SUPPORTING INFORMATION

Highly regioselective and chemoselective titanocene mediated Barbier-type allylations

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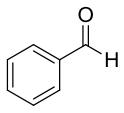
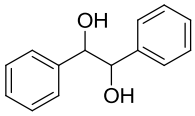
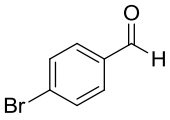
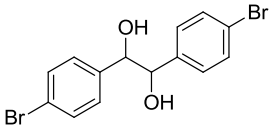
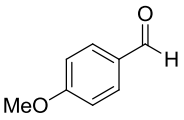
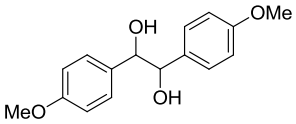
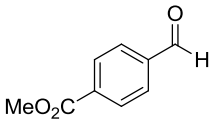
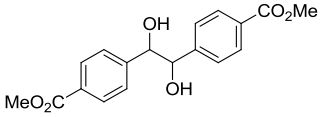
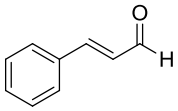
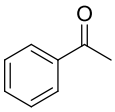
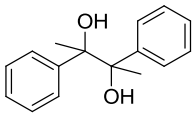
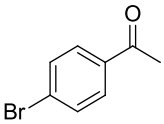
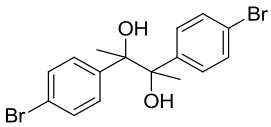
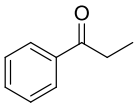
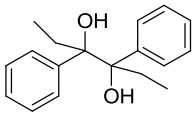
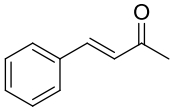
General Details. Deoxygenated solvents and reagents were used for all reactions involving Cp_2TiCl. THF was freshly distilled from Na. CH_2Cl_2 was freshly distilled from P_2O_5. Products were purified by flash chromatography on Merck silica gel 50. Yields refer to analytically pure samples. NMR spectra were recorded in a NMR 500, 400, and 300 MHz spectrometers. Citral is a 1:1 mixture of *E*:*Z* isomers. Pure geranial and neral samples isomerize at room temperature. The following known compounds were isolated as pure samples and showed NMR spectra matching those of the reported compounds: **6**,[1] **7**,[2] **9**,[3] **11**,[2] **13**,[2] **14**,[3] **15**,[2] **16**,[4] **17**,[5] **19**,[5] **20**,[6] **21**,[7] **24**,[8] **40**,[9] **41**,[10] **42**,[11] **43**,[12] **44**,[13] **45**,[14] **46**,[15] **47**,[16] **49**,[17] **50**,[18] **51**,[19] **52**,[16] **53**.[20]

General procedure for control pinacol coupling reactions mediated by titanocene complex 1. Rigorously deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 or complex **1** (1 mmol) and Zn dust (8.0 mmol) under Ar atmosphere, and the suspension was stirred at room temperature until it turned green (about 15 min). Then, a solution of carbonyl compound (1.0 mmol) in THF (2 mL) was added. The mixture was stirred for 16 h, and then diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (EtOAc/hexane mixtures). Results reported in Table S1 refer to the use of Cp_2TiCl. When complex **1** was used, the starting aldehydes **3**, **32**-**35** and ketones **36**-**39** were recovered unchanged.

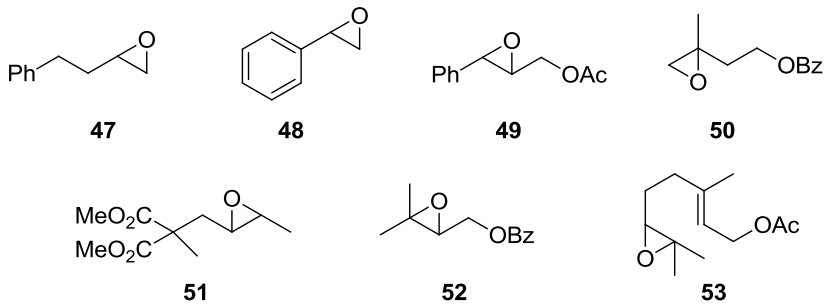
Table S1. Control pinacol coupling reactions of the corresponding aldehydes (**3**, **32**-**35**) and ketones (**36**-**39**) mediated by Cp_2TiCl.

Entry	Carbonyl compound	Product (Yield, %).
1	 **3**	 **40** (60%)
2	 **32**	 **41** (55%)

3	 **33**	 **42** (30%)
4	 **34**	 **43** (36%)
5	 **35**	---
6	 **36**	 **44** (50%)
7	 **37**	 **45** (52%)
8	 **38**	 **46** (46%)
9	 **39**	---

General procedure for control epoxide opening mediated by titanocene complex 1. Rigorously deoxygenated THF (20 mL) was added to a mixture of complex **1** (1 mmol) and Mn dust (8 mmol) under Ar atmosphere, and the suspension was stirred at room temperature until it turned green (about 15 min). Then, a solution of the corresponding epoxide (**47-53**) (1 mmol) in THF (2 mL) was added. The mixture was stirred for 6 h, and then diluted with EtOAc, washed with brine, and dried over anhydrous Na_2SO_4 and the solvent removed. The residue was submitted to flash chromatography (EtOAc/hexane mixtures) to mainly give the corresponding starting materials (see Scheme S-1). The only exception was styrene oxide (**48**), which was opened by cationic mechanisms mediated by $MnCl_2$ generated in the reaction medium.

Scheme S-1. Representative epoxides **47-53** used in this study.



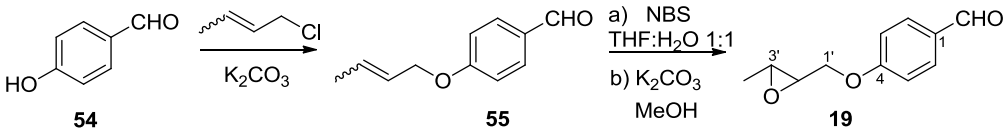
General procedure for Barbier-type reactions mediated by titanocene complex 1. Strictly deoxygenated THF (20 mL) was added to a mixture of titanocene(IV) complex **1** (1 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of the corresponding aldehyde or ketone (1 mmol) in THF (2 mL) was added. Subsequently, corresponding halide (**5** and **8**) (3 mmol) was slowly added and the solution was stirred for 6 h. The reaction was then quenched with 2N HCl and extracted with EtOAc. The organic layer was washed with brine, dried (anhyd. Na_2SO_4) and the solvent removed. Products **6-7**, **9-18** were purified by flash chromatography on silicagel (EtOAc/hexane) and characterized by spectroscopic techniques. Yields obtained are reported in Tables 1.

Compound 10: Colourless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.15 (t, *J* = 7.5 Hz, 1H), 4.63 (t, *J* = 5.7 Hz, 1H), 3.81 (s, 3H), 2.56-2.29 (m, 2H), 1.72 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 159.1 (C), 136.6 (C), 135.6 (C), 127.2 (CH), 120.0 (CH), 113.8 (CH), 73.8 (CH), 55.4 (CH_3), 38.3 (CH_2), 26.0 (CH_3), 18.1 (CH_3); HRMS (ES) m/z calcd for $C_{13}H_{17}O$ [M^+-OH] 189.1279, found 189.1272.

Compound 12: Colourless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.16–7.07 (m, 1H), 5.25 (t, *J* = 7.4 Hz, 1H), 5.05 (dd, *J* = 8.4, 4.0 Hz, 1H), 2.62-2.45 (m, 1H), 2.33 (dt, *J* = 15.3, 8.3 Hz, 1H), 2.25-2.14 (bs, 1H, OH), 1.75 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.2 (C), 136.2 (C), 132.7 (CH_2), 128.8 (CH), 127.7 (CH), 127.5 (CH), 121.9 (C), 119.6

(CH), 72.8 (CH), 36.6 (CH_2), 26.1 (CH_3), 18.1 (CH_3); HRMS (ES) m/z calcd for $C_{12}H_{14}Br$ [M^+-OH] 237.0279, found 237.0275.

Synthesis of compound 19:



Crotylation of compound **54**: To a solution of phenol **54** (610 mg, 5 mmol) in acetone (25 mL), K_2CO_3 (880 mg, 10 mmol) and crotyl chloride (675 mg, 7.5 mmol, Aldrich, 75:25 mixture of *E*:*Z* isomers) were added and the mixture was refluxed overnight. Then, water was added and the new mixture extracted with AcOEt, dry over anhyd. Na_2SO_4 and the solvent removed. The residue was purified by flash cromatography on silicagel (EtOAc/hexane, 2/8) to yield compound **55** (820 mg, 99%): Colorless oil; 75:25 mixture of *E*/*Z* isomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.80 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 5.97–5.60 (m, 2H), 4.66 (d, *J* = 6.2 Hz, 1H, *Z* isomer), 4.52 (d, *J* = 6.0 Hz, 2H, *E* isomer), 1.75 (d, *J* = 6.1 Hz, 3H, *E* isomer), 1.60 (bs, 3H, *Z* isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7 (CH), 163.7 (C), 131.8 (CH, *E* isomer), 131.2 (CH, *Z* isomer), 129.8 (C), 125.1 (CH, *E* isomer), 124.6 (CH, *Z* isomer), 114.9 (CH), 68.9 (CH_2, *E* isomer), 64.0 (CH, *Z* isomer), 17.8 (CH_3); HRMS (ES+) m/z calcd for $C_{11}H_{13}O_2$ [M^++H] 177.0916, found 177.0923.

Epoxidation of compound **55**: Powdered NBS (533 mg, 3 mmol) was gradually added to a solution of aldehyde **55** (500 mg, 3 mmol) in a mixture of THF/water (6 mL, 1:1) at 0º C. The reaction was stirred for 15 min, diluted with EtOAc, washed with water, dried over anhyd. Na_2SO_4, and the solvent removed. The residue was dissolved in 0.5 M methanolic K_2CO_3 (5 mL) and stirred for 30min at room temperature. The methanolic solution was then diluted with EtOAc, washed with water, dried over anhyd. Na_2SO_4, and the solvent removed. The residue was submitted to flash chromatography on silicagel (EtOAc/hexane, 2/8) to yield epoxide **19** (400 mg, 73 %) as a 75:25 mixture of isomers at C-3´: Colorless oil;. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.82 (d, *J* = 7.9 Hz, 2H, *Z* isomer), 7.80 (d, *J* = 7.9 Hz, 2H, *E* isomer), 7.01 (d, *J* = 9.5 Hz, 2H, *Z* isomer), 6.98 (d, *J* = 8.5 Hz, 2H, *E* isomer), 4.25 (dd, *J* = 11.1, 3.2 Hz, 2H), 4.23 (dd, *J*

= 11.0, 4.1 Hz, 2H, *Z* isomer), 4.17-4.07 (m, 2H, *Z* isomer), 4.06-3.97 (m 2H, *E* isomer), 3.33–3.15 (m, 1H, *Z* isomer), 3.10–2.99 (m, 1H, *E* isomer), 1.36 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.1 (C), 163.8 (C), 132.3 (CH), 130.6 (C), 115.28 (CH), 69.0 (CH_2, *E* isomer), 67.1 (CH_2, *Z* isomer), 57.1 (CH, *E* isomer), 54.5 (CH, *Z* isomer), 52.8 (CH, *E* isomer), 52.4 (CH, *Z* isomer), 17.6 (CH_3, E isomer), 13.9 (CH_3, Z isomer); HRMS (ES+) m/z calcd for $C_{11}H_{13}O_3$ [M^++H] 193.0865, found 193.0857.

General procedure for Barbier-type reactions mediated by titanocene complex 1 in the presence of epoxides. Strictly deoxygenated THF (20 mL) was added to a mixture of titanocene(IV) complex **1** (1.5 mmol) and Mn dust (8 mmol) under an Ar atmosphere and the suspension was stirred at room temperature until it turned lime green (after about 15 min). Then, a solution of aldehydes (**19**-**21**) or bromide **23** (1 mmol) in THF (2 mL) was added. Subsequently, the corresponding halide (**5**, **8**, and **22**-**23**) (3 mmol) was slowly added and the solution was stirred for additional 2 h. Finally, the solvent was removed. Products **24**-**31** were purified by flash chromatography on silicagel (deactivated with Et_3N) (EtOAc/hexane) and characterized by spectroscopic techniques. Yields obtained are reported in Tables 2.

Compound **24**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 5.08 (t, *J* = 7.2 Hz, 1H), 4.56 (t, *J* = 6.6 Hz, 1H), 4.08 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.92 (dd, *J* = 11.0, 5.1 Hz, 1H), 3.05–2.91 (m, 2H), 2.50–2.18 (m, 2H), 1.87 (bs, 1H, OH), 1.65 (s, 3H), 1.54 (s, 3H), 1.31 (d, *J* = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0 (C), 137.1 (C), 135.7 (C), 127.2 (CH), 120.0 (CH), 114.6 (CH), 73.8 (CH), 68.5 (CH_2), 57.2 (CH), 52.8 (CH), 38.4 (CH_2), 26.0 (CH_3), 18.1 (CH_3), 17.5 (CH_3). A good quality HRMS could not be obtained.

