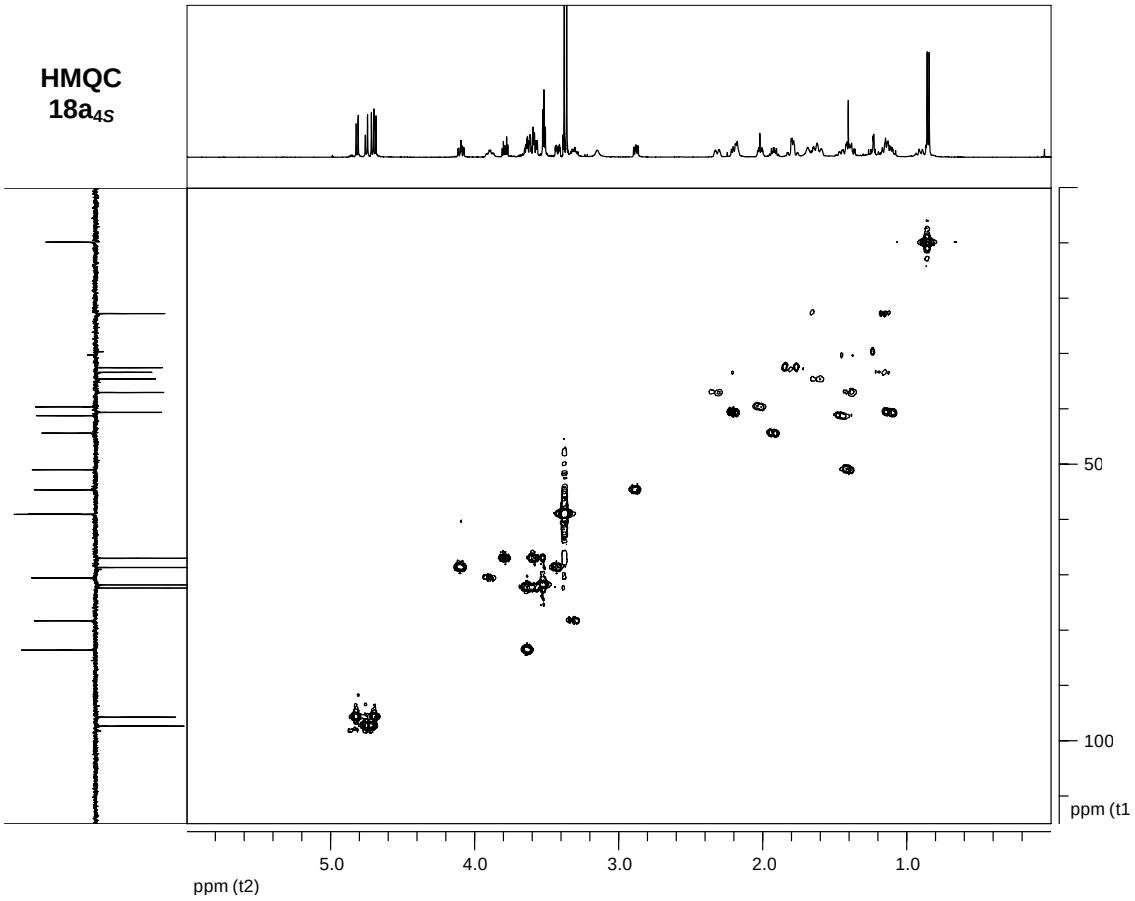
COSY
18a$_{4S}$



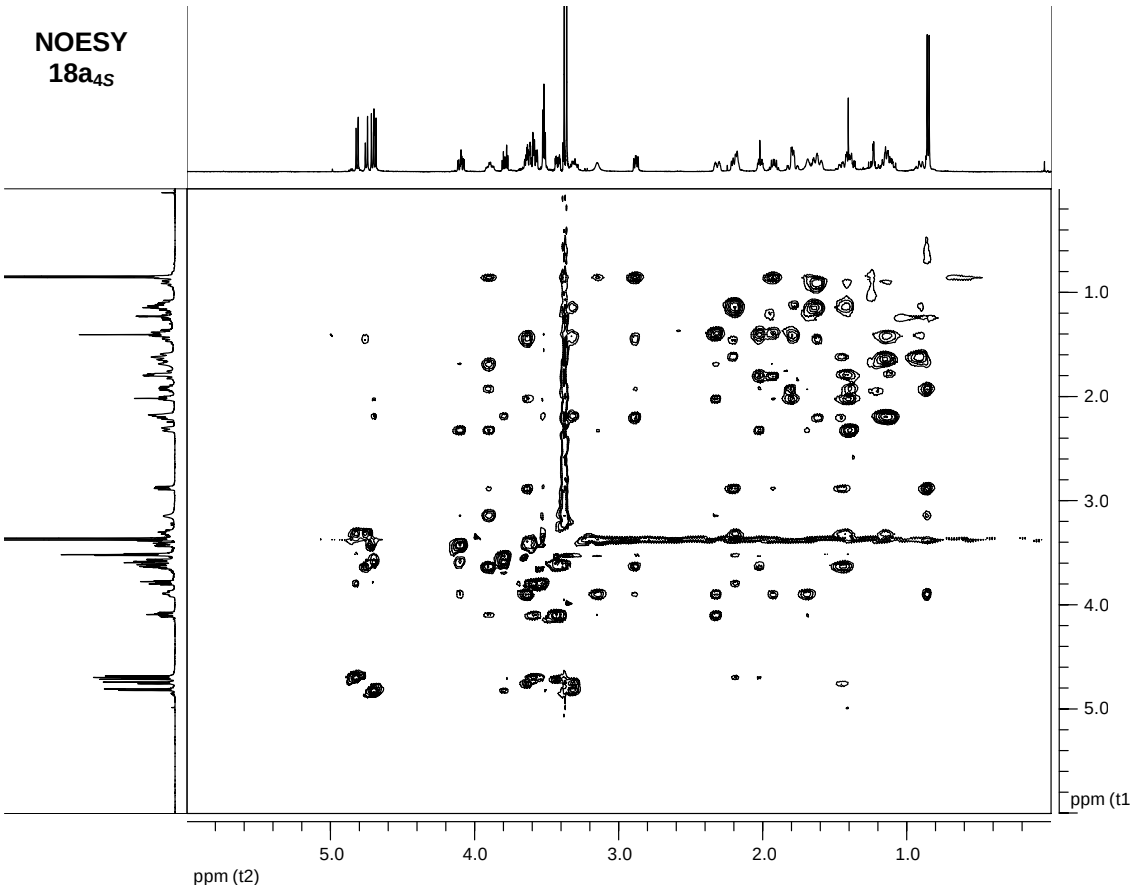
TOCSY
18a$_{4S}$

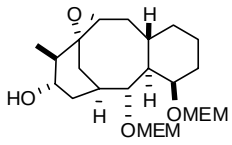


HMQC
18a$_{4S}$

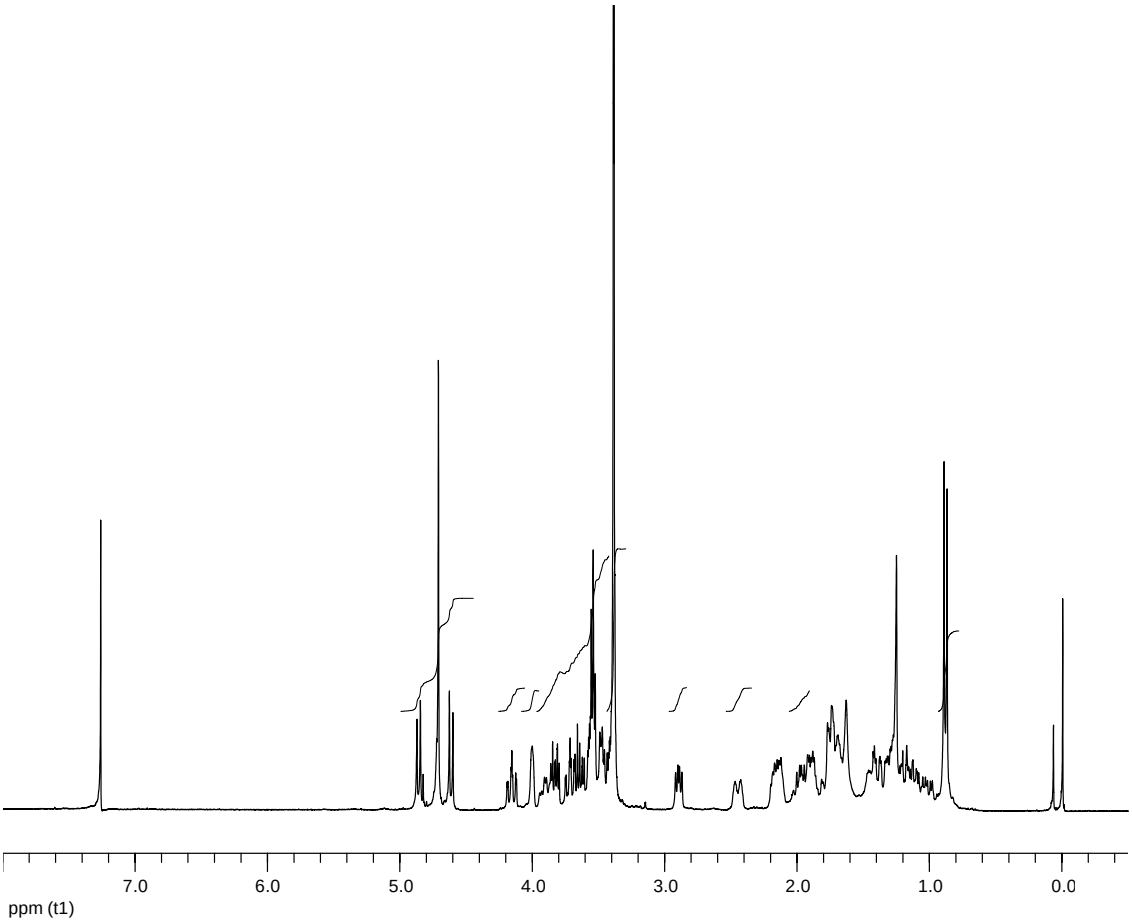


