Supporting Information

Late-stage C—H amination of abietane diterpenoids

María Ivana Lapuh,[a,b] Alejandro Dana,[b] Pablo H. Di Chenna,[b] Benjamin Darses,[a] Fernando J. Durán,[*b] and Philippe Dauban*[a]

[a] *Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Univ. Paris-Sud, Université Paris-Saclay, 1, av. de la Terrasse, 91198 Gif-sur-Yvette, France.* E-mail: philippe.dauban@cnrs.fr

[b] *Universidad de Buenos Aires, Consejo Nacional de Investigaciones Científicas y Técnicas, Unidad de Microanálisis y Métodos Físicos Aplicados a la Química Orgánica (UMYMFOR), Departamento de Química Orgánica, Facultad de Ciencias Exactas y Naturales, Pabellón 2, Ciudad Universitaria, Buenos Aires C1428EG, Argentina.* E-mail: fduran@qo.fcen.uba.ar

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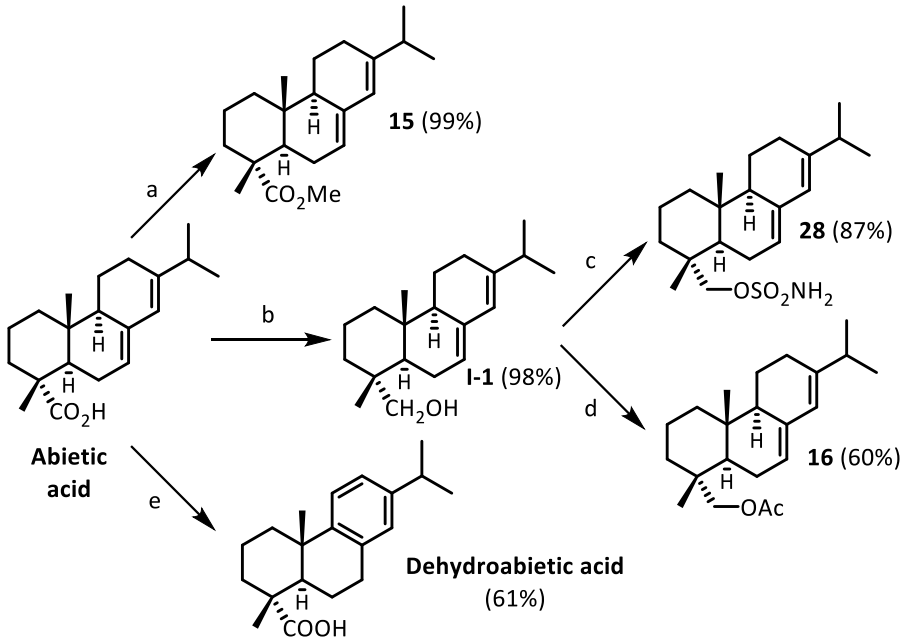
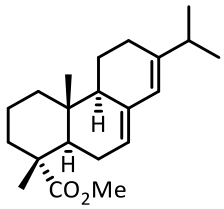


a) MeI, K_2CO_3, acetone, reflux, b) $LiAlH_4$, THF, 0 °C to r.t., c) Chlorosulfonyl isocyanate, HCO_2H, Py, DMA, d) AcCl, Et_3N, DCM, 0 °C, e) Pd(C), 250 °C

Scheme S.1

Methylabietadien-18-oate (15)

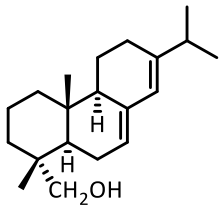


K_2CO_3 (9.36 g, 67.7 mmol) and MeI (5.10 ml, 81.3 mmol) were added to a stirred solution of abietic acid 87% (8.19 g, 23.6 mmol) in acetone (123 ml), and the resulting suspension was heated to reflux. After 14 h the reaction was allowed to cool down to r.t. and water (40 ml) was added. Then the crude material was extracted with Et_2O (2x). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography (hexane/EtOAc 97.5: 2.5) to afford the desired compound (7.38 g, 99% yield) as colorless viscous liquid. All the analytical data is in agreement with the literature.[1]

^{1}H NMR (500 MHz, CDCl3): δ 5.77 (s, 1H), 5.37 − 5.34 (m, 1H), 3.63 (s, 3H), 2.22 (sept, *J* = 6.8 Hz, 1H), 2.11 − 2.01 (m, 4H), 1.97 − 1.92 (m, 1H), 1.90 − 1.85 (m, 1H), 1.84 − 1.68 (m, 3H), 1.64 − 1.53 (m, 3H), 1.25 (s, 3H), 1.25 − 1.10 (m, 2H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.82 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 179.0, 145.3, 135.6, 122.4, 120.6, 51.8, 51.0, 46.6, 45.1, 38.3, 37.1, 34.9, 34.6, 27.5, 25.7, 22.5, 21.4, 20.8, 18.1, 17.0, 14.0.

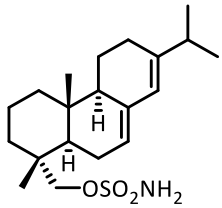
Abietadien-18-ol (**I-1**)



$LiAlH_4$ (250 mg, 6.59 mmol) was added in three portions to a solution of abietic acid 87% (1.00 g, 2.89 mmol) in anhydrous THF (17 ml) at 0 °C. The mixture was stirred overnight at r.t., then it was cooled to 0 °C and water (0.25 mL), 30% NaOH (0.25 mL) and water (0.75 ml) were added sequentially and dropwise. Afer drying over Na_2SO_4, the resulting white suspension was filtered through celite and washed with EtOAc. The filtrate was concentrated and purified by flash chromatography (petroleum ether/EtOAc 85:15) to afford the desired alcohol (813 mg, 98%) as a white amorphous solid. All the analytical data is in agreement with literature.[2]

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.42 – 5.38 (m, 1H), 3.36 (d, *J* = 10.8 Hz, 1H), 3.15 (d, *J* = 10.9 Hz, 1H), 2.22 (sept, *J* = 6.9 Hz, 1H), 2.10 – 2.04 (m, 2H), 2.04 – 1.93 (m, 2H), 1.92 – 1.78 (m, 3H), 1.63-1.50 (m, 2H), 1.53 (dd, *J* = 11.3, 5.6 Hz, 1H), 1.40 (td, *J* = 12.7, 3.9 Hz, 1H), 1.39 – 1.32 (m, 1H), 1.28 – 1.17 (m, 1H), 1.06 – 1.00 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 3H), 0.83 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 135.7, 122.5, 121.0, 72.2, 50.9, 43.8, 39.0, 37.6, 35.8, 35.0, 34.8, 27.6, 23.9, 22.8, 21.5, 21.0, 18.3, 17.8, 14.4.

Abietadien-18-yl sulfamate (28)



Chlorosulfonyl isocyanate (332 µl, 3.82 mmol) was added to a round bottom flask under an argon atmosphere and cooled to 0 °C with an ice bath. Formic acid (144 µl, 3.82 mmol) was then carefully added dropwise (important gas release). The resulting white slurry was stirred for 12 h. as the temperature was slowly allowed to reach r.t. Anhydrous DMA (0.88 ml) was then slowly added at 0°C followed by the alcohol **I-1** (550 mg, 1.91 mmol) in solution in anhydrous DMA (2.2 ml) and anhydrous pyridine (308 µl, 3.82 mmol). The mixture was stirred for 1 h in the ice bath and five h at r.t. Then water was added, followed by a saturated solution of NH_4Cl. The mixture was extracted with EtOAc (4 x 20 ml), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography (petroleum ether/EtOAc 8:2) to afford **26** (612 mg, 87%) as a yellow amorphous solid.

$[\alpha]_D^{20}$ = -51.2 (c = 1.00 in $CHCl_3$)

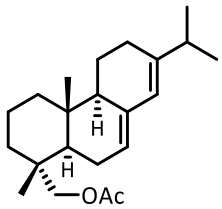
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.43 – 5.34 (m, 1H, H-7), 4.82 (s, 2H), 3.92 (d, *J* = 9.2 Hz, 1H), 3.73 (d, *J* = 9.3 Hz, 1H), 2.22 (sept, *J* = 13.5, 6.7 Hz, 1H), 2.14 – 1.97 (m, 4H), 1.95 – 1.75 (m, 3H), 1.61 – 1.50 (m, 3H), 1.50 – 1.40 (m, 2H), 1.29 – 1.15 (m, 1H), 1.03 (td, *J* = 12.7, 6.0 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.98 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (75 MHz, CDCl3) δ 145.7, 135.7, 122.4, 120.4, 79.0, 50.8, 43.8, 38.6, 36.9, 35.9 (C-3), 35.0, 34.9, 27.6, 23.9 (C-6), 22.7, 21.5, 21.0, 18.0, 17.6, 14.3.

IR (ATR, neat): ν = 3369, 3268, 2594, 2923, 2861, 2847, 1557, 1460, 1443, 1357, 1193, 1166, 970, 905, 842, 804, 774, 759, 709 cm^{-1}.

HRMS ESI (+): *m/z* $[M+Na]^+$ calcd. for $C_{20}H_{33}NNaO_3S^+$: 390.2073; found: 390.2045.

Abietadien-18-yl acetate (16)



Triethylamine (335 µl, 2.40 mmol) was added to a solution of **I-1** (347 mg, 1.20 mmol) in anhydrous DCM (4 ml) under an argon atmosphere. Then the mixture was cooled to 0°C and acetyl chloride (171 µl, 2.40 mmol) was added dropwise. The reaction was stirred for 1 h at the same temperature before being diluted with 10 ml of DCM. The organic phase was successively washed with 1N HCl (x2) and with H_2O, dried over Na_2SO_4, filtered and the filtrate was concentrated under pressure. The resulting yellow viscous liquid was purified by flash chromatography (petroleum ether/EtOAc 97.5:2.5) to afford the desired compound (240 mg, 60%) as a colorless viscous liquid.

$[\alpha]_D^{20}$ = -16.5 (c = 1.00 in $CHCl_3$).

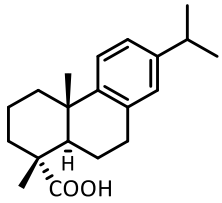
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (s, 1H), 5.43 – 5.38 (m, 1H), 3.80 (d, *J* = 11.0 Hz, 1H), 3.67 (d, *J* = 11.0 Hz, 1H), 2.23 (sept, *J* = 6.6 Hz, 1H), 2.11 – 2.05 (m, 2H), 2.04 (s, 3H), 2.04 – 1.97 (m, 2H), 1.93 –1.78 (m, 3H), 1.62-1.48 (m, 2H), 1.54 (dd, *J* = 11.1, 5.8 Hz, 1H), 1.45 – 1.38 (m, 1H), 1.37 (td, *J* = 12.7, 3.7 Hz, 1H), 1.27 – 1.16 (m, 1H), 1.06 – 1.00 (m, 1H), 1.02 (d, *J* = 4.6 Hz, 3H), 1.01 (d, *J* = 4.7 Hz, 3H), 0.94 (s, 3H), 0.83 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 145.5, 135.5, 122.5, 121.1, 72.8, 50.9, 44.3, 38.9, 36.5, 36.3, 35.0, 34.9, 27.7, 24.1, 22.8, 21.6, 21.2, 21.0, 18.2, 17.9, 14.3.

IR (ATR, neat): ν = 3402, 2930, 2877, 1736, 1716, 1463, 1443, 1380, 1236, 1035, 981, 890, 735 cm^{-1}.

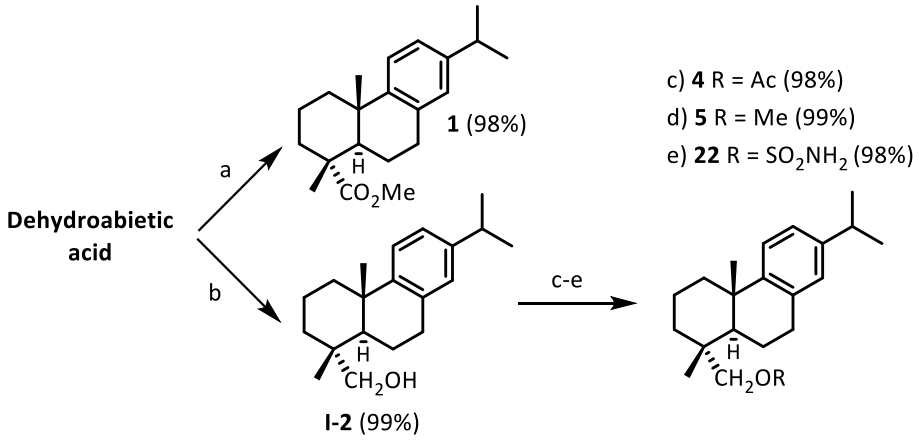
HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{22}H_{35}O_2^+$: 331.2632; found: 331.2623.

Dehydroabietic acid (8,11,13-Abietatrien-18-oic acid)



A round bottom flask was charged with abietic acid 87% (5.00 g, 13.6 mmol) and Pd(C) 5% (250 mg, 5 wt%) and it was connected to an oil bubbler. The reaction mixture was heated to 250 °C for 3 hs under an argon atmosphere. After cooling down to r.t., EtOAc was added (10 ml) and the black suspension was filtered through a pad of celite. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (hexane/EtOAc 80:20) to afford the desired product (2.50 g, 61%) as a white amorphous solid. All the analytical data is in agreement with the literature.[3]

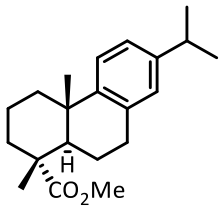
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H), 2.98 – 2.84 (m, 2H), 2.82 (sept, *J* = 6.9 Hz, 1H), 2.33 – 2.27 (m, 1H), 2.24 (dd, *J* = 12.5, 2.1 Hz, 1H), 1.91 – 1.67 (m, 5H), 1.58 – 1.45 (m, 2H), 1.28 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 6H), 1.21 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 184.9, 146.8, 145.8, 134.8, 127.0, 124.2, 124.0, 47.5, 44.7, 38.0, 37.0, 36.8, 33.6, 30.1, 25.2, 24.1 (1C + 1C), 21.9, 18.6, 16.3.



a) MeI, K_2CO_3, acetone, reflux, b) $LiAlH_4$, THF, 0 °C to r.t., c) NaH, MeI, DMSO, 40 °C to r.t., d) AcCl, Et_3N, DCM, 0 °C, e) Chlorosulfonyl isocyanate, HCO_2H, Py, DMA

Scheme S.2

Methyl 8,11,13-abietatrien-18-oate (1)

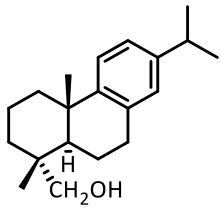


Prepared following the same procedure as for the preparation of **15**, starting from dehydroabietic acid (5.00 g, 16.6 mmol), K_2CO_3 (6.60 g, 47.7 mmol), MeI (3.60 ml, 57.3 mmol) and acetone (87 ml). The crude material was purified by flash chromatography (hexane/EtOAc 97.5: 2.5) to afford the desired compound **1** (5.13 g, 98% yield) as a white amorphous solid. All the analytical data is in agreement with the literature [4].

^{1}H RMN (300 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 3.66 (s, 3H), 2.96 – 2.72 (m, 3H), 2.36 – 2.25 (m, 1H), 2.24 (dd, *J* = 12.5, 2.2 Hz, 1H), 1.93 – 1.57 (m, 5H), 1.49 (td, *J* = 12.4, 4.5 Hz, 1H), 1.46-1.33 (m, 1H), 1.27 (s, 3H), 1.22 (d, *J* = 7.3 Hz, 6H), 1.21 (s, 3H).

^{13}C RMN (75 MHz, $CDCl_3$) δ 179.3, 147.0, 145.8, 134.8, 127.0, 124.3, 124.0, 52.0, 47.8, 45.0, 38.1, 37.1, 36.8, 33.6, 30.1, 25.2, 24.1 (1C + 1C), 21.8, 18.7, 16.6.

8,11,13-Abietatrien-18-ol (I-2)

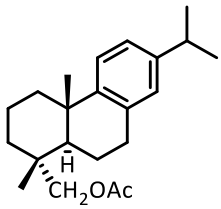


Prepared following the same procedure as for the preparation of **I-1**, starting from dehydroabietic acid (2.64 g, 8.8 mmol), $LiAlH_4$ (668 mg, 17.6 mmol) and anhydrous THF (60 ml).

The crude material was purified by flash chromatography (hexane/EtOAc 85:15) to afford **I-2** (2.48 g, 99%) as a colorless viscous liquid. All analytical data is in agreement with literature.[3]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.2 Hz, 1H), 6.98 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 3.47 (d, *J* = 10.9 Hz, 1H), 3.23 (d, *J* = 10.9 Hz, 1H), 2.92 – 2.84 (m, 2H), 2.81 (sept, *J* = 7.0 Hz, 1H), 2.33-2.23 (m, 1H), 1.85 – 1.74 (m, 2H), 1.74 – 1.63 (m, 2H), 1.64 (dd, *J* = 12.0, 3.0 Hz, 1H), 1.44 (td, *J* = 12.6, 4.0 Hz, 1H), 1.46 – 1.33 (m, 2H), 1.22 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 6H), 0.89 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 145.7, 134.9, 126.9, 124.4, 123.9, 72.4, 44.1, 38.6, 38.0, 37.5, 35.2, 33.6, 30.2, 25.4, 24.1 (1C + 1C), 19.0, 18.8, 17.5.

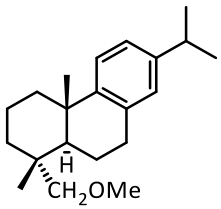
8,11,13-Abietatrien-18-yl acetate (4)



Prepared following the same procedure for the preparation of **16**, starting from **I-2** (405 mg, 1.42 mmol), triethylamine (396 µl, 2.84 mmol), acetyl chloride (203 µl, 2.84 mmol) and DCM (5 ml). The resulting yellow viscous liquid was purified by flash chromatography (petroleum ether/EtOAc 97.5:2.5) to afford **4** (459 mg, 98%) as a colorless viscous liquid. All the analytical data is in agreement with the literature.[5]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.2 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 3.98 (d, *J* = 11.0 Hz, 1H), 3.69 (d, *J* = 11.0 Hz, 1H), 2.95 – 2.79 (m, 2H), 2.82 (sept, *J* = 7.0 Hz, 1H), 2.32-2.25 (m, 1H), 2.03 (s, 3H), 1.81 – 1.63 (m, 4H), 1.67 (dd, *J* = 11.6, 2.4 Hz, 1H), 1.45 (td, *J* = 13.2, 4.1 Hz, 1H), 1.45 – 1.41 (m, 1H), 1.41 (td, *J* = 13.0, 4.0 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 6H), 1.22 (s, 3H), 0.94 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 147.3, 145.8, 134.9, 127.0, 124.4, 124.0, 72.6, 44.2, 38.4, 37.6, 36.9, 35.7, 33.6, 30.4, 25.5, 24.1 (1C + 1C), 21.1, 19.1, 18.7, 17.6.

18-methoxyabieta-8,11,13-triene (5)



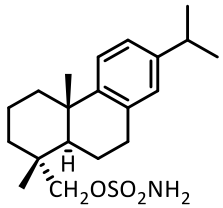
A solution of alcohol **I-2** (400 mg, 1.40 mmol) in DMSO (4.50 ml) was added to a suspension of NaH 60% in mineral oil (120 mg, 3.00 mmol) in DMSO (0.50 ml) (the mineral oil had previously been washed with hexane under an argon atmosphere). The reaction mixture was stirred at 40 °C for 1.5 h. and then MeI (200 µl, 3.21 mmol) was added. After 3 h. of stirring at r.t.,the mixture was cooled with and ice bath and water was added (10 ml) dropwise, then the resulting solution

was extracted with diethyl ether (2 x 20 ml) and the combined organic phases were washed with brine (3 x 10 ml), died over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 97.5:2.5) to afford **5** (420 mg, 99%) as a colorless viscous liquid.

$[\alpha]_D^{20}$ = +63.7 (c = 1.00 in $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.2 Hz, 1H), 6.97 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 3.30 (s, 3H), 3.18 (d, *J* = 9.0 Hz, 1H), 2.95 (d, *J* = 9.0 Hz, 1H), 2.90 – 2.84 (m, 2H), 2.81 (sept, *J* = 7.0 Hz, 1H), 2.30-2.20 (m, 1H), 1.85 – 1.57 (m, 4H), 1.69 (dd, *J* = 13.0, 3.0 Hz, 1H), 1.49 (td, *J* = 13.4, 4.0 Hz, 1H), 1.45 – 1.34 (m, 2H), 1.23 (d, *J* = 7.0 Hz, 6H), 1.20 (s, 3H), 0.88 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 147.7, 145.5, 135.1), 126.9, 124.4, 123.8, 82.8, 59.4, 44.4, 38.6, 37.6, 37.5, 35.9, 33.6, 30.3, 25.4, 24.1 (1C + 1C), 19.2, 18.9, 17.9.
IR (ATR, neat): ν= 2952, 2924, 2867, 1497, 1458, 1383, 1362, 1197, 1174, 1108, 973, 820 cm^{-1}.
HRMS ESI (+): *m/z* $[M+H]^+$ calc. for $C_{21}H_{33}O^+$: 301.2526, found: 301.2522.

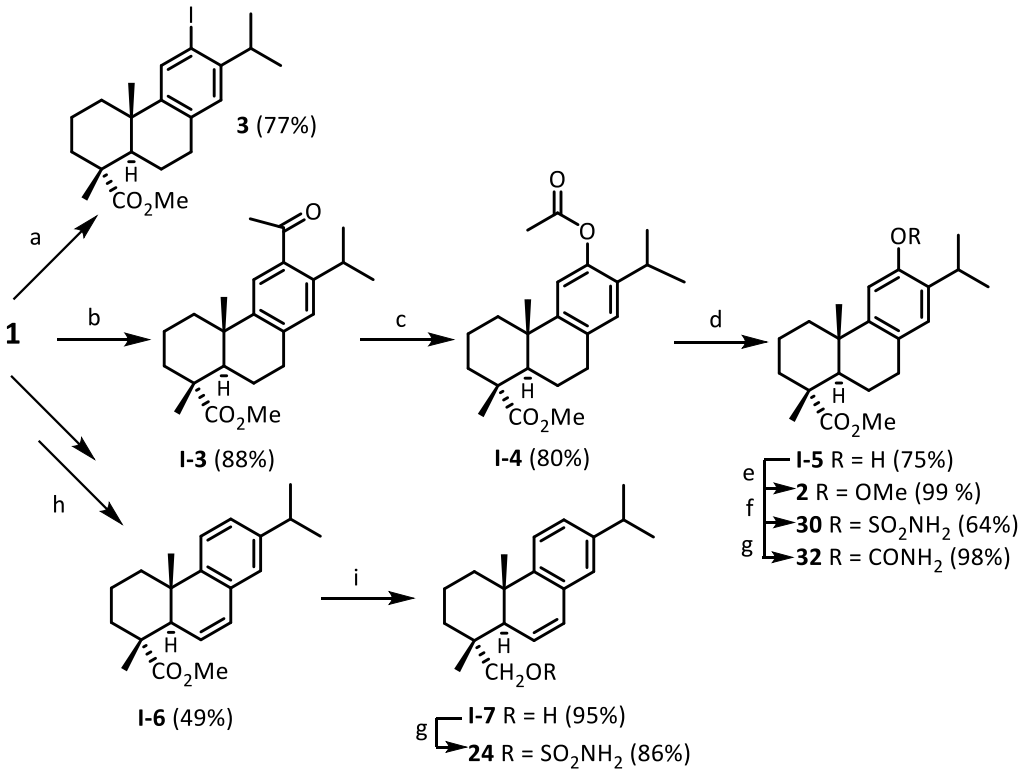
8,11,13-Abietatrien-18-yl sulfamate (22)



Prepared following the same procedure as for the preparation of **28** starting from **I-2** (500. mg, 1.74 mmol), chlorosulfonyl isocyanate (303 µl, 3.48 mmol), formic acid (131 µl, 3.48 mmol) and pyridine (280 µl, 3.48 mmol). After purification by flash chromatography (petroleum ether/EtOAc 75:25), product **22** was isolated (622 mg, 98%) as a white amorphous solid.

$[\alpha]_D^{20}$ = +32.3 (c = 1.00 in $CHCl_3$)

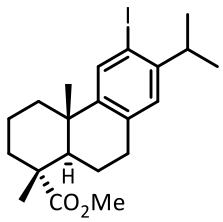
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.2 Hz, 1H), 6.99 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 4.71 (br s, 2H), 4.05 (d, *J* = 9.3 Hz, 1H), 3.79 (d, *J* = 9.3 Hz, 1H), 2.96 – 2.86 (m, 2H), 2.81 (sept, *J* = 7.1 Hz, 1H), 2.32 – 2.25 (m, 1H), 1.83 – 1.65 (m, 4H), 1.69 (dd, *J* = 12.0, 2.8 Hz, 1H), 1.52 (td, *J* = 13.0, 2.8 Hz, 1H), 1.49 – 1.44 (m, 1H), 1.41 (td, *J* = 13.2, 3.7 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.22 (s, 3H), 0.97 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 145.9, 134.7, 127.0, 124.3, 124.1, 78.8, 43.8, 38.2, 37.5, 37.3, 35.3, 33.6, 30.0, 25.3, 24.1 (1C + 1C), 19.1, 18.5, 17.3.
IR (ATR, neat): ν = 3386, 3280, 2952, 2872, 1718, 1698, 1555, 1460, 1355, 1175, 969, 928, 840, 820 cm^{-1}.
HRMS ESI (-): *m/z* $[M-H]^-$ calcd. for $C_{20}H_{30}NO_3S^-$: 364.1952; found: 364.1945



a) I_2, $AgNO_3$, MeOH, b) AcCl, $AlCl_3$, DCM, 0 °C to r.t., c) *m*CPBA, DCM, d) NaOMe, MeOH, e) dimethyl sulfate, K_2CO_3, acetone, reflux, f) Chlorosulfonyl isocyanate, HCO_2H, Py, DMA, g) Chlorosulfonyl isocyanate, DCM, then ice/H_2O, h) See ref. 7, i) $LiAlH_4$, THF, 0 °C to r.t.,

Scheme S.3

Methyl 12- Iodo-8,11,13-abietatrien-18-ate (3)



Dehydroabietic acid methyl ester **1** (1.00 g, 3.18 mmol) was dissolved in MeOH (31 ml) assisted by sonication. Then $AgNO_3$ (1.08 g, 6.36 mmol) was added followed by I_2 (1.78 g, 7.00 mmol). The mixture was stirred for 19 hours under an argon atmosphere and protected from light. AgI was then filtered off and washed with DCM. The filtrate was washed successively with a saturated solution of Na_2SO_3 and water. The organic phase was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was suspended in MeOH (25 ml) and was stirred vigorously for 30 min. Then it was filtered and purified by flash chromatography (petroleum ether/EtOAc 95:5) to afford **3** (1.09 g, 77%) as a white solid.

m.p.: 124 - 126 °C

$[\alpha]_D^{20}$ = +80.3 (c = 1.00 in $CHCl_3$)

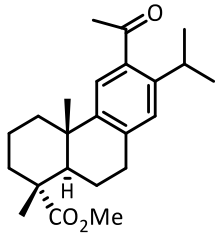
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1H), 6.89 (s, 1H), 3.68 (s, 3H), 3.10 (sept, *J* = 6.9 Hz, 1H), 2.89 – 2.79 (m, 2H), 2.30-2.20 (m, 1H), 2.19 (dd, *J* = 12.5, 2.3 Hz, 1H), 1.90 – 1.62 (m, 5H), 1.50 (td, *J* = 12.3, 4.6 Hz, 1H), 1.47 – 1.37 (m, 1H), 1.28 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 149.6, 147.2, 135.7, 135.5, 126.6, 98.2, 52.1, 47.7, 44.7, 38.0, 37.6, 37.0, 36.7, 29.7, 25.1, 23.4, 23.2, 21.6, 18.6, 16.6.

IR (ATR, neat): ν = 2962, 2927, 2869, 1714, 1463, 1447, 1429, 1385, 1249, 1173, 1132, 1082, 968, 904, 879, 755, 725 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{30}IO_2^+$: 441.1285 ; found: 441.1298.

Methyl 12- Acetyl-8,11,13-abietatrien-18-ate (I-3)



Freshly distilled acetyl chloride (1.12 mL, 15.70 mmol) was added to a solution of dehydroabietic acid methyl ester **1** (2.24 g, 7.12 mmol) in anhydrous DCM (30 mL) and under argon atmosphere. The resulting reaction mixture was stirred at 0 °C for 5 min. Then $AlCl_3$ (1.90 g, 14.24 mmol) was added at 0 °C. After 45 min. at 0 °C the reaction mixture was stirred at r.t. for 16 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL) at 0 °C. The resulting biphasic mixture was extracted with DCM (3 x 50 mL) and the combined organic phases were washed successively with a saturated solution of $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 90:10) to afford **I-3** (2.23 g, 88%) as a white solid.

m.p.: 130 – 131 °C

$[\alpha]_D^{20}$ = +60.1 (c = 1.00 in $CHCl_3$).

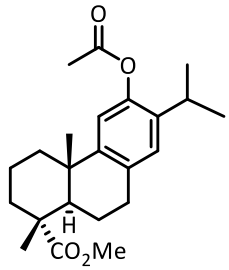
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.04 (s, 1H), 3.67 (s, 3H), 3.46 (sept, *J* = 6.8 Hz, 1H), 2.95 – 2.86 (m, 2H), 2.54 (s, 3H), 2.36-2.26 (m, 1H), 2.22 (dd, *J* = 13.0, 2.2 Hz, 1H), 1.93 – 1.62 (m, 5H), 1.52 (td, *J* = 12.5, 4.1 Hz, 1H), 1.50 – 1.39 (m, 1H), 1.28 (s, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.22 (s, 3H), 1.19 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 179.0, 146.7, 145.0, 138.9, 136.5, 127.2, 124.4, 52.1, 47.7, 44.9, 38.0, 37.1, 36.8, 30.7, 30.1, 28.8, 25.2, 24.4, 24.2, 21.6, 18.6, 16.6.

IR (ATR, neat): ν = 2948, 2925, 2867, 1725, 1682, 1552, 1448, 1435, 1363, 1248, 1225, 1174, 1134, 1107, 1084, 883 cm^{-1}.

HRMS ESI (+): *m/z* $[M+Na]^+$ calcd. for $C_{23}H_{32}NaO_3^+$: 379.2244; found: 379.2235.

Methyl 12- acetoxy-8,11,13-abietatrien-18-ate (I-4)



To a solution of **I-3** (2.50 g, 7.01 mmol) in anhydrous DCM (21 ml) was added *m*CPBA (2.42 g, 14.02 mmol). The resulting mixture was stirred at r.t. for 72 h, then water (100 ml) and DCM were added. After phase separation, the aqueous phase was extracted with DCM (2 x 50 ml) and the combined organic phases were successively washed with a saturated solution of $NaHCO_3$ (2 x 100 ml) and brine (200 ml), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 90:10) to afford **I-4** (2.08 g, 80%) as a colorless viscous liquid.

$[\alpha]_D^{20}$ = +54.1 (c = 0.68 in $CHCl_3$)

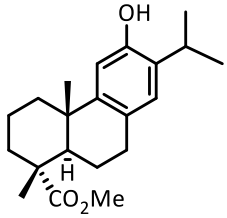
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.82 (s, 1H), 3.66 (s, 3H), 2.90 (sept, *J* = 6.9 Hz, 1H), 2.90 – 2.82 (m, 2H), 2.31 (s, 3H), 2.23 (dd, *J* = 12.4, 2.3 Hz, 1H), 2.24-2.14 (m, 1H), 1.91 – 1.59 (m, 5H), 1.50 (td, *J* = 12.0, 3.9 Hz, 1H), 1.45 – 1.35 (m, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 170.1, 148.2, 146.4, 137.1, 133.0, 127.2, 118.0, 52.1, 47.7, 44.6, 38.0, 37.1, 36.7, 29.6, 27.3, 25.1, 23.2, 23.1, 21.8, 21.1, 18.6, 16.6.

IR (ATR, neat): ν = 2933, 2866, 1757, 1724, 1496, 1433, 1366, 1244, 1205, 1133, 1113, 1017, 910, 731 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{33}O_4^+$: 373.2373; found: 373. 23735

Methyl 12- hydroxyl-8,11,13-abietatrien-18-ate (I-5)



A solution of NaOMe (235 mg, 4.34 mmol) in MeOH (8.0 ml) was added dropwise to a solution of **I-4** (1.09 g, 2.90 mmol) in MeOH (8.1 ml). The resulting reaction mixture was stirred for 1 h at r.t. Then HCl (0.1 N) was added until pH=3 and the resulting suspension was extracted with EtOAc (2 x 30 ml), dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 90:10) to afford **I-5** (718 mg, 75%) as a pale yellow solid.

m.p.: 150 - 152 °C

$[\alpha]_D^{20}$ = +58.3 (c = 1.00 in $CHCl_3$)

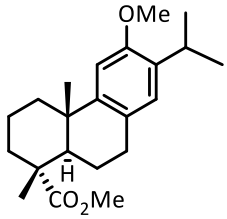
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.62 (s, 1H), 4.66 (br s, 1H), 3.66 (s, 3H), 3.11 (sept, *J* = 6.9 Hz, 1H), 2.85 – 2.76 (m, 2H), 2.21 (dd, *J* = 12.4, 2.2 Hz, 1H), 2.22 – 2.14 (m, 1H), 1.85-1.59 (m, 5H), 1.48 (td, *J* = 12.3, 4.1 Hz, 1H), 1.44 – 1.32 (m, 1H), 1.26 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.19 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 150.9, 148.0, 131.9, 127.1, 126.8, 110.9, 52.1, 47.8, 45.0, 38.1, 37.1, 36.7, 29.4, 27.0, 25.1, 22.9, 22.7, 22.0, 18.7, 16.6.

IR (ATR, neat): ν = 3442, 2942, 2925, 1694, 1507, 1417, 1327, 1253, 1230, 1174, 1134, 1115, 1059, 1048, 1000, 964, 909, 888, 860, 794, 764, 724 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{31}O_3^+$: 331.2268; found: 331.2253.

Methyl 12- methoxy-8,11,13-abietatrien-18-ate (2)



K_2CO_3 (249 mg, 1.80 mmol) and dimethyl sulfate (256 µl, 2.70 mmol) were added to a solution of **I-5** (297 mg, 0.899 mmol) in acetone (5 ml). The reaction mixture was heated to reflux for 12 h, after that water (5ml) was added and the resulting solution was extracted with DCM (2 x 15 ml). The combined organic phases were washed with water, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 97.5: 2.5) to afford compound **2** (307 mg, 99%) as a colorless viscous liquid.

$[\alpha]_D^{20}$ = +63.3 (c = 1.00 in $CHCl_3$)

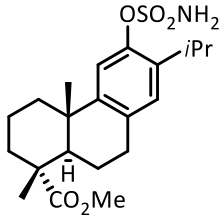
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H), 6.71 (s, 1H), 3.79 (s, 3H), 3.66 (s, 3H), 3.22 (sept, *J* = 6.8 Hz, 1H), 2.85 – 2.77 (m, 2H), 2.32 – 2.23 (m, 1H), 2.24 (dd, *J* = 12.5, 2.1 Hz, 1H), 1.93 – 1.67 (m, 4H), 1.66 – 1.61 (m, 1H), 1.53 (td, *J* = 12.5, 3.2 Hz, 1H), 1.45 – 1.32 (m, 1H), 1.27 (s, 3H), 1.23 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 155.2, 147.5, 134.6, 126.8, 126.6, 106.5, 55.7, 52.0, 47.9, 45.1, 38.2, 37.4, 36.8, 29.5, 26.6, 25.2, 23.0, 22.8, 22.0, 18.8, 16.7.

IR (ATR, neat): ν = 2932, 2872, 1724, 1612, 1500, 1462, 1406, 1380 1327, 1243, 1193, 1174, 1132, 1041, 959, 886, 847, 790, 733 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{22}H_{33}O_3^+$: 345.2424; found: 345.2422

12-sulfamoyloxy-8,11,13-abietatrien-18-ate (30)

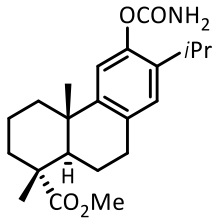


Chlorosulfonyl isocyanate (114 µl, 1.32 mmol) was added to a round bottom flask under an argon atmosphere and cooled to 0 °C with an ice bath. Formic acid (50 µl, 1.32 mmol) was then carefully added dropwise (important gas release). The resulting white slurry was stirred for 12 hours as the temperature was slowly allowed to reach r.t. Anhydrous DMA (166 µl) was then slowly added at 0 °C followed by the phenol **I-5** (110 mg, 0.33 mmol) in solution in anhydrous DMA (240 µl) and anhydrous pyridine (106 µl, 1.32 mmol). The mixture was stirred for 1 h in ice bath and five h at r.t. Then water (5 ml) was added, followed by a saturated solution of NH_4Cl (5 ml) and the mixture was extracted with EtOAc (4 x 10 ml), dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography (petroleum ether/EtOAc 85:15) affording **30** (87 mg, 64%) as a white amorphous solid.

$[\alpha]_D^{20}$ = +51.2 (c = 1.00, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.98 (s, 1H), 4.95 (br s, 2H), 3.67 (s, 3H), 3.28 (sept, *J* = 6.9 Hz, 1H), 2.92-2.83 (m, 2H), 2.29 – 2.19 (m, 1H), 2.19 (dd, *J* = 12.5, 2.0 Hz, 1H), 1.90 – 1.59 (m, 5H), 1.56 – 1.36 (m, 2H), 1.27 (s, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.20 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 148.7, 145.9, 138.3, 134.4, 127.7, 117.6, 52.1, 47.7, 44.7, 38.1, 37.3, 36.7, 29.6, 26.7, 25.1, 23.5, 23.4, 21.6, 18.6, 16.6.
IR (ATR, neat): ν = 3360, 3278, 2968, 2934, 2874, 1725, 1557, 1495, 1456, 1361, 1245, 1188, 1133, 1108, 993, 945, 886, 832, 816, 753, 725 cm^{-1}.
HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{21}H_{32}NO_5S^+$: 410.1996; found: 410.1980

Methyl 12-carbamoyloxy-8,11,13-abietatrien-18-ate (32)



Chlorosulfonyl isocyanate (125 µl, 1.44 mmol) was added to a stirred slurry of phenol **I-5** (452 mg, 1.37 mmol) in anhydrous DCM (1.40 ml) under argon atmosphere. The reaction mixture was stirred at room temperature for 3 hours until the starting material was fully consumed and then solvent was removed under reduced pressure. The residue was stirred with water (5 ml) containing crushed ice. The solution was extracted with EtOAc (3 x 20 ml), and the combined organic phases were washed successively with water (10 mL) and brine (3 X 10 mL), dried over

Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 65:35) to afford product **32** (425 mg, 98%) as a white amorphous solid.

$[\alpha]_D^{20}$ = +61.6 (c = 1.00 in $CHCl_3$)

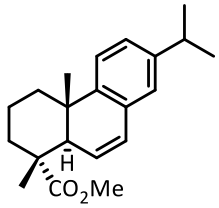
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.90 (s, 1H), 5.04 (br s, 2H), 3.66 (s, 3H), 3.03 (sept, *J* = 6.9 Hz, 1H), 2.89 – 2.83 (m, 2H), 2.23 (dd, *J* = 12.6, 2.2 Hz, 1H), 2.23 – 2.18 (m, 1H), 1.87 – 1.78 (m, 1H), 1.78 – 1.65 (m, 3H), 1.65 – 1.61 (m, 1H), 1.51 (td, *J* = 12.4, 4.3 Hz, 1H), 1.43 – 1.37 (m, 1H), 1.26 (s, 3H), 1.21 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 155.7, 148.2, 146.2, 137.7, 133.0, 127.1, 118.2, 52.0, 47.7, 44.6, 38.0, 37.1, 36.7, 29.6, 27.1, 25.1, 23.3, 23.1, 21.7, 18.6, 16.6.

IR (ATR, neat): ν= 3474, 3340, 3199, 2932, 2869, 1723, 1715, 1597, 1497, 1460, 1352, 1337, 1323, 1246, 1168, 1134, 1115, 1018, 1006, 939, 911, 889, 754 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{22}H_{32}NO_4^+$: 374.2326; found: 374.2355.

Methyl 6,8,11,13-abietatetraen-18-oate (I-6)

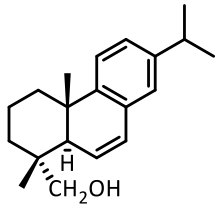


Prepared according the procedure described by Monteiro *et. al.* [6] starting from dehydroabietic acid methyl ester **1**. All the analytical data is in agreement with the literature.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 – 7.05 (m, 2H), 6.93 (d, *J* = 1.6 Hz, 1H), 6.53 (dd, *J* = 9.6, 3.1 Hz, 1H), 5.73 (dd, *J* = 9.5, 2.7 Hz, 1H), 3.66 (s, 3H), 2.94 (t, *J* = 3.0 Hz, 1H), 2.87 (sept, *J* = 6.9 Hz, 1H), 2.28 – 2.16 (m, 1H), 1.91 – 1.62 (m, 5H), 1.42 (s, 3H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.10 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 146.5, 145.3, 132.7, 130.0, 128.5, 125.9, 124.9, 121.8, 52.2, 46.8, 46.6, 37.3, 35.8, 35.5, 33.8, 24.2 (1C + 1C), 21.0, 18.6, 18.1.

6,8,11,13-Abietatetraen-18-ol (I-7)



Prepared following the same procedure as for the preparation of **I-1** starting from **I-6** (744 mg, 2.38 mmol), $LiAlH_4$ (180 mg, 4.77 mmol) and anhydrous THF (12 ml). The crude material was purified by flash chromatography (petroleum ether/ EtOAc 85:15) to afford **I-7** (646 mg, 95%) as a colorless viscous liquid.

$[\alpha]_D^{20}$ = -49.0 (c = 1.00 in $CHCl_3$)

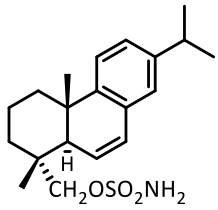
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.54 (dd, *J* = 9.6, 3.1 Hz, 1H), 5.96 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.48 (d, *J* = 11.1 Hz, 1H), 3.27 (d, *J* = 11.1 Hz, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 2.39 (t, *J* = 3.0 Hz, 1H), 2.22-2.12 (m, 1H), 1.86 – 1.69 (m, 2H), 1.61 (td, *J* = 12.5, 4.5 Hz, 1H), 1.46 (td, *J* = 12.8, 4.4 Hz, 1H), 1.46 – 1.40 (m, 1H), 1.23 (d, *J* = 7.1 Hz, 3H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.08 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 146.3, 145.8, 132.7, 128.9, 128.7, 125.8, 124.7, 121.9, 71.7, 45.3, 37.5, 37.3, 35.9, 34.6, 33.7, 24.1 (1C + 1C), 20.9, 18.5, 18.3.

IR (ATR, neat): ν= 33361, 1958, 2925, 1867, 1709, 1489, 1460, 1382, 1366, 1043, 1027, 888, 823, 773, 768, 698, 687 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{20}H_{29}O^+$: 285.2213; found: 285.2229

6,8,11,13-Abietatetraen-18-yl sulfamate (24)



Prepared following the same procedure as for the preparation of **28**, starting from **I-7** (632 mg, 2.22 mmol), chlorosulfonyl isocyanate (390 µl, 4.50 mmol), formic acid (170 µl, 4.50 mmol), pyridine (360 µl, 4.50 mmol) and anhydrous DMA (3.6 ml). After purification by flash chromatography (petroleum ether/EtOAc 75:25), compound **24** was isolated (698 mg, 86%) as a white amorphous solid.

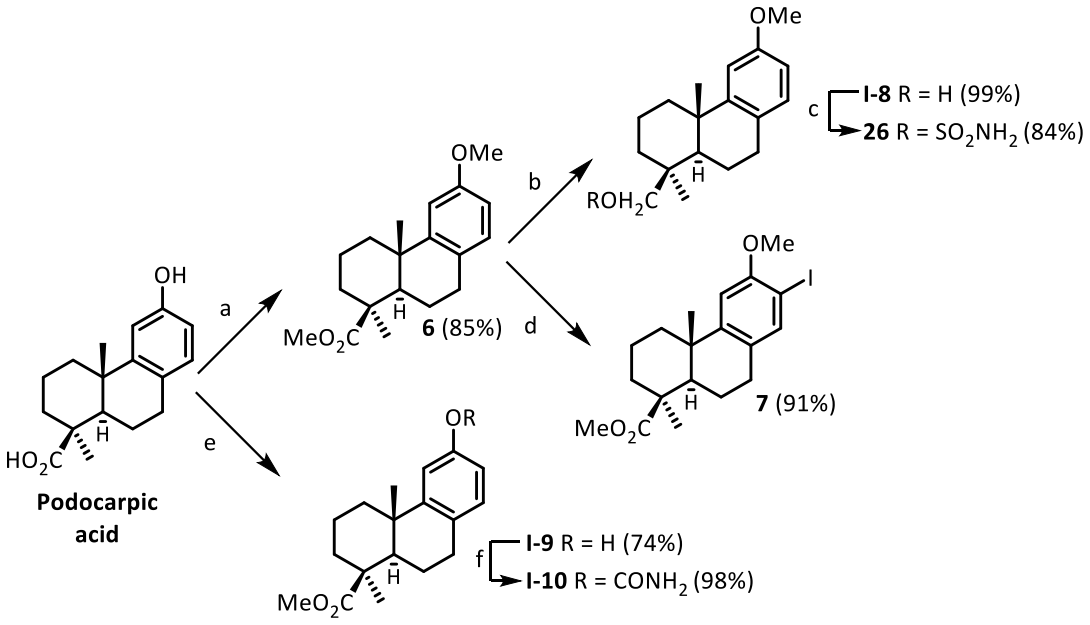
$[\alpha]_D^{20}$ = -47.5 (c = 1.00 in $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 – 7.03 (m, 2H), 6.92 (s, 1H), 6.56 (dd, *J* = 9.8, 3.0 Hz, 1H), 5.93 (dd, *J* = 9.7, 2.6 Hz, 1H), 4.67 (br s, 2H), 4.03 (d, *J* = 9.4 Hz, 1H), 3.86 (d, *J* = 9.5 Hz, 1H), 2.86 (sept, *J* = 6.9 Hz, 1H), 2.43 (t, *J* = 3.0 Hz 1H), 2.24-2.13 (m, 1H), 1.86 – 1.72 (m, 2H), 1.61 (td, *J* = 12.3, 5.0 Hz, 1H), 1.62 – 1.47 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.11 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 145.4, 132.5, 129.1, 127.8, 126.1, 124.9, 121.9, 78.4, 45.4, 37.6, 36.6, 35.5, 34.7, 33.7, 24.1 (1C + 1C), 20.9, 18.2, 18.1.

IR (ATR, neat): ν = 3377, 3266, 2961, 2928, 2869, 1742, 1717, 1640, 1462, 1383, 1366, 1250, 1175, 966, 905, 838, 810, 762, 727, 686 cm^{-1}.

