

Domino alkylation/oxa-Michael of 1,3-cyclohexanediones: Steering the C/O-chemoselectivity to reach tetrahydrobenzofuranones

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General Information

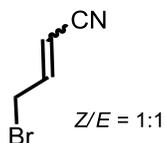
Water and 2,2,2-trifluoroethanol (TFE) used for the preparation of tetrahydrobenzofuran-4-one were degasified by sparging of N₂ during 2 h. Otherwise noted, solvents were technical grade and used as they were. Substituted 1,3-cyclohexanediones (**1** and **11**) were prepared according to Ishikawa and Saito.¹ 1,3-Cyclohexanedione, dimedone, methyl 4-bromocrotonate and all other reagents were purchased from Aldrich/Alfa Aesar and used without purification. *E/Z*-4-Bromocrotonitrile (**B**) and *E/Z*-4-bromopent-2-enitrile (**C**) are known compounds.² Hydrogenations on Pd/C (10% on charcoal) were conducted in Schlenk system or two neck flask. All reactions were monitored by ¹H NMR or TLC (visualization with UV and/or by KMnO₄). Chromatography refers to column chromatography on silica gel (100-200 mesh) unless otherwise noted. Neutral aluminium oxide was purchased from Aldrich (activated, Brockmann I). NMR spectra were recorded at 300 MHz (¹H) and 75 MHz (¹³C) and chemical shifts are reported in ppm. The residual signal of the undeuterated solvent was used as the internal standard. Melting points were determined using a Kopfler hot stage apparatus and are uncorrected. Mass spectra were recorded by the University of Rouen Spectrometry Laboratory using electron impact (EI), electrospray (ESI) or chemical (CI) ionization techniques. IR data was obtained on a PerkinElmer Spectrum 100 FT-IR-spectrometer with only major peaks being reported.

¹ T. Ishikawa, R. Kadoya, M. Arai, H. Takahashi, Y. Kaisi, T. Mizuta, K. Yoshikai and S. Saito, *J. Org. Chem.*, 2001, **66**, 8000.

² (a) A. Padwa, S. S. Murphree, Z. Ni and S. H. Watterson, *J. Org. Chem.*, 1996, **61**, 3829; (b) E. D. Matveeva, T. A. Podrugina, E. V. Tishkovskaya and N. S. Zefirov, *Mendeleev Commun.*, 2003, **13**, 260.

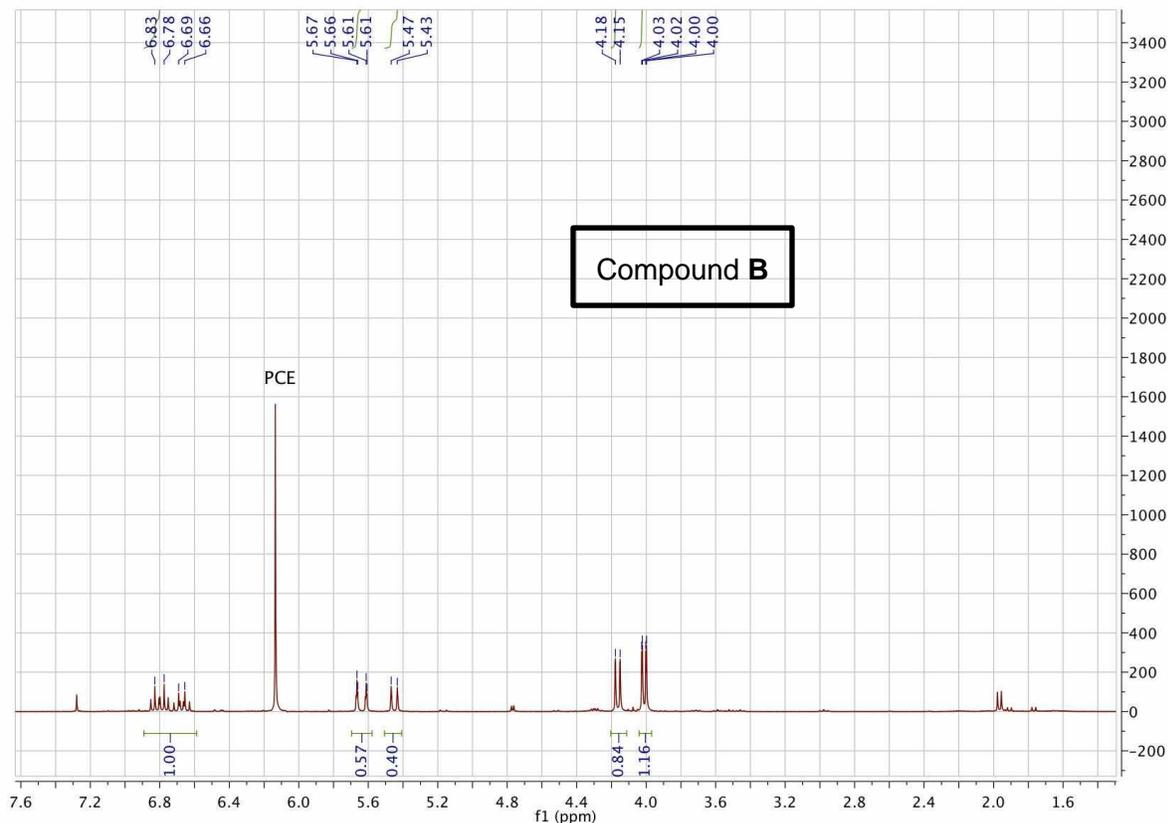
E/Z-4-bromocrotonitrile (**B**)

CAS Registry Number: 37590-23-1

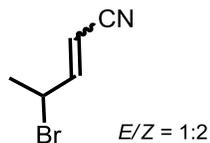


To a solution of crotonitrile (10.0 g, 0.149 mol) in *n*BuCl (149 mL) was added NBS (39.5 g, 0.223 mol). This mixture was heated at 100°C (bp = 78°C) with efficient condensation during 13 h (conversion \approx 80%) and the reaction mixture was cooled to room temperature, diluted with pentane (100 mL) and filtered through Celite[®]. After removal of the volatiles and the remaining starting material, the title compound is obtained by distillation of the crude (50°C, 1 mbar, 10.0 g, 47%) as a pale yellow oil (*Z/E* = 1:1). The purity of **B** was determined by NMR titrations with 1,1,1,2,2-pentachloroethane (PCE) as an internal reference.

¹H NMR [300 MHz, CDCl₃]: δ = 6.82-6.72 (m, 1H), 6.69-6.59 (*m*, 1H), 5.60 (dd, *J* = 16.0, 1.4 Hz, 1H), 5.42 (*d*, 1H, *J* = 11.0 Hz, 1H), 4.12 (*d*, *J* = 8.0 Hz, 2H), 3.96 (*d*, *J* = 7.0, 2H); ¹³C NMR [75 MHz, CDCl₃]: δ = 148.3, 147.6, 116.2, 114.4, 103.6, 102.3, 28.8, 26.3; MS (EI, M⁺) 147, 145.

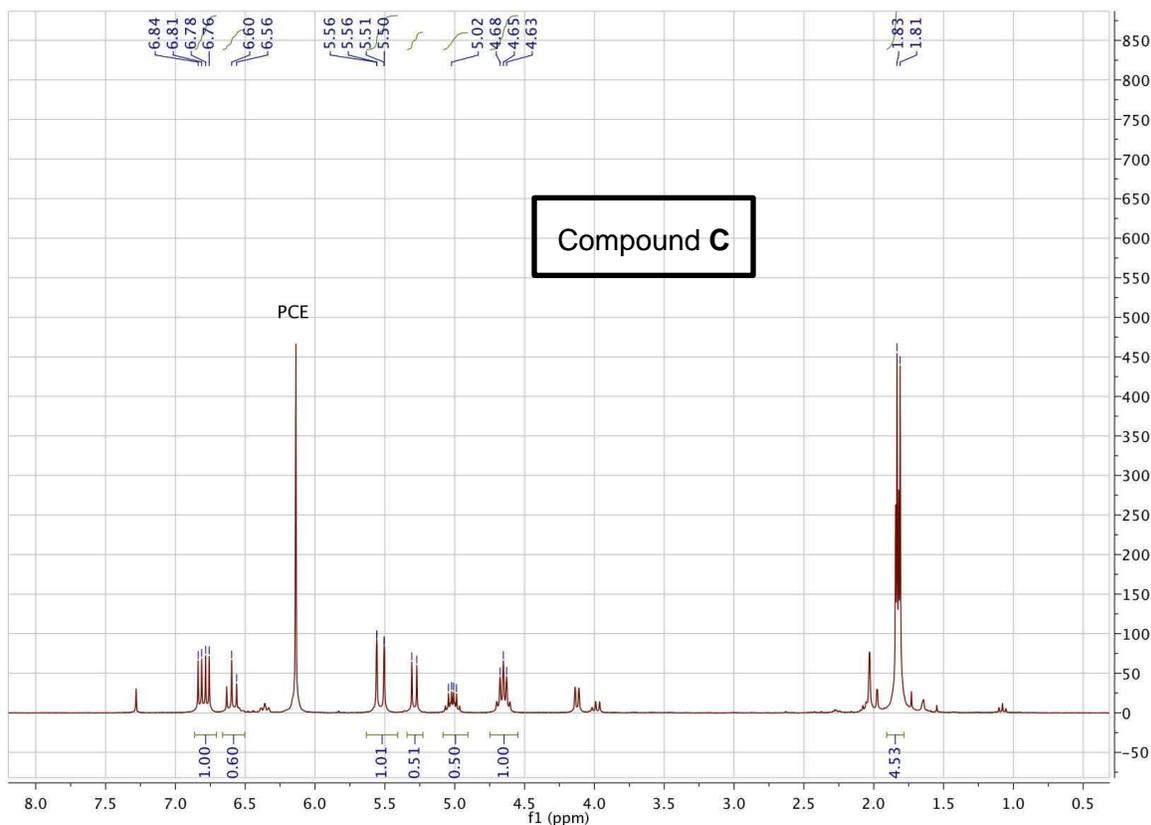


E/Z-4-bromopent-2-enitrile (C)



To a solution of 2-pentenenitrile (11.1 g, 70% pure, = 7.77 g, 97.1 mmol) in nBuCl (90 mL) was added NBS (15.5 g, 97.1 mmol) and catalytic amount of AIBN. The suspension was heated at 80°C for 5 h during which additional catalytic amounts of AIBN were added every hours. Then the mixture was cooled to rt, diluted with pentane, cooled to 0°C during 5 h and filtered through Celite®. The filtrate was concentrated under reduced pressure to afford the crude bromide **C**. The crude was purified by distillation through a Vigreux column to yield 9.6 g (61%) of **C**, b.p. 40–43°C (0.3 mbar, T bath = 75°C).

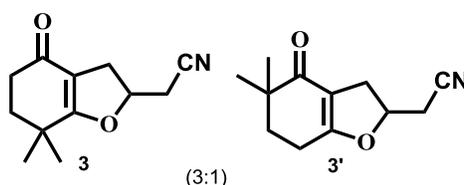
¹H NMR [300 MHz, CDCl₃]: δ = 6.73 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.54 (*t*, *J* = 10.6 Hz, 1H), 5.47 (dd, *J* = 16.1, 1.1, 1H), 5.23 (*d*, *J* = 10.8 Hz, 1H), 4.95 (*m*, 1H), 4.59 (*m*, 1H), 1.76 (*d*, *J* = 6.6 Hz), 1.75 (*d*, *J* = 6.7 Hz); ¹³C NMR [75 MHz, CDCl₃]: δ = 153.9, 153.3, 116.5, 116.3, 100.3, 98.7, 44.0, 42.6, 25.1, 24.2; MS (EI, M⁺) 162, 160.



General Procedure for Alkylation/ oxa-Michael Cyclization Process

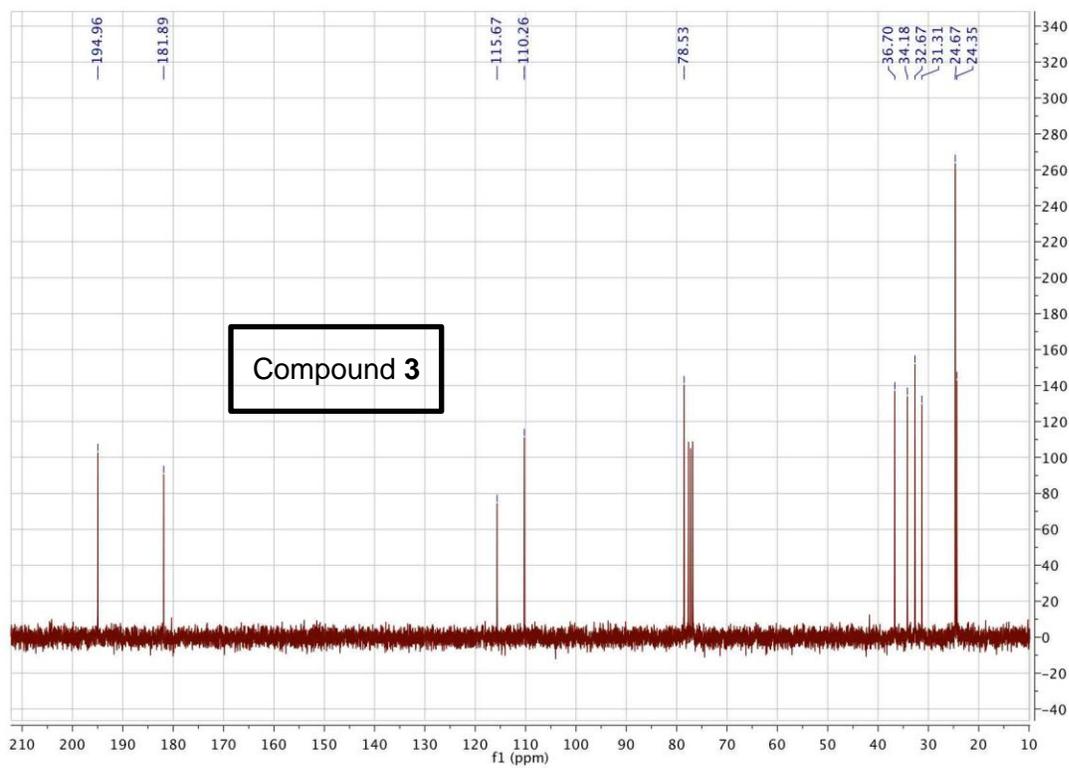
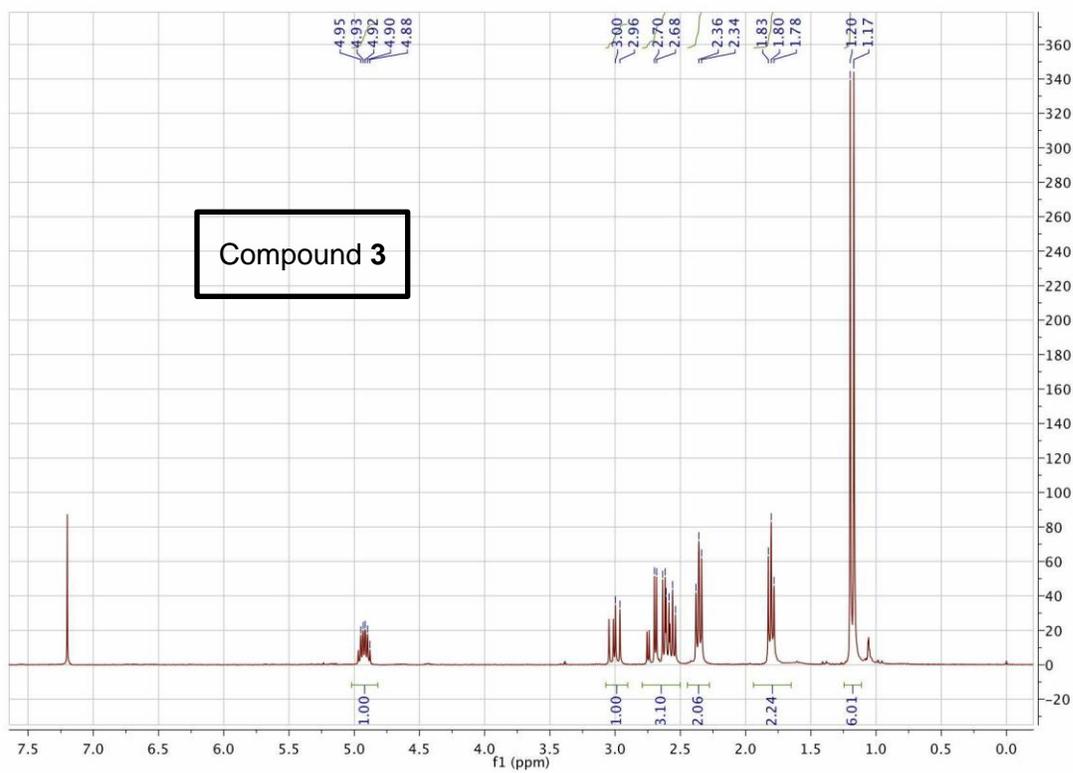
To a stirred solution of cyclic 1,3-diketone (1 equiv) and LiOH (1.2 equiv) in TFE:H₂O (7:3, v/v, C = 2.2 M, degassed by N₂ sparging during 2 h) was added the electrophile (1 equiv). The mixture was stirred during 1 day to 5 days at 45°C or 60°C under an atmosphere of N₂. Then, citric acid (10% solution in water) was added and the aqueous layer was extracted with CH₂Cl₂ (3x). The organic layer was brined and dried on Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the crude was purified by crystallization/trituration or by distillation or by column chromatography (neutral alumina, elution with AcOEt/PET) to give the products. In order to ease the purification of some adducts, the *O*-alkylated product was decomposed by heating the crude in TFE at 160-180°C overnight prior to any isolation attempts.

2-(7,7-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (**3**) and 2-(5,5-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (**3'**)

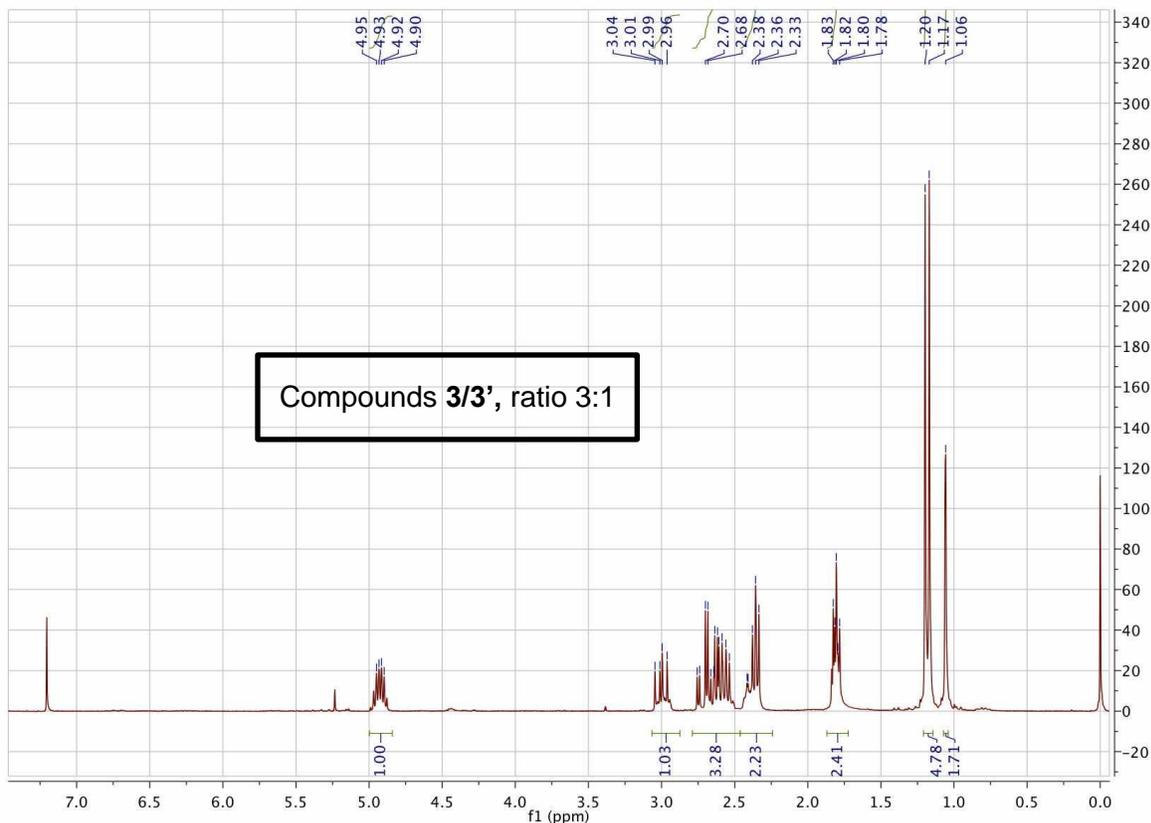


Prepared according to general procedure (27 h of heating at 45°C). The crude was taken up in TFE for heating overnight at 160°C in a sealed tube. After removal of the solvent under reduced pressure, the crude was distilled in a Kugelrohr apparatus to yield 160-180 mg (61-68%) of **3/3'** (0.2 mbar, T = 160°C). The major isomer **3** (65 mg, 25%) can be obtained after trituration with a mixture of pentane/Et₂O at -20°C.