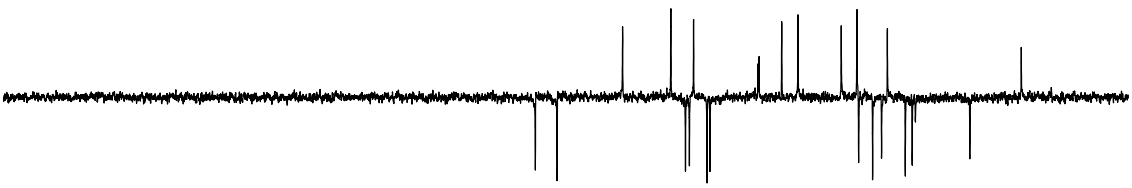
NOESY
18a$_{4S}$

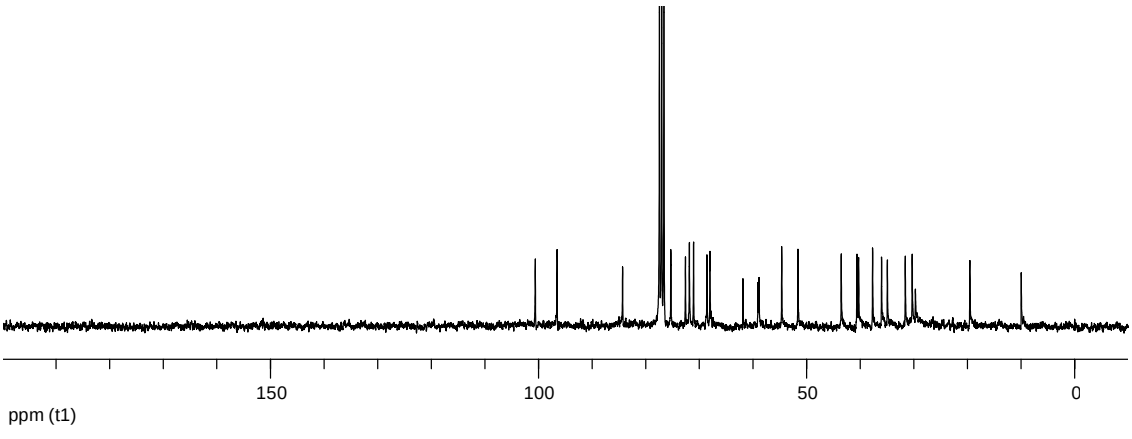


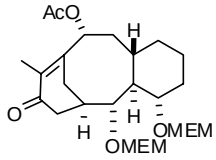


18a$_{4R}$

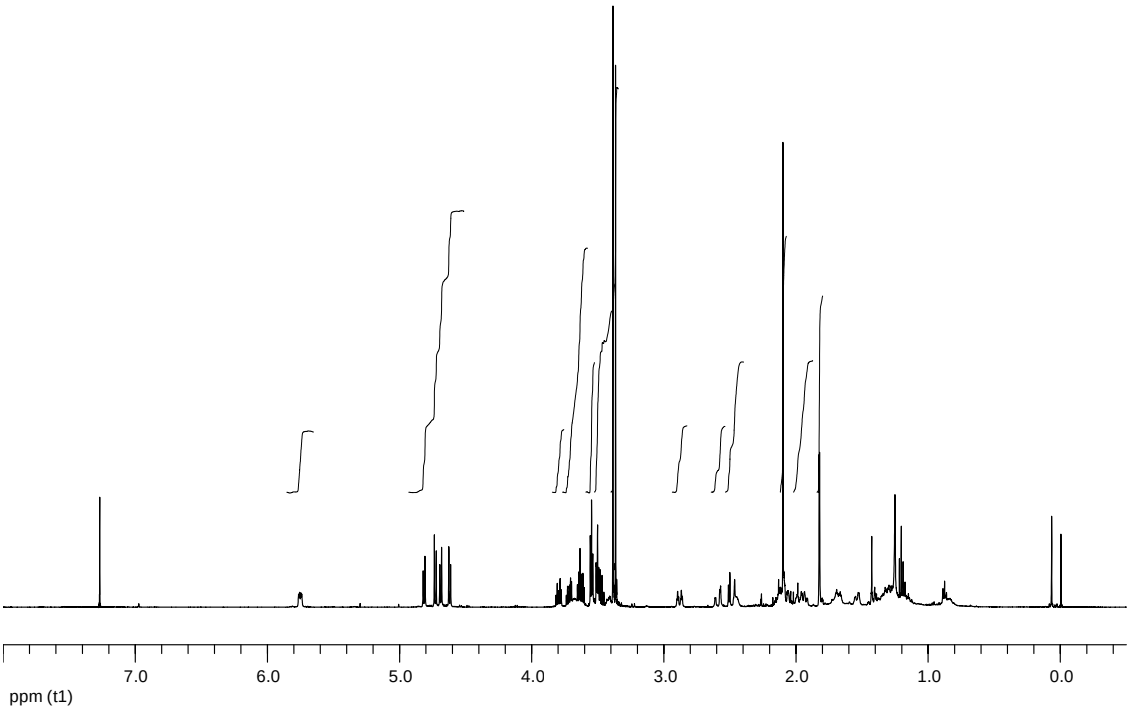


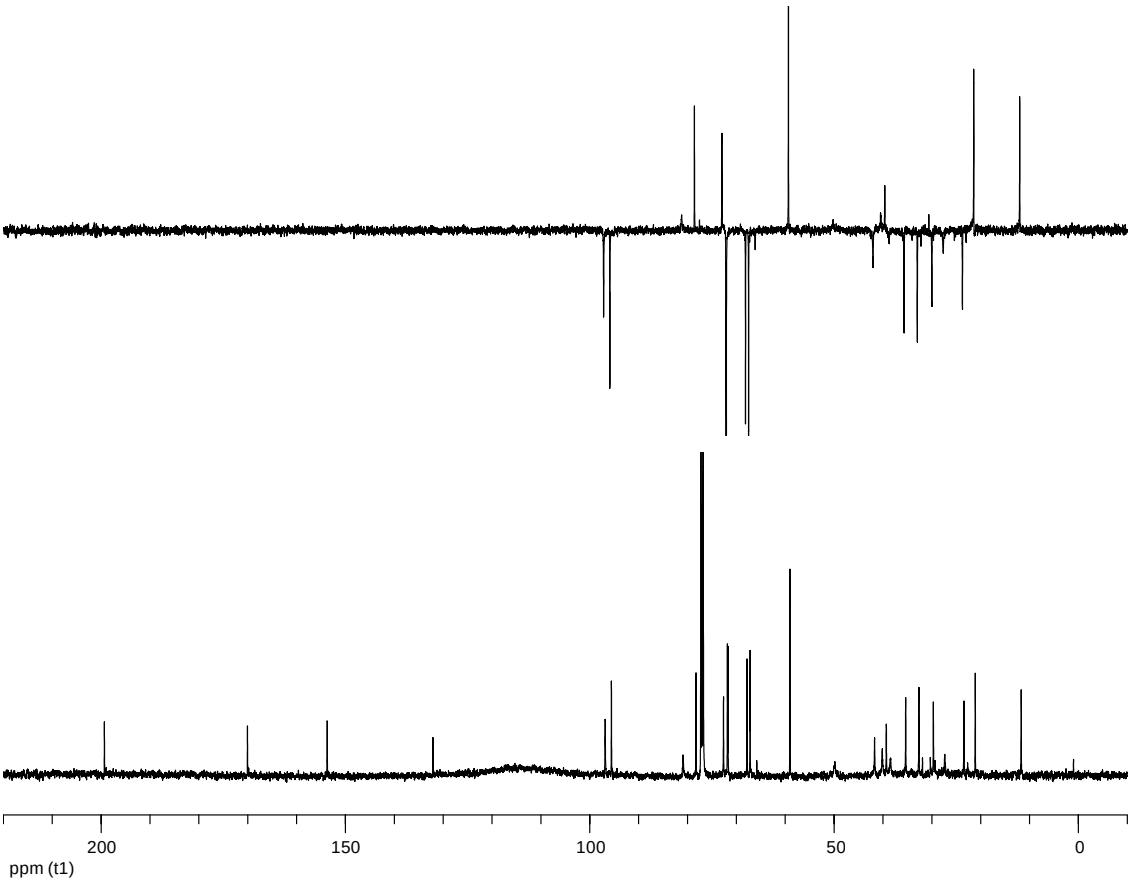