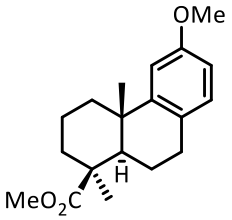
HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{20}H_{30}NO_3S^+$: 285.2213 ; found: 285.2229



a) MeI, K_2CO_3, acetone, reflux, b) $LiAlH_4$, THF, 0 °C to r.t., c) Chlorosulfonyl isocyanate, formic acid, Py, DMA, d) I_2, AgNO3, MeOH, 40 °C, e) $TMSCHN_2$, MeOH, $PhCH_3$ f) Chlorosulfonyl isocyanate, DCM, then ice/H_2O

Scheme S.4

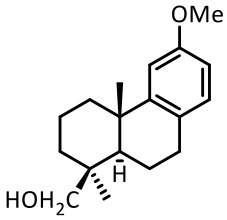
Methyl O-methylpodocarpate (6)



K_2CO_3 (5.03 g, 36.4 mmol) and MeI (2.72 ml, 43.7 mmol) were added to a stirred solution of podocarpic acid (2.00 g, 7.29 mmol) in acetone (32 ml). The resulting suspension was heated to reflux. After 14 h the reaction was allowed to cool to r.t., then water (40 ml) was added, and then the crude material was extracted with DCM (3 x 30 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc 95: 5) to afford compound **6** (1.87 g, 85 % yield) as a colorless solid. All the analytical data is in agreement with the literature.[7]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 6.70 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 2.88 (ddd, *J* = 16.9, 5.4, 1.7 Hz, 1H), 2.76 (ddd, *J* = 16.3, 12.7, 6.3 Hz, 1H), 2.34 -2.15 (m, 3H), 2.11-1.87 (m, 2H), 1.71 – 1.59 (m, 1H), 1.55 (dd, *J* = 12.3, 1.7 Hz, 1H), 1.42 (td, *J* = 13.3, 4.2 Hz, 1H), 1.30 (s, 3H), 1.13 (td, *J* = 13.5, 4.3 Hz, 1H), 1.06 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 157.8, 149.4, 130.0, 127.8, 111.3 (1C + 1C), 55.4, 52.9, 51.4, 44.1, 39.5, 38.8, 37.8, 31.4, 28.7, 23.0, 21.2, 20.1.

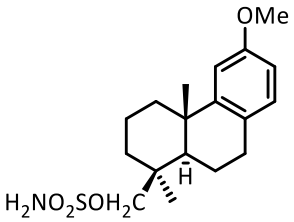
O-methylpodocarp-16-ol (I-8)



Prepared following the same procedure as for the preparation of **I-1** starting from **6** (920 mg, 3.04 mmol), $LiAlH_4$ (231 mg, 6.08 mmol) and anhydrous THF (18 ml). The crude material was purified by flash chromatography (hexane/ EtOAc 85:15) to afford **I-8** (822 mg, 99 %) as a white solid. All the analytical data is in agreement with the literature.[8]

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.3 Hz, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 6.66 (dd, *J* = 8.4, 2.7 Hz, 1H), 3.85 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 3H), 3.55 (dd, *J* = 10.9, 1.2 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.82 – 2.72 (m, 1H), 2.32 – 2.24 (m, 1H), 2.00 – 1.93 (m, 1H), 1.92 – 1.85 (m, 1H), 1.77 – 1.58 (m, 3H), 1.49 (dd, *J* = 12.8, 2.0 Hz, 1H), 1.44 (td, *J* = 12.7, 4.0 Hz, 1H), 1.18 (d, *J* = 0.8 Hz, 3H), 1.05 (s, 3H), 1.02 (tdd, J = 13.8, 4.3, 1.3 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 151.1, 129.9, 127.2, 111.0, 110.4, 65.4, 55.4, 51.3, 39.0, 38.9, 38.1, 35.3, 30.3, 26.9, 25.8, 19.4, 19.1.

O-methylpodocarp-16-yl sulfamate (26)

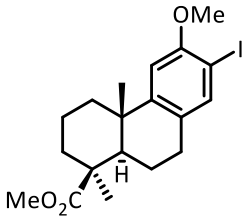


Prepared following the same procedure as for the preparation of **28**, starting from **I-8** (400 mg, 1.46 mmol), chlorosulfonyl isocyanate (354 µl, 2,92 mmol), formic acid (110 µl, 2.92 mmol), pyridine (235 µl, 2.92 mmol) and anhydrous DMA (2.3 ml). After purification by flash chromatography (hexane/EtOAc 75:25), compound **24** was isolated (431 mg, 84 %) as a white solid.

m.p.: 136-137 °C
$[\alpha]_D^{20}$ = +44.1 (c = 1.00 in $CHCl_3$)
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.6 Hz, 1H), 4.82 (br s, 2H), 4.46 (d, *J* = 9.3 Hz, 1H), 4.09 (d, *J* = 9.3, 1H), 3.77 (s, 3H), 2.92 – 2.85 (m, 1H), 2.83 – 2.74 (m, 1H), 2.34 – 2.26 (m, 1H), 2.03 – 1.96 (m, 1H), 1.93 – 1.86 (m, 1H), 1.78 – 1.61 (m, 3H), 1.54 (dd, *J* = 12.9, 1.9 Hz, 1H), 1.46 (td, *J* = 12.9, 4.4 Hz, 1H), 1.20 (s, 3H), 1.11 (s, 3H), 1.10 (td, *J* = 13.6, 4.4 Hz, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 150.5, 130.0, 127.0, 111.3, 110.4, 74.3, 55.4, 51.3, 38.7, 38.0, 37.6, 35.4, 30.0, 27.1, 25.8, 19.3, 18.9.

IR (ATR, neat): ν = 3356, 3261, 2921, 1612, 1572, 1501, 1480, 1452, 1440, 1362, 1293, 1281, 1265, 1251, 1188, 1172, 1158, 1044, 971, 919, 846, 655, 547 cm^{-1}.
HRMS ESI (+): *m/z* $[M+Na]^+$ calcd. for $C_{18}H_{27}NNaO_4S^+$: 376.1553; found: 376.1560

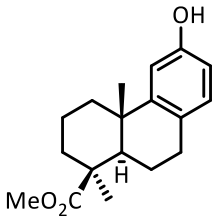
Methyl 13-Iodo-O-methylpodocarpate (7)



Methyl *O*-methylpodocarpate **6** (1.73 g, 5.72 mmol) was dissolved in methanol (75 ml) at 40 °C. $AgNO_3$ (1.94 g, 11.4 mmol) was then added, followed by I_2 (3.19 g, 12.6 mmol). The mixture was stirred for 12 hours at 40 °C under an argon atmosphere and protected from light. AgI was then filtered off and washed with DCM, and the filtrate was washed with a saturated solution of Na_2SO_3 (2 x 20 ml). The organic phase was washed with water, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc 9:1) to afford **7** (2.24 g, 91%) as a white solid. All the analytical data is in agreement with the literature [7].

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.70 (s, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 2.80 (ddd, *J* = 16.7, 5.7, 1.5 Hz, 1H), 2.69 (ddd, *J* = 16.7, 12.9, 6.3 Hz, 1H), 2.32 - 2.25 (m, 1H), 2.25 -2.19 (m, 1H), 2.18 -2.12 (m, 1H), 1.99 (qt, *J* = 13.7, 3.8 Hz, 1H), 1.97 – 1.85 (m, 1H), 1.68 – 1.60 (m, 1H), 1.50 (dd, *J* = 12.2, 1.8 Hz, 1H), 1.40 (td, *J* = 13.4, 4.1 Hz, 1H), 1.27 (s, 3H), 1.09 (td, *J* = 13.6, 4.3 Hz, 1H), 1.03 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 156.4, 149.9, 139.6, 130.3, 108.5, 83.1, 56.5, 52.7, 51.4, 44.1, 39.5, 38.9, 37.7, 30.9, 28.6, 23.0, 21.0, 20.0.

Methyl podocarpate (I-9)

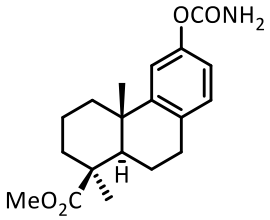


To a solution of podocarpic acid (500 mg, 1.82 mmol) in MeOH (3 mL) and toluene (6 mL) was added dropwise 2.0 M $TMSCHN_2$ in Et_2O (1.20 mL, 2.40 mmol) over 5 min. The resulting mixture was stirred at r.t. for 30 min. and the excess $TMSCHN_2$ was quenched with AcOH. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (petroleum ether/EtOAc 85:15) to afford **I-9** (390 mg, yield 74 %) as a colorless solid. All the analytical data is in agreement with literature [9].

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 6.58 (dd, *J* = 8.1, 2.6 Hz, 1H), 3.66 (s, 3H), 2.83 (ddd, *J* = 16.5, 5.2, 1.5 Hz, 1H), 2.71 (ddd, *J* = 16.5, 12.5, 5.9 Hz, 1H), 2.31 - 2.24 (m, 1H), 2.21 - 2.13 (m, 2H), 1.99 (qt, *J* = 13.8, 4.0 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.67 – 1.58 (m, 1H), 1.52 (dd, *J* = 12.2, 1.8 Hz, 1H), 1.39 (td, *J* = 13.3, 4.1 Hz, 1H), 1.27 (s, 3H), 1.08 (td, *J* = 13.6, 4.3 Hz, 1H), 1.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.1, 153.7, 149.7, 130.2, 127.8, 113.1, 112.2, 52.9, 51.4, 44.8, 39.5, 38.7, 37.8, 31.4, 28.7, 23.0, 21.3, 20.1.

Methyl 12-(carbamoyloxy)podocarpate (I-10)



Prepared following the same procedure as for the preparation of **32**, starting from **I-8** (374 mg, 1.30 mmol) and chlorosulfonyl isocyanate (119 µl, 1.37 mmol). Purification by flash chromatography (petroleum ether/EtOAc 7:3) affords product **I-10** (425 mg, 98%) as a white amorphous solid.

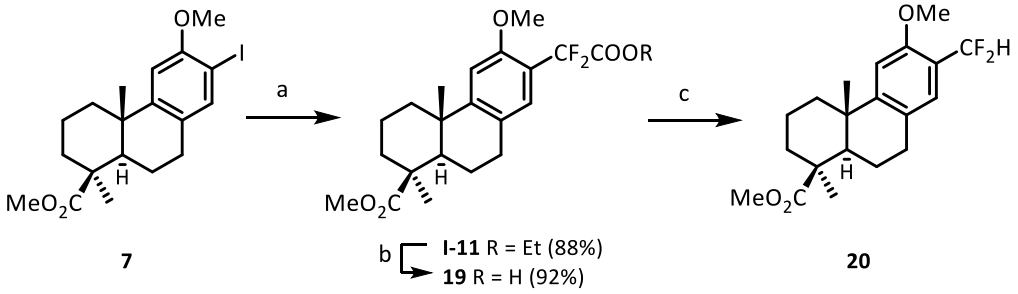
$[\alpha]_D^{20}$ = +102.5 (c = 0.76 in $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.4 Hz, 1H), 4.97 (br s, 2H), 3.66 (s, 3H), 2.89 (ddd, *J* = 17.1, 5.6, 2.0 Hz, 1H), 2.76 (ddd, *J* = 17.0, 12.5, 6.0 Hz, 1H), 2.32 - 2.23 (m, 1H), 2.23 – 2.13 (m, 2H), 2.09 – 1.87 (m, 2H), 1.68 – 1.57 (m, 1H), 1.52 (dd, *J* = 12.2, 1.8 Hz, 1H), 1.41 (td, *J* = 13.3, 4.2 Hz, 1H), 1.27 (s, 3H), 1.10 (td, *J* = 13.7, 4.0 Hz, 1H), 1.02 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.0, 155.4, 149.5, 149.0, 132.9, 130.0, 119.0, 118.6, 52.7, 51.4, 44.1, 39.4, 38.7, 37.7, 31.6, 28.7, 23.1, 21.0, 20.0.

IR (ATR, neat): ν = 3495, 3433, 3343, 3271, 2956, 2852, 1718, 1708, 1599, 1496, 1435, 1357, 1241, 1207, 1179, 1149, 1134, 992, 973, 774 cm^{-1}.

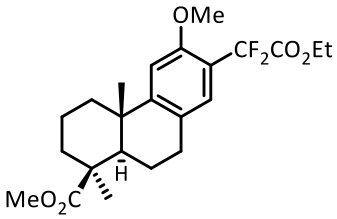
HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{26}NO_4^+$: 332.1856 ; found: 332.1865



a) BrF_2CCO_2Et, Cu, DMSO, 55 °C, b) LiOH 0.25 M, MeCN, THF,
c) 2-mercaptopyridine *N*-oxide sodium salt, DMAP, *n*-Bu_3SnH, toluene, reflux

Scheme S.5

Methyl 13-(2-ethoxy-1,1-difluoro-2-oxoethyl) -O-methylpodocarpate (I-11)



To a slurry of **7** (673 mg, 1.57 mmol) and ethyl bromodifluoroacetate 98% (500 µl, 3.90 mmol) in DMSO (4 ml) was added activated copper powder (519 mg, 8.16 mmol). The resulting mixture was stirred at 60 °C for 15 h. The reaction mixture was then cooled down to r.t., diluted with EtOAc (3 mL) and poured in an aqueous solution of 1.27 M KH_2PO_4 (5 ml). After stirring for 30 min., the resulting suspension was filtered through a pad of celite and the copper salts were washed with EtOAc (100 mL). The organic phase of the filtrate was recovered and washed with water (2 x 40 ml), dried over Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (hexane /EtOAc 85:15) to afford **I-11** as a white solid (591 mg, 88% yield).

m.p.: 133-134 °C

$[\alpha]_D^{20}$ = +94.1 (c = 1.00 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.79 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 2.89 (ddd, *J* = 16.7, 5.5, 1.5 Hz, 1H), 2.76 (ddd, *J* = 16.6, 12.8, 5.9 Hz, 1H), 2.32 – 2.26 (m, 1H), 2.24 – 2.15 (m, 2H), 2.01 (qt, *J* = 14.2, 3.8 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.68 – 1.60 (m, 1H), 1.53 (dd, *J* = 12.3, 1.8 Hz, 1H), 1.42 (td, *J* = 13.4, 3.8 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.28 (s, 3H), 1.09 (td, *J* = 13.6, 4.2 Hz, 1H), 1.04 (s, 3H).

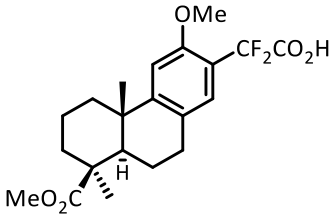
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 164.5 (t, *J* = 33.9 Hz), 154.8 (t, *J* = 4.9 Hz), 152.4 (t, *J* = 2.0 Hz), 128.0, 127.0 (t, *J* = 6.9 Hz), 119.6 (t, *J* = 24.0 Hz), 112.5 (t, *J* = 248.0 Hz), 108.7, 62.8, 55.9, 52.6, 51.4, 44.1, 39.5, 39.1, 37.7, 31.4, 28.6, 22.9, 21.0, 20.0, 14.1.

^{19}F NMR (471 MHz, $CDCl_3$) δ -101.7 (d, *J* = 273.0 Hz), -102.4 (d, *J* = 273.0 Hz).

IR (ATR, neat): ν = 2991, 2957, 2889, 2853, 1755, 1720, 1624, 1502, 1472, 1457, 1433, 1364, 1308, 1293, 1272, 1237, 1190, 1173, 1143, 1093, 1073, 1029, 913, 769, 734, 716, 641cm^{-1}.

HRMS ESI(+): *m/z* $[M+H]^+$ calcd. for $C_{23}H_{31}F_2O_5^+$: 425.2134; found: 425.2128

Methyl 13-(1,1-difluoro-2-oxoethyl)-O-methylpodocarpate (19)



An aqueous solution of $LiOH.H_2O$ 1.25 M (5.8 ml) and THF (0.7 ml) were added to a solution of **I-10** (500 mg, 1.18 mmol) in MeCN (5.8 ml). The resulting mixture was stirred at r.t. for 2 h, and then HCl 1N was added until pH=2. The resulting suspension was extracted with EtOAc (3 x 20ml), dried over Na_2SO_4, filtered, and the filtrated was concentrated under reduced pressure. The residue was purified using reverse phase (C-18) flash chromatography ($MeOH/H_2O$ 7:3) to afford the desired product **19** (400 mg, 92%) as a white amorphous solid.

$[\alpha]_D^{20}$ = 98.4 (c = 1.00 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.83 (s, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 2.89 (ddd, *J* = 16.5, 5.7, 1.7 Hz, 1H), 2.75 (ddd, *J* = 16.6, 12.9, 6.1 Hz, 1H), 2.32 - 2.25 (m, 1H), 2.24 – 2.16 (m, 2H), 2.01 (qt, *J* = 14.2, 3.7 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.68 – 1.61 (m, 1H), 1.52 (dd, *J* = 12.3, 1.8 Hz, 1H), 1.41 (td, *J* = 13.3, 4.0 Hz, 1H), 1.28 (s, 3H), 1.09 (td, *J* = 13.6, 4.2 Hz, 1H), 1.04 (s, 3H).

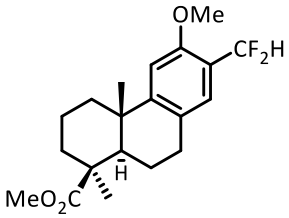
^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 167.3 (t, *J* = 34.6 Hz), 154.6 (t, *J* = 4.4 Hz), 152.7, 128.2, 127.0 (t, *J* = 6.7 Hz), 118.7 (t, *J* = 24.0 Hz), 112.3 (t, *J* = 248.0 Hz), 108.9, 56.0, 52.4, 51.4, 44.0, 39.3, 39.0, 37.5, 31.2, 28.5, 22.8, 20.8, 19.9.

^{19}F NMR (471 MHz, $CDCl_3$) δ -102.3 (d, *J* = 272.0 Hz), -103.1 (d, *J* = 272.0 Hz).

IR (ATR, neat): ν = 2953, 2874, 2850, 1761, 1722, 1699, 1620, 1504, 1464, 1438, 1411, 1345, 1240, 1216, 1194, 1168, 1144, 1109, 1080, 1071, 1033, 976, 899, 852, 801, 720, 701, 659 cm^{-1}.

HRMS ESI(+): *m/z* $[M+Na]^+$ calcd. for $C_{21}H_{26}F_2NNaO_5^+$: 419.1640; found: 419.1632.

Methyl 13-difluoromethyl-O-methylpodocarpate (20)



DMF (4.9 µl, 64 µmol) and oxalyl chloride (109 µl, 1.28 mmol) were added dropwise to solution of **19** (254 mg, 0.640 mmol) in DCM (2 ml) under an argon atmosphere and in ice bath. After 3 h of stirring, the volatiles were removed under reduced pressure and the resulting white amorphous solid was redissolved in anhydrous toluene (3.2 ml). This solution was added dropwise and over a period of 30 min. to a solution of 2-mercaptopyridine *N*-oxide sodium salt (115 mg, 0.768 mmol), DMAP (7.8 mg, 64 µmol) and Bu_3SnH (1.03 ml, 3.84 mmol) in toluene (9 ml) heated to reflux. The heating was continued for 1.5 more h and after cooling down to r.t.,

the mixture was purified by flash chromatography (hexane/EtOAc 95:5) to afford the desired product (70 mg, 31%) as a white solid.

mp: 118-119 °C.

$[\alpha]_D^{20}$ = 109.5 (c = 1.00 in $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (br s, 1H), 6.88 (t, *J* = 55.9 Hz, 1H), 6.80 (br s, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 2.88 (ddd, *J* = 16.5, 5.6, 1.7 Hz, 1H), 2.74 (ddd, *J* = 16.5, 12.6, 6.1 Hz, 1H), 2.32 – 2.26 (m, 1H), 2.26 - 2.16 (m, 2H), 2.02 (qt, *J* = 14.0, 3.7 Hz, 1H), 2.00 – 1.89 (m, 1H), 1.68 – 1.61 (m, 1H), 1.52 (dd, *J* = 12.3, 1.8 Hz, 1H), 1.41 (td, *J* = 13.4, 4.1 Hz, 1H), 1.28 (s, 3H), 1.09 (td, *J* = 13.6, 4.3 Hz, 1H), 1.04 (s, 3H).

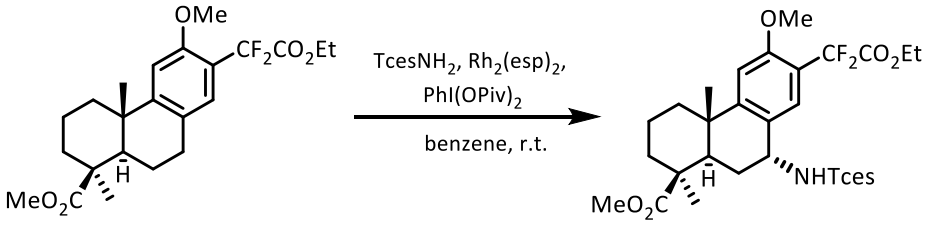
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9 (s), 155.4 (t, *J* = 5.7 Hz), 152.1 (t, *J* = 1.9 Hz), 127.9 (s), 126.9 (t, *J* = 5.6 Hz), 120.4 (t, *J* = 22.1 Hz), 111.9 (t, *J* = 235.0 Hz), 108.1 (s), 55.8 (s), 52.7 (s), 51.5 (s), 44.1 (s), 39.6 (s), 39.1 (s), 37.7 (s), 31.3 (s), 28.6 (s), 23.0 (s), 21.1 (s), 20.1 (s).

^{19}F NMR (471 MHz, $CDCl_3$) δ -114.3 (d, *J* = 298.0 Hz), -115.0 (d, *J* = 298.0 Hz).

IR (ATR, neat): ν= 2994, 2839, 1716, 1618, 1503, 1456, 1381, 1329, 1302, 1258, 1239, 1219, 1185, 1142, 1053, 1018, 902, 853, 729, 629 cm^{-1}.

HRMS ESI (+): *m/z* $[M+Na]^+$ calcd. for $C_{20}H_{26}F_2NaO_3^+$: 375.1742; found: 375.1739.

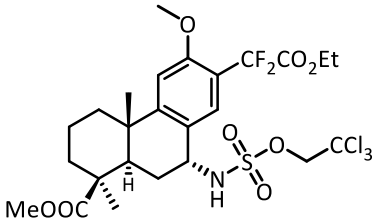
2. C(sp^3)–H amination of ethyl ester of 19 *(cf. reference #17 of the manuscript)*



I-11 **I-12**

Scheme S.6

Methyl 7α-(((2,2,2-trichloroethoxy)sulfonyl)amino)-13-(2-ethoxy-1,1-difluoro-2-oxoethyl)-O-methylpodocarpate (I-12)



Prepared following the general amination procedure **1** starting from **I-10** (255 mg, 0.600 mmol) and using 5 mol% of $Rh_2(esp)_2$ (22.7 mg, 30.0 µmol). After purification by flash chromatography (Petroleum ether/EtOAc 80:20), the desired compound was obtained as a white amorphous solid (336 mg, 85%).

m.p.: 183-184 °C.

$[\alpha]_D^{20}$ = +66.5 (c = 1.00 in $CHCl_3$).

^{1}H RMN (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 6.83 (s, 1H), 4.95 (d, *J* = 6.0 Hz, 1H), 4.89 – 4.85 (m, 1H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.75 (d, *J* = 10.8 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 2.70 - 2.64 (m, 1H), 2.41 - 2.35 (m, 1H), 2.28 – 2.22 (m, 1H), 2.23 (ddd, *J* = 14.9, 13.1, 4.2 Hz, 1H), 2.03 (qt, *J* = 13.8, 3.5 Hz, 1H), 1.73 (dd, *J* = 13.1, 1.6 Hz, 1H), 1.75 – 1.67 (m, 1H), 1.42 (td, *J* = 13.2, 4.0 Hz, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.35 (s, 3H), 1.16 (td, *J* = 13.6, 4.2 Hz, 1H), 1.03 (s, 3H).

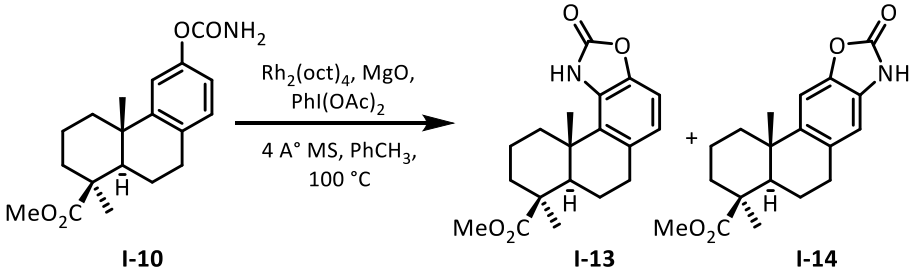
^{13}C NMR (126 MHz, $CDCl_3$) δ 177.5, 164.1 (t, *J* = 33.6 Hz), 157.0 (t, *J* = 4.6 Hz), 153.9, 128.7 (t, *J* = 6.9 Hz), 124.7, 121.3 (t, *J* = 24.3 Hz,), 112.0 (t, *J* = 249.0 Hz), 108.4 , 93.7, 78.1, 63.0, 55.9, 54.0, 51.6, 46.2, 43.7, 39.2 , 39.1, 37.5, 28.4, 27.7, 22.1, 19.8, 14.1.

^{19}F RMN (471 MHz, $CDCl_3$) δ -102.46 (s), -102.47 (s).

IR (ATR, neat): ν = 3281, 2985, 2951, 2922, 2855, 1734, 1719, 1504, 1447, 1433, 1355, 1335, 1227, 1184, 1147, 1108, 1085, 1053, 1035, 1011, 985, 906, 848, 750, 729, 638 cm^{-1}

HRMS ESI(+): *m/z* $[M+Na]^+$ calcd. for $C_{25}H_{32}Cl_3F_2NNaO_8S^+$: 672.0775; found: 672.0806.

3. C(sp^3)–H amination applied to a podocarpic acid-derived carbamate *(cf. reference #24 of the manuscript)*

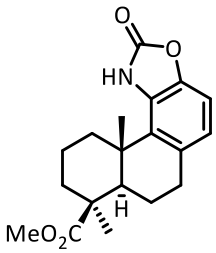


I-10 **I-13** **I-14**

Scheme S.7

Prepared following the previously described procedure for the synthesis of **33** starting from carbamate **I-10** (189 mg, 0.570 mmol). After purification by flash chromatography (petroleum ether/EtOAc 97.5: 2.5 to 75:25) two major cyclized products were obtained: **I-13** (pale yellow solid, 50 mg, 27 %) and **I-14** (pink solid, 36 mg, 19%).

Methyl(7aR,8S,11aS)-8,11a-dimethyl-2-oxo-1,2,6,7,7a,8,9,10,11,11a-decahydrophenanthro [4,3-d]oxazole-8-carboxylate (I-13)



m.p: 215-218 °C (melting with decomposition)**.**

$[\alpha]_D^{20}$ = +128.2 (c = 1.00 in $CHCl_3$)

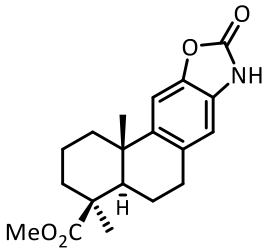
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 3.68 (s, 3H), 2.97 – 2.75 (m, 2H), 2.40 – 2.29 (m, 2H), 2.27 – 2.16 (m, 1H), 2.08 (qt, *J* = 13.5, 3.4 Hz, 1H), 1.89 (qd, *J* = 13.1, 5.7 Hz, 1H), 1.74 – 1.60 (m, 1H), 1.56 (d, *J* = 12.0 Hz, 1H), 1.42 (td, *J* = 13.2, 3.8 Hz, 1H), 1.30 (s, 3H), 1.15 (s, 3H), 1.08 (td, *J* = 13.4, 4.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 156.2, 142.6, 132.7, 131.6, 126.5, 123.8, 108.0, 54.2, 51.6, 44.0, 38.9, 37.5, 37.3, 33.2, 28.9, 21.0, 19.7, 18.5.

IR (ATR, neat): ν = 3184, 2945, 2875, 1749, 1717, 1708, 1471, 1437, 1386, 1310, 1274, 1243, 1233, 1192, 1177, 1149, 1112, 1099, 1034, 974, 909, 813, 728 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{24}NO_4^+$: 330.1700; found: 330.1967.

Methyl(4S,4aR,11bS)-4,11b-dimethyl-9-oxo-1,2,3,4,4a,5,6,8,9,11b-decahydrophenanthro [2,3-d]oxazole-4-carboxylate (I-14)



m.p.: decomposition at 238 °C.

$[\alpha]_D^{20}$= +157.3 (c = 0.60, $CHCl_3$)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (s, 1H), 7.10 (s, 1H), 6.72 (s, 1H), 3.67 (s, 3H), 2.92 (ddd, *J* = 16.7, 5.8, 1.9 Hz, 1H), 2.81 (ddd, *J* = 16.5, 12.1, 6.0 Hz, 1H), 2.34 - 2.25 (m, 1H), 2.25 – 2.14 (m, 2H), 2.10 – 1.89 (m, 2H), 1.70 – 1.59 (m, 1H), 1.53 (dd, *J* = 12.1, 1.7 Hz, 1H), 1.39 (td, *J* = 13.3, 4.1 Hz, 1H), 1.28 (s, 3H), 1.10 (td, *J* = 13.0, 4.0 Hz, 1H), 1.03 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9, 156.2, 143.3, 142.9, 131.6, 127.2, 109.7, 107.2, 52.8, 51.5, 44.1, 40.0, 38.9, 37.7, 32.3, 28.6, 23.4, 21.0, 20.1.

IR (ATR, neat): ν = 3235, 2979, 2949, 2908, 2099, 1769, 1728, 1713, 1486, 1435, 1378, 1305, 1257, 1236, 1177, 1145, 1098, 939, 894, 857, 846, 823, 715 cm^{-1}.

HRMS ESI (+): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{24}NO_4^+$: 330.1700; found: 330.1704.

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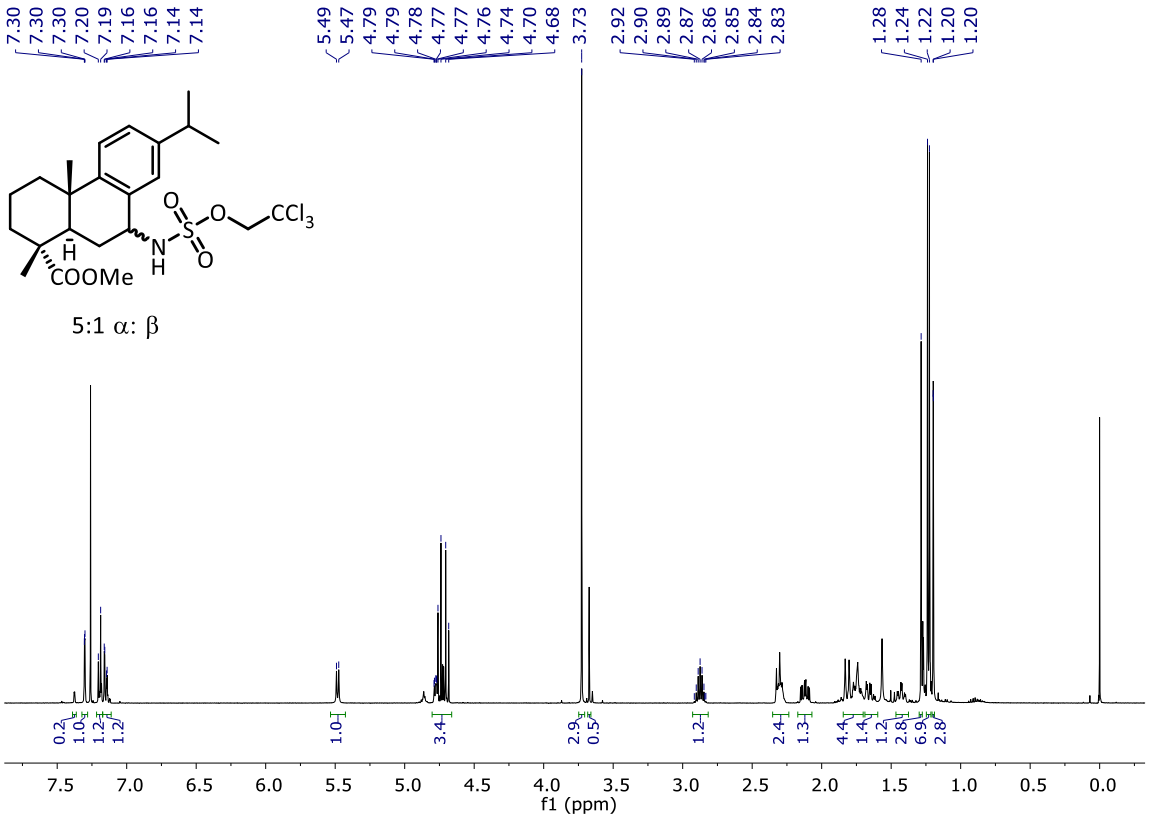
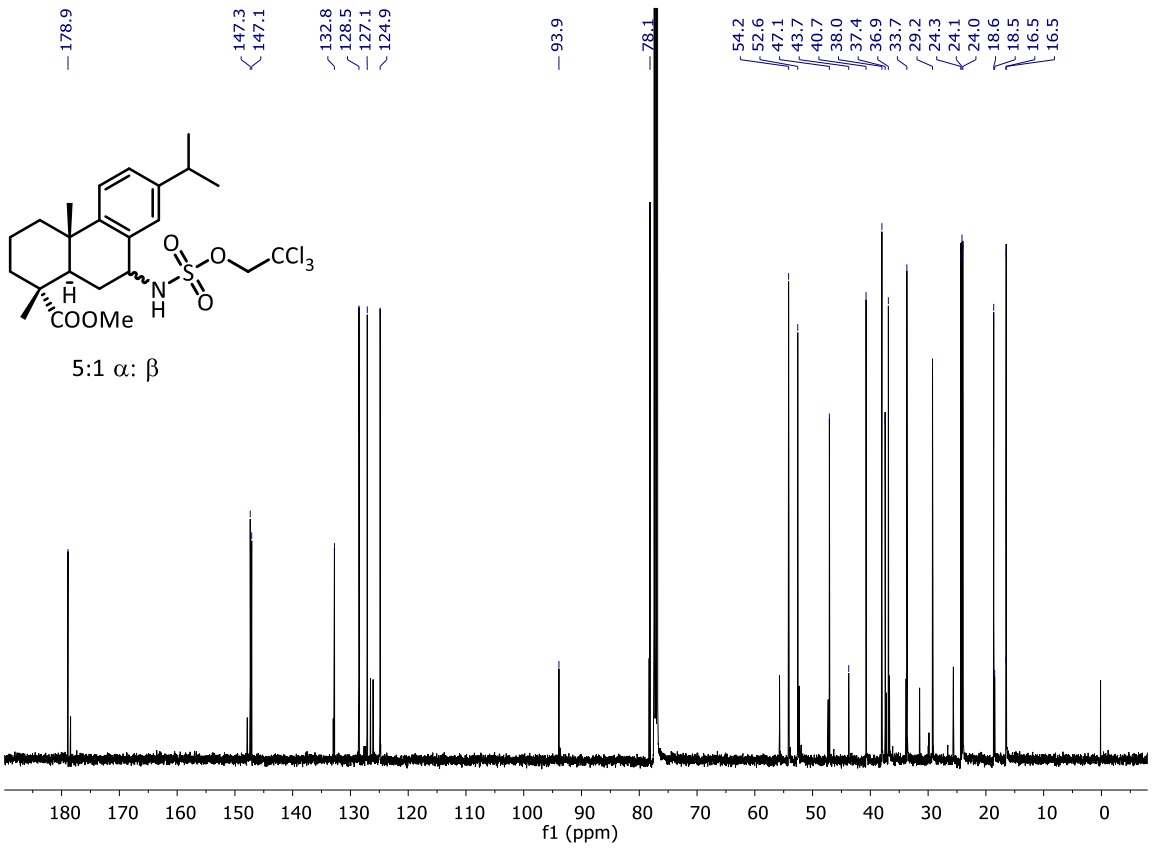
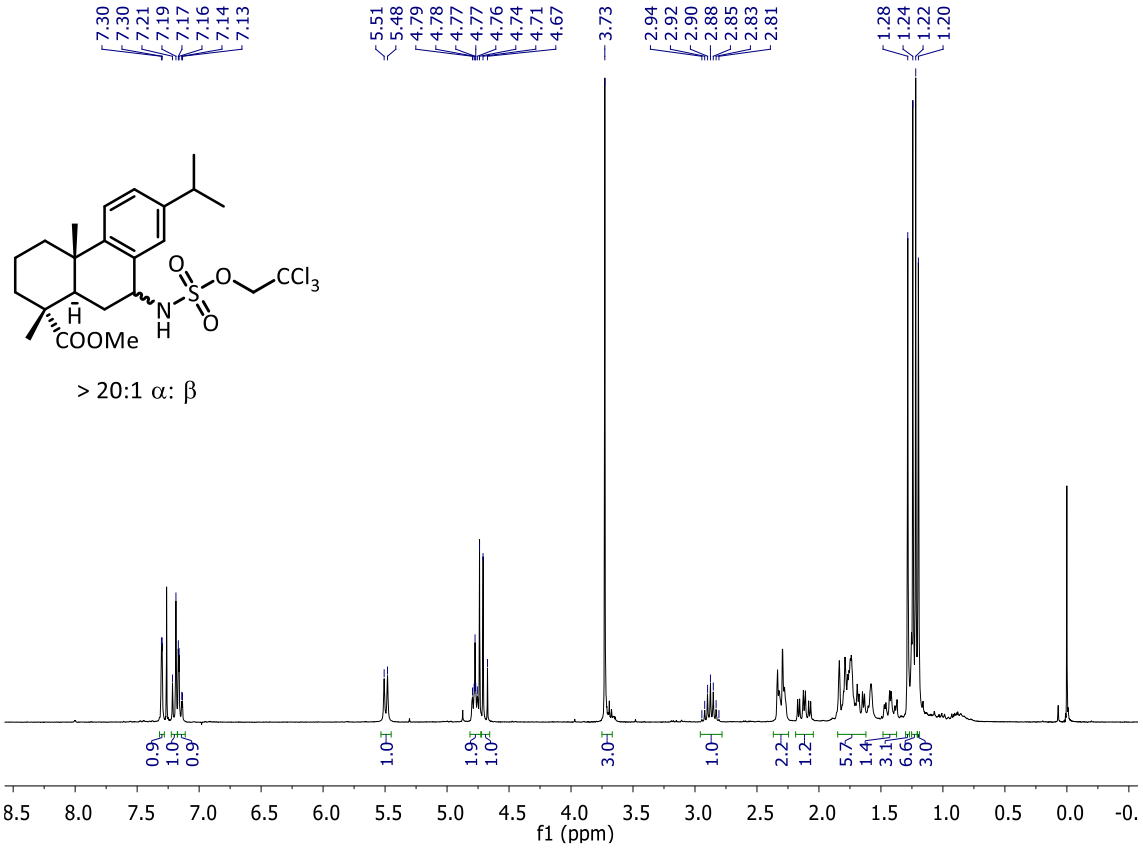
4. ^{1}H, ^{13}C, ^{19}F and NOESY spectra of compounds **8**, **13**, **14**, **21**, **23**, **25** and **27**

*Compound **8***: ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)

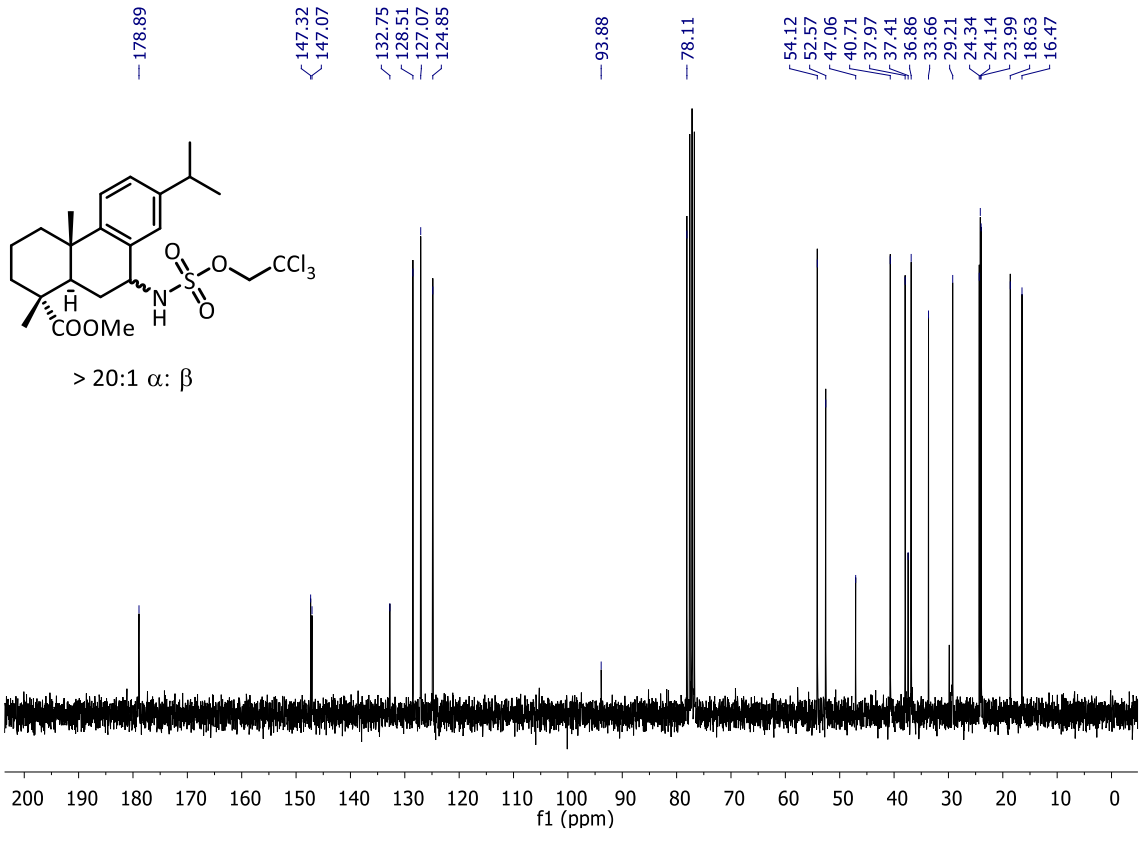




*Compound **8***: ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz)}

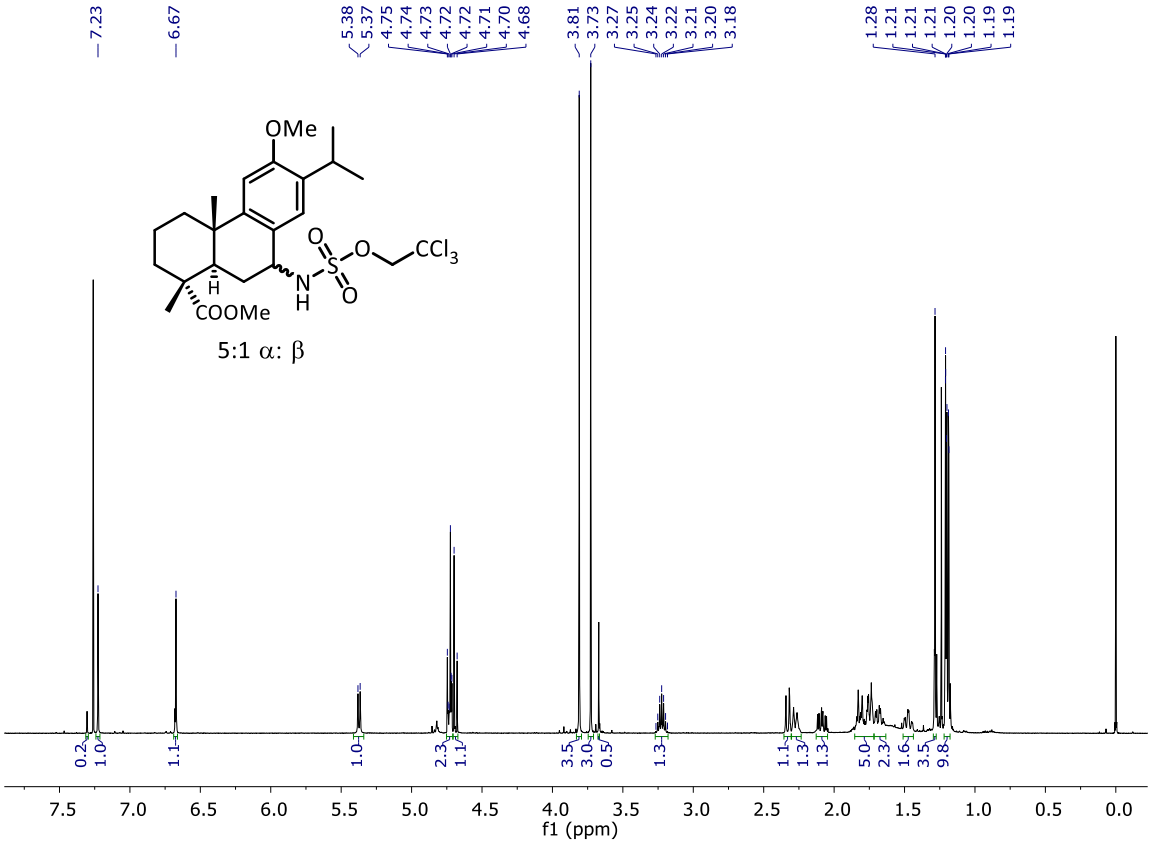


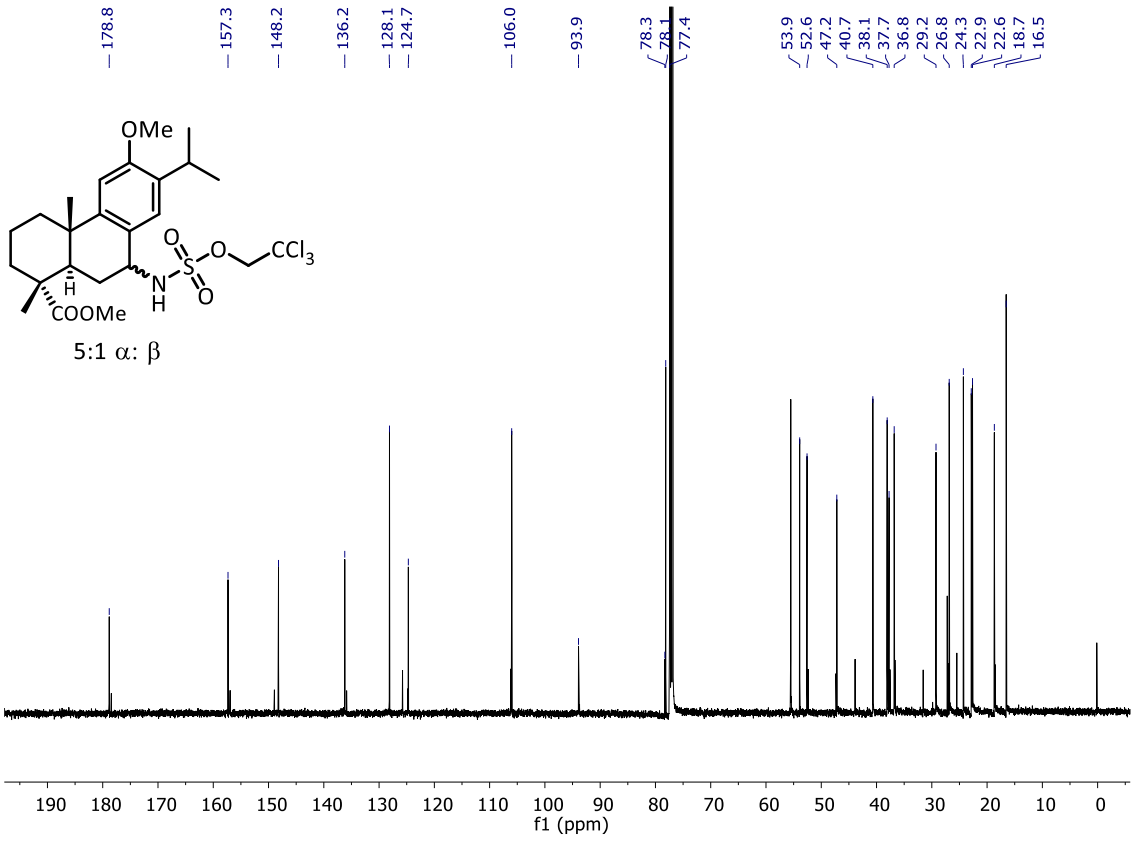
> 20:1 α: β



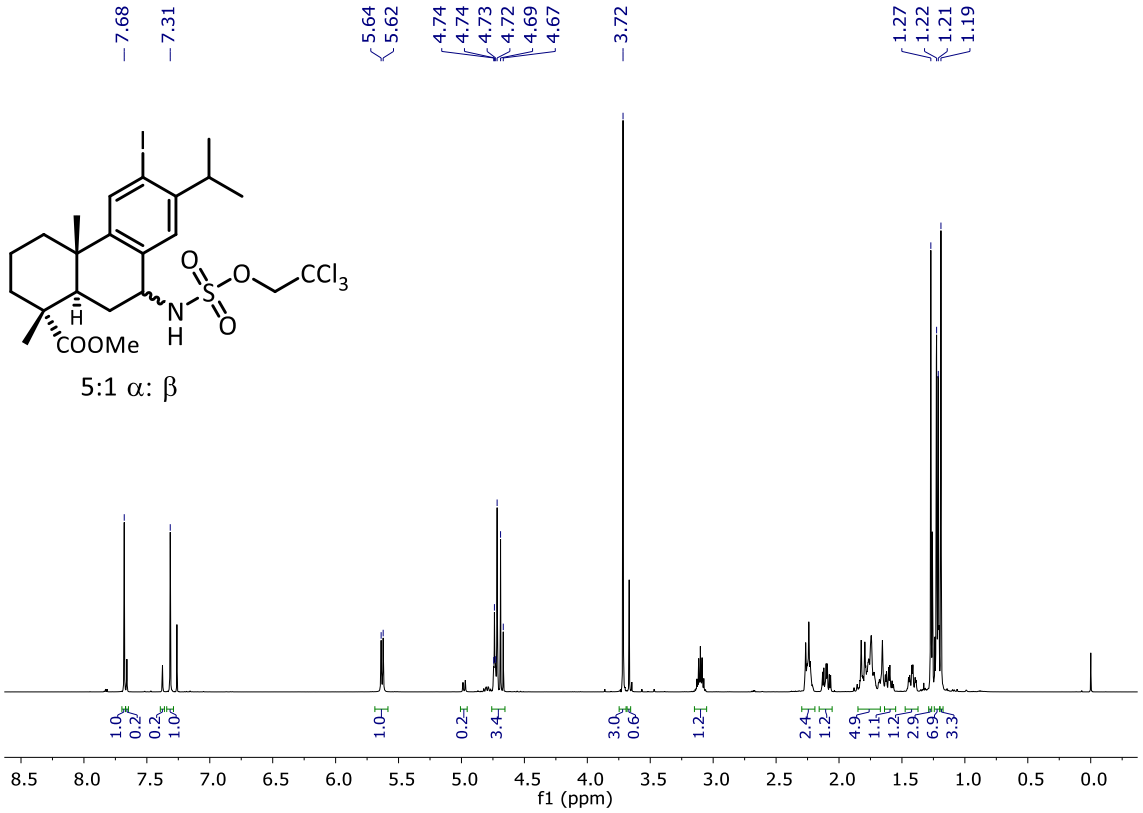
> 20:1 α: β

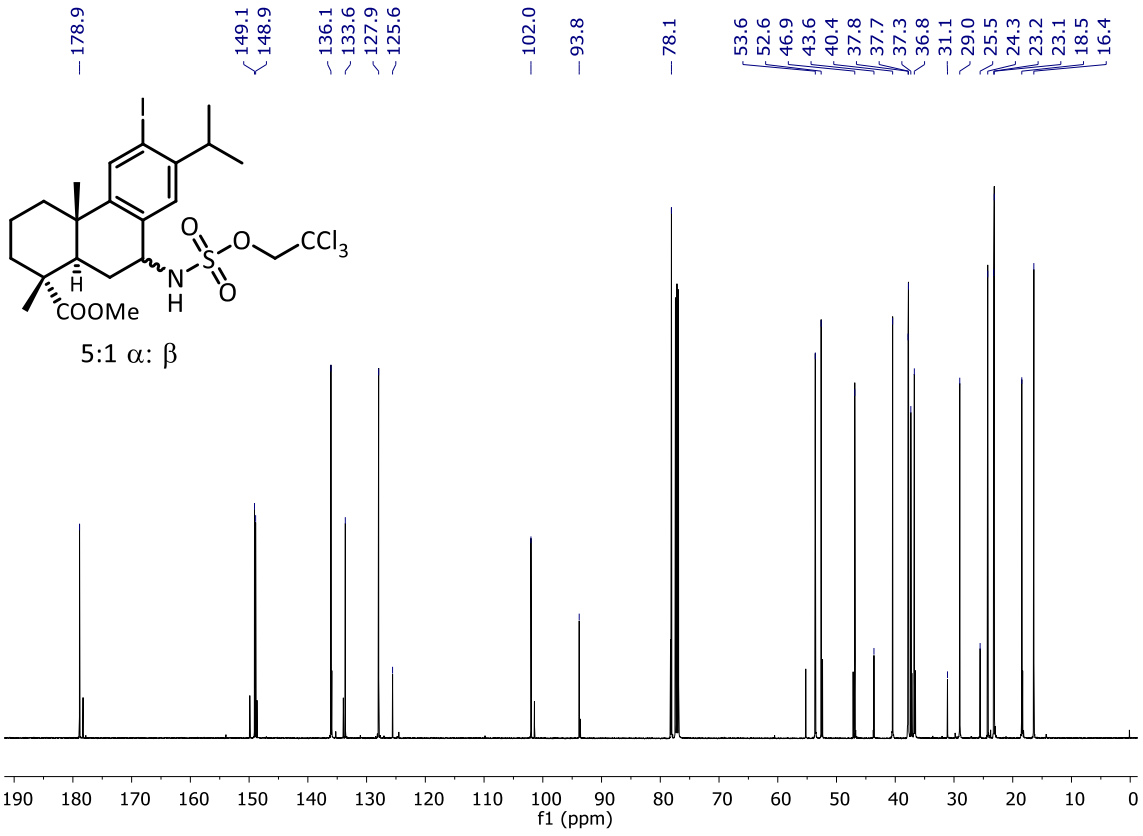
*Compound **9***: ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)