Compound **25**: 1:1 mixture of *E*/*Z* diastereoisomers and at C-3 and C-8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (t, *J* = 9.1 Hz, 1H), 5.15 (t, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.74 (ddd, *J* = 2.8 Hz, 1H), 2.40–2.04 (m, 4H), 1.76 (s, 3H, Z isomer), 1.71–1.51 (m, 2H), 1.73 (s, 3H, *E* isomer), 1.71 (s, 3H, *Z* isomer), 1.64 (s, 3H, *E* isomer), 1.31 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9 (C, one isomer), 137.5 (C, one isomer), 137.4 (C, one isomer), 137.3 (C, one isomer), 135.0 (C, one isomer), 134.9 (C, one isomer), 134.8 (C, one isomer), 134.6 (C, one isomer), 129.6 (CH, one isomer), 129.0 (CH, one isomer), 128.1 (CH), 120.1 (CH, one isomer), 120.0

(CH, one isomer), 119.9 (CH, one isomer), 119.8 (CH, one isomer), 68.5 (CH, one isomer), 68.4 (CH, one isomer), 68.1 (CH, one isomer), 67.9 (CH, one isomer), 64.3 (CH, one isomer), 64.1 (CH, one isomer), 64.0 (CH, one isomer), 63.8 (CH, one isomer), 59.2 (C, one isomer), 59.1 (C, one isomer), 58.5 (C, one isomer), 58.4 (C, one isomer), 36.7 (CH_2, one isomer), 36.61 (CH_2, one isomer), 36.57 (CH_2, one isomer), 36.5 (CH_2, one isomer), 36.4 (CH_2, one isomer), 36.3 (CH_2, one isomer), 29.8 (CH_2, one isomer), 29.7 (CH_2, one isomer), 29.3 (CH_2, one isomer), 28.8 (CH_2, one isomer), 27.6 (CH_2, one isomer), 27.4 (CH_2, one isomer), 27.3 (CH_2, one isomer), 27.0 (CH_2, one isomer), 26.0 (CH_3), 24.9 (CH_3), 23.4 (CH_3, one isomer), 23.3 (CH_3, one isomer), 18.9 (CH_3, one isomer), 18.83 (CH_3, one isomer), 18.81 (CH_3, one isomer), 18.1 (CH_3, one isomer), 16.7 (CH_3, one isomer); HRMS (EI) m/z calcd for $C_{13}H_{17}O$ [M^+-OH_2] 220.1827, found 220.1831.

Compound **26**: 1:1 mixture of *E*/*Z* isomers and at C-3 and C-8: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29–5.22 (m, 1H), 5.20–5.12 (m, *J* = 6.4 Hz, 1H), 5.08 (t, *J* = 6.8 Hz, 1H), 4.35 (dt, *J* = 16.8, 6.5 Hz, 1H), 2.80–2.68 (m, 1H), 2.42 – 1.99 (m, 4H), 1.85–1.53 (m, 4H), 1.76 (s, 3H, minor isomer), 1.71 (s, 3H, minor isomer), 1.69 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H), 1.32 (s, 6H), 1.29 (s,3H, minor isomer), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (C, one isomer), 139.0 (C, one isomer), 138.9 (C, one isomer), 138.7 (C, one isomer), 138.0 (C, one isomer), 137.7 (C, one isomer), 137.6 (C, one isomer), 137.5 (C, one isomer), 131.84 (C, one isomer), 131.83 (C, one isomer), 131.80 (C, one isomer), 131.79 (C, one isomer), 129.5 (CH, one isomer), 129.0 (CH, one isomer), 128.0 (CH, one isomer), 127.9 (CH, one isomer), 124.35 (CH, one isomer), 124. 32 (CH, one isomer), 124.29 (CH, one isomer), 119.9 (CH, one isomer), 119.8 (CH, one isomer), 119.7 (CH, one isomer), 119.6 (CH, one isomer), 68.5 (CH, one isomer), 68.4 (CH, one isomer), 68.0 (CH, one isomer), 67.8 CH, one isomer), 64.3 (CH, one isomer), 64.2 (CH, one isomer), 64.1 (CH, one isomer), 63.8 (CH, one isomer), 58.51 (C, one isomer), 58.50 (C, one isomer), 58.48 (C, one isomer), 58.46 (C, one isomer), 40.10 (CH_2), 36.62 (CH_2, one isomer), 36.59 (CH_2, one isomer), 36.56 (CH_2, one isomer), 36.5 (CH_2, one isomer), 36.39 (CH_2, one isomer), 36.38 (CH_2, one isomer), 36.37 (CH_2, one isomer), 29.8 (CH_2), 29.90 (CH_2, one isomer), 29.5 (CH_2, one isomer), 29.3 (CH_2, one isomer), 29.1 (CH_2, one isomer), 28.9 (CH_2, one isomer), 27.7 (CH_2, one isomer), 27.43 (CH_2, one isomer), 27.39 (CH_2, one isomer), 27.1 (CH_2, one isomer), 26.83 (CH_2, one isomer), 26.81 (CH_2, one isomer), 26.79 (CH_2, one isomer),

25.9 (CH_3), 25.03 (CH_3, one isomer), 25.01 (CH_3, one isomer), 24.6 (CH_3, one isomer), 23.9 (CH_3, one isomer), 23.7 (CH_3, one isomer), 23.5 (CH_3, one isomer), 23.4 (CH_3, one isomer), 23.1 (CH_3, one isomer), 22.8 (CH_3, one isomer), 19.0 (CH_3, one isomer), 18.9 (CH_3, one isomer), 18.89 (CH_3, one isomer), 18.88 (CH_3, one isomer), 17.8 (CH_3), 16.9 (CH_3, one isomer), 16.8 (CH_3, one isomer), 16.5 (CH_3, one isomer); HRMS (EI) m/z calcd for $C_{13}H_{17}O$ [M^+-OH_2] 288.2453 found 288.2453.

Compound **27**: 1:1 mixture of *E*/*Z* isomers and at C-3 and C-8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.04 (m, 5H), 5.21 (d, *J* = 7.8 Hz, 1H), 4.52 (dt, *J* = 4.5 Hz, 1H), 2.74 (dd, *J* = 10.6, 4.0 Hz, 2H), 2.61 (t, *J* = 5.0 Hz, 1H), 2.22–1.99 (m, 2H), 1.63–1.33 (m, 2H), 1.51 (s, 3H), 1.23 (s, 3H), 1.21 (s, 3H), 1.19 (s, 6H), 1.17 (s, 3H, minor isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3 (C, one isomer), 138.9 (C, one isomer), 129.7 (CH, one isomer), 129.6 (CH, one isomer), 128.52 (CH, one isomer), 128.49 (CH, one isomer), 127.46 (C), 126.54 (CH, one isomer), 126.53 (CH, one isomer), 126.46 (CH), 69.73 (CH, one isomer), 69.70 (CH, one isomer), 69.3 (CH, one isomer), 69.0 (CH, one isomer), 64.2 (CH, one isomer), 64.07 (CH, one isomer), 64.06 (CH, one isomer), 63.8 (CH, one isomer), 59.2 (C, one isomer), 58.4 (C, one isomer), 44.4 (CH_2, one isomer), 44.35 (CH_2, one isomer), 44.32 (CH_2, one isomer), 44.30 (CH_2, one isomer), 36.4 (CH_2, one isomer), 36.38 (CH_2, one isomer), 36.36 (CH_2, one isomer), 36.35 (CH_2, one isomer), 28.8 (CH_2, one isomer), 27.40 (CH_2, one isomer), 27.36 (CH_2, one isomer), 26.8 (CH_2, one isomer), 25.01 (CH_3, one isomer), 24.99 (CH_3, one isomer), 24.98 (CH_3, one isomer), 24.97 (CH_3, one isomer), 23.4 (CH_3, one isomer), 23.3 (CH_3, one isomer), 19.0 (CH_3, one isomer), 18.89 (CH_3, one isomer), 18.88 (CH_3, one isomer), 18.8 (CH_3, one isomer); HRMS (ES) m/z calcd for $C_{13}H_{17}O$ [M^+-OH_2] 242.1671, found 242.1674.

Compound **28**: 1:1 mixture of diasteroisomers at C-3 and C-9: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.29 (m, 5H), 5.32–5.19 (m, 1H), 4.77–4.66 (m, 1H), 2.73–2.65 (m, 1H), 2.59–2.38 (m, 2H), 2.30–2.10 (m, 2H), 1.63 (s, 3H, one isomer), 1.62 (s, 3H, one isomer), 1.30 (s, 3H, one isomer), 1.29 (s, 3H, one isomer), 1.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (C), 138.5 (C, one isomer), 138.4 (C, one isomer),128.42 (CH), 127.44 (CH), 125.93 (CH, one isomer), 125.90 (CH, one isomer), 120.8 (CH), 120.4 (CH), 74.1 (CH, one isomer), 74.0 (CH, one isomer), 64.4 (CH, one isomer), 64.3 (CH, one isomer), 58.4 (C, one isomer), 58.2 (C, one isomer), 38.6 (CH_2, one isomer), 38.1 (CH_2, one isomer major), 37.0 (CH_2, one isomer), 36.8 (CH_2, one isomer), 27.4 (CH_2,

one isomer), 27.2 (CH_2, one isomer), 25.00 (CH_3), 18.93 (CH_3, one isomer), 18.90 (CH_3, one isomer), 16.43 (CH_3, one isomer), 16.37 (CH_3, one isomer); HRMS (ES+) m/z calcd for $C_{17}H_{25}O_2$ [M^++H] 261.1855, found 261.1845.

Compound **29**: 1:1 mixture of *E*/*Z* isomers and at C-3 and C-9: ^{1}H NMR (300 MHz, CDCl3) δ 5.26–5.16 (m, 2H), 5.16–5.04 (m, 1H), 4.35 (m, 1H), 2.69 (t, *J* = 6.2 Hz, 1H), 2.39–1.85 (m, 6H), 1.73 (dd, *J* = 6.7, 1.2 Hz, 4H), 1.68 (s, 3H), 1.67 (s, 3H), 1.66 (s, 3H, one isomer), 1.65 (s, 3H, one isomer), 1.59 (s, 3H), 1.29 (s, 3H, one isomer), 1.29 (s, 3H,one isomer), 1.25 (s, 3H,one isomer), 1.24 (s, 3H,one isomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8 (C, one isomer), 138.7 (C, one isomer),138.4 (C, one isomer), 138.3 (C, one isomer), 137.7 (C, one isomer), 137.6 (C, one isomer), 137.5 (C, one isomer), 137.4 (C, one isomer), 132.44 (C, one isomer), 132.40 (C, one isomer), 131.75 (C, one isomer), 131.74 (C, one isomer), 128.6 (CH, one isomer), 127.5 (CH, one isomer), 124.9 (CH, one isomer), 124.1 (CH, one isomer), 120.8 (CH, one isomer), 120.7 (CH, one isomer), 120.6 (CH, one isomer), 120.5 (CH, one isomer), 77.4 (CH), 64.4 (CH, one isomer), 64.3 (CH, one isomer), 64.2 (CH, one isomer) 64.1 (CH, one isomer), 58.5 (C, one isomer) , 58.4 (C, one isomer), 58.3 (C, one isomer), 58.2 (C, one isomer), 39.7 (CH_2), 36.9 (CH_2, one isomer), 36.83 (CH_2, one isomer), 36.77 (CH_2, one isomer), 36.7 (CH_2, one isomer), 32.5 (CH_2), 27.6 (CH_2, one isomer), 27.5 (CH_2, one isomer), 27.4 (CH_2, one isomer), 27.3 (CH_2, one isomer), 26.73 (CH_2, one isomer), 26.72 (CH_2, one isomer), 26.56 (CH_2, one isomer), 26.54 (CH_2, one isomer), 25.82 (CH_3, one isomer), 25.79 (CH_3, one isomer), 25.02 (CH_3, one isomer), 25.01 (CH_3, one isomer), 25.00 (CH_3, one isomer), 24.99 (CH_3, one isomer), 23.5 (CH_3), 18.9 (CH_3, one isomer), 18.8 (CH_3, one isomer), 17.83 (CH_3, one isomer), 17.81 (CH_3, one isomer), 16.8 (CH_3, one isomer), 16.5 (CH_3, one isomer), 16.4 (CH_3, one isomer), 16.2 (CH_3, one isomer); HRMS (ES+) m/z calcd for $C_{20}H_{35}O_2$ [M^++H] 307.2637, found 307.2623.