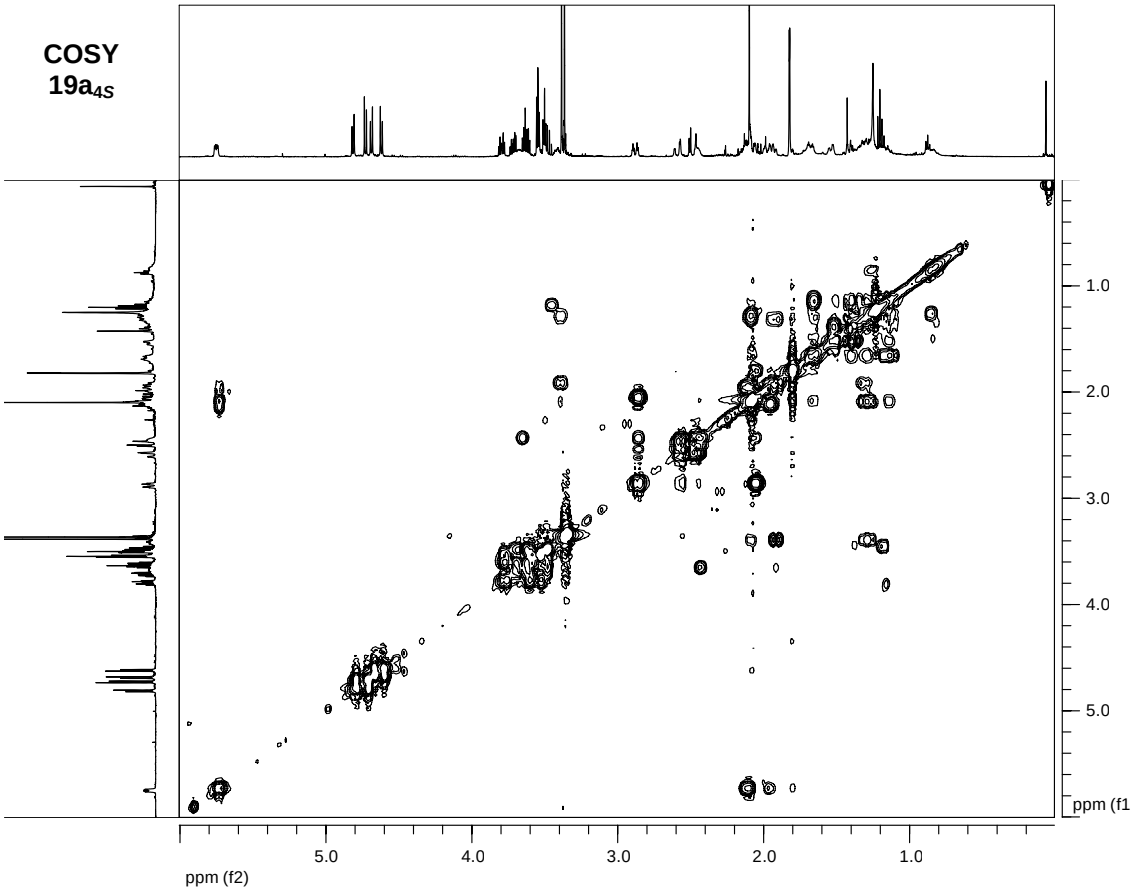

AcO
H
O
H
H
OMEM
OMEM

19a$_{4S}$

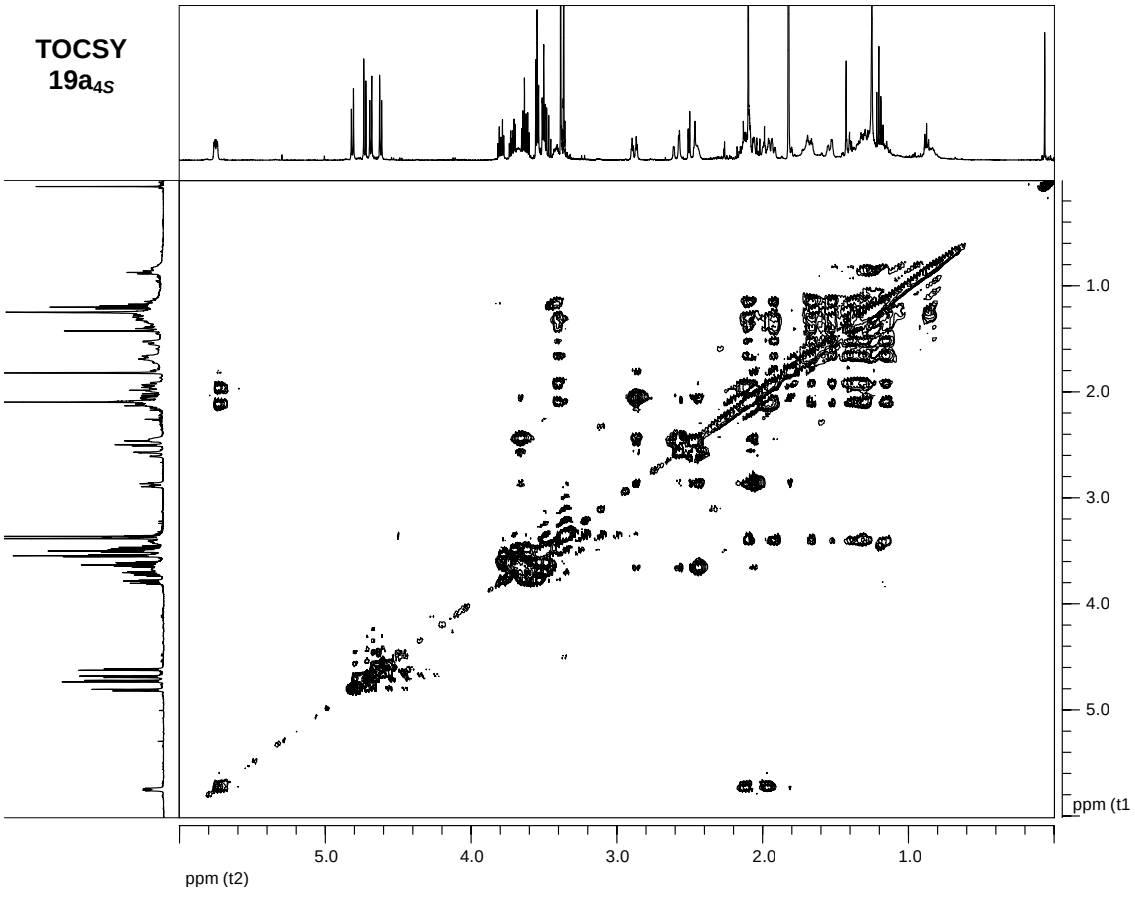

7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

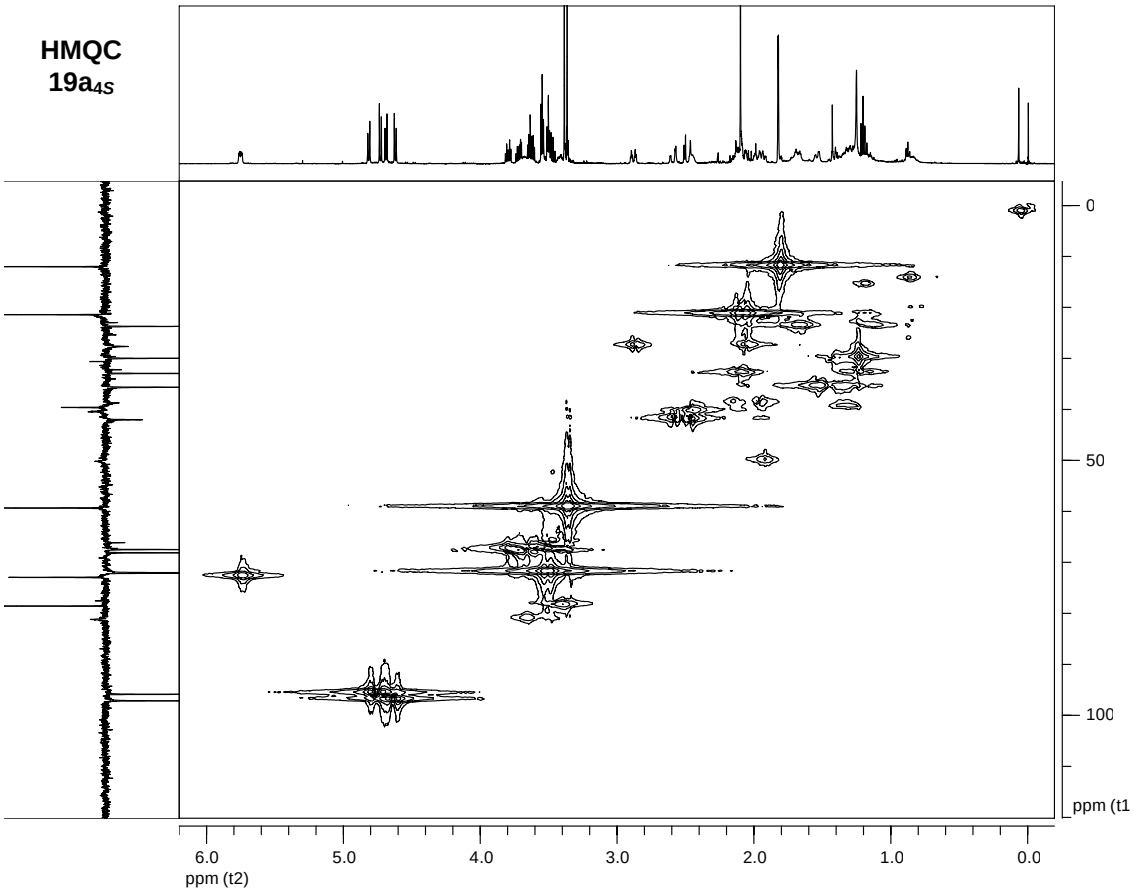
COSY
19a$_{4S}$



