Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Stereoselective Rearrangement of Guaianolides to tricyclic δ-Valerolactones

Martin Schanderl, Won Boo Jeong, Michael Schwarz and Oliver Reiser*

Universität Regensburg, Institut für Organische Chemie, Universitätsstr. 31, 93053 Regensburg, Germany. Fax: +49 941-943-4121; Tel: +49 941-943-4631; E-mail: oliver.reiser@chemie.uni-regensburg.de

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General Methods

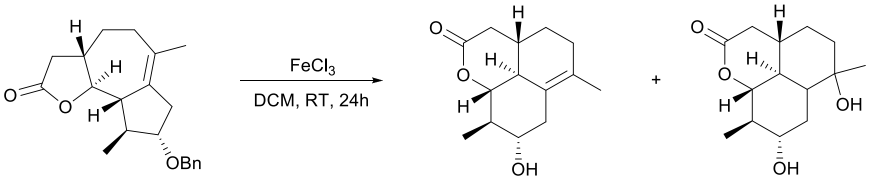
Anhydrous dichloromethane was taken from the MB-SPS solvent purification system. Ethyl acetate and hexanes (40-60 °C) were purified by distillation before use. All reagents were of p.a. quality. Reactions were performed in oven dried and in vacuo heated reaction flasks under a predried nitrogen or argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance 300, and Bruker Avance 600 Kryo, with a H/C/P/F QNP gradient probe. The chemical shift δ is given in ppm. Calibration was set on chloroform-d$_1$ as internal standard (7.26 ppm for ^{1}H and 77.00 ppm for ^{13}C). The spectra were evaluated in 1st order and the coupling constants are given in Hertz (Hz). The following abbreviations for the spin multiplicity were used: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dt = doublet of a triplet, dd = double doublet, ddd = doublet of a double doublet. The multiplicity of the signals were detected by DEPT 135 and 90 and are given as: + = primary und tertiary C-atom (positive DEPT 135 signal; tertiary C-atom: DEPT 90 signal), - = secondary C-atom (negative DEPT 135 signal), Cq = quaternary C-atom (DEPT-signal intensity zero).

Melting points were measured on a Büchi SMP 20 in a silicon oil bath. The melting points are uncorrected. Infrared-Spectra were recorded on a Biorad FT-IR Excalibur FTS 3000. Masspectrometry was performed on Varian MAT 311A, Finnigan MAT 95, Thermoquest Finnigan TSQ 7000, Nermag quadrupoles, VG ZAB high-resolution double-focusing and VG Autospec-Q tandem hybrid with EBEqQ configuration. Optical rotation was measured on a 241 MC Perkin-Elmer polarimeter at a wavelength of 589 nm (Na-D) in a 1 dm cell and the $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. X-ray analysis was performed by the crystallography laboratory of the University of Regensburg (STOE-IPDS, Stoe & Cie GmbH).

In Vitro Cell Assays: All stock cultures (MCF 7, breast cancer) were grown in T-25 flasks. Freshly trypsinized cell suspensions were seeded in 96-well microtiter plates at densities of 30000 cells per well and incubated 24 h at 37 °C with 5 % CO$_2$ in 1x RPMI 1640, 10 % fetal calf serum. The compound was added afterwards from DMSO-diluted stock and incubated for another 24 hours. Cell medium was removed and the cells were washed twice with 1x RPMI 1640 without fetal calf serum. Afterwards the cells were incubated at 37 °C in 10 % Resazurin solution for 2 h. The absorbency at 595 nm was measured using a microplate reader. The mean IC$_{50}$ is the concentration of agent that reduces cell growth by 50% under the experimental conditions and is the average from three determinations that were reproducible and statistically significant.

Xray structures of 6, 10, 12, 14, 15: Cif files are included as separate files with the supporting information. Moreover, the data are deposited at the Cambridge Crystallographic Data Centre (CCDC 798357 – 798361).

(3a*S*,8*S*,9*R*,9a*R*,9b*S*)-8-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydrobenzo[*de*]chromen-2(3*H*)-one (12) and (3a*S*,8*S*,9*R*,9a*R*,9b*S*)-6,8-dihydroxy-6,9-dimethyldecahydrobenzo[*de*]chromen-2(3*H*)-one (19)