Compound **30**: 1:1 mixture of diasteroisomers at C-3 and C-9: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (dt, *J* = 13.4, 6.7 Hz, 2H), 5.15 (dd, *J* = 12.4, 6.4 Hz, 1H), 4.55 (d, *J* = 7.0 Hz, 2H), 4.05–3.87 (m, 1H), 2.74–2.56 (m, 1H), 2.38–2.03 (m, 6H), 2.04 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.33–1.24 (m, 4H), 1.26 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 142.0 (C, one isomer), 141.9 (C, one isomer), 137.5 (C, one isomer), 137.4 (C, one isomer), 125.35 (CH, one isomer), 125.31 (CH, one isomer), 121.1 (CH, one isomer), 120.9 (CH, one isomer), 118.7 (CH, one isomer),

118.6 (CH, one isomer), 77.1 (CH, one isomer), 77.0 (CH, one isomer), 64.4 (CH, one isomer), 64.3 (CH, one isomer), 61.5 (CH_2), 58.4 (C, one isomer), 58.2 (C, one isomer), 39.2 (CH_2), 36.9 (CH_2, one isomer), 36.7 (CH_2, one isomer), 34.4 (CH_2, one isomer), 34.1 (CH_2, one isomer), 27.5 (CH_2, one isomer), 27.3 (CH_2, one isomer), 25.80 (CH_2), 25.0 (CH_3), 21.15 (CH_3), 18.9 (CH_3, one isomer), 18.8 (CH_3, one isomer), 16.6 (CH_3), 16.43 (CH_3, one isomer), 16.38 (CH_3, one isomer), 11.89 (CH_3, one isomer), 11.87 (CH_3, one isomer); HRMS (ES+) m/z calcd for $C_{22}H_{37}O_4$ [M^++H] 365.2692, found 365.2692.

Compound **31**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.18 (t, *J* = 5.9 Hz, 2H), 2.70 (t, *J* = 6.2 Hz, 2H), 2.21–2.04 (m, 4H), 2.04–1.98 (m, 4H), 1.75 (s, 3H), 1.78–1.55 (m, 4H), 1.61 (s, 3H), 1.30 (s, 6H), 1.26 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.31 (C), 125.6 (C), 124.8 (CH), 64.2 (CH), 58.3 (C), 36.2 (CH_2), 28.2 (CH_2), 27.4 (CH_2), 25.0 (CH_3), 18.9 (CH_3), 16.0 (CH_3), 16.0 (CH_3); HRMS (ES+) m/z calcd for $C_{20}H_{35}O_2$ [M^++H] 307.2637, found 307.2634. In ^{1}H NMR, a 14% of isomer with α,γ-regioselectivity was also observed. Significant signals: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77–5.64 (m, 1H), 5.03–4.86 (m, 2H), 3.54 (ddd, *J* = 15.5, 10.4, 5.9 Hz, 1H), 3.30–3.06 (m, 2H), 2.66 (t, *J* = 6.2 Hz, 2H), 1.70 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.34 (C), 124.7 (CH), 112.2 (CH_2), 64.1 (CH), 58.3 (C), 36.7 (CH_2), 28.1 (CH_2), 27.4 (CH_2), 25.0 (CH_3), 18.9 (CH_3).

Computational details

The calculations were carried out at the DFT-B3LYP level [21-23] with the Gaussian 09 program.[24] The geometries were fully optimized by the gradient technique with the following basis: for Ti the standard LANL2DZ basis set,[25] whereas the carbon, oxygen and hydrogen atoms were described by the polarized 6-31G* basis set.[26] The nature of the optimized structures, either transition states or intermediates, was assessed through a frequency calculation, and the changes of Gibbs free reaction energies (Δ*G* values) were obtained by taking into account zero-point energies, thermal motion, and entropy contribution at standard conditions (temperature of 298.15K, pressure of 1 atm). We have concentrated our discussion on the corresponding enthalpic values.

Cartesian coordinates of the calculated structures

2a

E = –790.4634898, *H* = –790.160058, *G* = –790.223140

C	0.584533000	-2.211026000	0.932673000
C	0.639758000	-2.336348000	-0.477898000
C	-0.554086000	-1.431290000	1.255954000
C	-1.219433000	-1.070225000	0.048929000
C	-0.455425000	-1.622668000	-1.025120000
H	1.290342000	-2.625186000	1.641122000
H	1.397603000	-2.862050000	-1.044222000
H	-0.862264000	-1.156843000	2.256218000
C	-2.536274000	-0.311323000	-0.088604000
H	-0.682848000	-1.534676000	-2.080347000
C	-2.329405000	1.023077000	-0.864958000
C	-1.388071000	1.971008000	-0.133935000
O	-0.126473000	1.538290000	-0.054667000
O	-1.753047000	3.020979000	0.355073000
C	-3.531882000	-1.187676000	-0.883754000
C	-3.147192000	-0.007658000	1.294043000
H	-3.292517000	1.526745000	-0.987283000
H	-1.925299000	0.805038000	-1.861353000
H	-3.697028000	-2.145606000	-0.377723000
H	-3.166121000	-1.399349000	-1.894393000
H	-4.498325000	-0.677949000	-0.974971000
H	-2.496127000	0.627667000	1.903449000
H	-3.344342000	-0.932486000	1.847795000
H	-4.098072000	0.522361000	1.173474000
Ti	0.948475000	-0.026651000	0.034622000
C	3.059786000	0.278926000	1.098168000
C	3.257145000	-0.668854000	0.058285000
C	2.727407000	1.520024000	0.491511000
C	2.697229000	1.334078000	-0.910004000
C	3.011110000	-0.023325000	-1.182835000
H	3.169328000	0.096234000	2.159896000

H	3.526966000	-1.708109000	0.190568000
H	2.465713000	2.432309000	1.011022000
H	2.419948000	2.083491000	-1.639904000
H	3.071550000	-0.479729000	-2.163017000

2a-THF

E = –1022.9193377, *H* = –1022.490267, *G* = –1022.566580

C	-0.946990000	1.926833000	1.810912000
C	-0.278821000	0.795390000	2.326882000
C	-1.960428000	1.473678000	0.918641000
C	-1.949623000	0.055632000	0.900800000
C	-0.892223000	-0.355849000	1.758018000
H	-0.724892000	2.959049000	2.045418000
H	0.539027000	0.805453000	3.035688000
H	-2.629584000	2.108443000	0.353646000
C	-2.876594000	-0.861472000	0.117967000
H	-0.581408000	-1.378931000	1.925470000
C	-2.086126000	-2.058272000	-0.456098000
C	-0.858462000	-1.752067000	-1.328822000
O	-0.400244000	-0.527176000	-1.334236000
O	-0.349628000	-2.667379000	-1.971583000
C	-3.950629000	-1.404487000	1.093224000
C	-3.585893000	-0.110737000	-1.026348000
H	-2.753390000	-2.691019000	-1.052875000
H	-1.735600000	-2.702308000	0.362058000
H	-4.547977000	-0.586619000	1.512614000
H	-3.491823000	-1.947960000	1.926991000
H	-4.629689000	-2.091107000	0.572742000
H	-2.865062000	0.288488000	-1.745543000
H	-4.197429000	0.715687000	-0.646091000
H	-4.256425000	-0.795385000	-1.558741000
Ti	0.167313000	0.866662000	-0.019567000
C	1.453601000	2.972692000	-0.013725000
C	2.215106000	2.027863000	-0.735797000

C	0.237786000	3.182138000	-0.722519000
C	0.249916000	2.362607000	-1.877007000
C	1.470283000	1.640048000	-1.879657000
H	1.739797000	3.446528000	0.916851000
H	3.184088000	1.641134000	-0.446629000
H	-0.559191000	3.852969000	-0.429650000
H	-0.541148000	2.274337000	-2.609710000
H	1.754875000	0.893898000	-2.608311000
C	3.741000000	-1.789104000	1.255400000
C	3.215723000	-2.575084000	0.043167000
C	2.594071000	-0.809275000	1.553470000
O	1.800438000	-0.727768000	0.343250000
C	2.438304000	-1.507027000	-0.713220000
H	4.652167000	-1.242769000	0.986118000
H	3.973065000	-2.421045000	2.117777000
H	2.539964000	-3.378705000	0.356955000
H	4.014377000	-3.015452000	-0.561095000
H	1.938376000	-1.170379000	2.352158000
H	2.946887000	0.193602000	1.817956000
H	3.112519000	-0.845802000	-1.274939000
H	1.653046000	-1.881133000	-1.369548000

2a-B

E = –1136.0461333, *H* = –1135.622813, *G* = –1135.703725

C	-2.405810000	1.275185000	1.898706000
C	-1.217524000	0.669197000	2.361209000
C	-3.064243000	0.354449000	1.033053000
C	-2.304631000	-0.841693000	0.977526000
C	-1.153282000	-0.631057000	1.786953000
H	-2.755065000	2.268519000	2.146064000
H	-0.481472000	1.112021000	3.019980000
H	-3.992095000	0.539922000	0.509190000
C	-2.637895000	-2.106786000	0.200615000
H	-0.339996000	-1.331495000	1.924717000

C	-1.355482000	-2.718404000	-0.407671000
C	-0.471616000	-1.814681000	-1.283013000
O	-0.734902000	-0.536225000	-1.310087000
O	0.462438000	-2.325787000	-1.901412000
C	-3.248313000	-3.131239000	1.189093000
C	-3.662817000	-1.833991000	-0.918678000
H	-1.614358000	-3.596604000	-1.010959000
H	-0.707644000	-3.102539000	0.392123000
H	-4.173917000	-2.744262000	1.630879000
H	-2.554165000	-3.355989000	2.006664000
H	-3.483121000	-4.070700000	0.673303000
H	-3.273932000	-1.117245000	-1.647331000
H	-4.606115000	-1.447813000	-0.515552000
H	-3.891859000	-2.767343000	-1.446343000
Ti	-0.976194000	0.966515000	0.014914000
C	-1.114524000	3.422428000	-0.002138000
C	0.093837000	3.058464000	-0.633641000
C	-2.188501000	2.912112000	-0.784578000
C	-1.640465000	2.236615000	-1.900781000
C	-0.227760000	2.312714000	-1.799826000
H	-1.205525000	3.976807000	0.923016000
H	1.089485000	3.273747000	-0.267782000
H	-3.242130000	3.018234000	-0.560250000
H	-2.193066000	1.710592000	-2.667583000
H	0.475804000	1.852873000	-2.480493000
C	5.559950000	-1.116179000	-0.575824000
C	4.207513000	-0.942795000	-0.862704000
C	3.397406000	-0.190688000	0.004859000
C	6.104519000	-0.536325000	0.573086000
C	5.300712000	0.213896000	1.442034000
C	3.950295000	0.385881000	1.162929000
H	6.187581000	-1.700556000	-1.242103000
H	3.763473000	-1.395080000	-1.745937000
C	1.983122000	-0.032895000	-0.331362000

H	7.159903000	-0.668894000	0.795860000
H	5.734257000	0.659532000	2.332823000
H	3.307371000	0.961663000	1.821399000
O	1.173719000	0.545613000	0.408701000
H	1.635872000	-0.472753000	-1.276396000

2a-Ep

E = –1062.2150263, *H* = –1061.759373, *G* = –1061.841294

C	2.230433000	-1.843924000	-0.207985000
O	1.804889000	-0.544148000	0.276233000
C	2.940027000	-1.189840000	0.919659000
H	1.527725000	-2.631689000	0.067764000
C	2.710655000	-1.944861000	-1.630871000
C	2.676642000	-1.671146000	2.331922000
C	4.267365000	-0.486927000	0.728992000
H	3.281567000	-2.873087000	-1.759266000
H	1.836121000	-1.987440000	-2.287604000
H	3.346273000	-1.102631000	-1.916430000
H	4.344869000	0.368412000	1.411092000
H	5.092209000	-1.171382000	0.960125000
H	4.396266000	-0.124609000	-0.292491000
H	3.447286000	-2.389526000	2.635765000
H	2.703259000	-0.834549000	3.040410000
H	1.702046000	-2.160772000	2.410462000
C	-1.134407000	1.909718000	1.857230000
C	-0.371683000	0.817752000	2.327170000
C	-2.146777000	1.403723000	0.992855000
C	-2.041108000	-0.010340000	0.947580000
C	-0.929968000	-0.361676000	1.761860000
H	-0.977197000	2.951417000	2.101016000
H	0.478275000	0.867258000	2.995785000
H	-2.879247000	2.001169000	0.467232000
C	-2.928179000	-0.975932000	0.177337000
H	-0.545169000	-1.362667000	1.901766000

C	-2.081497000	-2.116083000	-0.431137000
C	-0.928061000	-1.732598000	-1.374283000
O	-0.455155000	-0.515601000	-1.306589000
O	-0.479426000	-2.589247000	-2.132101000
C	-3.942313000	-1.593701000	1.171864000
C	-3.711199000	-0.261562000	-0.942284000
H	-2.730337000	-2.802154000	-0.986578000
H	-1.642605000	-2.721714000	0.374408000
H	-4.578399000	-0.817922000	1.613671000
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H	-4.362326000	0.522980000	-0.540104000
H	-4.351141000	-0.982141000	-1.464666000
Ti	-0.026871000	0.947243000	-0.028396000
C	0.917084000	3.219258000	-0.062787000
C	1.866592000	2.341772000	-0.627974000
C	-0.237739000	3.211499000	-0.894555000
C	0.008143000	2.339401000	-1.981456000
C	1.301981000	1.787335000	-1.809372000
H	1.039700000	3.782542000	0.853176000
H	2.838389000	2.107170000	-0.215263000
H	-1.145682000	3.775679000	-0.724191000
H	-0.686382000	2.089750000	-2.772453000
H	1.755375000	1.039202000	-2.444178000

References:

1.- M. Atobe, F. Amemiya, K. Fuse, T. Kashiwagi, T. Fuchigami, M. Matsumoto and C. Kurodo, *Org. Biomol. Chem*. 2011, **9**, 4256-4265.