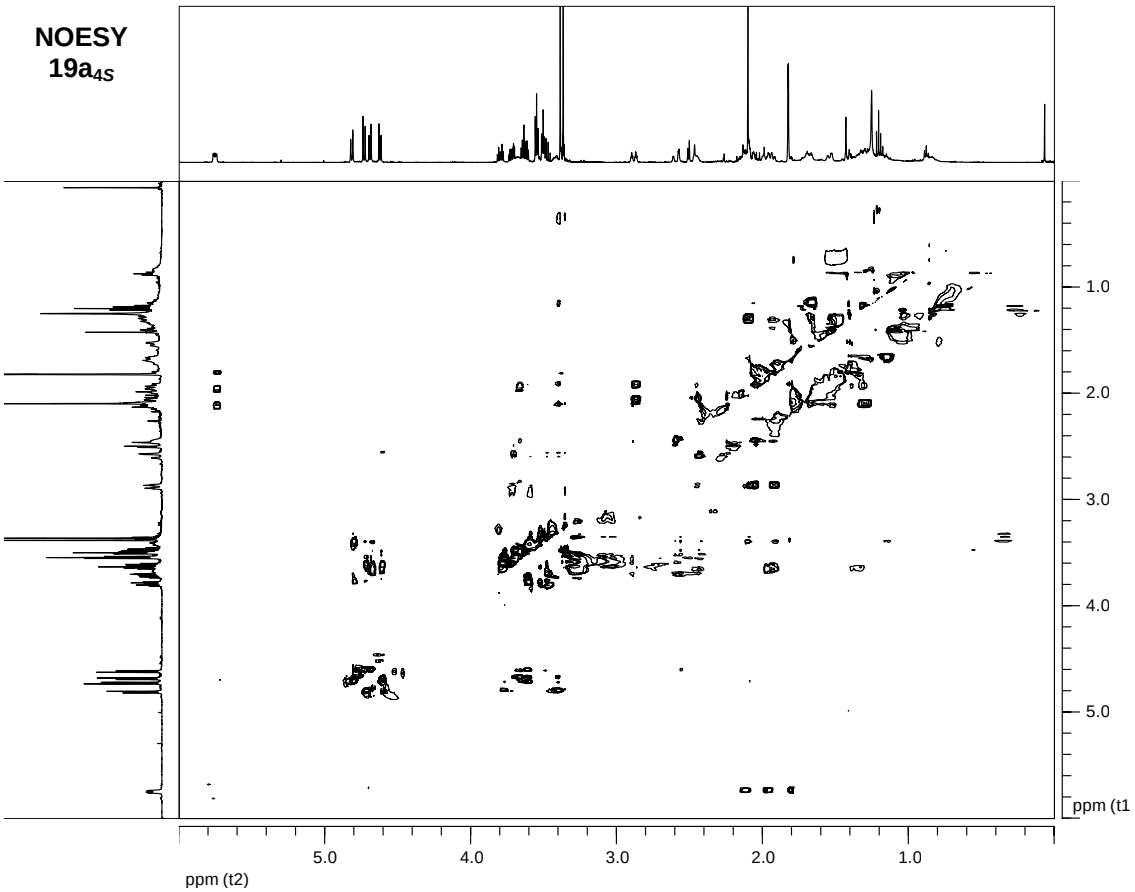
TOCSY
19a$_{4S}$

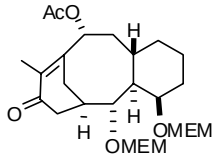


HMQC
19a$_{4S}$

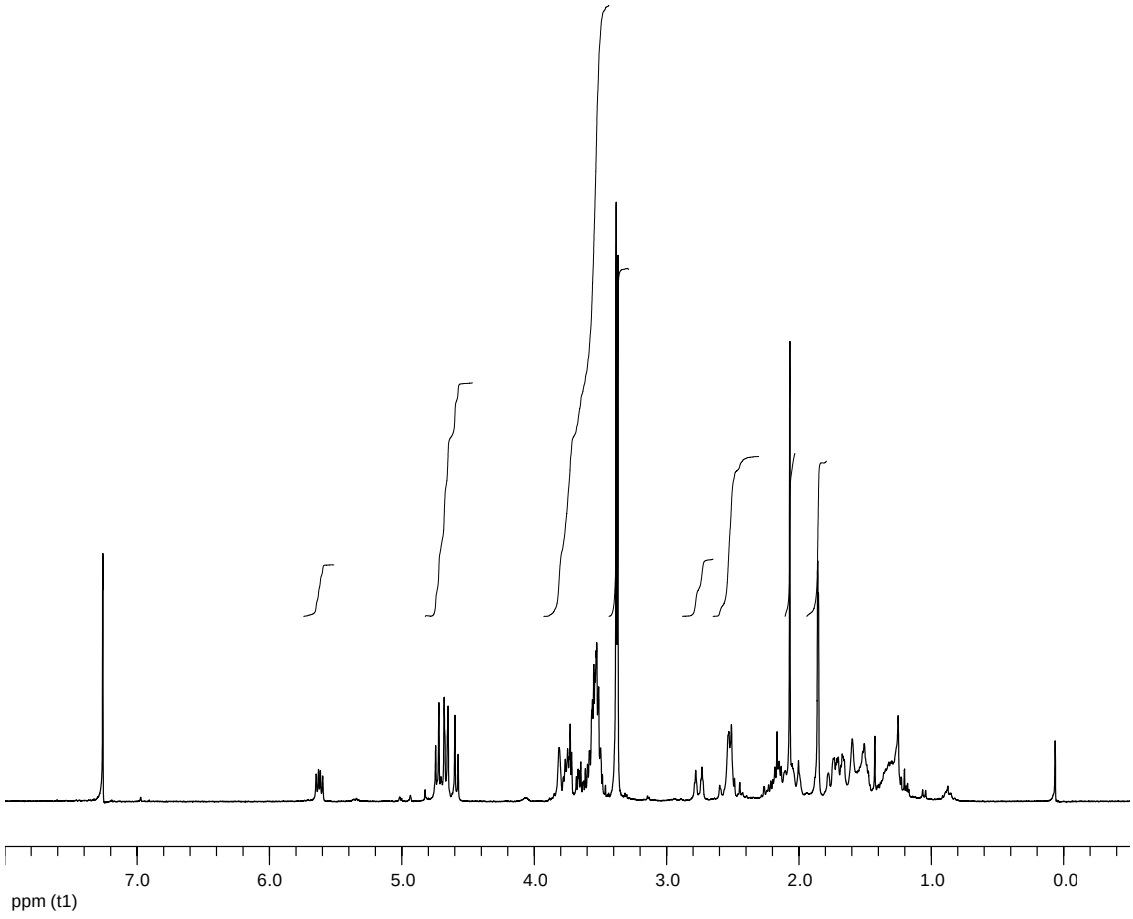


NOESY
19a$_{4S}$




AcO
H
O
H
H
OMEM
OMEM

19a$_{4R}$


7.0
6.0