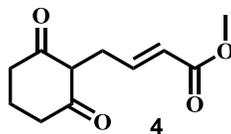
Data for (3): m.p 110°C ; ¹H NMR [300 MHz, CDCl₃]: δ = 4.93 (m, 1H), 3.00 (dd, AB, J = 15.0, 10.5 Hz, 1H), 2.70 (dd, AB, J = 16.9, 5.0 Hz), 2.64-2.56 (m, 2H), 2.36 (m, 2H), 1.80 (m, 2H), 1.20 (s, 3H), 1.17 (s, 3H); ¹³C NMR [75 MHz, CDCl₃]: δ = 195.0, 181.9, 115.7, 110.3, 78.5, 36.7, 34.2, 32.7, 31.3, 24.7, 24.3; IR (ν̄/cm⁻¹, neat): 2929, 2244, 1618, 1399, 1256, 1151, 965, 576; HRMS (ESI) Calculated for C₁₃H₁₈NO₂: 220.1338 (M+H)⁺; Found: 220.1330.



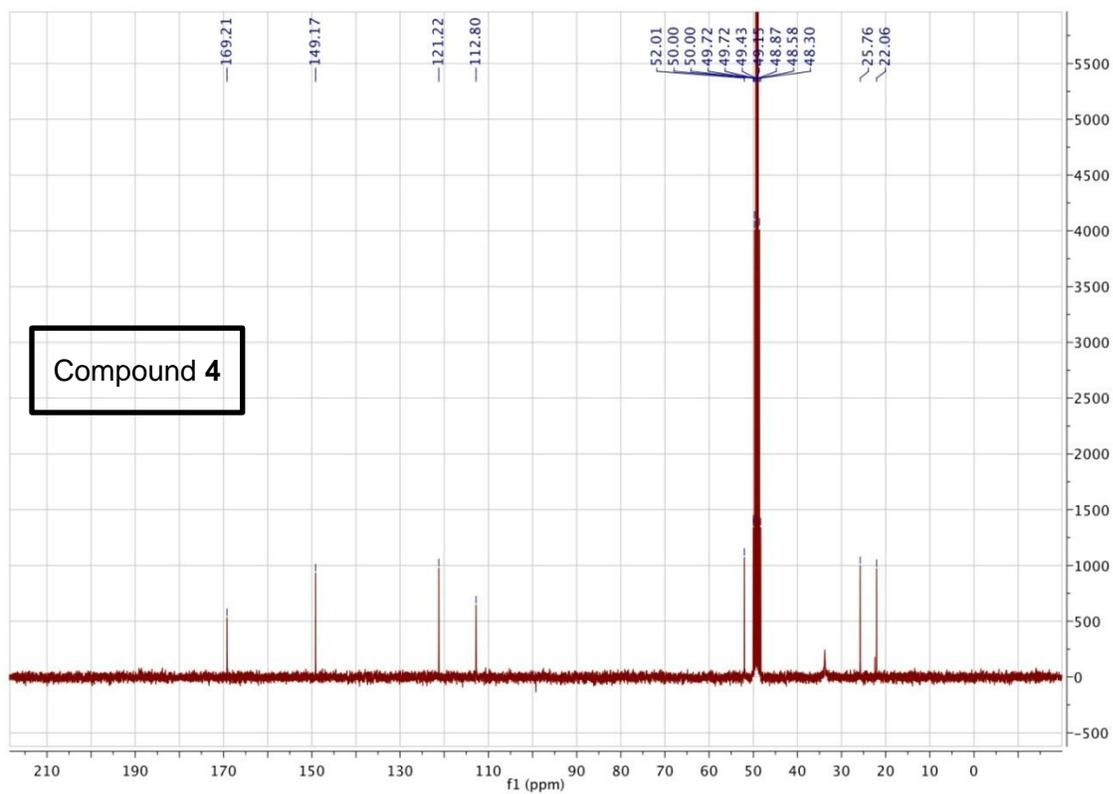
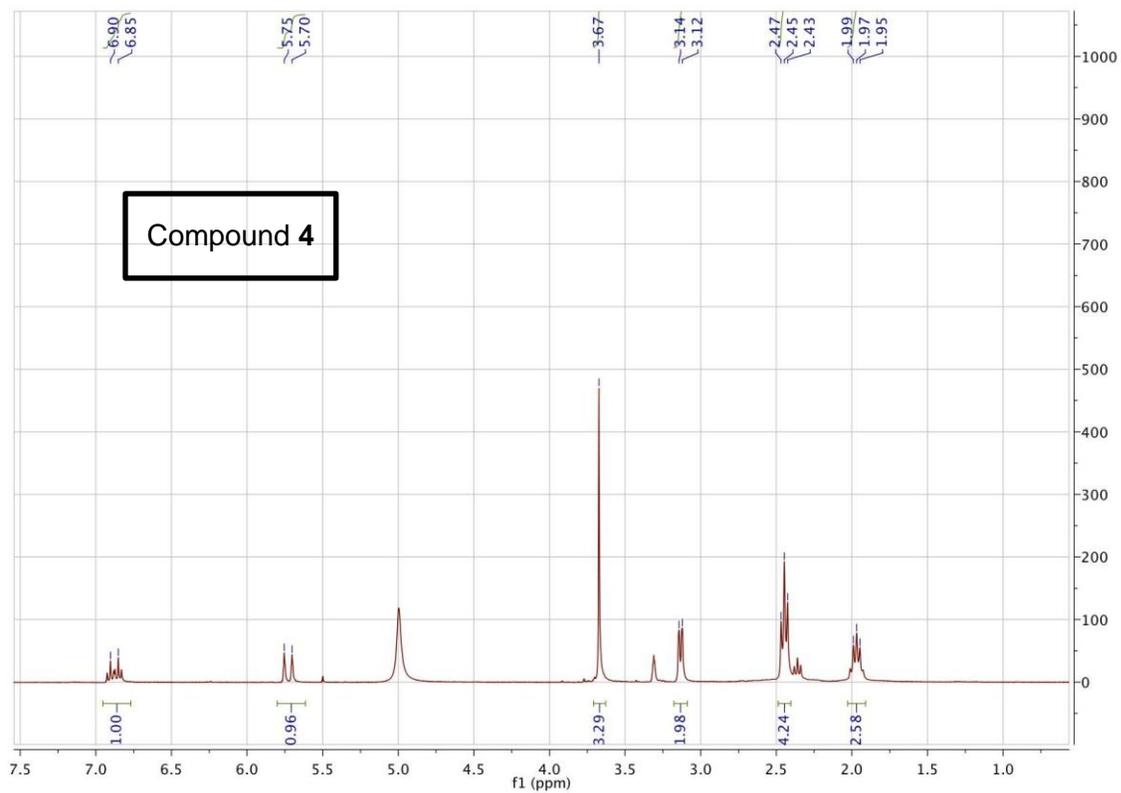
Data for (3/3') = 3:1; ^1H NMR [300 MHz, CDCl_3]: δ = 4.93 (m, 1H), 3.00 (dd, AB, J = 15.0, 10.5 Hz, 1H), 3.00 (m, 1H), 2.70 (dd, AB, J = 16.9, 5.0 Hz), 2.64-2.56 (m, 2H), 2.42 (m, 2H), 2.36 (m, 2H), 1.80 (m, 2H), 1.20 (s, 3H), 1.17 (s, 3H), 1.06 (s br, 6H).



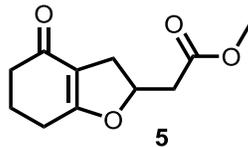
(E)-Methyl 4-(2,6-dioxocyclohexyl)but-2-enoate (4)



m.p. 165 °C. ^1H NMR [300 MHz, CD_3OD]: δ = 6.88 (dt, J = 15.5, 6.4 Hz, 1H), 5.73 (dt, J = 15.5, 1.6 Hz, 1H), 3.68 (s, 3H), 3.12 (dd, br, J = 6.4, 1.3 Hz, 1H), 2.45 (t, J = 6.2 Hz, 4H), 1.97 (t, J = 6.5 Hz, 2H); ^{13}C NMR [75 MHz, CD_3OD]: δ = 169.2, 149.2, 121.2, 112.8, 52.0, 25.8, 22.1. C=O bonds not visible; **IR** ($\tilde{\nu}$ / cm^{-1} , neat): 2944, 2832, 1731, 1375, 1268, 1029, 738; **HRMS (EI)** Calculated for $\text{C}_{11}\text{H}_{14}\text{O}_4$: 210.0892 (M^+); Found: 210.0888.

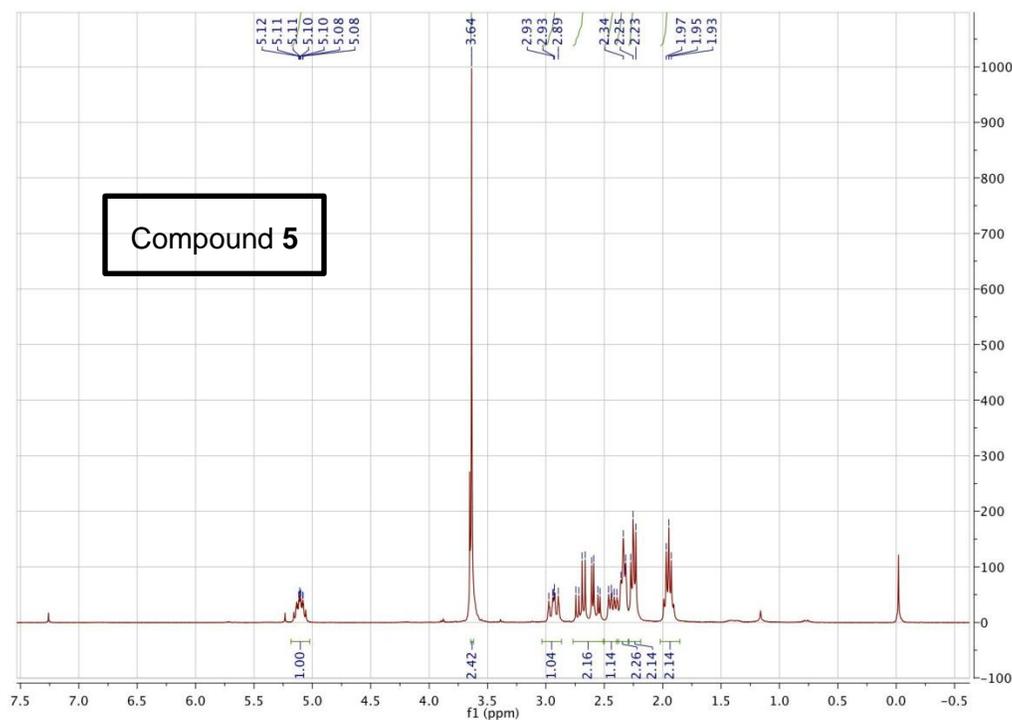


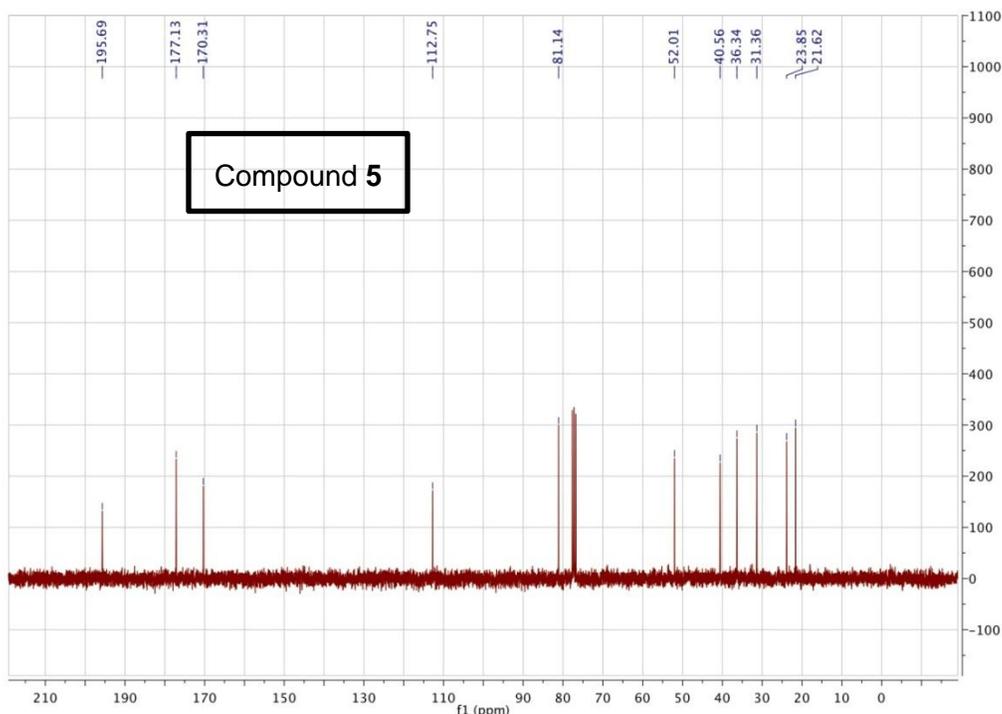
Methyl 2-(4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetate (5)



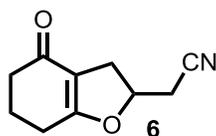
Prepared according to general procedure (48 h of reaction at 45°C). The crude was purified by distillation through Vigreux column to yield 3.38-3.80 g (64-72%) of methyl 2-(4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetate, b.p. 130°C (0.3 mbar, T bath = 200°C).

¹H NMR [300 MHz, CDCl₃]: δ = 5.11 (m, 1H), 3.64 (s, 3H), 2.93 (dt, *J* = 10.2, 1.7 Hz, 1H), 2.73 (dd, AB *J* = 16.0, 7.8 Hz, 1H), 2.57 (dd, AB *J* = 16.0, 5.5 Hz, 1H), 2.43 (dt, *J* = 7.0, 1.7 Hz, 1H), 2.34 (m, 2H), 2.25 (t, *J* = 6 Hz, 2H), 1.95 (t, *J* = 6.3 Hz, 2H); **¹³C NMR** [75 MHz, CDCl₃]: δ = 195.7, 171.1, 170.3, 112.7, 81.1, 52.0, 40.6, 36.3, 31.4, 23.8, 21.6; **IR** ($\tilde{\nu}$ /cm⁻¹, neat): 2951, 1733, 1623, 1403, 1231, 1179, 972, 586; **HRMS: (EI)** Calculated for C₁₁H₁₄O₄: 210.0892 (M⁺); Found: 210.0896.



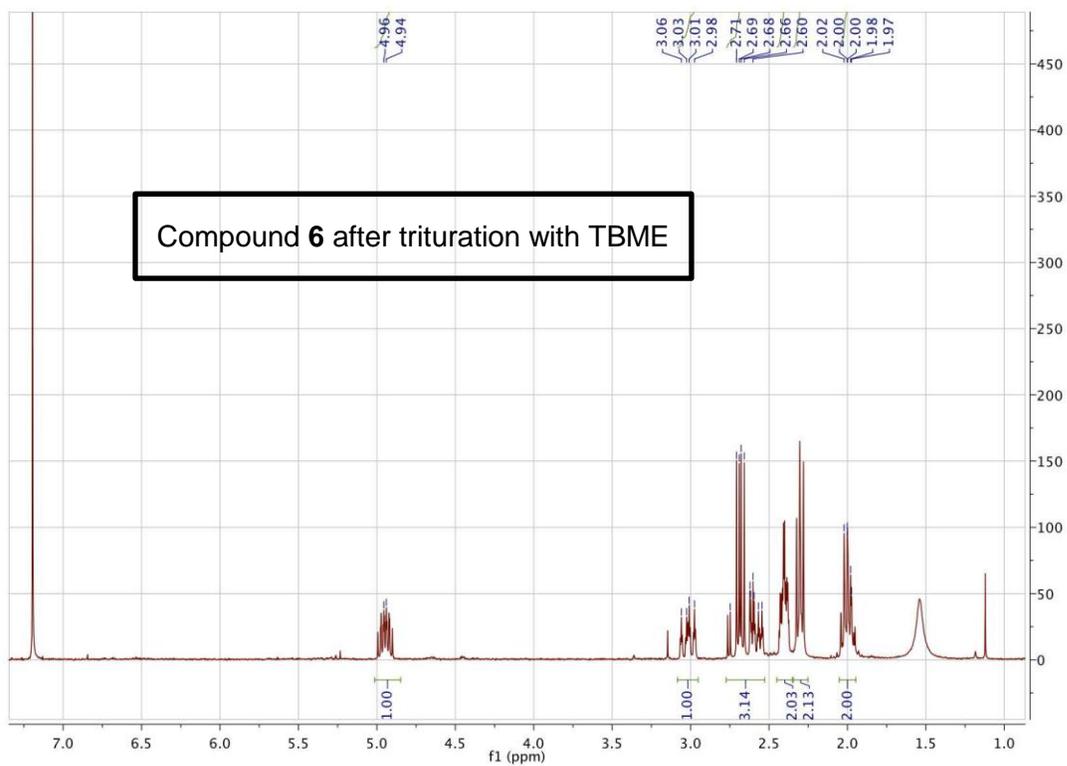
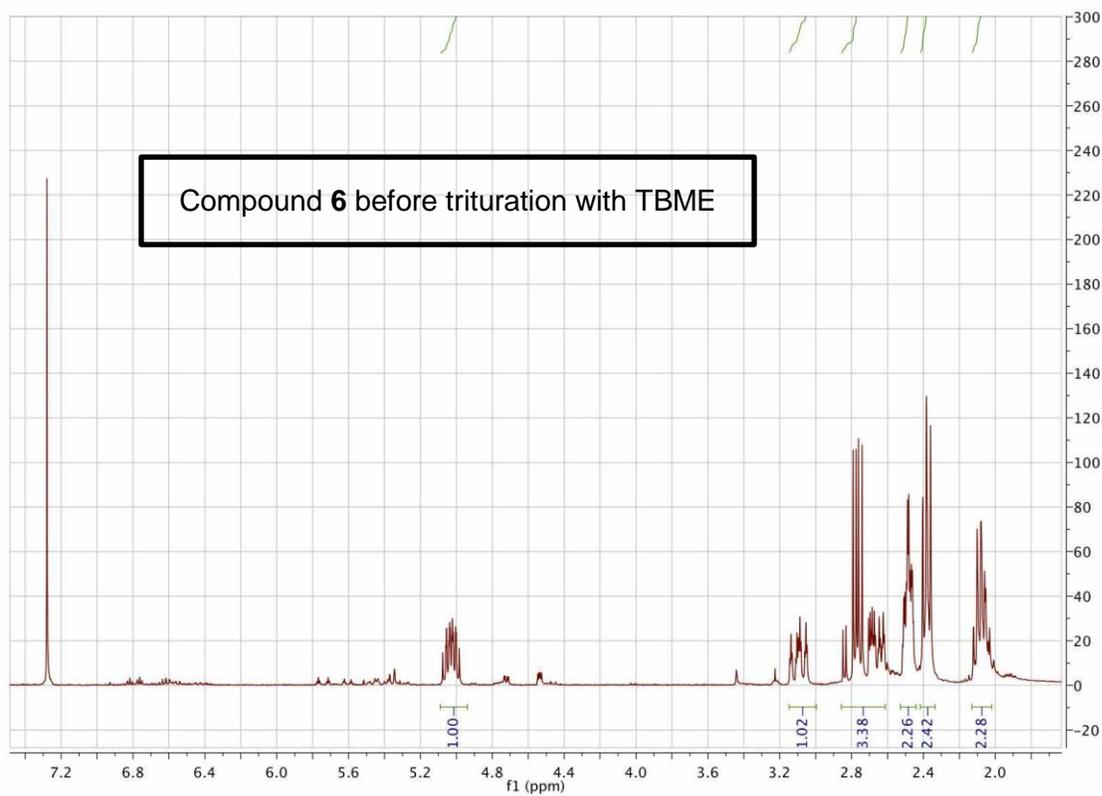