2.- L-H. Zhao, H-S. Jin, L-J. Wan and L-H. Zhang, *J. Org. Chem*. 2011, **76**, 1831-1837.

3.- F. Amemiya, K. Fuse, T. Fuchigami and M. Atobe, *Chemm. Comm*. 2010, **46**, 2730-2732.

4.- T. Jiménez, S. P. Morcillo, A. Martín-Lasanta, D. Collado-Sanz, D. J. Cárdenas, A. Gansäuer, J. Justicia and J. M. Cuerva, *Chem. Eur. J.* 2012, **18**, 12825-12833.

5.- H. J. Kim, L. Su and S. Koo, *Org. Lett.* 2011, **13**, 2682-2685.

6.- K. Surenda and C. J. Corey, *J. Am. Chem. Soc.* 2008, **130**, 8865-8869.

7.- G. R. Labadie, R. Viswanathan and C. D. Poulter, *J. Org. Chem.* 2007, **72**, 9291-9297.

8.- M. A. Tarselli, J. L. Zucarello, S. J. Lee and M. R. Gagne *Org. Lett.* 2009, **11**, 3490-3492.

9.- S.Voltrova and J. Srogl, *Synlett* 2013, **24**, 394-396.

10.- A. Clerici, N. Pastori and O. Porta, *Tetrahedron Lett*. 2004 , **45**, 1825–1828.

11.- B. Basu, S. Das, Saja, P. Das, A. Nanda and K. Ashish, *Tetrahedron Lett*. 2005, **46**, 8591-8593.

12.- K. Fukui, *J. Org. Chem.* 1972 , **37**, 3176 – 3181

13.- M. Paradas, A. G. Campaña, R. E. Estevez, L. Álvarez de Cienfuegos, T. Jiménez, R. Robles, J. M. Cuerva and J. E. Oltra, *J. Org. Chem.* 2009, **74**, 3616-3619.

14.- T. Hayashi and K. Sasaki, *Chem. Lett*. 2011 , **40**, 492–494.

15.- H. Mosher, *J. Org. Chem*. 1963, **28**, 2154-2155.

16.- T. Jiménez, A. G. Campaña, B. Bazdi, M. Paradas, D. Arráez-Román, A. Segura-Carretero, A. Fernández-Gutiérrez, J. E. Oltra, R. Robles, J. Justicia and J. M. Cuerva, *Eur. J. Org. Chem.* 2010, **22**, 4288-4295.

17.- J. Nokami, K. Maruoka, T. Souda and N. Tanaka, *Tetrahedron* 2007, **63**, 9016–9022.

18.- T. Mukaiyama, K. Imagawa, T. Yamada and T. Toshihiro, *Chem. Lett.* 1992, **2**, 231-234.

19.- J. Justicia, T. Jiménez, S. P. Morcillo, J. M. Cuerva and J. E. Oltra, *Tetrahedron* 2009, **65**, 10837-10841.

20.- A. F. Barrero, J. M. Cuerva, M. M. Herrador and M. Valdivia, *J. Org. Chem.* 2001, **66**, 4074-4078.

21.- A. D. Becke, *Phys. Rev. A* 1988, **38**, 3098-3100.

22.- C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B* 1988, **37**, 785-789.

23.- A. D. Becke, *J. Chem. Phys.* 1993, **98**, 5648-5652.

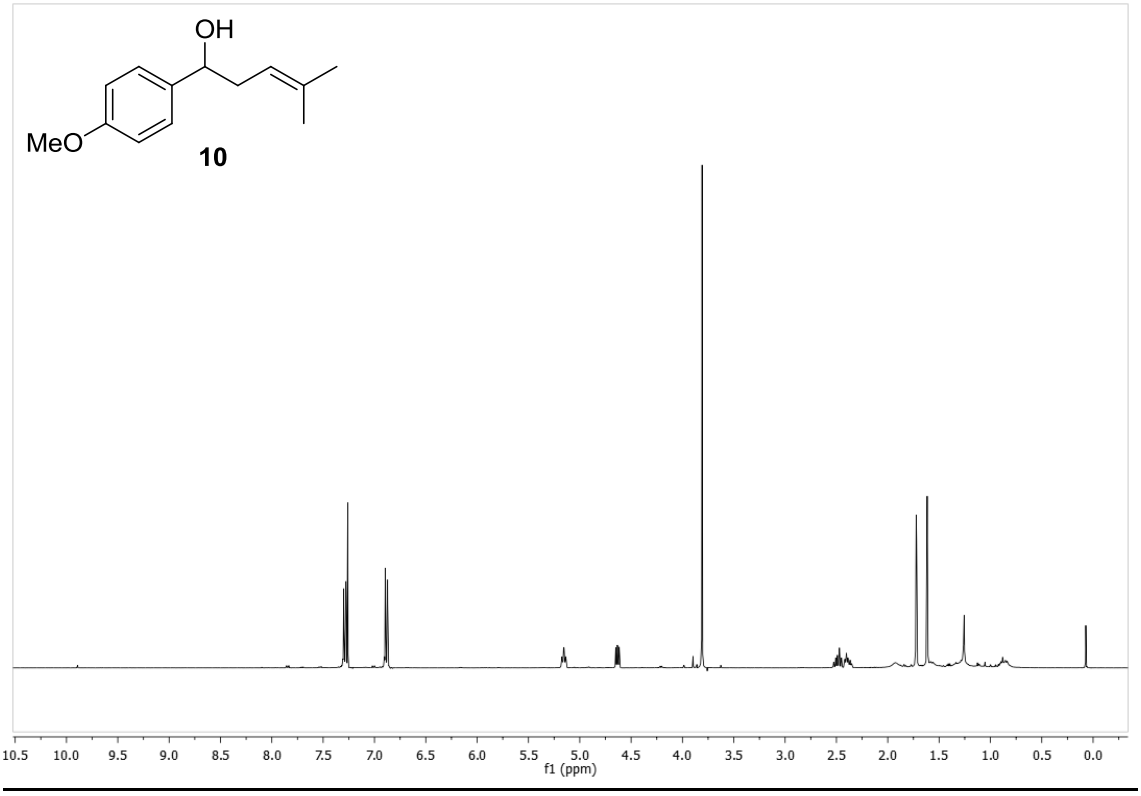
24.- Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Li, X. Caricato, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery

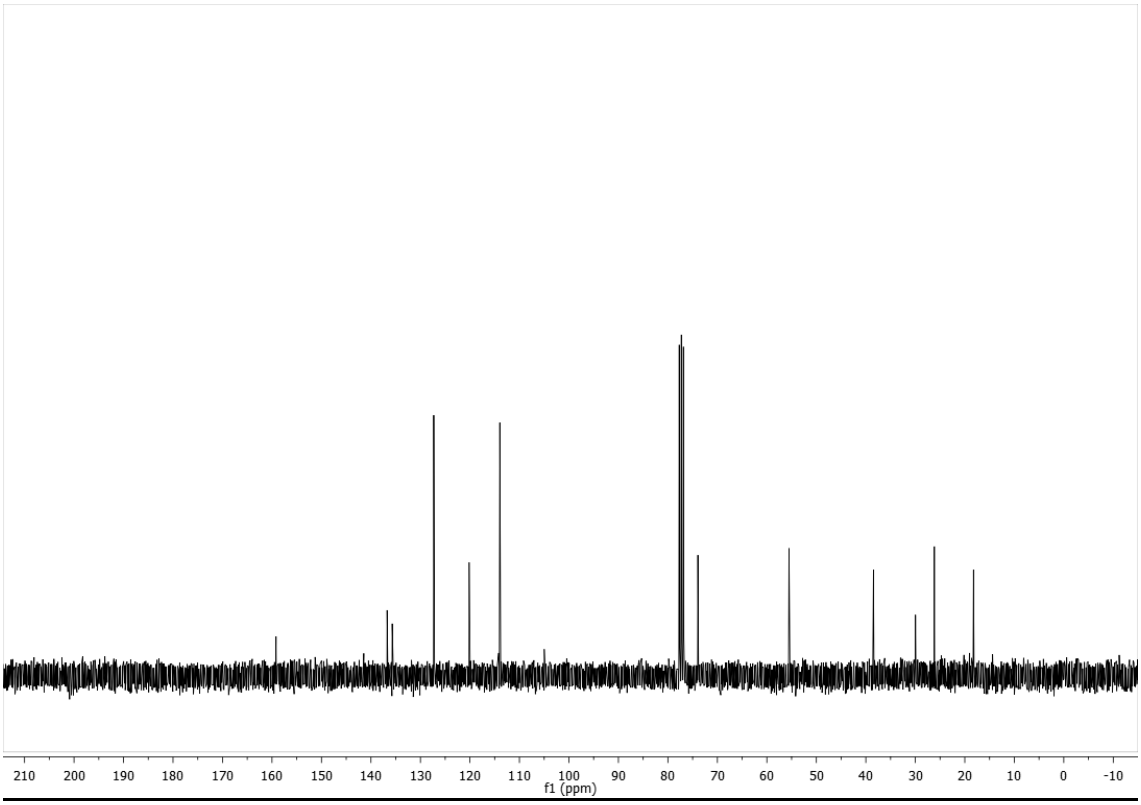
Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010.

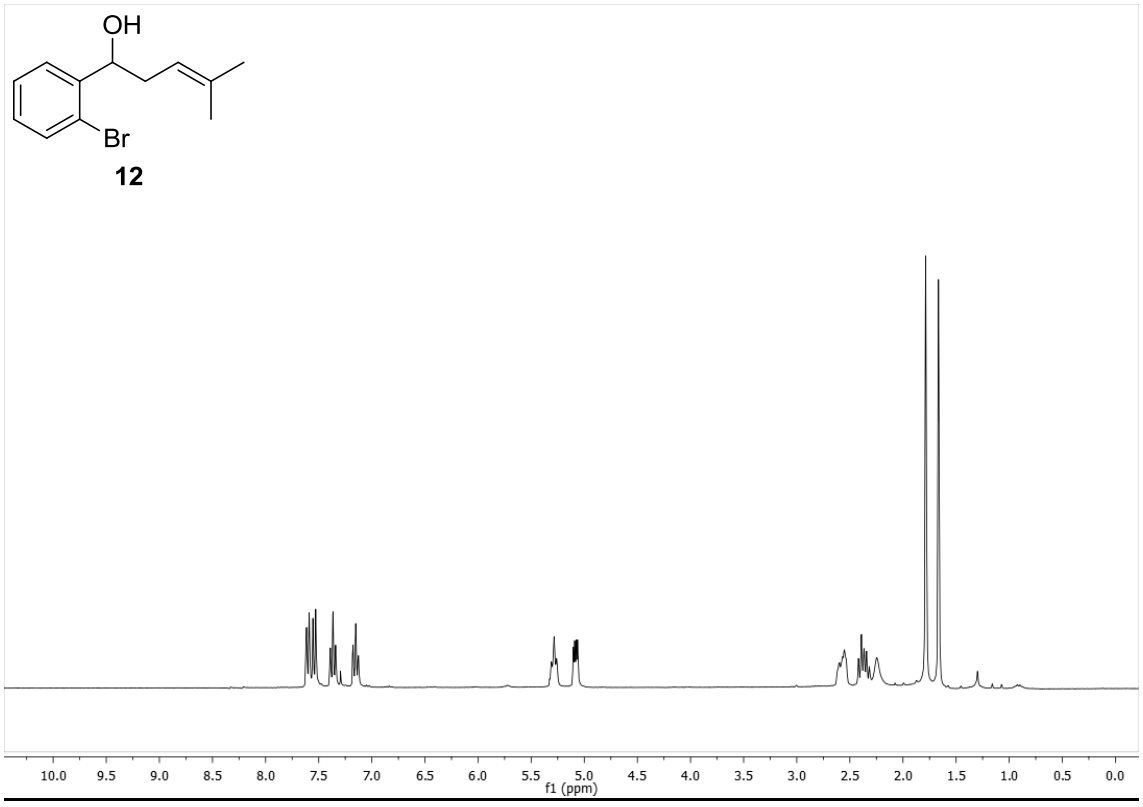
25.- (a) P. J. Hay and W. R. Wadt, *J. Chem. Phys.* 1985, **82**, 270-283. (b) W. R. Wadt and P. J. Hay, *J. Chem. Phys.* 1985, **82**, 284-298. (c) P. J. Hay and W. R. Wadt, *J. Chem. Phys.* 1985, **82**, 299-310.