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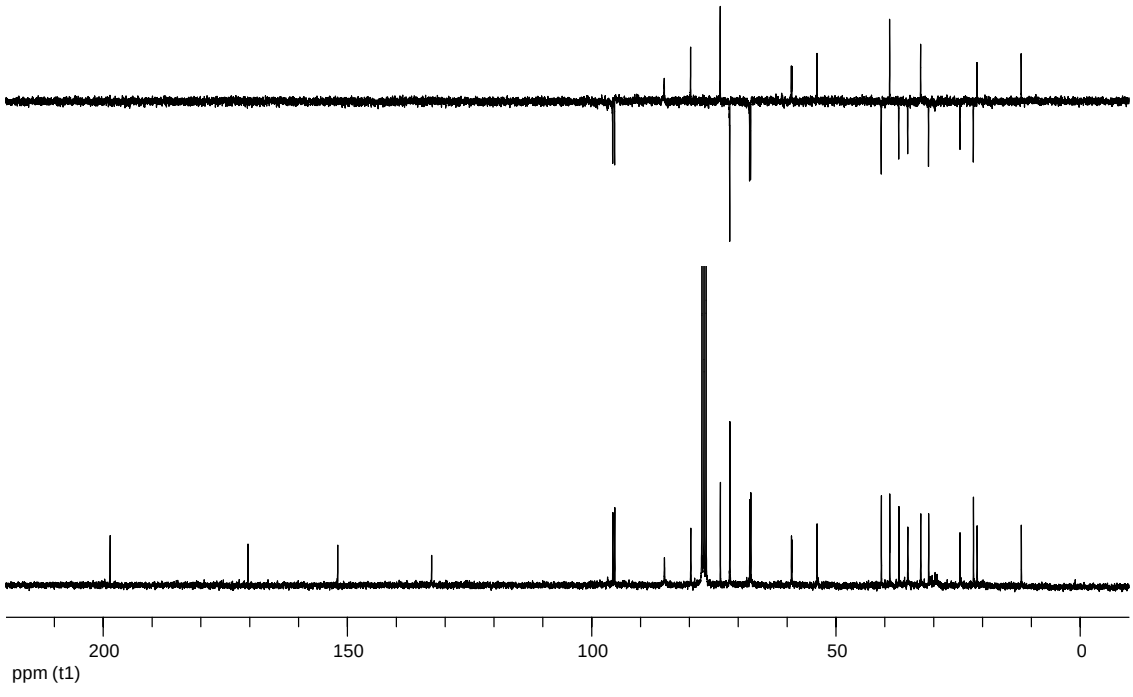
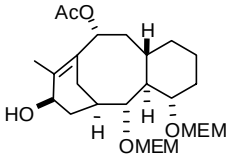
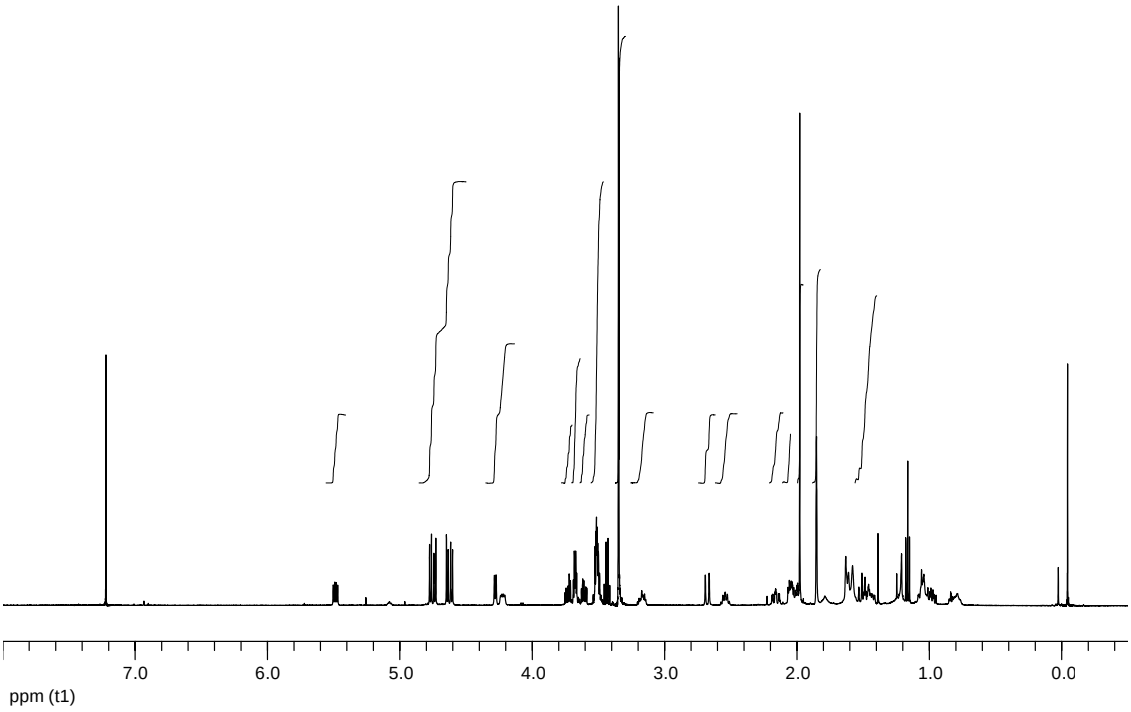
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)