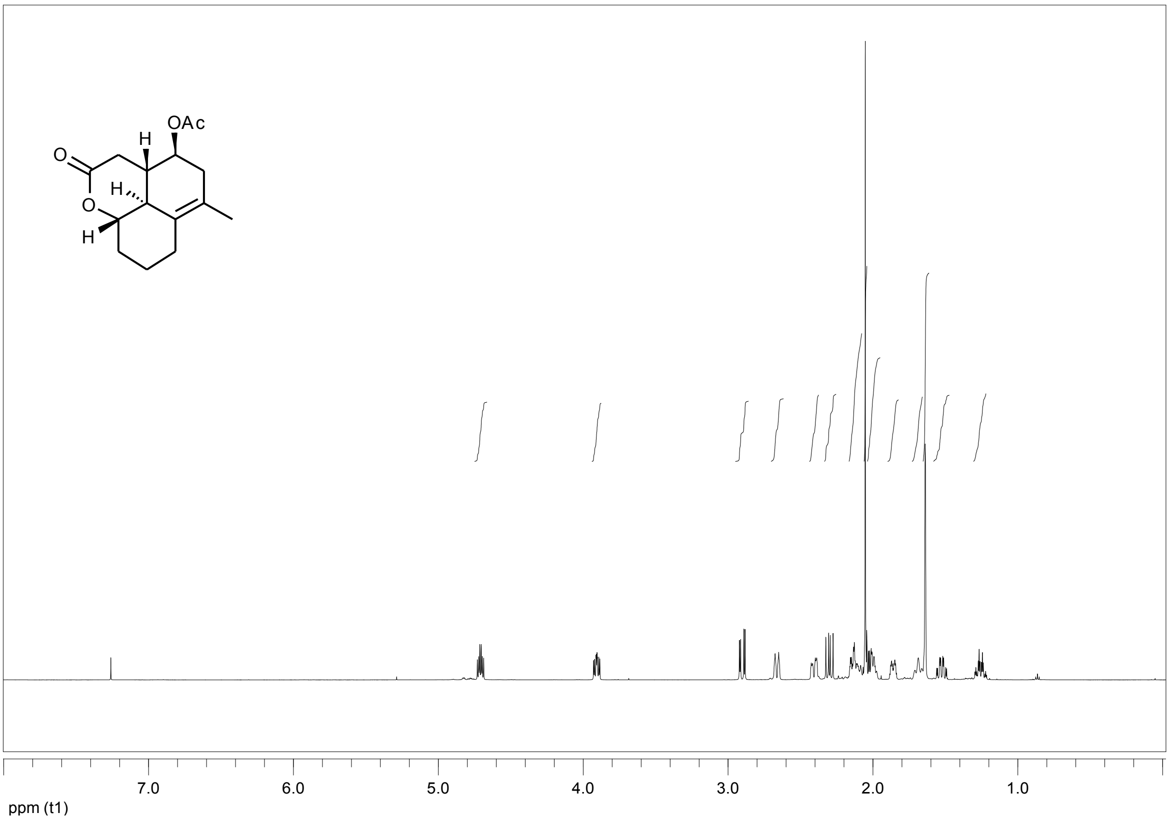
11 **12**, 71% **19**, 29%

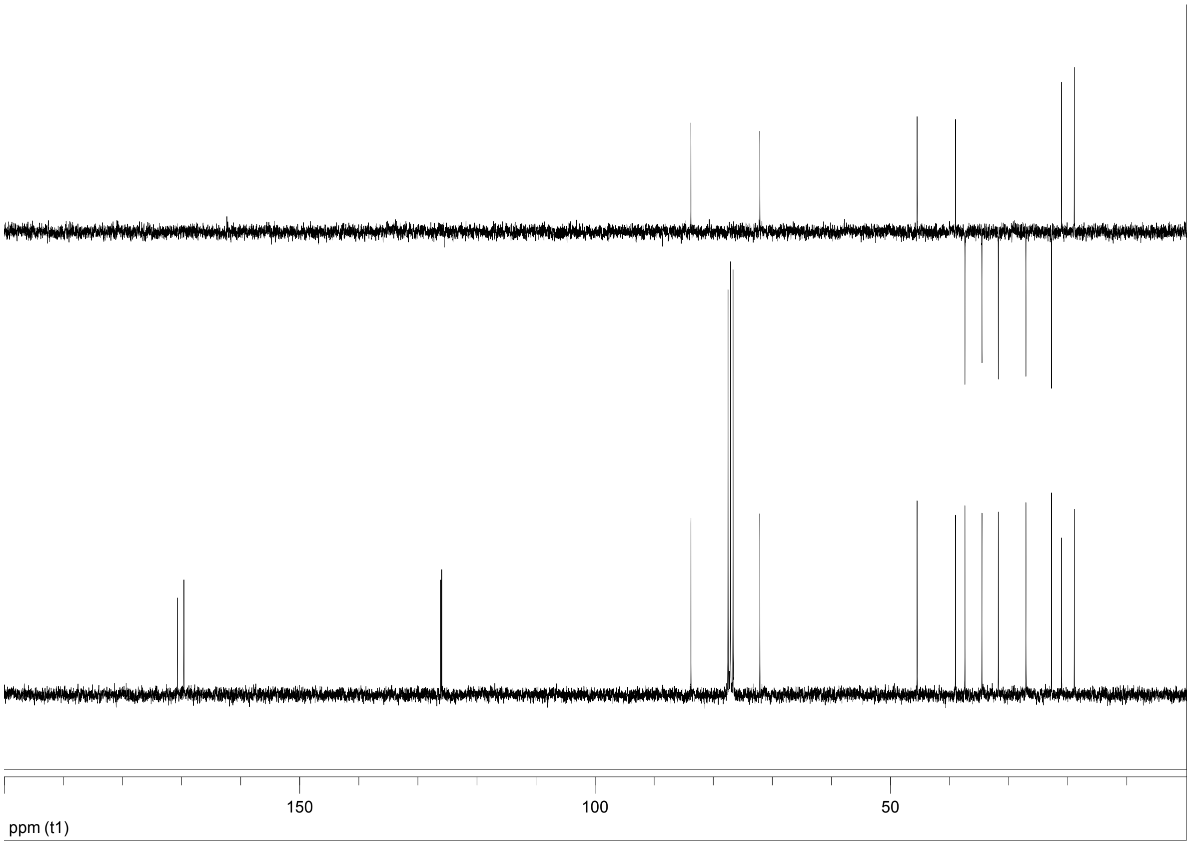
Compound **11** (60 mg, 0.18 mmol, 1 equiv) was dissolved under a nitrogen atmosphere in anhydrous CH_2Cl_2 (5 ml) in a flame dried Schlenk flask. Anhydrous $FeCl_3$ (29 mg, 0.18 mmol, 1.0 equiv) was added in one portion. After 14 and 18 hours reaction time, another portions of $FeCl_3$ were added (1.0 and 3.0 equiv). After 24 h hours total reaction time H_2O (1 ml) and CH_2Cl_2 (10 ml) were poured into the reaction mixture and the layers were separated. The aqueous layer was again extracted with CH_2Cl_2 (1x4 ml/mmol). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography on silica gel (hexanes:ethylacetate 1:1) afforded **12** (31 mg, 71%). Furthermore, **19** could be isolated (12 mg, 29 %), which was generated by water addition to **12** onto the C-6, C-6a double bond.