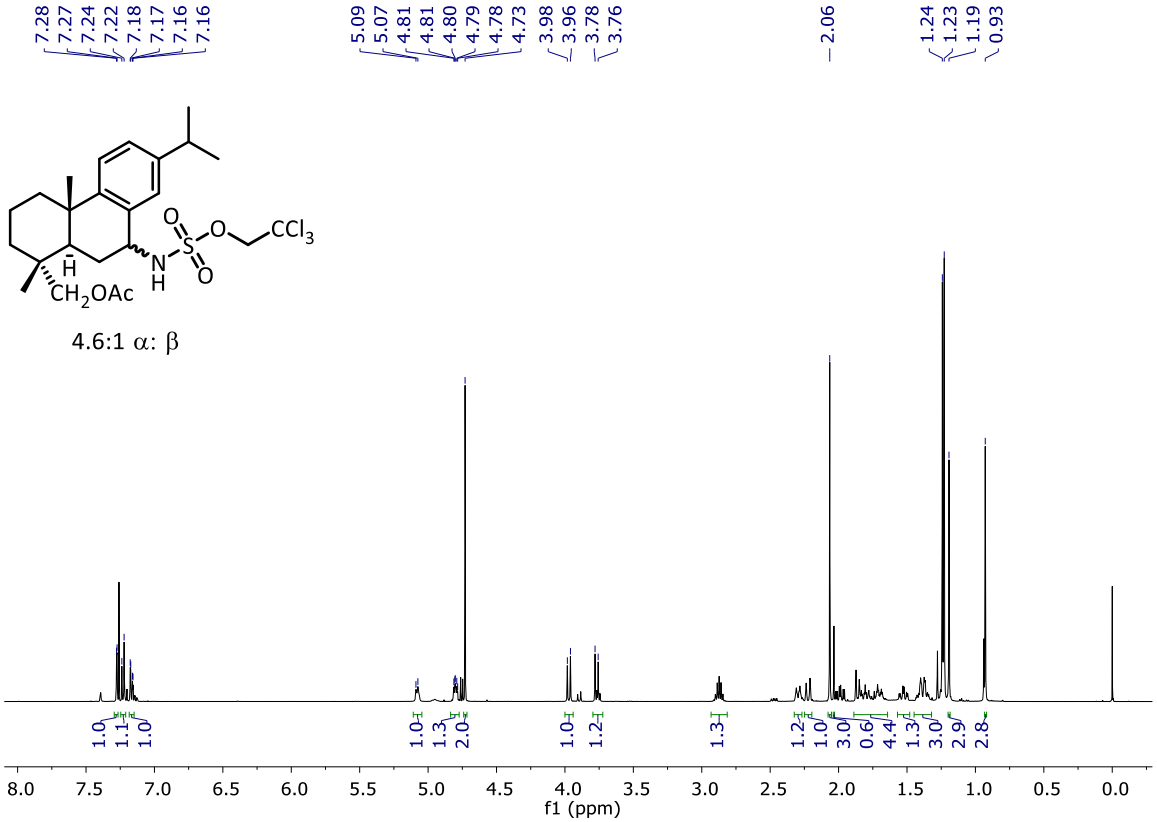


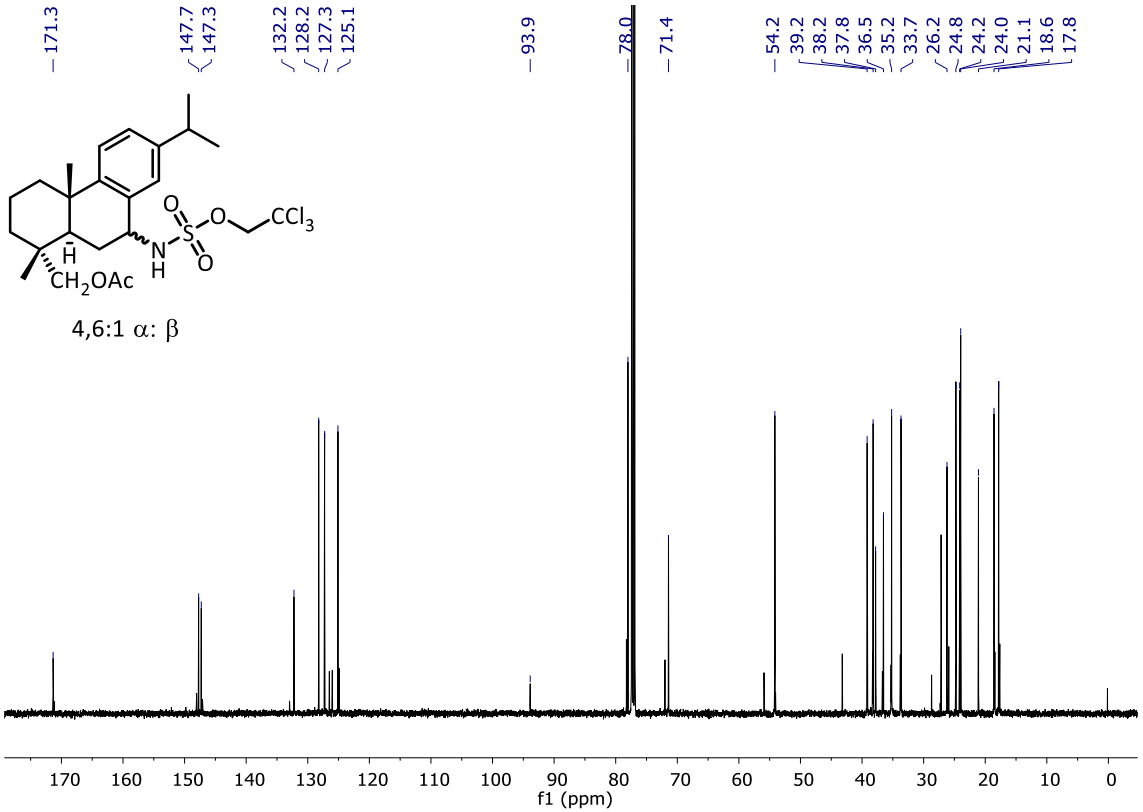
*Compound **10**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)



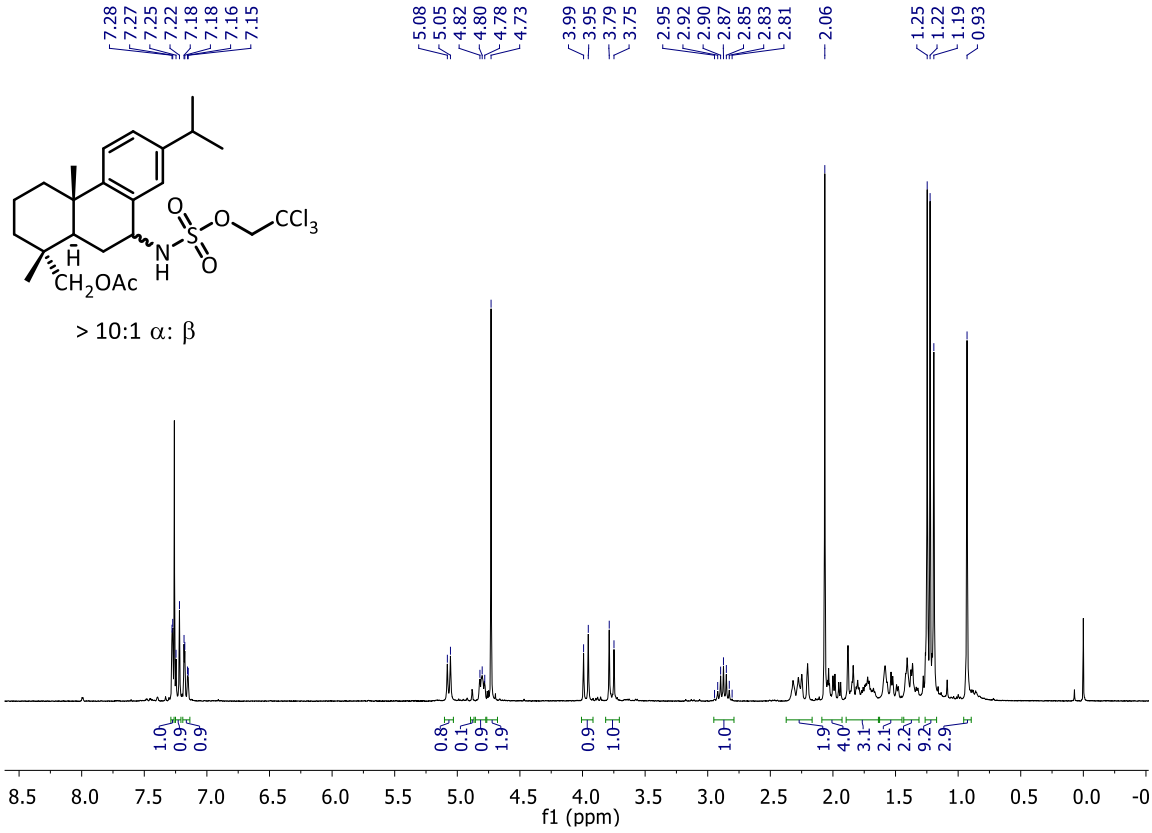


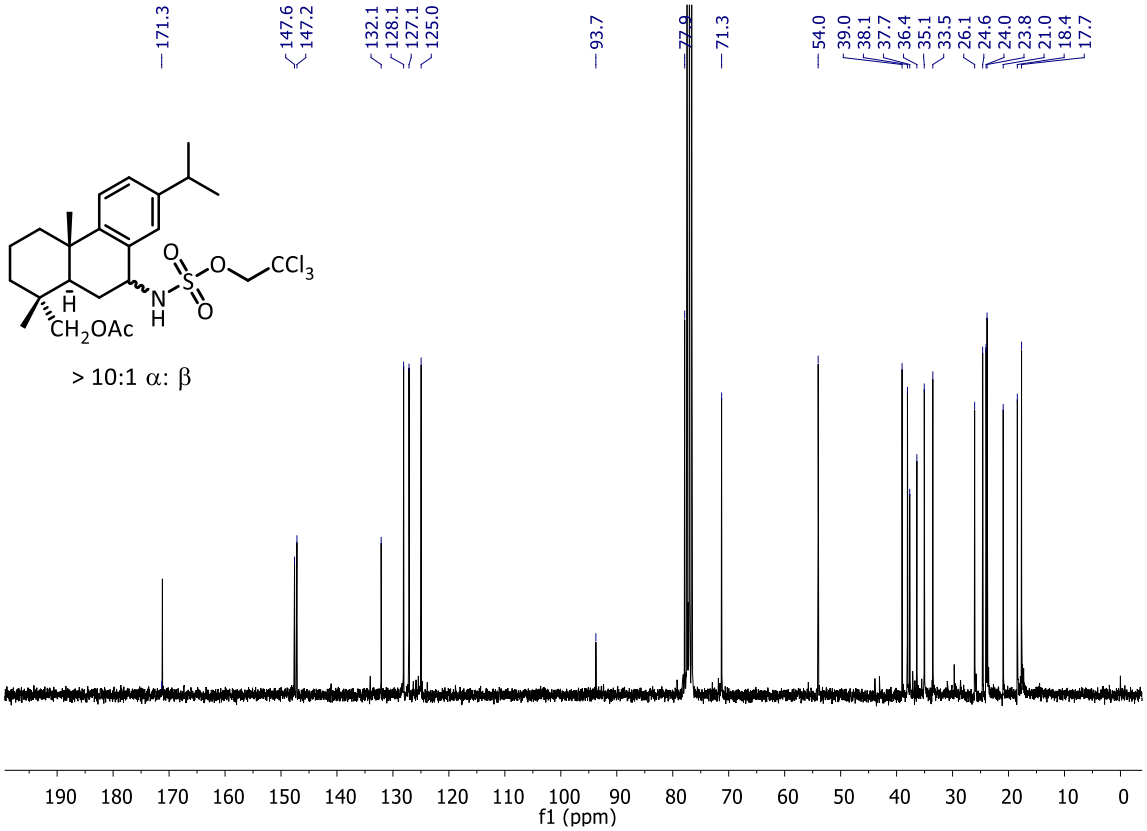
*Compound **11**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)



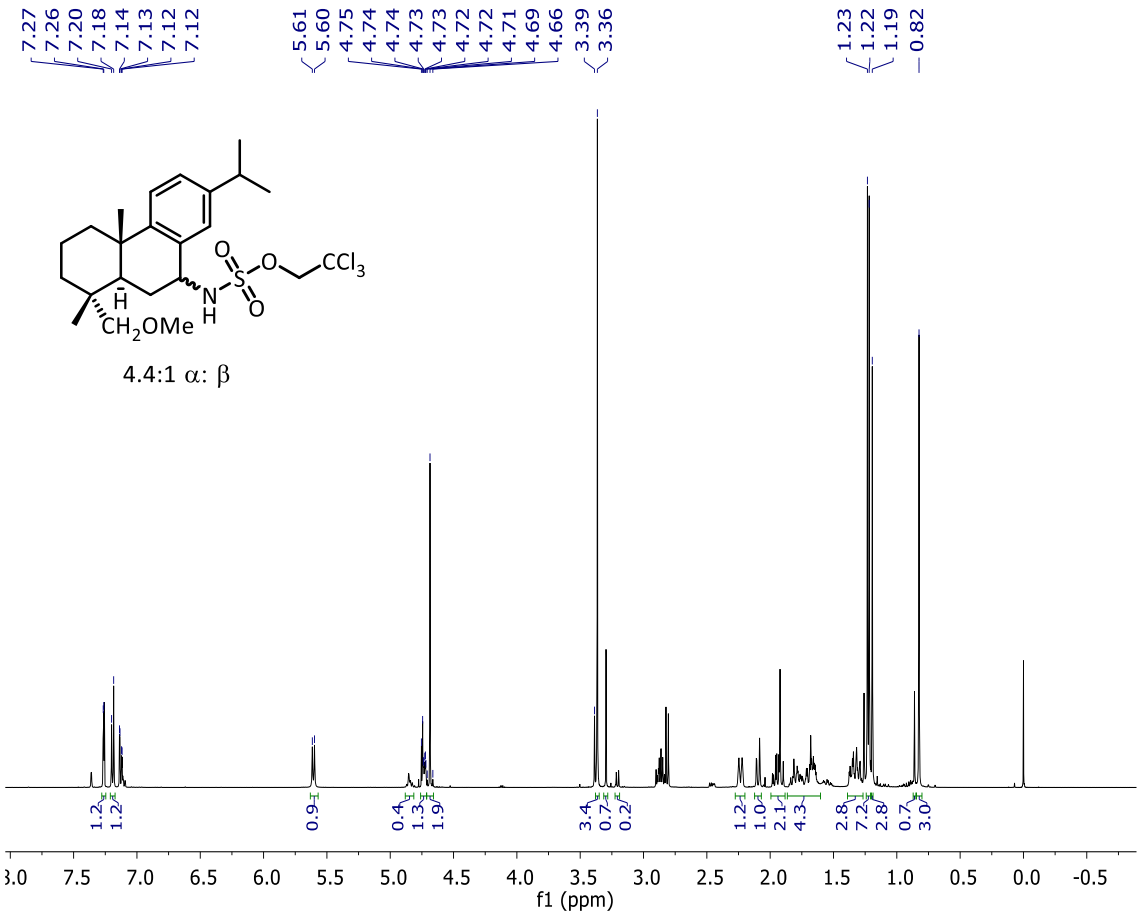


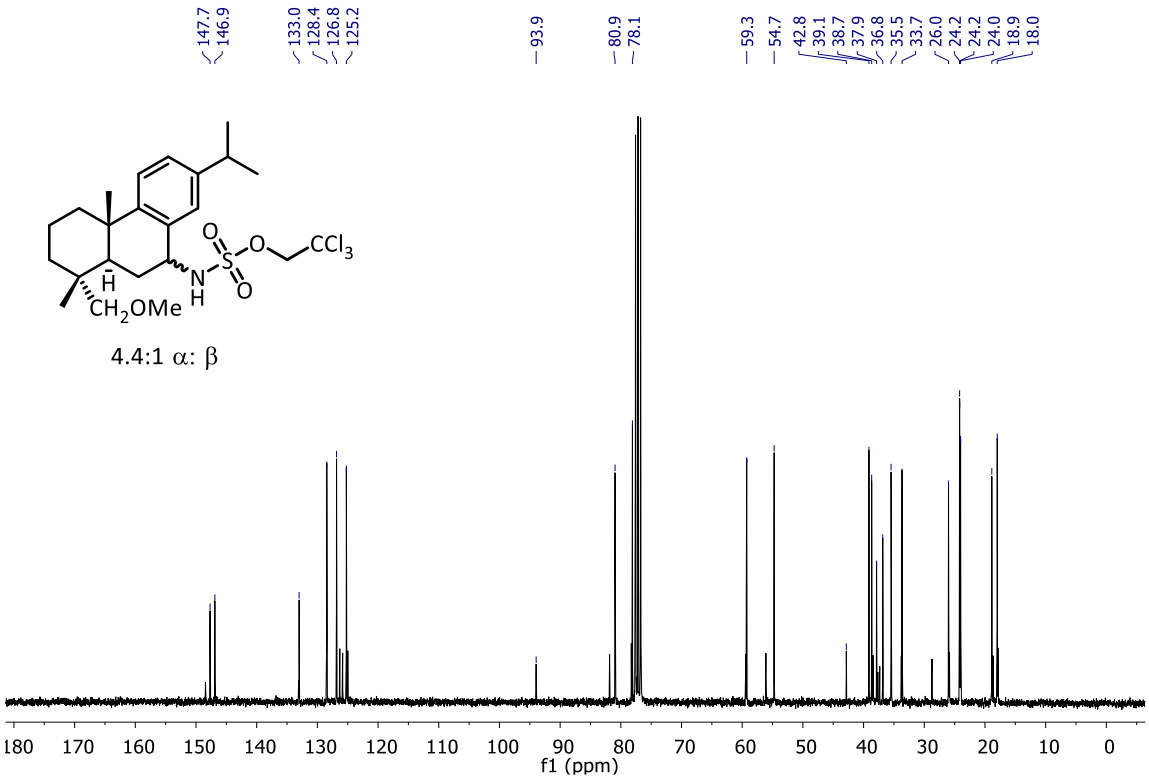
*Compound **11***: ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



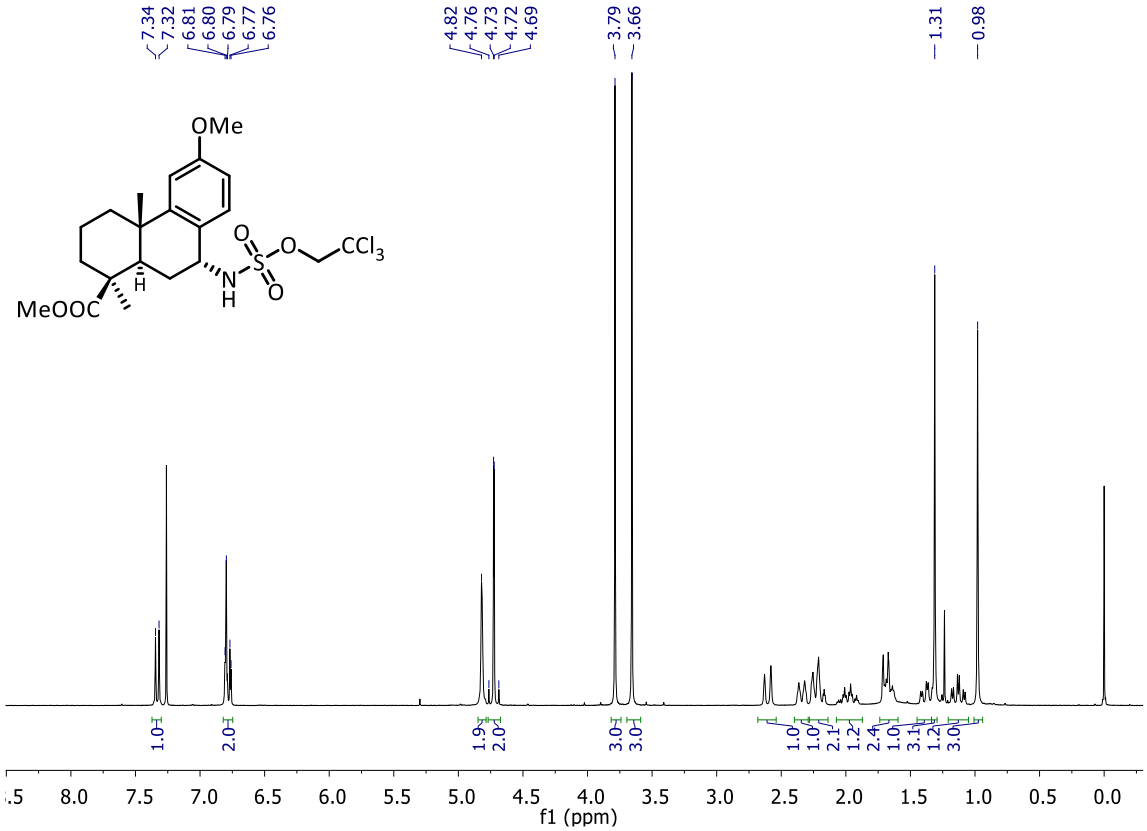


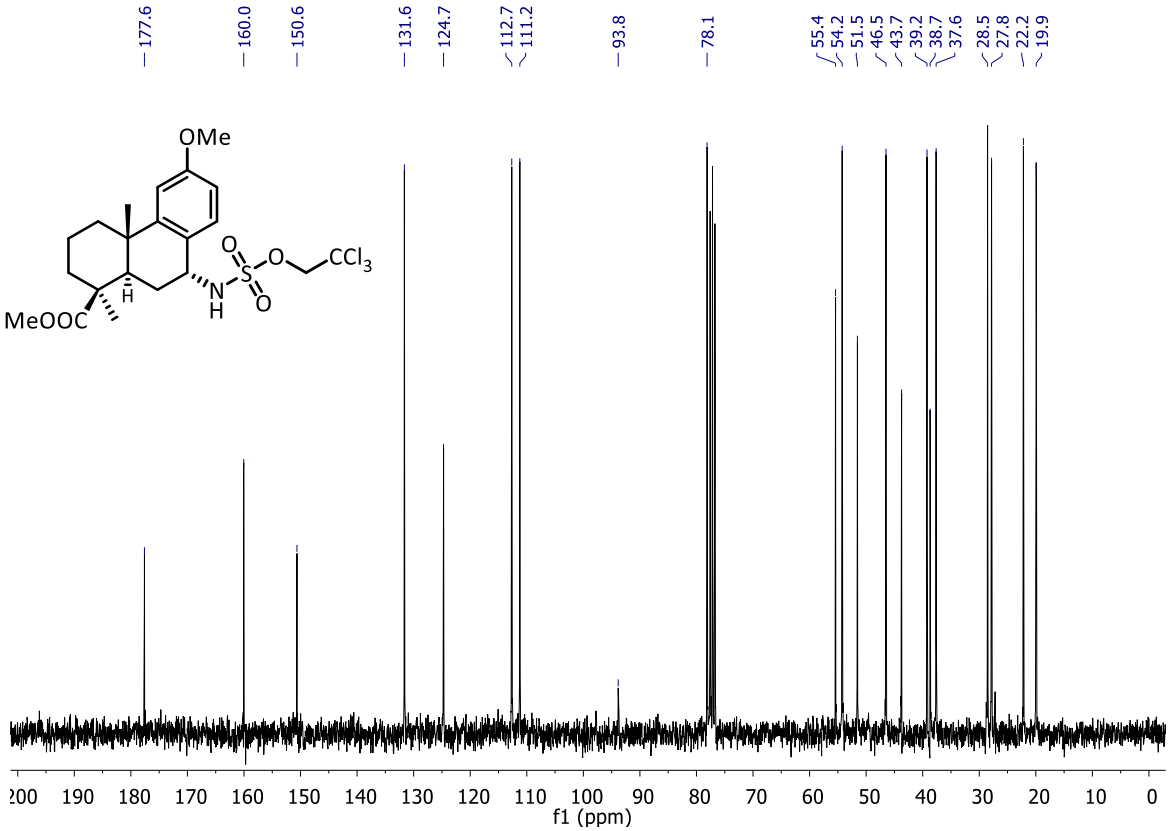
*Compound **12**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



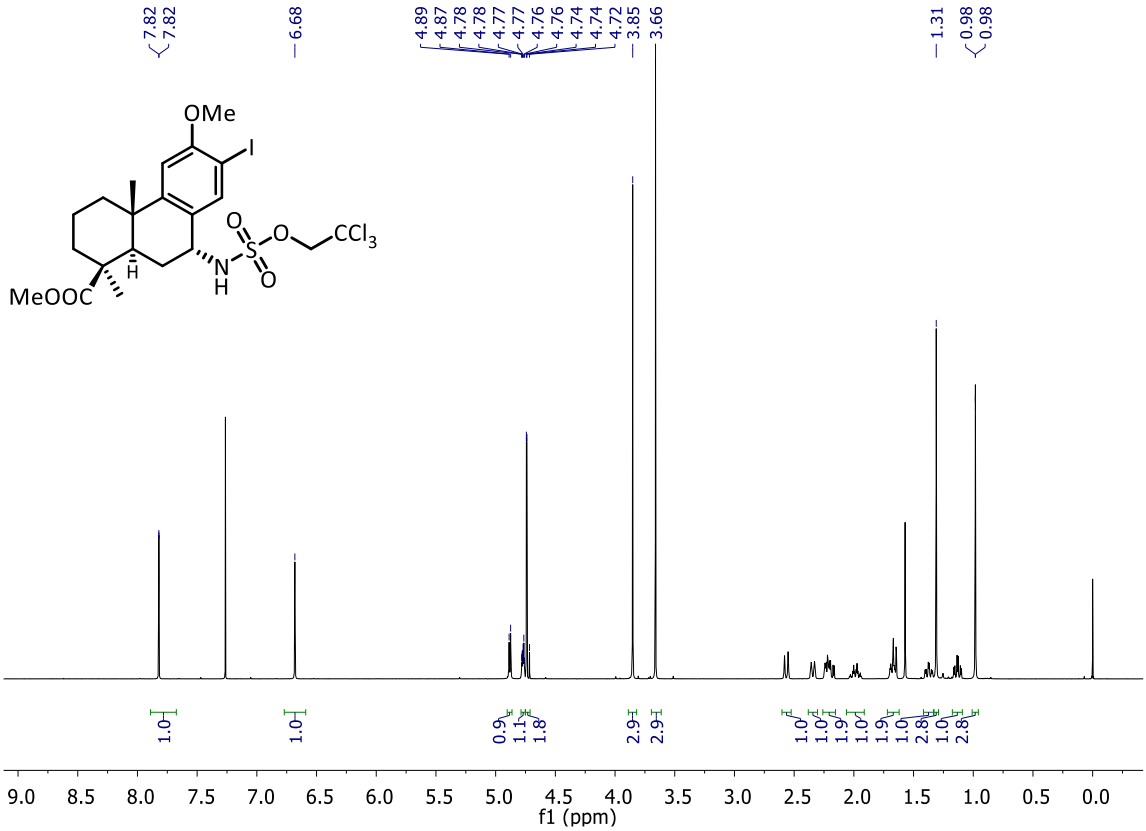


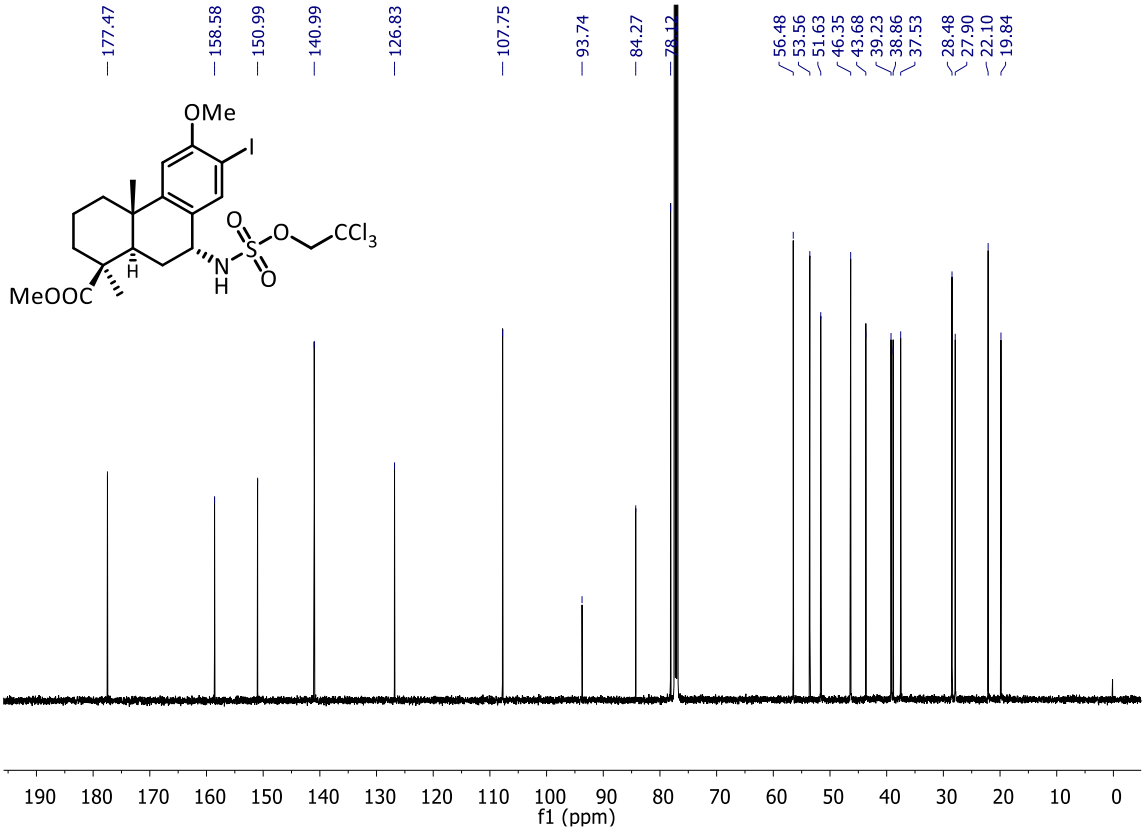
*Compound **13**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



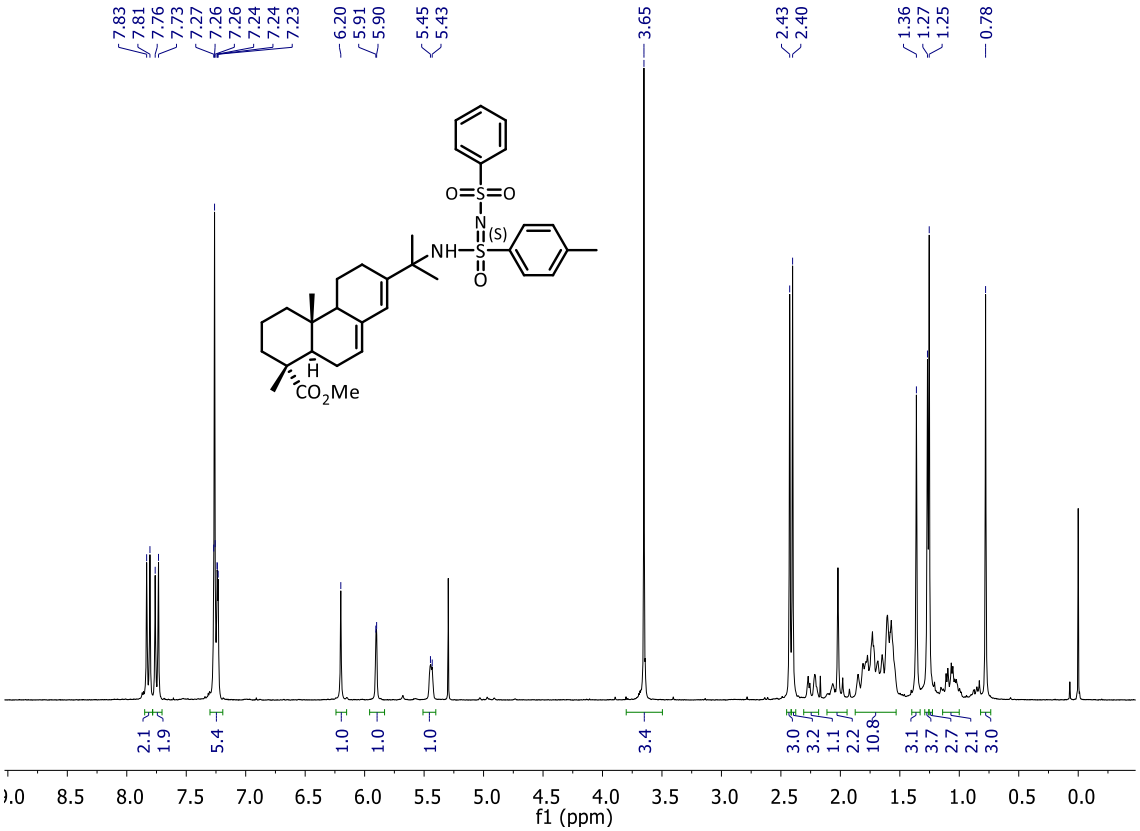


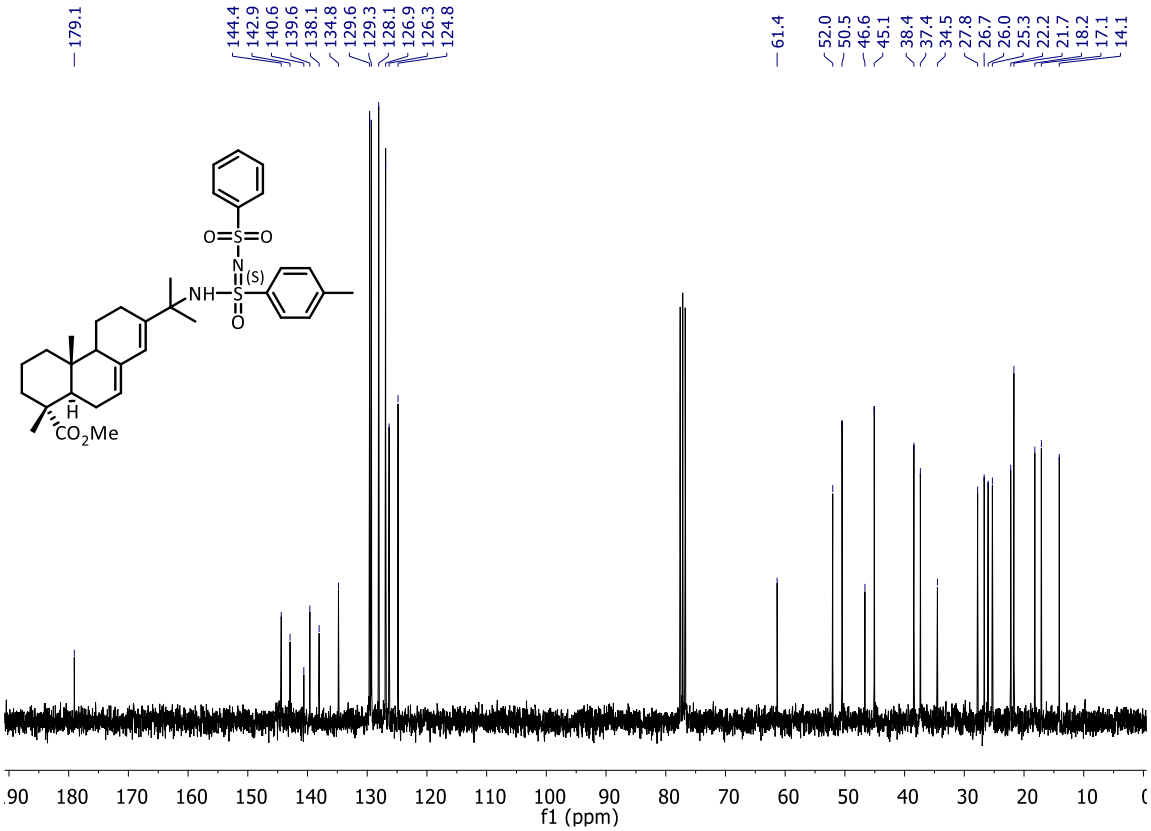
*Compound **14**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)



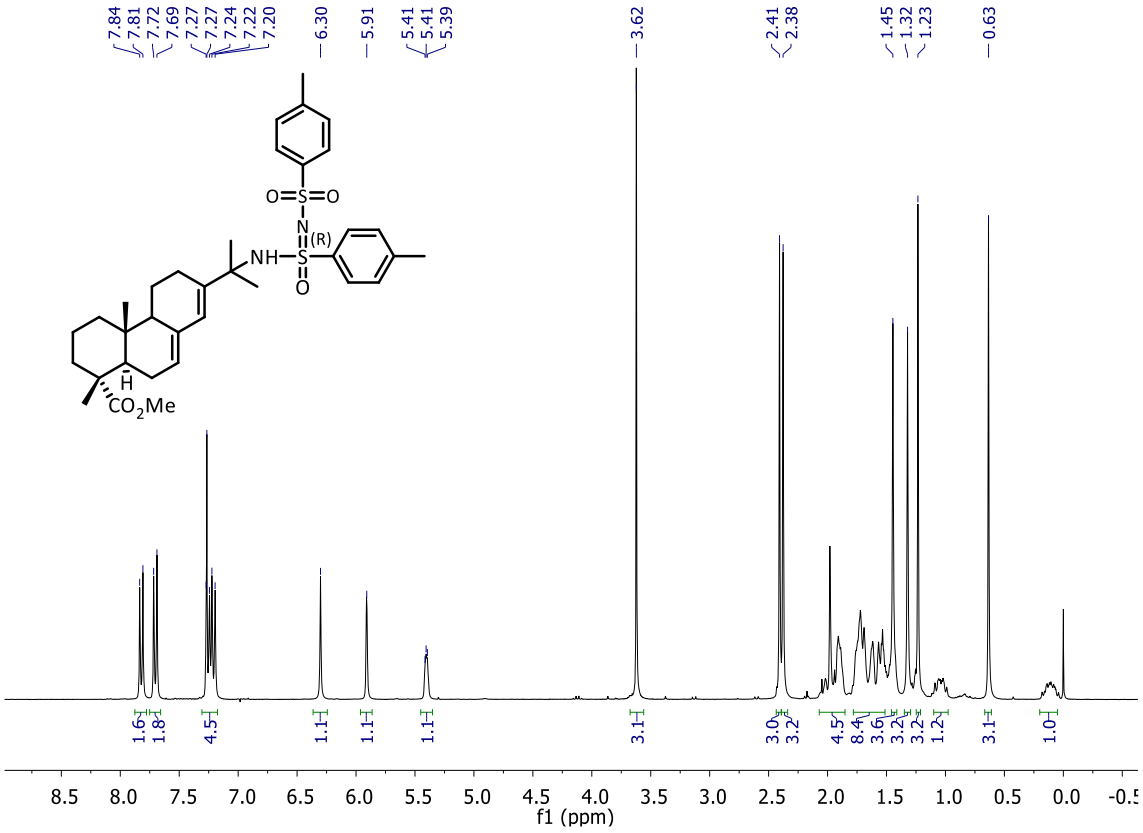


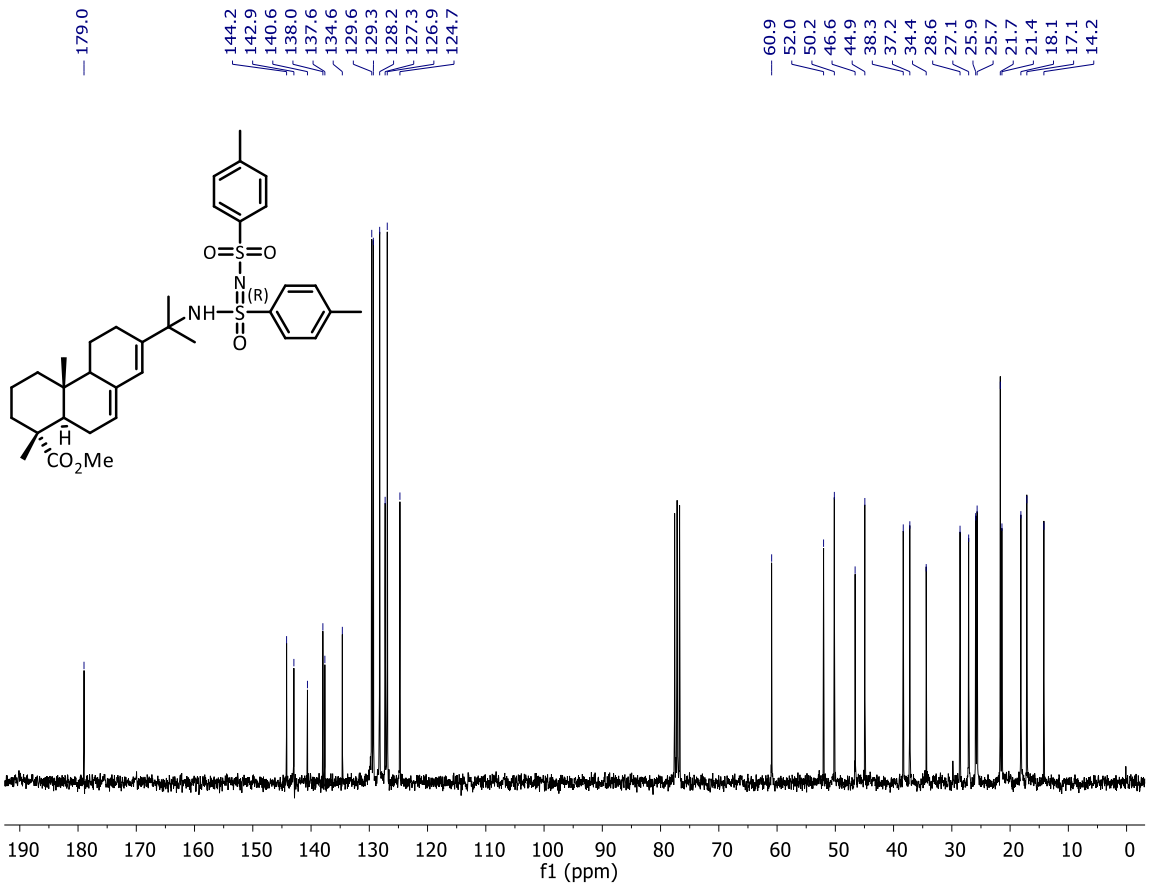
*Compound **17a**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