AcO
H
HO
H
H
OMEM
OMEM

20a$_{4S}$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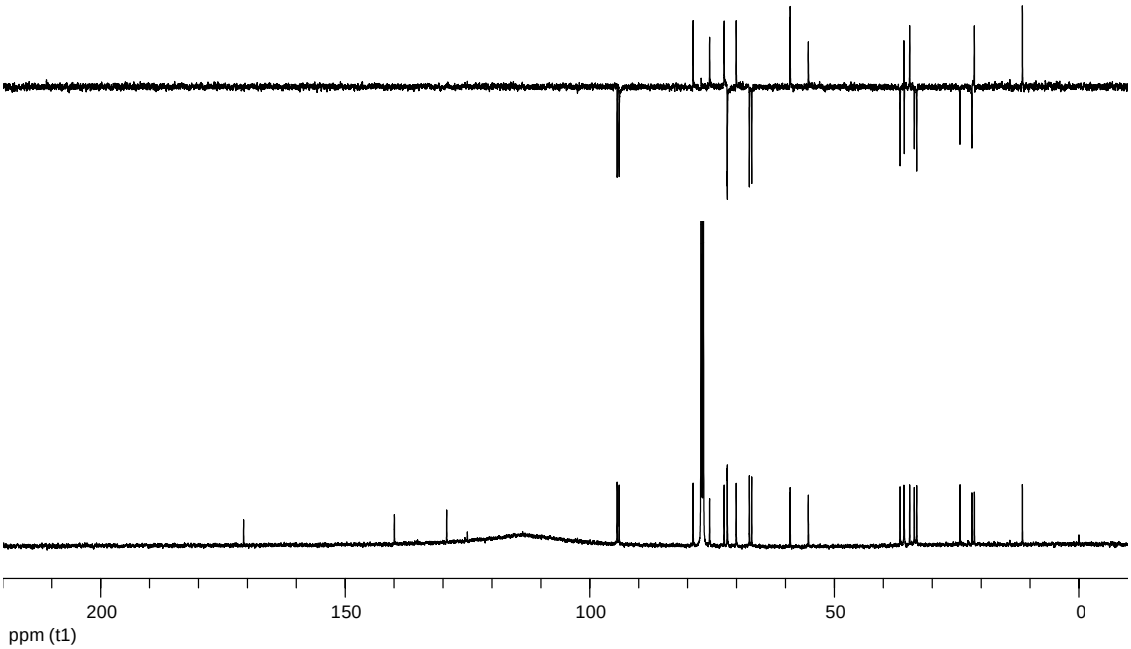
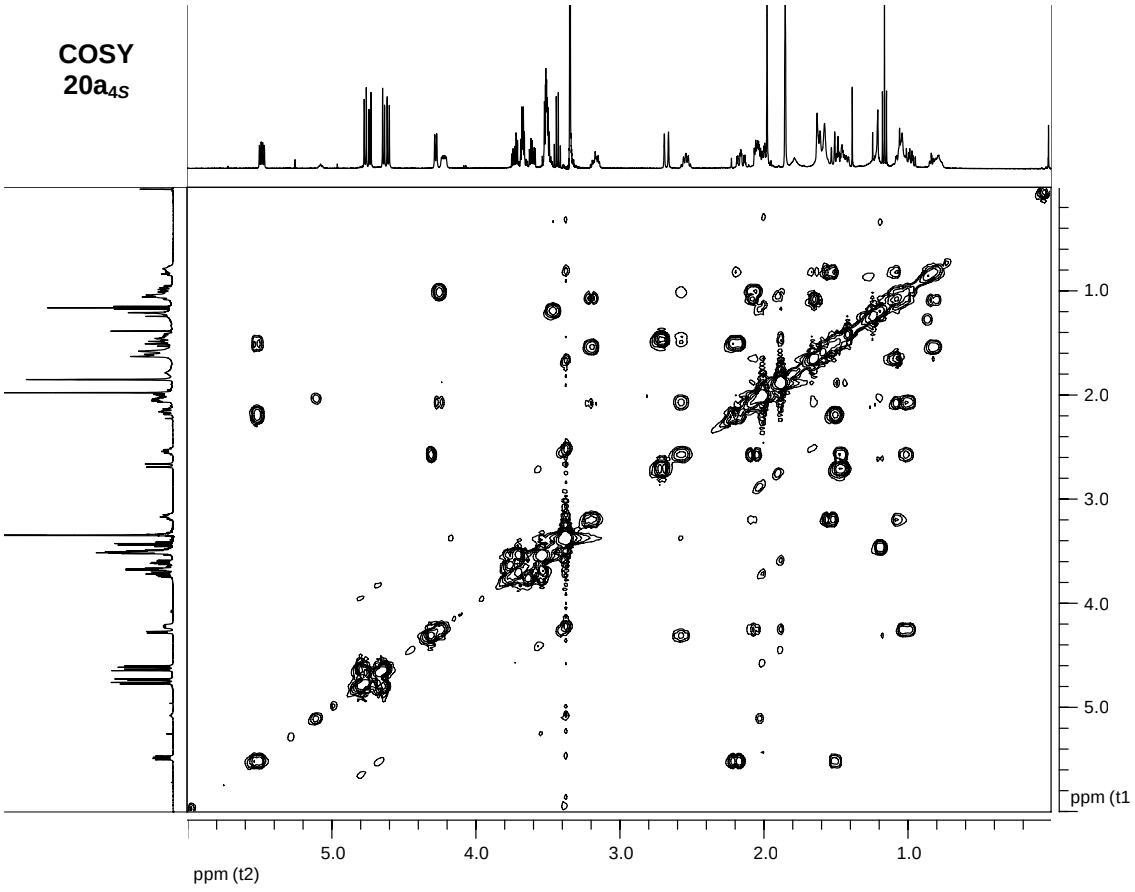
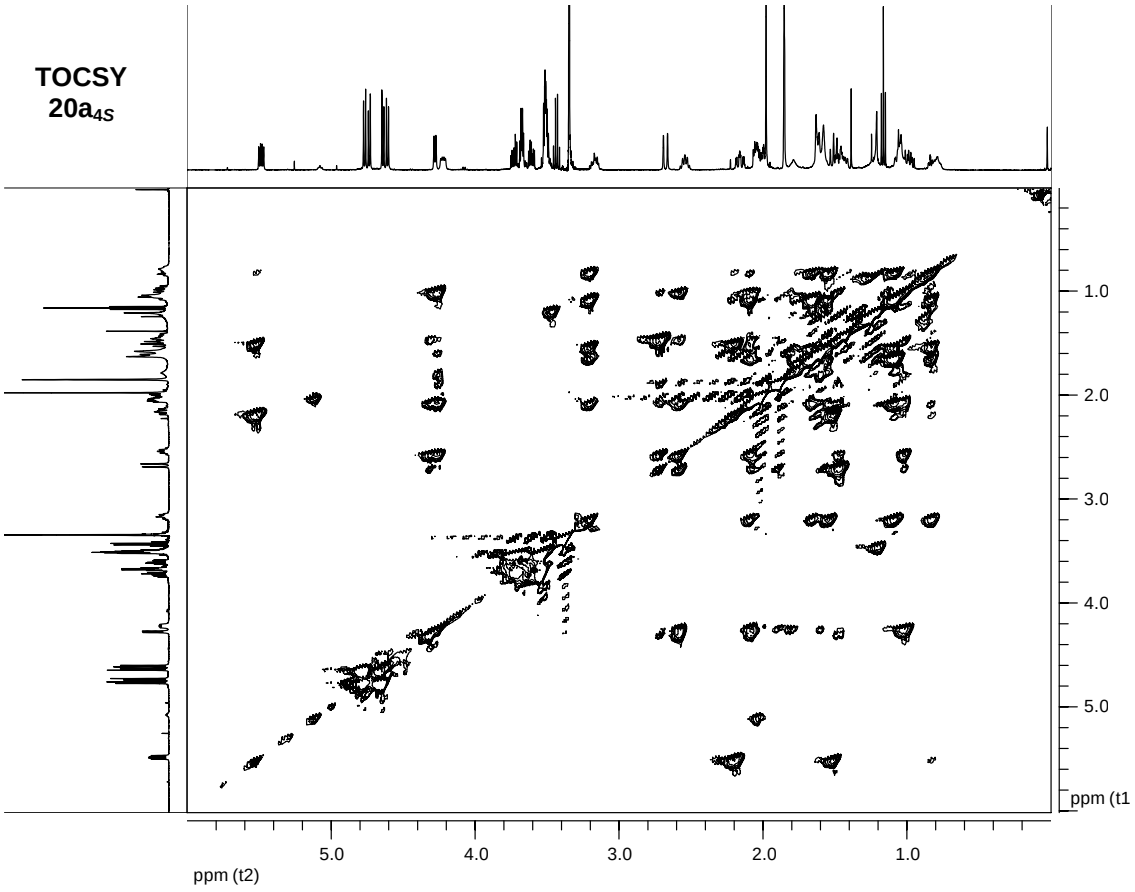
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)