δ-Valerolactone 12: R_f (hexanes/ethyl acetate 1 :1, Mostain) = 0.31; $[\alpha]_D^{20}$ = +98.5 (c = 0.540, $CHCl_3$).- ^1H NMR (300 MHz): δ 1.20 (d, *J* = 6.4 Hz, 3H, 9-C*H*$_3$), 1.66 (s, 3H, 6-C*H*$_3$), 1.68-1.78 (m, 2H), 1.79 1.90 (m, 2H), 1.91-2.17 (m, 4H), 2.20 (dd, *J* = 18.3 Hz, 12.2 Hz, 1H, 7-H_b), 2.73 (dd, *J* = 18.3 Hz, 5.2 Hz, 1H, 7-H_a), 2.92 (dd, *J* = 14.0 Hz, 4.7 Hz, 1H, 3-H_a), 3.11 (ddd, *J* = 10.8 Hz, 10.4 Hz, 4.6 Hz , 1H, 8-H), 3.42 (dd, *J* = 10.4 Hz, 10.4 Hz, 1H, 9a-H).- ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.5 (+, 9-*C*H_3), 19.2 (+, 6-*C*H_3), 27.6 (-), 31.6 (-), 34.9 (+), 36.9 (-), 37.8 (-), 44.7 (+), 44.9 (+), 72.5 (+, 8-C), 86.6 (+, 9a-C), 122.0 (Cq, 6-C), 130.7 (C_q, 6a-C), 170.9 (Cq, 2-C)- IR (KBr): $\tilde{\nu}$ 3408, 3323, 2925, 1732, 1690, 1233, 1055, 799, 645 cm^{-1}. -HRMS (EI, 70 eV): calcd for $C_{14}H_{20}O_3$: 236.1412 [M^+], found: 236.1408 [M^+]).

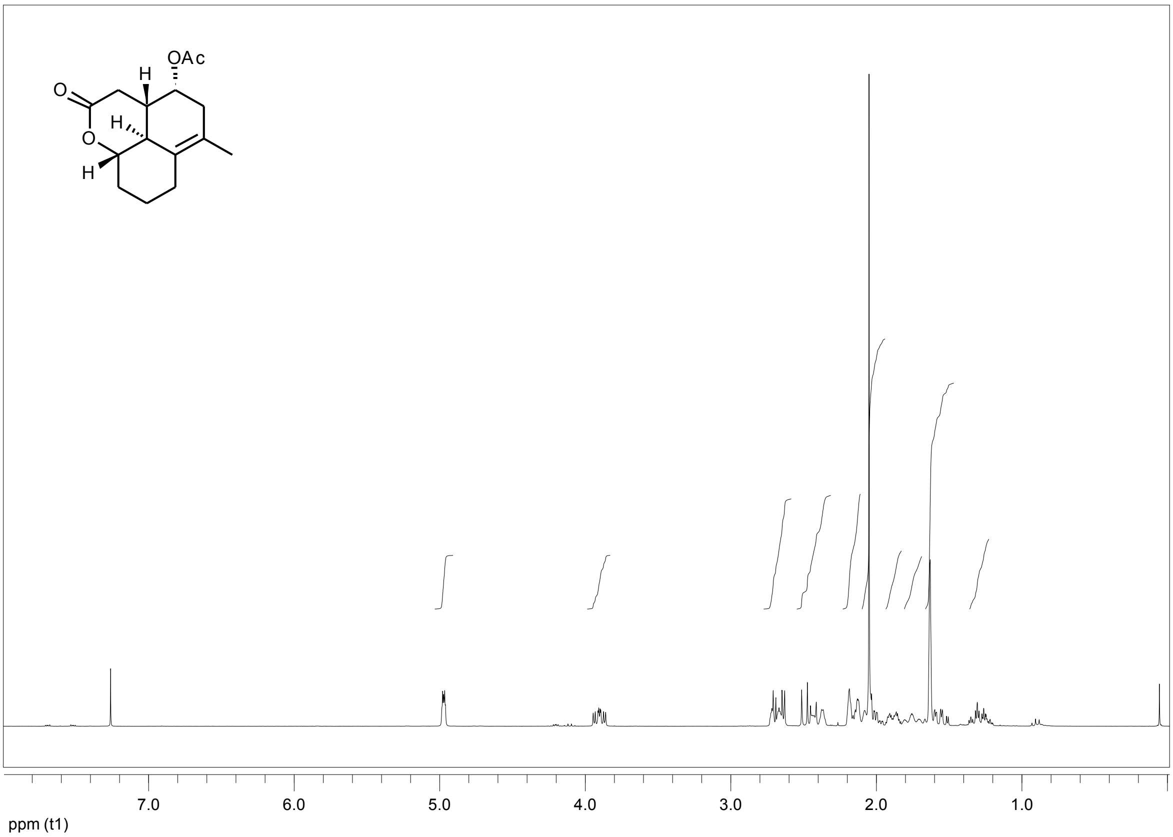
δ-Valerolactone 19 (1:1 mixture of C-6-epimers: R_f (hexanes/ethyl acetate 1 :1, Mostain) = 0.16. - ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, *J* = 6.3 Hz, 3H, 9-C*H*$_3$), 1.18-1.28 (m, 1H), 1.60 (s, 3H, 6-C*H*$_3$), 1.40-1.74 (m, 7H), 1.75-1.95 (br s, 1H, O*H*), 2.20-2.33 (m, 3H), 2.74 (dd, *J* = 18.5 Hz, 4.8 Hz, 1H), 3.30 (ddd, *J* = 11.0 Hz, 10.3 Hz, 4.4 Hz, 1H), 3.56 (dd, *J* = 10.2 Hz, 10.2 Hz, 1H, diastereomer-1), 3.65, *J* = 10.4 Hz. 1H, diastereomer-2). - ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.7 (+, 9-*C*H_3), 28.0 (-), 31.3 (+, 6-C*H*$_3$), 35.0 (-), 35.4 (+), 36.9 (-), 41.4 (-), 42.2 (+), 45.3 (+), 72.8 (Cq, 6-C), 73.0 (+), 85.4 (+), 170.3 (Cq, *C*=O). IR (Film): $\tilde{\nu}$ 3418, 2930, 1723, 1233, 1016, 756 cm^{-1}. - MS (EI-MS, 70 eV): *m/z* (%) = 236.0 (M^+, 4), 218.0 ($[M-H_2O]^+$, 7), 175.9 (19), 159.2 (100), 158.1 (94), 143.1 (44), 91.1 (26), 28.1 (62).

