Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Electronic Supporting Information for:

Activation of Molecular Oxygen and its Use in Stereoselective Tetrahydrofuran-Syntheses from δ,ε-Unsaturated Alcohols

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Contents

1 General Remarks

(i) The compound numbering in the electronic supporting information (ESI) is consistent with that of the accompanying publication. (ii) References refer exclusively to the ESI.

2 Instrumentation

Melting points [°C] were determined on a Koffler hot-plate melting point microscope (*Reichert*). ^{1}H-, ^{13}C- and ^{19}F-NMR spectra were recorded with FT-NMR DPX 200, DPX 400 and DMX 600 instruments (*Bruker*). Chemical shifts refer to the δ-scale (coupling constants J are given in Hz). The resonances of residual protons and the corresponding carbons of deuterated solvents $CDCl_3$ (δ_H 7.26, δ_C 77.0) or DMSO-d_6 (δ_H 2.49, δ_C 39.5) were used as internal standards. Mass spectra (EI, 70 eV) were recorded with a Mass Selective Detector HP 6890 (*Hewlett Packard*). MALDI-TOF spectra were meassured with an Ultraflex TOF/TOF (*Bruker*) using DHB as matrix. UV/Vis-spectra were recorded in 1 cm-quartz cuvettes with a Cary 100 spectrometer (*Varian*) at 20 °C using analytical grade solvents. Molar extinction coefficients (ε) are reported in $m^3 \times mol^{-1} \times cm^{-1}$. GC Analyses were performed on a HP 6890 Series (*Hewlett Packard*) with a ZB5 column (*Phenomenex*, 30 m x 0.25 mm, 0.25 µm). Temperature program: 40 °C (3 min), linear temperature rise (10 °C min-1) to 280 °C, final temperature 280 °C (10 min). Combustion analyses were performed with an Elemental Analyser 2400 CHN (*Perkin Elmer*). Volumetric measurements of water were made on a 702 SM Titrino (*Metrohm*). IR spectra were recorded on a FT-IR 1000 spectrometer (*Perkin Elmer*). HPLC analysis: L-4250 UV/VIS detector, L-6200 A Intelligent Pump (*Merck*), Delta Bond (AK) column (*Keystone Scientific*, Inc., 4.6 mm × 150 mm length, particle size 5 µm, pore size 300 Å) and Delta Bond (AK) pre-concentration column (*Keystone Scientific*, Inc., 4.0 mm × 10 mm length).

3 Synthesis of (1*R*,4*R*)-3-Acyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ones

(1*R*,4*R*)-3-[(2,2-Dimethyl-1-oxo)prop-1-yl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**1**). A solution of (1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one [(+)-camphor)] (10.5 g, 69.0 mmol) in DME (25 mL) was added in a dropwise manner over a period of 1 h to a refluxing solution of $NaNH_2$ (3.0 g, 69.2 mmol) in DME (40 mL) under an atmosphere of nitrogen. Heating was continued for 1 h followed by addition of a solution of pivaloyl chloride (2.5 g, 20.7 mmol) in DME (15 mL) within 5 min. The reaction mixture was boiled for further 14 h. It was then cooled to 20 °C, poured onto 50 g of crushed ice and 6 mL of conc. HCl. The pH of the mixture was adjusted with additional conc. HCl to 6–7. It was extracted with Et_2O (2 × 50 mL) and the combined

organic layers were washed with H_2O (5 × 20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining oil was purified by column chromatography to give product **1** (553 mg, 11 %). Red solid, mp 63.0 °C, R_f 0.56 [SiO_2, pentane/diethylether = 3:1 (*v*/*v*)]. $[\alpha]_D^{20}$ +57.0 (*c* 0.98 in $CHCl_3$). λ_{max} (MeOH)/nm 277 (lg ε 1.72). ν_{max} (KBr)/cm^{-1} 2967 and 2870 (CH), 1750 and 1690 (CO) and 1079. δ_H (400 MHz; $CDCl_3$) 0.90 (6 H, s, 2 × 7-Me), 1.00 (3 H, s, 1-Me), 1.15 (9 H, s, 3 × 12-Me), 1.37–1.79 (4 H, m, 5-H, 6-H), 2.34 (1 H, m$_c$, 4-H) and 3.83 (1 H, dd, *J* 4.8 and 1.3, 3-H). δ_C (100 MHz; $CDCl_3$) 9.6 (1-Me), 19.0 (7-Me), 19.7 (7-Me), 21.7 (C5), 26.2 (3 × 2'-Me), 29.3 (C6), 45.1 (C2'), 46.7 (C7), 48.8 (C4), 57.9 (C3), 58.4 (C1), 212.8 (C1') and 213.7 (C2), *m*/*z* (EI, 70 eV) 236 (M$^+$, 28 %), 221 (3), 208 (17), 193 (6), 179 (86), 151 (100), 137 (13), 127 (21), 123 (38), 109 (45), 83 (46) and 57 (95). Calc. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23 %. Found: C, 76.49; H, 10.37 %.