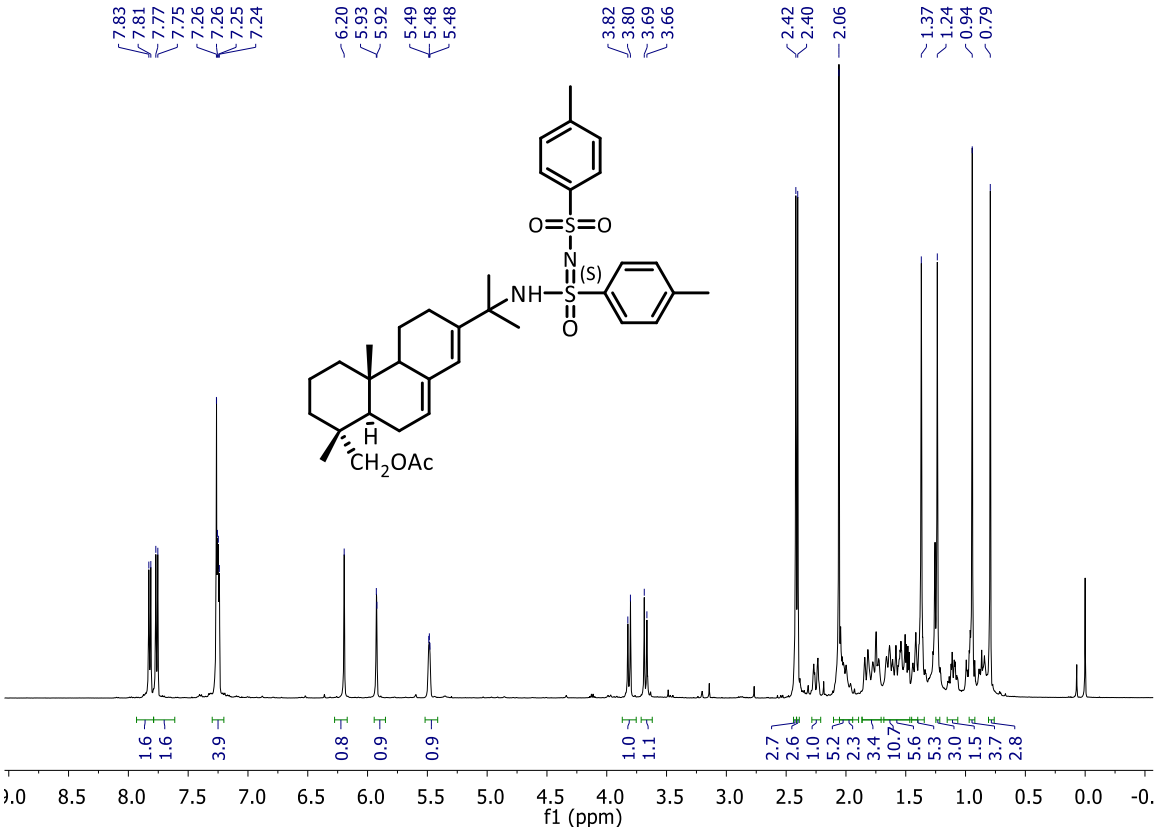


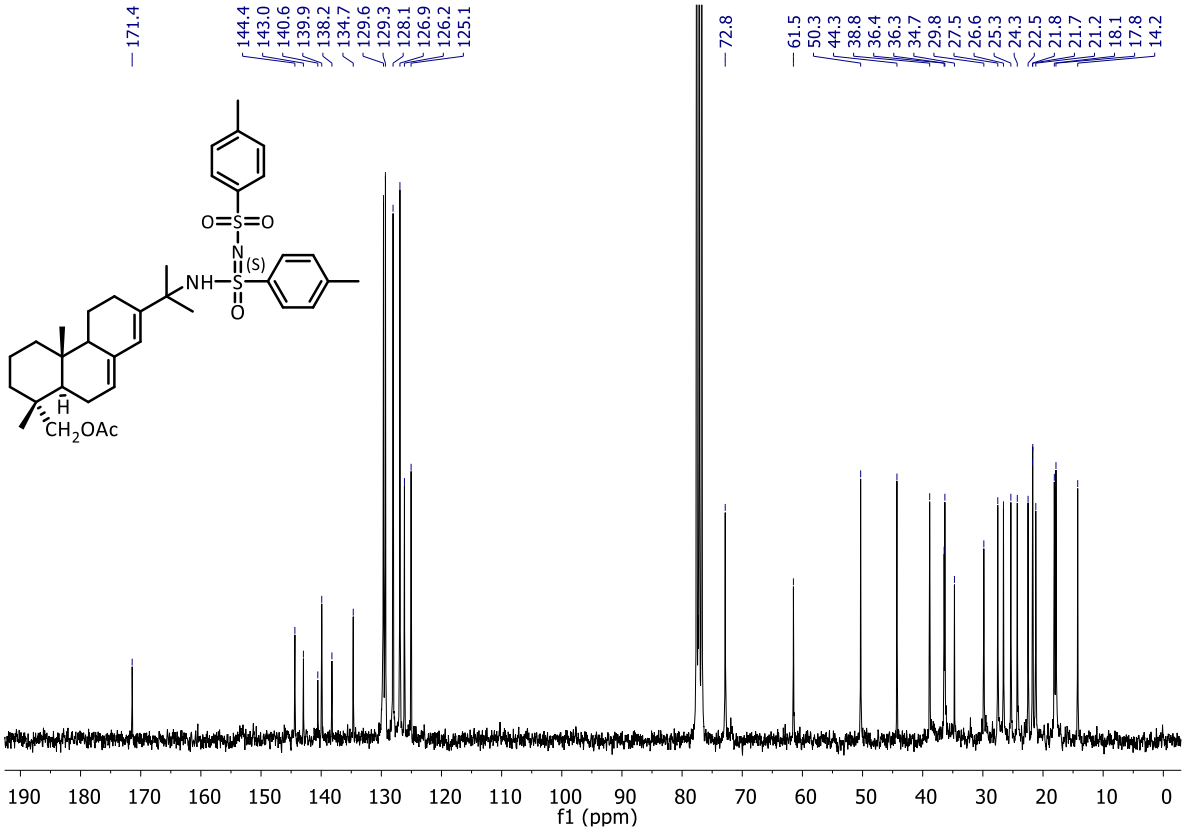
*Compound **17b**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



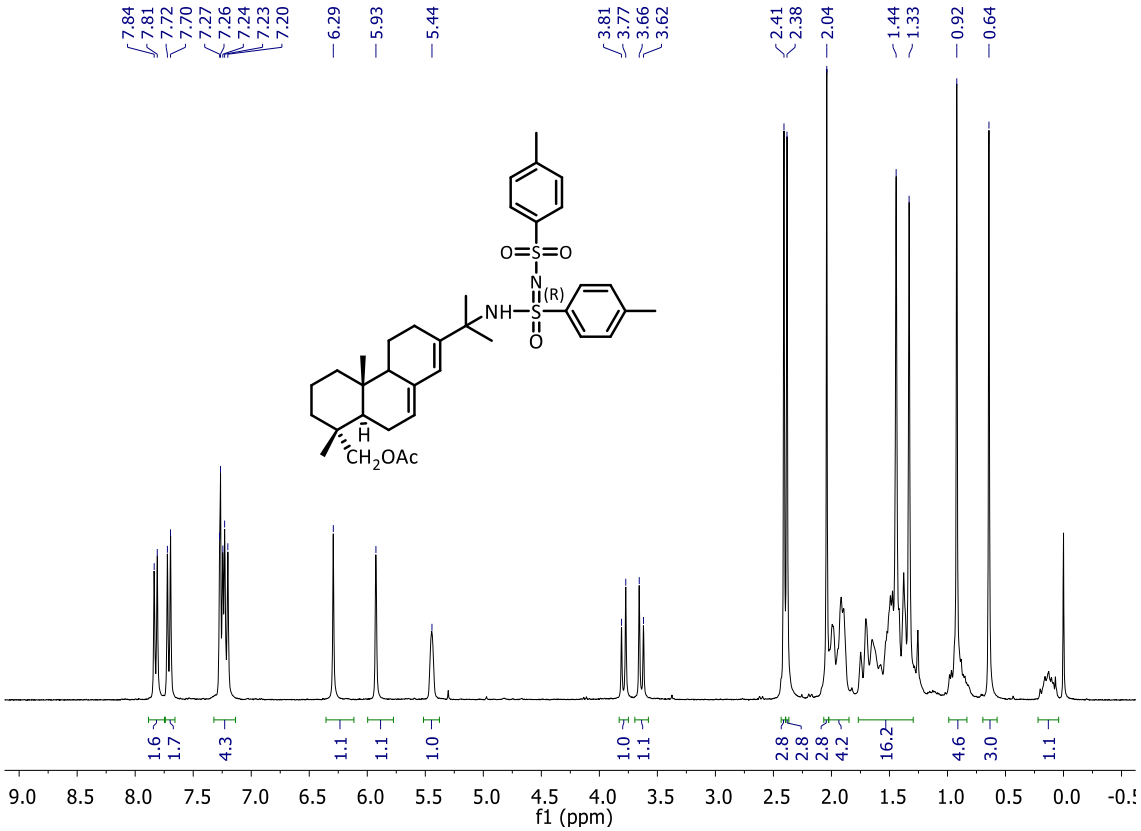


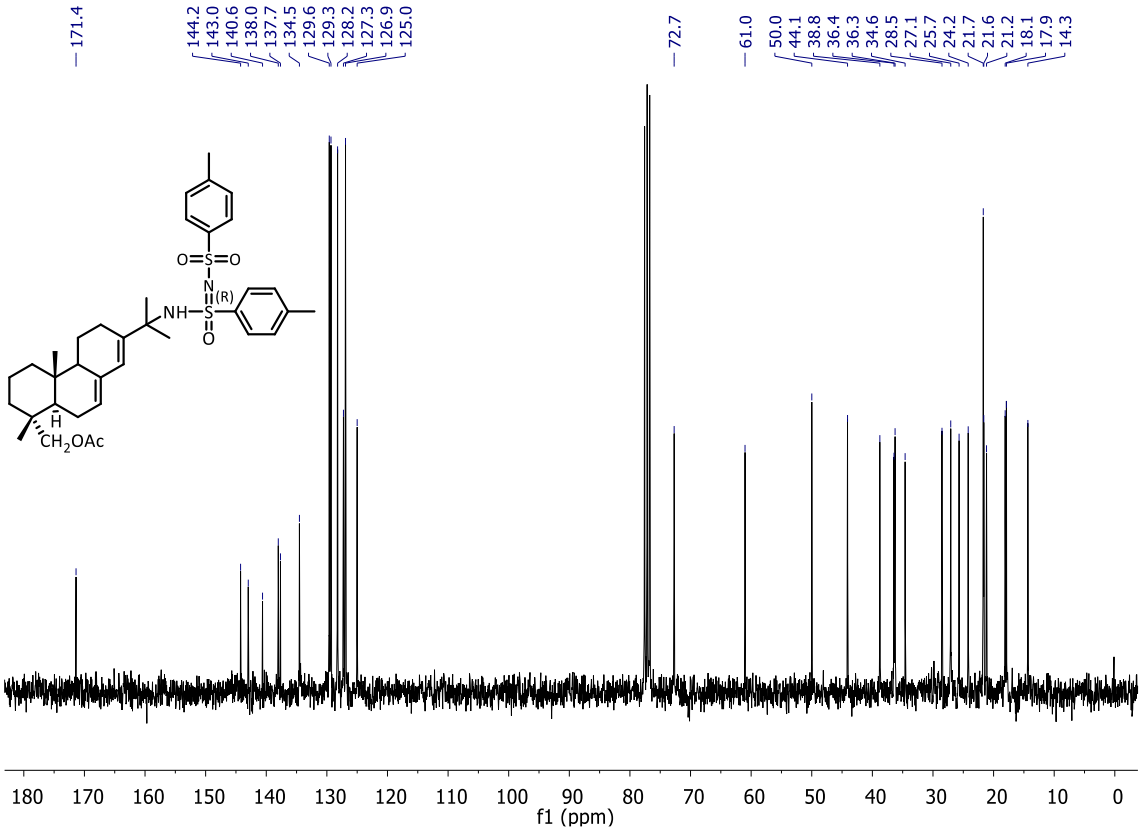
*Compound **18a:*** ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



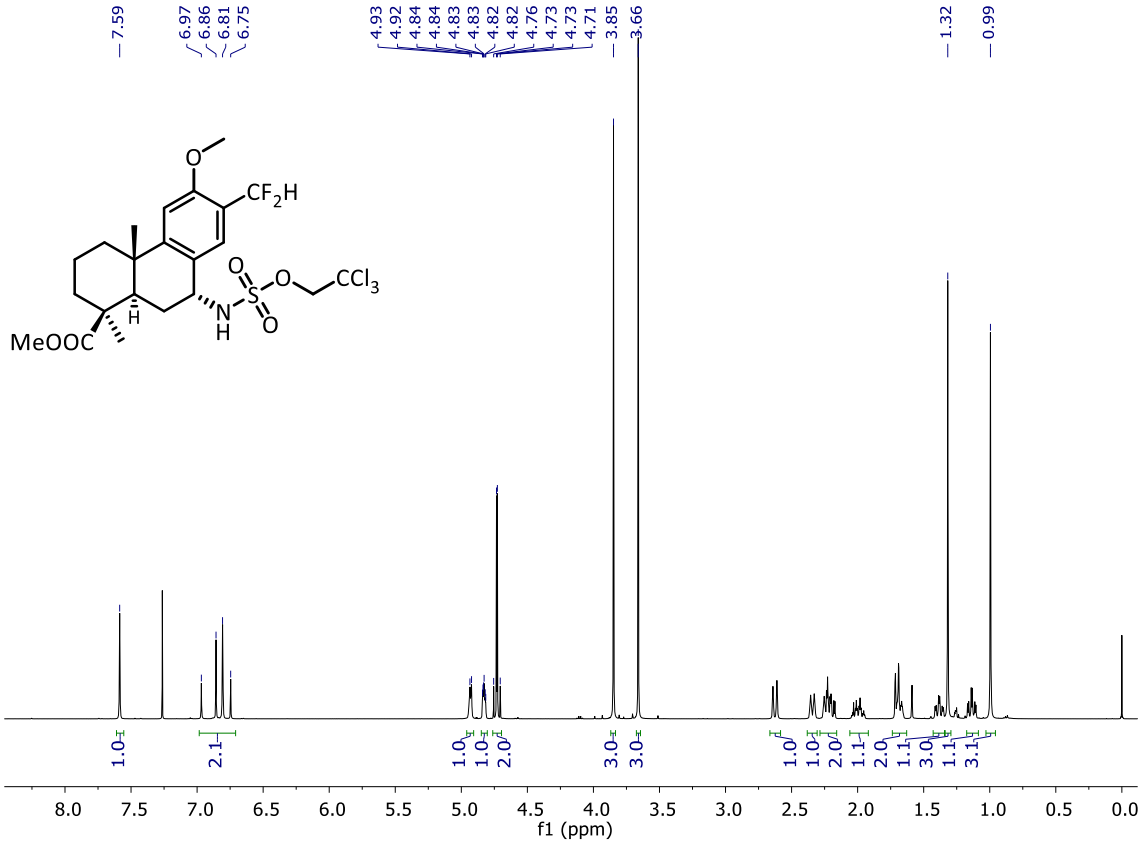


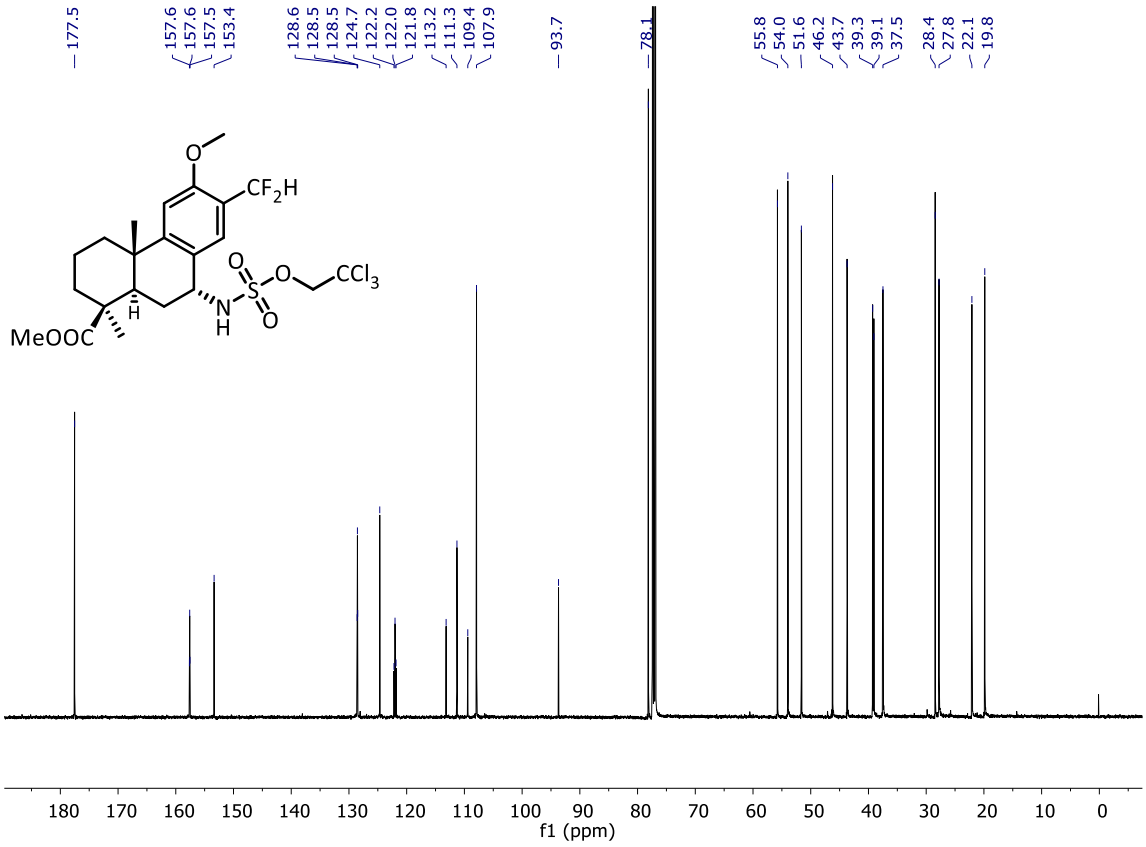
Compound ***18b:*** ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)

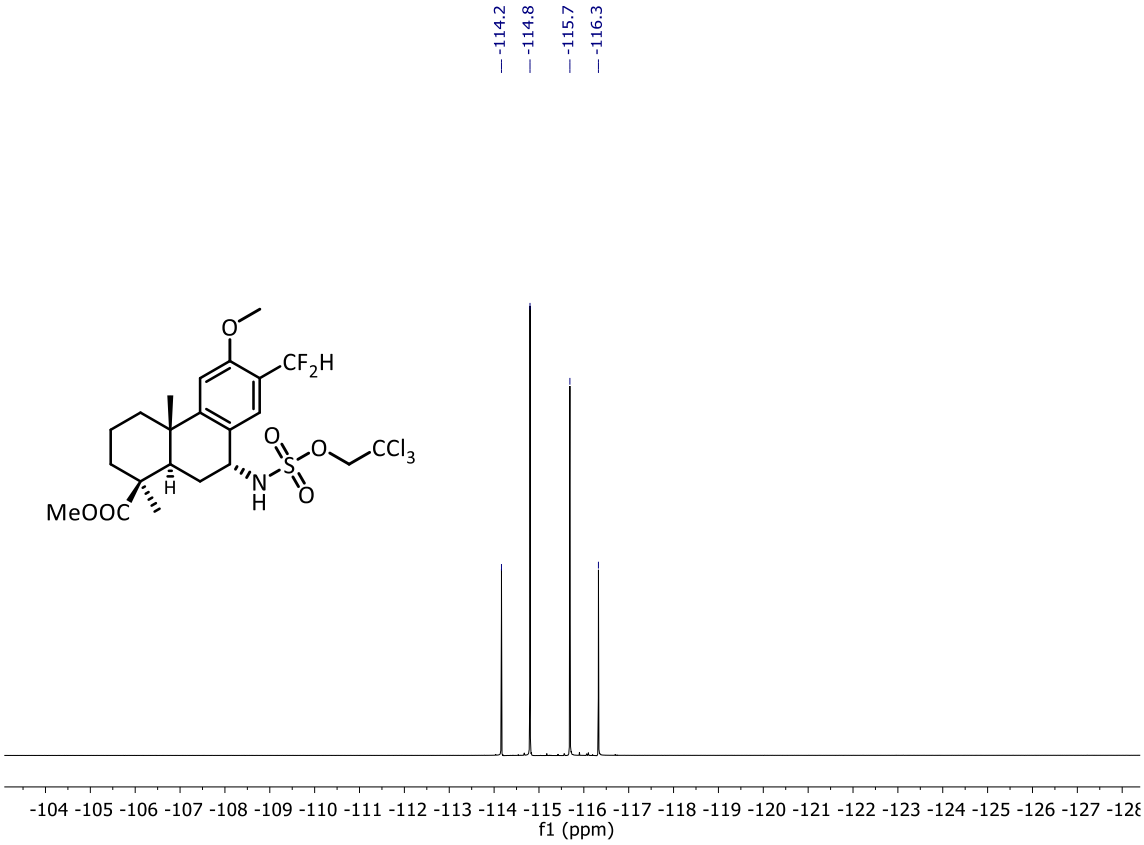




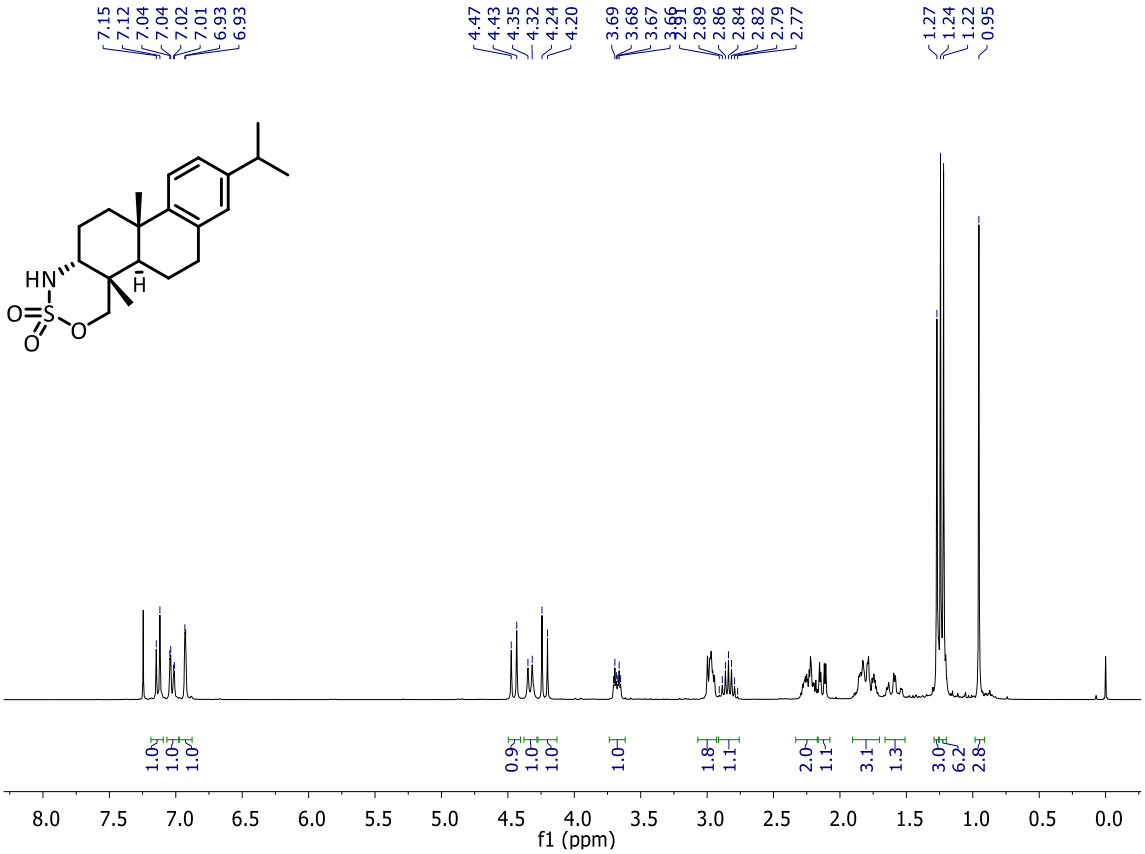
*Compound **21**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$), ^{19}F (470 MHz, $CDCl_3$)

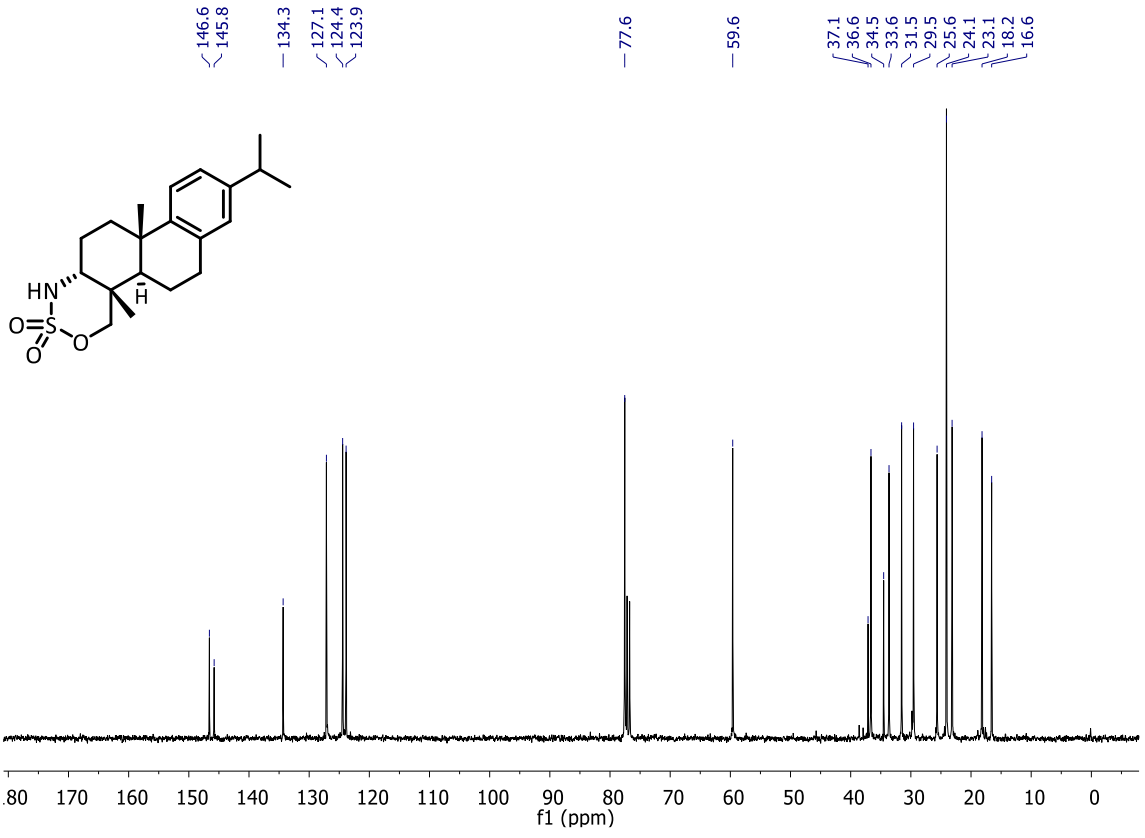




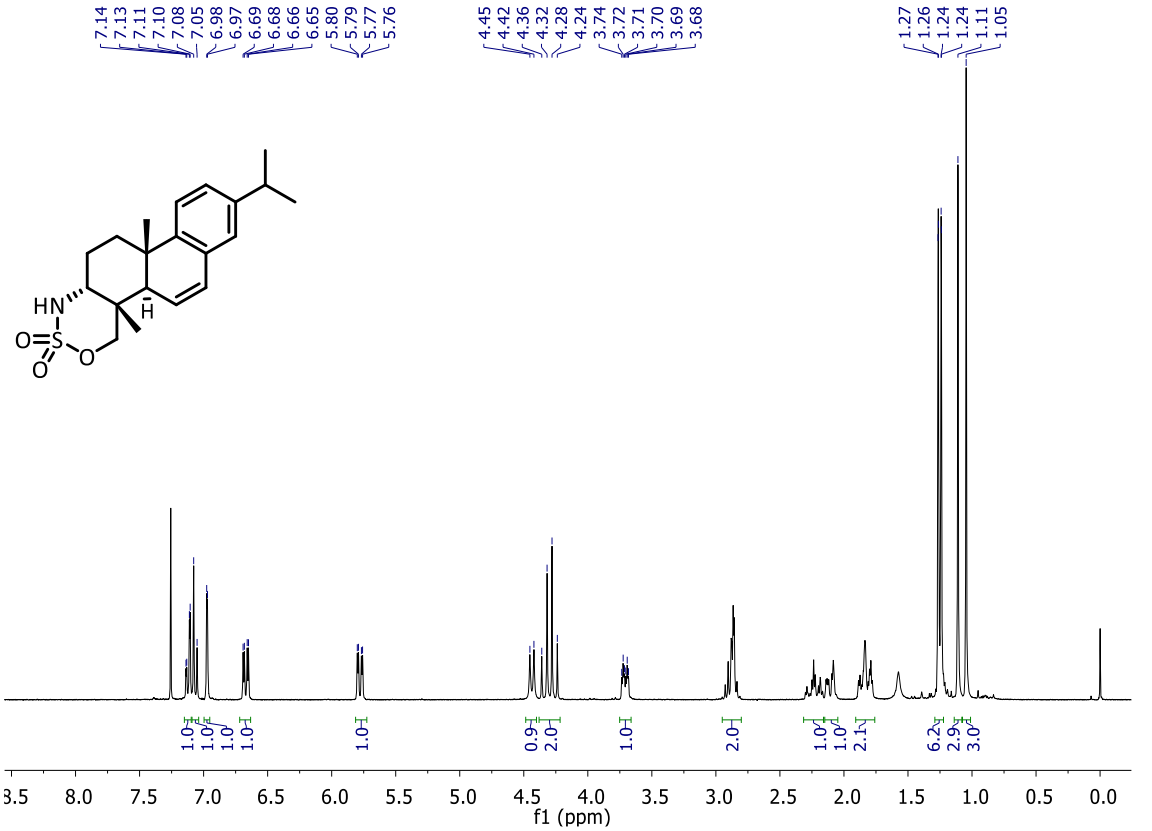

-114.2
-114.8
-115.7
-116.3
O
CF2H
O
O
CCl3
N
H
S
O
H
MeOOC
-104 -105 -106 -107 -108 -109 -110 -111 -112 -113 -114 -115 -116 -117 -118 -119 -120 -121 -122 -123 -124 -125 -126 -127 -128
f1 (ppm)

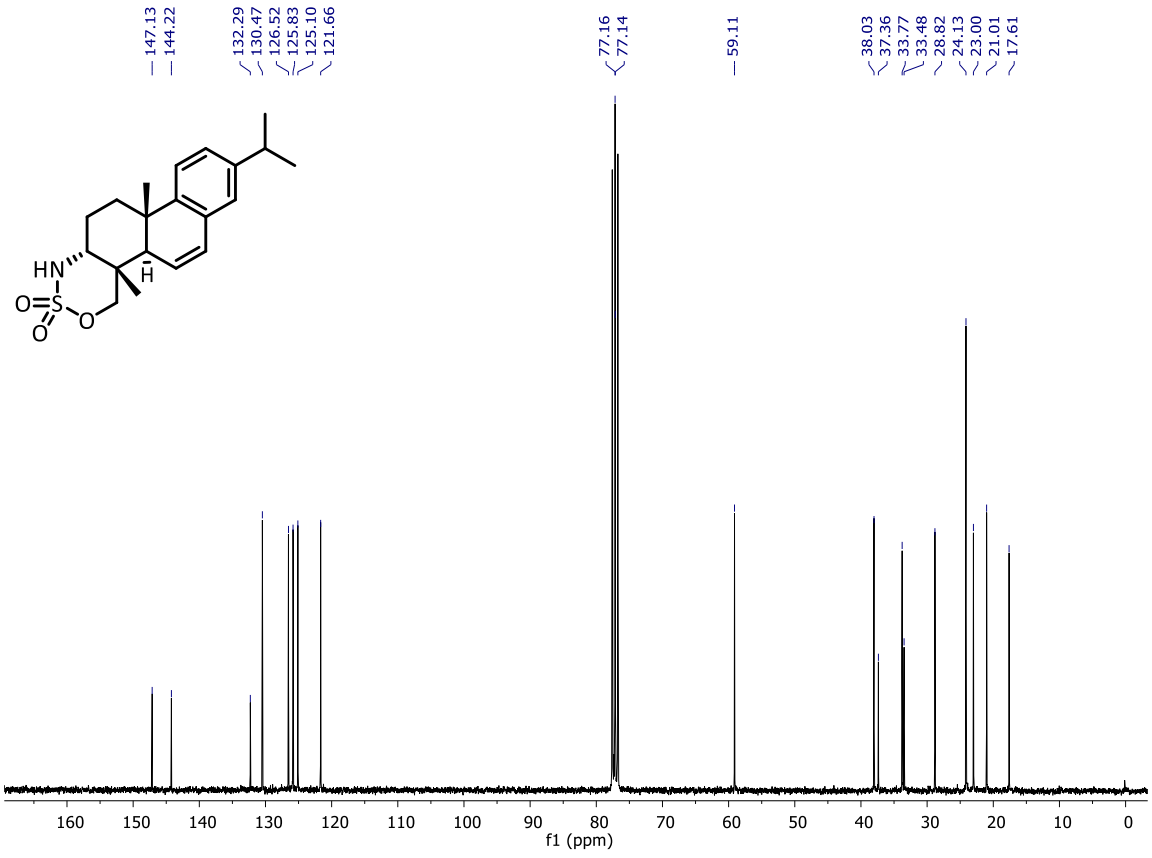
*Compound **23**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



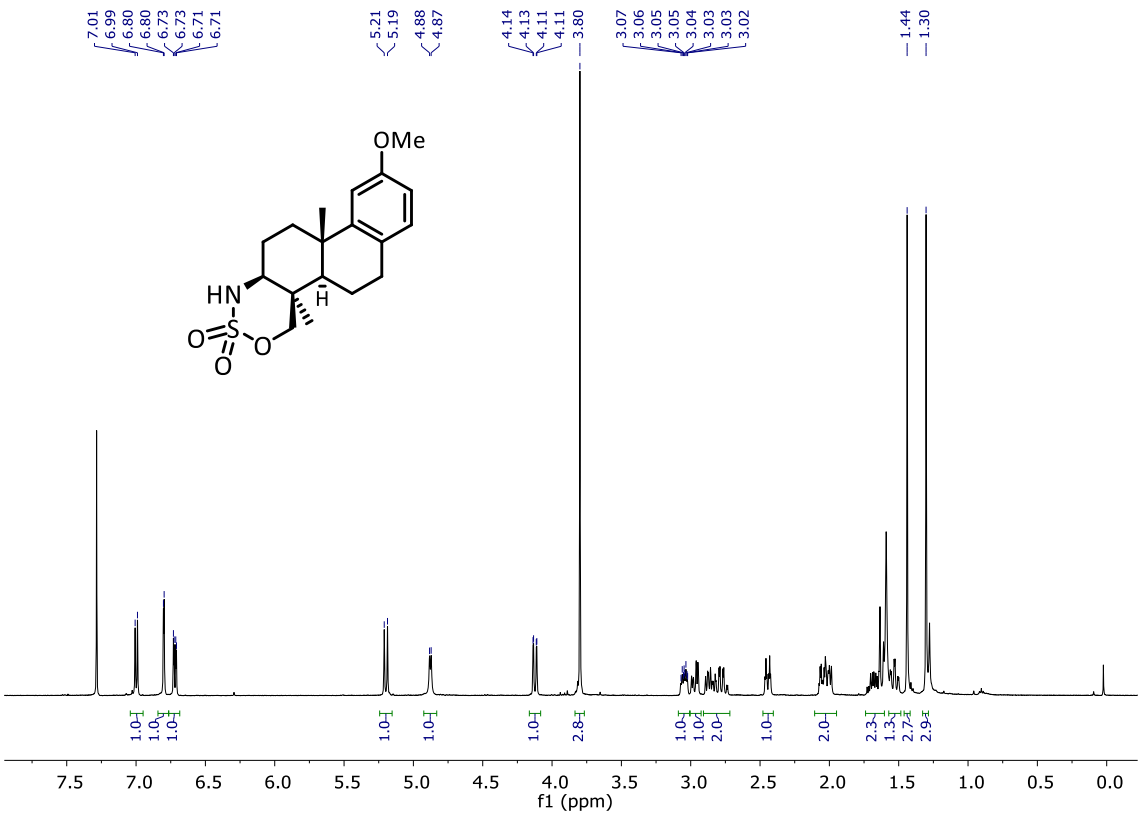


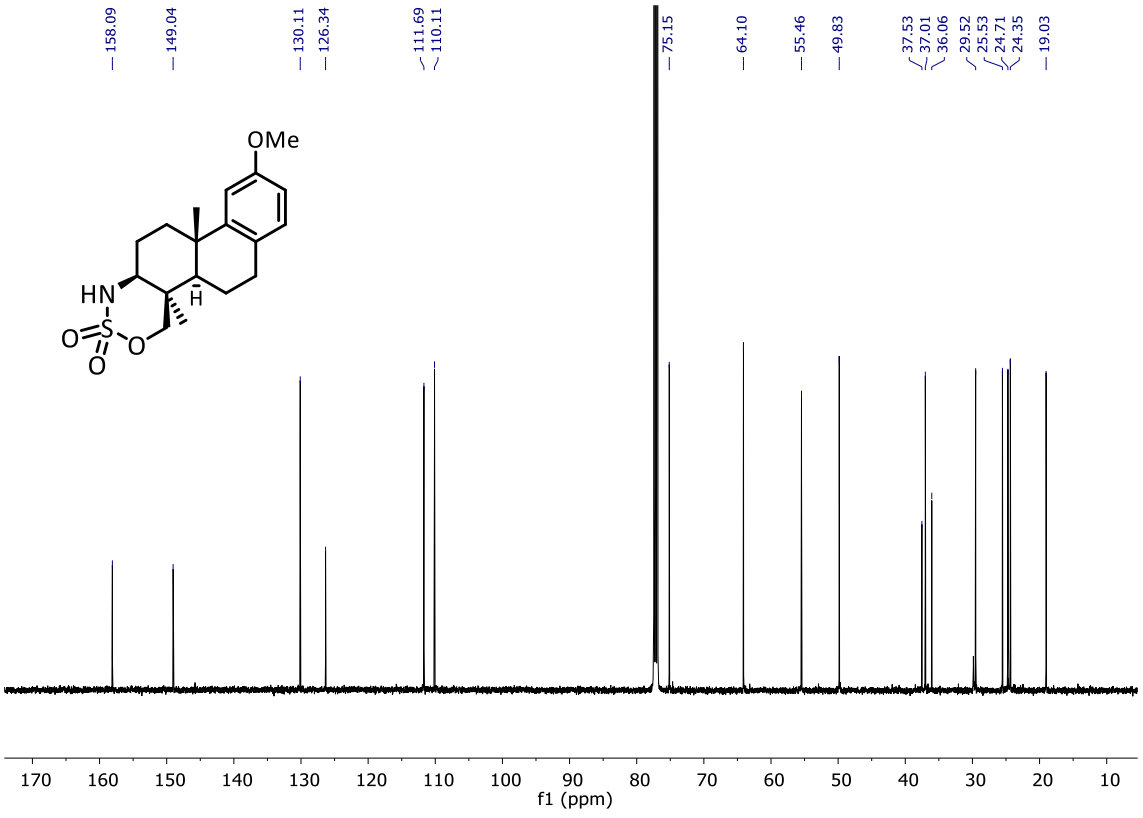
*Compound **25:*** ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



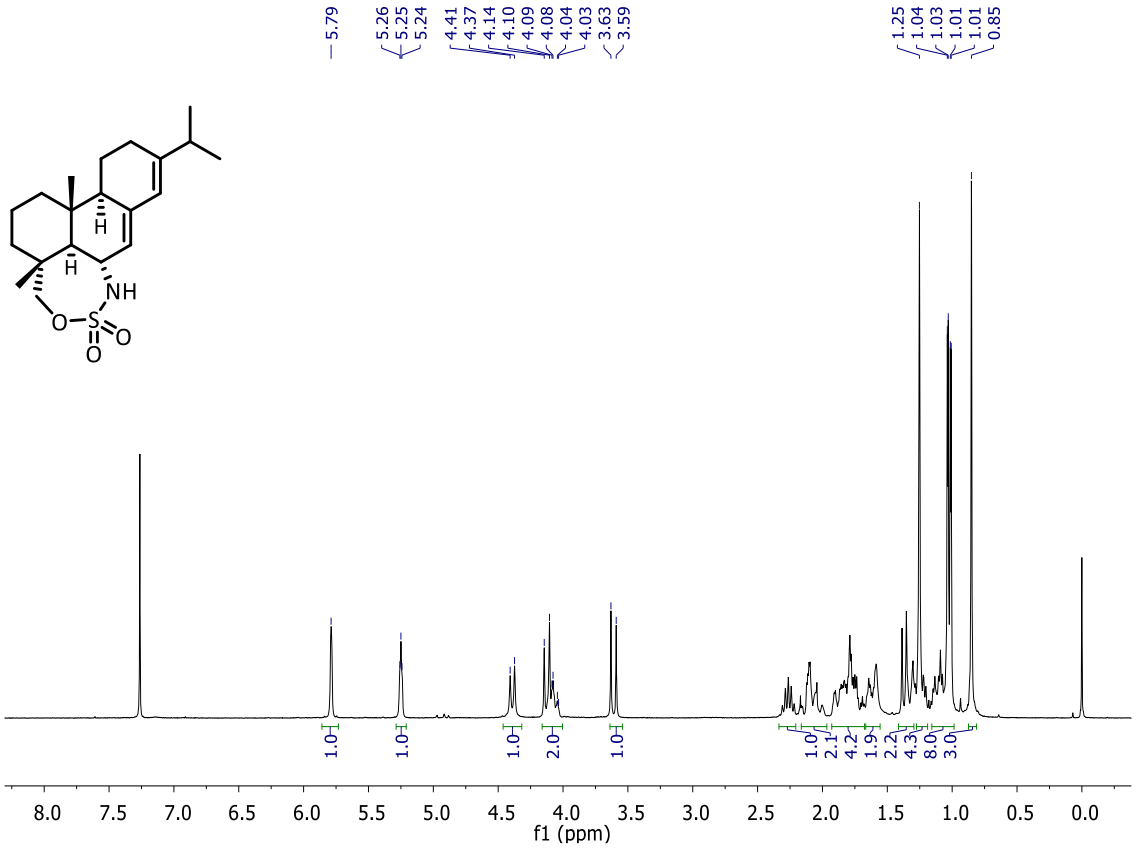


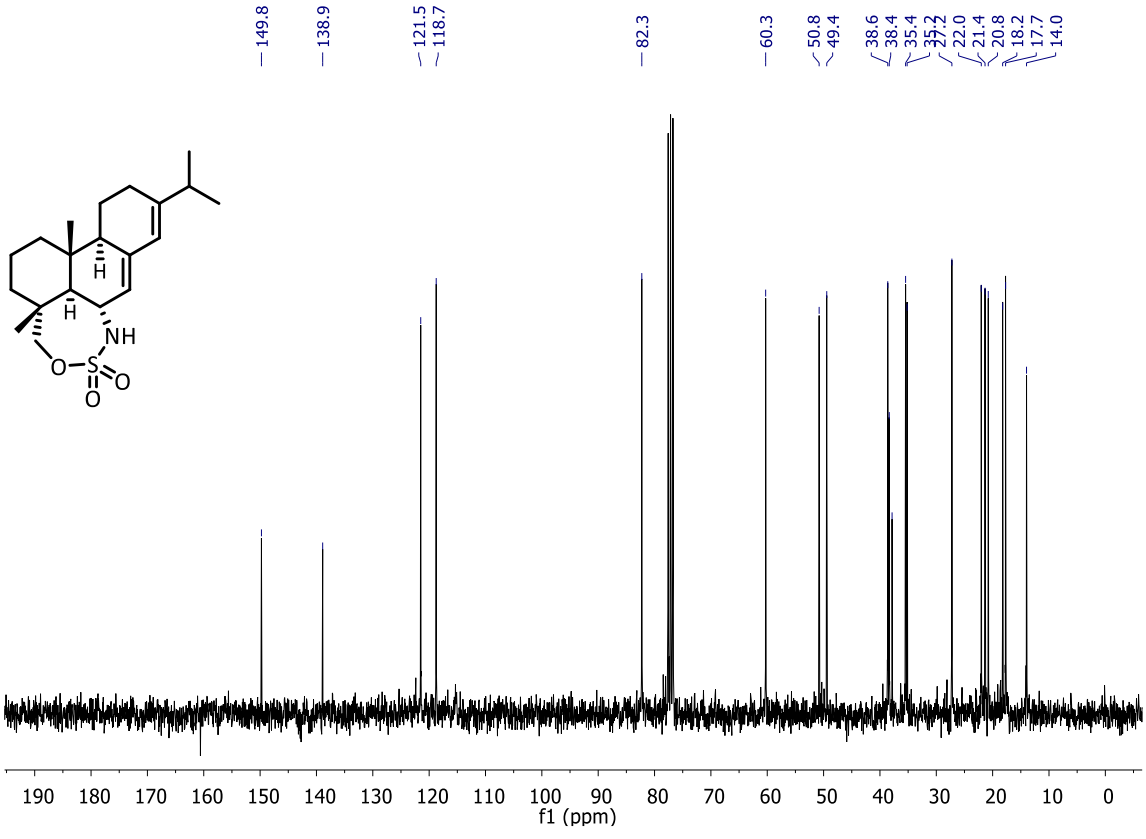
*Compound **27:*** ^{1}H (500 MHz $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)