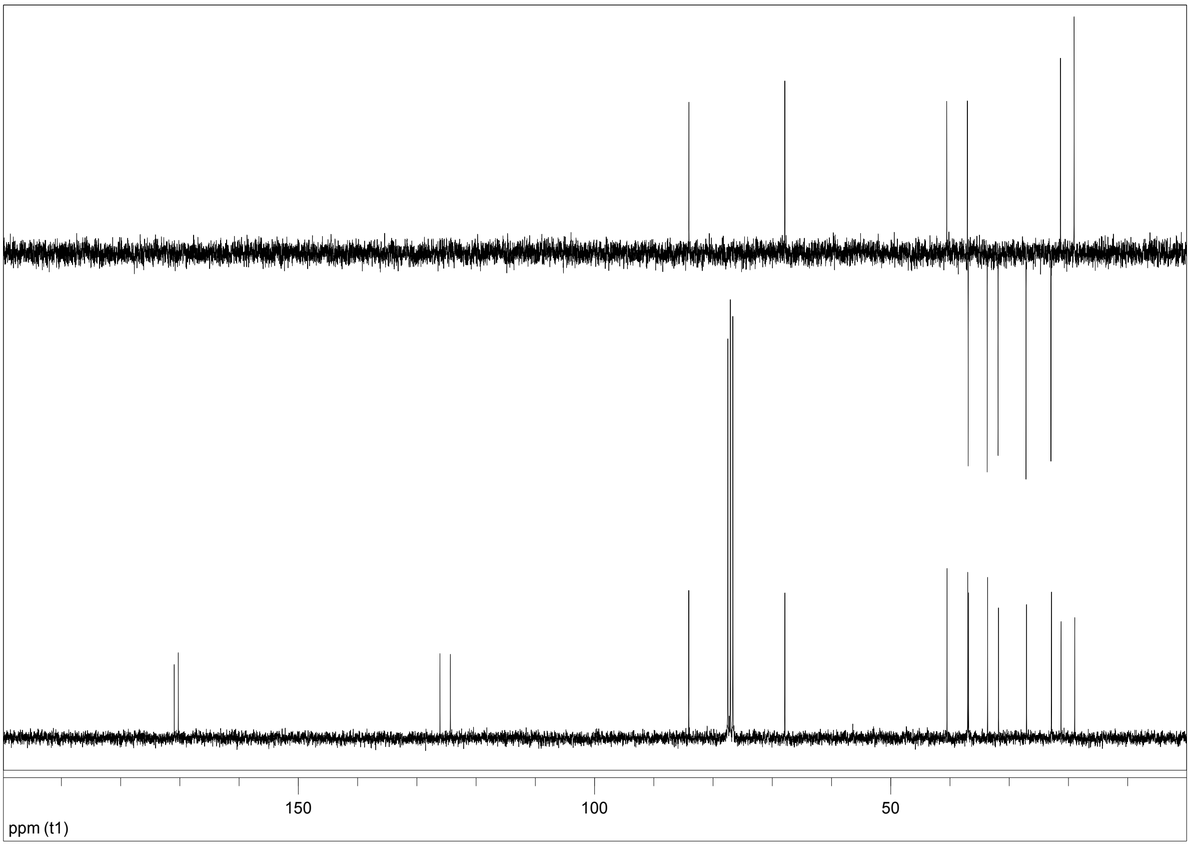
(3a*S*,4*S*,9a*S*,9b*S*)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydrobenzo[*de*]chromen-4-yl acetate (6)