(1*R*,4*R*)-3-Trifluoracetyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**2**). (1*R*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one (15.2 g, 100 mmol) was added to a suspension of NaH (9.0 g, 375 mmol) in DME (150 mL). The mixture was refluxed for 1 h. A solution of ethyl trifluoroacetate (15.7 g, 110 mmol) in DME (50 mL) was added into the boiling solution in a dropwise manner within 1 h. Heating was continued for 2 h. The mixture was hereafter cooled down to 0 °C. EtOH (15 mL) was added. The deep red mixture was poured into H_2O (300 mL), acidified with conc. HCl (pH 1) and extracted with pentane (4 × 100 mL). Combined organic extracts were washed with 5 % aqueous $NaHCO_3$ solution (2 × 150 mL) and H_2O (150 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining oil was distilled to afford compound **2** (18.2 g, 73 %). Colorless liquid, bp 62 °C / 0.25 mbar, R_f 0.63 [SiO_2, petrolether/diethylether = 5:1 (*v*/*v*)]. $[\alpha]_D^{20}$ +150.0 (*c* 1.07 in $CHCl_3$). λ_{max} (MeOH)/nm 258 (lg ε 0.08) and 313 (0.52). ν_{max} (NaCl)/cm^{-1} 2965 and 2876 (CH), 1705 and 1655 (CO), 1452, 1374, 1321, 1264, 1223, 1192, 1147, 1106, 1073, 1038, 1003, 919, 817, 808, 761 and 678. δ_H (400 MHz; $CDCl_3$) 0.87 (3 H, s, 1-Me), 1.00 (3 H, s, 7-Me), 1.04 (3 H, s, 7-Me), 1.48 (2 H, m$_c$, 6-H), 1.75–1.84 (1 H, m, 5-H), 2.07–2.16 (1 H, m, 5-H), 2.90–2.91 (1 H, m, 4-H) and 11.48 (1 H, br s, OH). δ_C (100 MHz; $CDCl_3$) 8.4 (1-Me), 18.1 (7-Me), 20.3 (7-Me), 26.6 (C5), 30.2 (C6), 47.2 (C4), 48.9 (C7), 58.0 (C1), 117.7 (C3), 119.4 (q, *J* 273.9 Hz, CF_3), 148.2 (q, *J* 37.7 Hz, C1') and 214.0 (C2). δ_F (565 MHz; EtOD) –75.3; *m*/*z* (EI, 70 eV) 248 (M$^+$, 100 %), 233 (47), 220 (51), 205 (42), 151 (36), 135 (32), 123 (35) and 69 (22).

(1*R*,4*R*)-3-Benzoyl-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**3**) was prepared from a solution of methyl benzoate (4.9 g, 36.1 mmol) in DME (20 mL), (1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (5.0 g, 32.8 mmol) and a suspension of NaH (1.85 g, 77.1 mmol) in DME (50 mL) in extension to the procedure described for derivative **2**. Yield: 4.9 g (58 %), colorless solid, mp 97.5 °C (pentane). $[\alpha]_D^{20}$ +270.0 (*c* 1.00 in $CHCl_3$). λ_{max} (MeOH)/nm 235sh, 244 (lg ε 2.86) and 308 (3.00). ν_{max} (KBr)/cm^{-1} 2965 and 2868 (CH), 1750 and 1667 (CO), 1615, 1074, 1033, 824, 795, 775 and 698; δ_H (600 MHz; $CDCl_3$) 0.83 (3 H, s, 1-Me), 0.94 (3 H, s, 7-Me), 1.03 (3 H, s, 7-Me), 1.51–1.57 (1 H, m, 5-H), 1.58–1.84 (2 H, m, 5-H, 6-H), 2.16 (1 H, ddt, J_d 11.2, J_t 4.3, 6-H), 2.84 (1 H, d, *J* 3.8, 4-H), 7.41–7.45 (3 H, m, Ph-H) and 7.64–7.69 (2 H, m, Ph-H). δ_C (150 MHz; $CDCl_3$) 8.9 (1-Me), 18.8 (7-Me), 20.3 (7-Me), 27.1 (C5), 30.6 (C6), 46.4 (C7), 48.4 (C4), 58.8 (C1), 115.4 (C3), 127.8, 128.3, 130.3 and 134.1 (Ph), 161.8 (C1') and 213.3 (C2) (ketoenol). δ_H (600 MHz; $CDCl_3$) 0.98 (3 H, s, 1-Me), 1.02 (3 H, s, 7-Me), 1.03 (3 H, s, 7-Me), 1.33–1.39 (1 H, m, 6-H), 1.58–1.84 (3 H, m, 5-H, 6-H), 2.52 (1 H, dd, *J*, 4.4, 4-H), 4.24 (1 H, dd, *J* 4.7, 1.5, 3-H), 7.45–7.50 (2 H, m, Ph-H), 7.54–7.60 (2 H, m, Ph-H) and 7.90–7.94 (2 H, m, Ph-H); δ_C (150 MHz; $CDCl_3$) 9.6 (1-Me), 19.0 (7-Me), 19.7 (7-Me), 22.1 (C5), 28.9 (C6), 45.2 (C7), 48.6 (C4), 50.1 (C1), 57.6 (C3), 128.4, 128.7, 133.5 and 136.4 (Ph), 197.2 (C1') and 212.9 (C2) (diketone). *m*/*z* (EI, 70 eV) 256 (M^+, 32 %), 241 (7), 228 (15), 213 (15), 147 (19), 105 (100) and 77 (36).

(1*R*,4*R*)-3-[3,5-Bis-(trifluoromethyl)benzoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (**4**) was prepared from ethyl 3,5-bis(trifluoromethyl)benzoate (5.0 g, 17.5 mmol) in DME (10 mL), (1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (3.0 g, 19.7 mmol) and a suspension of NaH (2.0 g, 83.3 mmol) in DME (40 mL) in extension to the procedure described for derivative **2**. Yield: 3.4 g (50 %) R_f 0.76 [SiO_2, pentane/diethylether = 12:1 (*v*/*v*)], reddish solid, mp 73.2 °C (pentane). $[\alpha]_D^{20}$ +159.0 (*c* 1.03 in $CHCl_3$). λ_{max} (MeOH)/nm 224 (lg ε 2.86) and 309 (2.96). ν_{max} (KBr)/cm^{-1} 2967 and 2932 (CH), 1684 and 1638 (CO), 1300, 1278, 1173, 1132, 1041, 907, 706 and 681. δ_H (200 MHz; $CDCl_3$) 0.84 (3 H, s, 1-Me), 0.98 (3 H, s, 7-Me), 1.05 (3 H, s, 7-Me), 1.43–1.90 (4 H, m, 5-H, 6-H), 2.13–2.30 (1 H, m, 4-H), 2.77 (1 H, d, *J* 3.7, 3-H), 7.93 (1 H, s, Ph-H), 8.09 (2 H, s, Ph-H) and 12.34 (1 H, br s, OH). δ_C (150 MHz; $CDCl_3$) 8.8 (1-Me), 18.6 (7-Me), 20.4 (7-Me), 26.8 (C5), 30.5 (C6), 46.4(C7), 48.3 (C4), 57.8 (C3), 58.9(C1), 123.0 (q, *J* 270.3, CF_3), 123.6 (1 × Ph-C), 127.7 (2 × Ph-C), 132.0 (q, *J* 33.1, 2 × Ph-C), 136.2 (1 × Ph-C), 157.6 (C1') and 213.5 (C2). δ_F (565 MHz; EtOD) –68.13 and –68.15 (ketoenol) and –68.36 (diketone). *m*/*z* (EI, 70 eV) 392 (M^+, 20 %), 373 (9),