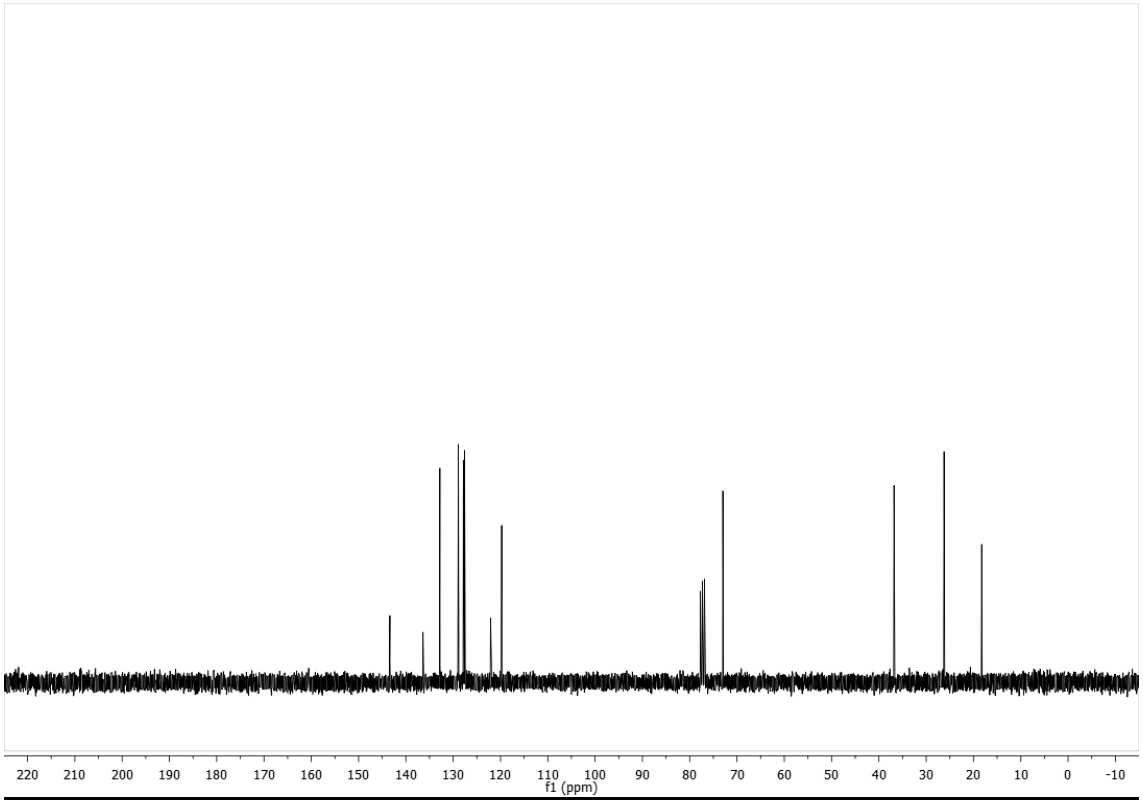
26.- P. C. Hariharana and J. A. Pople, *Mol. Phys.* 1974, **27**, 209-214.

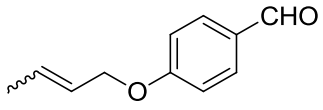
^{1}H and ^{13}C NMR FOR NEW COMPOUNDS







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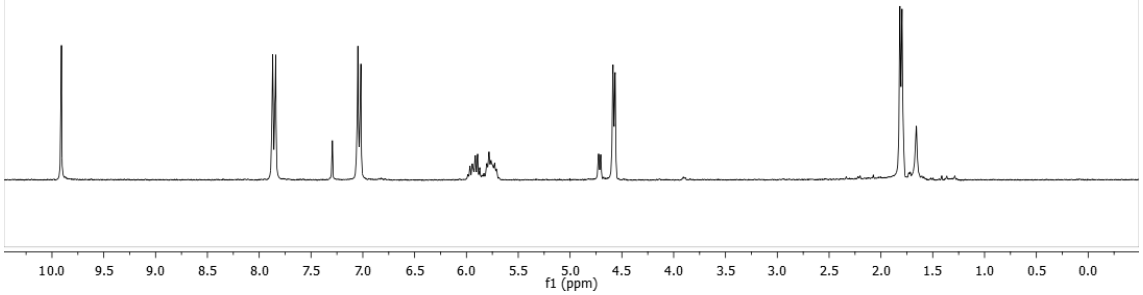
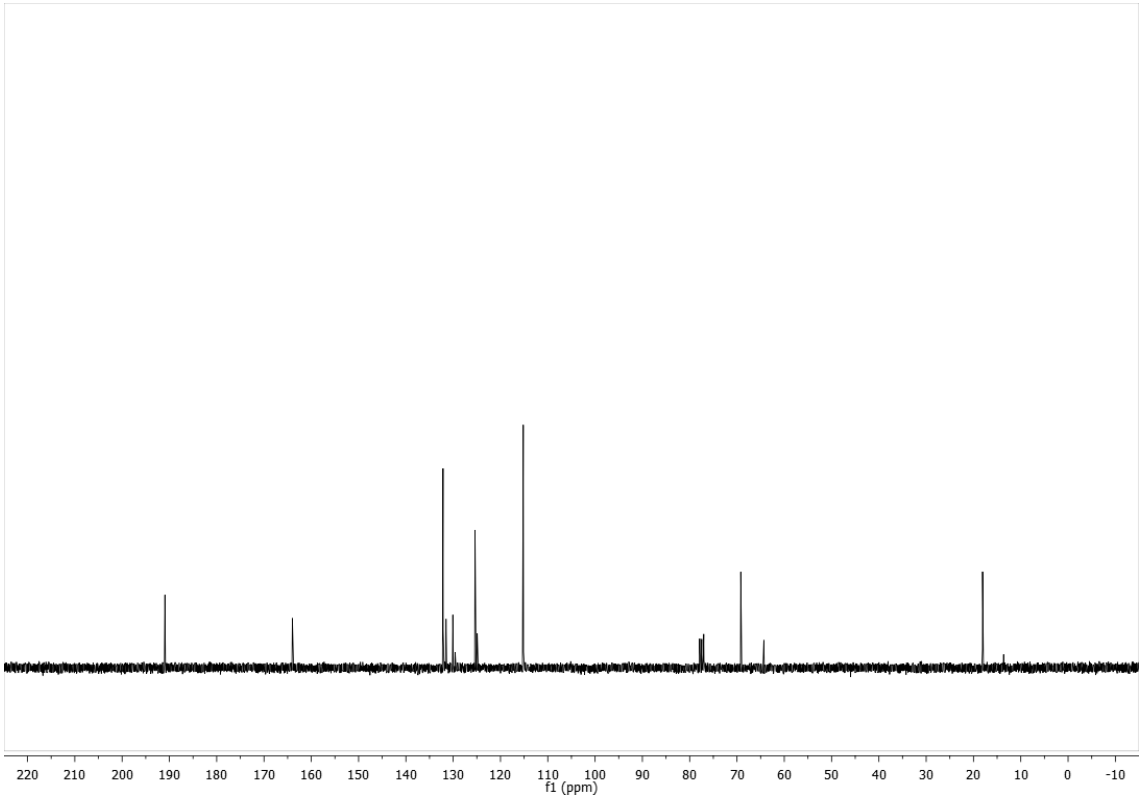
O

55


10.0 9.5 9.0 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 0.0
f1 (ppm)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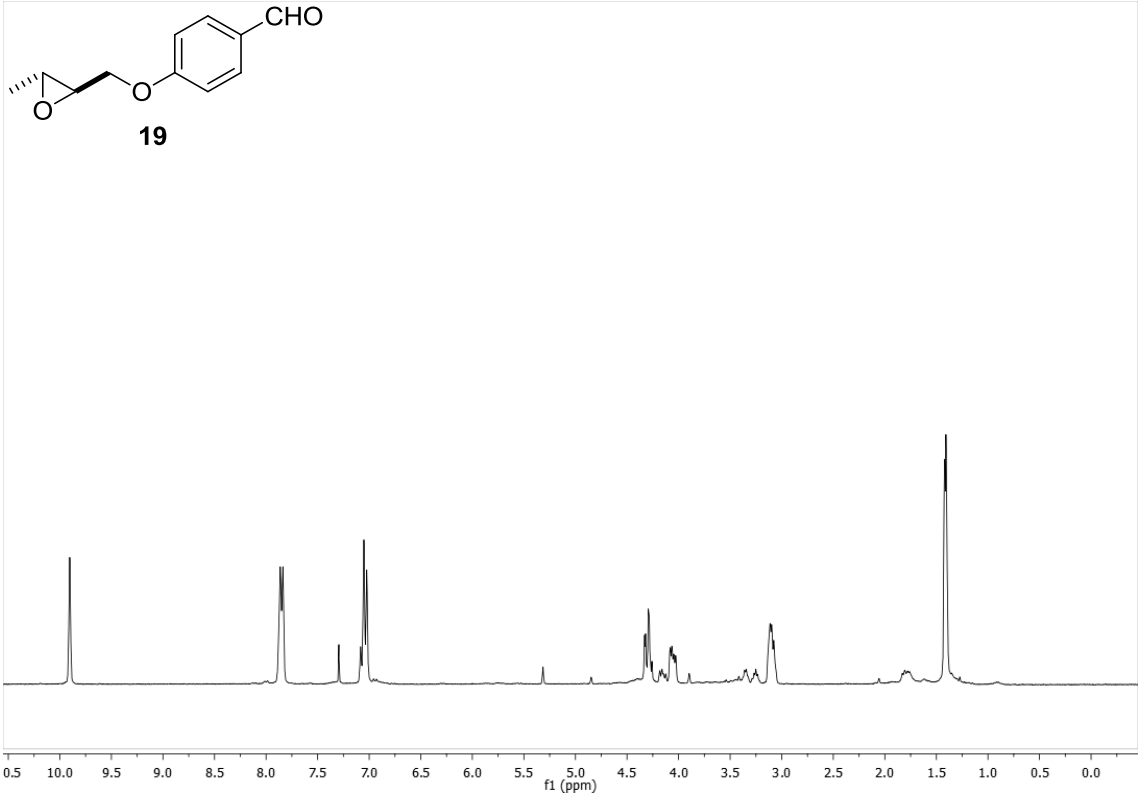
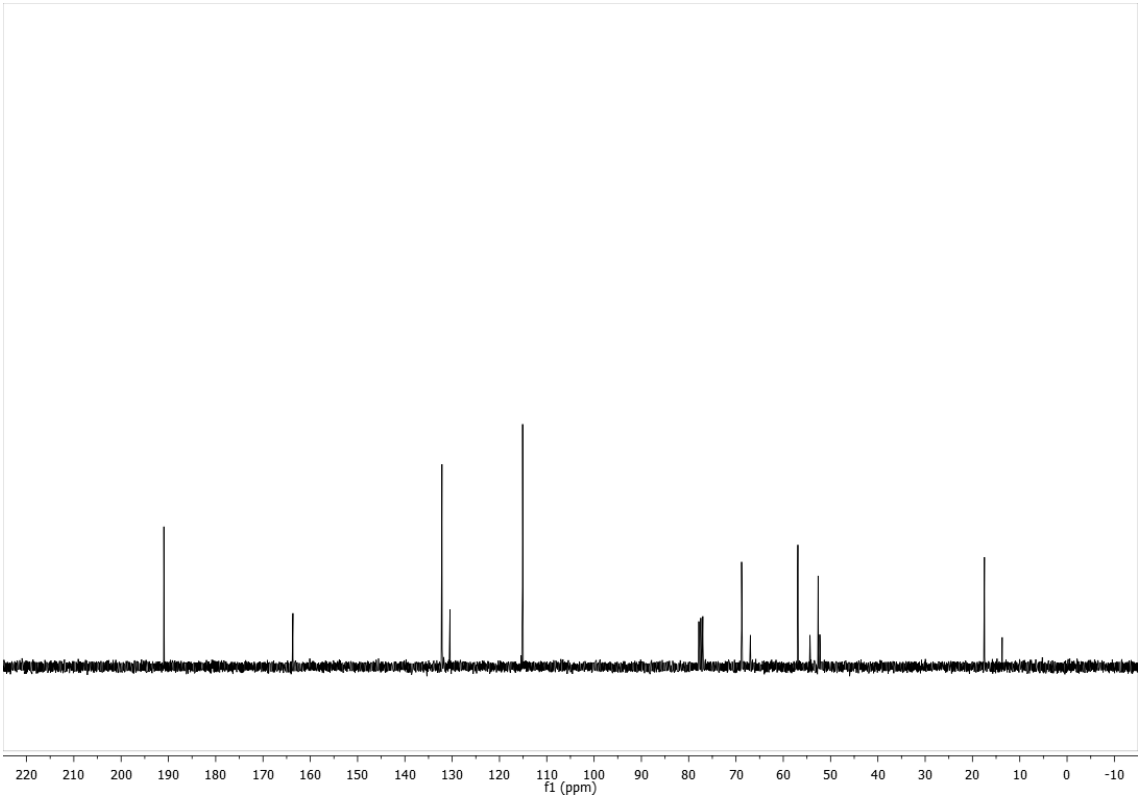

CHO
O
O
19
0.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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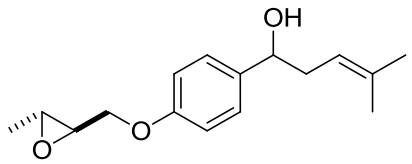
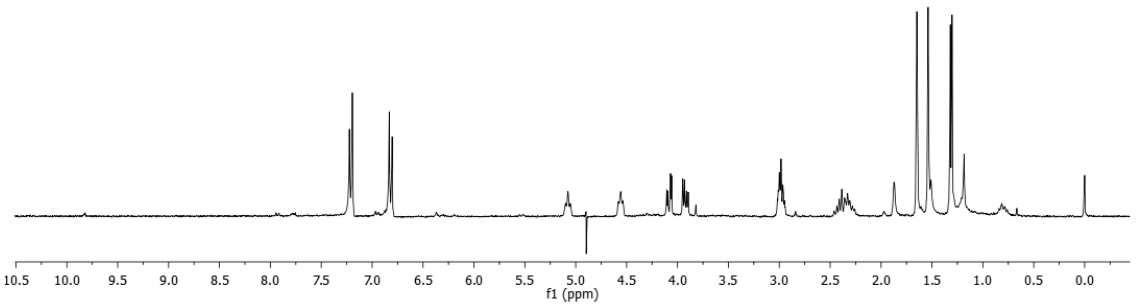
f1 (ppm)