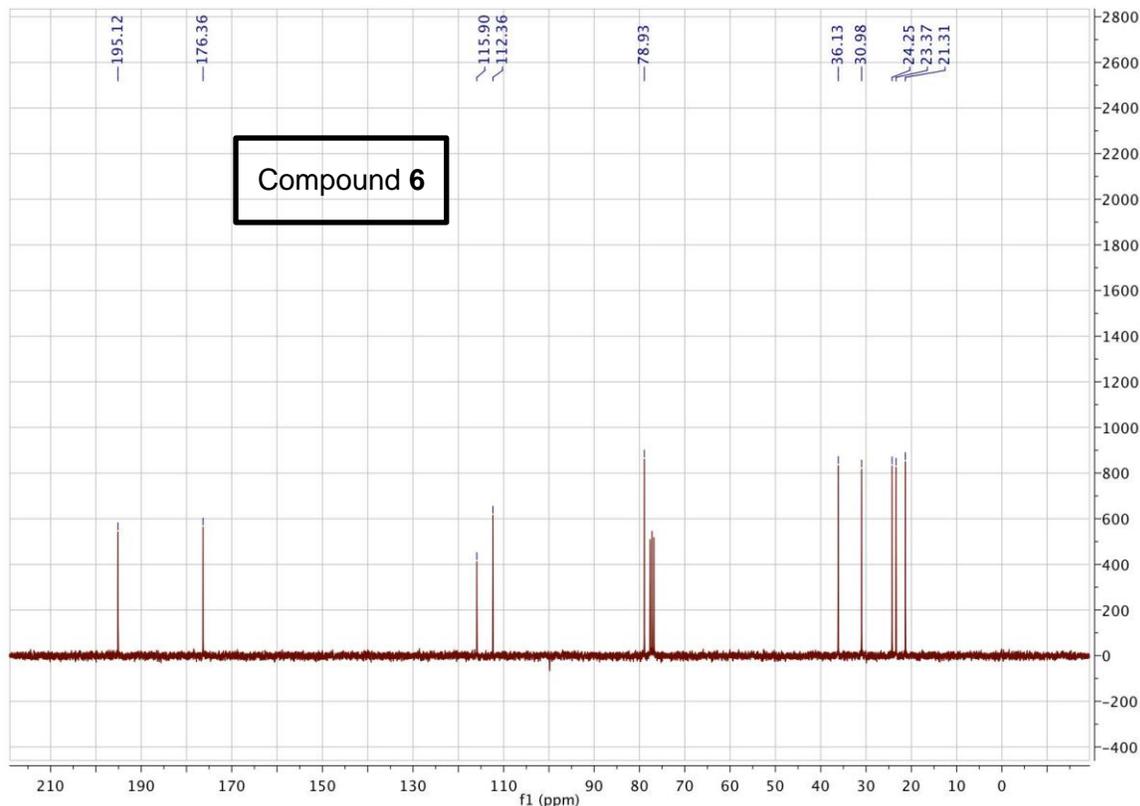
2-(4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (**6**)



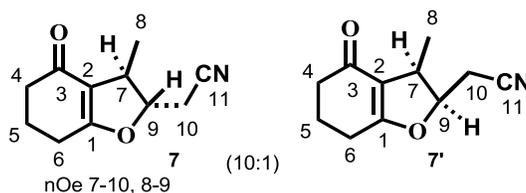
Prepared according to general procedure (24 h of heating at 45°C). The crude was triturated in pentane/tBuOMe at 0°C and the solids were filtrated, collected and solubilized in CH₂Cl₂. The solvent was slowly evaporated to provide of **6** (900 mg, 75%) as crystals with a purity of ≈ 90%. Trituration of this material with tBuOMe (TBME) at -20°C afforded **6** with higher purity (m = 697 mg, 58%).

m.p. 120°C. **¹H NMR** [300 MHz, CDCl₃]: δ = 5.00 (m, 1H), 3.10 (m, 3H), 2.77 (dd AB, *J* = 17.0, 5.0 Hz, 1H), 2.70 (dd AB, *J* = 17.0, 6.0 Hz, 1H), 2.60 (ddt, *J* = 15.0, 6.8, 1.7 Hz, 1H), 2.42 (m, 2H), 2.34 (m, 2H), 2.04 (m, 2H), 1.35 (t, *J* = 6.7 Hz, 2H); **¹³C NMR** [75 MHz, CDCl₃]: δ = 195.3, 176.4, 115.7, 112.6, 79.0, 45.8, 36.3, 31.3, 24.5, 23.6, 21.5; **IR** ($\tilde{\nu}$ /cm⁻¹, neat): 2924, 2244, 1612, 1404, 1228, 1184, 971, 570; **HRMS: (ESI)** Calculated for C₁₀H₁₂NO₂: 178.0868 (**M+H**)⁺; Found: 178.0870.



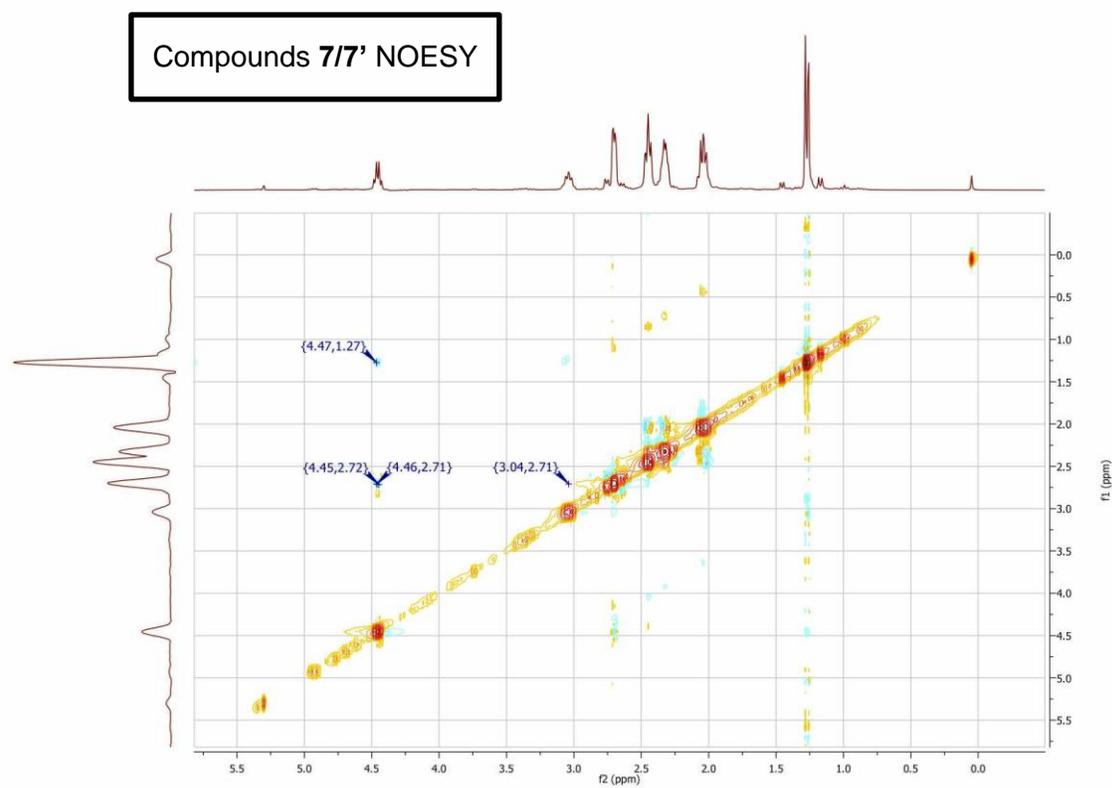
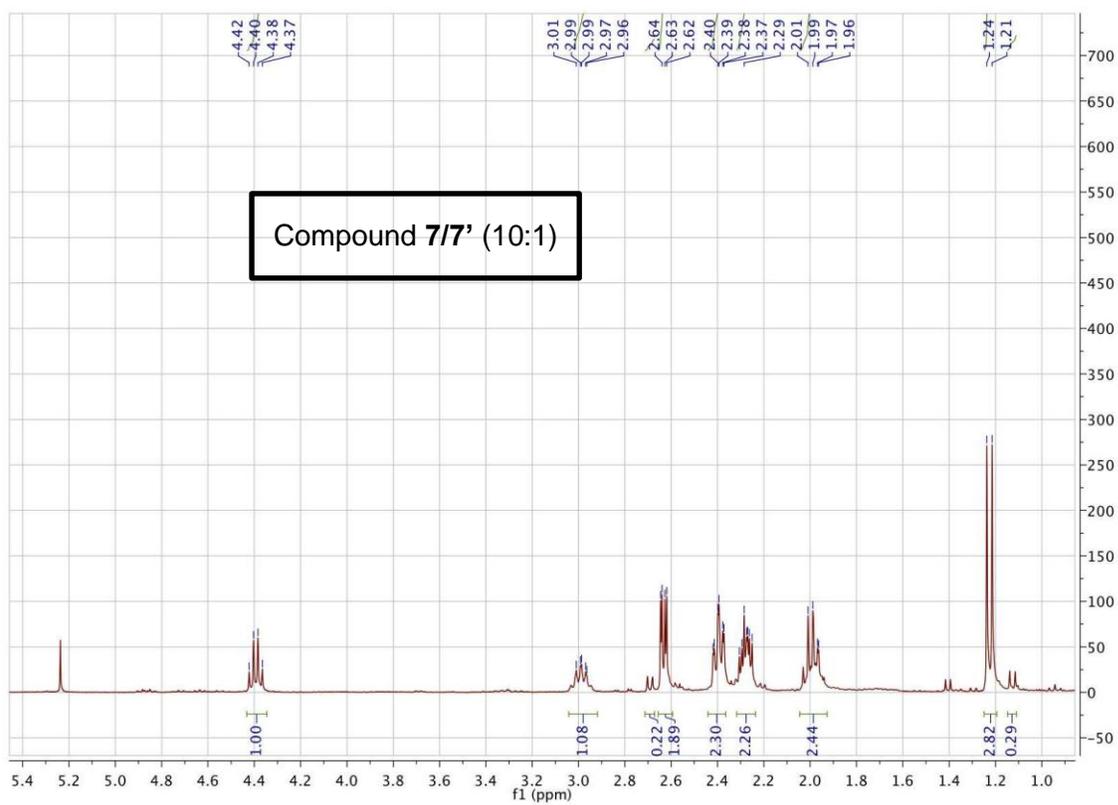


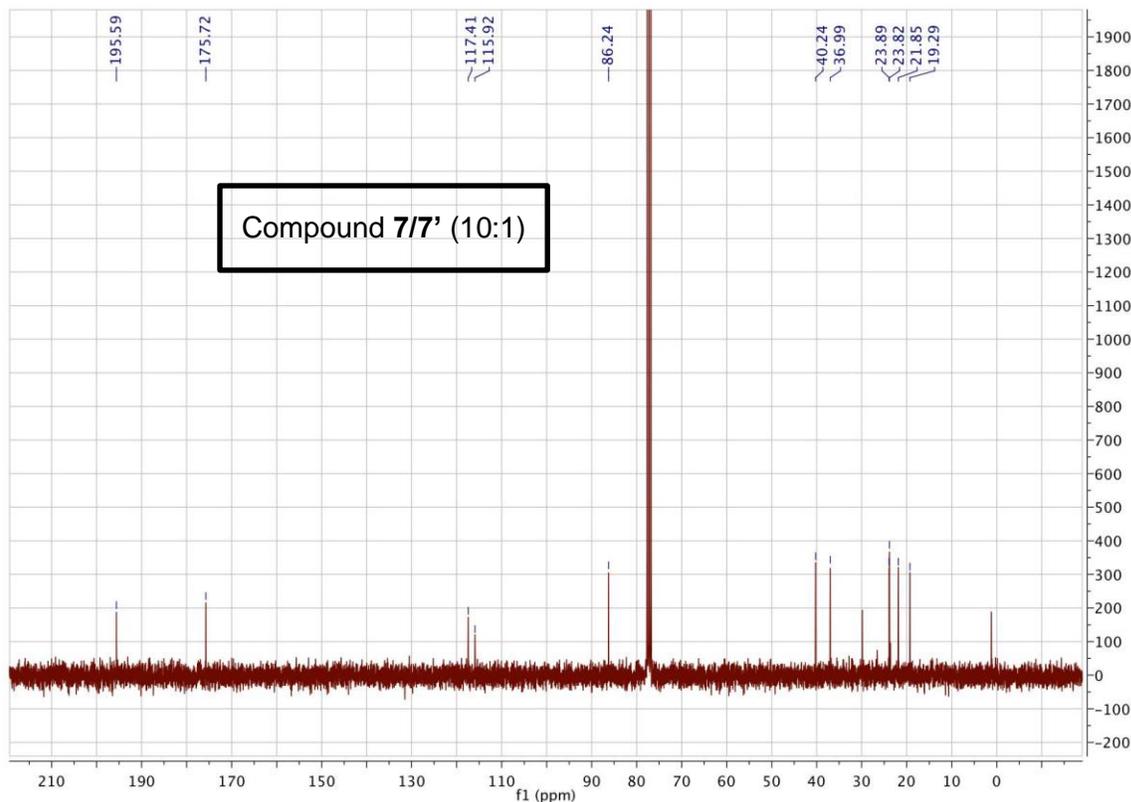
2-(3-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (7)



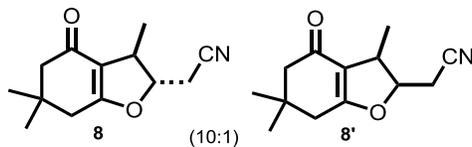
Prepared according to general procedure (60 °C during 5 days). The crude was taken up in TFE (10 mL) and heated at 160 °C overnight in a sealed reactor. After removal of the solvent under reduced pressure, the crude was distilled (160 °C, P = 0.2 mbar) in a Kugelrohr apparatus to afford the products **7/7'** (471 mg, 40%). The residue obtained was distilled a second time (0.2 mbar, T = 200 °C) to afford 67 mg of additional **7/7'** (45% global).

Data of (7/7'): $^1\text{H NMR}$ [300 MHz, CDCl_3]: δ = 4.40 (q, J = 5.8 Hz, 1H, H9), 2.99 (m, 1H, H7), 2.64 (d, J = 1.4 Hz, 1H, H10), 2.62 (d, J = 2.4 Hz, 1H, H10), 2.40 (dt, J = 6.4, 1.6 Hz, 2H, H6), 2.28 (m, 2H, H4), 1.99 (m, 2H, H5), 1.22 (d, J = 6.2 Hz, 3H, H8), 1.13 (d, J = 6.5 Hz, 3H, H8); $^{13}\text{C NMR}$ [75 MHz, CDCl_3]: δ = 195.6 (C3), 175.7 (C1), 117.4 (C2), 115.9 (C11), 86.2 (C9), 40.2 (C7), 37.0 (C4), 23.9 (C10), 23.8 (C6), 21.8 (C5), 19.3 (C8); **IR** ($\tilde{\nu}$ / cm^{-1} , neat): 2946, 2249, 1613, 1399, 1179, 976, 823; **HRMS (ESI)** Calculated for $\text{C}_{11}\text{H}_{14}\text{NO}_2$: 192.1025 ($\text{M}+\text{H}$)⁺; Found: 192.1034.



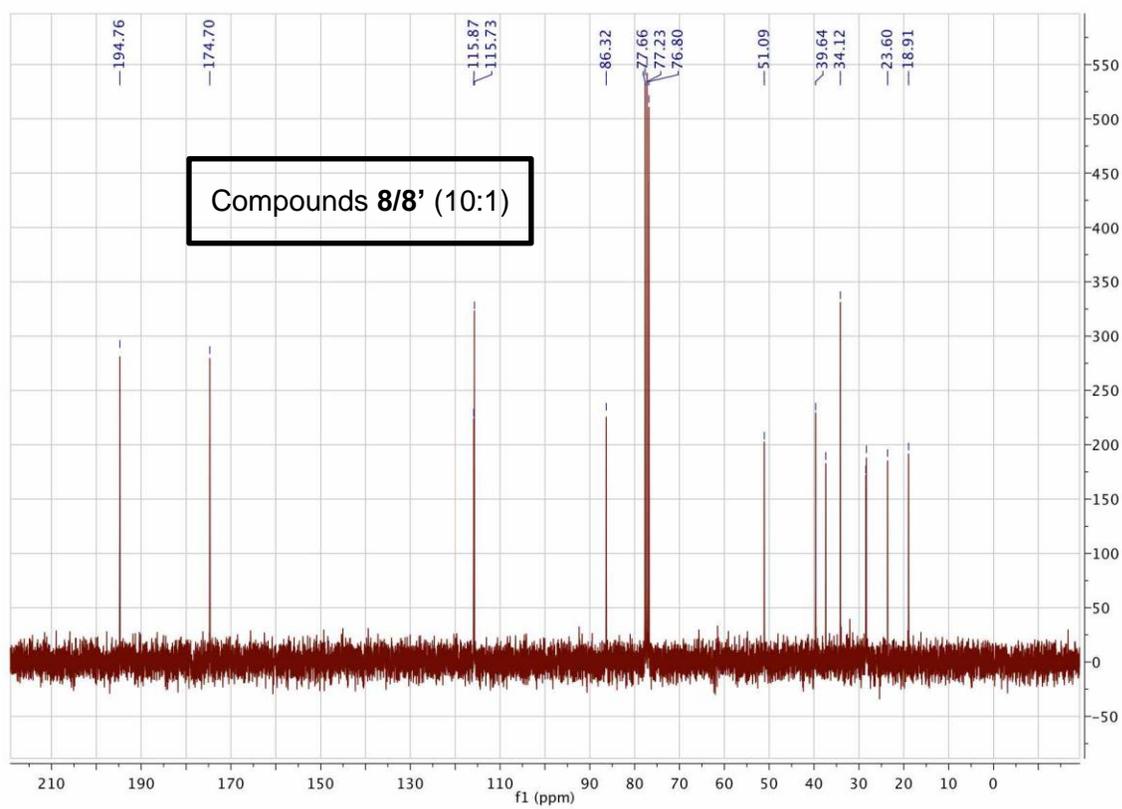
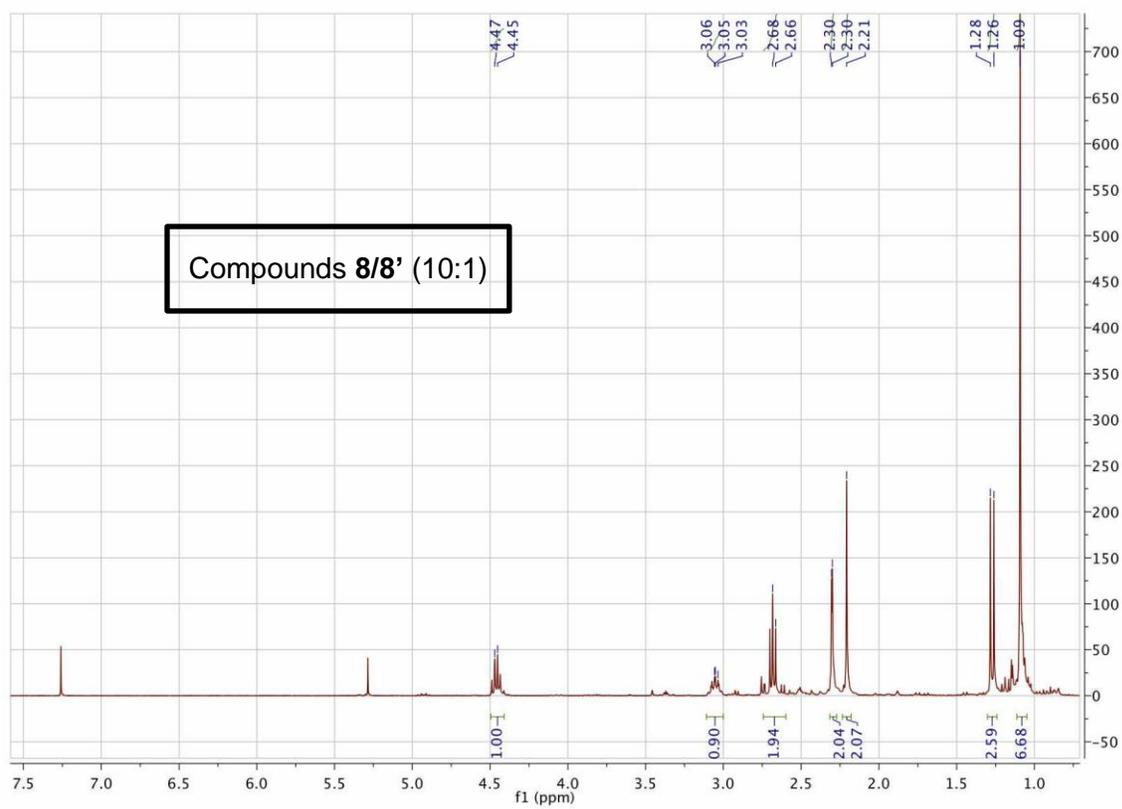


2-(3,6,6-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (**8**)

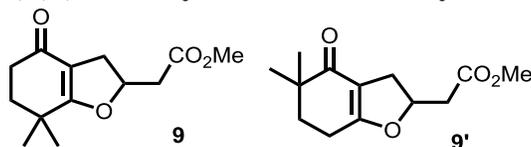


Prepared according to general procedure (60°C during 5 days). The crude (1.6 g) was taken up in TFE (10 mL) and heated overnight at 170°C in a sealed reactor. After removal of the volatile, the residue was distilled in a Kugelrohr system to yield 605 mg (44%) of **8**, b.p. 160°C (0.2 mbar, T = 160°C). The residue was distilled a second time (0.2 mbar, T = 200 °C) to afford 130 mg of additional **8** (53% global).