364 (17), 349 (15), 241 (100), 213 (40), 151 (8) and 123 (42). Calc. for $C_{19}H_{18}O_2F_6$: C, 58.17; H, 4.62 %. Found: C, 58.20; H, 4.56 %.

4 Synthesis of Tetrahydrofur-2-ylcarbaldehydes

General procedure. To a solution of tetrahydrofur-2-ylmethanol *trans*-**10a** (1.75 mmol) or *trans*-**10b** (2.99 mmol) in CH_2Cl_2 (4 mL/mmol) was added NEt_3 (1 mL/mmol) and DMSO (0.7 mL/mmol) at 0 °C. Stirring at 0 °C was continued for 15 min. Afterwards, pyridine/SO_3 complex (3 equiv.) was added at 0 °C. The reaction mixture was stirred for 4 h at 20 °C. It was diluted with CH_2Cl_2 (7 mL/mmol) and washed with 2 M aq. HCl, aq. satd. $NaHCO_3$ soln., and brine. The organic layer was dried with $MgSO_4$ and the volatiles were removed under reduced pressure to leave an oily residue, which was purified by column chromatography (SiO_2).

Tetrahydro-5-(1,1-dimethylethyl)fur-2-ylcarbaldehyde (**12a**). Yield: 146 mg (54 %) from **10a** (276 mg, 1.75 mmol), R_f 0.61 [SiO_2, acetone/pentane = 1:8 (*v*/*v*)], colorless oil, $C_9H_{16}O_2$ (156.22). ν_{max} (NaCl)/cm^{-1} 2956, 2926 and 2869 (CH), 1735 (CO), 1465, 1363 and 1074. δ_H (600 MHz; $CDCl_3$) 0.91 (9 H, s, Me-H), 1.67 (1 H, m_c, 3-H), 1.82–1.94 (2 H, m, 3-H, 4-H), 2.10–2.17 (1 H, m, 4-H), 3.74 (1 H, dd, *J* 9.1, 6.0, 5-H), 4.25 (1 H, td, J_t 7.6, J_d 1.8, 2-H) and 9.65 (1 H, d, *J* 1.8, CHO); δ_C (100 MHz; $CDCl_3$) 25.7 (3 × Me), 26.3 (C4), 27.6 (C3), 33.9 (C1'), 83.1 (C2), 89.1 (C5), 203.3 (CHO). *m*/*z* (EI, 70 eV) 156 (M^+, < 1 %), 127 (45), 109 (100), 83 (64), 69 (51), 67 (28), 57 (54), 55 (52).

Tetrahydro-5-phenylfur-2-ylcarbaldehyde (**12b**). Yield: 235 mg (45 %) from **10b** (533 mg, 2.99 mmol), R_f 0.31 [SiO_2, Et_2O/pentane = 5:3 (*v*/*v*)], colorless oil, $C_{11}H_{12}O_2$ (176.21). ν_{max} (NaCl)/cm^{-1} 3061, 3029, 2936, 1731, 1450, 1063, 757 and 700. δ_H (600 MHz; $CDCl_3$) 1.91 (1 H, m_c, 3-H), 2.11 (1 H, m_c, 4-H), 2.26–2.39 (2 H, m, 3-H, 4-H), 4.57 (1 H, dd, *J* 7.4, 7.2, 2-H), 5.11 (1 H, dd, *J* 7.5, 6.6, 5-H), 7.27–7.31 (1 H, m, Ph), 7.32–7.38 (4 H, m, Ph), 9.77 (1 H, s, CHO). δ_C (150 MHz; $CDCl_3$) 27.4 (C3), 34.3 (C4), 82.2, 83.2 (C2 and C5), 125.5, 127.6, 128.4, 141.6 (Ph), 202.7 (CHO). *m*/*z* (EI, 70 eV) 176 (M^+, 1 %), 158 (8), 147 (90), 129 (48), 117 (12), 105 (12), 91 (100), 77 (18).