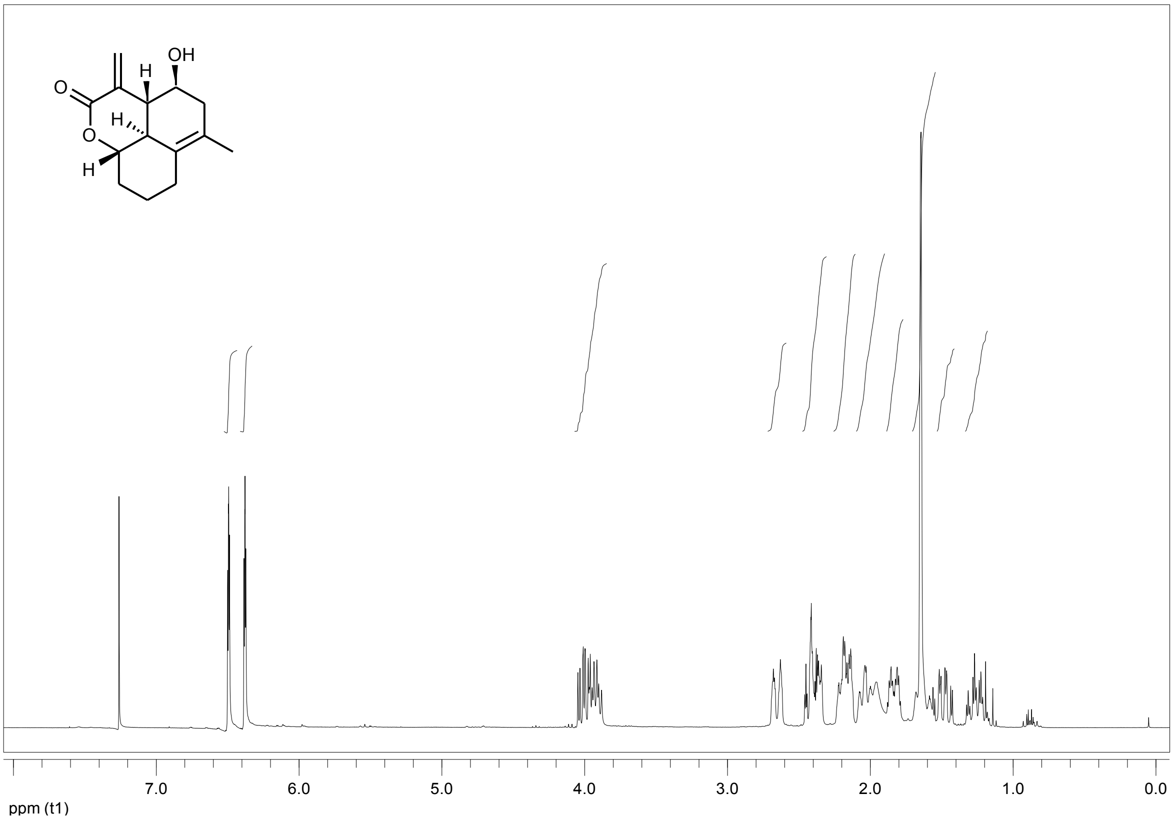


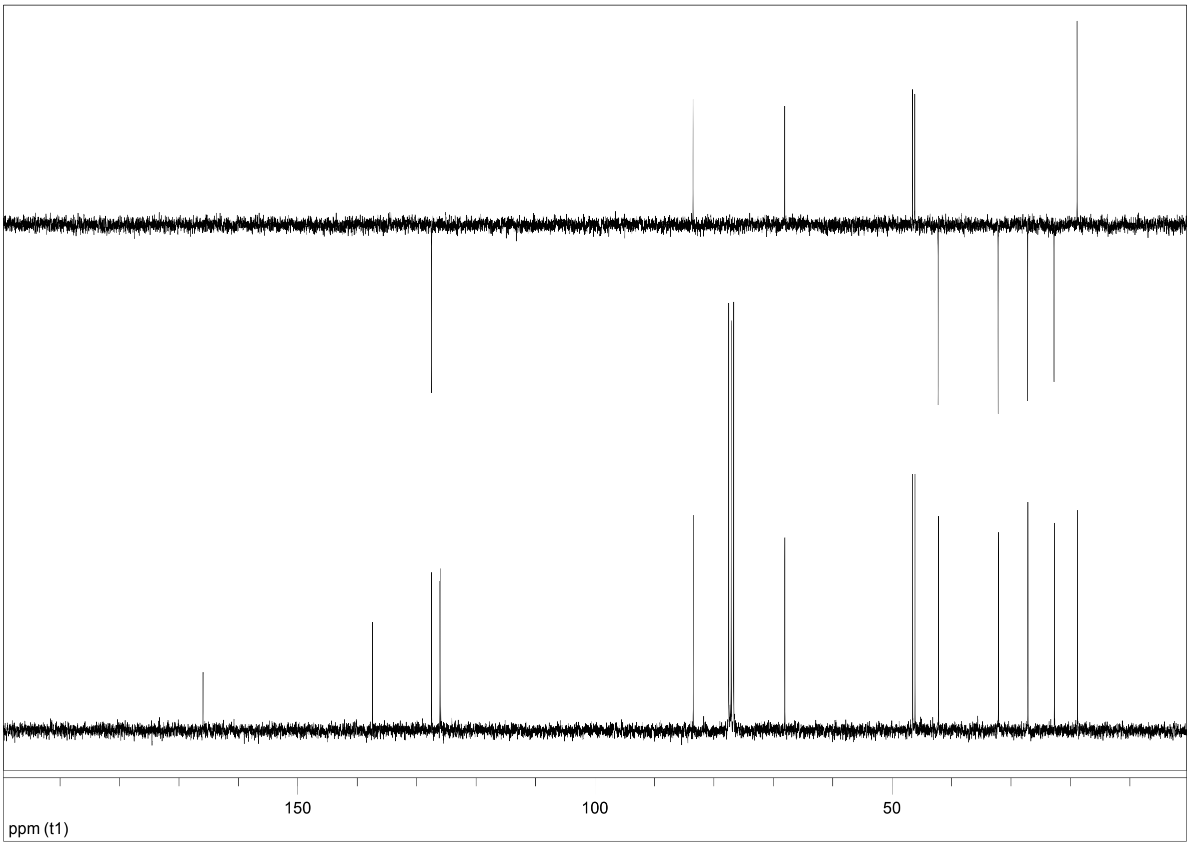
(3a*S*,4*R*,9a*S*,9b*S*)-6-methyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydrobenzo[*de*]chromen-4-yl acetate (8)