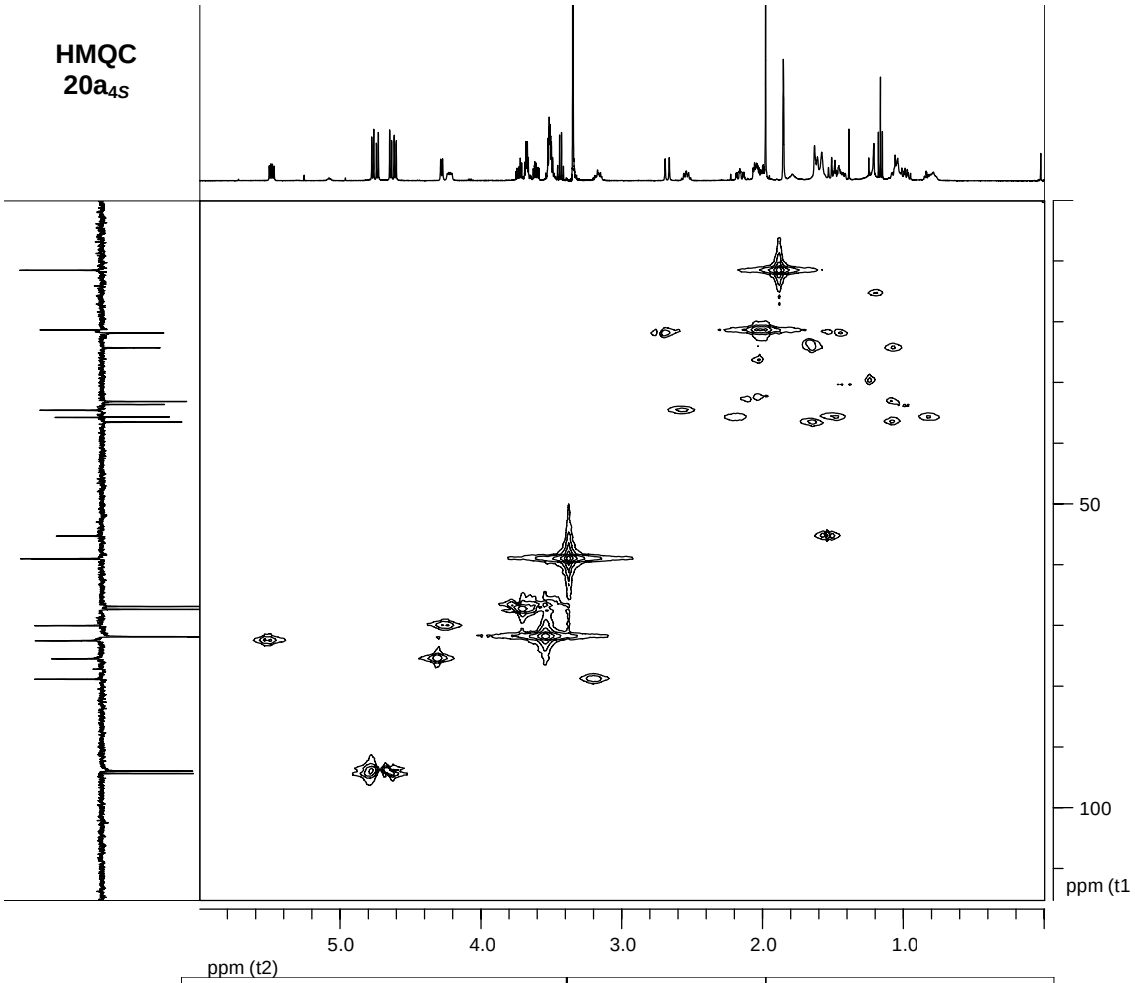
COSY
20a$_{4S}$



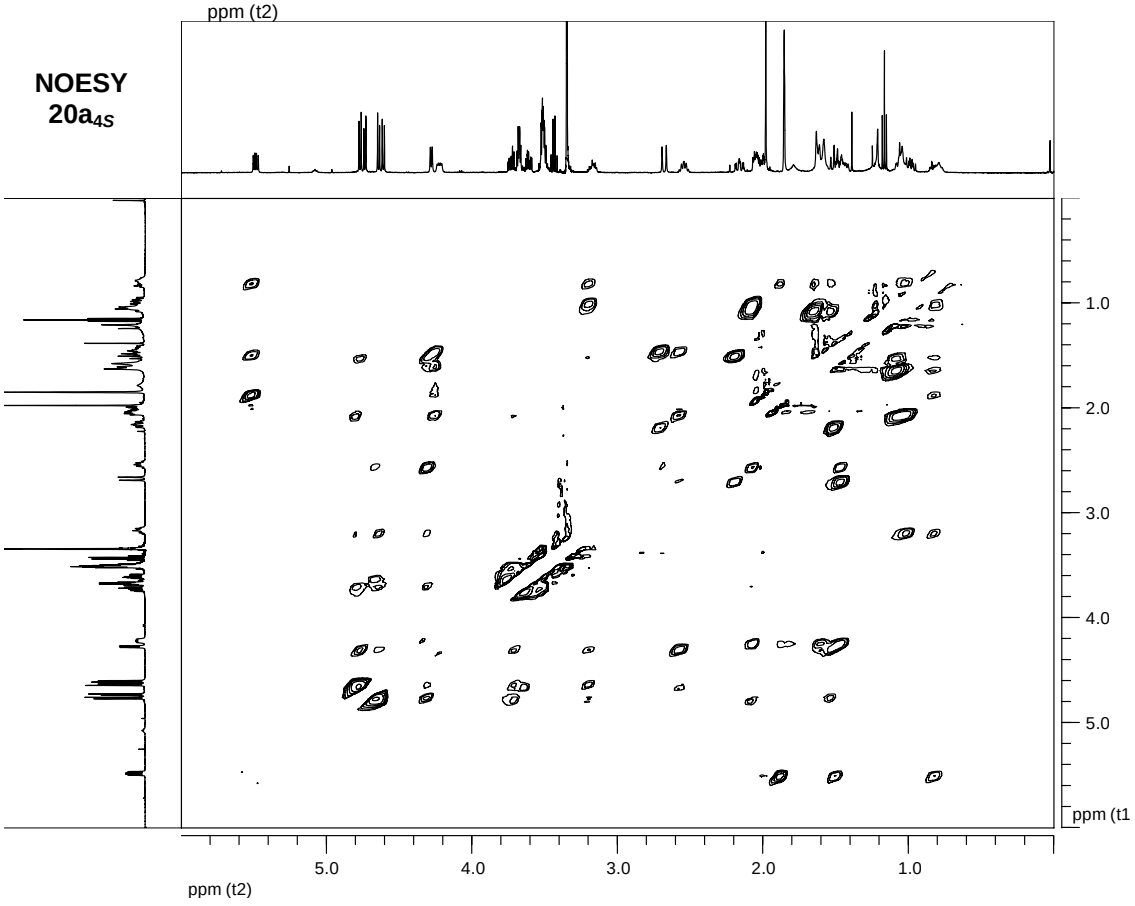
TOCSY
20a$_{4S}$

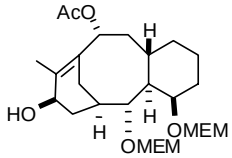


HMQC
$20a_{4S}$

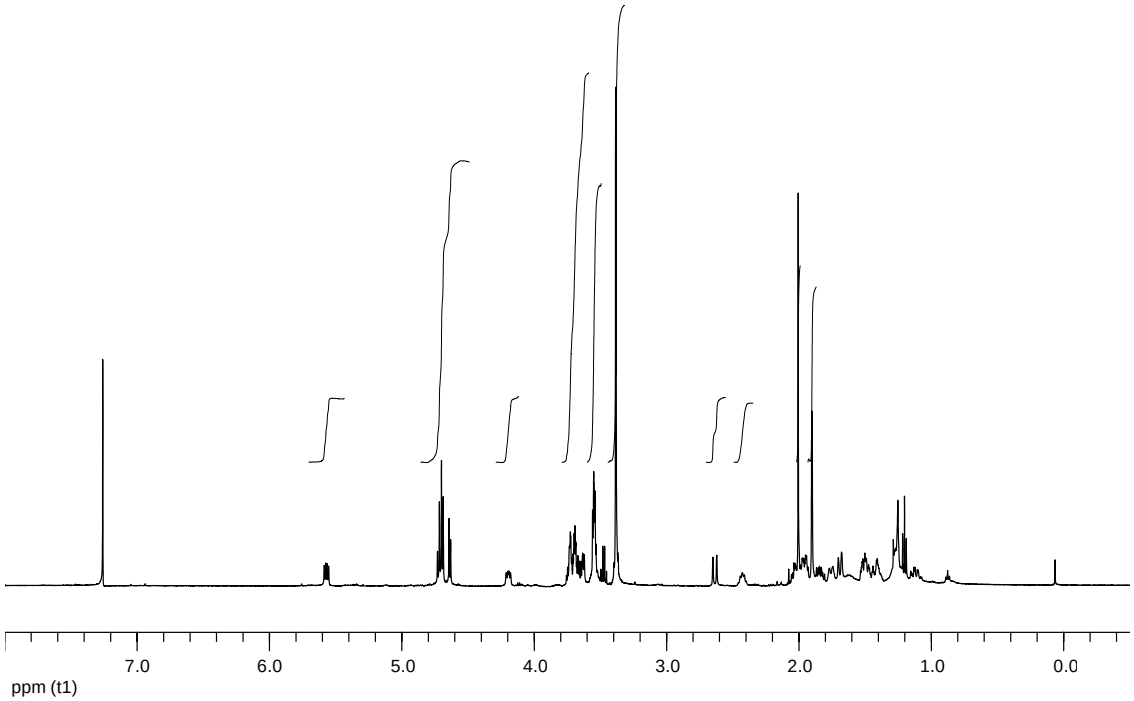