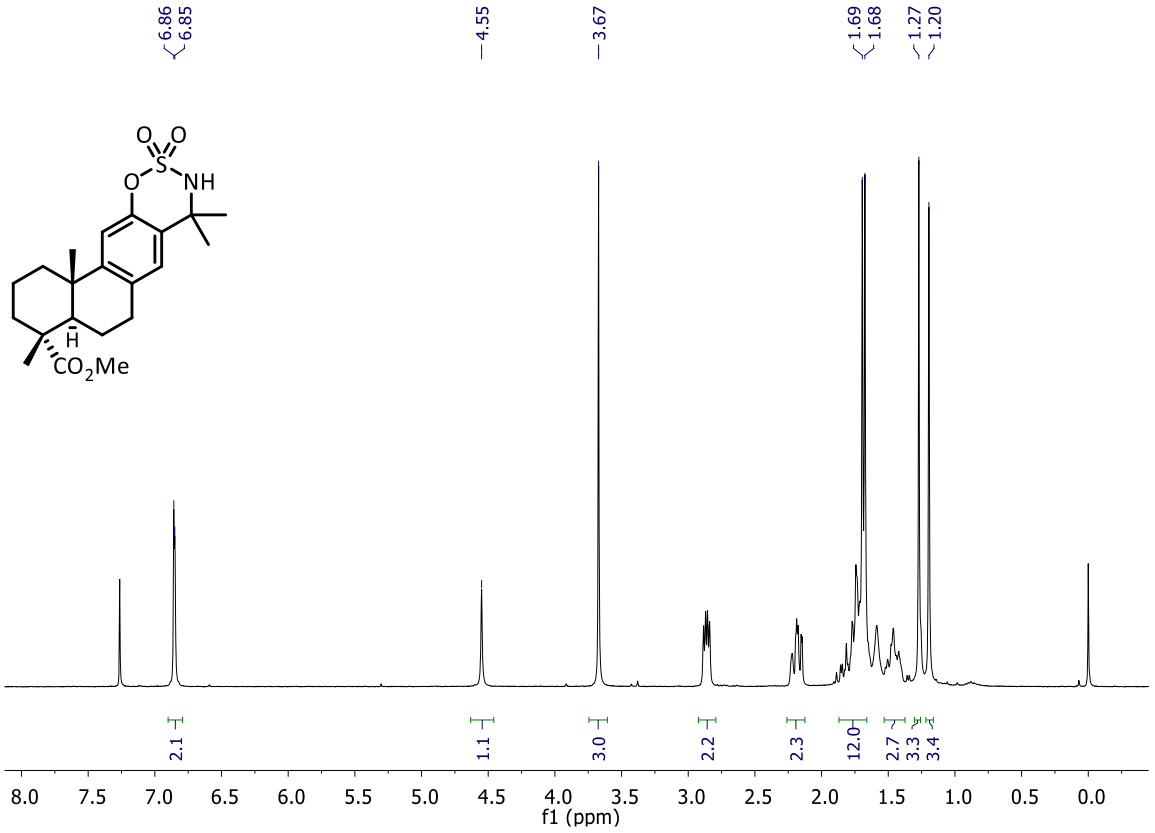


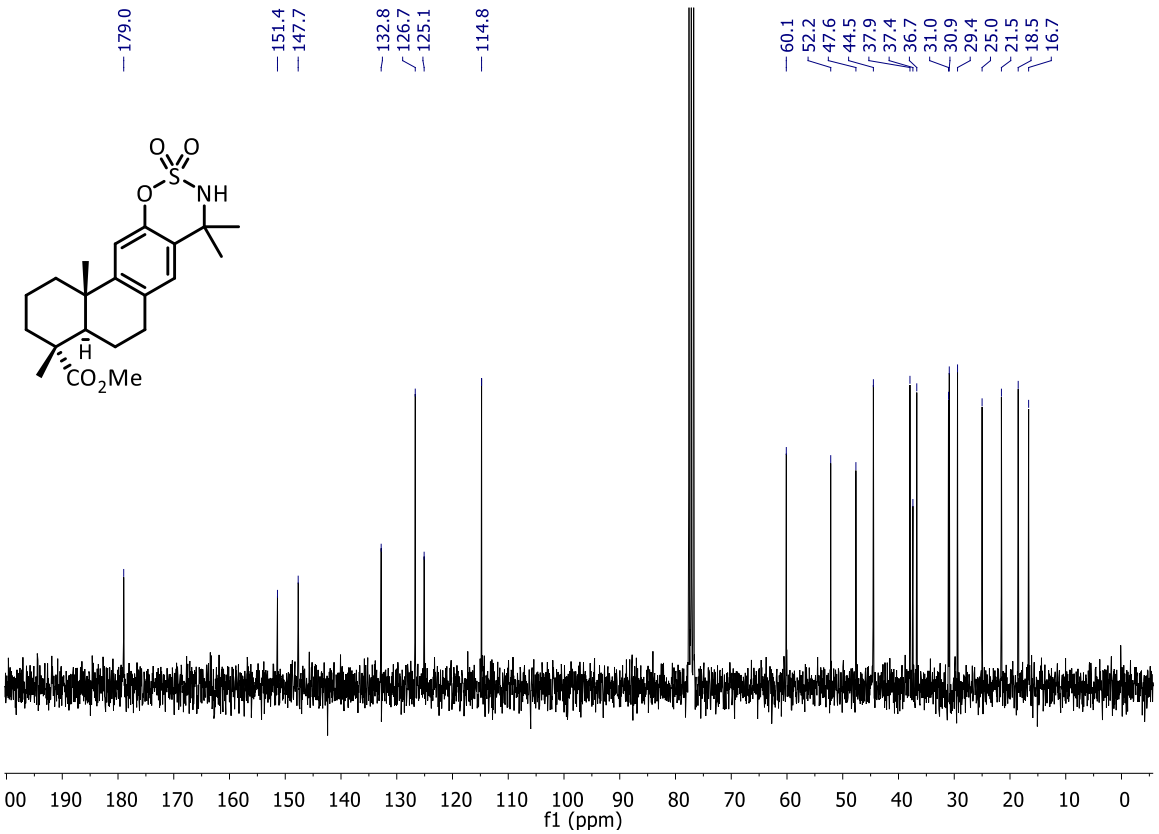
*Compound **29:*** ^{1}H (300 MHz $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



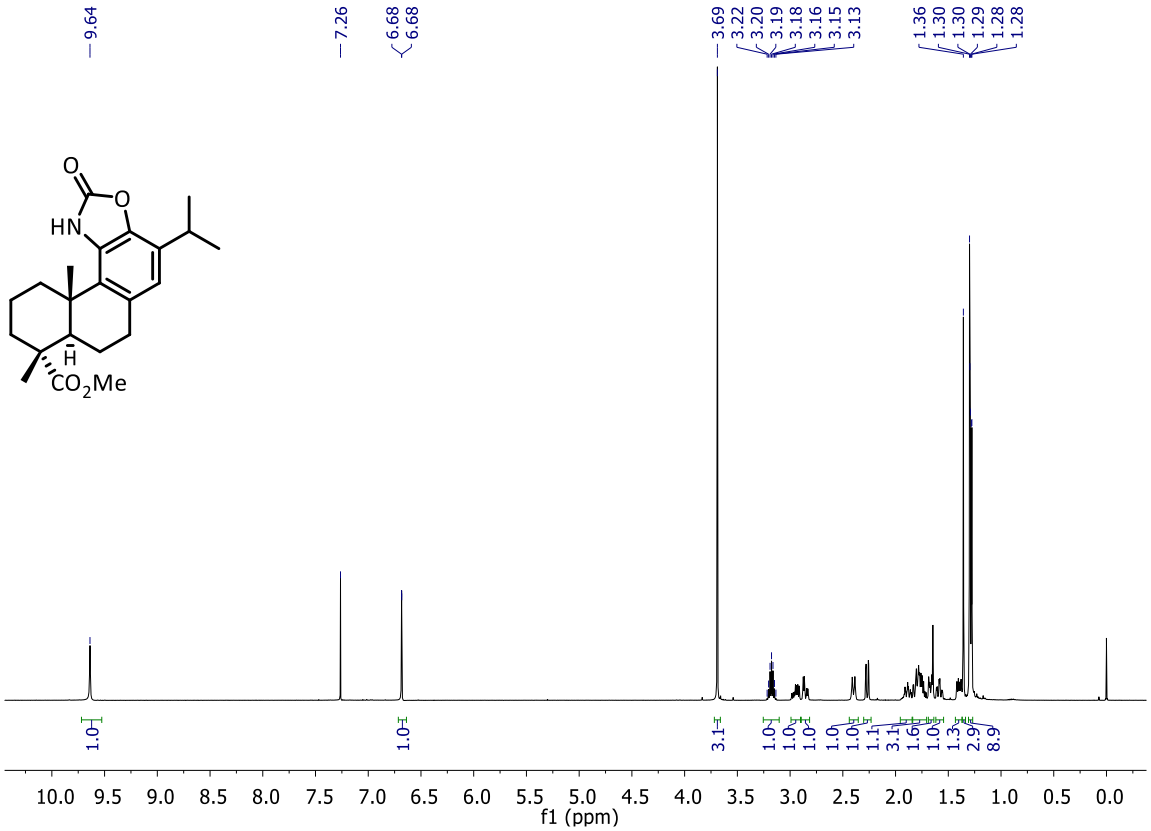


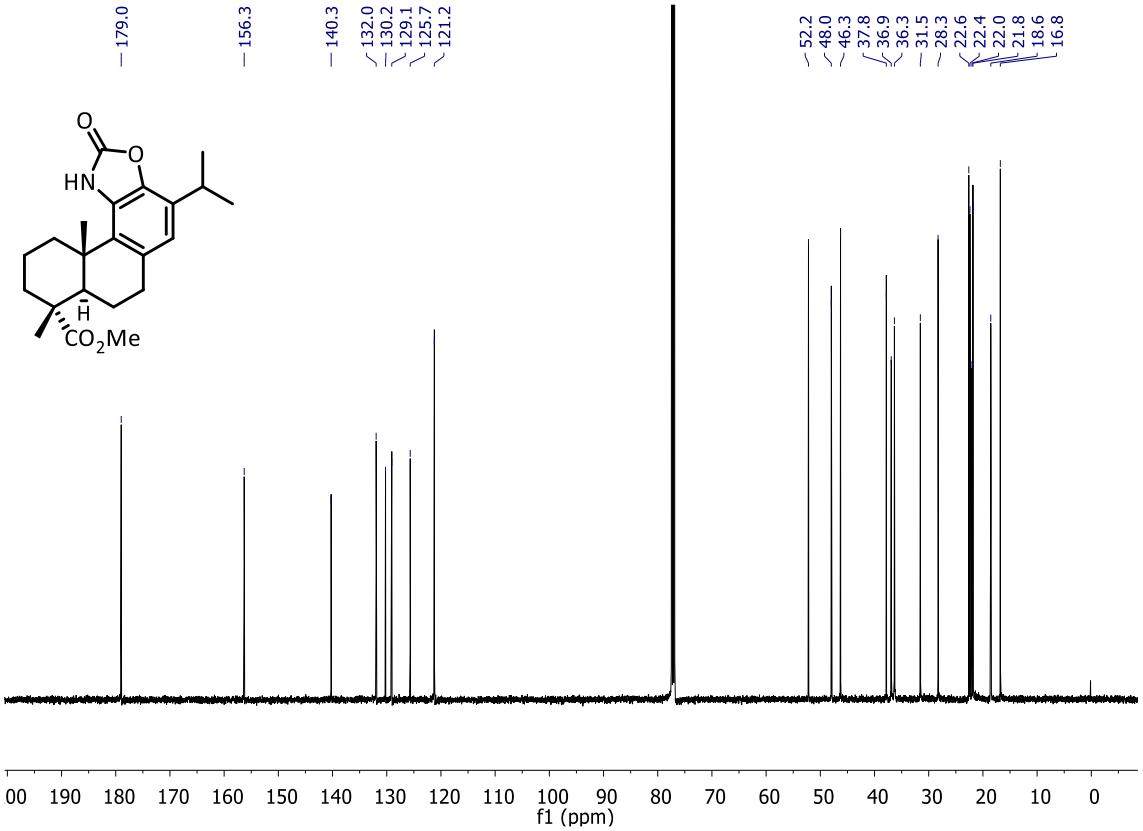
*Compound **31:*** ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



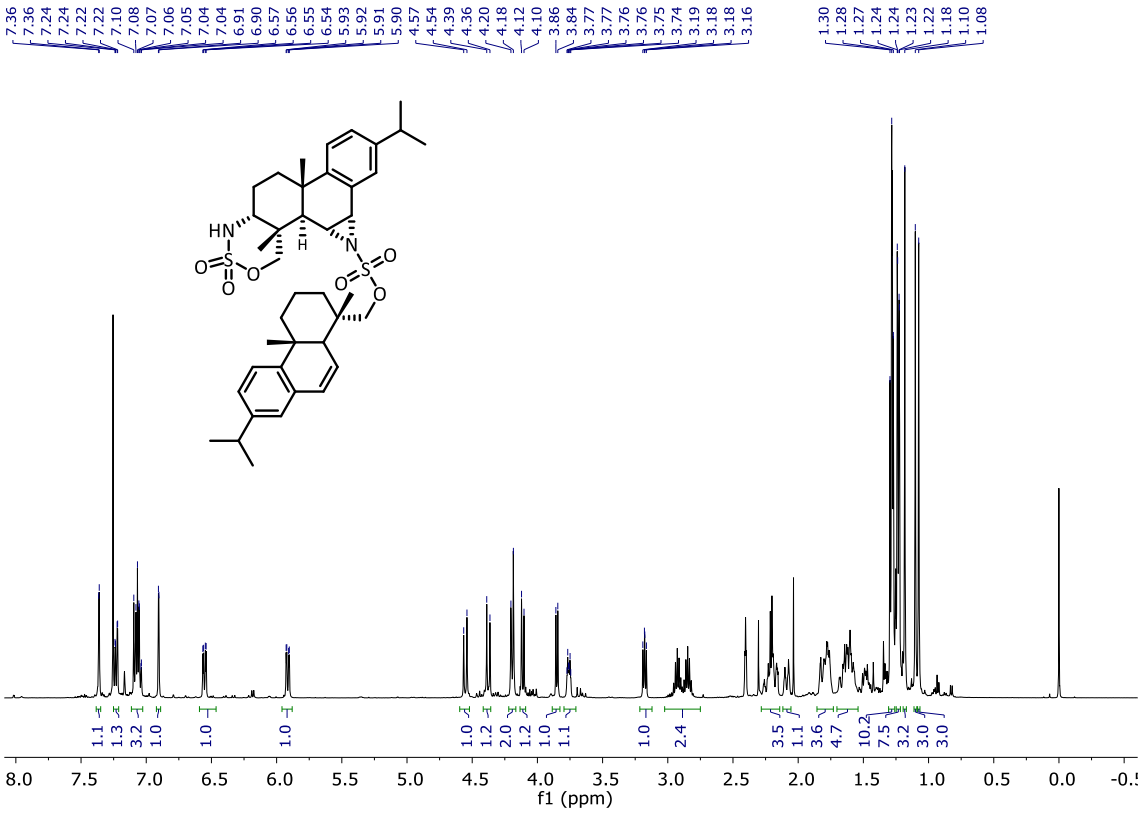


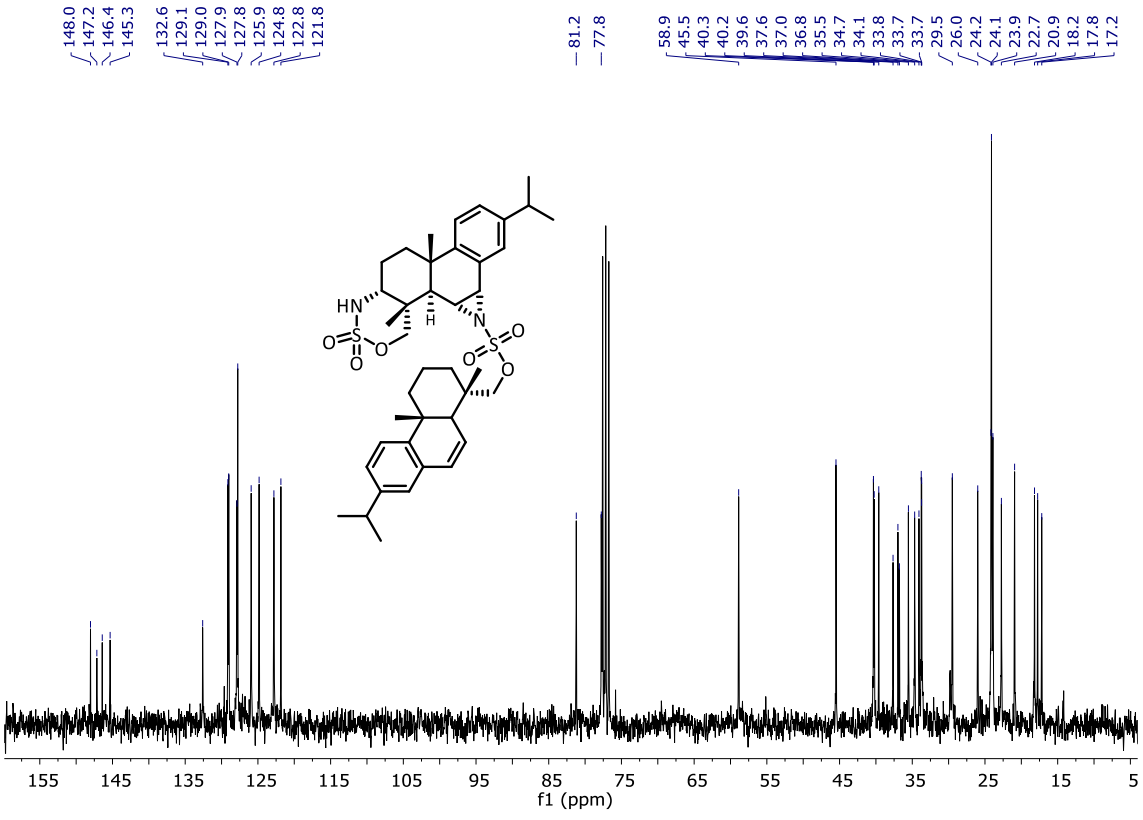
*Compound **33:*** ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)



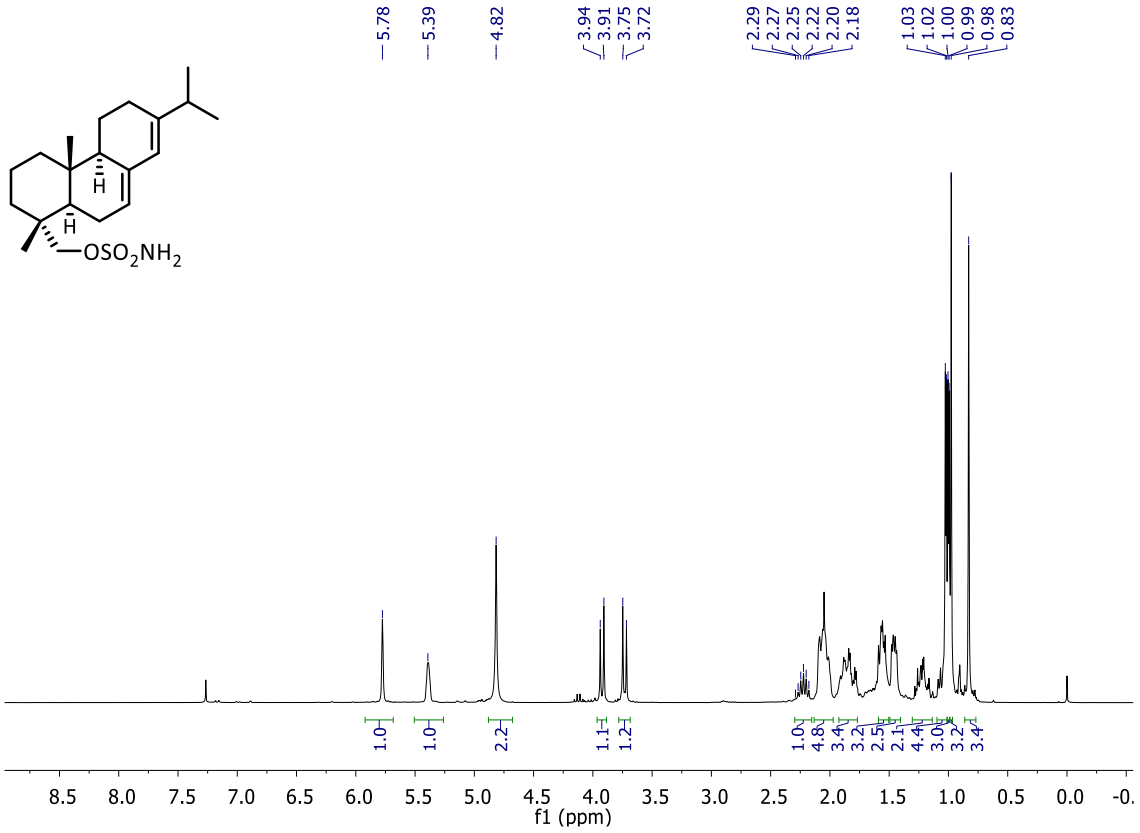


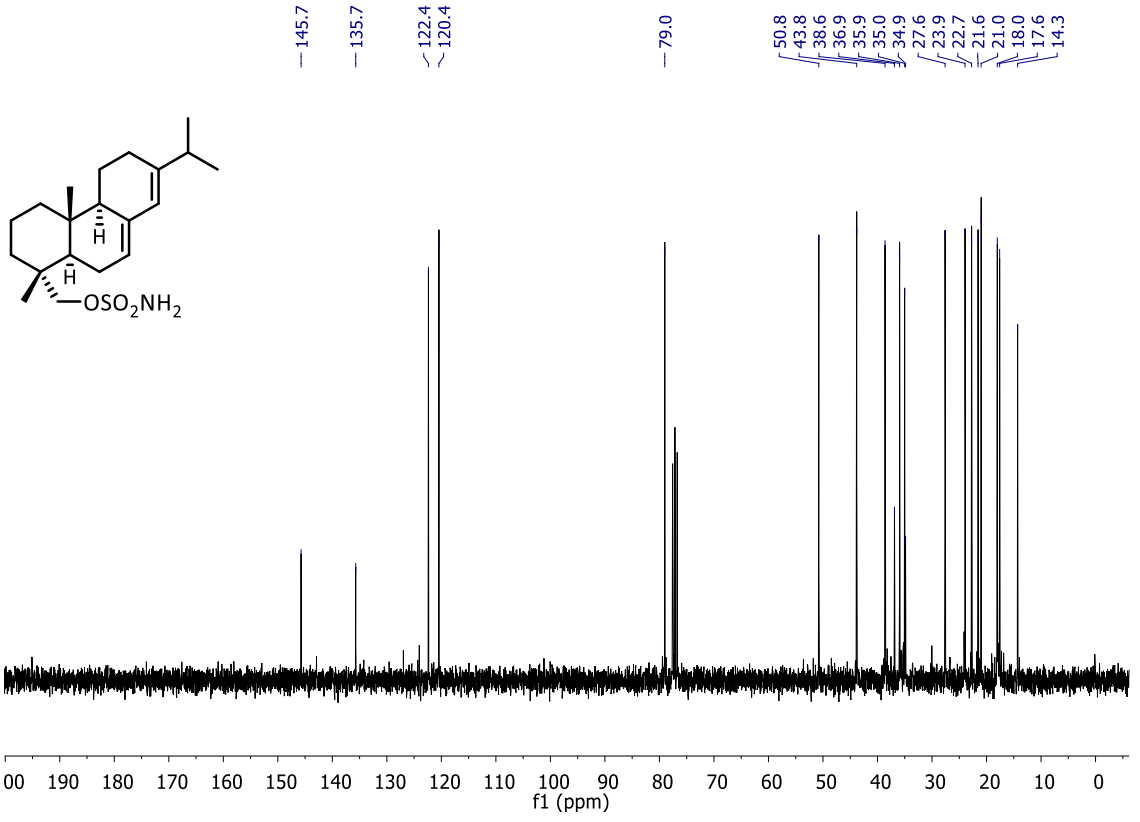
*Compound **34**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



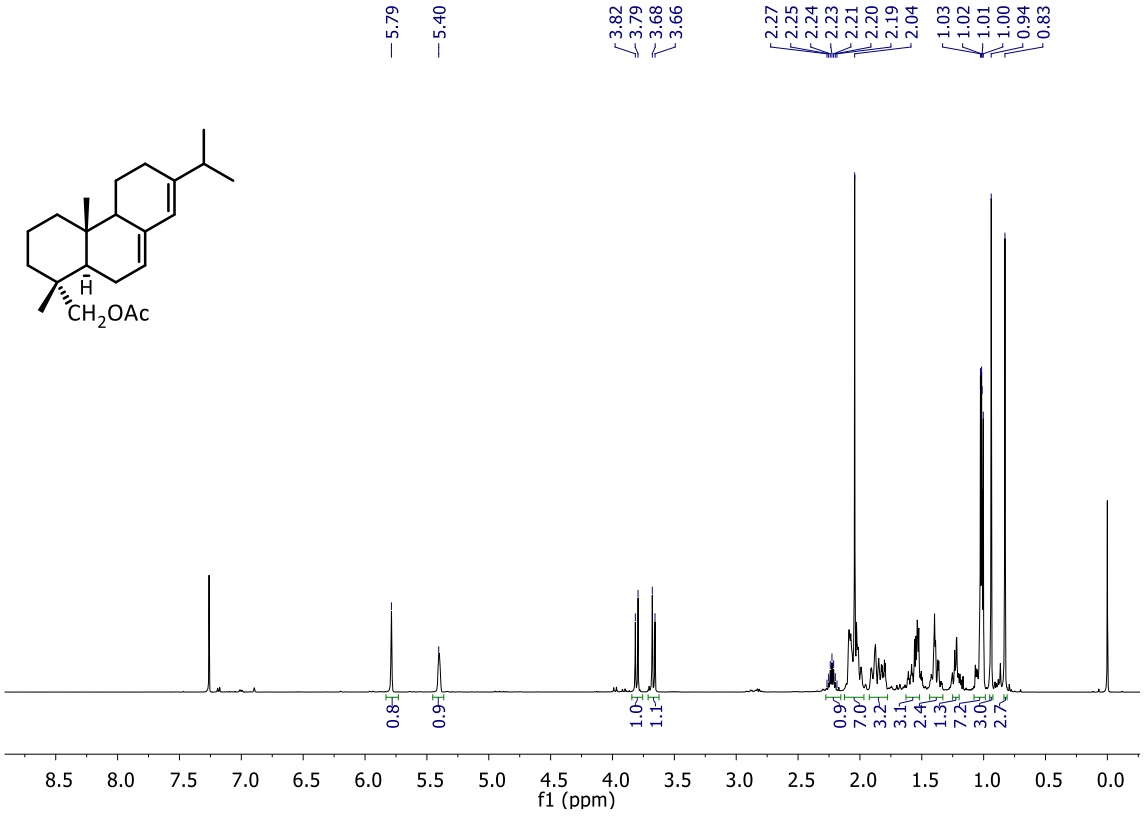


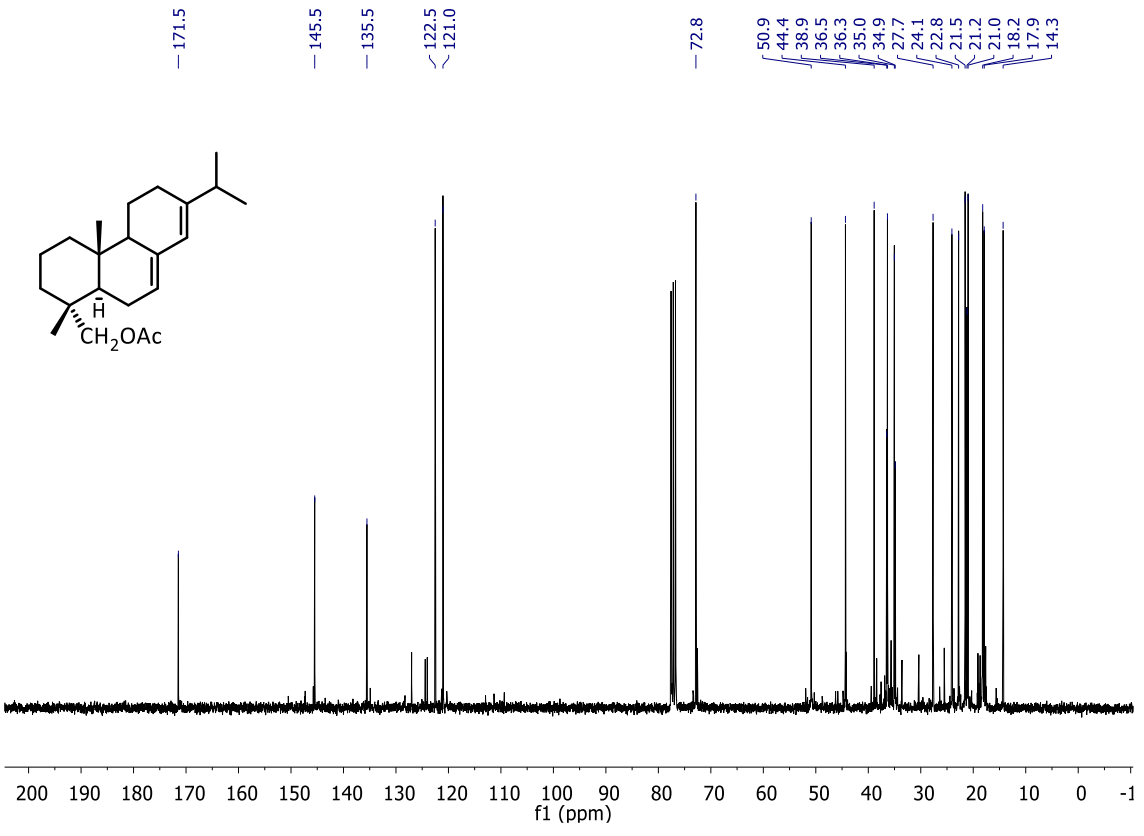
*Compound **28***: ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



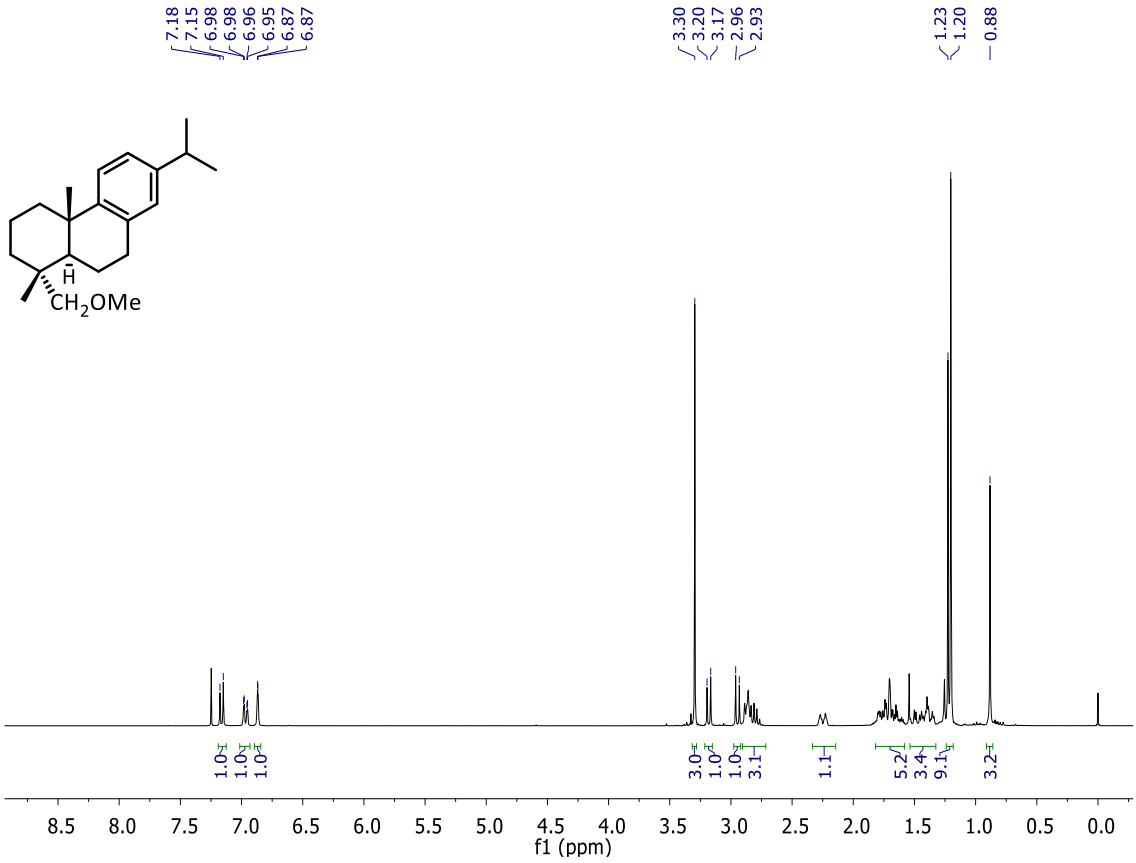


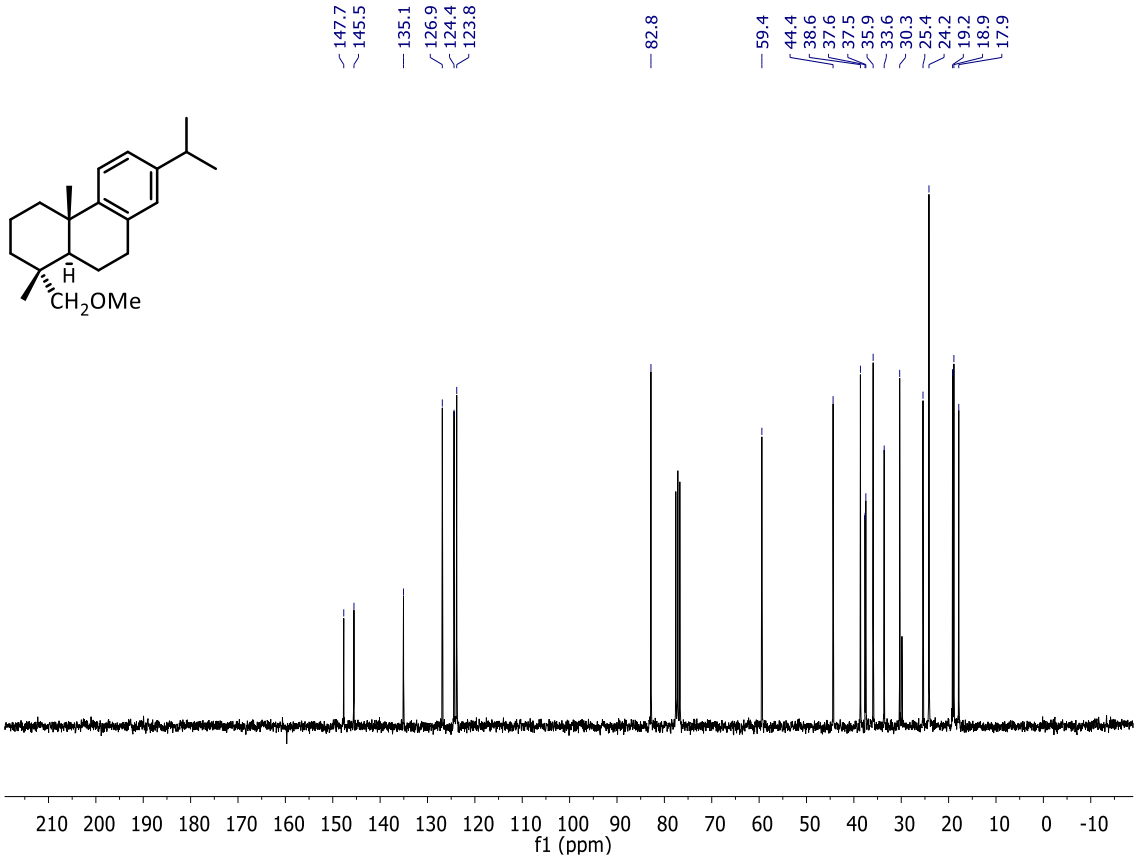
*Compound **16**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



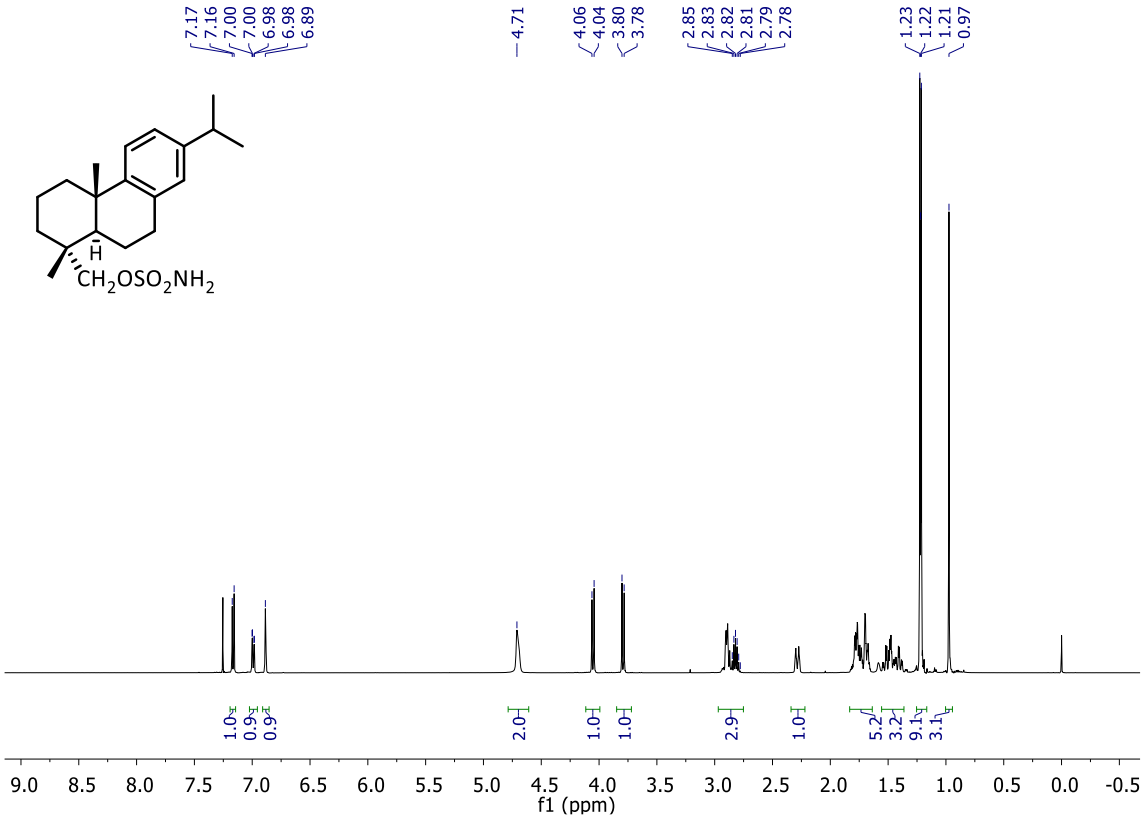


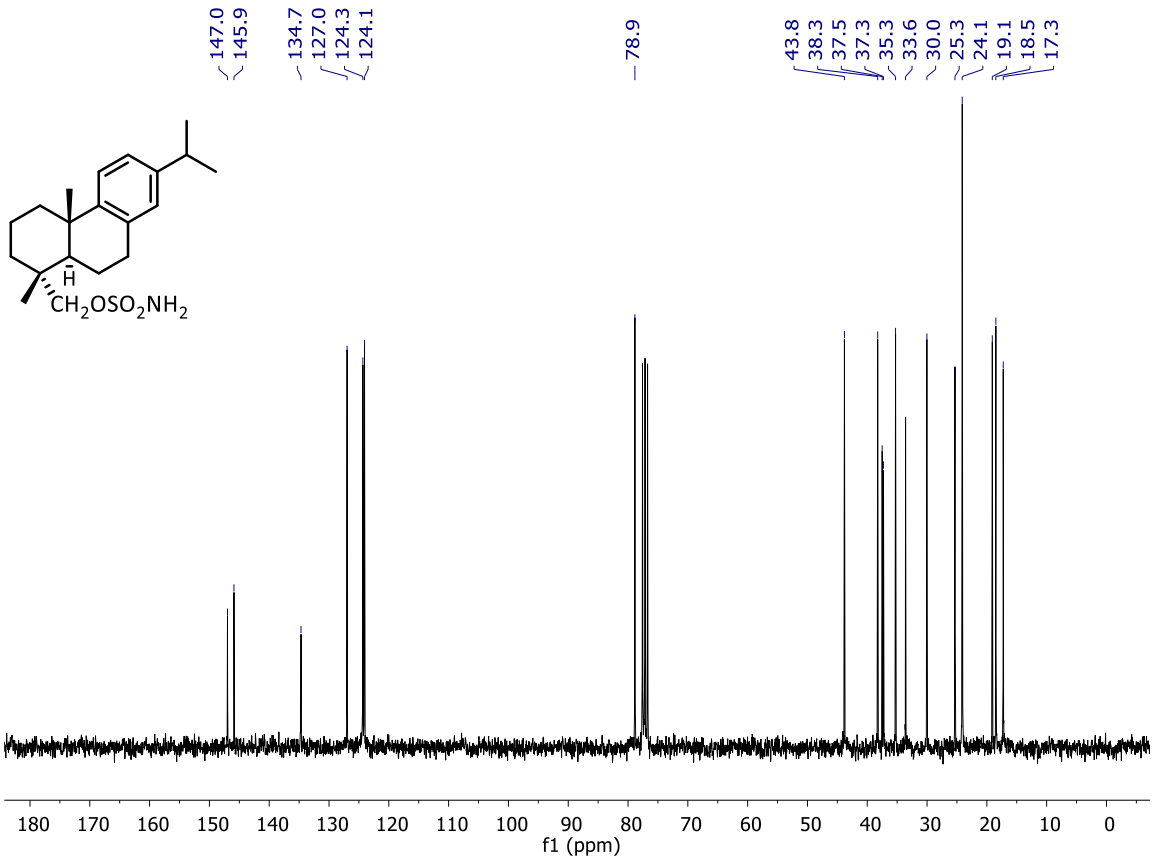
*Compound **5:*** ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



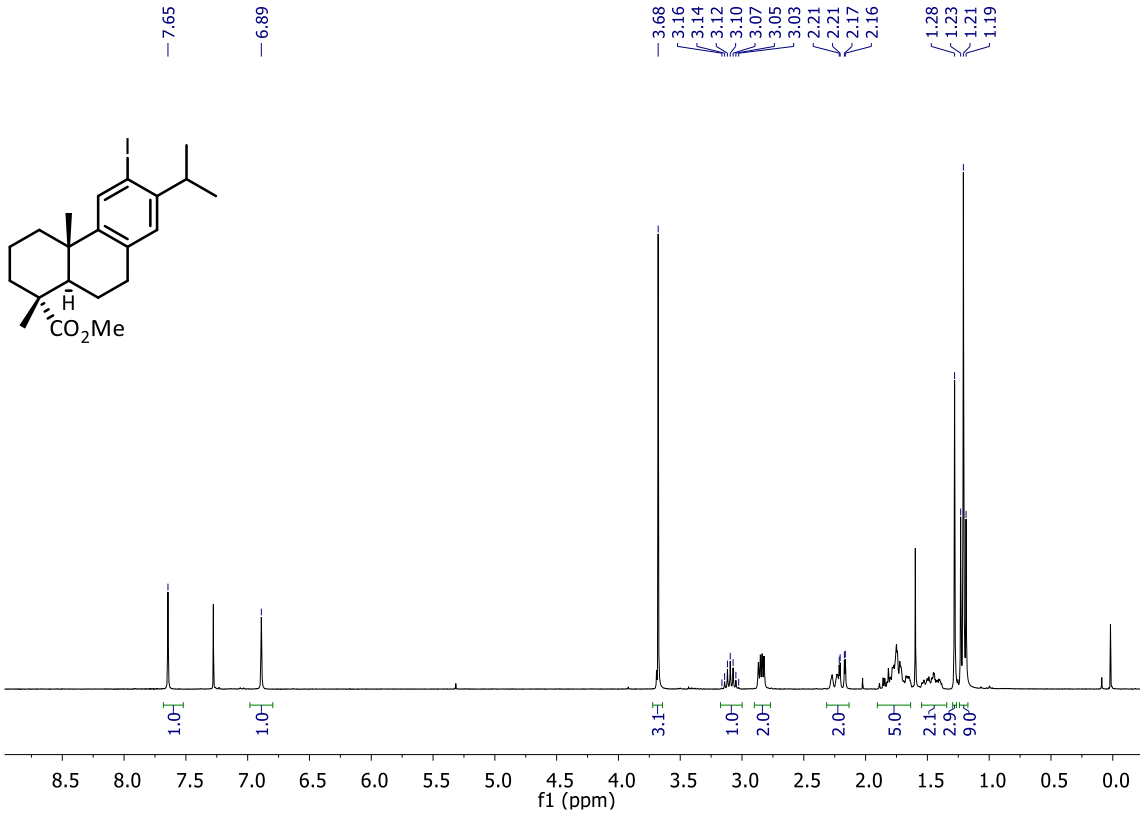


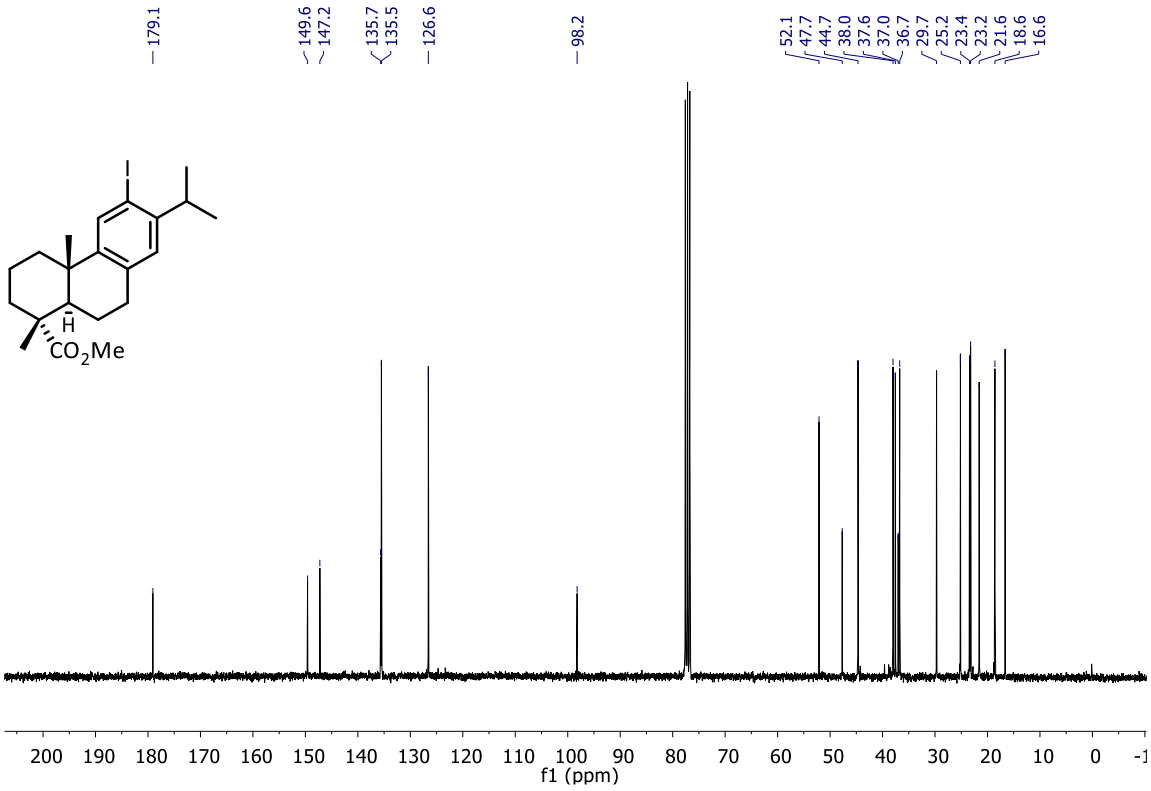
Compound ***22***: ^{1}H (500 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