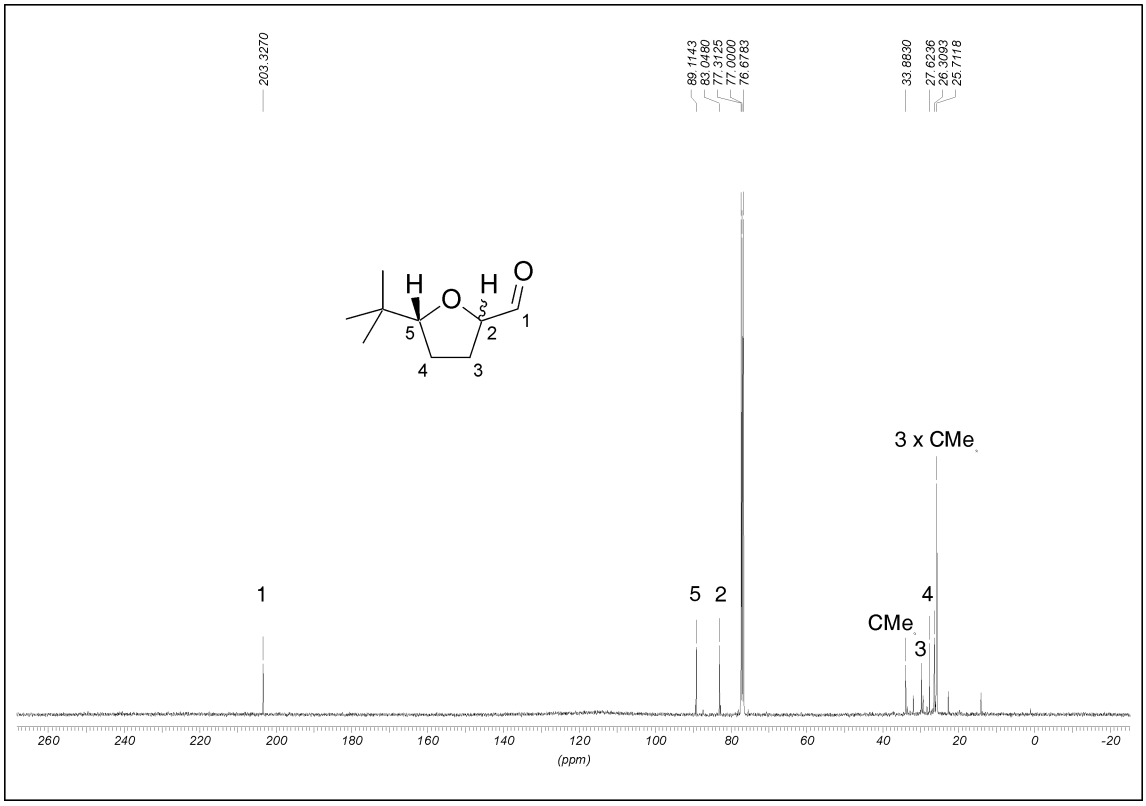

Figure S1. ^{13}C-NMR spectrum (100 MHz) of tetrahydrofurylcarbaldehyde **12a**.

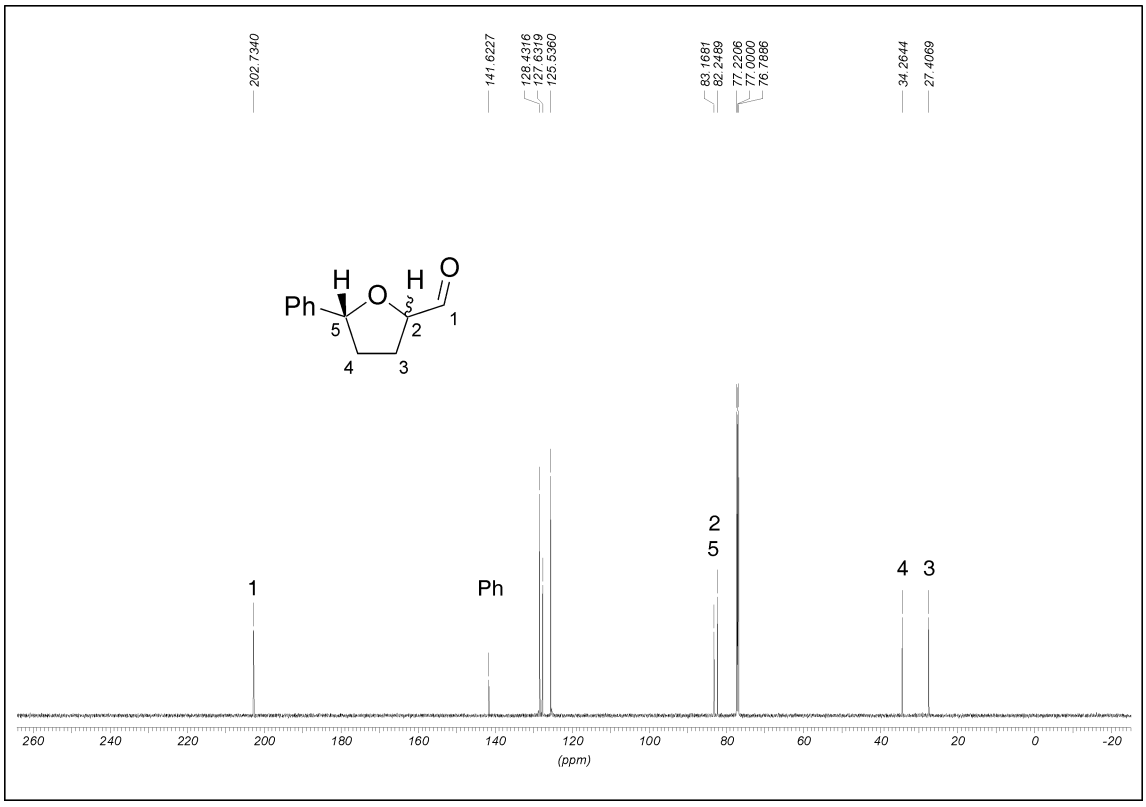

Figure S2. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofurylcarbaldehyde **12b**.

5 Spectral Data of Selected Oxidation Products

1-*trans*-6-*trans*-Oxabicyclo[4.3.0]non-8-ylmethanol (10f).[1] Yield: 318 mg (68 %, *cis*:*trans* < 1:99) from **9f** (421 mg, 3.00 mmol), R_f 0.29 [SiO_2, acetone/petroleum ether = 1:3 (*v*/*v*)], colorless oil, $C_9H_{16}O_2$ (156.22). δ_H (400 MHz; $CDCl_3$) 1.12–1.32 (3 H, m, CH_2), 1.35–1.64 (5 H, m, CH_2, OH), 1.71 (2 H, dd, *J* 7.7, 3.4, CH_2), 1.87 (1 H, m_c, CH), 2.02 (1 H, m_c, CH_2), 3.49 (1 H, dd, *J* 11.5, 6.5, CH_2OH), 3.64 (1 H, dd, *J* 11.5, 3.2, CH_2OH), 3.95 (1 H, dd, *J* 7.2, 3.4, CH), 4.25 (1 H, qd, J_q 7.5, J_d 3.2, CH). δ_C (100 MHz; $CDCl_3$) 20.5 (CH_2), 24.0 (CH_2), 27.6 (CH_2), 28.1 (CH_2), 34.2 (CH_2), 38.3 (CH), 65.8 (CH_2OH), 76.9 (CH), 77.7 (CH). *m*/*z* (EI, 70 eV) 155 (M^+–H, 1 %), 138 (1), 125 (72), 107 (40), 81 (100), 67 (8), 55 (12), 41 (8).