OH
O
O

24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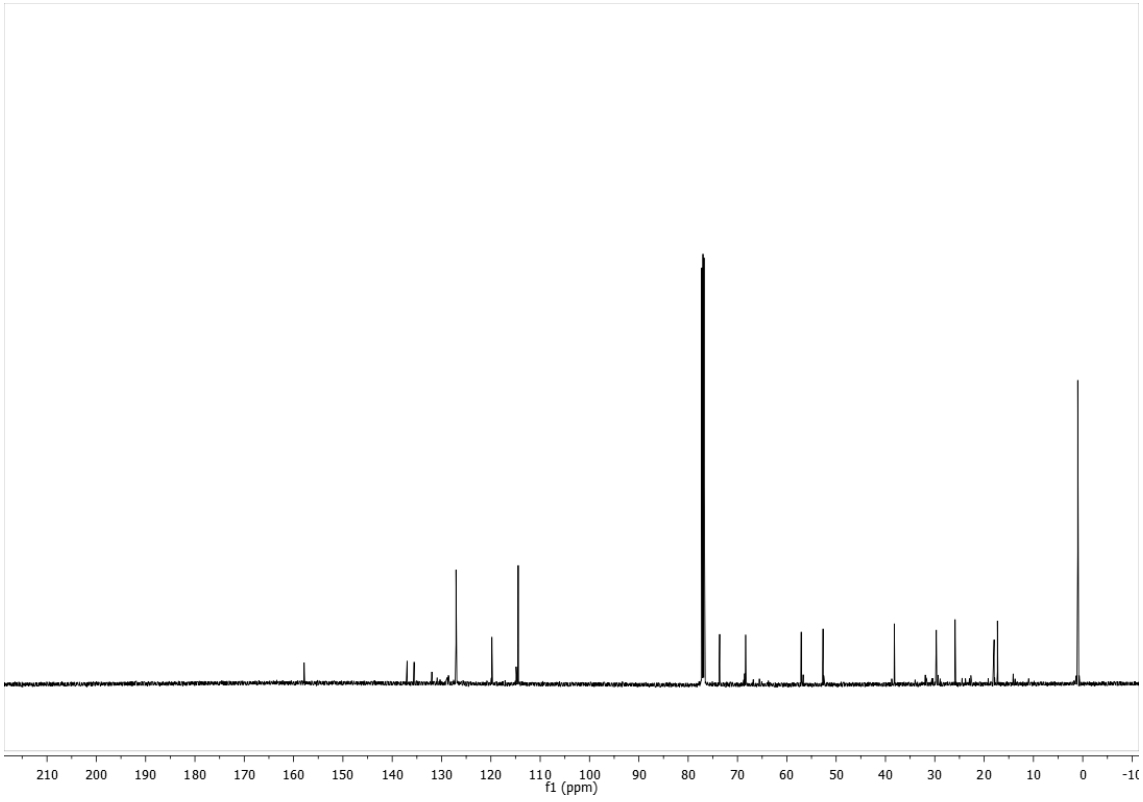
f1 (ppm)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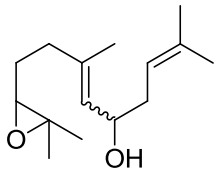

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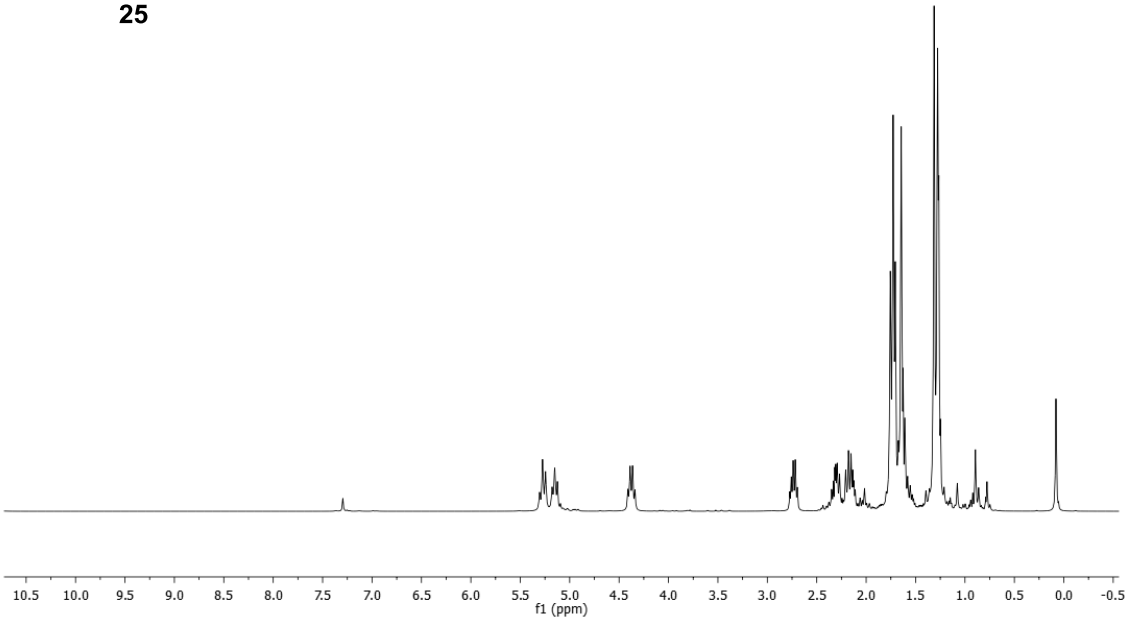
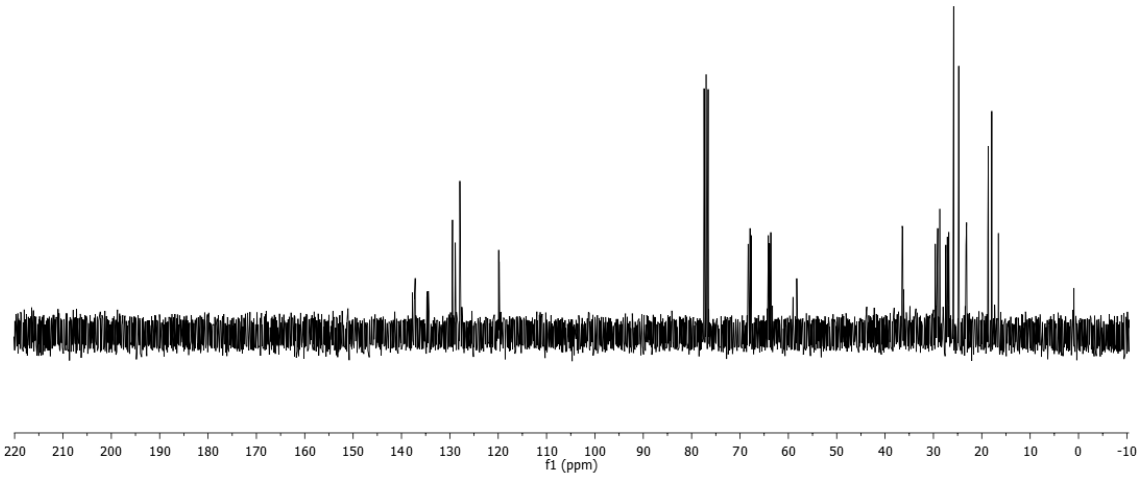
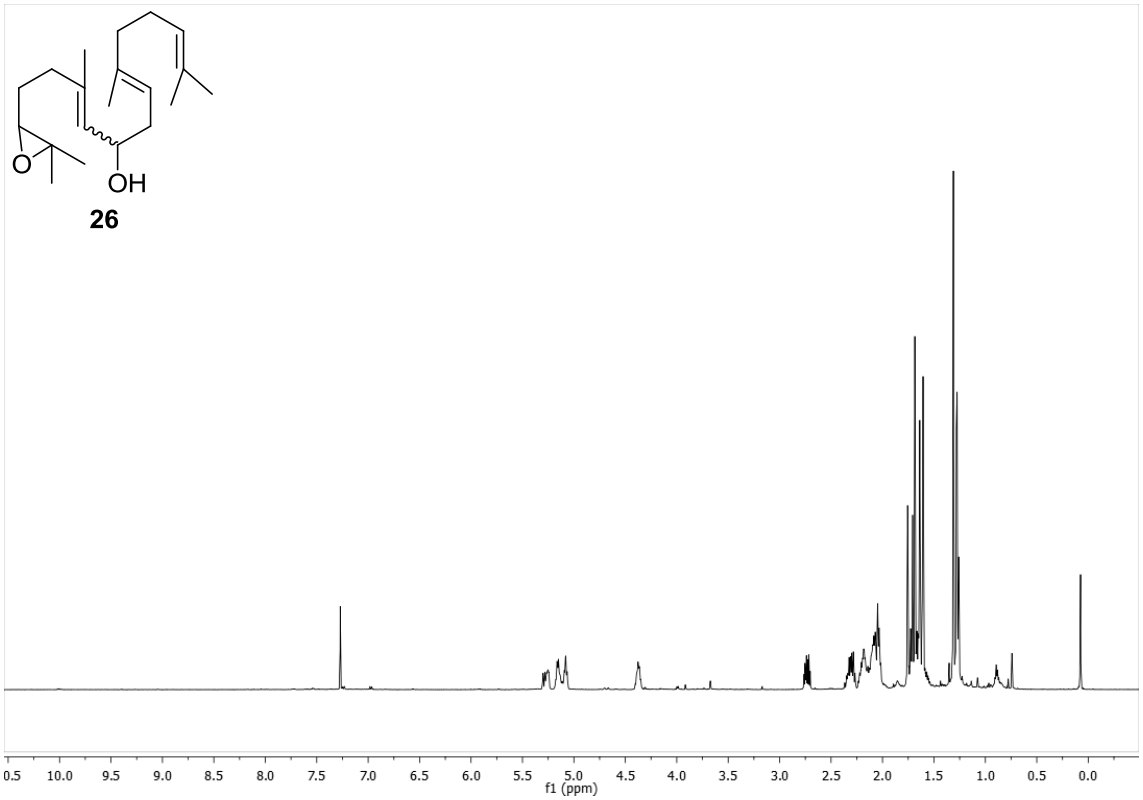
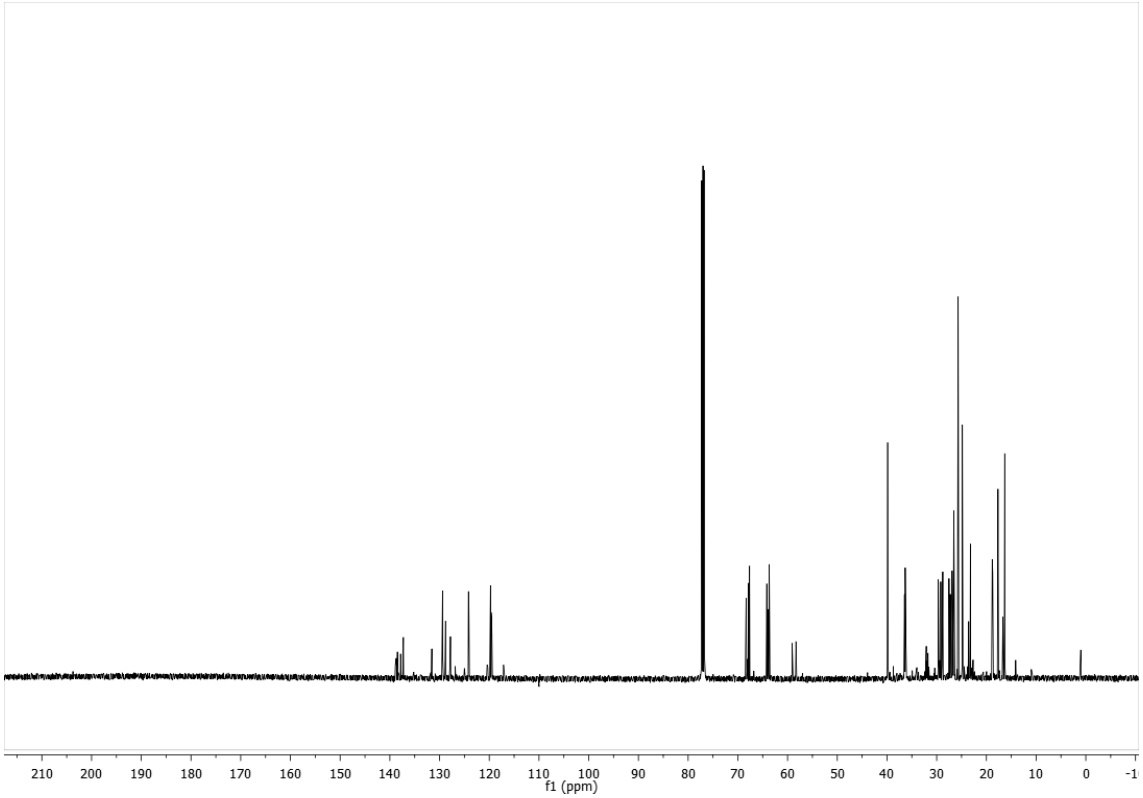