¹H NMR [300 MHz, CDCl₃]: δ = 4.45 (q, *J* = 5.4 Hz, 1H), 3.06 (m, 1H), 2.68 (m, 2H), 2.30 (m, 2H), 2.21 (s, 2H), 1.27 (d, *J* = 6.7 Hz, 3H), 1.09 (s, 6H); **¹³C NMR** [75 MHz, CDCl₃]: δ = 194.8, 174.6, 115.9, 115.8, 86.3, 51.2, 39.7, 37.4, 34.2, 28.5, 28.4, 23.7, 19.0; **IR** ($\tilde{\nu}$ /cm⁻¹, neat): 2963, 2249, 1629, 1404, 1223, 1031, 976; **HRMS (ESI)** Calculated for C₁₃H₁₈NO₂: 220.1338 (**M+H**)⁺; Found: 220.1329.

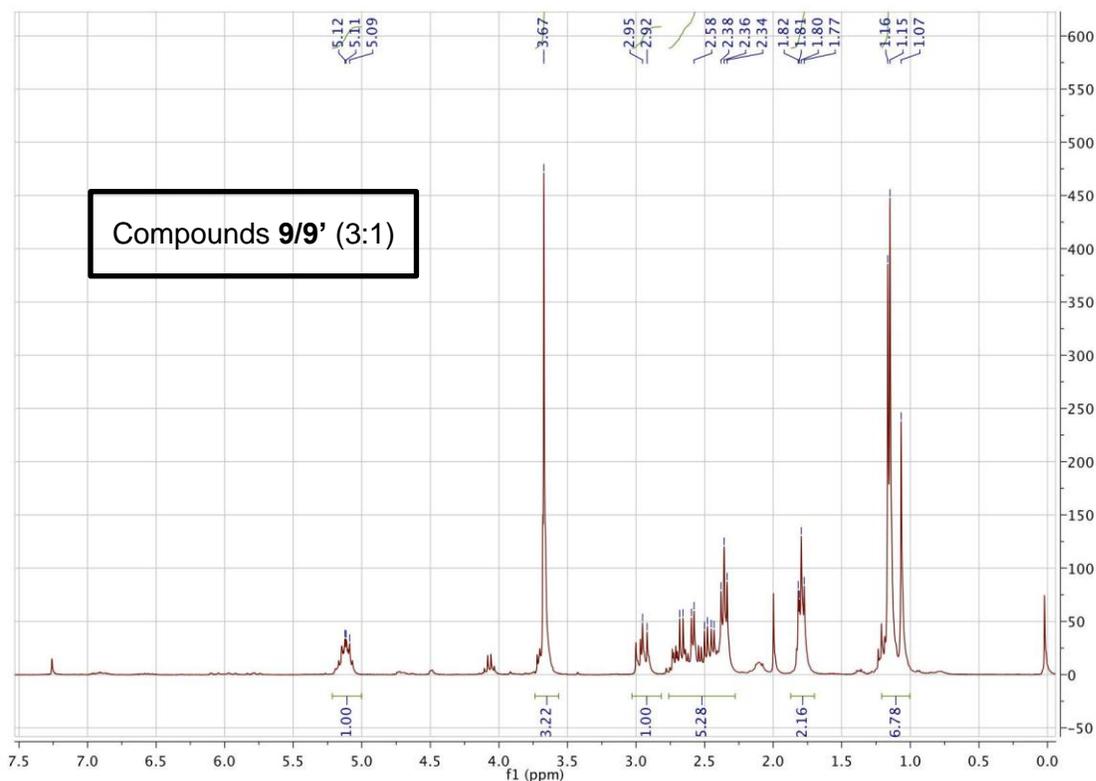


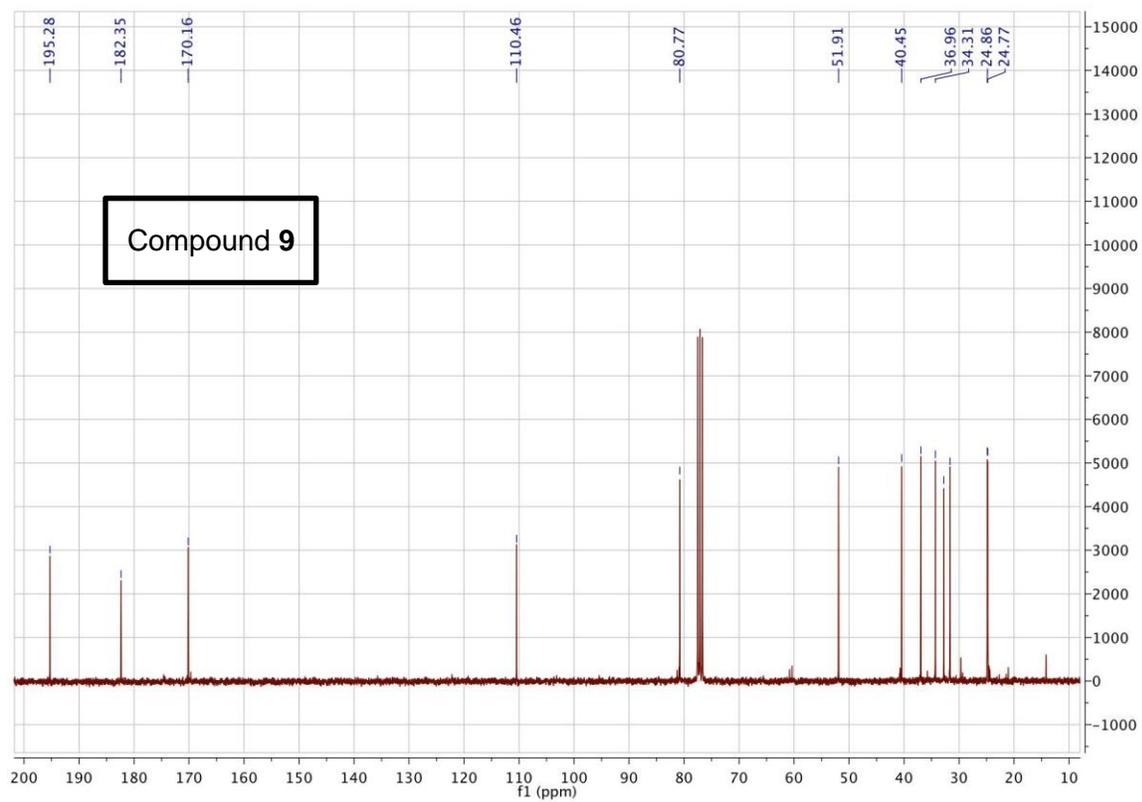
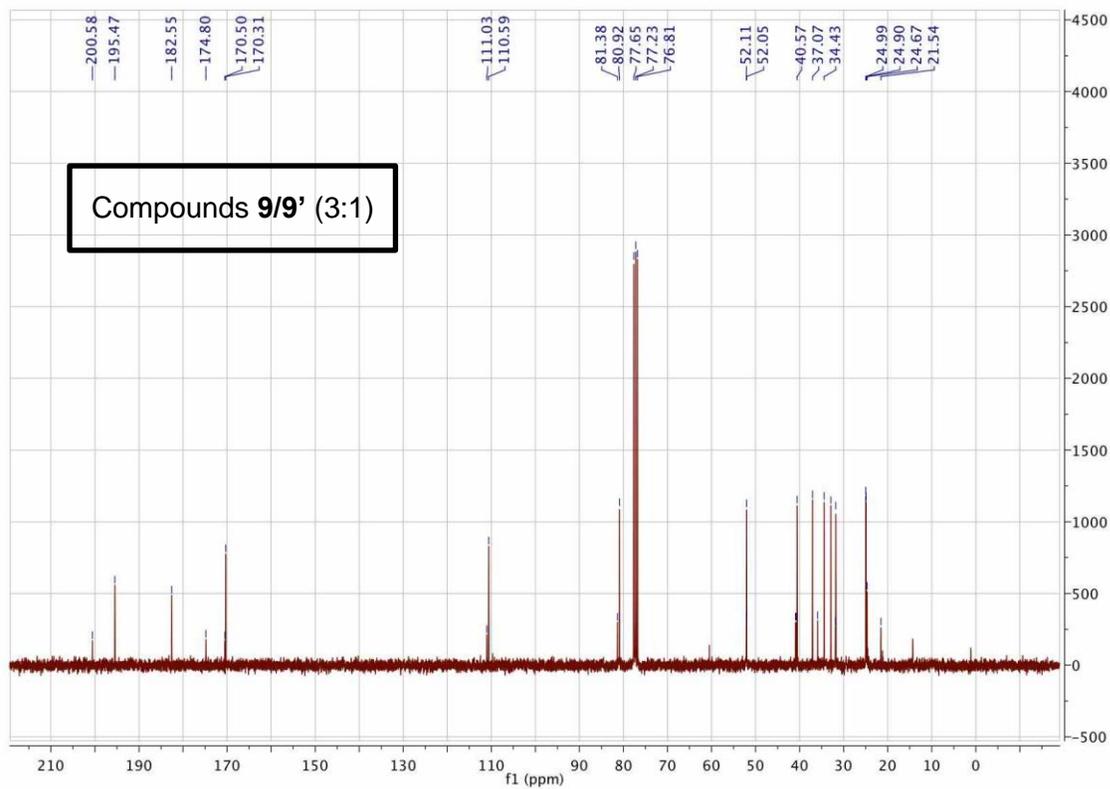
Methyl 2-(7,7-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetate (9) and methyl 2-(5,5-dimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetate (9')



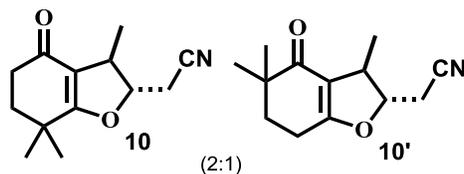
Prepared according to general procedure (27 h of heating at 45°C). The crude was distilled in a Kugelrohr apparatus to yield 493 mg (58%) of **9/9'** (2:1), b.p. 140°C (0.27 mbar, T = 140°C). Further purification of **9/9'** can be carried out by column chromatography on neutral alumina.

Data of (9/9', 3:1): ¹H NMR [300 MHz, CDCl₃]: δ = 5.18 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.95 (m, 1H), 2.74-2.51 (m, 2H), 2.45 (dd, *J* = 14.5, 6.0 Hz, 1H), 2.36 (t, *J* = 6.9 Hz, 2H), 1.79 (m, 2H), 1.20 (s, 3H), 1.19 (s, 3H), 1.11 (s, 6H); ¹³C NMR [75 MHz, CDCl₃]: δ = 200.6, 195.5, 182.5, 174.8, 170.5, 170.3, 111.0, 110.6, 81.4, 80.9, 52.1, 52.05, 40.95, 40.8, 40.6, 37.1, 35.9, 34.4, 32.9, 31.9, 31.8, 25.0, 24.9, 24.7(2C), 21.5; IR (ν̄ /cm⁻¹, neat): 2929, 1739, 1629, 1404, 1190, 943; HRMS (ESI) Calculated for C₁₀H₁₂NO₂: 239.1283 (M+H)⁺; found: 239.1275.



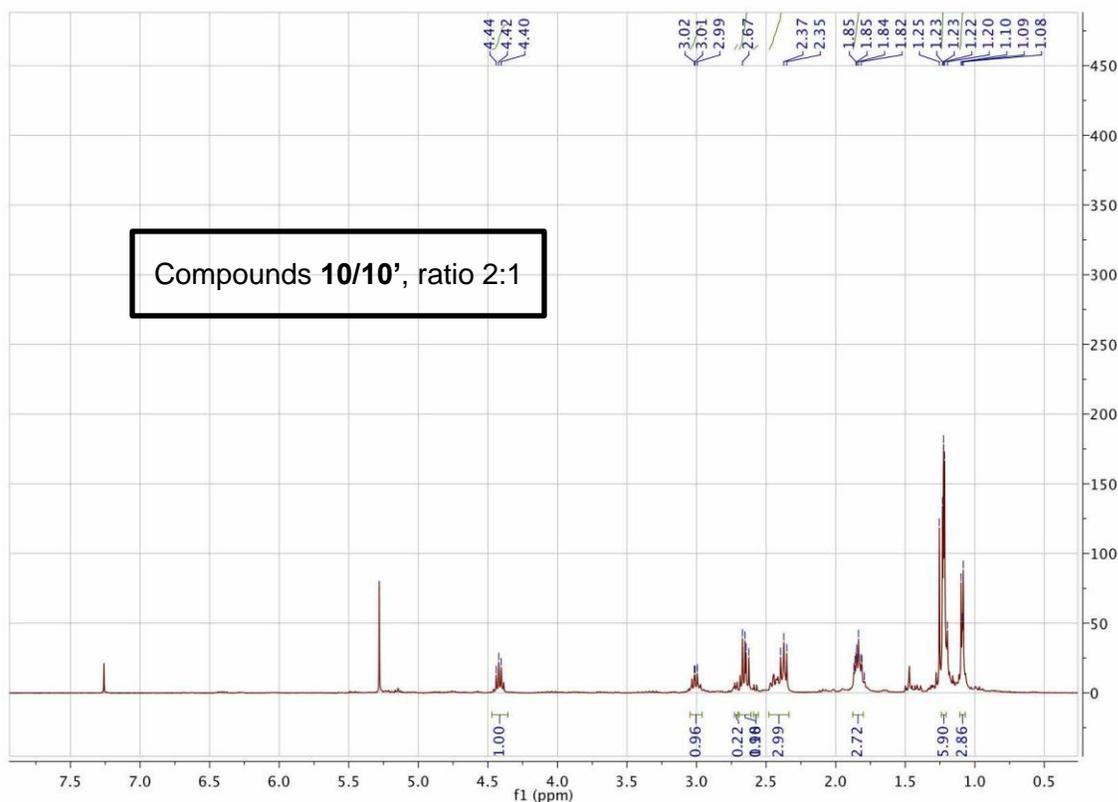


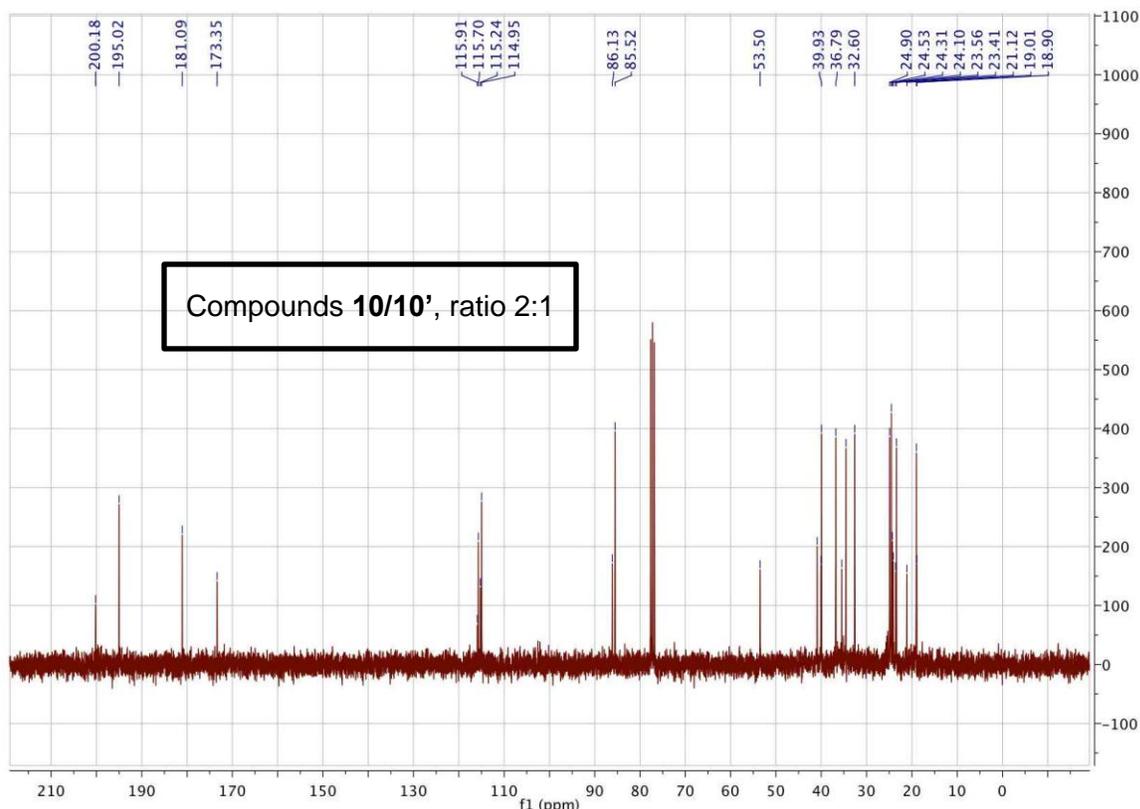
2-(3,7,7-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (10) and 2-(3,5,5-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (10')



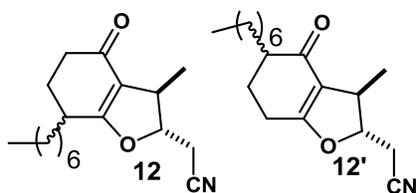
Prepared according to the general procedure (60°C during 5 days). The crude was taken up in TFE (10 mL) and heated at 160°C overnight in a sealed reactor. After removal of the solvent under reduced pressure, the products **10/10'** (367 mg, ratio 2:1, 46%) were obtained after distillation of the crude in a Kugelrohr apparatus (160°C, P = 0.2 mbar).

Data for (10/10') : $^1\text{H NMR}$ [300 MHz, CDCl_3]: δ = 4.42 (m, 1H), 3.01 (m, 1H), 2.72-2.57 (m, 2H), 2.47-2.35 (m, 2H), 1.84 (m, 2H), 1.23 (m, 6H), 1.09 (m, 3H); $^{13}\text{C NMR}$ [75 MHz, CDCl_3]: δ = 200.2, 195.0, 181.1, 173.3, 115.9, 115.7, 115.2, 114.9, 86.1, 85.5, 40.9, 40.0, 39.9, 36.8, 35.4, 34.5, 32.6, 24.9, 24.5, 24.3, 24.1, 23.6, 23.4, 21.1, 19.0, 18.9; **IR** ($\tilde{\nu}$ / cm^{-1} , neat): 2957, 2249, 1629, 1453, 1399, 1157, 976; **HRMS (ESI)** Calculated for $\text{C}_{13}\text{H}_{18}\text{NO}_2$: 220.1338 (**M+H**) $^+$; found: 220.1333.