1-*cis*-6-*trans*-Oxabicyclo[4.3.0]non-8-ylmethanol (10g).[1,2] Yield: 284 mg (61 %, *cis*:*trans* = 5:95) from **9g** (421 mg, 3.00 mmol), R_f 0.29 [SiO_2, acetone/petroleum ether = 1:3 (*v*/*v*)], colorless oil, $C_9H_{16}O_2$ (156.22). δ_H (400 MHz; $CDCl_3$) 1.07 (1 H, qd, J_q 11.9, J_d 3.1, CH_2), 1.14–1.34 (5 H, m, CH_2), 1.36–1.49 (1 H, m, CH_2), 1.69 (1 H, dd, *J* 9.6, 2.7, CH_2), 1.79 (1 H, m_c, CH_2), 1.92 (1 H, m_c, CH_2), 1.99 (1 H, m_c, CH), 2.04 (1 H, s, OH), 3.10 (1 H, td, J_t 10.2, J_d 3.3, CH), 3.53 (1 H, dd, *J* 11.9, 3.1, CH_2OH), 3.67 (1 H, m_c, CH_2OH), 4.14 (1 H, m_c, CH). δ_C (100 MHz; $CDCl_3$) 24.3 (CH_2), 25.6 (CH_2), 29.0 (CH_2), 31.3 (CH_2), 33.3 (CH_2), 46.0 (CH), 65.4 (CH_2OH), 78.8 (CH), 82.6 (CH). *m*/*z* (EI, 70 eV) 155 (M^+–H, 1 %), 138 (2), 125 (60), 107 (38), 81 (100), 67 (12), 55 (15), 41 (10).

5-*tert*-Butyl-2-isopropoxy-tetrahydrofuran (13a). **Isomer A**: R_f 0.80 [SiO_2, acetone/pentane = 1:8 (*v*/*v*)], colorless oil. ν_{max} (KBr)/cm^{-1} 3419, 2956, 2926, 2868, 1733, 1465, 1363, 1261, 1075, 1014, 986 and 802. δ_H (600 MHz; $CDCl_3$) 0.88 (9 H, s, 3 × Me), 1.13 (3 H, d, *J* 6.4, $CH(CH_3)_2$-H), 1.19 (3 H, d, *J* 6.5, $CH(CH_3)_2$-H), 1.50–1.55 (1 H, m, 4-H), 1.77–1.81 (1 H, m, 3-H), 1.83–1.87 (1 H, m, 4-H), 1.88–1.94 (1 H, m, 3-H), 3.74 (1 H, dd, *J* 7.4, 5-H), 3.88 (1 H, sept, *J* 6.4, $CH(CH_3)_2$-H), 5.22 (1 H, dd, *J* 5.3, 1.7, 2-H). δ_C (150 MHz; $CDCl_3$) 22.1 ($CH(CH_3)_2$), 23.8 ($CH(CH_3)_2$), 24.3 (C4), 25.7 (3 × Me), 32.7 (C3), 33.2 ($C(CH_3)_3$), 68.6 ($CH(CH_3)_2$), 85.1 (C5), 102.2 (C2). *m*/*z* (EI, 70 eV) 185 (M^+–H, <1 %), 143 (1), 129 (65), 109 (21), 87 (100), 83 (12), 70 (22) and 57 (17). **Isomer B**: R_f 0.74 [SiO_2, acetone/pentane = 1:8 (*v*/*v*)], colorless oil; ν_{max} (KBr)/cm^{-1} 3419, 2956, 2927, 2869, 1735, 1466, 1363, 1262, 1076, 1014 and 803. δ_H (600 MHz; $CDCl_3$) 0.87 (9 H, s, 3 × Me), 1.11–1.14 (3 H, m, $CH(CH_3)_2$), 1.23 (3 H, d, *J* 6.2, $CH(CH_3)_2$-H), 1.60–1.95 (4 H, m, 3-H, 4-H), 3.94 (1 H, dd, *J* 6.1, 5-H), 4.03 (1 H,

sept, *J* 6.2, C*H*(CH_3)$_2$-H), 5.18 (1 H, d, *J* 4.4, 2-H). δ_C (150 MHz; $CDCl_3$) 21.0 (CH(*C*H_3)$_2$), 23.5 (CH(*C*H_3)$_2$), 24.5 (C4), 26.0 (3 × Me), 33.3 (C3), 33.7 (*C*(CH_3)$_3$), 67.3 (*C*H(CH_3)$_2$), 89.4 (C5), 100.5 (C2). *m*/*z* (EI, 70 eV) 143 (M^+–CH(CH_3)$_2$, 1 %), 129 (45), 109 (43), 87 (100), 83 (25), 70 (29) and 57 (38).