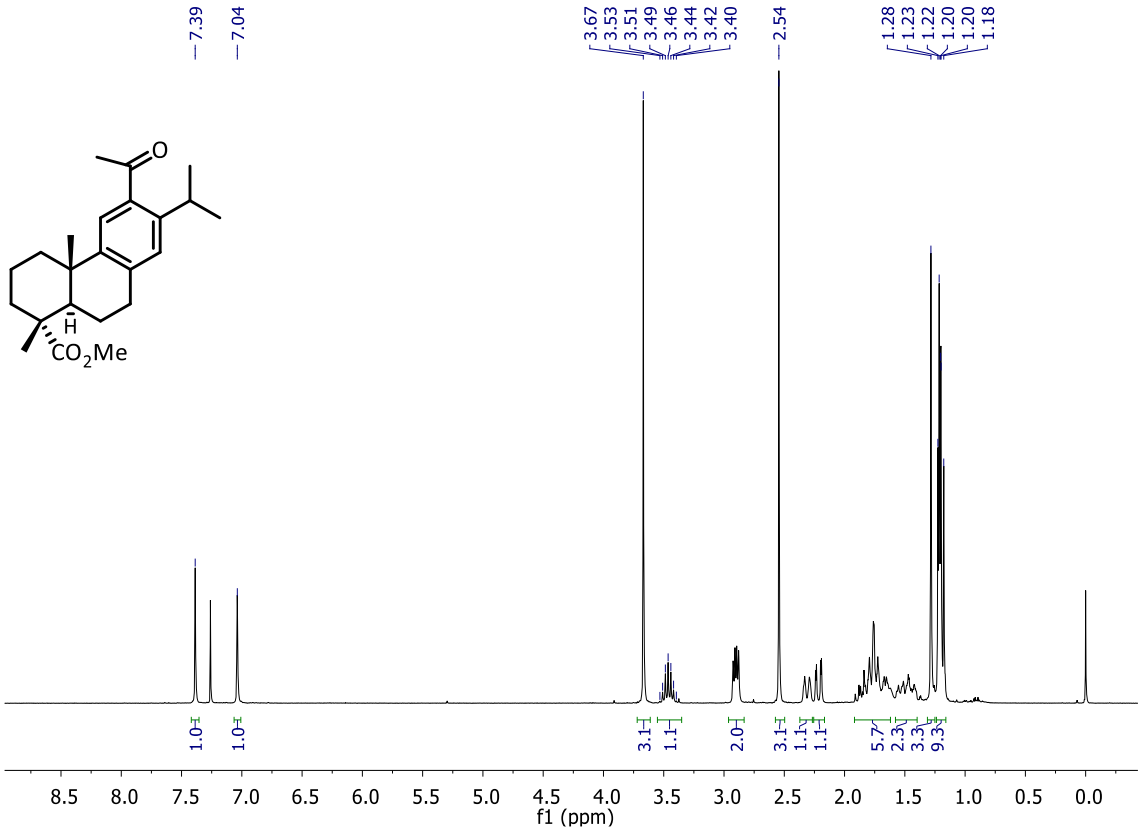


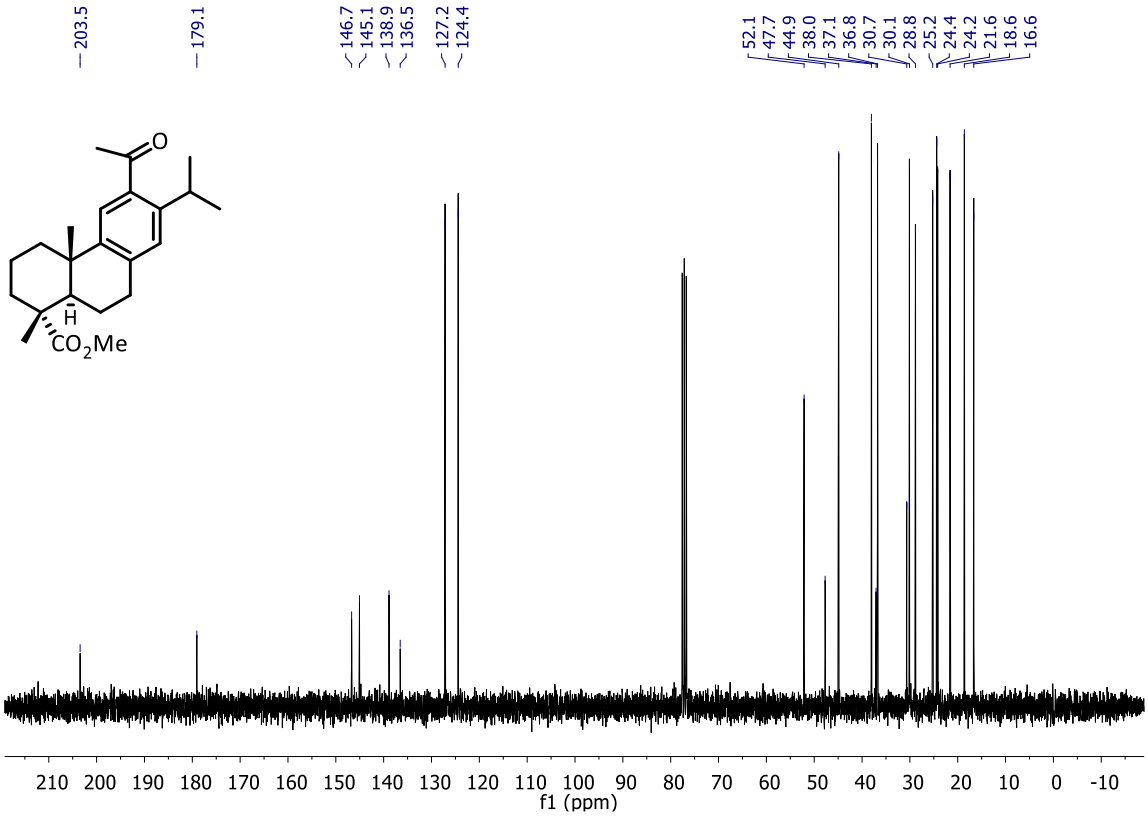
*Compound **3**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



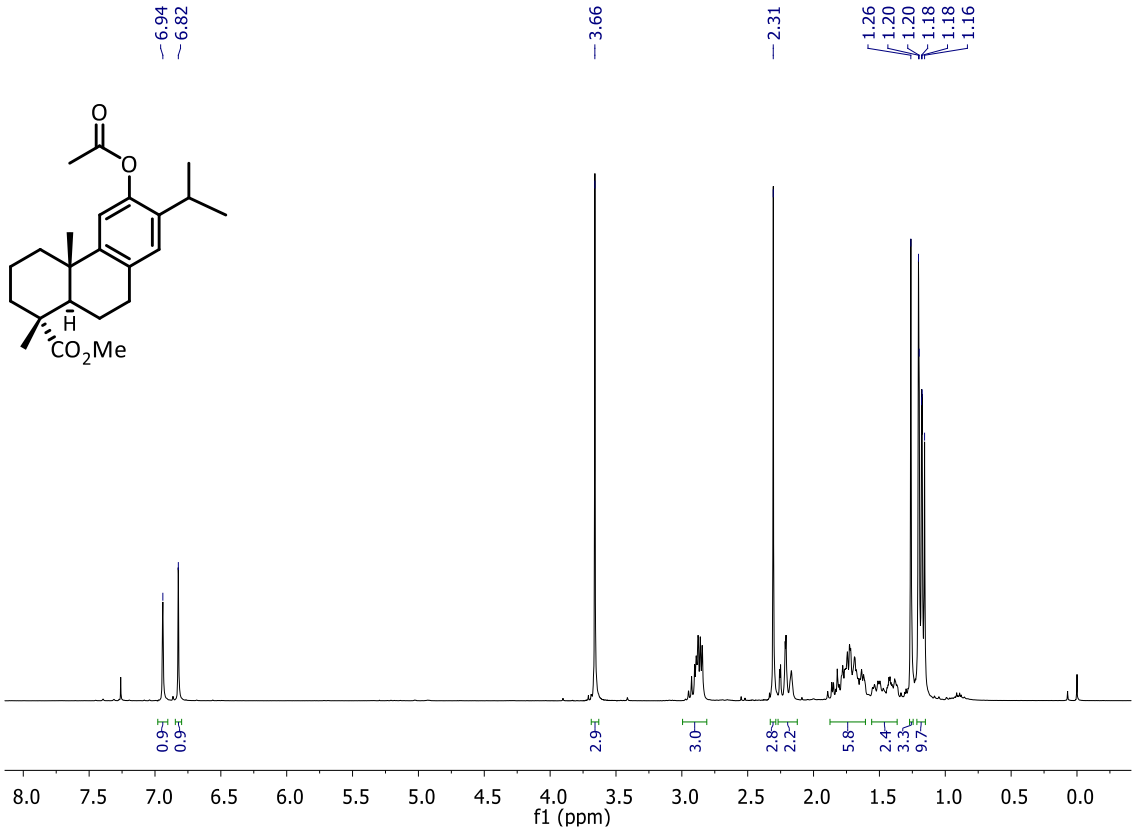


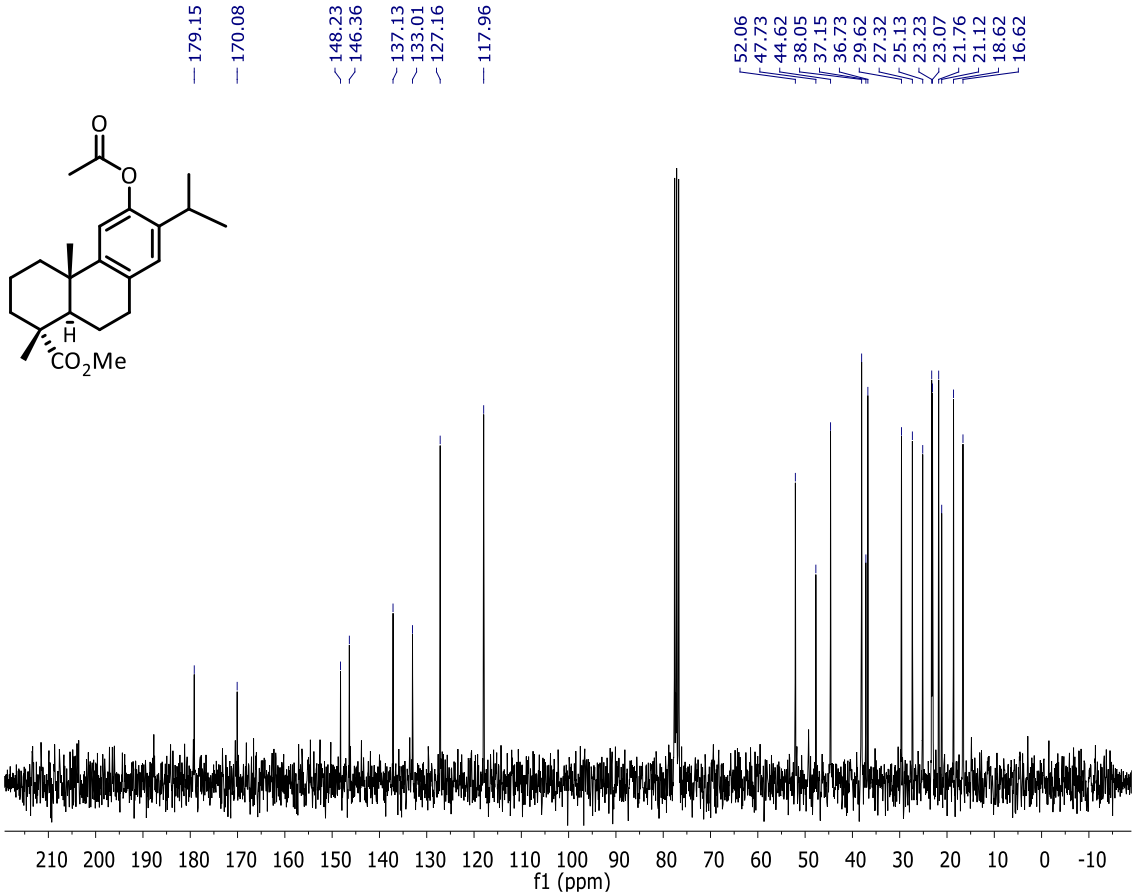
*Compound **I-3**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



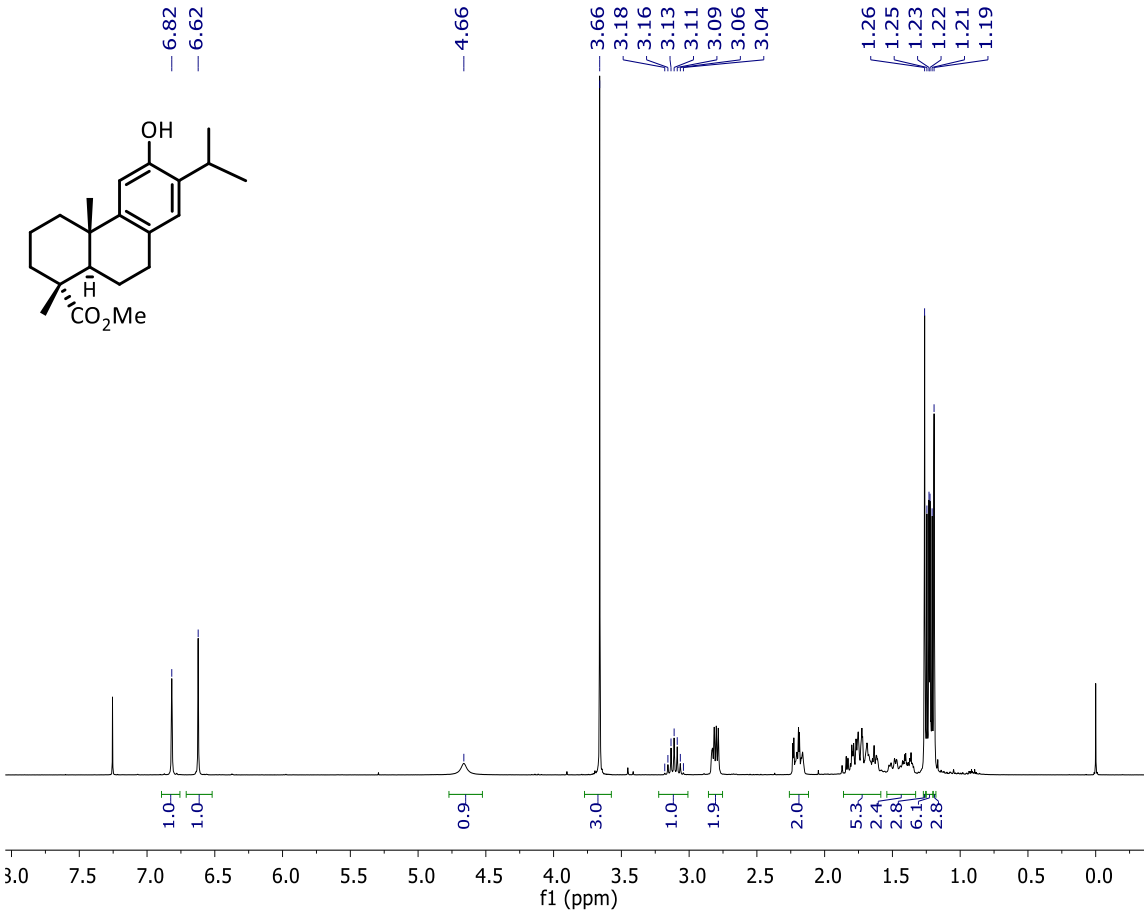


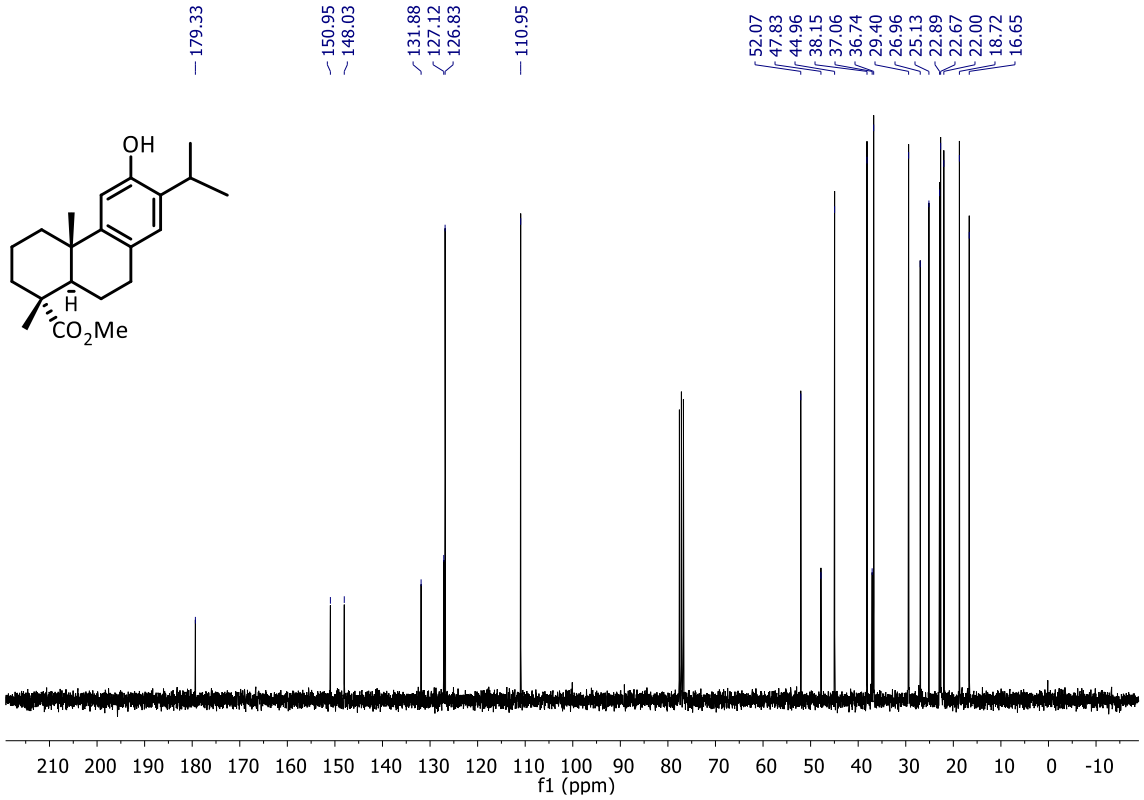
*Compound **I-4**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C(75 MHz, $CDCl_3$)



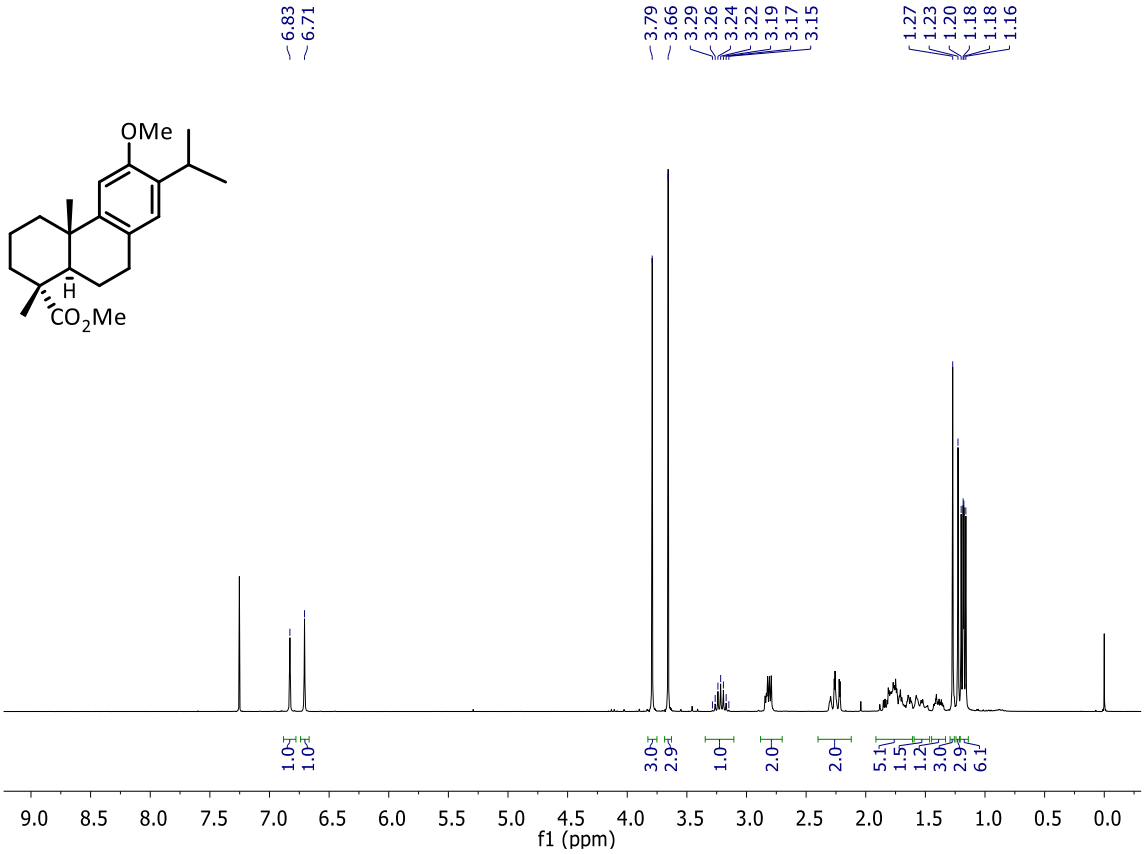


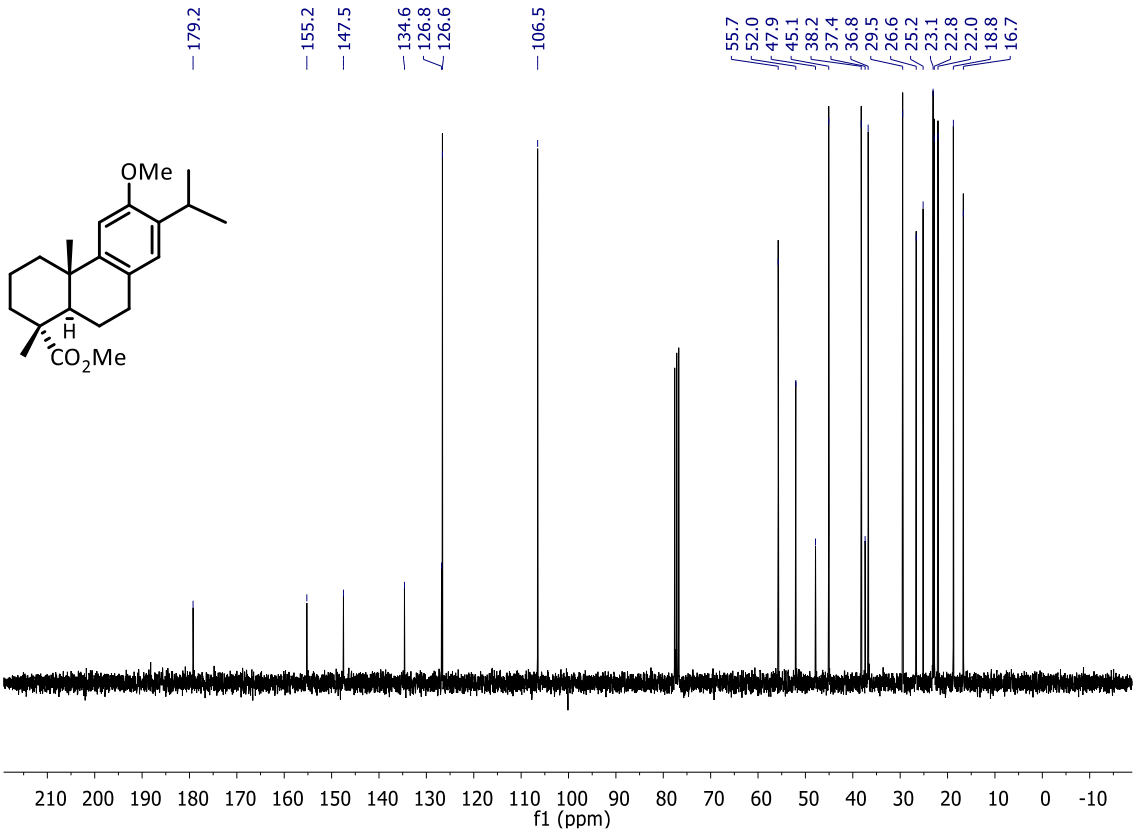
*Compound **I-5:*** ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



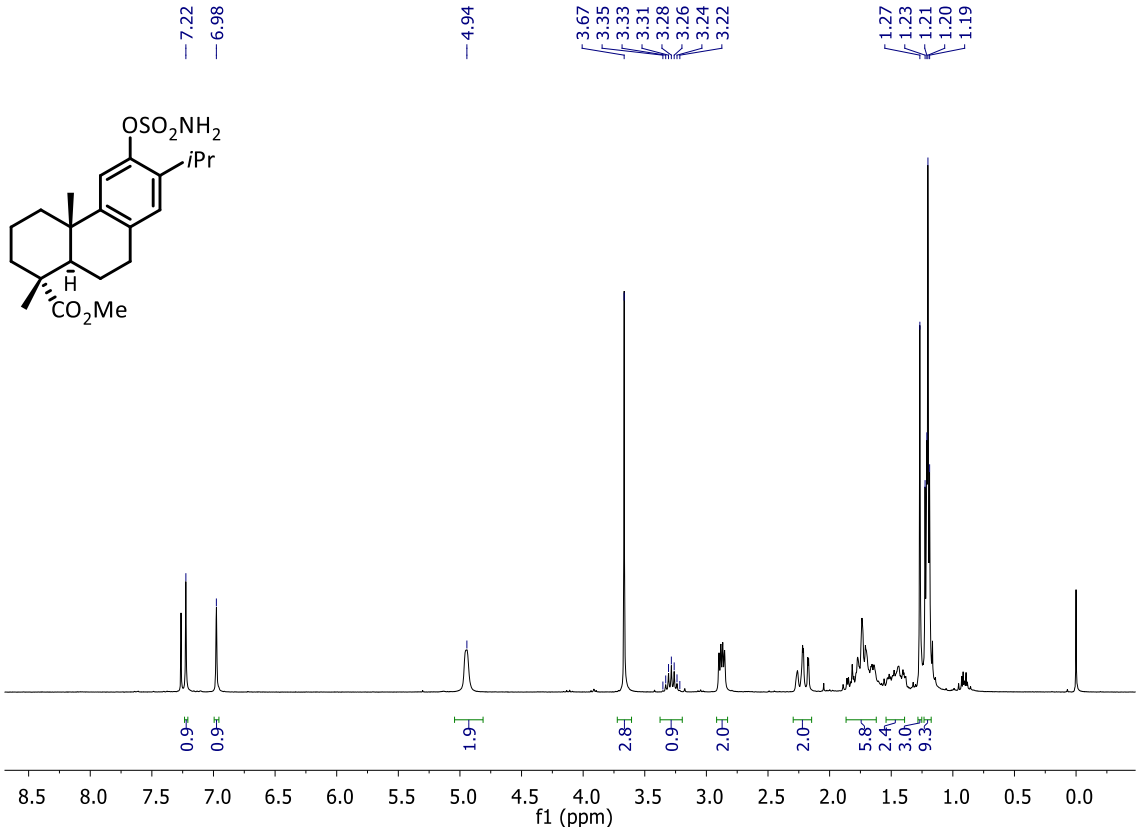


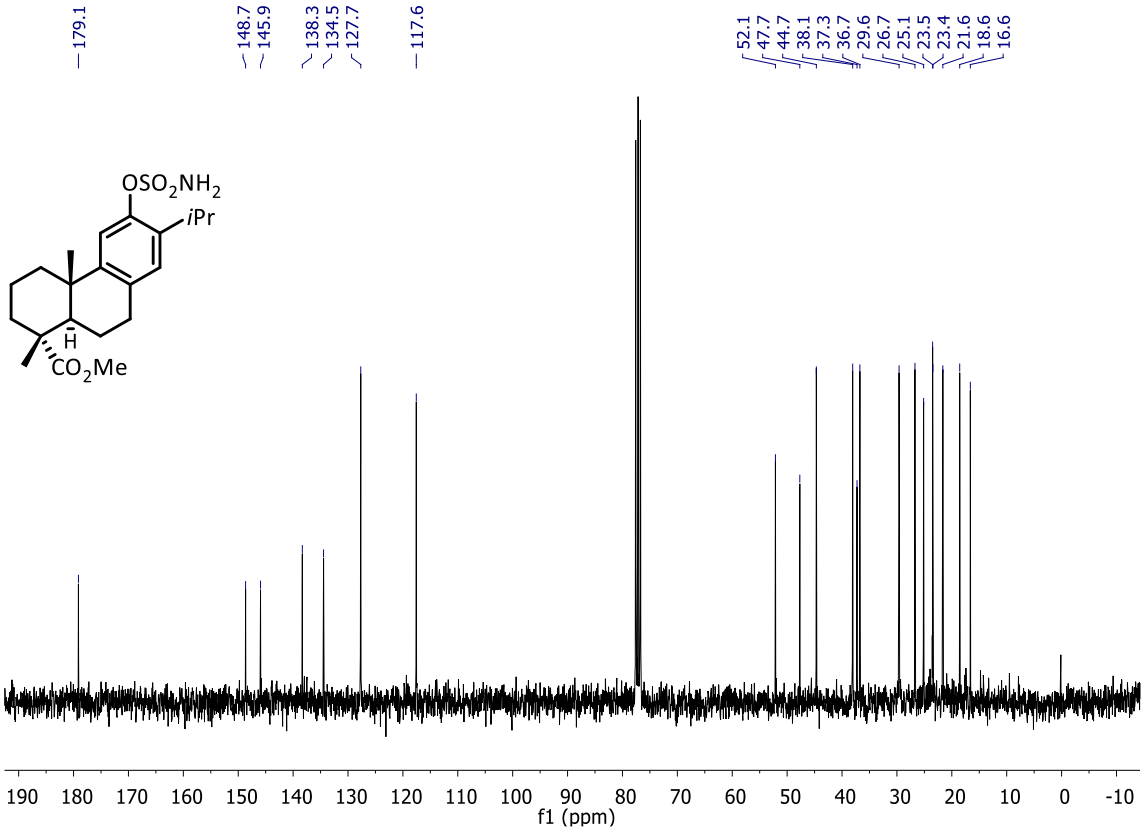
*Compound **2**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



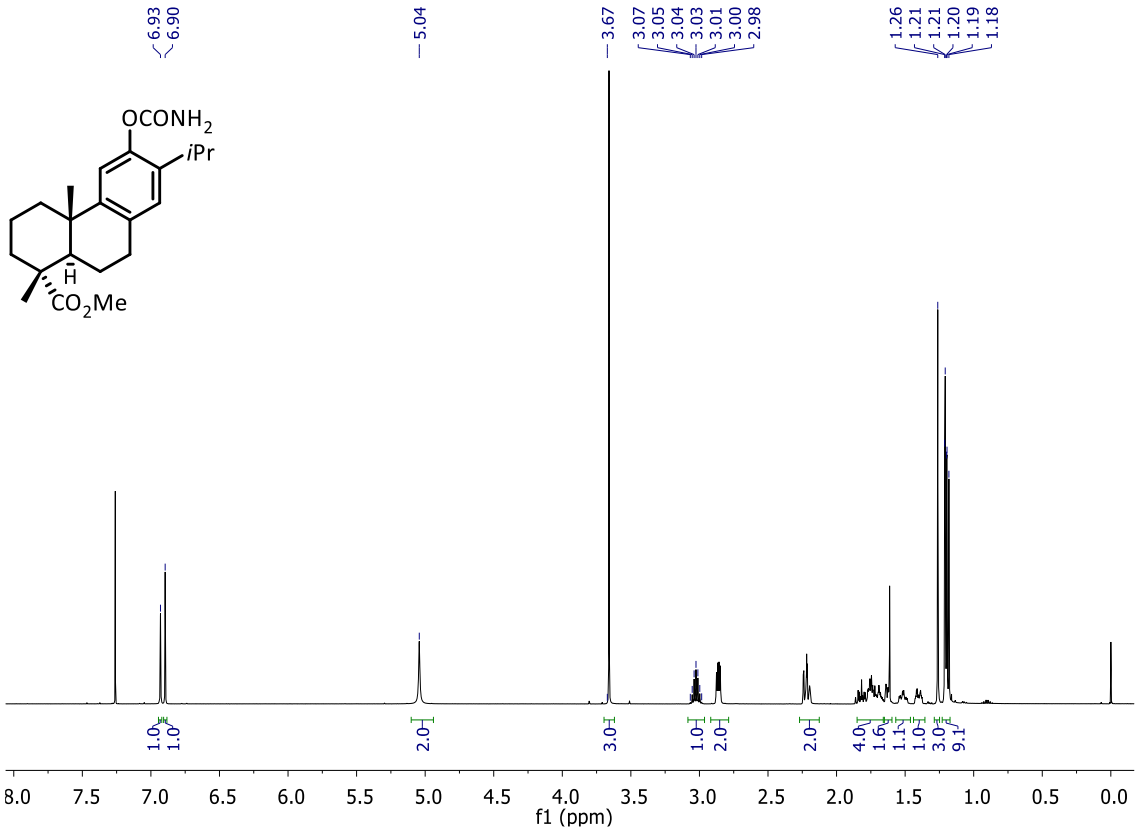


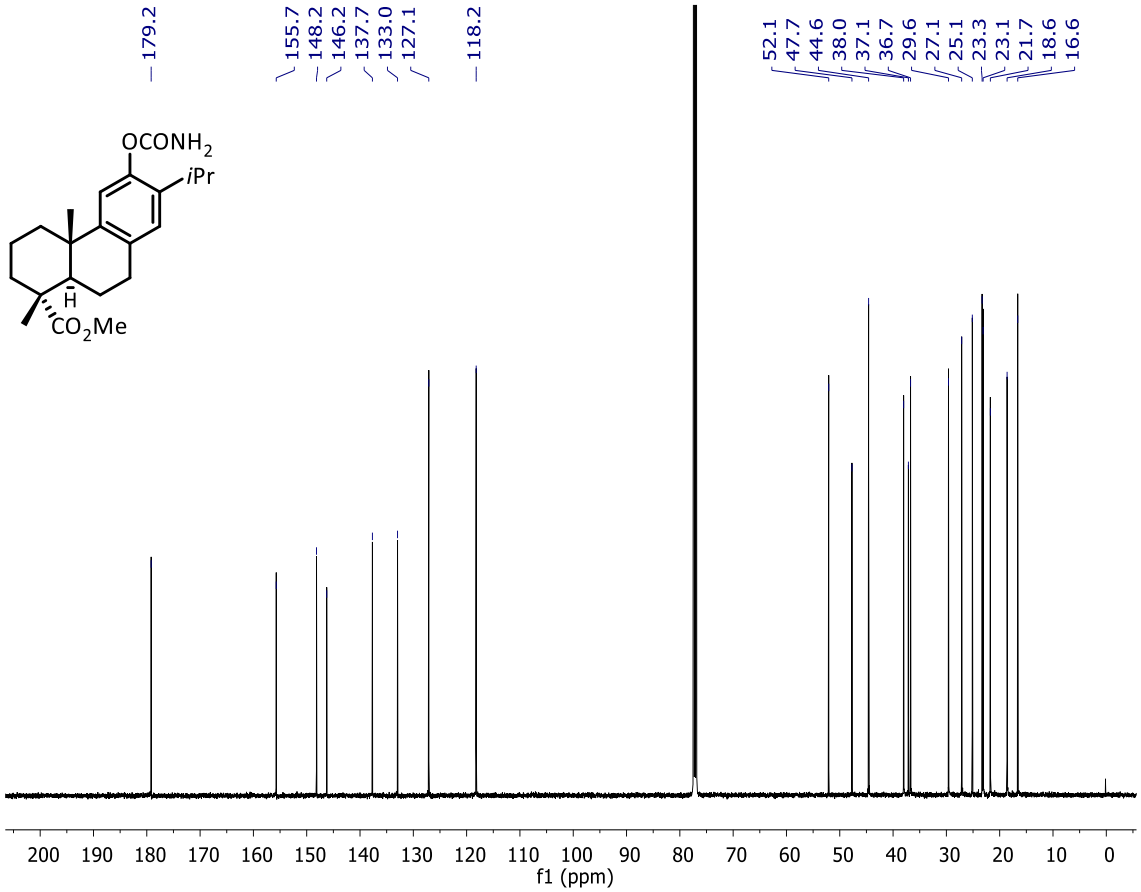
*Compound **30***:^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



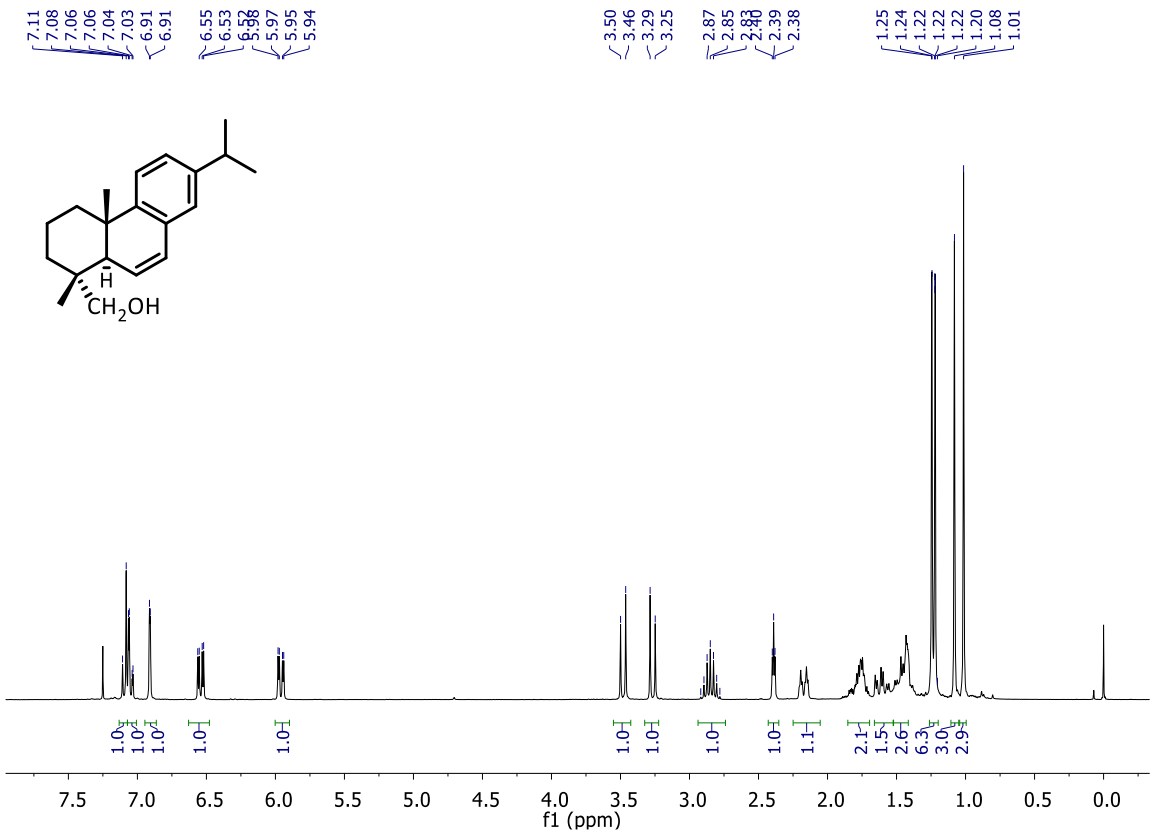


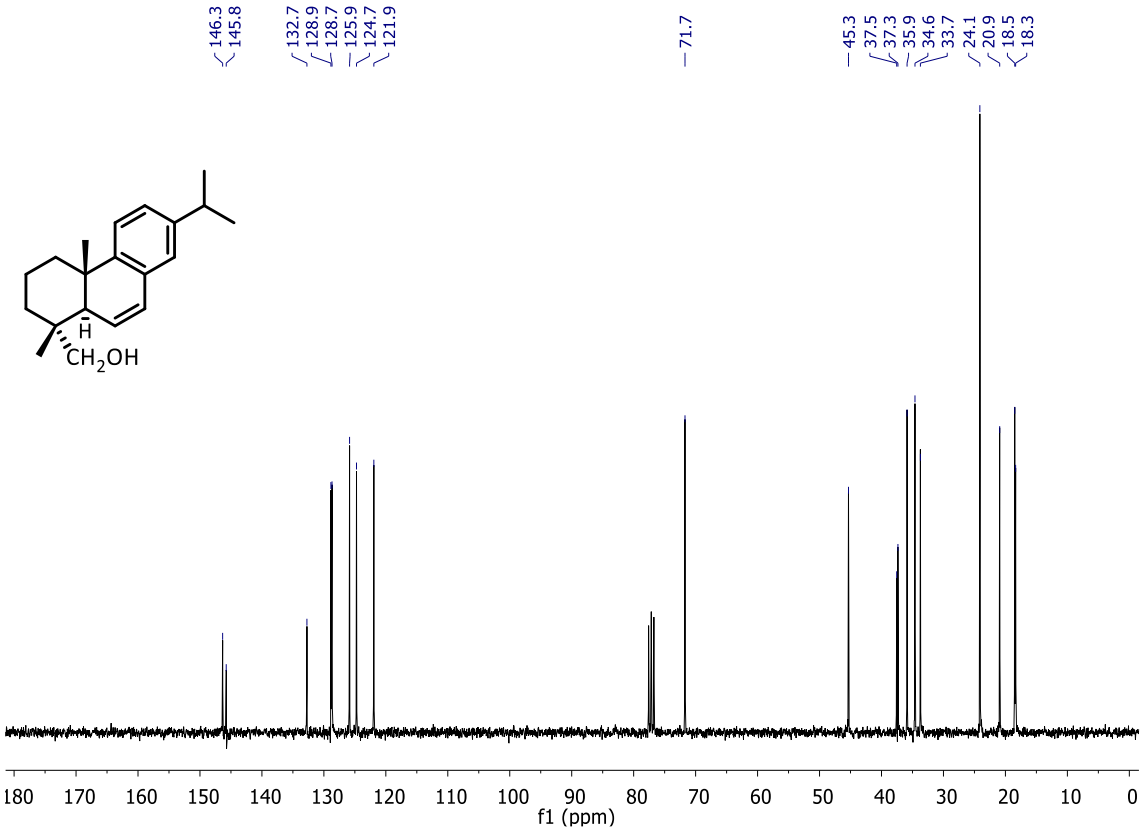
*Compound **32***: ^{1}H (500 MHz, $CDCl_3$), ^{13}C(126 MHz, $CDCl_3$)



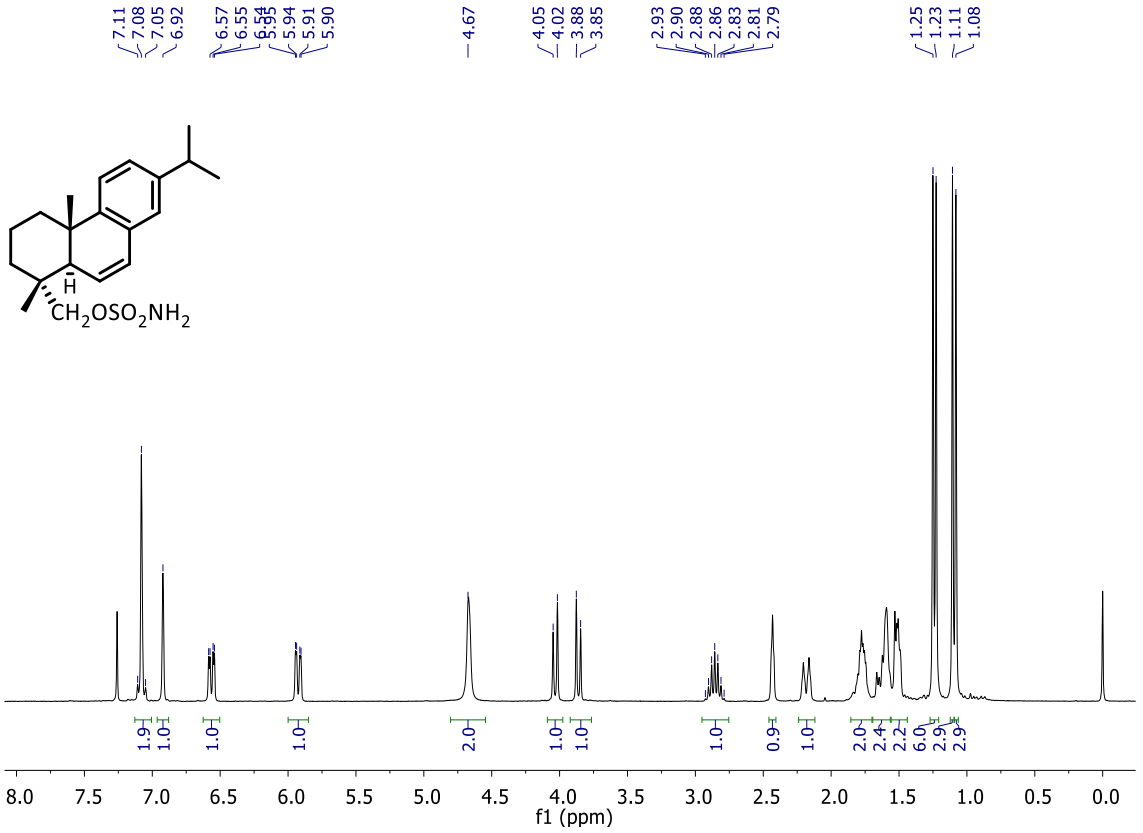


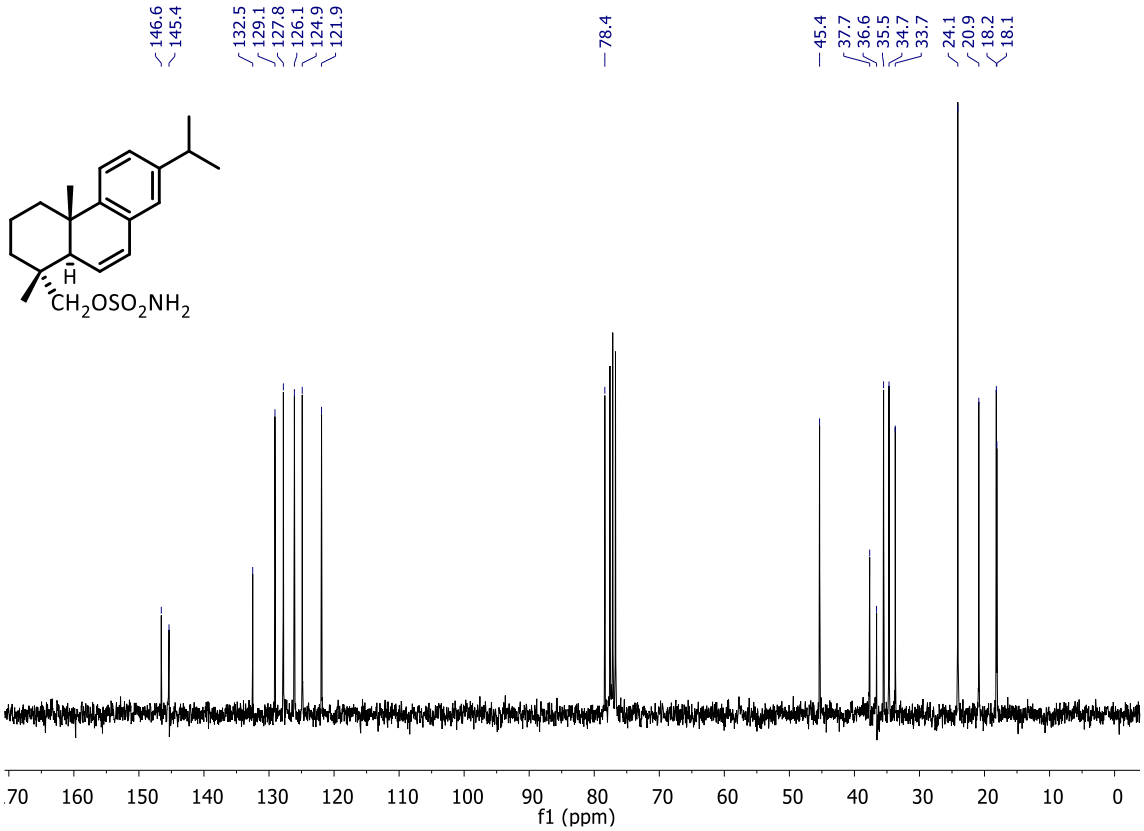
*Compound **I-7***:^{1}H (300 MHz, $CDCl_3$), 13C (75 MHz, $CDCl_3$)