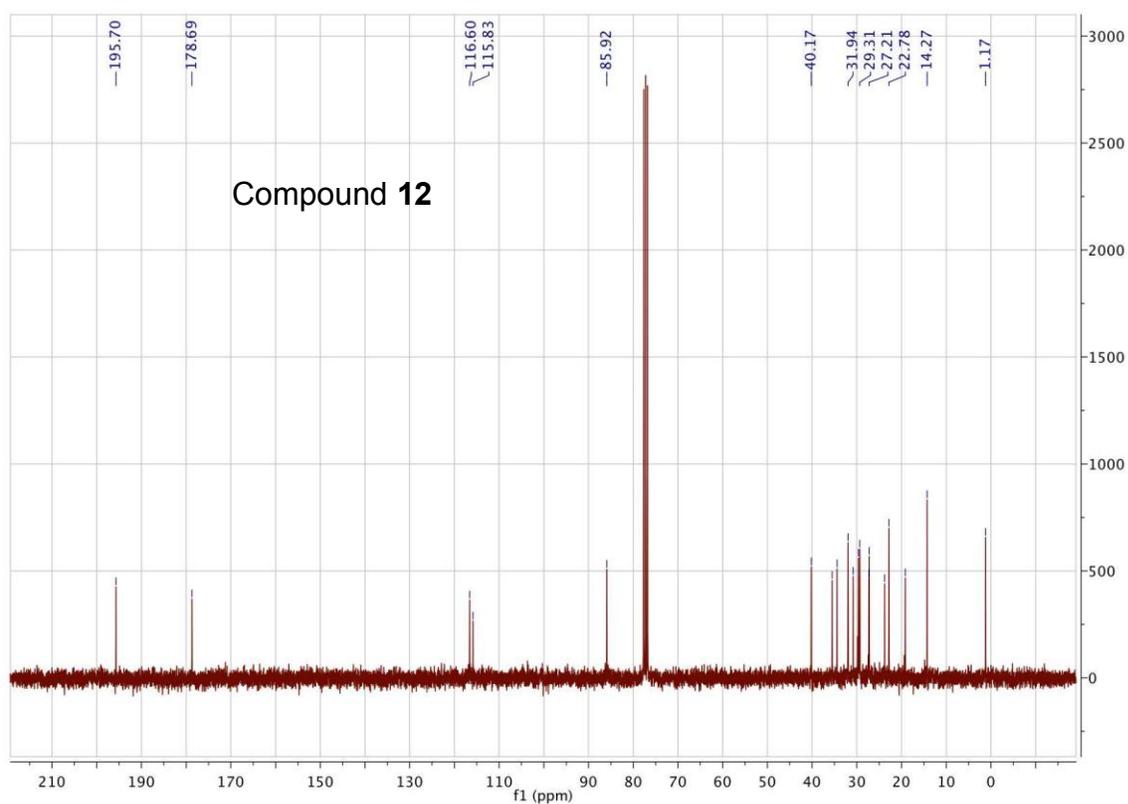
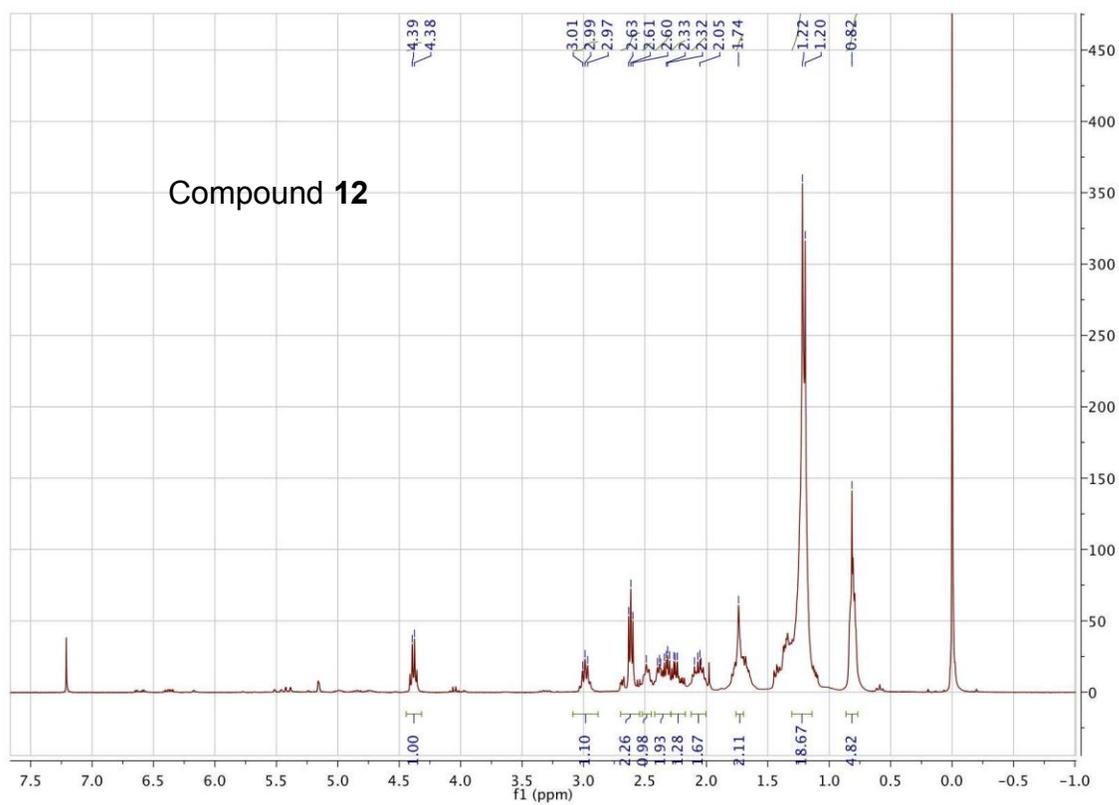


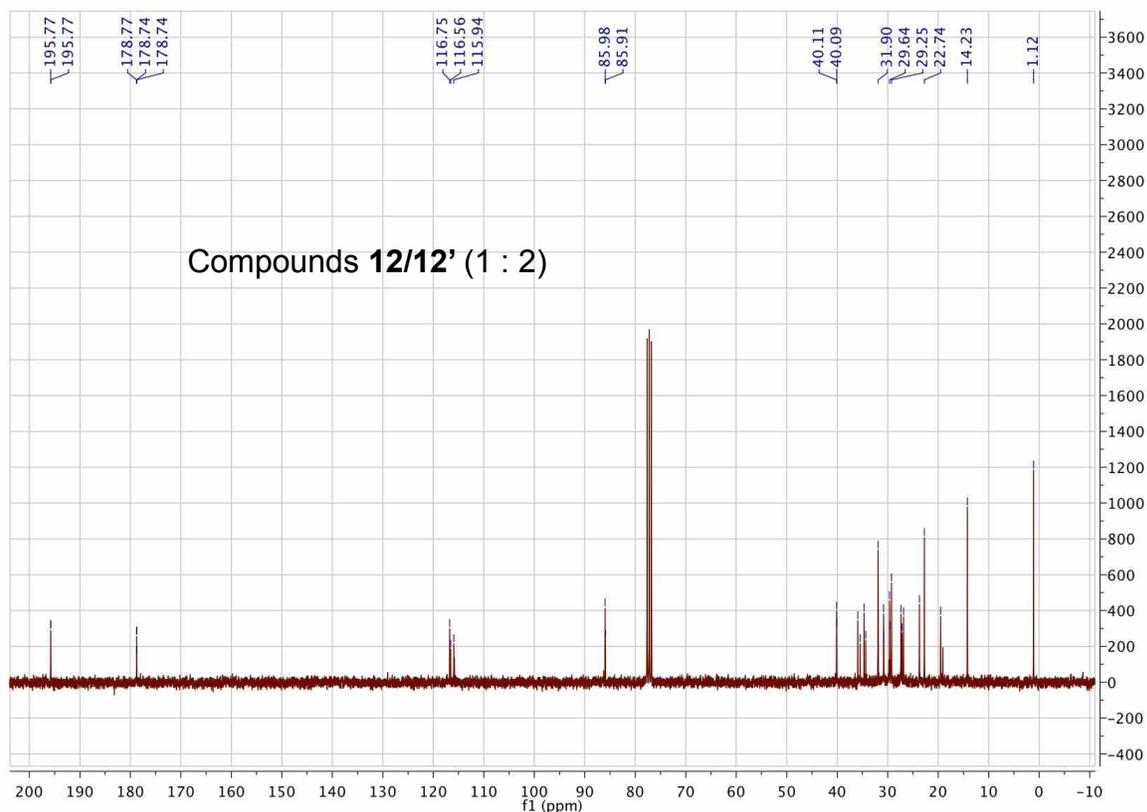
2-(7-heptyl-3-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (12) and 2-(5-heptyl-3-methyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetonitrile (12')



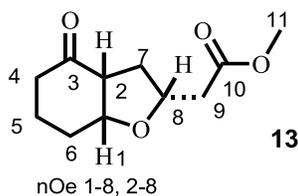
Prepared according to the general procedure (60°C during 5 days). Purification of the crude on neutral alumina (PE:AcOEt, 1:1) yielded 342 mg of the products **12** and **12'**.

Data for (12/12') : $^1\text{H NMR}$ [300 MHz, CDCl_3]: δ = 4.38 (q, 1H, J = 5.5 Hz), 2.99 (m, 1H), 2.69-2.54 (m, 2H), 2.49 (m, 1H), 2.40-2.18 (m, 3H), 2.11-2.03 (m, 1H), 1.79-1.65 (m, 2H), 1.22 (m, 13H), 0.82 (m, 3H); $^{13}\text{C NMR}$ [75 MHz, CDCl_3]: **12/12'** = **1:2**, δ = 119.8, 199.7 (*minor isomer*), 178.8, 178.7, 116.7, 116.6, 115.9, 115.8, 114.1, 86.0, 85.9, 40.1, 40.1, 35.5, 35.9, 34.7, 34.4, 31.9, 31.9, 30.8, 30.8, 29.6, 29.6, 29.3, 29.3, 27.4, 27.3, 27.2, 26.9, 23.8, 23.8, 22.8, 22.8, 19.5, 19.2, 14.3, 14.3; **IR** ($\tilde{\nu}/\text{cm}^{-1}$, neat): 2924, 2254, 1629, 1454, 1399, 1185, 976; **HRMS (ESI)** Calculated for $\text{C}_{18}\text{H}_{28}\text{NO}_2$: 290.2120 ($\text{M}+\text{H}$) $^+$; Found: 290.2106.





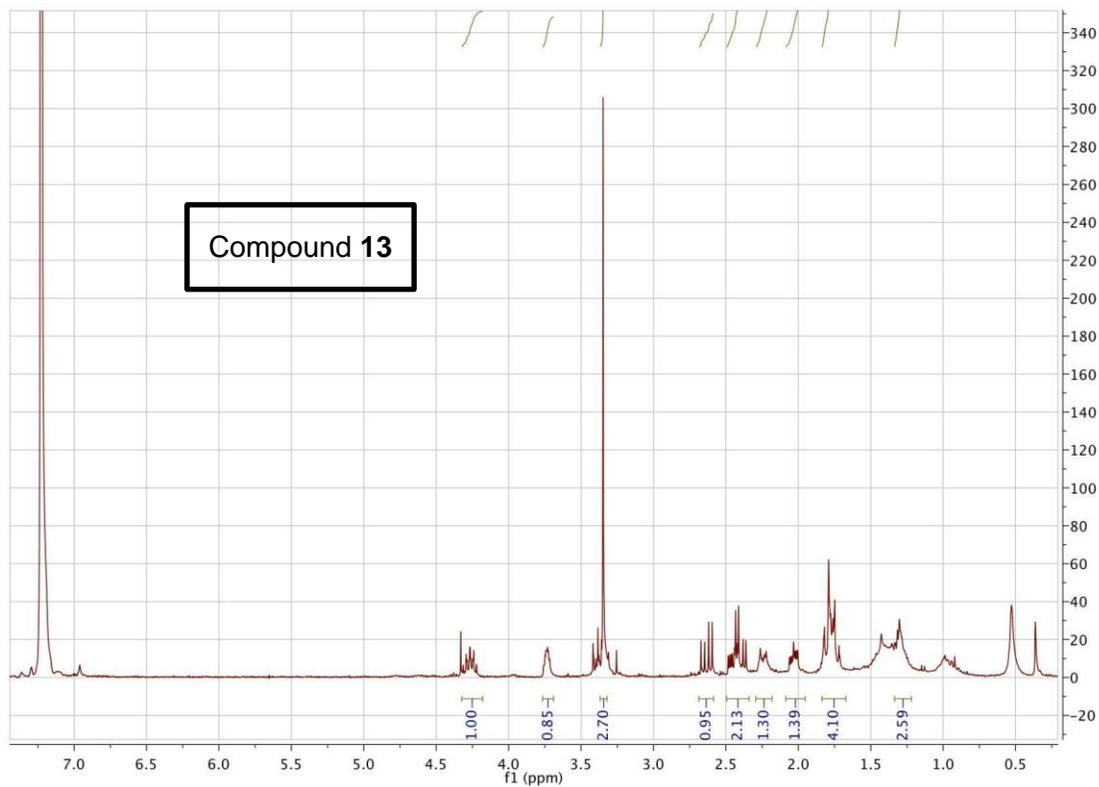
Methyl 2-(4-oxooctahydrobenzofuran-2-yl)acetate (**13**)



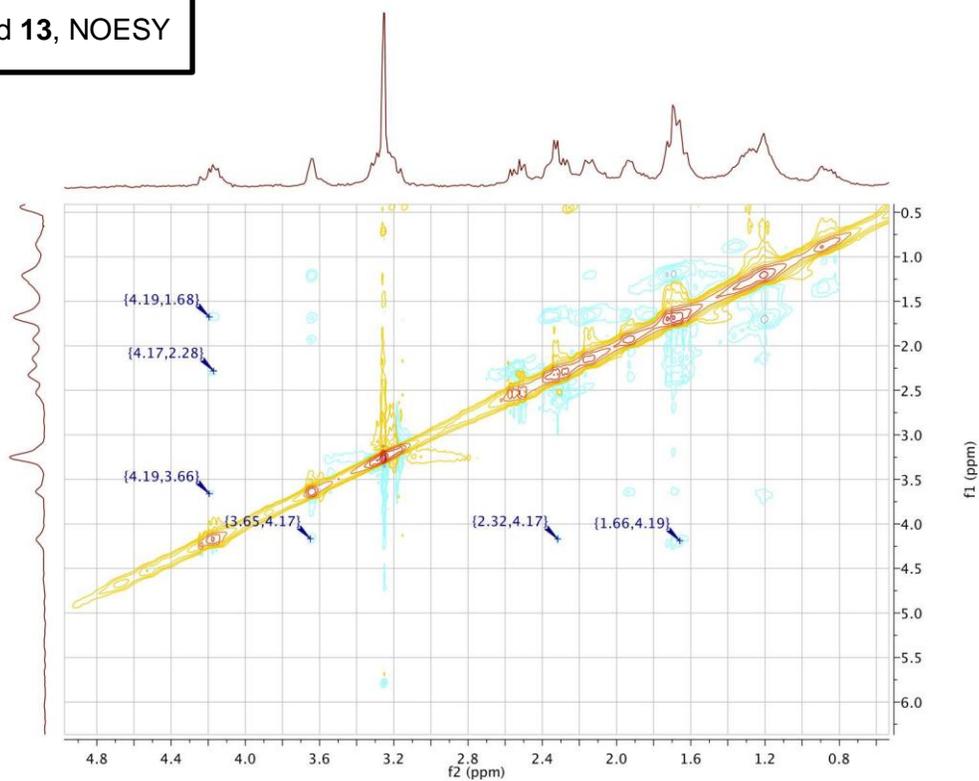
To a solution of **5** (370 mg, 1.762 mmol) in ethanol (30 mL) was added Pd/C (150 mg). Light vacuum (20 mbar) was applied and trifluoroacetic acid (270 μ L, 3.524 mmol) was added followed by an atmosphere of hydrogen. The mixture was stirred at rt for 5 h and was filtered through Celite[®] and the pad was washed with CH₂Cl₂. The organic layer obtained was washed with a solution of aqueous NaHCO₃, brined and dried on MgSO₄. After filtration and removal of the volatiles under reduced pressure, the crude was purified on silica gel (Pentane/AcOEt, 1:1) to afford the product **13** (m = 253 mg, 68%) as a colorless oil.

¹H NMR [300 MHz, C₆D₆]: δ = 4.20 (m, 1H, H8), 3.66 (m, 1H, H1), 3.28 (s, 3H), 2.57 (dd AB, J = 15.6, 7.5 Hz, 1H, H9), 2.39 (m, 1H, H4), 2.34 (dd AB, J = 15.6, 6.0 Hz, 1H, H9), 2.20 (m, 1H, H4), 1.97 (m, 1H, H2), 1.75 (m, 4H, H7,6), 1.24 (m, 2H, H5); ¹³C NMR [75 MHz, C₆D₆]: δ = 210.9 (C3), 171.8 (C10), 80.3 (C1), 74.1 (C8), 51.9 (C11), 51.7 (C2), 41.1 (C4), 40.7 (C9),

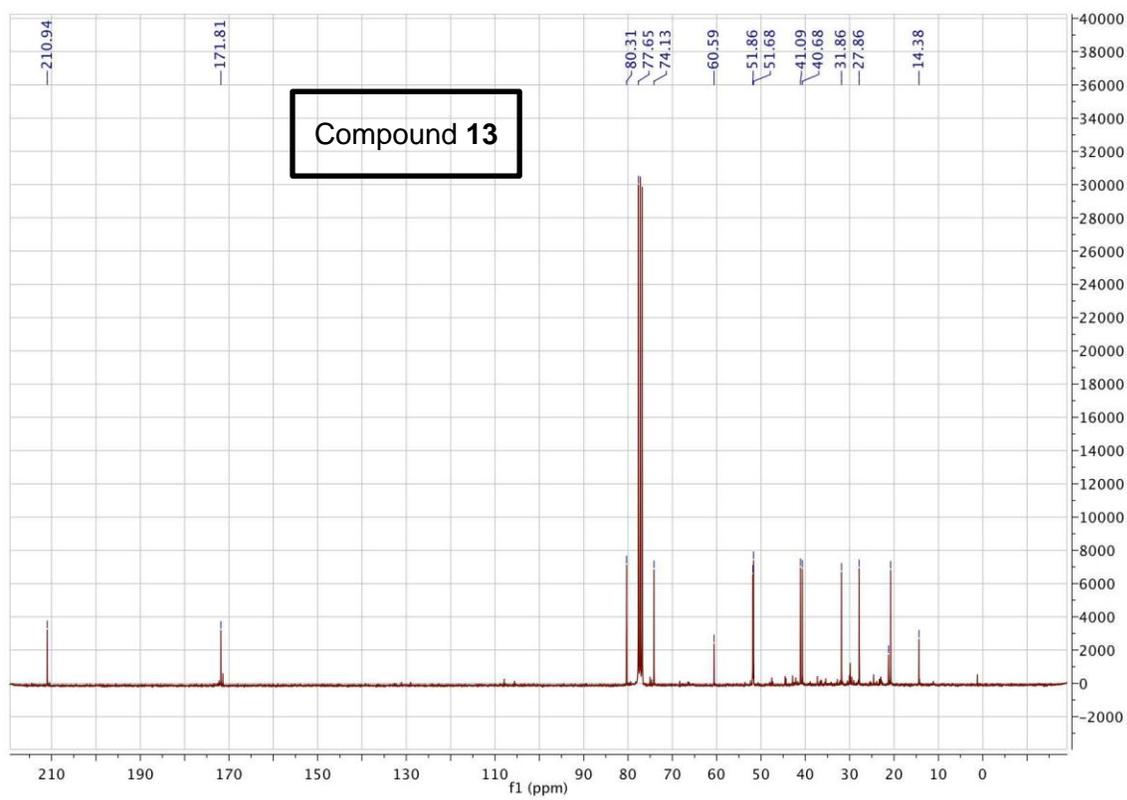
31.9 (C7), 27.9 (C6), 20.8 (C5); **IR** ($\tilde{\nu}$ /cm⁻¹, neat): 2982, 1738, 1372, 1240, 1046; **HRMS (EI)**
Calculated for C₁₁H₁₆O₄: 212.1049 (**M**)⁺; Found: 212.1046.