2-Phenylhexane-2,5-diol (**18**).[3] Yield: 153 mg (39 %, *dr* = 50:50) from **9e** (357 mg, 2.03 mmol), R_f 0.42 [SiO_2, Et_2O], colorless oil, $C_{12}H_{18}O_2$ (194.27). δ_H (400 MHz; $CDCl_3$) 1.13 (3 H, d, *J* 6.2, 6-H), 1.15 (3 H, d, *J* 6.2, 6-H), 1.28–1.53 (2 × 2 H, m, 4-H), 1.56 (3 H, s, 1-H), 1.57 (3 H, s, 1-H), 1.83–2.06 (2 × 2 H, m, 3-H), 3.78 (2 × 1 H, m_c, 5-H), 7.20–7.27 (2 × 1 H, m, Ph), 7.30–7.38 (2 × 2 H, m, Ph), 7.40–7.46 (2 × 2 H, m, Ph). δ_C (150 MHz; $CDCl_3$) 23.3 and 23.7 (C6), 30.3 and 31.0 (C1), 33.3 and 33.4 (C4), 39.8 and 40.6 (C3), 67.9 and 68.6 (C5), 74.3 (C2), 124.7 and 124.8, 126.3 and 126.4, 128.1, 147.8 and 148.0 (Ph). *m*/*z* (EI, 70 eV) 194 (M^+, 1 %), 179 (2), 161 (9), 121 (100), 117 (10) 105 (39), 91 (9), 77 (17).

5-Methyl-1-phenyl-hexane-1,5-diol (**21**).[4] Yield: 58.0 mg (18 %) from **9j** (295 mg, 1.55 mmol), R_f 0.29 [SiO_2, acetone/pentane = 1:3 (*v*/*v*)], colorless oil, $C_{13}H_{20}O_2$ (208.30). δ_H (400 MHz; $CDCl_3$) 1.19 (2 × 3 H, s, Me), 1.31–1.88 (6 H, m, 2-H, 3-H, 4-H), 4.69 (1 H, dd, *J* 7.8, 5.4, 1-H), 7.24–7.30 (1 H, m, Ph), 7.31–7.38 (4 H, m, Ph). δ_C (100 MHz; $CDCl_3$) 20.6 (C3), 29.1 and 29.3 (Me), 39.5, 43.5 (C2 and C4), 71.1 (C5), 74.4 (C1), 125.8, 127.5, 128.4, 144.9 (Ph). *m*/*z* (EI, 70 eV) 190 (M^+–H_2O, 7 %), 175 (7), 147 (6), 133 (13), 117 (36), 107 (100), 104 (53), 91 (15), 79 (48), 77 (38), 59 (33), 56 (36).

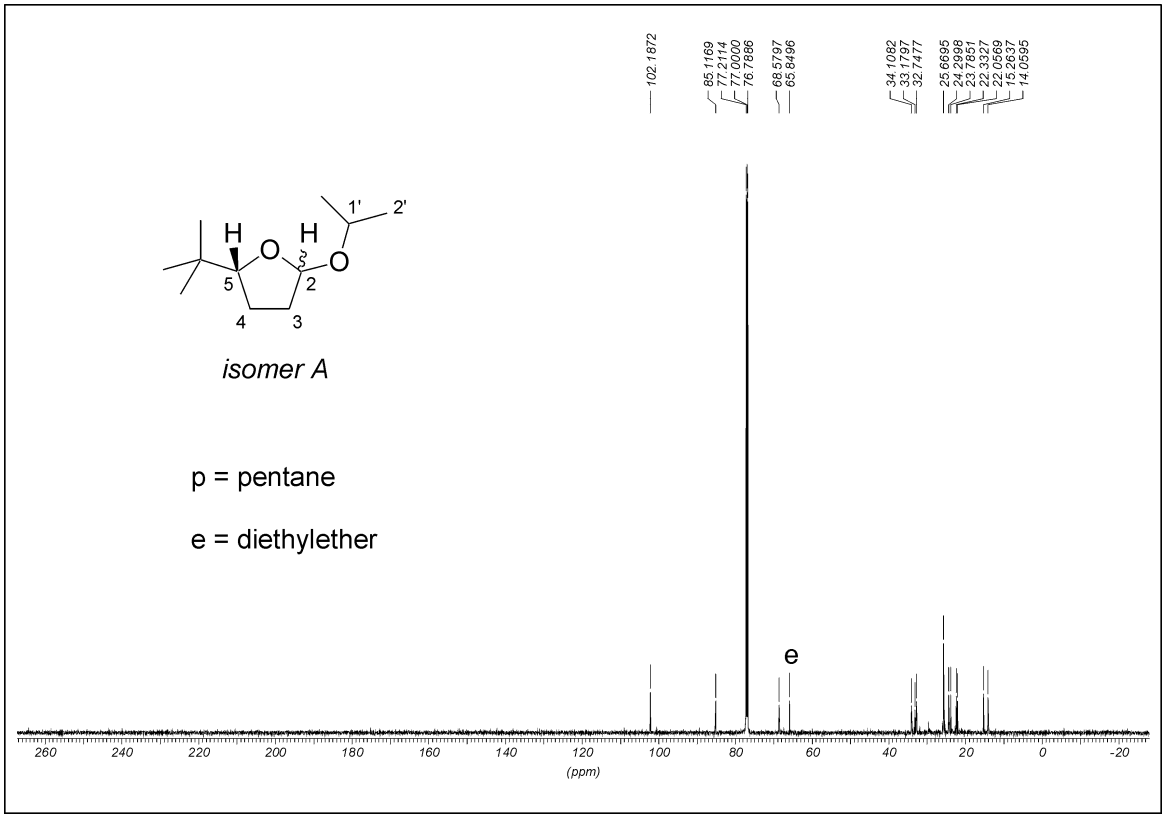

Figure S3. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran **13a** (isomer A).