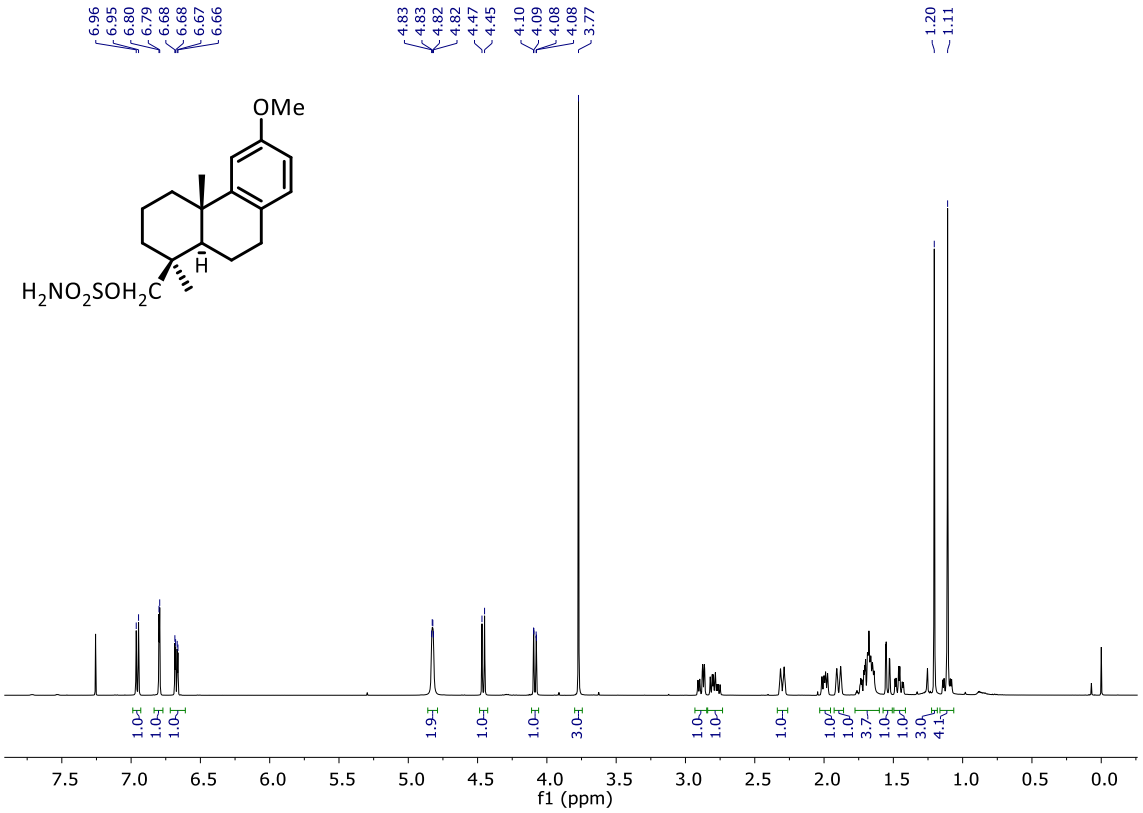


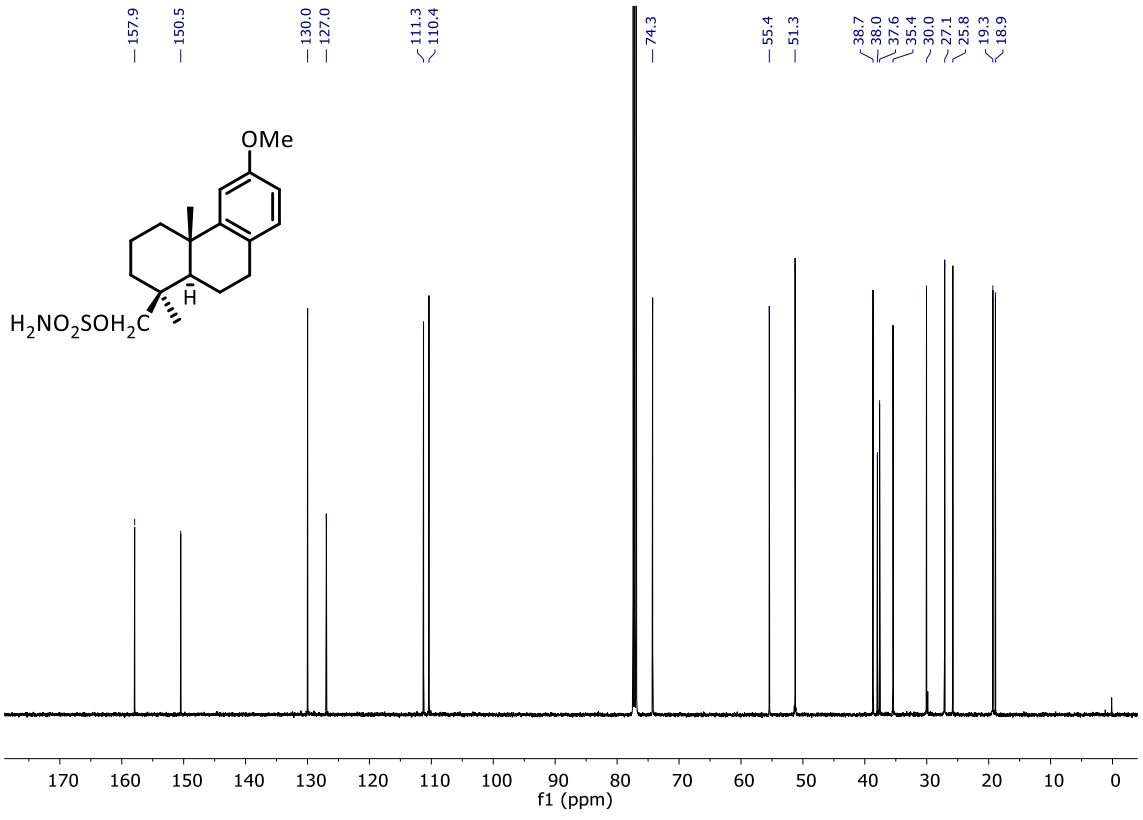
*Compound **24***:^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)



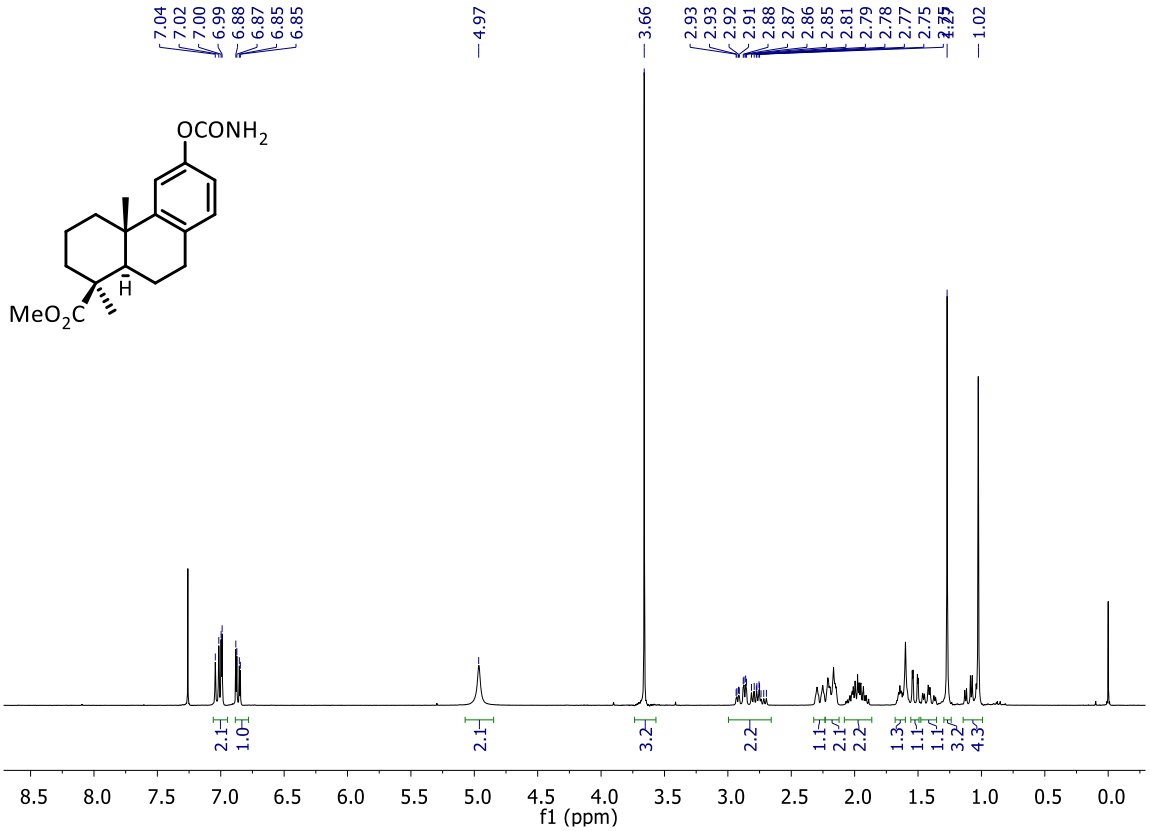


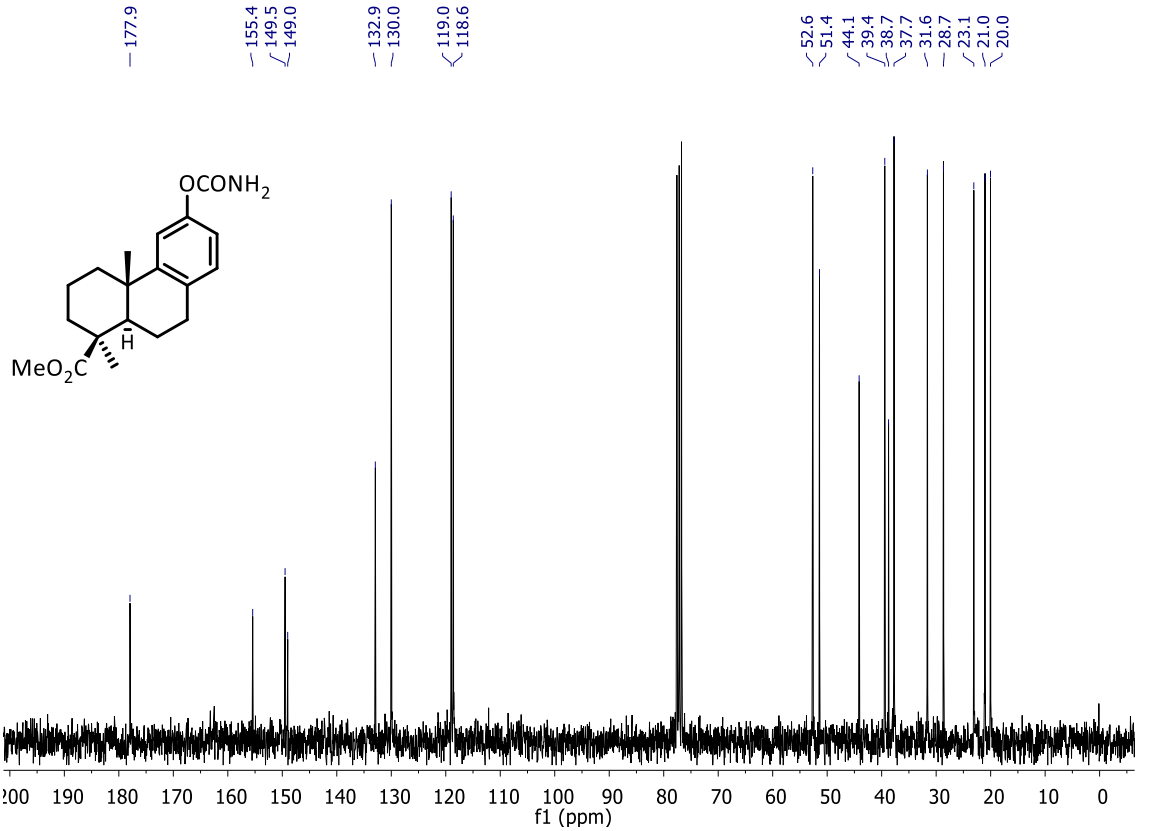
*Compound **26***:^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$)



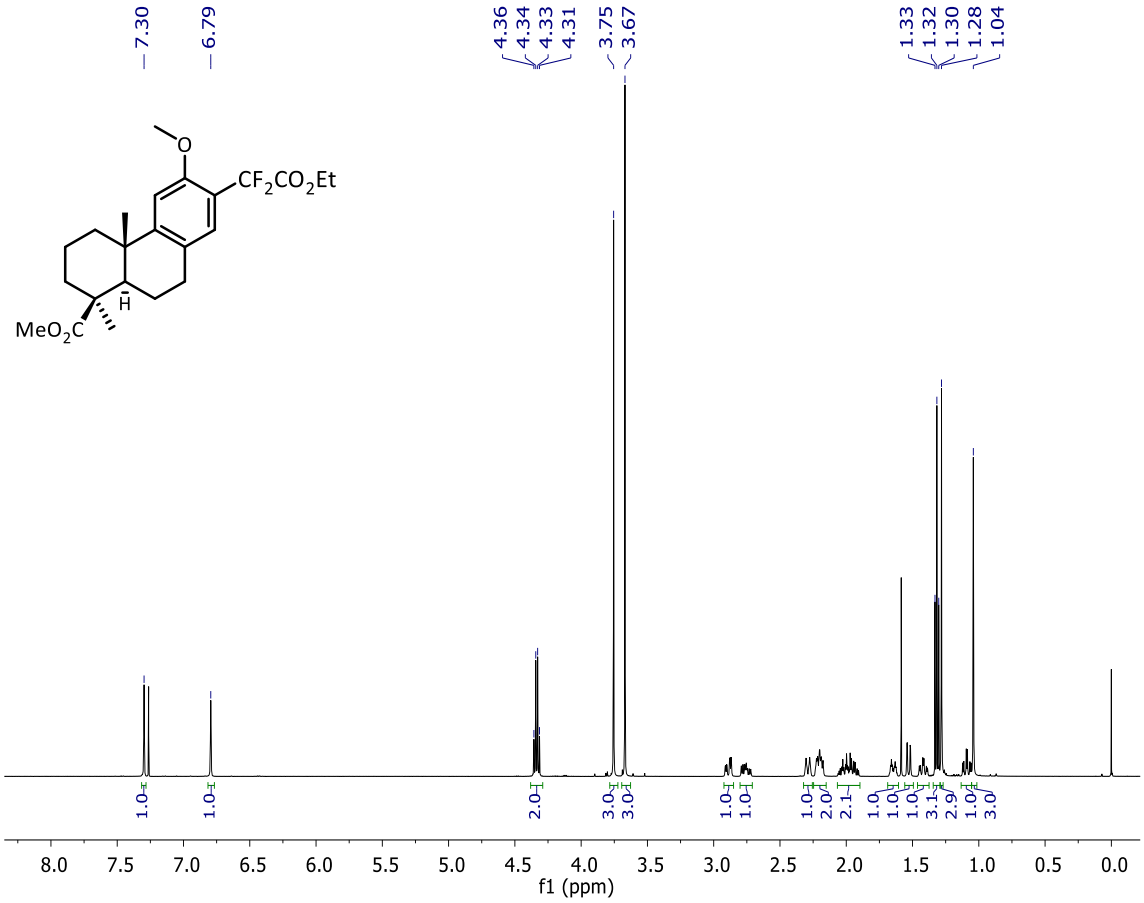


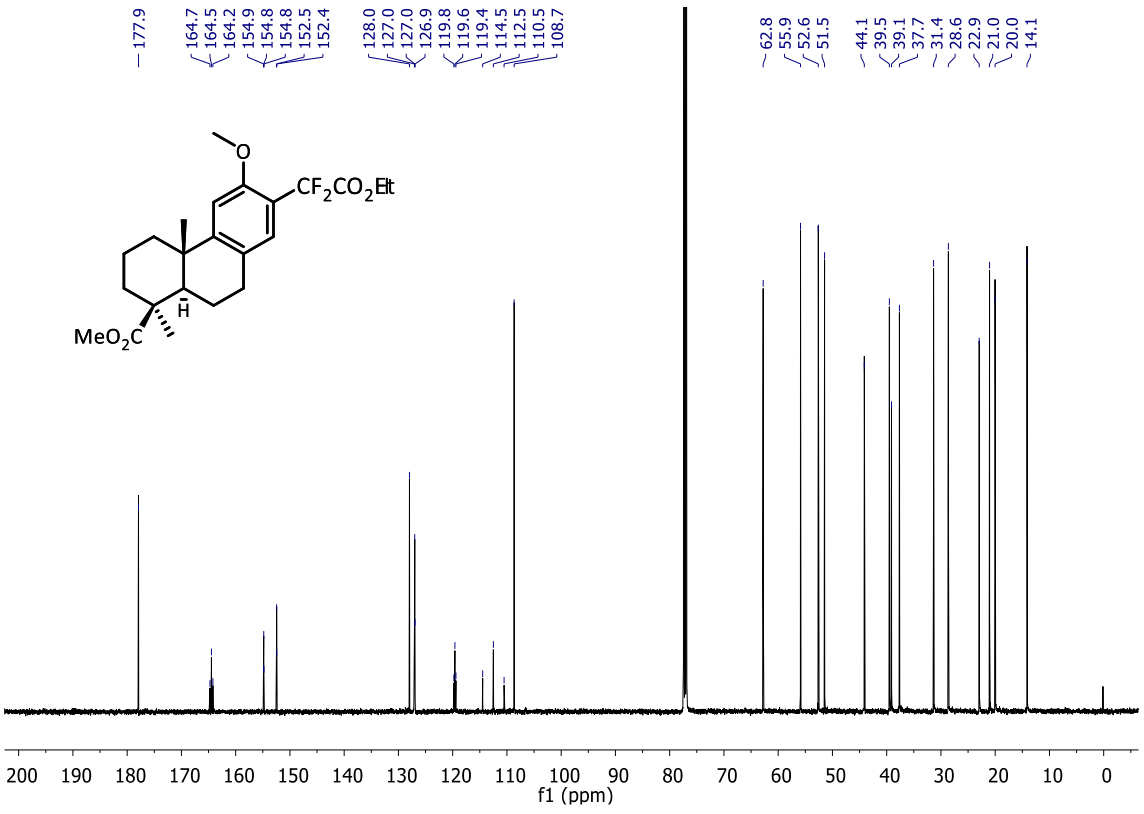
*Compound **I-10***:^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)

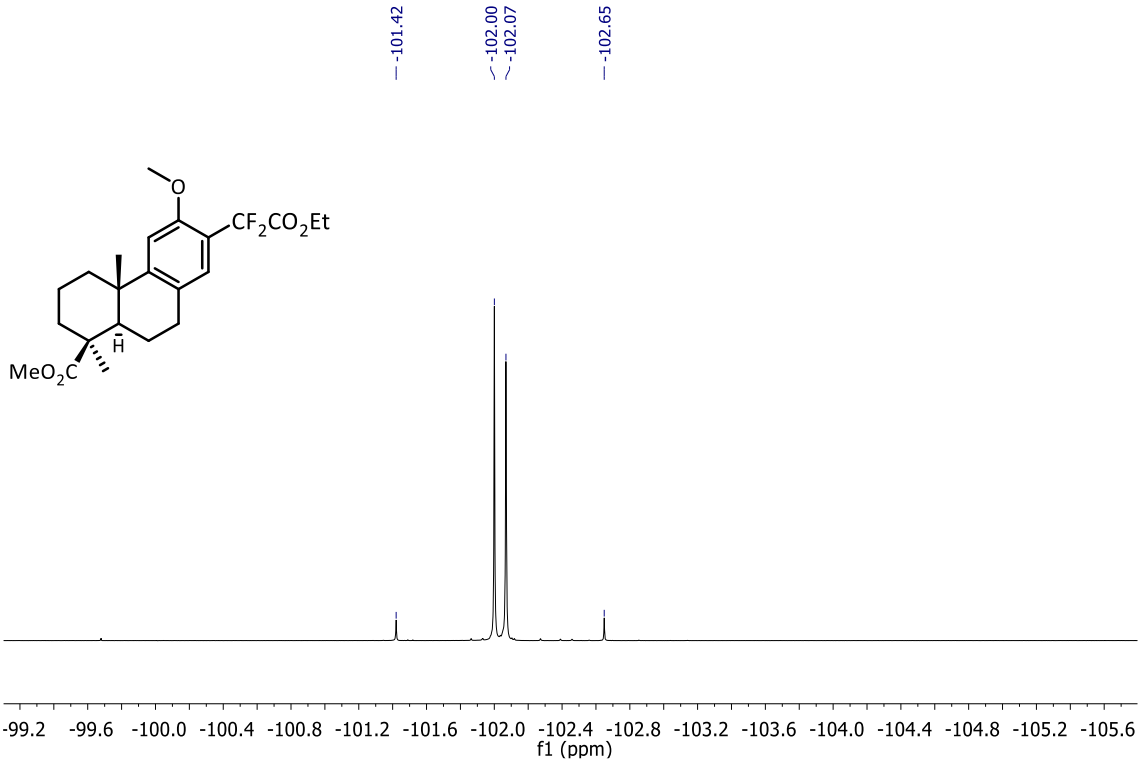




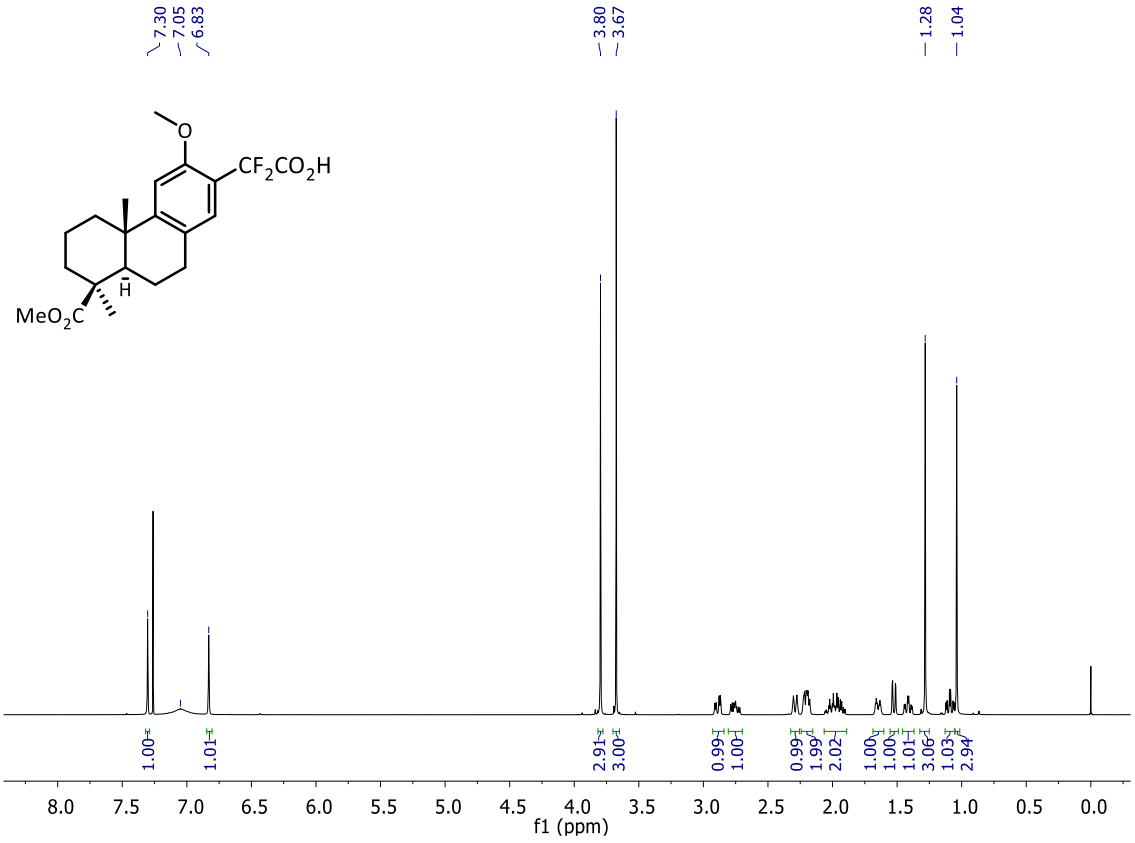
*Compound **I-11**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$), ^{19}F (470 MHz, $CDCl_3$)

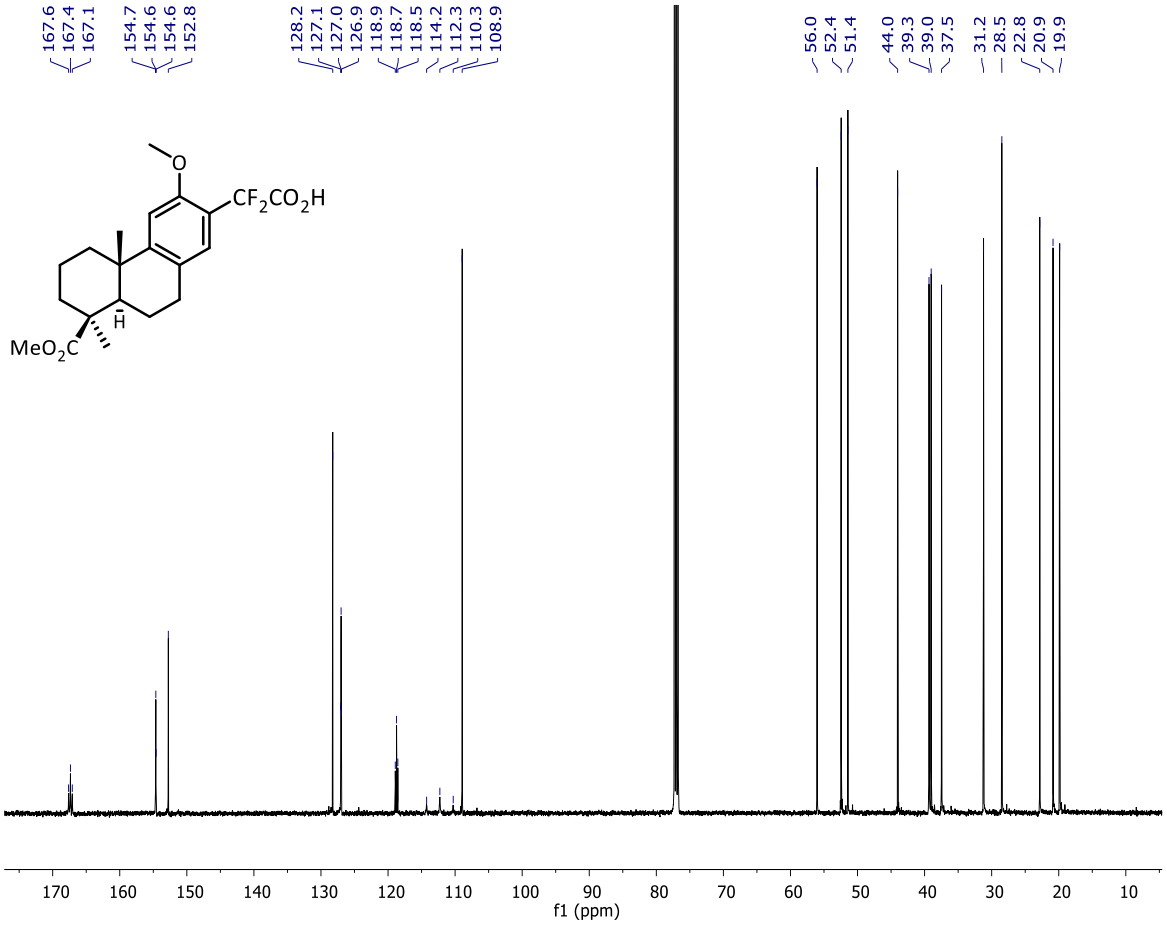


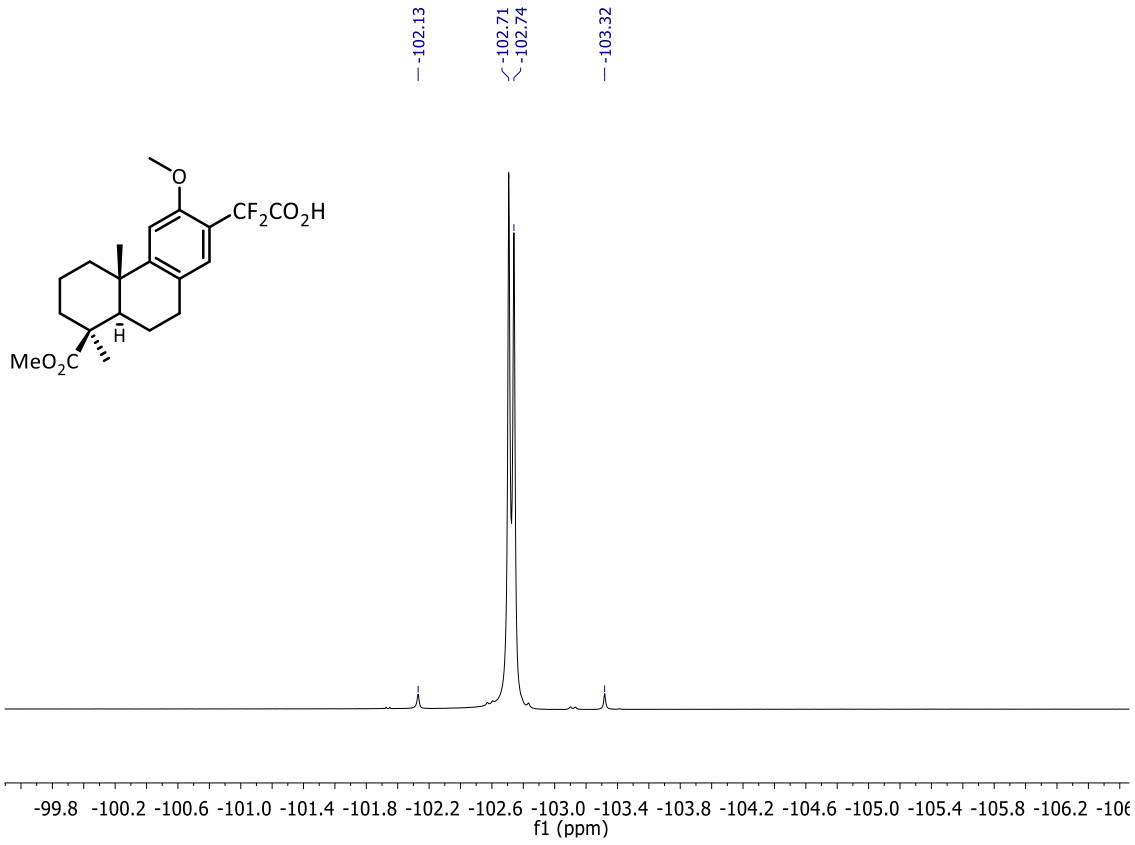




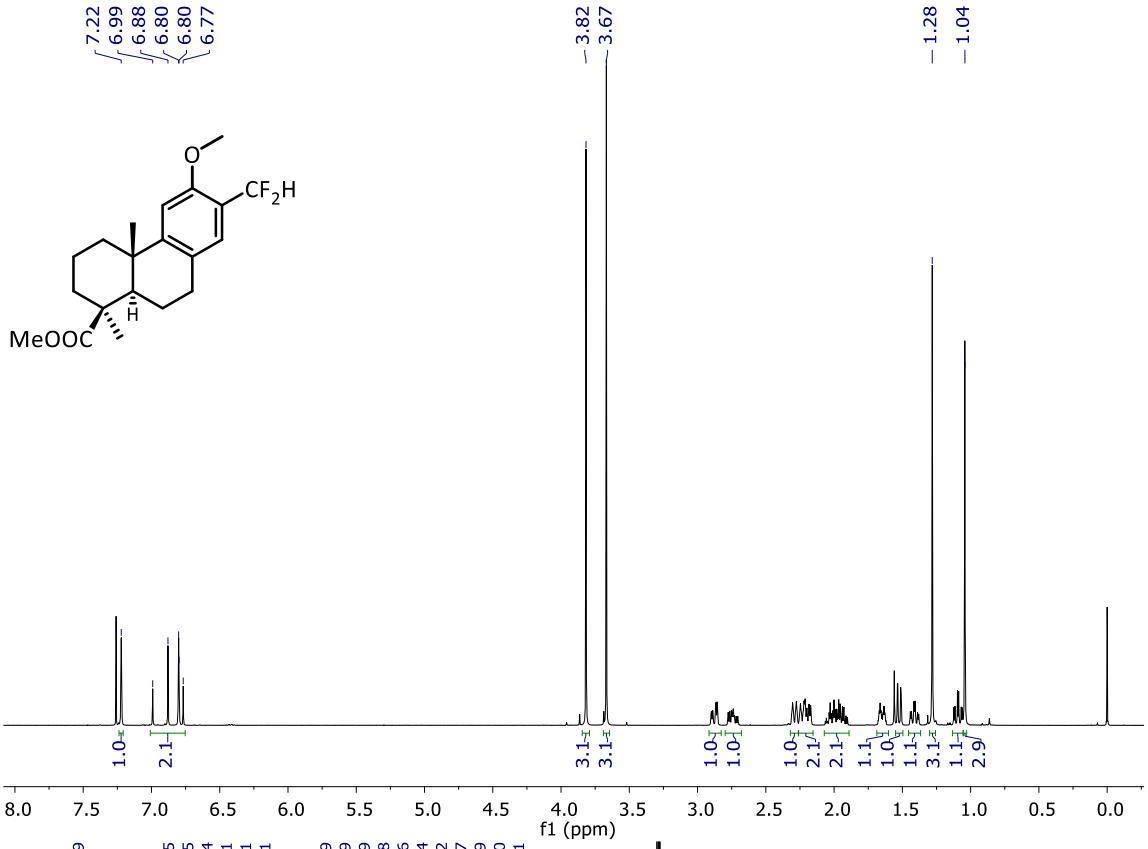
*Compound **19**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$), ^{19}F (470 MHz, $CDCl_3$)

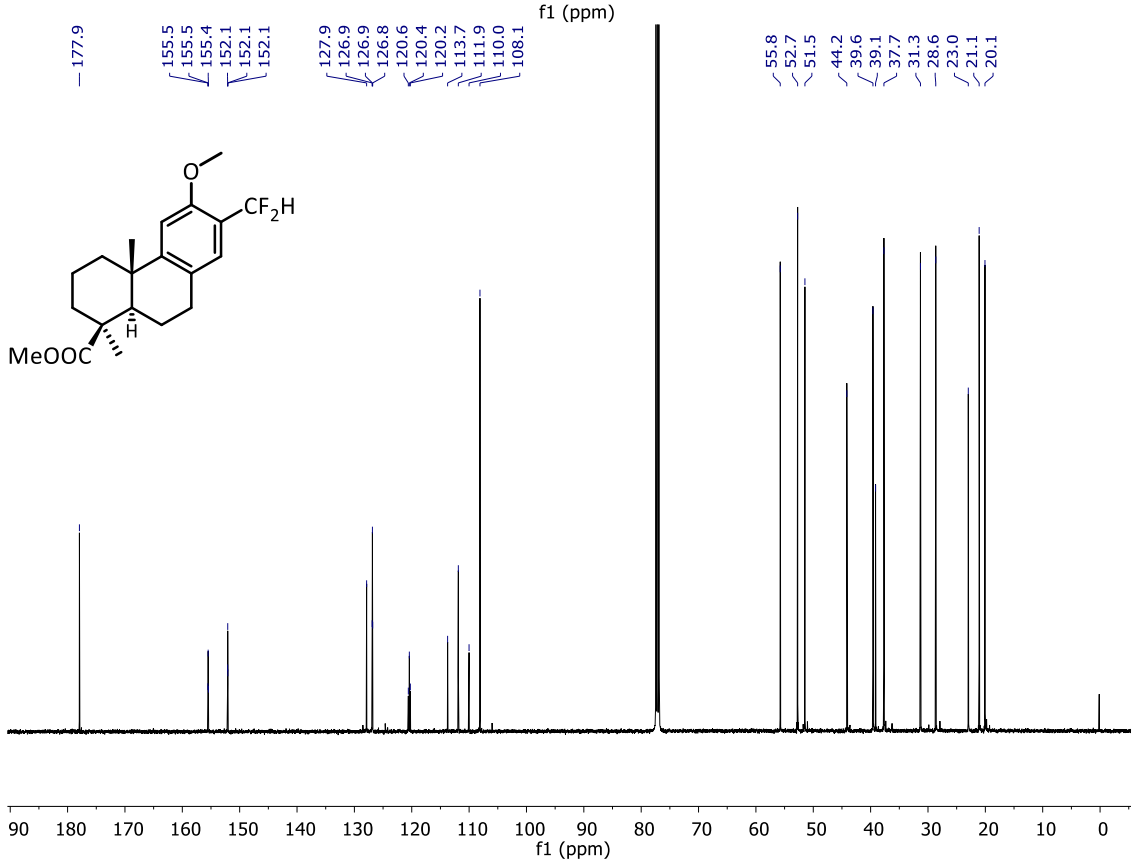


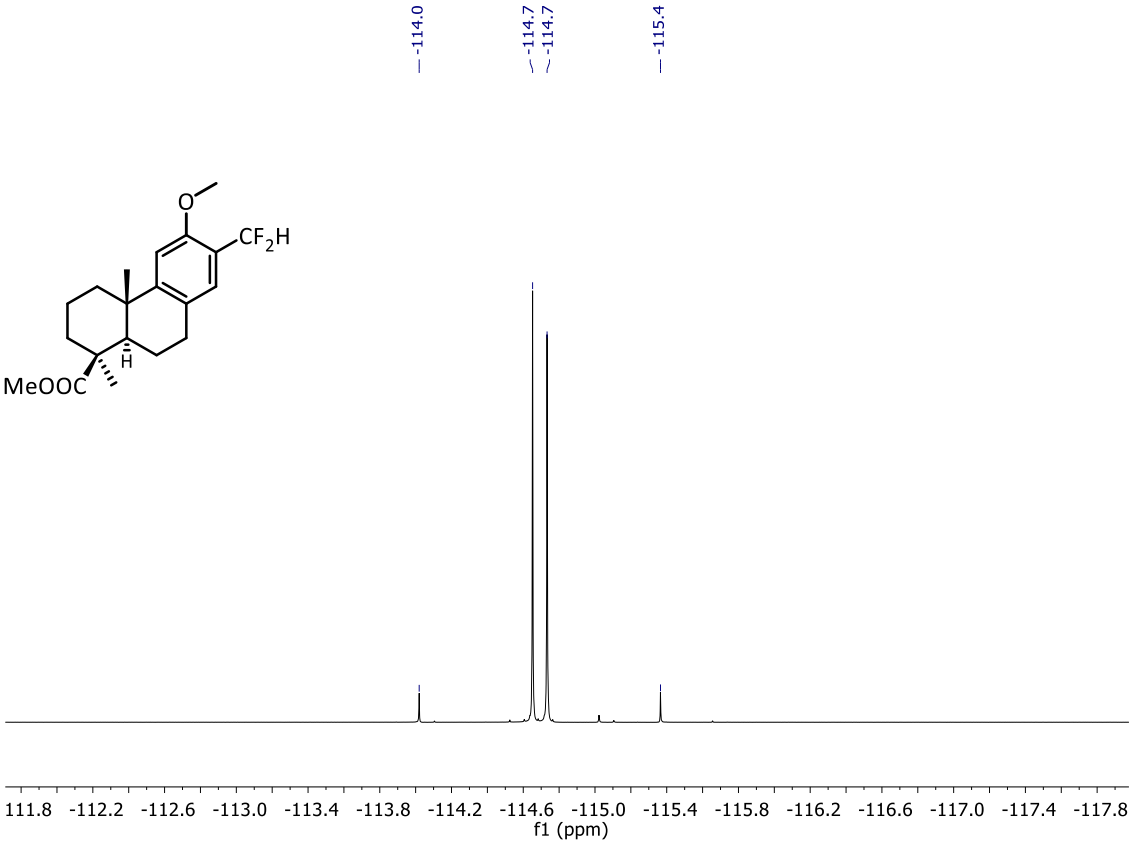

167.6
167.4
167.1
154.7
154.6
154.6
152.8
128.2
127.1
127.0
126.9
118.9
118.7
118.5
114.2
112.3
110.3
108.9
56.0
52.4
51.4
44.0
39.3
39.0
37.5
31.2
28.5
22.8
20.9
19.9
O
CF2CO2H
H
MeO2C
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


-102.13
-102.71
-102.74
-103.32
O
CF2CO2H
H
MeO2C
-99.8 -100.2 -100.6 -101.0 -101.4 -101.8 -102.2 -102.6 -103.0 -103.4 -103.8 -104.2 -104.6 -105.0 -105.4 -105.8 -106.2
f1 (ppm)

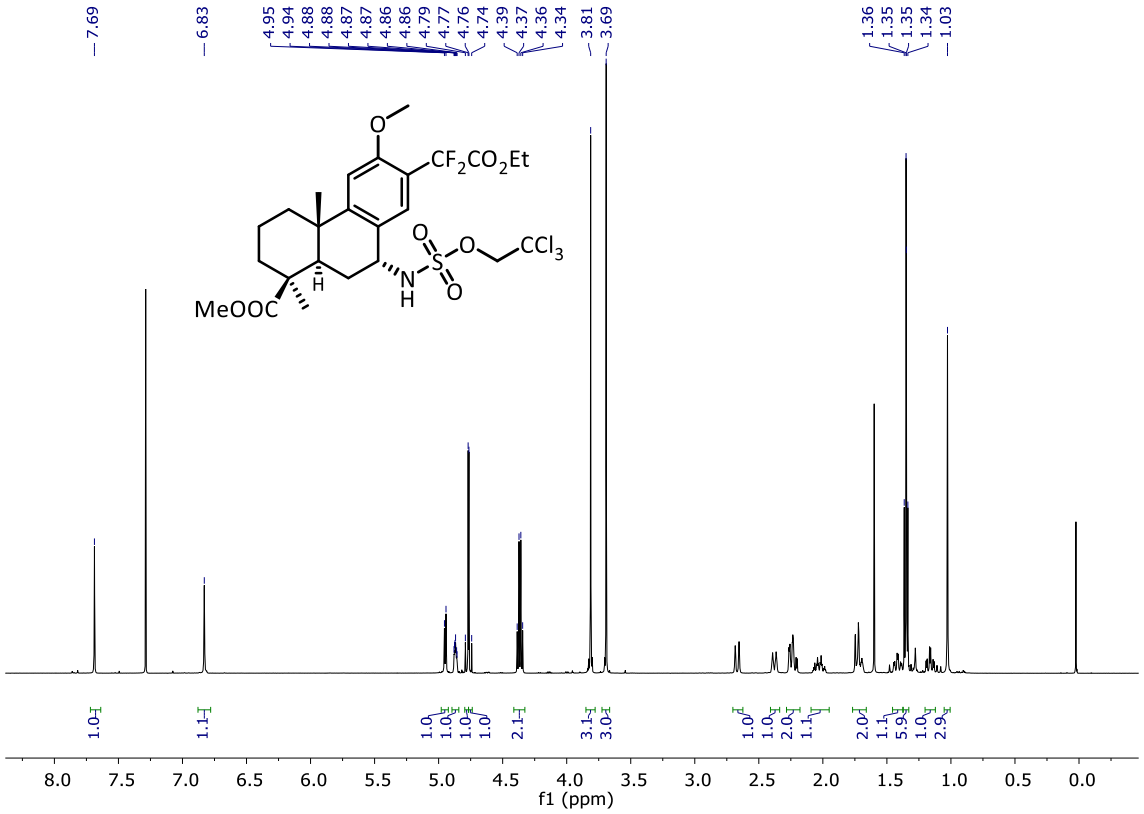
*Compound **20**:* ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$), ^{19}F (470 MHz, $CDCl_3$)

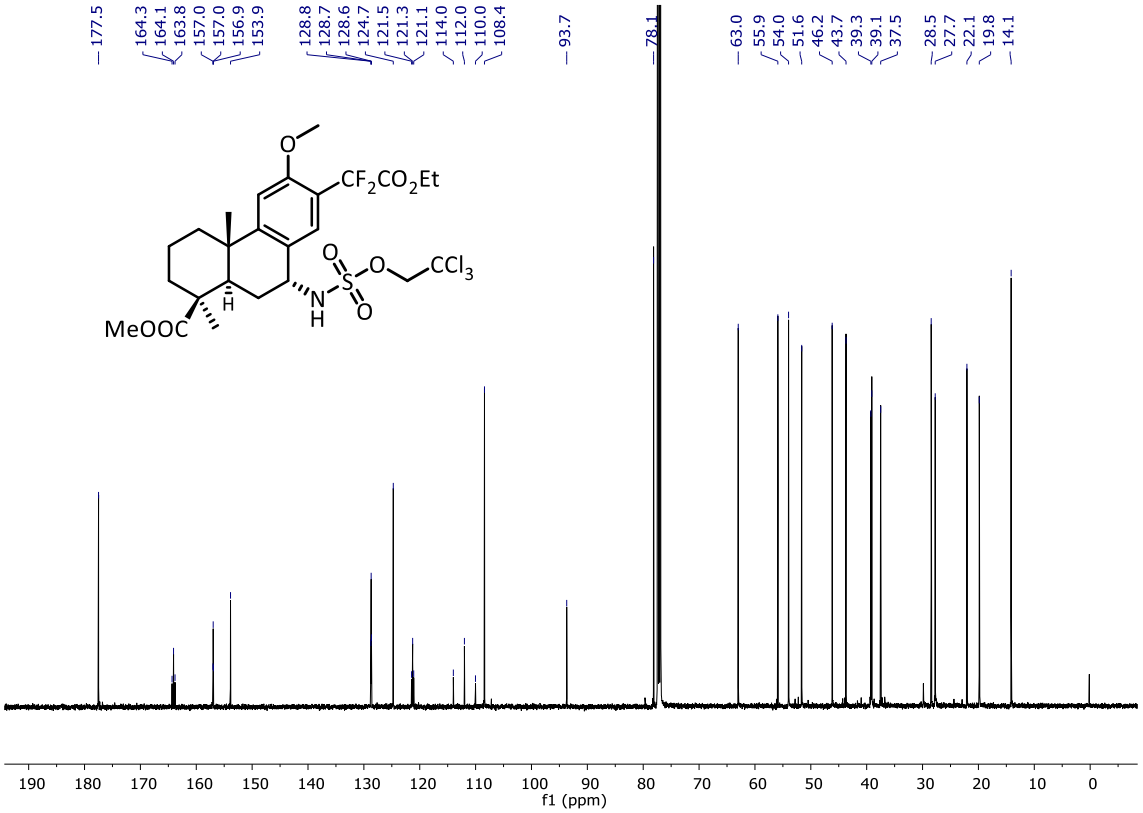


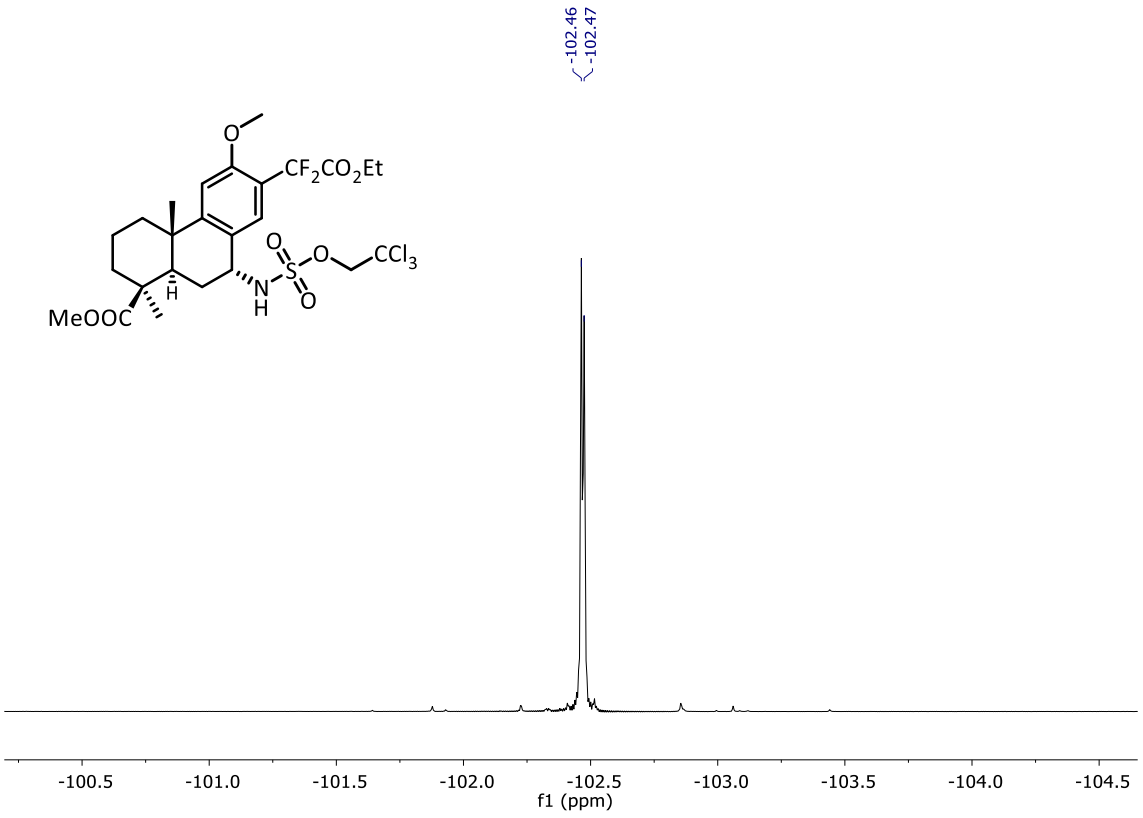




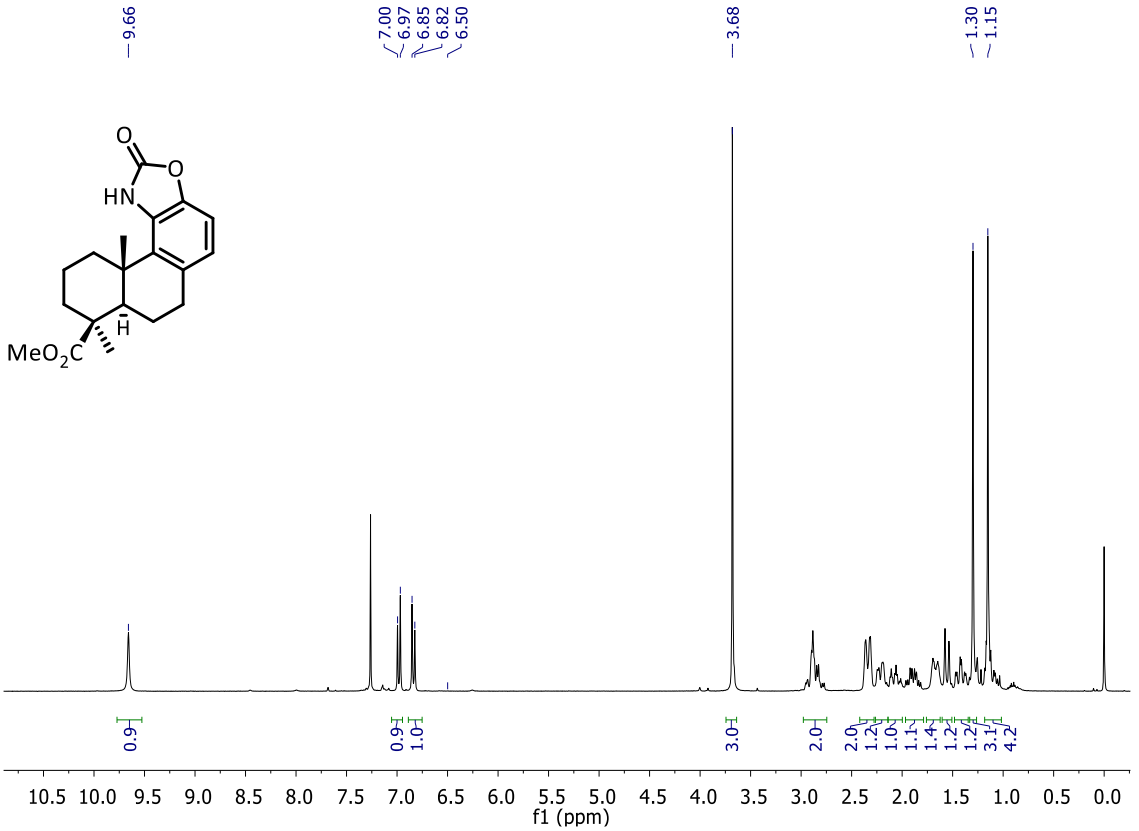
*Compound **I-12***: ^{1}H (500 MHz, $CDCl_3$), ^{13}C (126 MHz, $CDCl_3$), ^{19}F (470 MHz, $CDCl_3$)