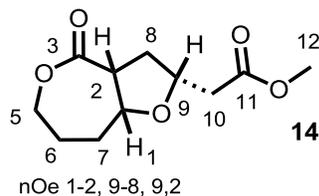
Compound 13, NOESY



Compound 13

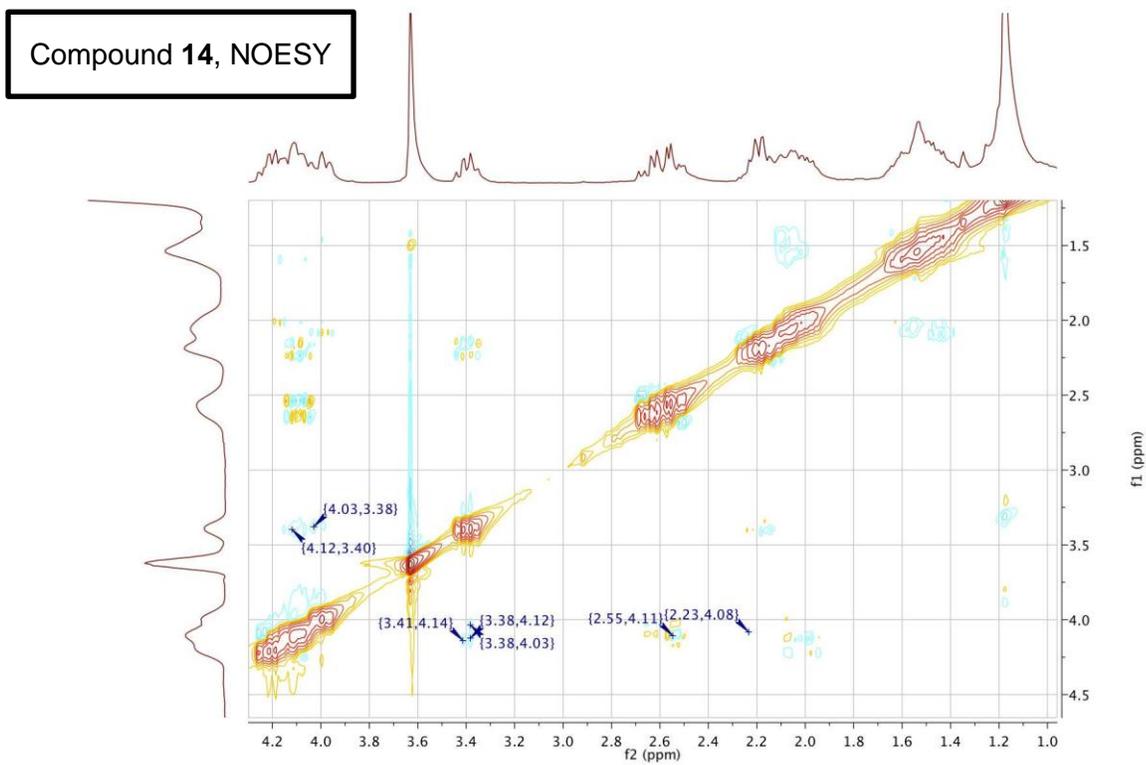
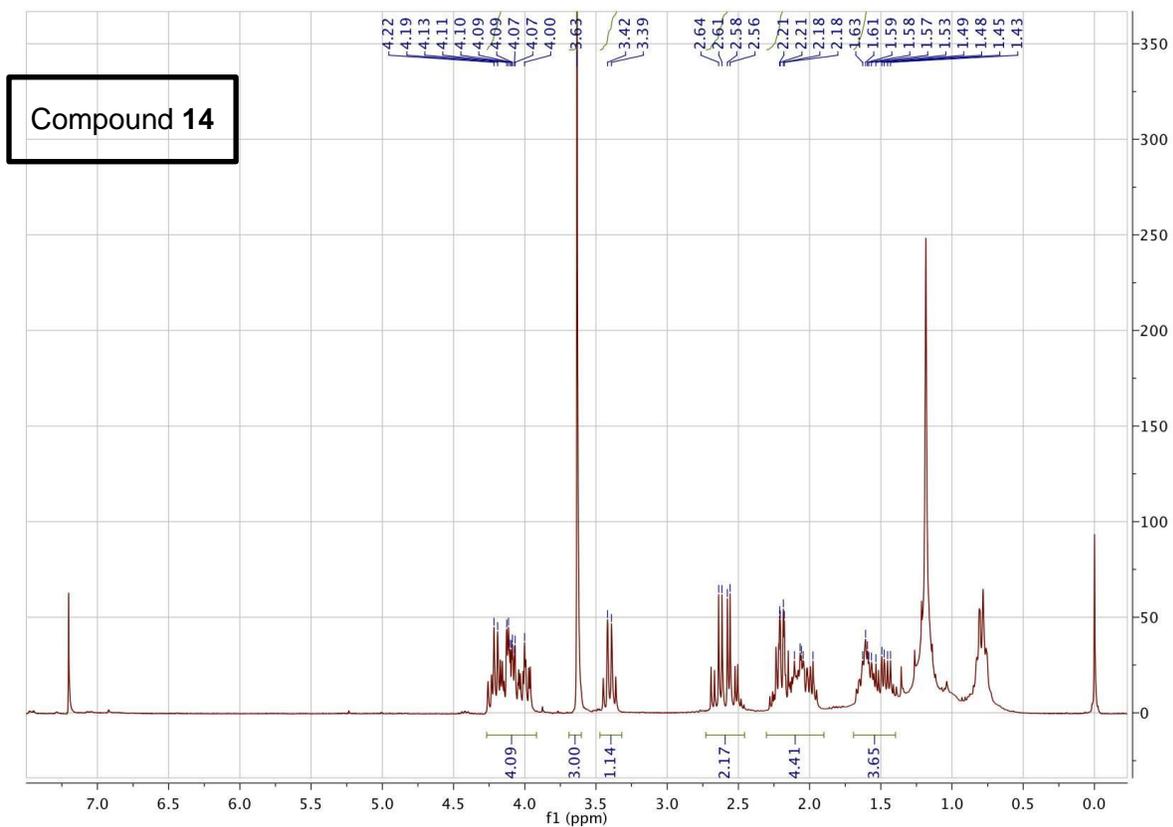


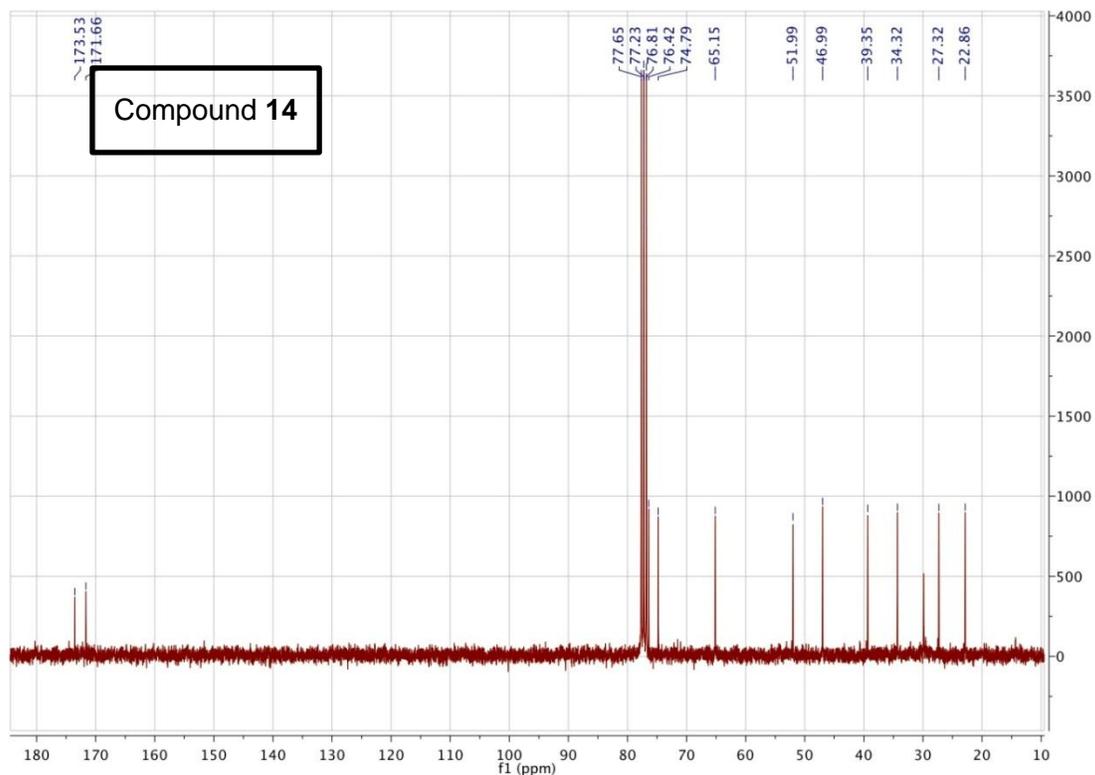
Methyl 2-(4-oxooctahydrofuro[3,2-c]oxepin-2-yl)acetate (**14**)



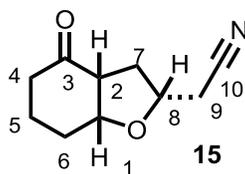
To a solution of **13** (90 mg, 0.425 mmol) in dry CH_2Cl_2 (3 mL) at 0°C and under an atmosphere of argon was added urea hydrogen peroxide complex (201 mg, 2.12 mmol) followed by the dropwise addition of freshly distilled trifluoroacetic anhydride (129 mg, 1.27 mmol). The reaction mixture was slowly warmed to rt and stirred for 12 h at this temperature. A solution of sodium thiosulfate was added and stirring was continued for 5 minutes. Additional CH_2Cl_2 was introduced and the organic layer was separated, washed with NaHCO_3 (10% solution in H_2O , 2 x 10 mL), dried over MgSO_4 . After filtration and removal of the solvent under reduced pressure, the crude was purified by column chromatography on neutral alumina (Pentane/AcOEt, 2:1) to afford the product **14** (48 mg, 50%) as a pale yellow oil.

^1H NMR [300 MHz, CDCl_3]: δ = 4.27-4.13 (m, 3H, H5,1), 4.06 (m, 1H, H9), 3.69 (s, 3H, H12), 3.48 (q, J = 8.8 Hz, 1H, H2), 2.70 (dd AB, J = 16.0, 7.3 Hz, 1H, H10), 2.60 (dd AB, J = 16.0, 5.5 Hz, 1H, H10), 2.26 (m, 2H, H8), 2.12-2.03 (m, 2H, H6,7), 1.69-1.49 (m, 2H, H6,7); **^{13}C NMR** [75 MHz, CDCl_3]: δ = 173.5 (C3), 171.7 (C11), 76.4 (C1), 74.8 (C2), 65.1 (C5), 52.0 (C12), 47.0 (C2), 39.3 (C10), 34.3 (C8), 27.3 (C6), 22.9 (C7); **IR** ($\tilde{\nu}$ / cm^{-1} , neat): 2984, 1741, 1446, 1374, 1243, 1047, 736; **HRMS (CI)** Calculated for $\text{C}_{11}\text{H}_{16}\text{O}_5$: 229.1076 (**M+H**)⁺; Found: 229.1077.





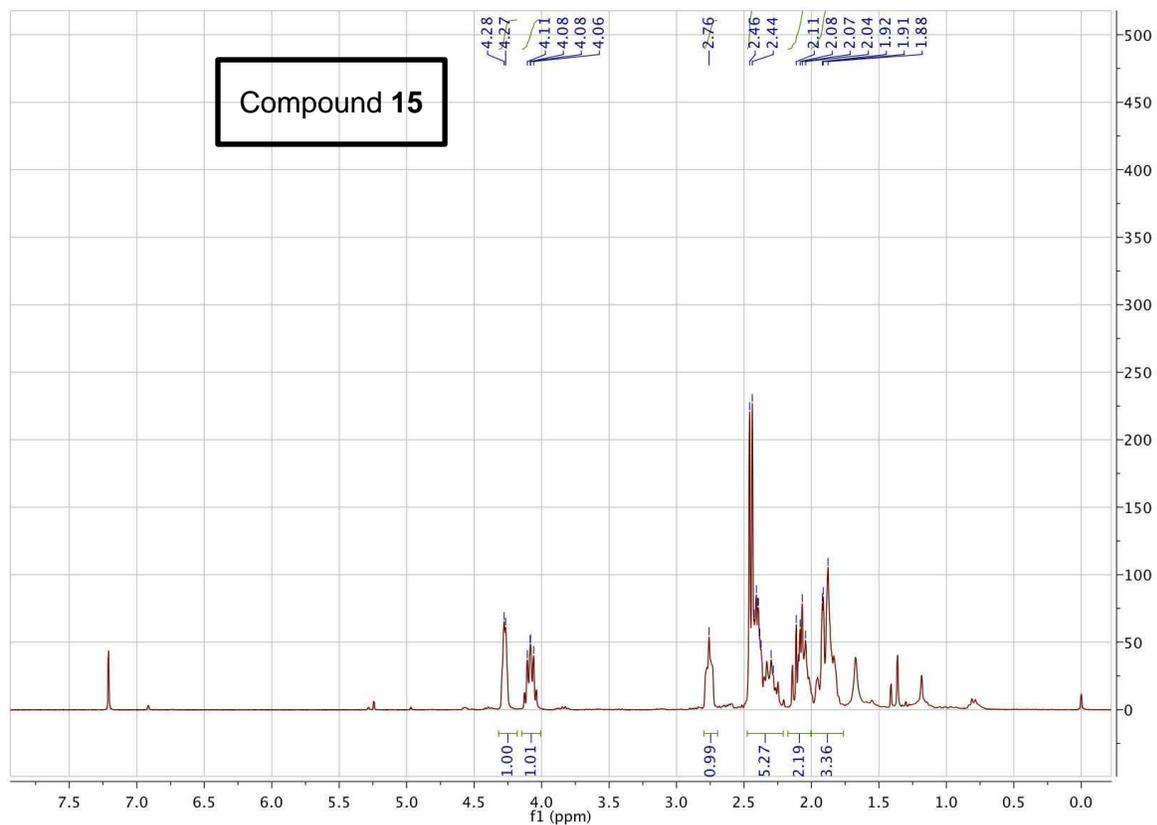
2-(4-Oxooctahydrobenzofuran-2-yl)acetonitrile (**15**)

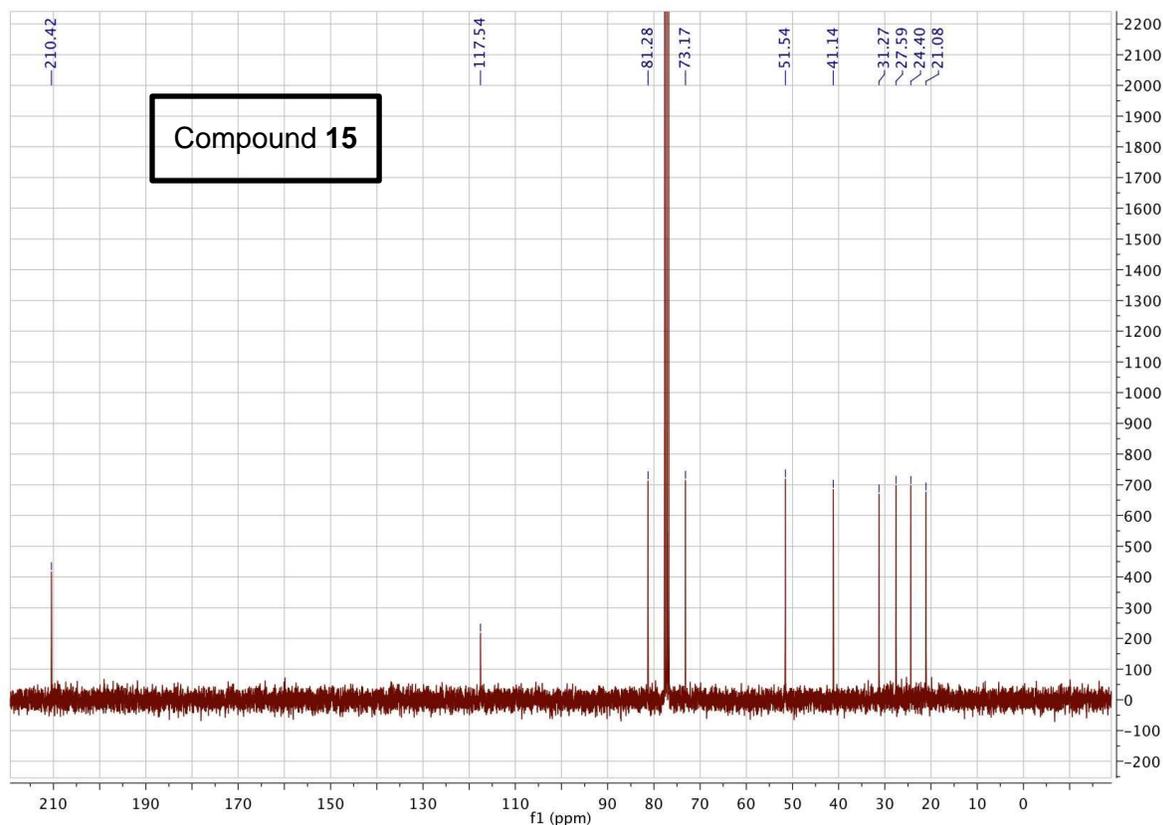


Configuration attributed by comparison with ester **13** and amine **17**

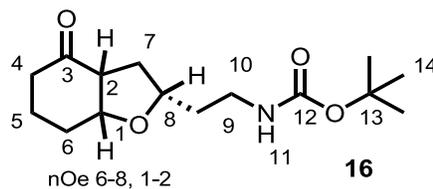
To a solution of **6** (50 mg, 0.28 mmol) in ethanol (2 mL) was added Pd/C (5 mg, 10 mol%). Light vacuum (20 mbar) was applied to the mixture before the vessel was connected to an atmosphere of hydrogen. The mixture was stirred at rt for 5 h before additional Pd/C (3 mg) was introduced to complete the reaction. After 2 h, the mixture was filtered through Celite[®], washed with EtOH and concentrated under reduced pressure. The crude was purified by filtration on a pad of silica gel and elution with AcOEt delivering the compound **15** after removal of the solvent (36 mg, 71%).

¹H NMR [300 MHz, CDCl₃]: δ = 4.33 (m, 1H, H1), 4.13 (m, 1H, H8), 2.81 (m, 1H, H2), 2.5 (d, *J* = 5.7 Hz, 2H, H9), 2.46 (m, 2H, H4), 2.36 (m, 1H, H7), 2.20-2.10 (m, 2H, H6, H7'), 2.01-1.89 (m, 3H, H5, H6'); **¹³C NMR** [75 MHz, CDCl₃]: δ = 210.3 (C3), 117.4 (C10), 81.1 (C1), 73.0 (C8), 51.4 (C2), 41.0 (C4), 31.1 (C7), 27.4 (C6), 24.2 (C9), 20.9 (C5); **IR** ($\tilde{\nu}$ /cm⁻¹, neat): 2946, 2255, 1706, 1075, 1025, 970; **MS** (CI)⁺ 180 (M+1, 100%); **HRMS (ESI)** Calculated for C₁₀H₁₄NO₂: 180.1025 (M+H)⁺; Found: 180.1018.



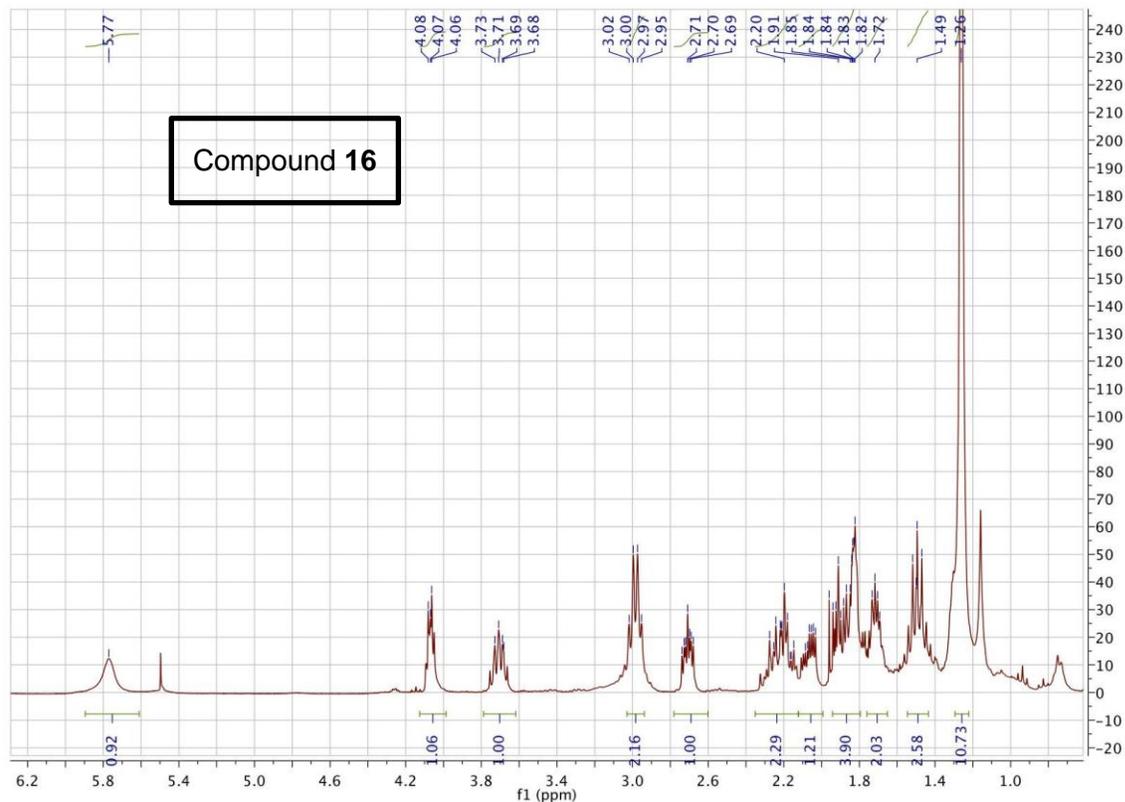


tert-Butyl 2-(4-oxooctahydrobenzofuran-2-yl)ethylcarbamate (**16**)