O
OH
26
f1 (ppm)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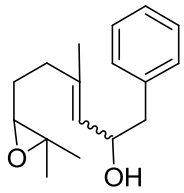

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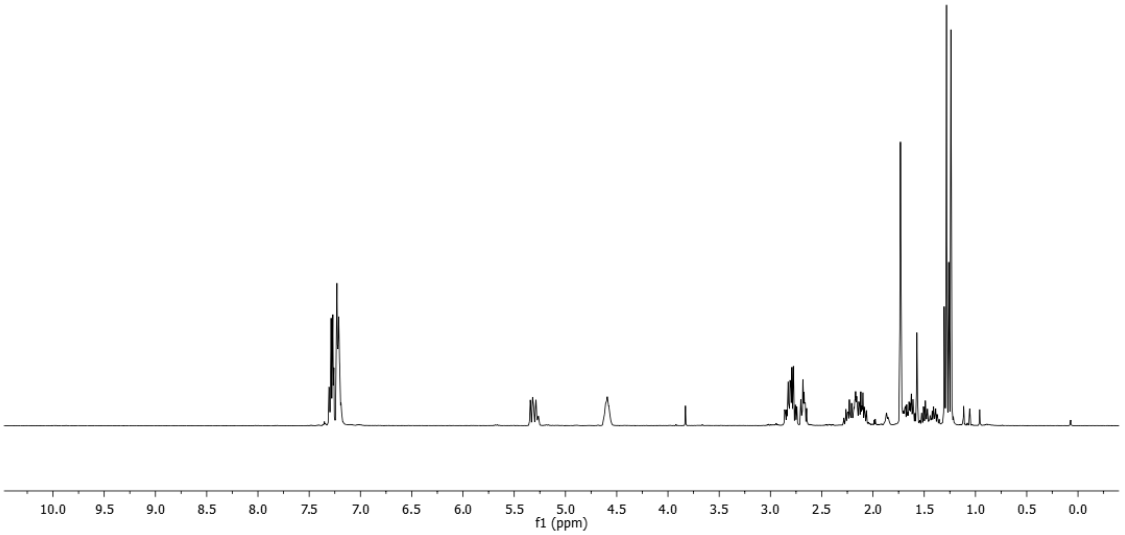

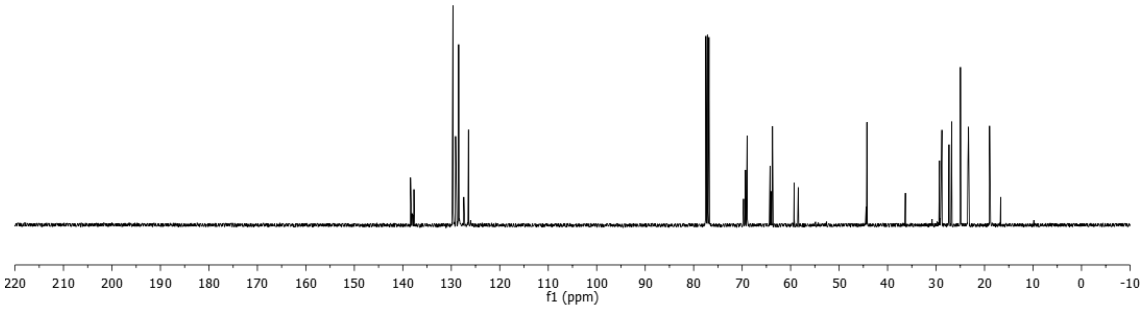

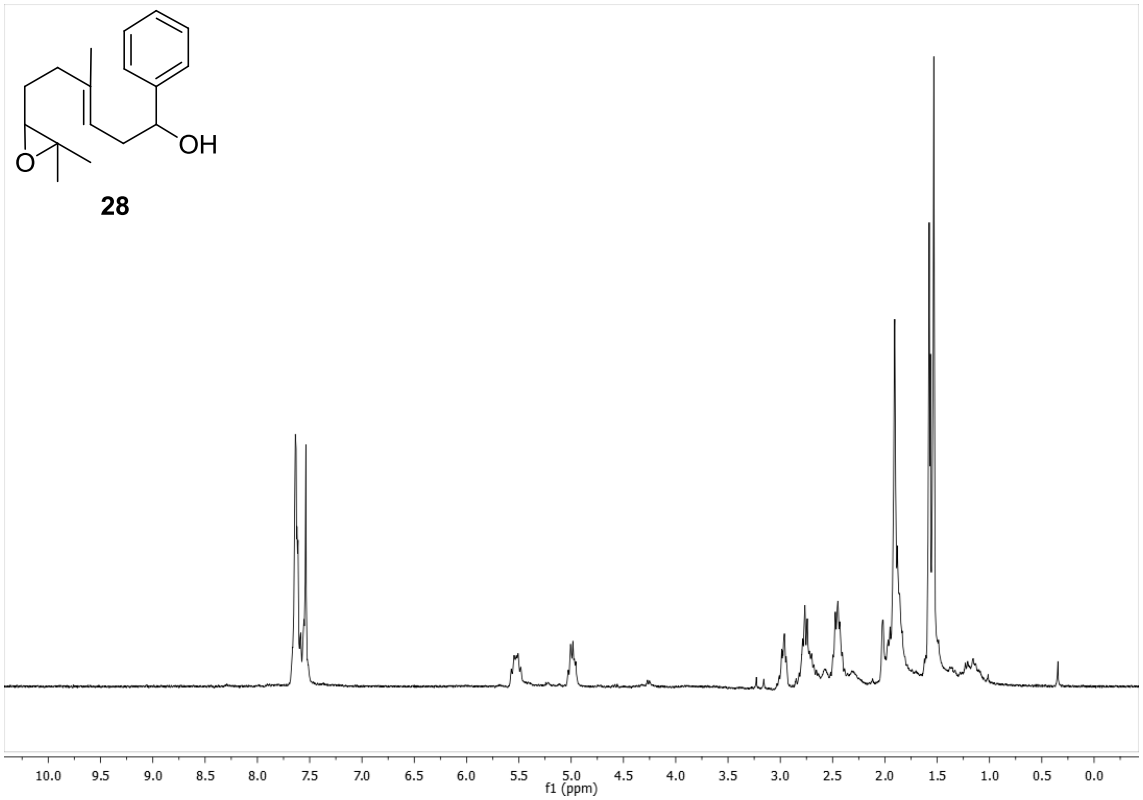

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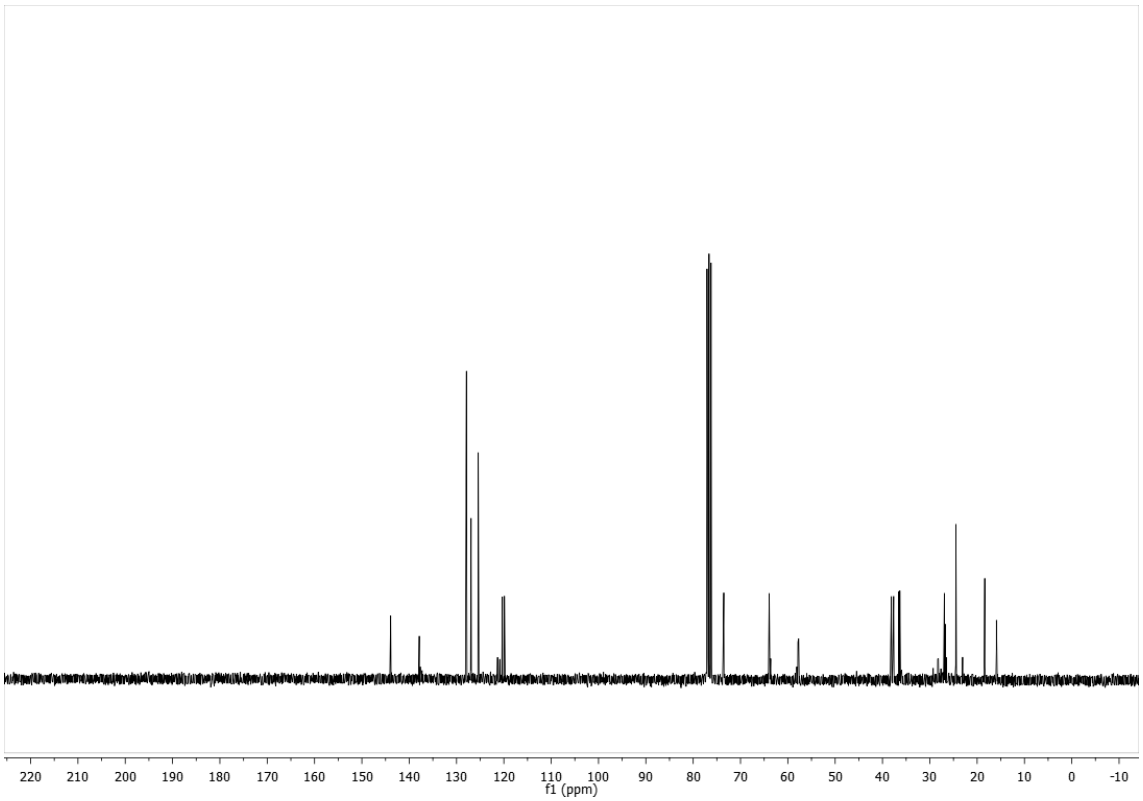