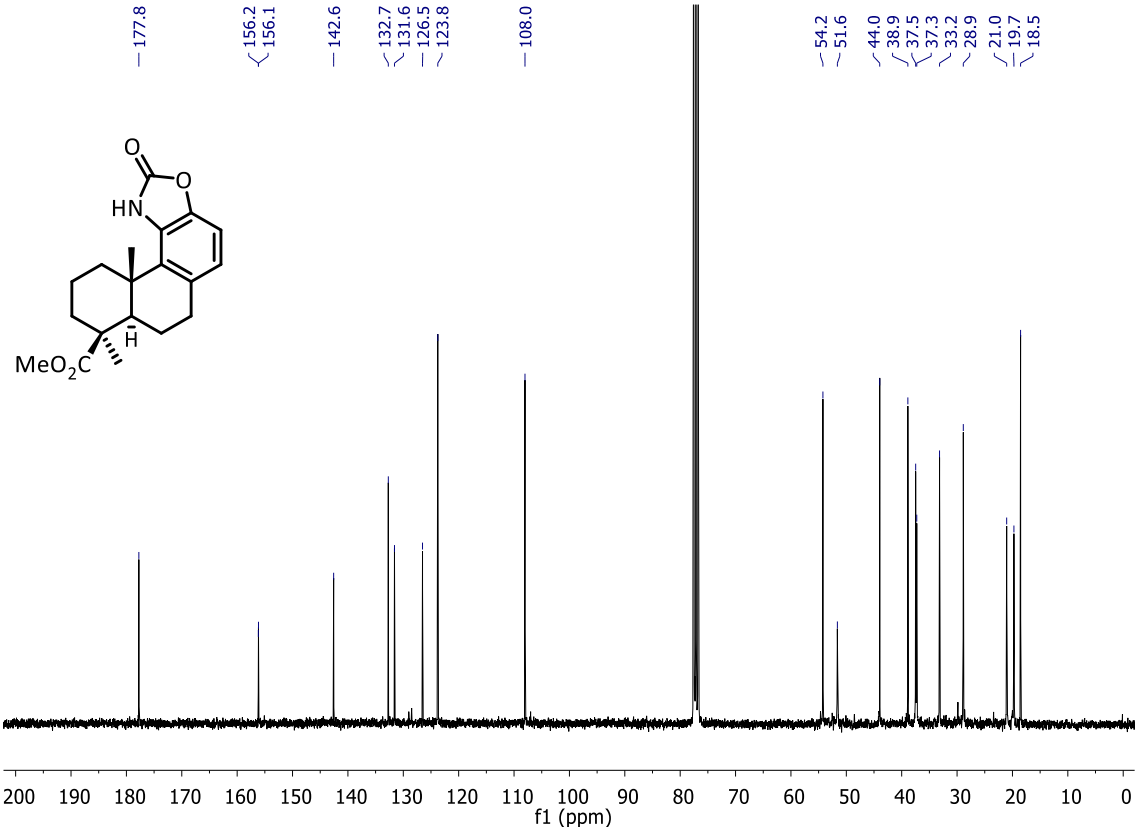



177.5
164.3
164.1
163.8
157.0
157.0
156.9
153.9
128.8
128.7
128.6
124.7
121.5
121.3
121.1
114.0
112.0
110.0
108.4
93.7
78.1
63.0
55.9
54.0
51.6
46.2
43.7
39.3
39.1
37.5
28.5
27.7
22.1
19.8
14.1
O
CF2CO2Et
O
O
S
O
CCl3
N
H
H
MeOOC
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

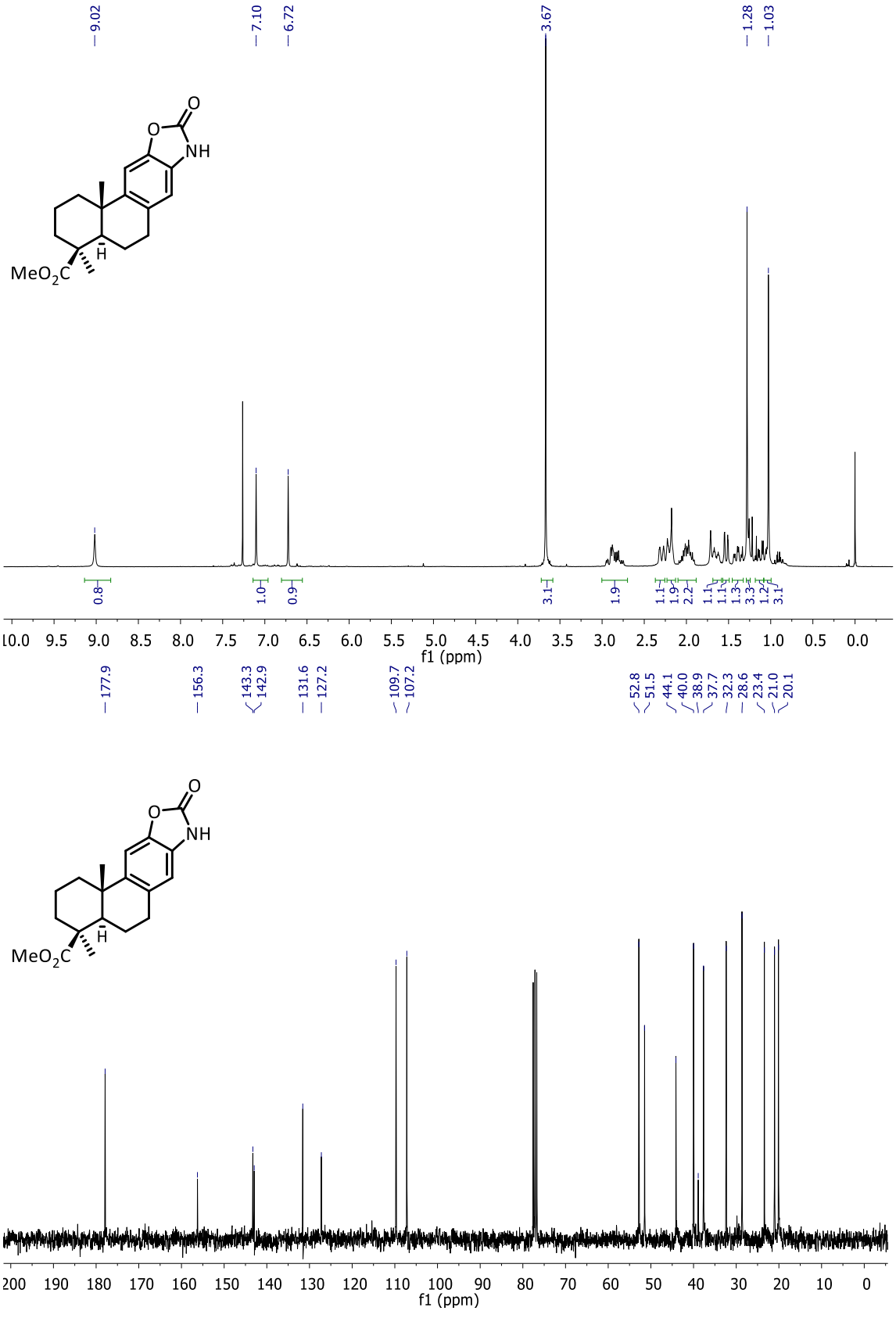

-102.46
-102.47
O
CF2CO2Et
O
O
S
O
CCl3
N
H
H
MeOOC
-100.5 -101.0 -101.5 -102.0 -102.5 -103.0 -103.5 -104.0 -104.5
f1 (ppm)

*Compound **I-13**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)

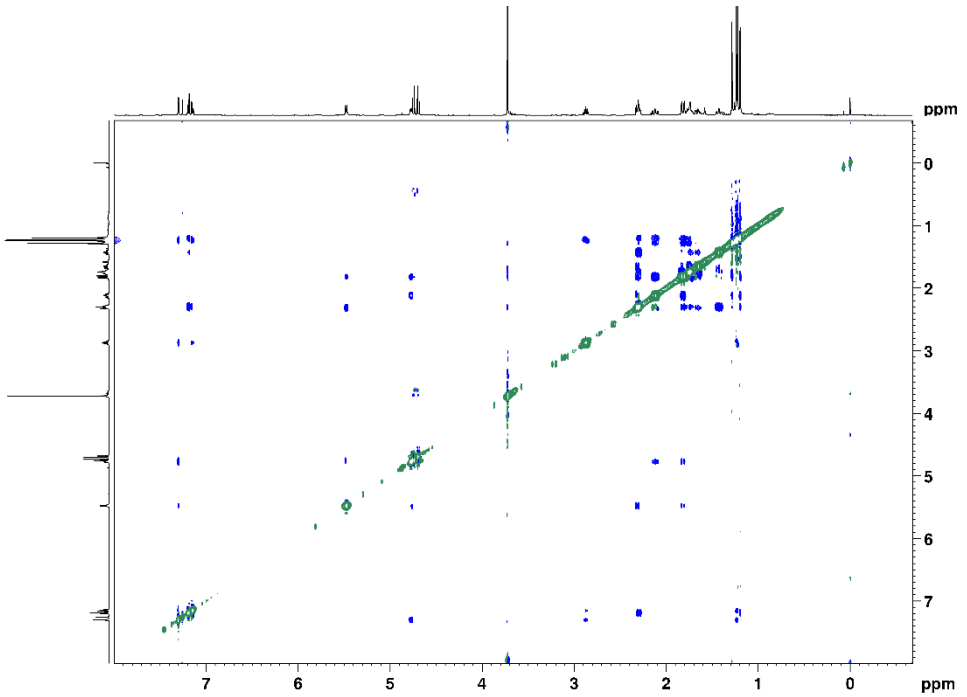


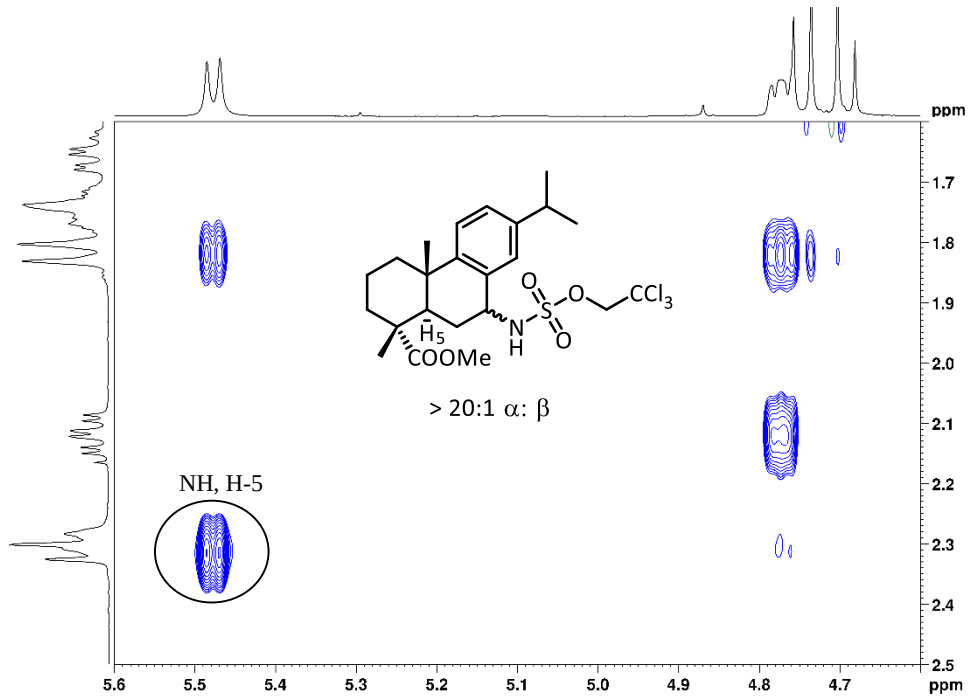


*Compound **I-14**:* ^{1}H (300 MHz, $CDCl_3$), ^{13}C (75 MHz, $CDCl_3$)

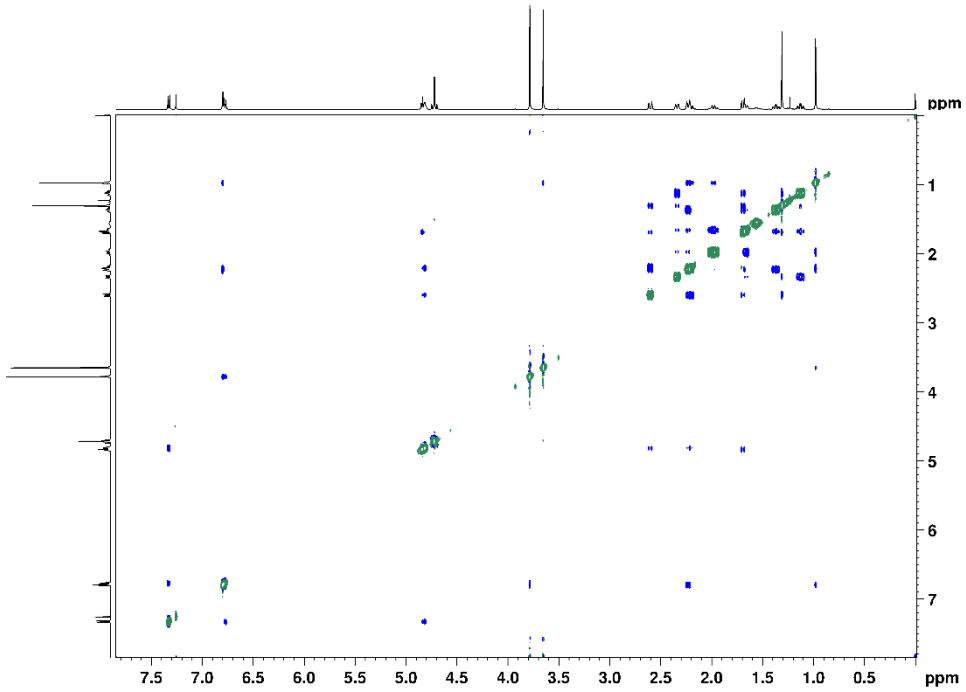


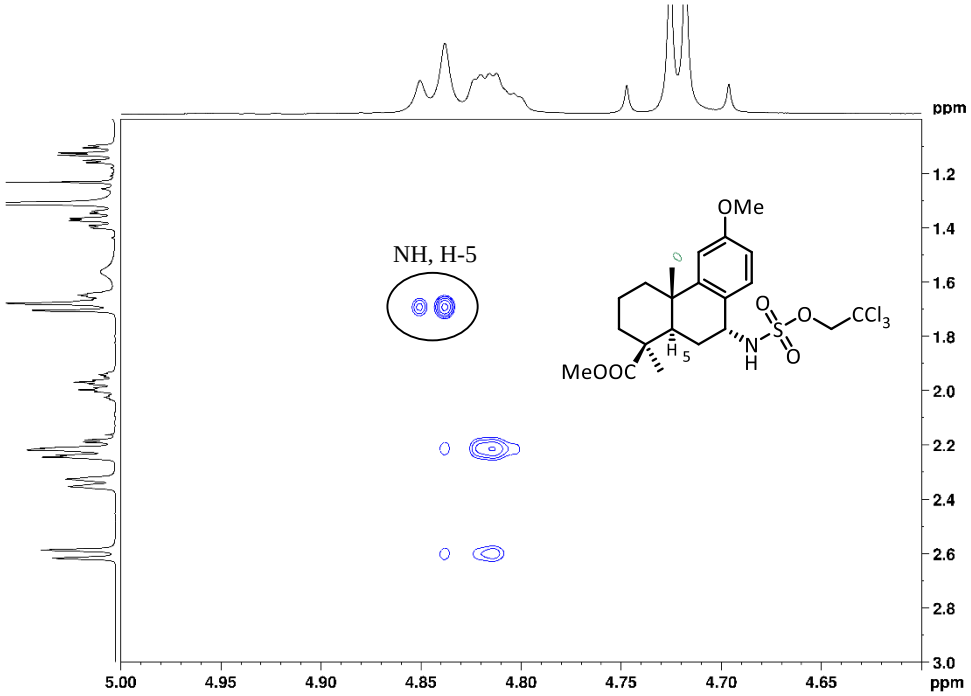
*Compound **8***


ppm
0
1
2
3
4
5
6
7
7
6
5
4
3
2
1
0
ppm

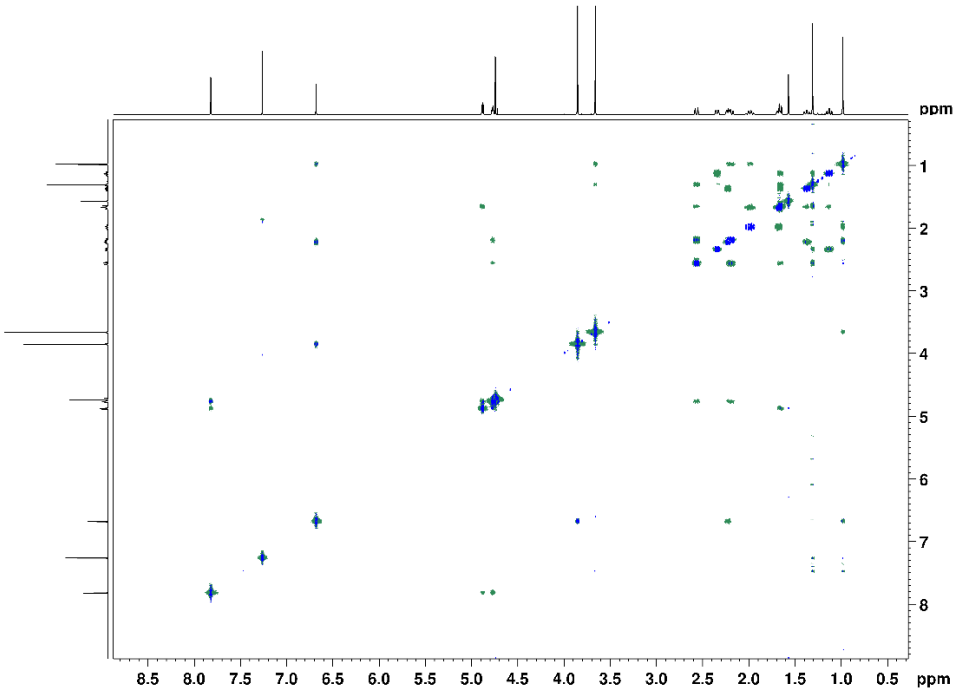

ppm
1.7
1.8
1.9
2.0
2.1
2.2
2.3
2.4
2.5
5.6
5.5
5.4
5.3
5.2
5.1
5.0
4.9
4.8
4.7
ppm
NH, H-5
O
O
CCl3
S
O
N
H
H5
COOMe
> 20:1 α: β

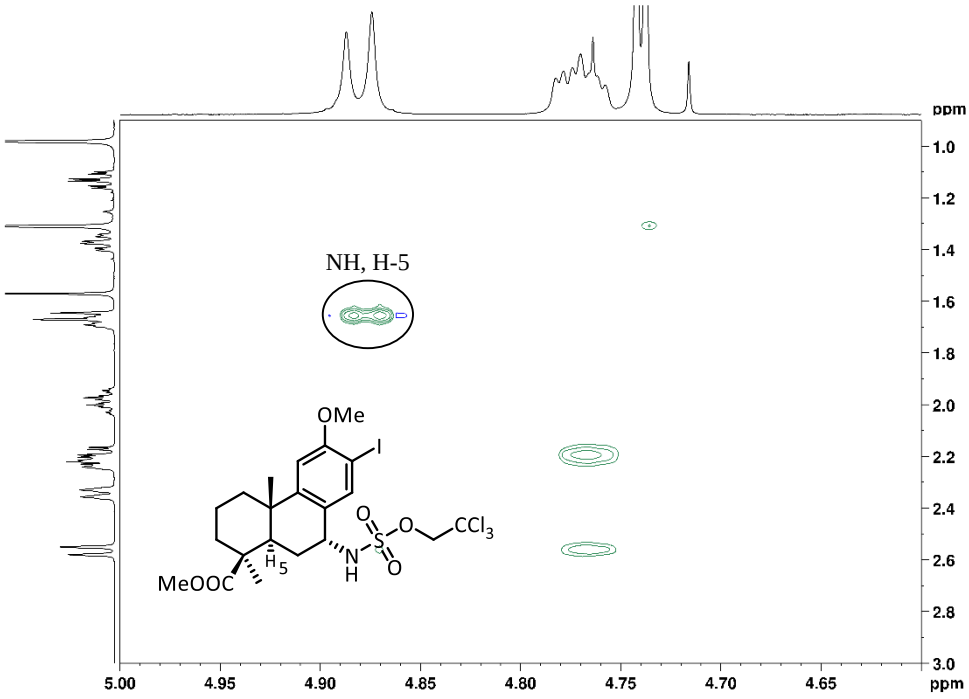
*Compound **13***


ppm
1
2
3
4
5
6
7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

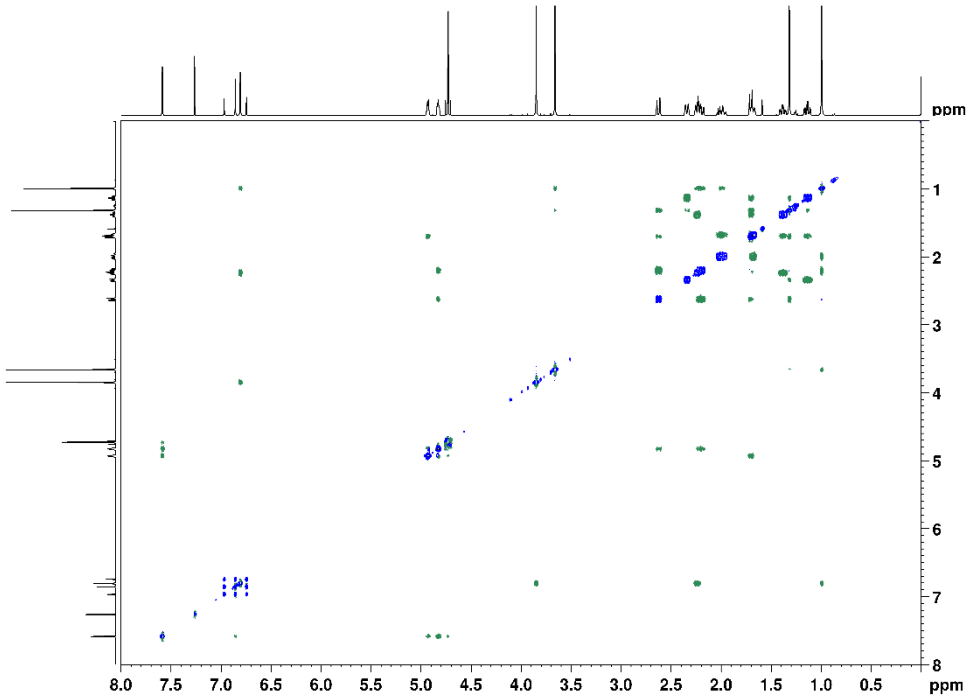

ppm
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
5.00
4.95
4.90
4.85
4.80
4.75
4.70
4.65
ppm
NH, H-5
OMe
MeOOC
H 5
N
H
O
S
O
O
CCl3

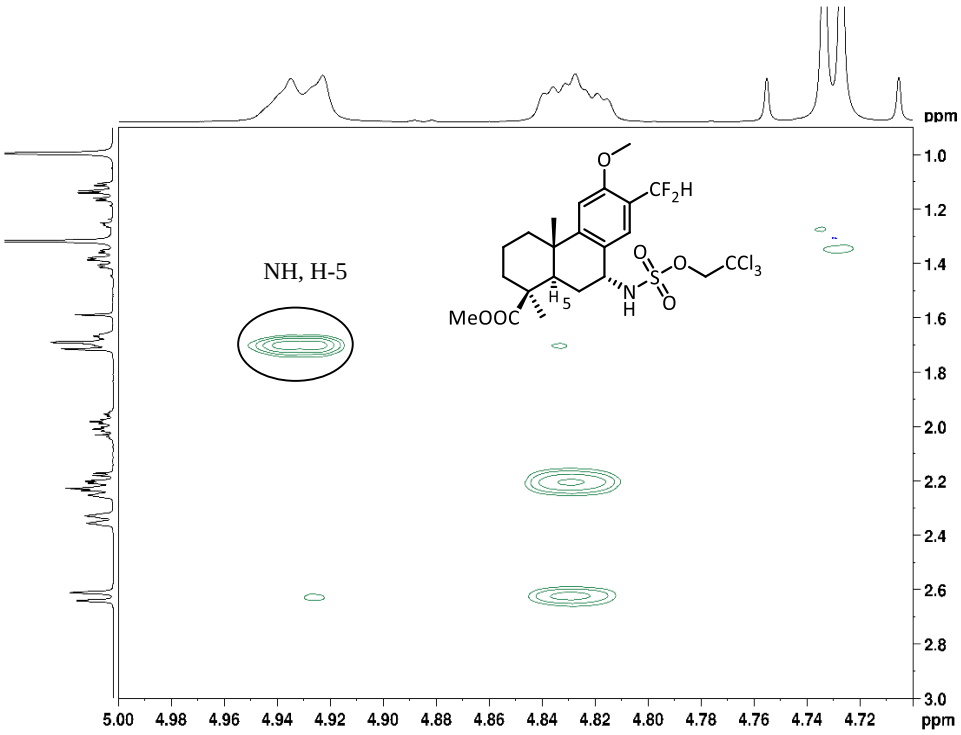
*Compound **14***


ppm
1
2
3
4
5
6
7
8
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

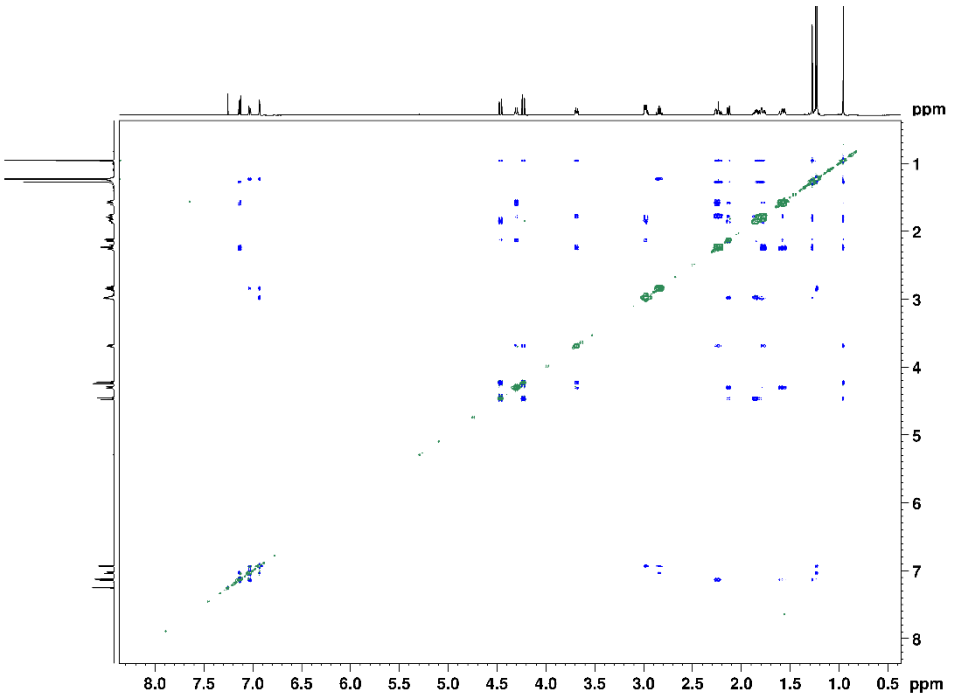

ppm
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
NH, H-5
OMe
I
O
O
CCl3
S
O
N
H
H5
MeOOC
5.00 4.95 4.90 4.85 4.80 4.75 4.70 4.65 ppm

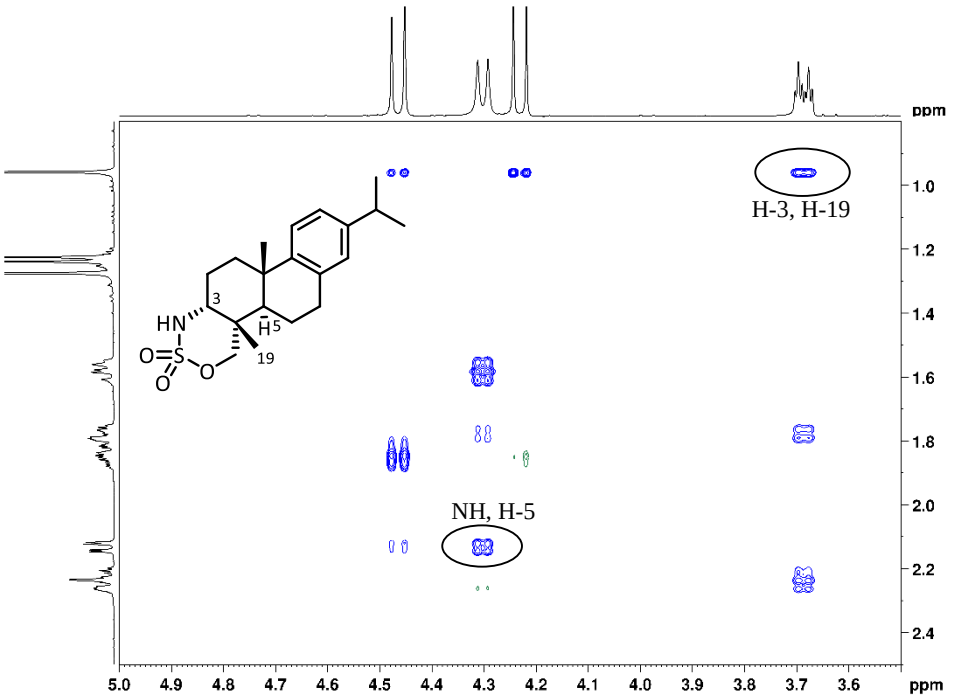
*Compound **21***


ppm
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

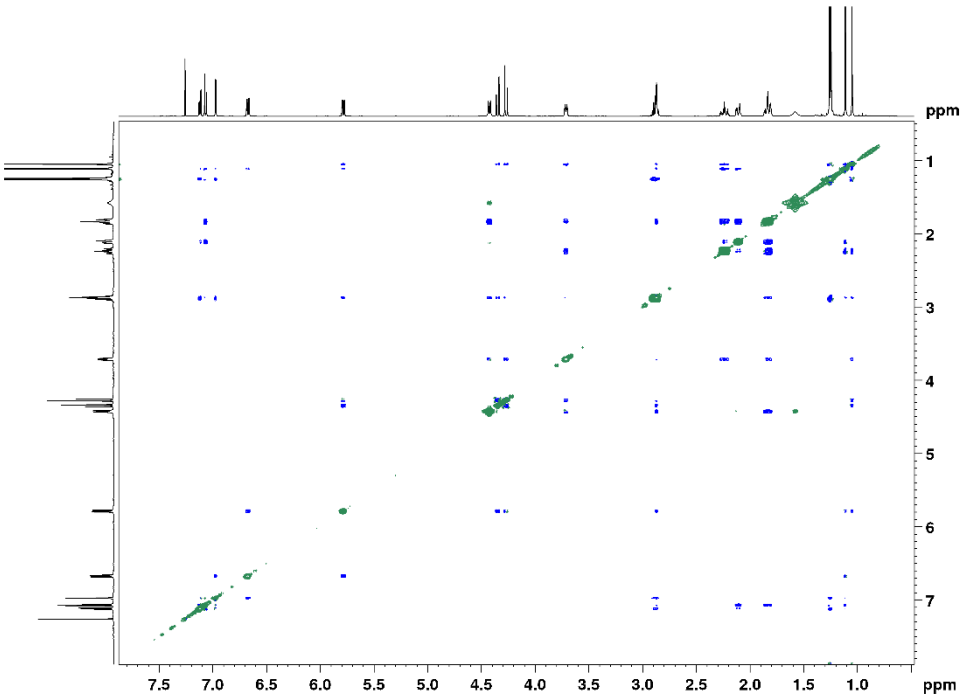

NH, H-5
O
CF2H
O
S
O
O
CCl3
N
H
H5
MeOOC
ppm
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
5.00 4.98 4.96 4.94 4.92 4.90 4.88 4.86 4.84 4.82 4.80 4.78 4.76 4.74 4.72 ppm

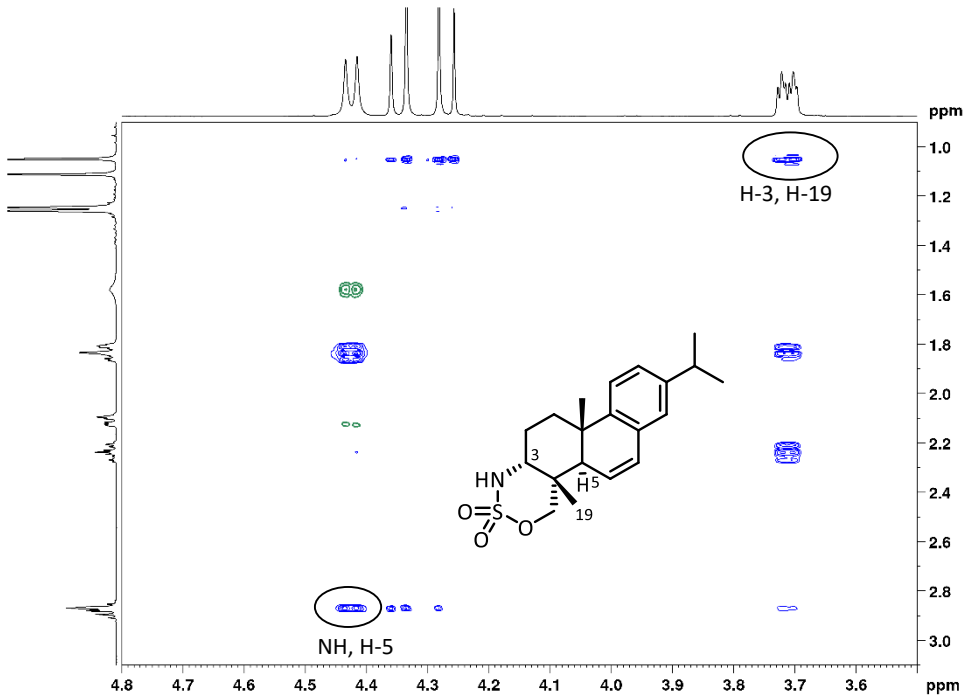
*Compound **23***


ppm
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

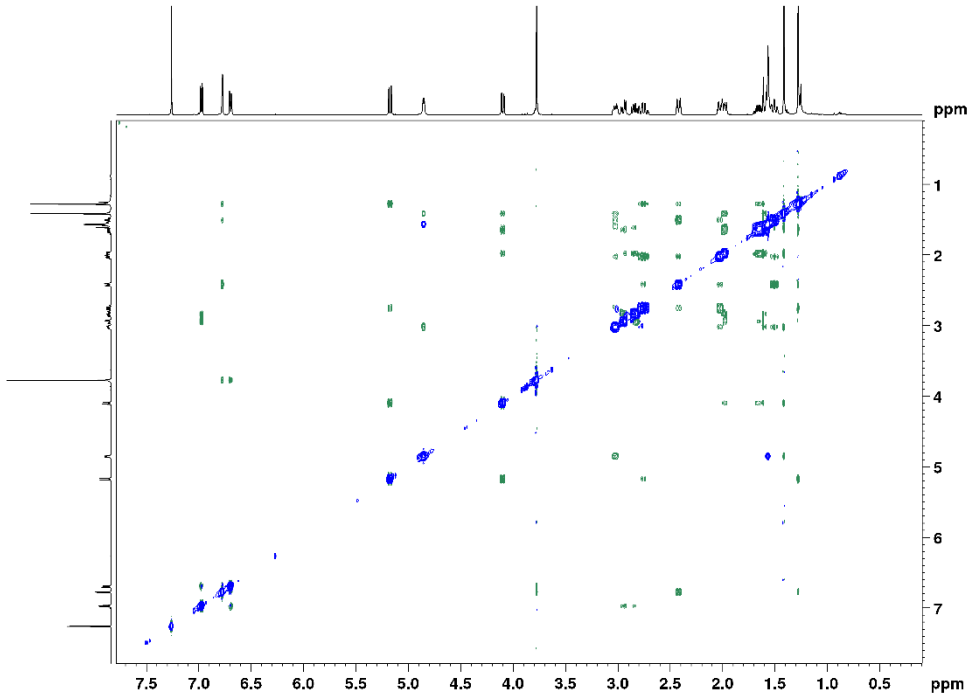

ppm
H-3, H-19
NH, H-5
HN
O
S
O
O
3
H
5
19
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 ppm

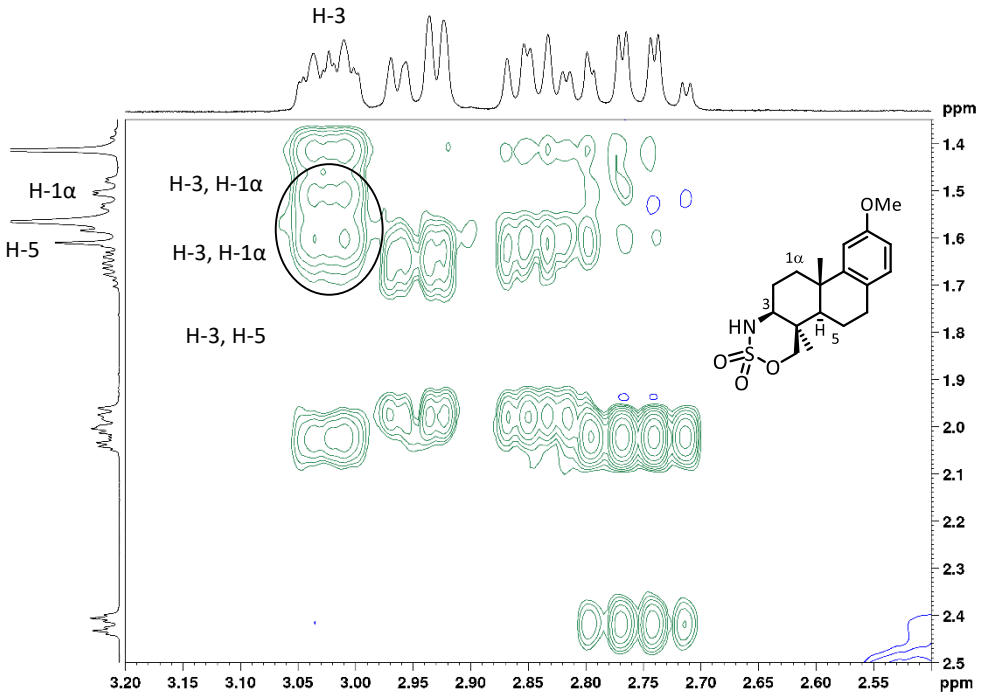
*Compound **25***


ppm
1
2
3
4
5
6
7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

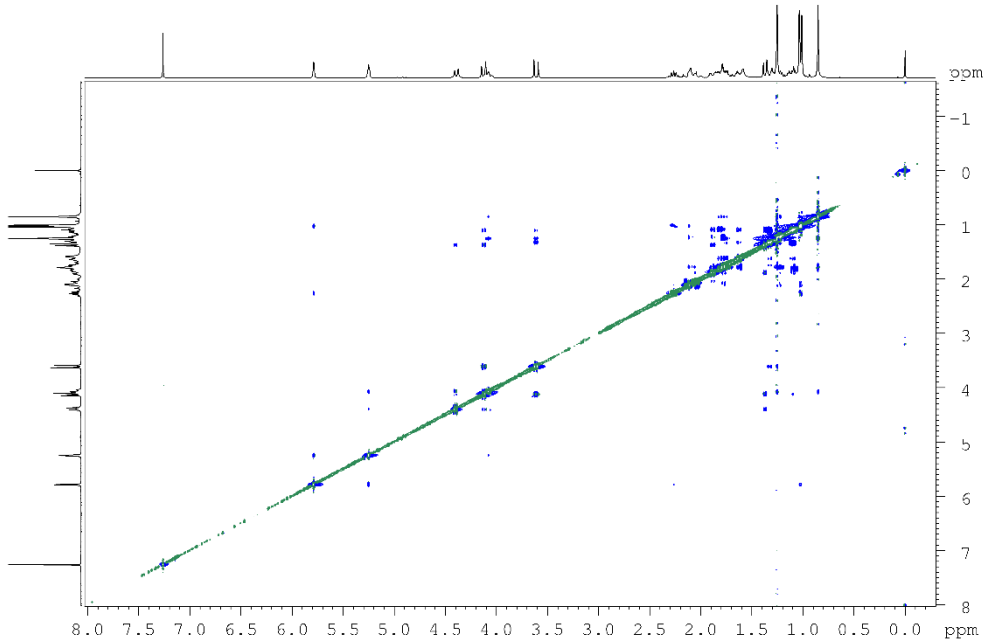

ppm
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
ppm
H-3, H-19
NH, H-5
HN
O
S
O
O
3
H
5
19

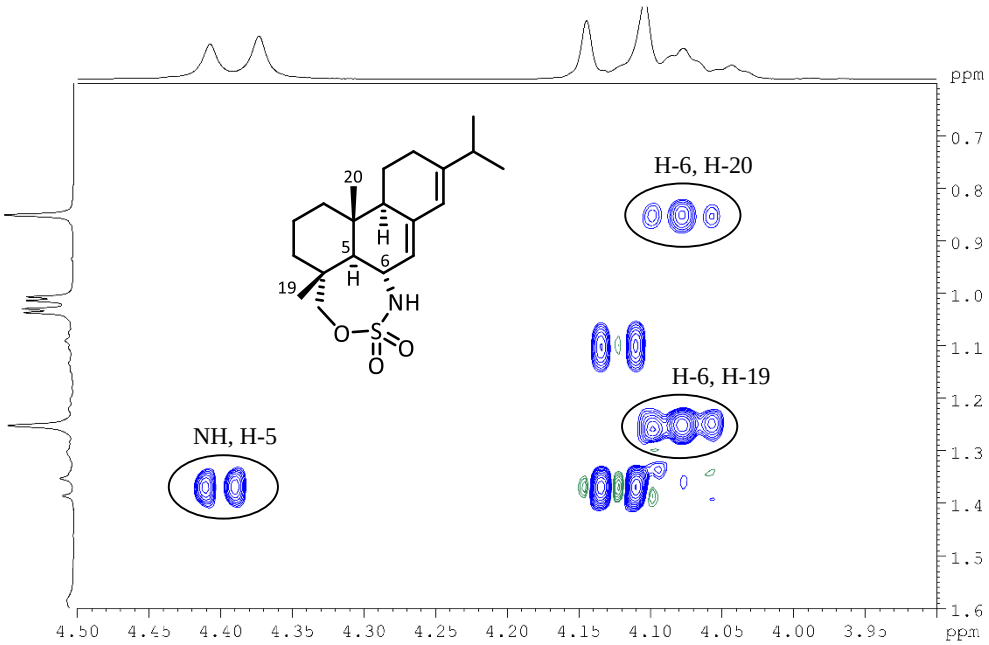
*Compound **27***


ppm
1
2
3
4
5
6
7
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


H-3
H-1α
H-5
H-3, H-1α
H-3, H-1α
H-3, H-5
OMe
1α
3
HN
H
5
O
S
O
O
ppm
1.4
1.5
1.6
1.7
1.8
1.9
2.0
2.1
2.2
2.3
2.4
2.5
3.20
3.15
3.10
3.05
3.00
2.95
2.90
2.85
2.80
2.75
2.70
2.65
2.60
2.55
ppm

*Compound **29***


ppm
-1
0
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm


ppm
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
1.5
1.6
4.50 4.45 4.40 4.35 4.30 4.25 4.20 4.15 4.10 4.05 4.00 3.95 ppm
20
H
5
H
6
19
NH
O
S
O
O
H-6, H-20
H-6, H-19
NH, H-5