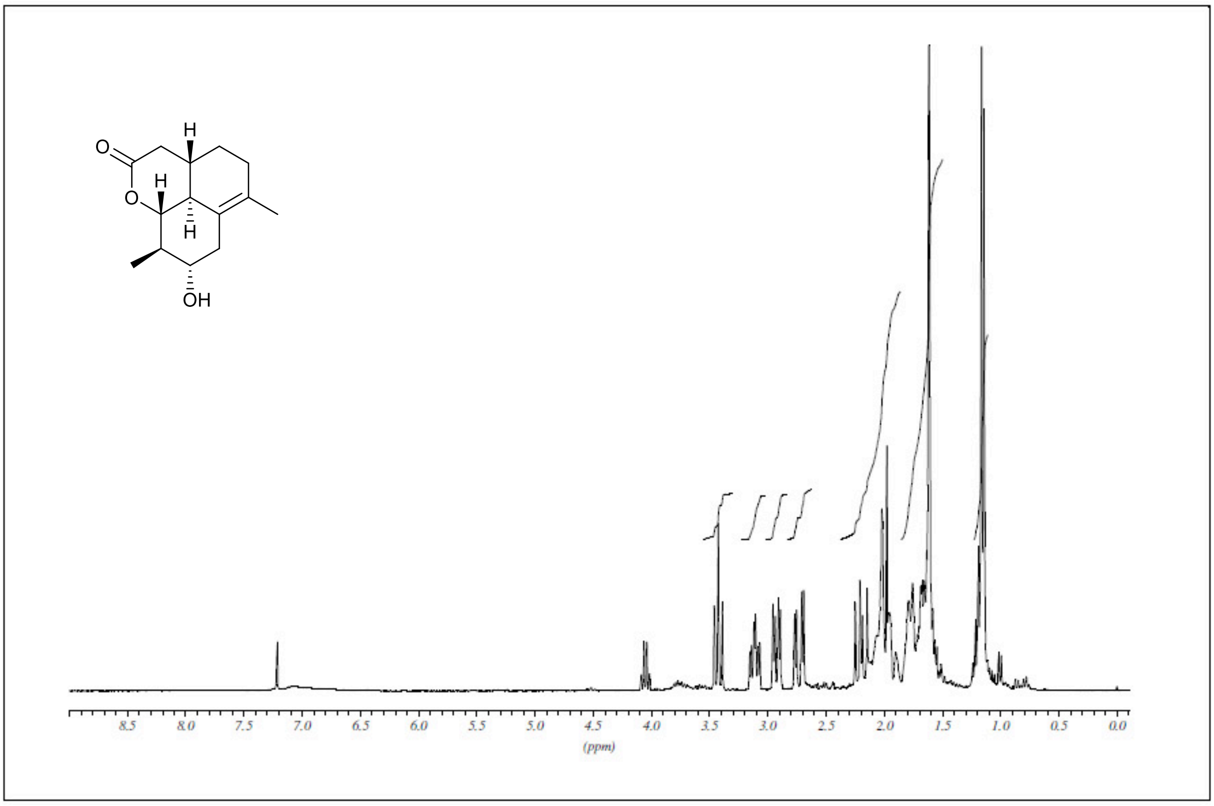


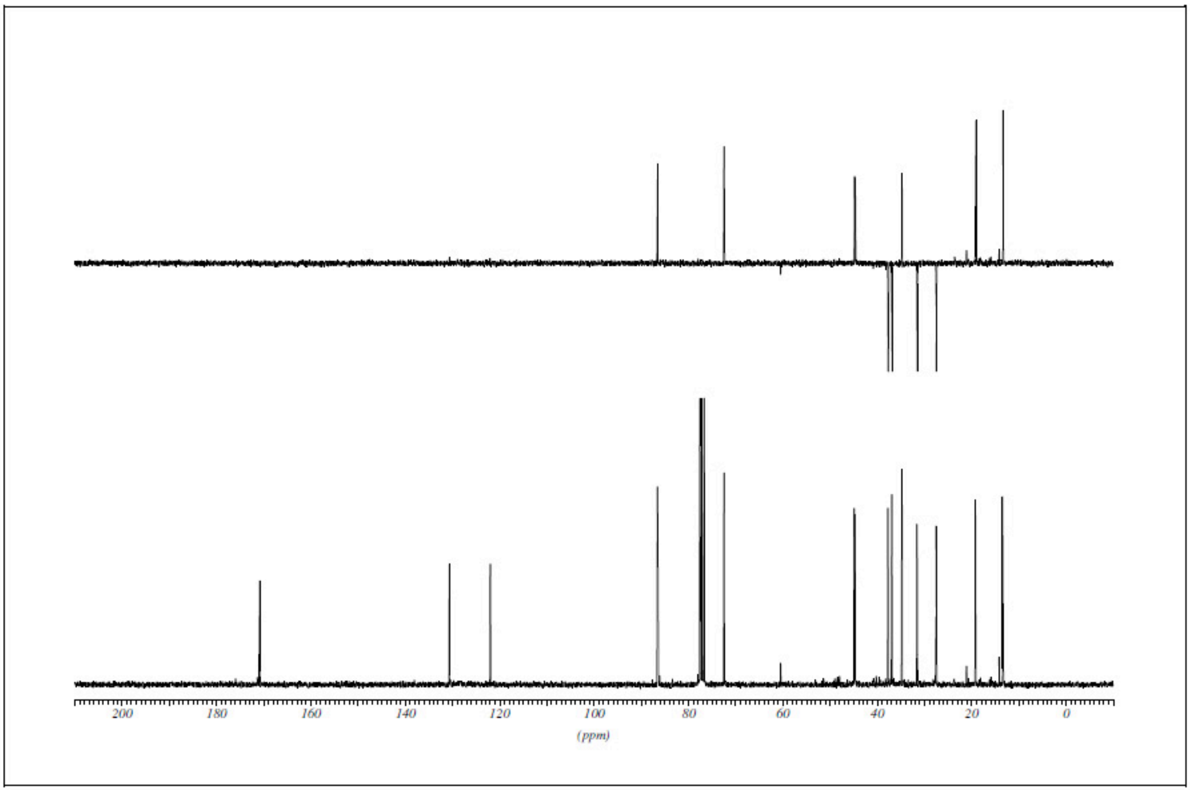
(3a*R*,4*S*,9a*S*,9b*S*)-4-hydroxy-6-methyl-3-methylidene-3a,4,5,7,8,9,9a,9b-octahydrobenzo[*de*]chromen-2(3*H*)-one (10)