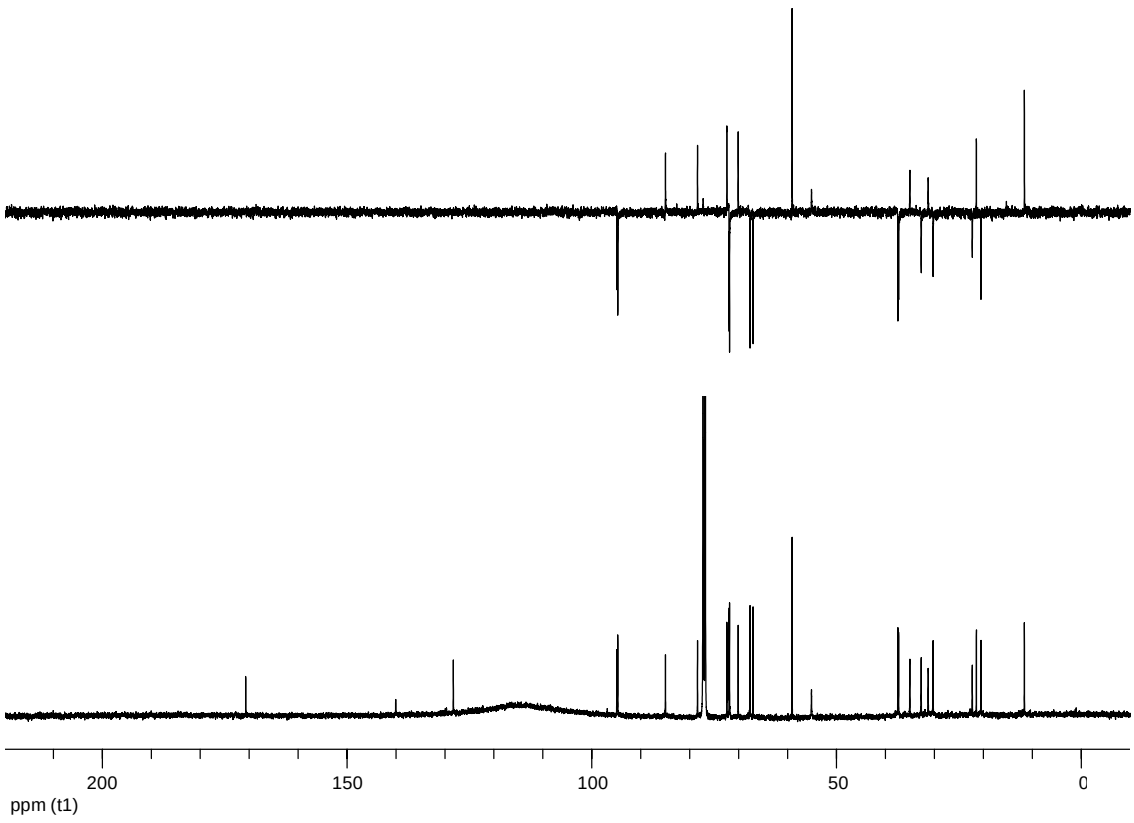
NOESY
$20a_{4S}$




AcO
H
HO
H
H
OMEM
OMEM

20a$_{4R}$


7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


200
150
100
50
0
ppm (t1)