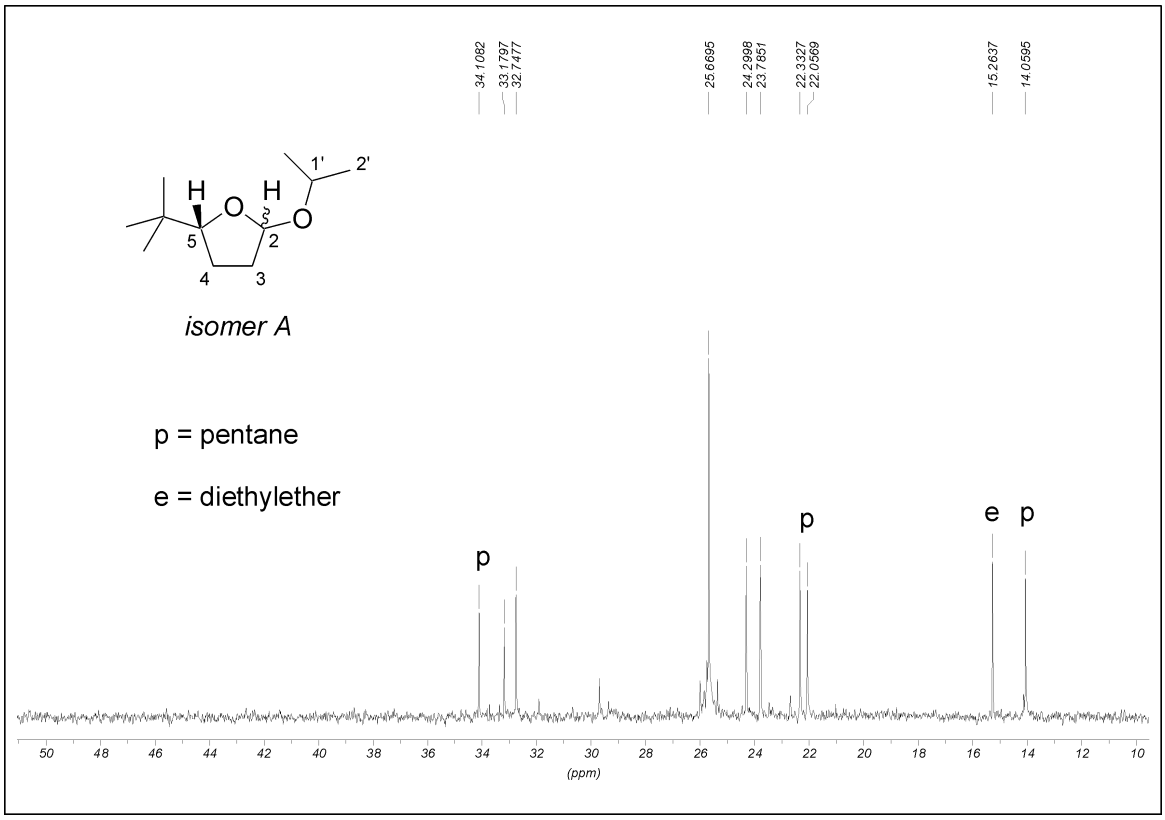

Figure S4. Zoom into the ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran **13a** (isomer A).

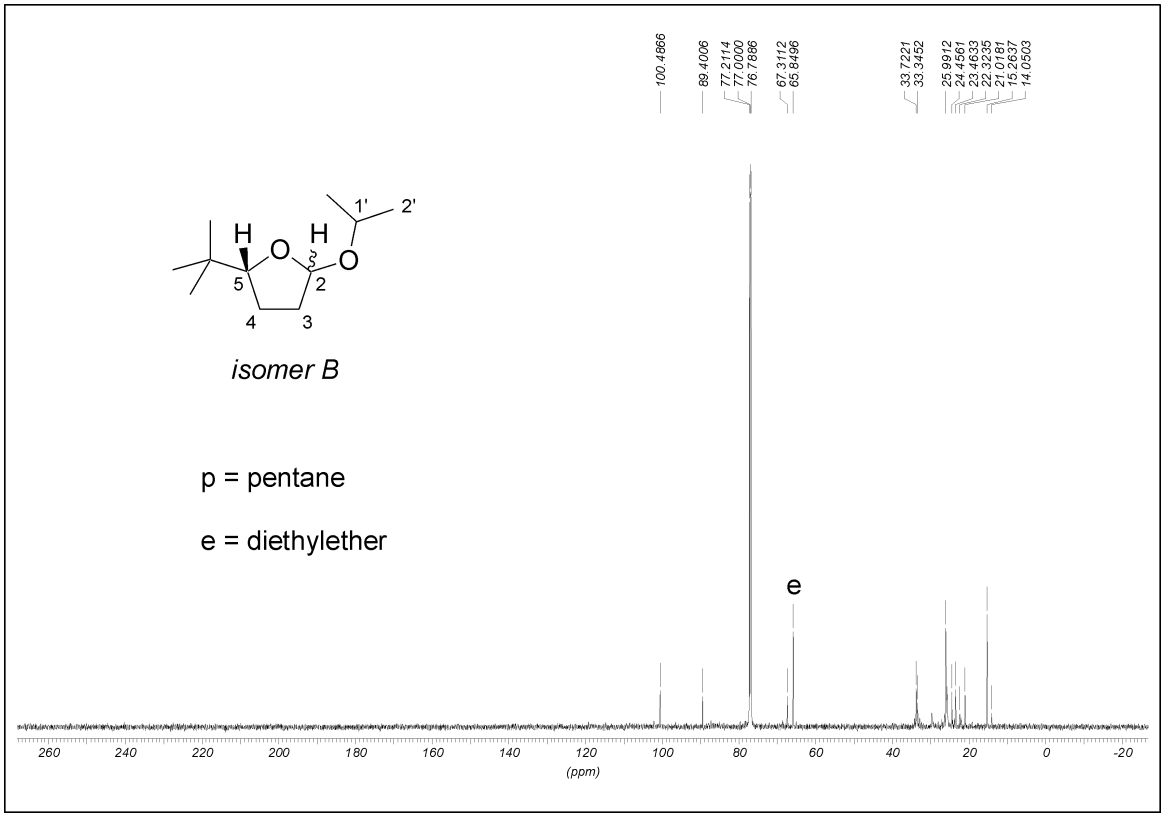

Figure S5. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran **13a** (isomer B).