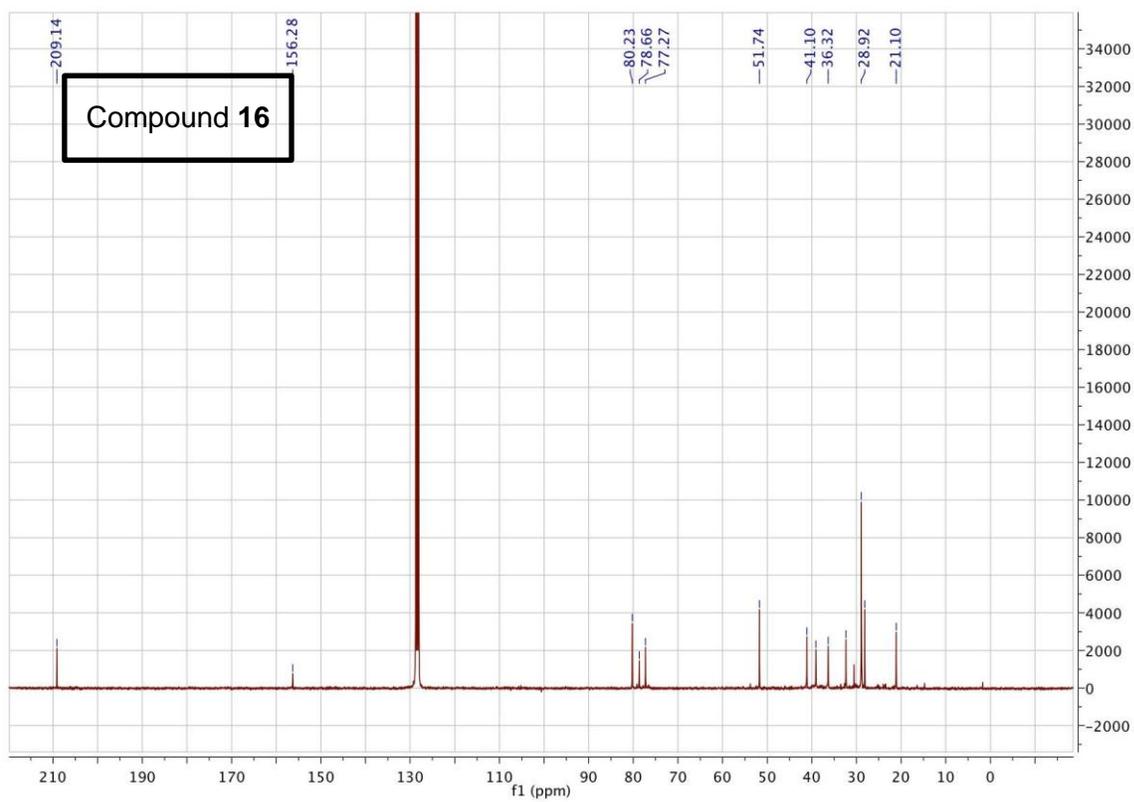
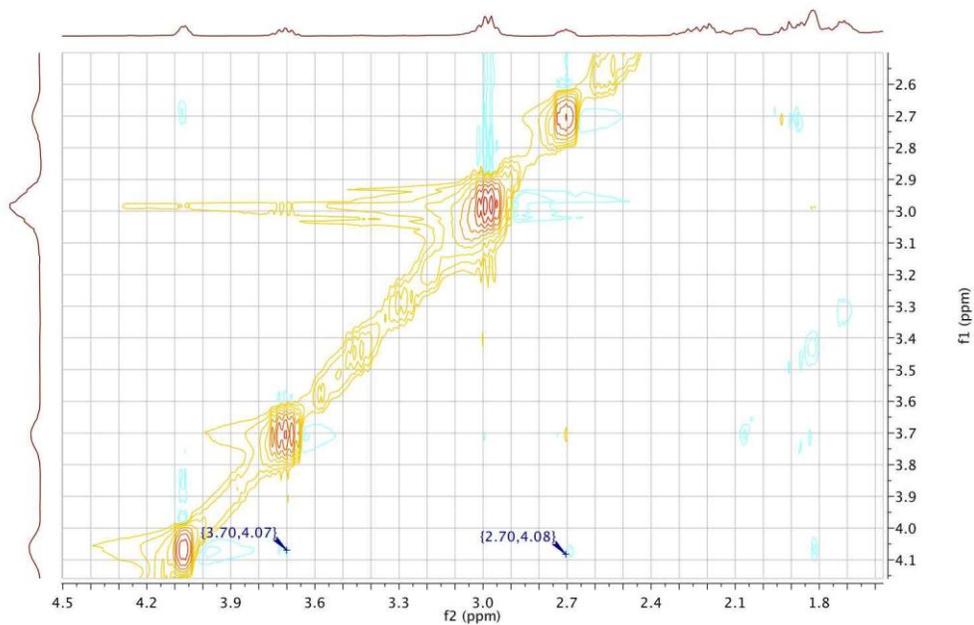


To a solution of **6** (50 mg, 0.28 mmol) in ethanol (2 mL) was added Pd/C (25 mg). Light vacuum (20 mbar) was applied to the reactor and trifluoroacetic acid (43 μ L, 64 mg, 0.56 mmol) was added. The vessel was connected to an atmosphere of hydrogen. The mixture was stirred at rt for 4.5 h and was filtered through Celite[®]. The pad was washed with CH₂Cl₂ and the solvent were removed under reduced pressure. The crude was taken up in CH₂Cl₂ (2 mL) and Et₃N (76 μ L, 0.56 mmol) then Boc₂O (62 mg, 0.28 mmol) were added. The mixture was stirred overnight before citric acid (10% aqueous) and CH₂Cl₂ were introduced in the flask. The aqueous layer was extracted with CH₂Cl₂ and the organic layers were brined and dried on MgSO₄. The solvents were removed on reduced pressure and the crude was purified on silica gel (AcOEt/Pentane, 1:1) to afford **16** (44 mg, 56 % yield over two steps).

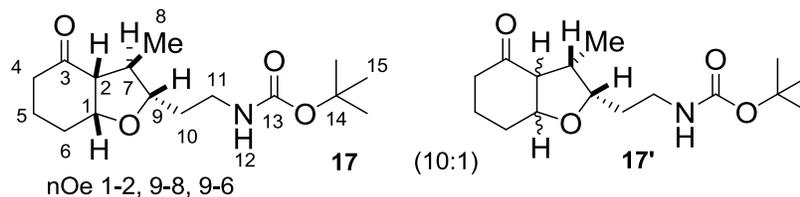
^1H NMR [300 MHz, CD_3COCD_3]: δ = 5.77 (s br, 1H, H11), 4.07 (m, 1H, H1), 3.71 (m, 1H, H8), 2.99 (q, J = 6.6 Hz, 2H, H10), 2.71 (m, 1H, H2), 2.22 (m, 2H, H4), 2.09 (m, 1H, H7), 1.94-1.82 (m, 4H, H7',6), 1.72 (m, 2H, H5), 1.50 (m, 2H, H9), 1.26 (s, 9H, H14); **^{13}C NMR** [75 MHz, C_6D_6]: δ = 209.1, 156.3, 80.2, 78.7, 77.3, 51.7, 41.1, 39.1, 36.3, 32.4, 28.9, 28.1, 21.1; **IR** ($\tilde{\nu}/\text{cm}^{-1}$, neat): 3358, 2973, 1701, 1514, 1366, 1251, 1168, 1070; **HRMS (ESI)** Calculated for $\text{C}_{15}\text{H}_{26}\text{NO}_4$: 284.1862 ($\text{M}+\text{H}$) $^+$, Found: 284.1857.



Compound 16, NOESY

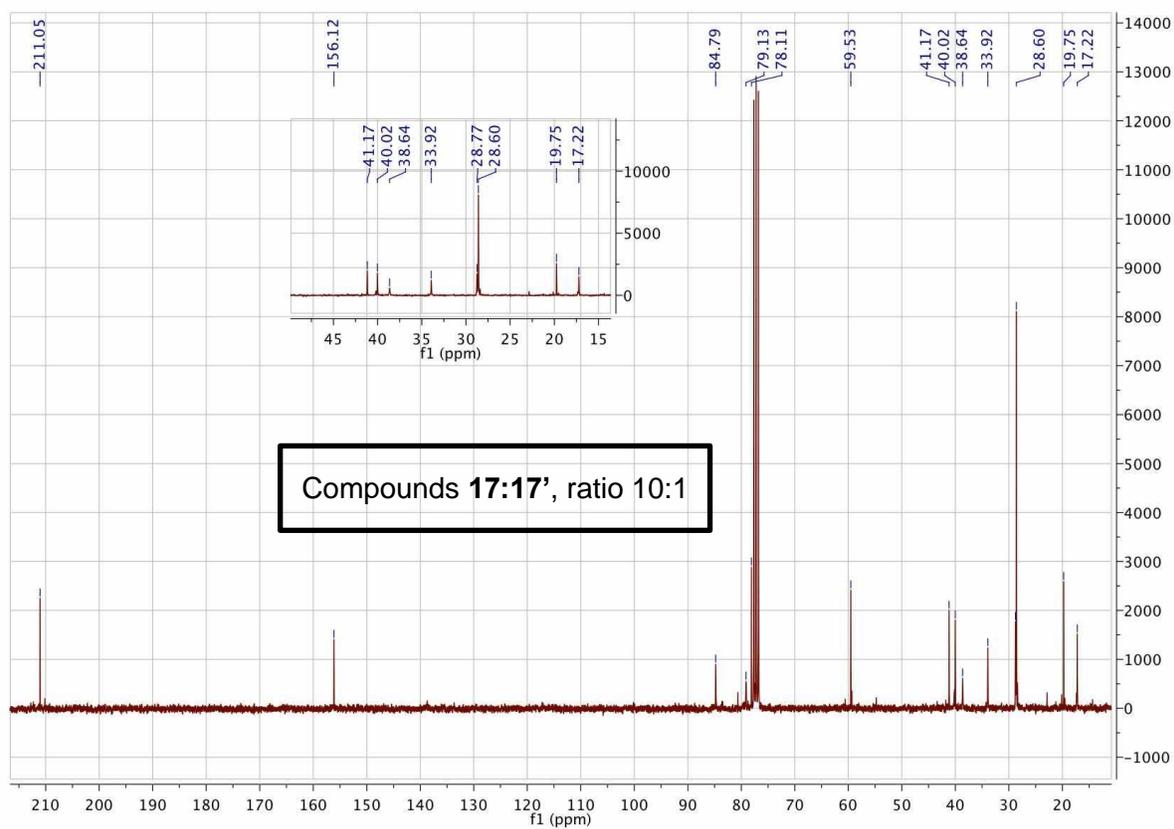
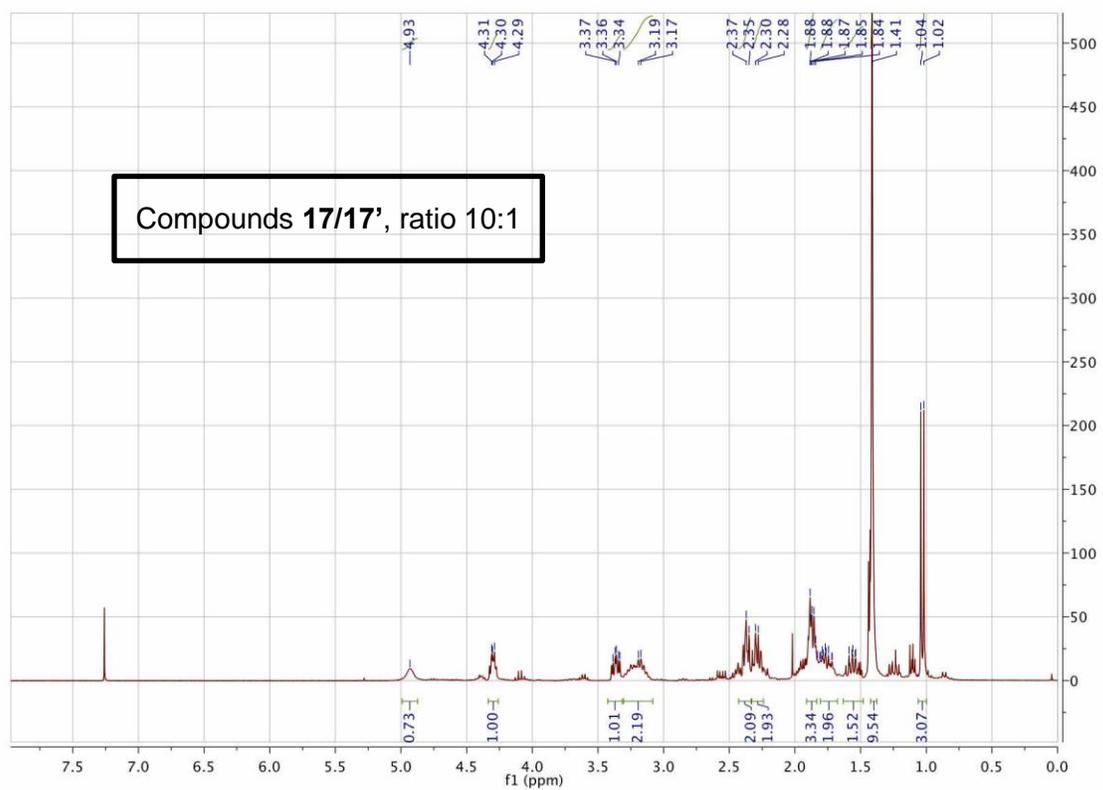


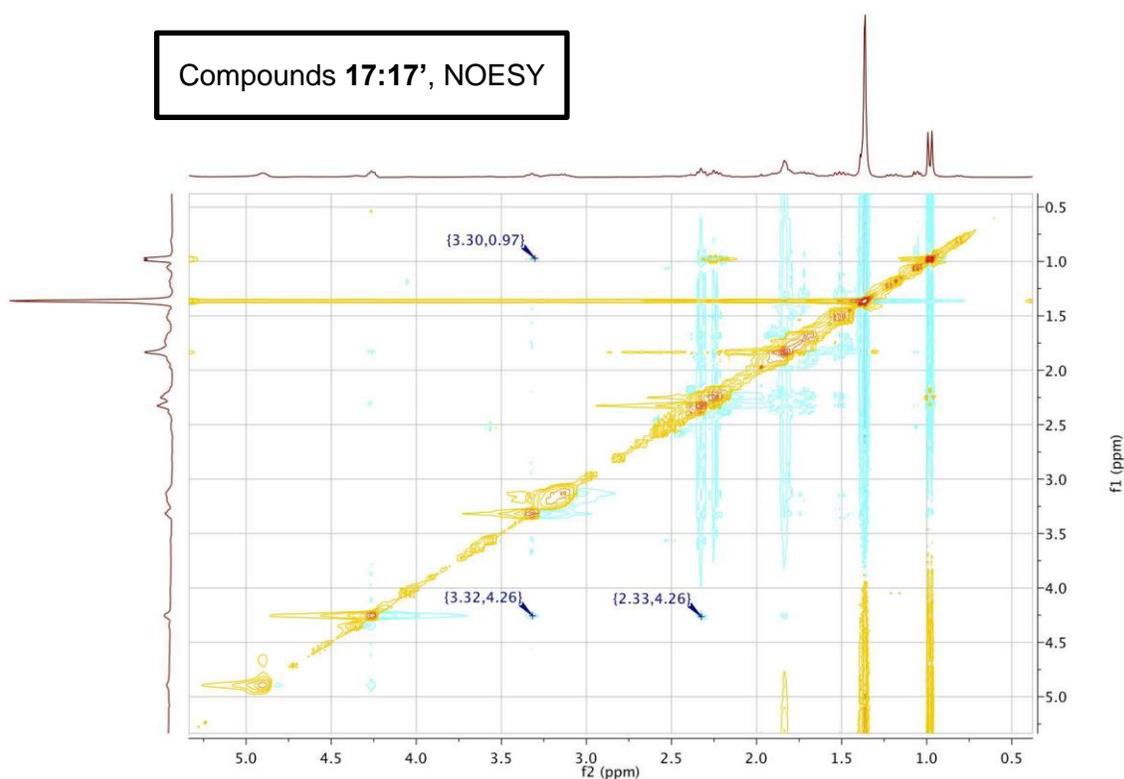
tert-Butyl 2-(3-methyl-4-oxooctahydrobenzofuran-2-yl)ethylcarbamate (17)



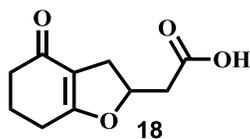
To a solution of **7** (100 mg, 0.523 mmol) in ethanol (4 mL) were added Pd/C (60 mg) and Boc₂O (114 mg, 0.523 mmol). Light vacuum (20 mbar) was applied to the vessel, trifluoroacetic acid (80 μL, 119 mg, 1.046 mmol) was added and the flask was connected to an atmosphere of hydrogen. The mixture was stirred at rt for 7 h and was filtered through a pad of cotton. The pad was washed with CH₂Cl₂ and the organic layer was washed with NaHCO₃ saturated, brined and dried on MgSO₄. Volatiles were removed on reduced pressure and the crude was purified on silica gel (AcOEt/CH₂Cl₂, 1:2) to afford product **17** (80 mg, 46 % yield).

¹H NMR [300 MHz, CDCl₃]: δ = 4.93 (s br, 1H, H12), 4.30 (m, 1H, H1), 3.36 (m, 1H, H9), 3.30-3.19 (m, 2H, H11), 2.38-2.26 (m, 4H, H7, H2, H4), 1.84-1.82 (m, 3H, H5, H6), 1.79-1.72 (m, 2H, H5, H10), 1.55 (m, 1H, H10), 1.41 (s, 9H, H14), 1.03 (d, *J* = 6.8 Hz, 3H); **¹³C NMR** [75 MHz, CDCl₃]: δ = 211.5, 156.1, 84.8, 79.1, 78.1, 59.5, 41.2, 40.0, 36.3, 33.9, 28.8, 28.6, 19.7, 17.2; **IR** ($\tilde{\nu}$ /cm⁻¹, neat): 3352, 2935, 1701, 1514, 1366, 1245, 1168; **HRMS (ESI)** Calculated for C₁₆H₂₈NO₄: 298.2018 (**M+H**)⁺, Found: 298.2006.



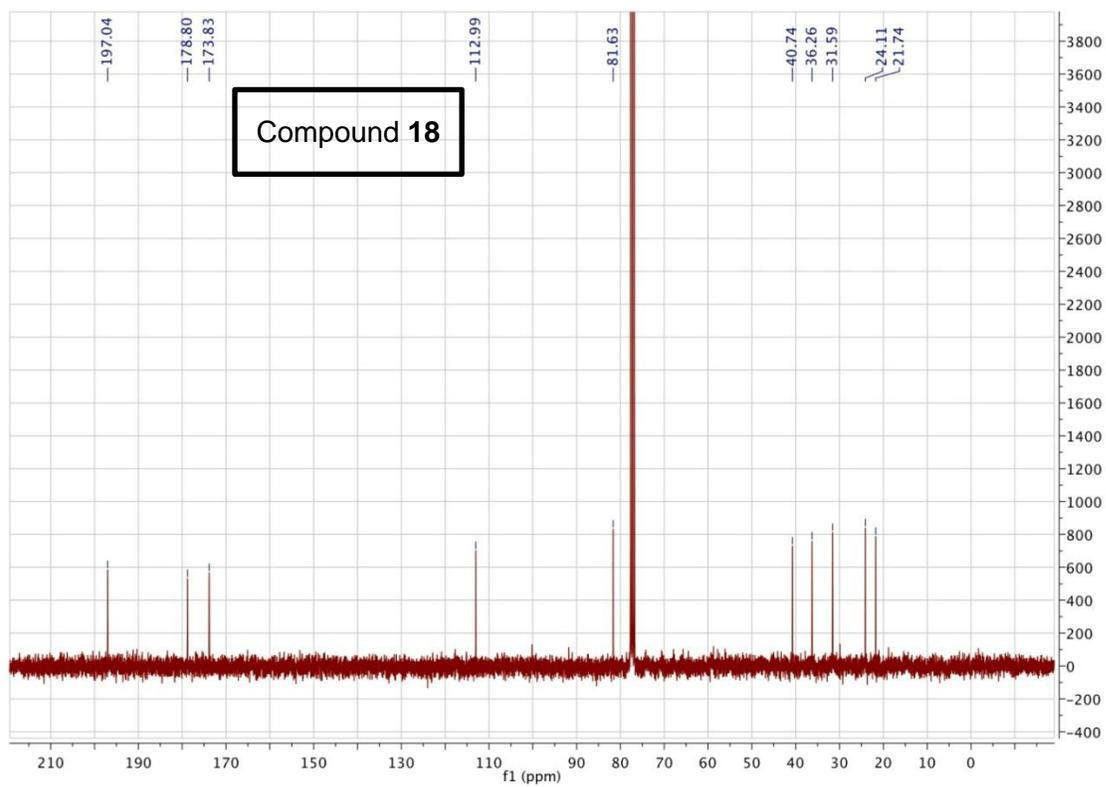
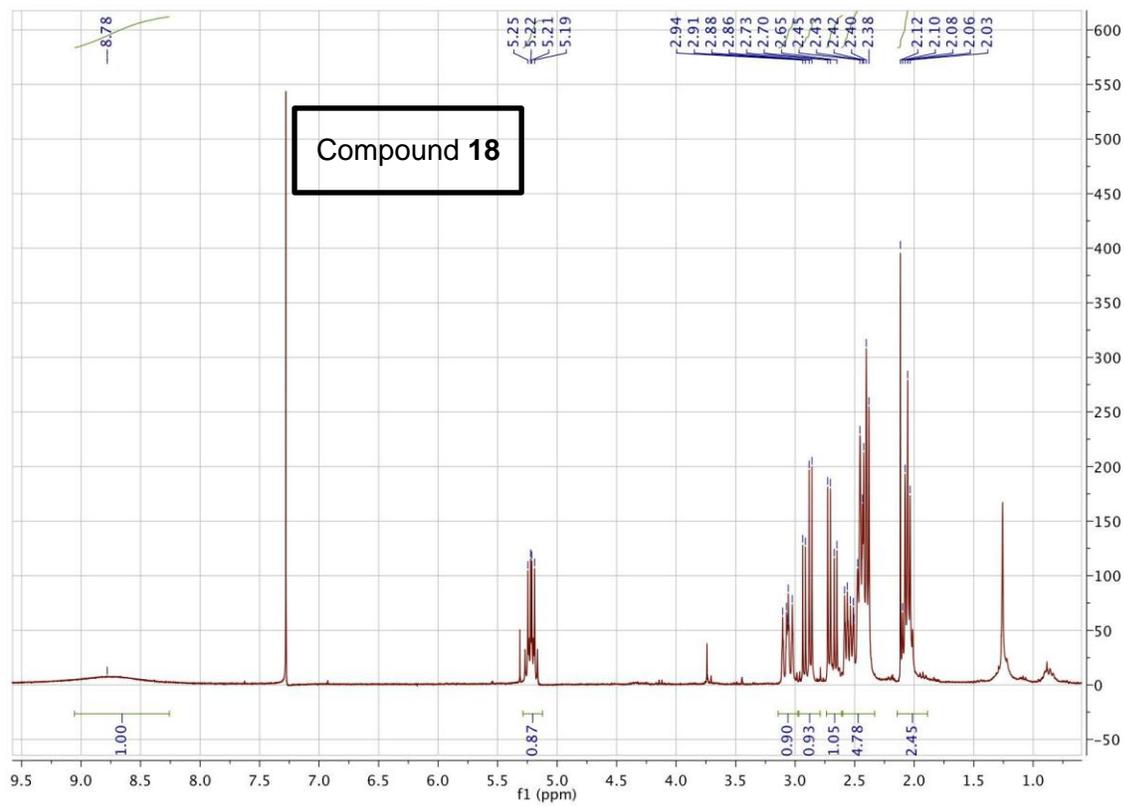