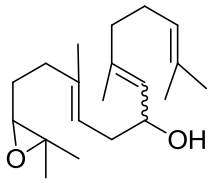

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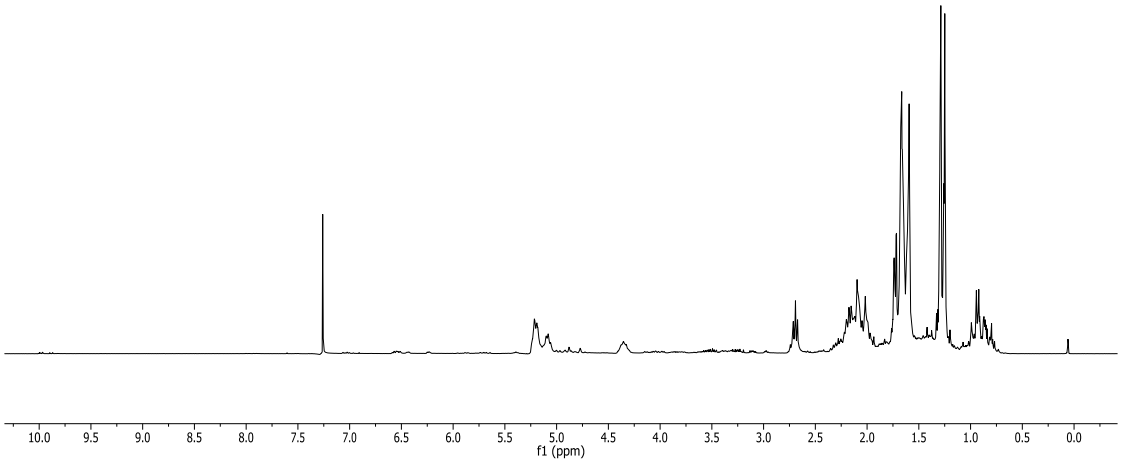
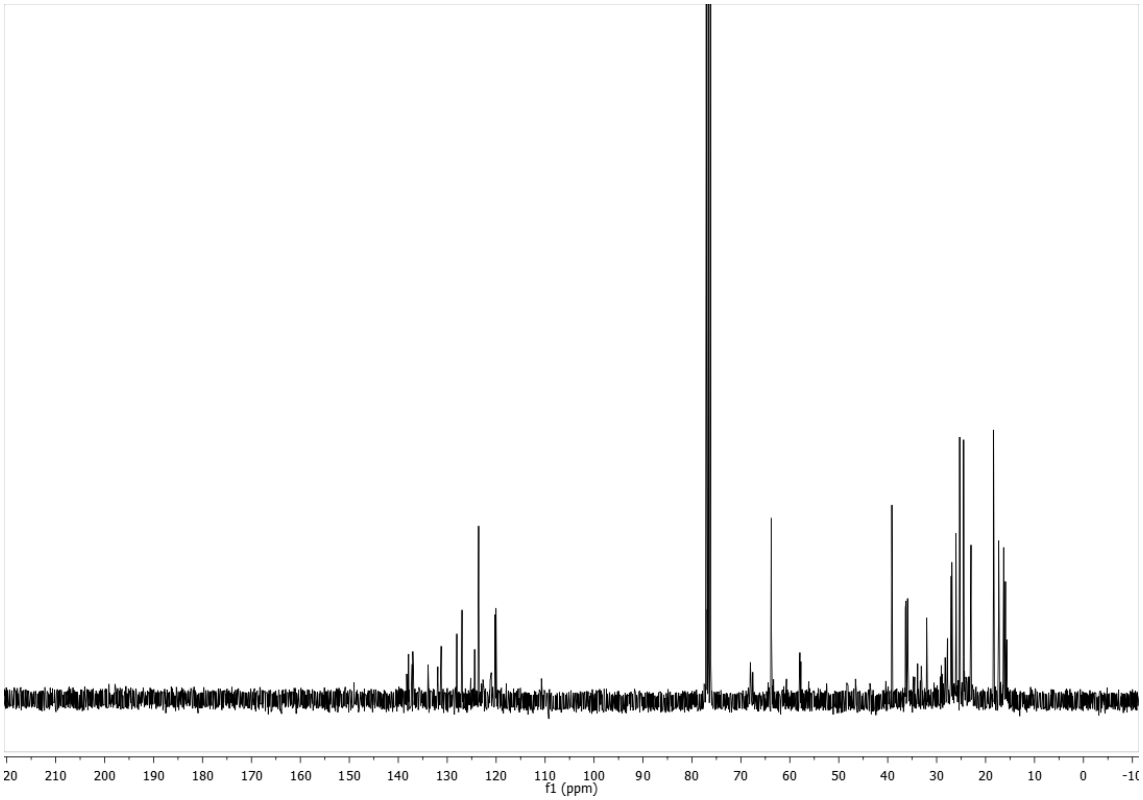
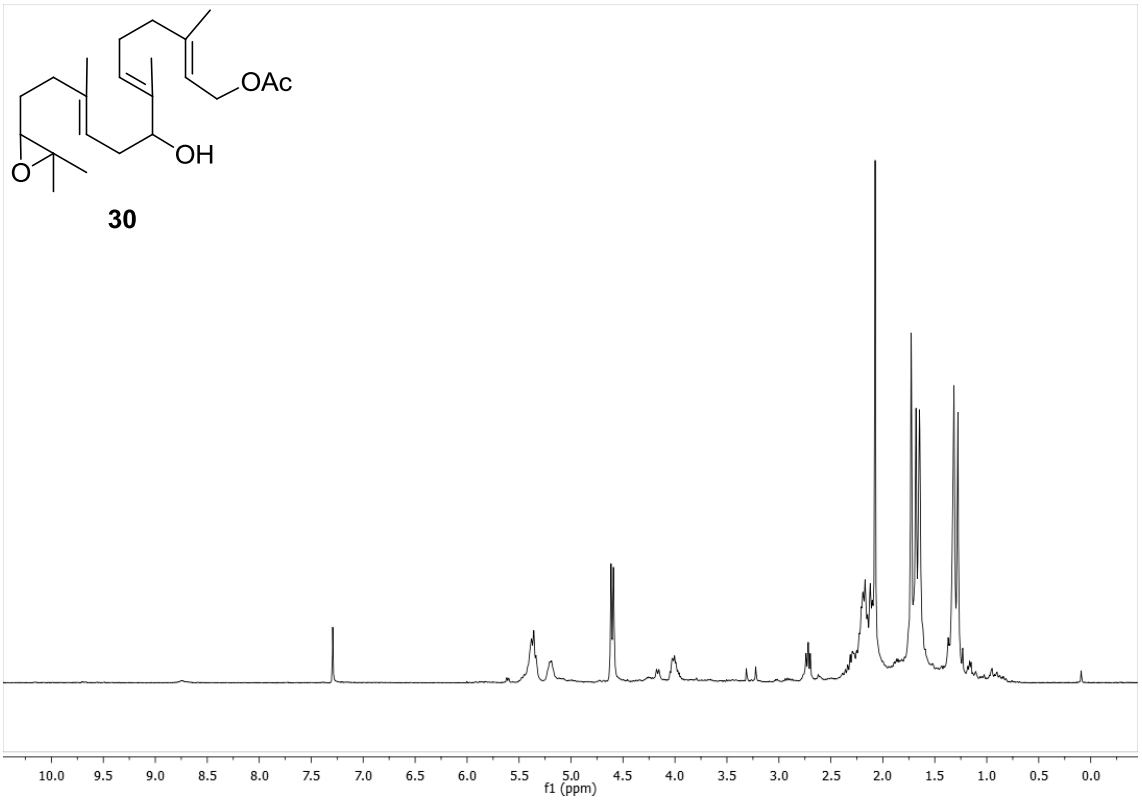




Traces of dienes can be also observed in NMR spectra. They derived from decomposition of minor amounts of γ-addition products.



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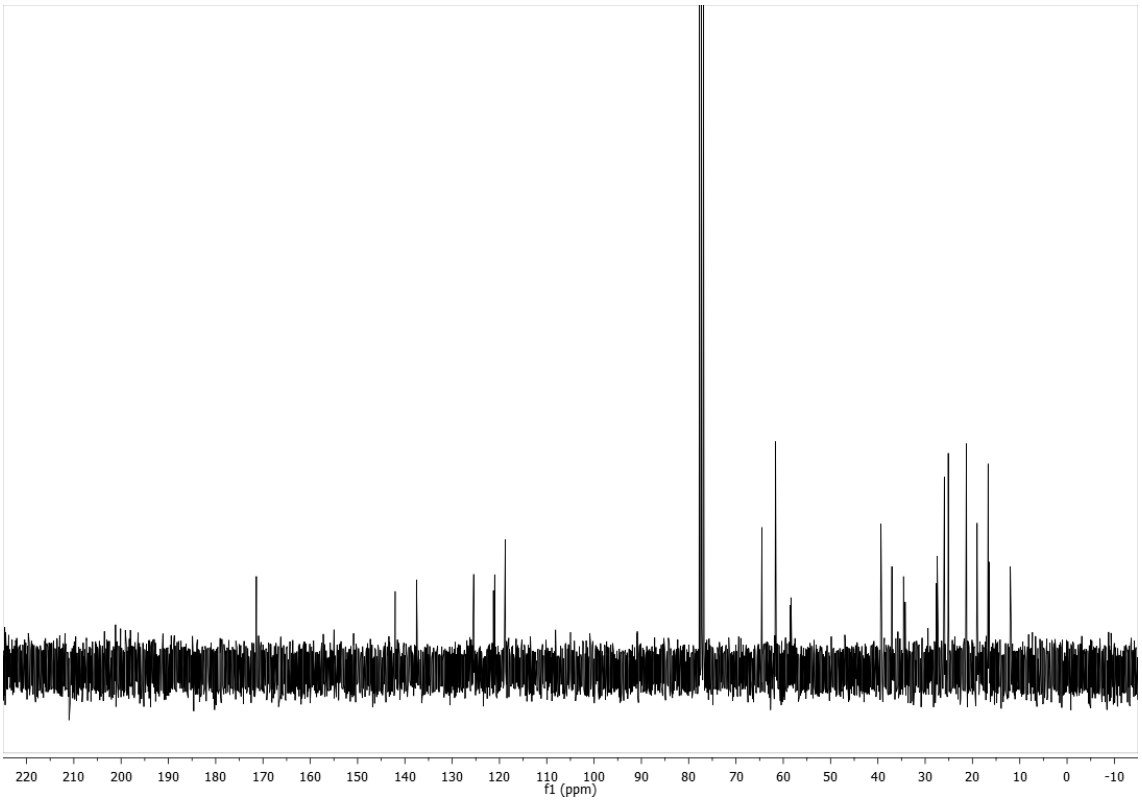
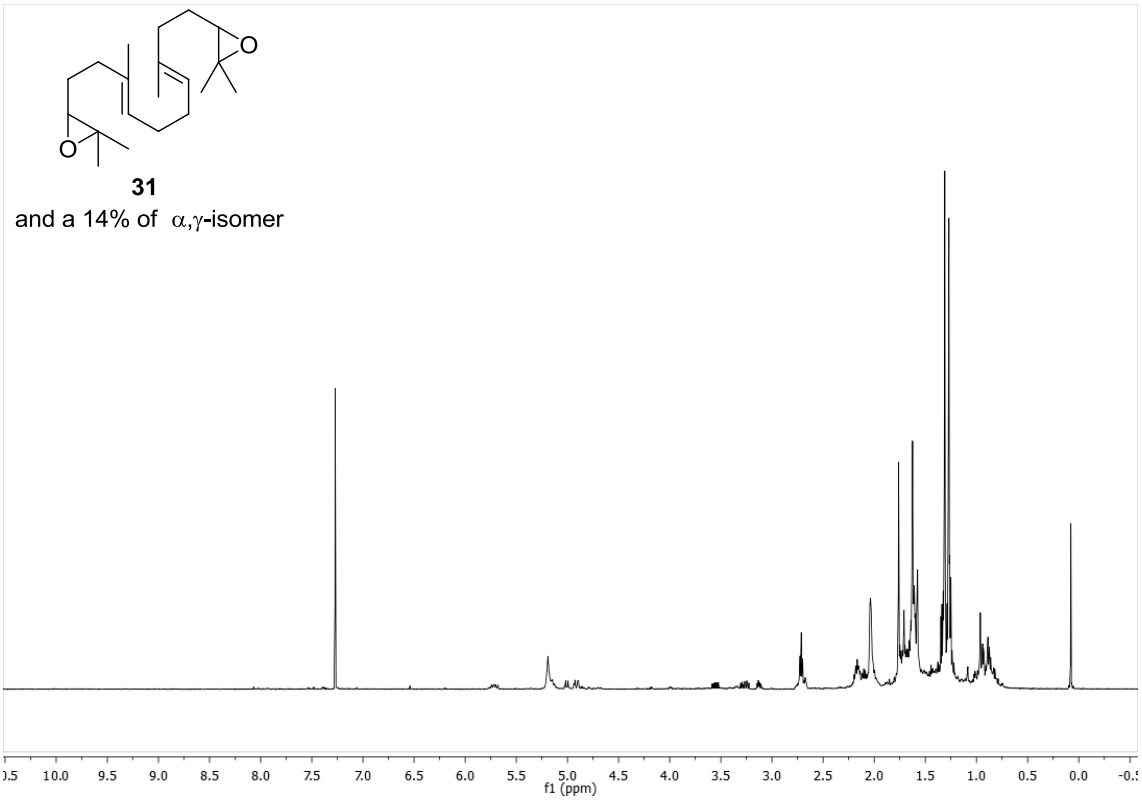
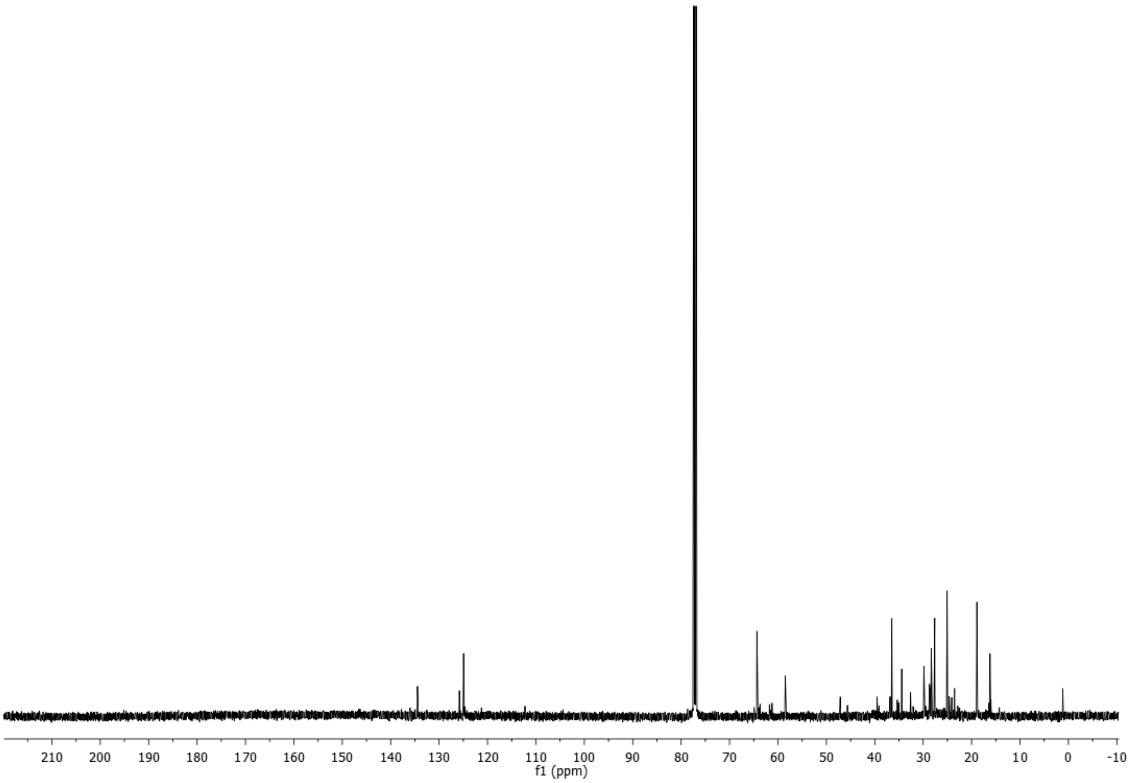



O
O
31
and a 14% of α,γ-isomer
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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f1 (ppm)