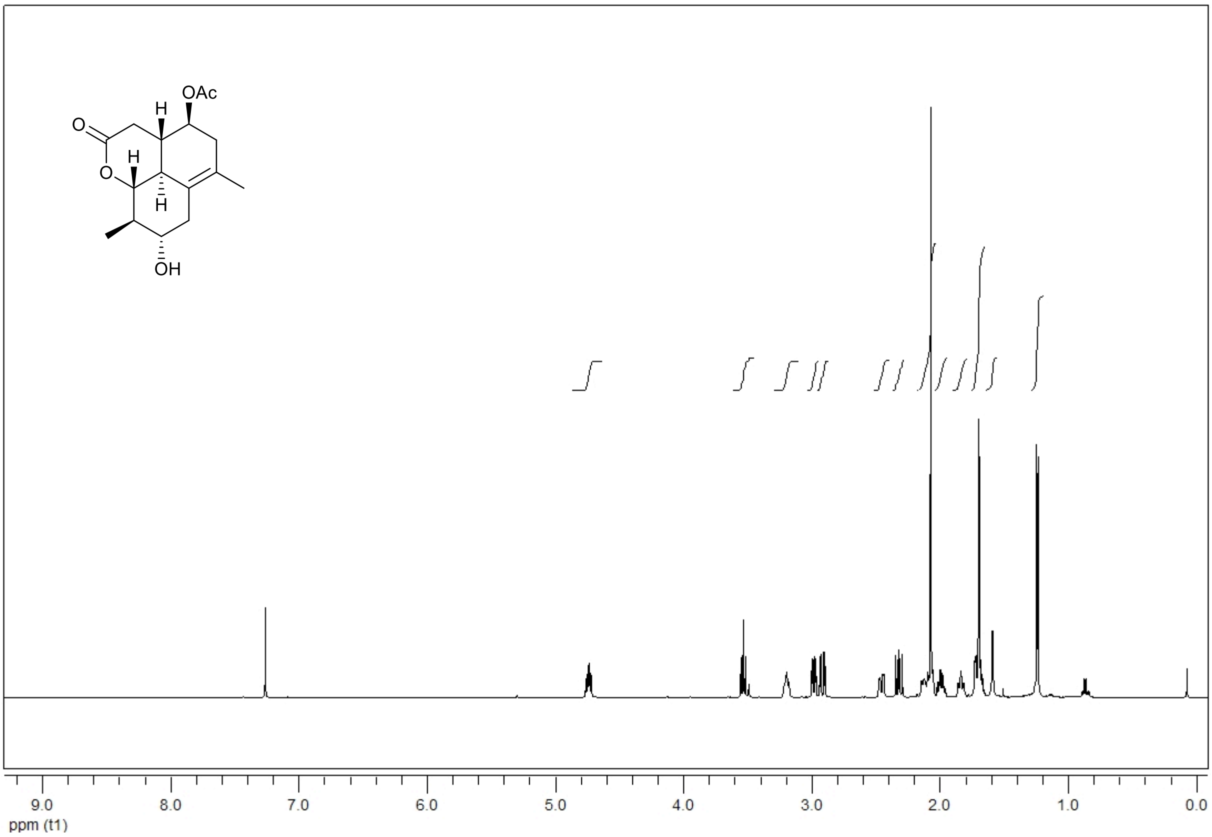


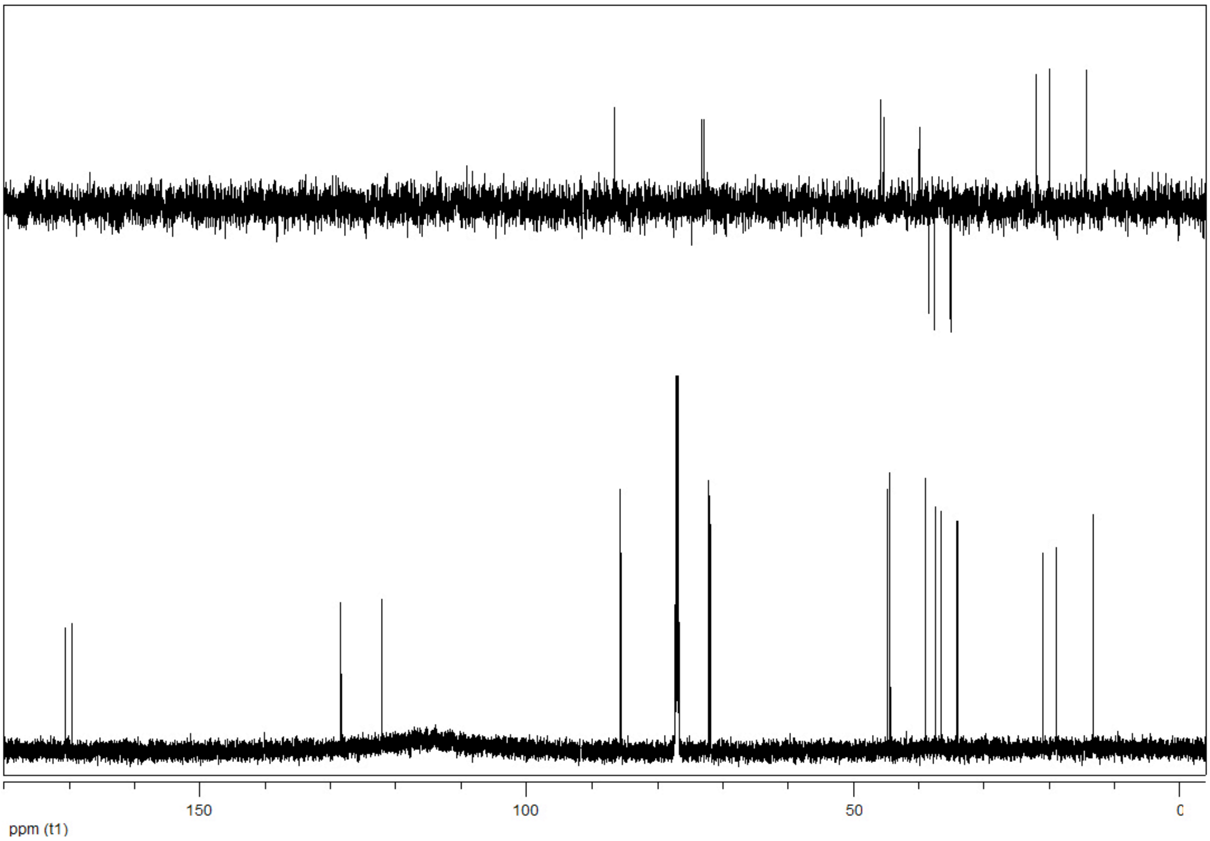
(3a*S*,8*S*,9*R*,9a*R*,9b*S*)-8-hydroxy-6,9-dimethyl-3a,4,5,7,8,9,9a,9b-octahydrobenzo[*de*]chromen-2(3*H*)-one (12)