2-(4-Oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)acetic acid (**18**)

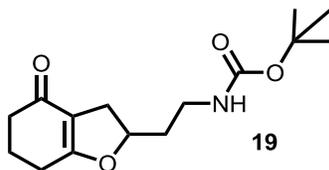


To a solution of **5** (80 mg, 0.380 mmol) in glacial acetic acid (1 mL) was added HBr (65 μ L, 0.380 mmol, 48% in H₂O) and the mixture was heated at 60 °C for 14 h. The reaction was diluted with cold water, washed first with Et₂O/pentane (1:1, v/v) then the aqueous layer was back extracted with CH₂Cl₂ (3x). The organic extracts obtained were combined, dried (MgSO₄) and the solvent removed under reduced pressure to deliver compound **18** as a pale beige solid (45 mg, 60 %).

m.p. 175 °C. ¹H NMR [300 MHz, CDCl₃]: δ = 8.78 (s br, 1H), 5.20 (dq, J = 10.0, 7.0 Hz, 1H), 3.04 (ddt, J = 14.5, 10.0, 1.5 Hz 1 H), 2.86 (dd, AB J = 16.0, 7.0 Hz, 1H), 2.57 (dd, AB J = 16.0, 7.0 Hz, 1H), 2.5 (ddt, J = 14.5, 7.0, 1.5 Hz 1 H), 2.42 (m, 2H), 2.37 (m, 2H), 2.03 (m, 2H); ¹³C NMR [75 MHz, CDCl₃]: δ = 197.0, 178.8, 173.8, 113.0, 81.6, 40.7, 36.3, 31.6, 24.1, 21.7; IR ($\tilde{\nu}$ /cm⁻¹, neat): 2984, 1742, 1446, 1373, 1243, 1047, 741; HRMS (EI) Calculated for C₁₀H₁₂O₄: 196.0736 (M⁺); Found: 196.0736.

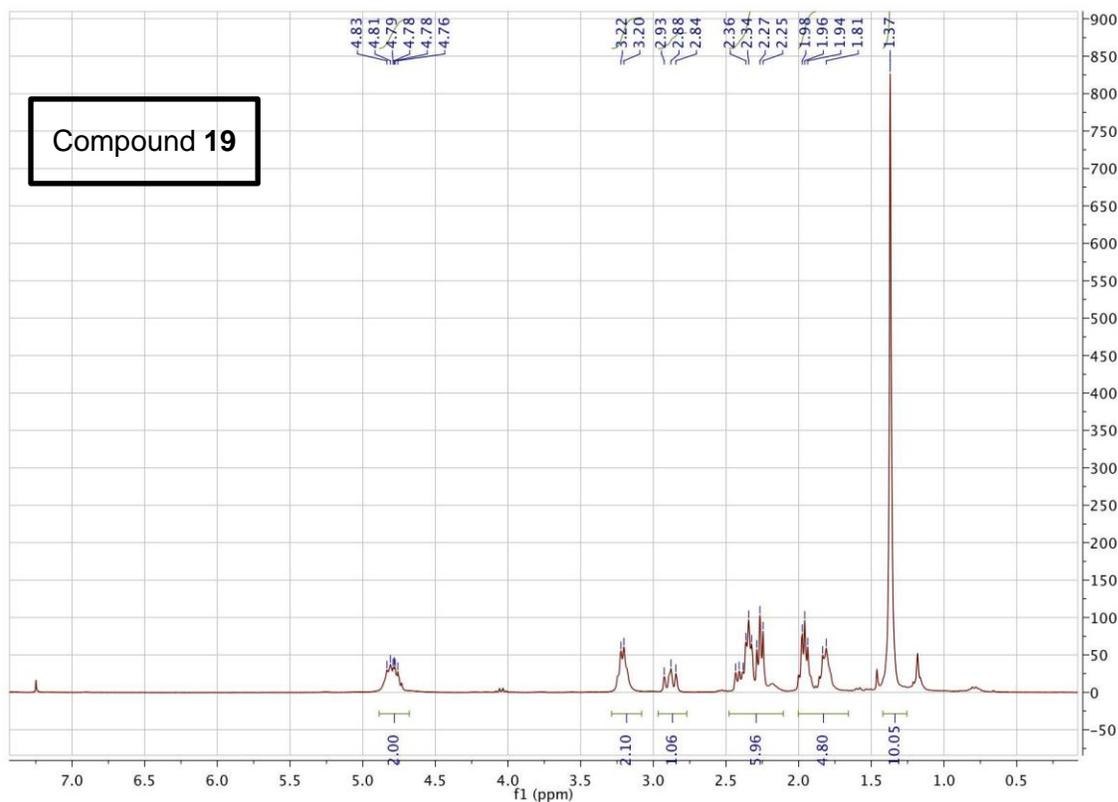


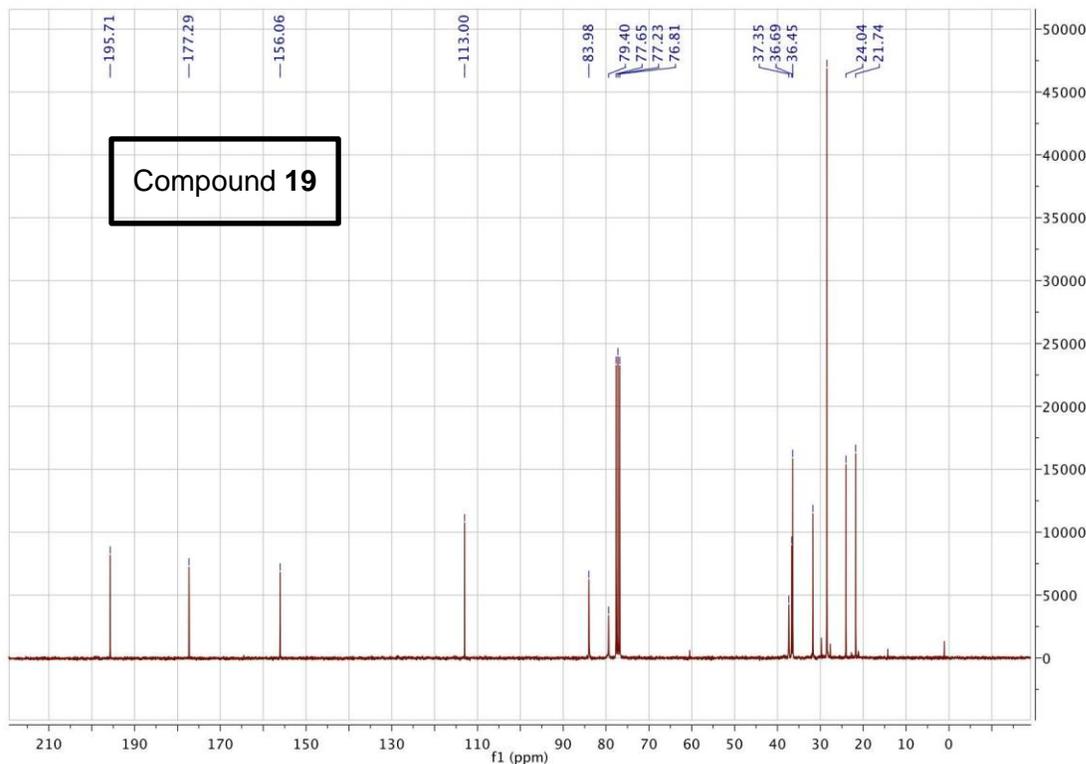
tert-Butyl 2-(4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-yl)ethylcarbamate (19)



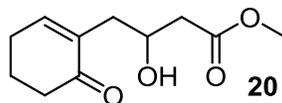
To a solution of **6** (185 mg, 1.045 mmol) in MeOH (3 mL) was added Boc₂O (230 mg, 1.045 mmol) followed by an excess of Ni Raney (≈50% in water). The mixture was stirred at rt for 16 h before filtration through Celite[®]. To the filtrate was added CH₂Cl₂ and water. After extraction of the aqueous layer with CH₂Cl₂, the organic layers were combined, brined, dried on Na₂SO₄. After filtration, the solvent was removed under reduced pressure and the crude was purified by chromatography on silica gel (pentane:AcOEt, 1/1) to yield product **19** (155 mg, 53 % yield).

¹H NMR [300 MHz, CDCl₃]: δ = 4.83 (m, 1H), 4.68 (s br, 1H), 3.30 (m, 2H), 2.95 (m, 1H), 2.48 (m, 1H), 2.41 (m, 2H), 2.34 (m, 2H), 2.03 (m, 2H), 1.90 (m, 2H), 1.44 (s, 9H); **¹³C NMR** [75 MHz, CDCl₃]: δ = 194.6, 176.2, 154.9, 111.9, 82.9, 36.2, 35.6, 30.9, 27.3, 22.9, 21.7; **HRMS (ESI)** Calculated for C₁₅H₂₄NO₄: 282.1705 (**M+H**)⁺; Found: 282.1696.



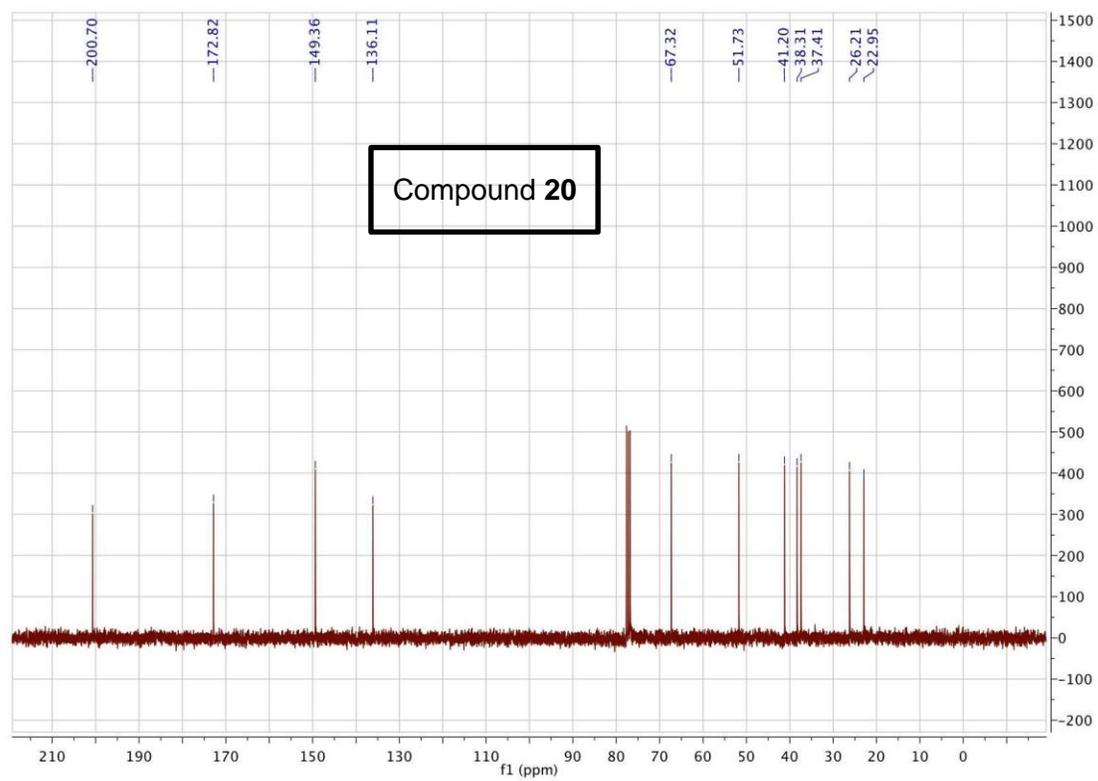
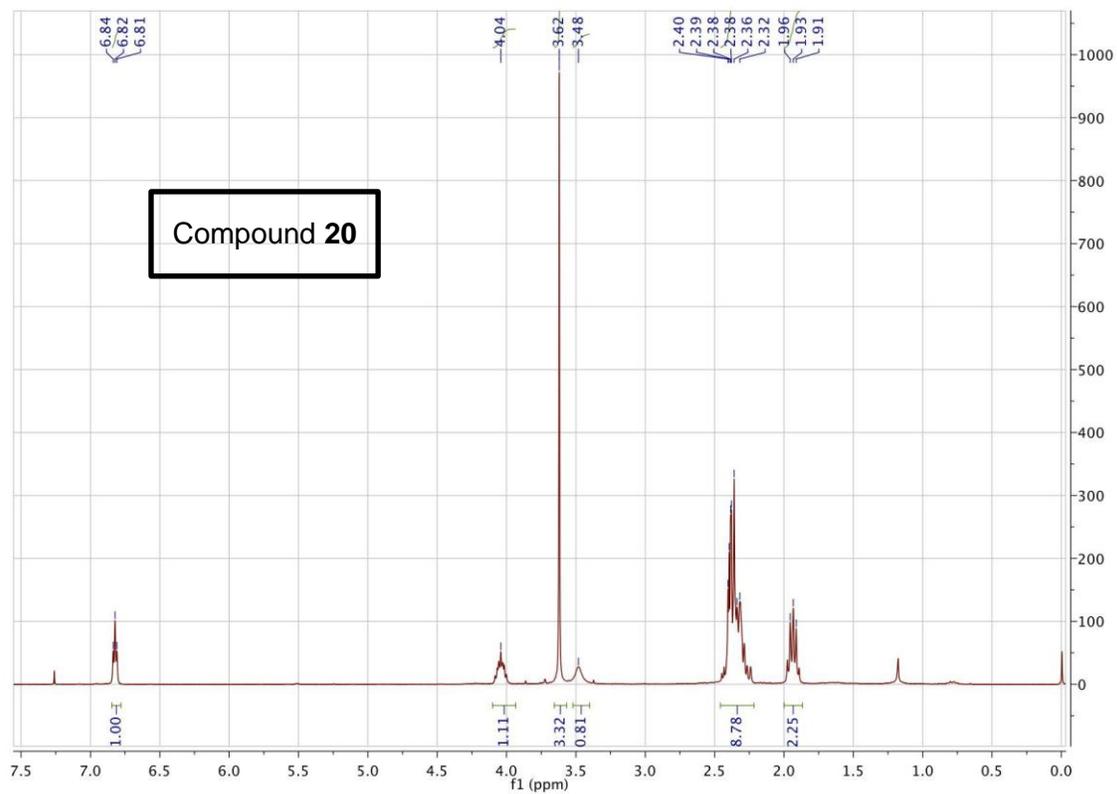


Methyl 3-hydroxy-4-(6-oxocyclohex-1-enyl)butanoate (**20**)

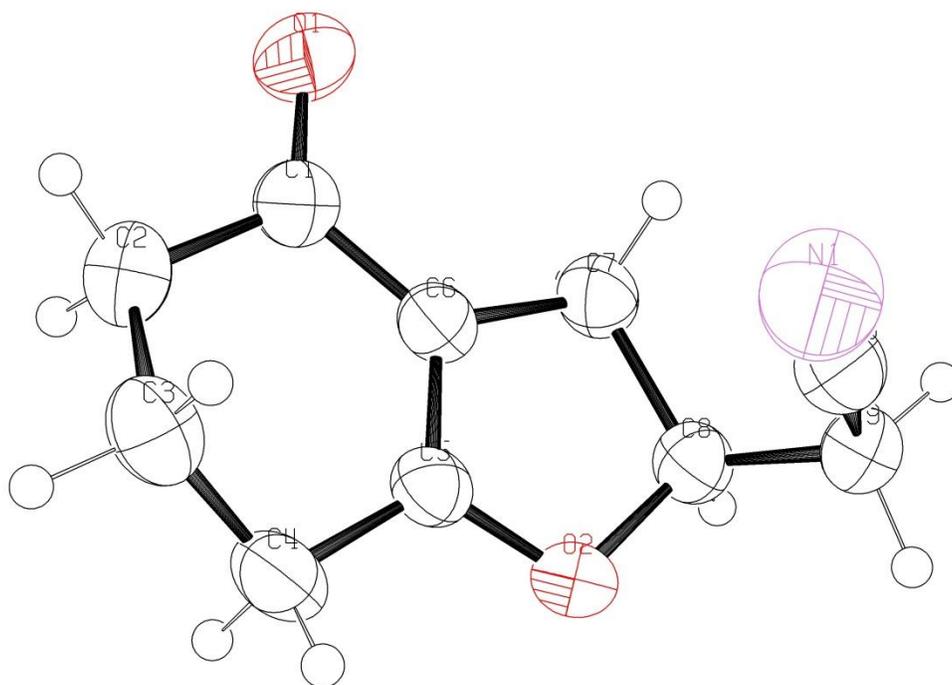


To a solution of **5** (100 mg, 0.476 mmol) in MeOH/EtOH (10 mL, 1:1, v/v) was added CeCl₃·7H₂O (355 mg, 0.952 mmol). The mixture was cooled to -90°C and stirred at the same temperature for 15 minutes before addition of NaBH₄ (50 mg, 1.29 mmol). The reaction was warmed to -10°C over 2 h 30 then water was added. After extraction with CH₂Cl₂ (3x), the organic layers were dried over MgSO₄, filtered and the solvent were removed under reduced pressure to afford the pure product **20** (98 mg, > 95%).

¹H NMR [300 MHz, CDCl₃]: δ = 6.82 (t, *J* = 4.1 Hz, 1H), 4.04 (m, 1H), 3.62 (s, 3H), 3.48 (s br, 1H), 2.40-2.32 (m, 8H), 1.93 (q, *J* = 6.2 Hz, 2H); ¹³C NMR [75 MHz, CDCl₃]: δ = 200.7, 172.8, 149.4, 136.1, 67.3, 51.7, 41.2, 38.3, 37.4, 26.2, 22.9; IR (ν̄/cm⁻¹, neat): 3396, 2946, 1723, 1651, 1443, 1278, 1163; HRMS (EI) Calculated for C₁₁H₁₅O₃: 195.1021 (M-H₂O)⁺; Found 195.1023.



Crystallographic study of 6: A colorless prism monoclinic, space group $P2_1$ (No. 4), $a = 8.4105(17)$ Å, $b = 5.6321(11)$ Å, $c = 10.022(2)$ Å, $\beta = 107.78$ 0(3), $V = 452.05(16)$ Å³, $Z = 2$, $d_{\text{calcd}} = 1.302$, $\mu = 0.71073$ mm⁻¹ was used for data collection. Diffraction intensities were measured using a Bruker SMART APEX diffractometer equipped with a CCD area Detector using Mo K α radiation at ambient temperature. Unit cell parameters and orientation matrix were determined by using the SMART software.⁴⁵ Intensities were integrated, corrected for Lorentz polarization. Absorption and unit cell parameters were refined by using SAINT plus and SADABS Softwares. The SHELX 97 Software package was used to solve and to refine the structural model. The final cycle of full-matrix least-squares refinement was based on 1631 observed reflections (for $I > 2\sigma(I)$) and 460 variable parameters and gave $R_1 = 0.0354$, $wR_2 = 0.0966$. The value of the goodness of fit indicator was 1.061 (Summary of Data CCDC 818360). ORTEP representation has been made using ORTEP III software.³



³ Michael N. Burnett and Carroll K. Johnson, ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL-6895, 1996.