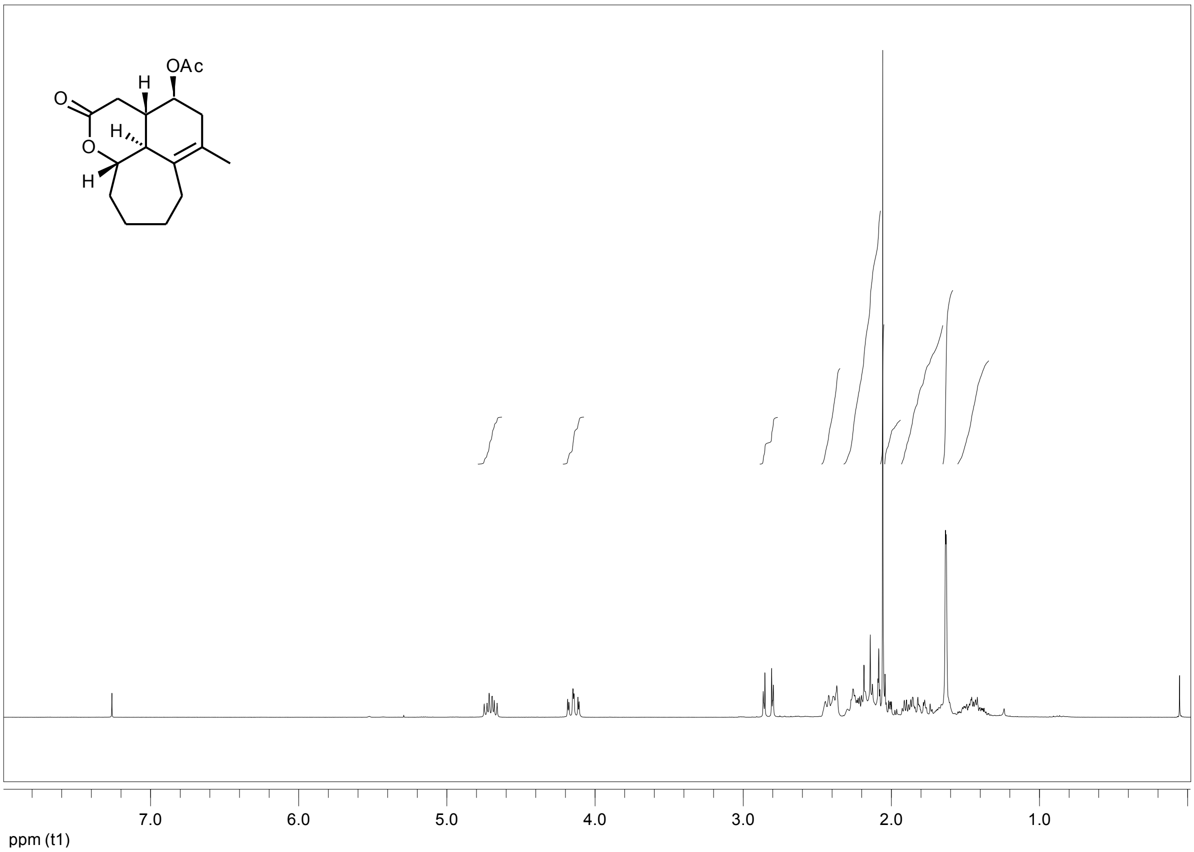


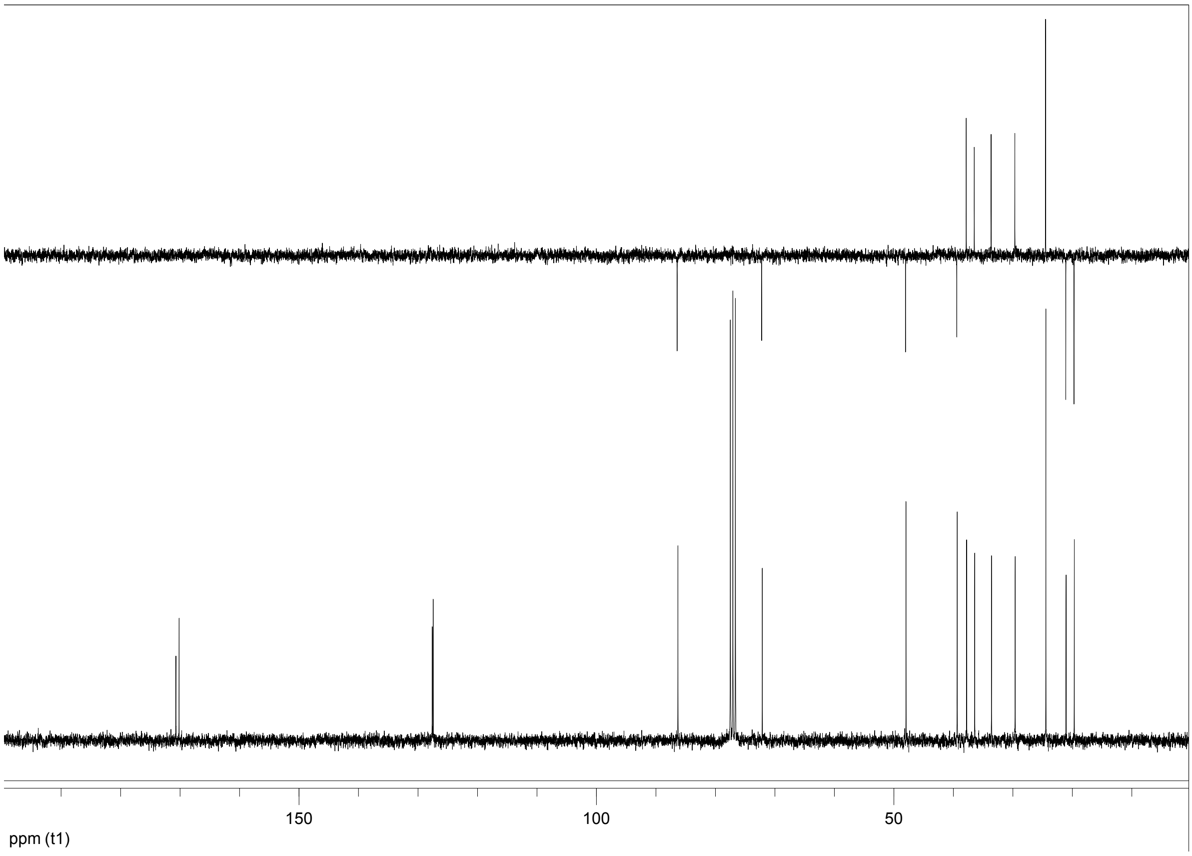
(3a*S*,4*S*,8*S*,9*R*,9a*R*,9b*S*)-8-hydroxy-6,9-dimethyl-2-oxo-2,3,3a,4,5,7,8,9,9a,9b-decahydrobenzo[*de*]chromen-4-yl acetate (14)





(3a*S*,4*S*,10a*S*,10b*S*)-6-methyl-2-oxo-3,3a,4,5,7,8,9,10,10a,10b-decahydro-2*H*-cyclohepta[*ij*]isochromen-4-yl acetate (16)





(3a*S*,8*S*,9*R*,9a*R*,9b*S*)-6,8-dihydroxy-6,9-dimethyldecahydrobenzo[*de*]chromen-2(3*H*)-one (19)