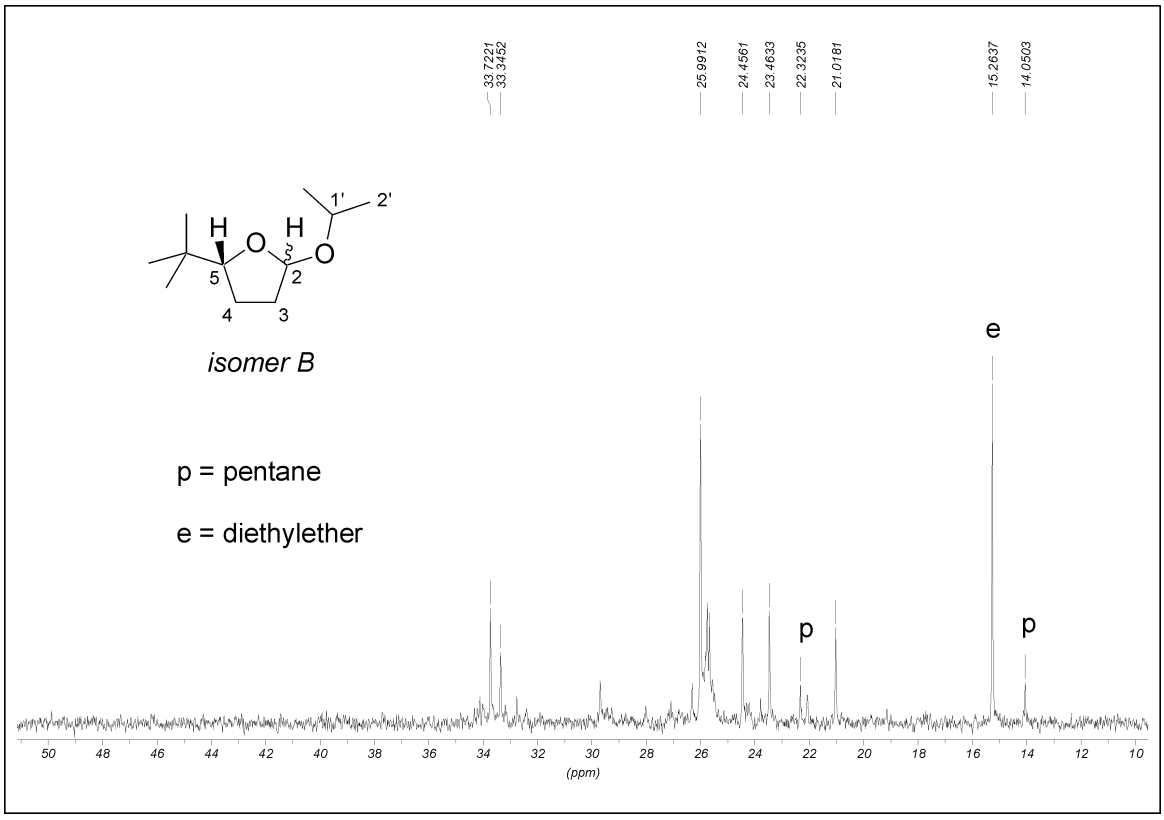

Figure S6. Zomm into the ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran **13a** (isomer B).

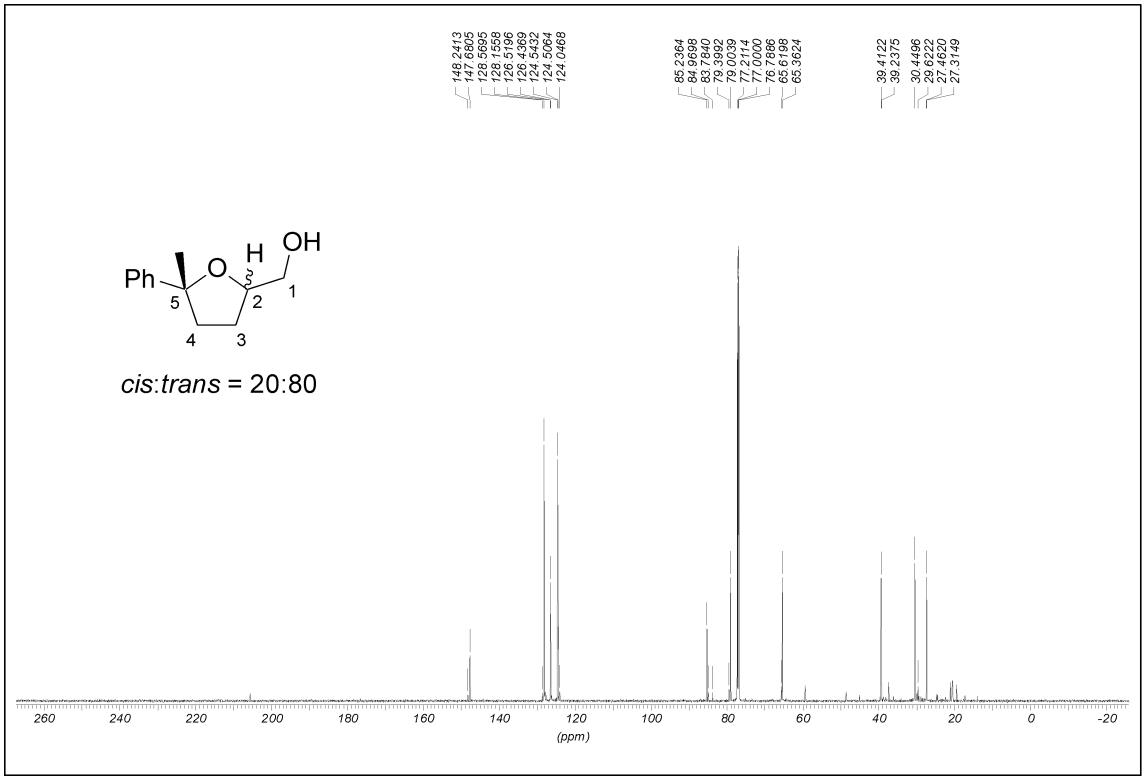

Figure S7. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofurylmethanol **10e**.

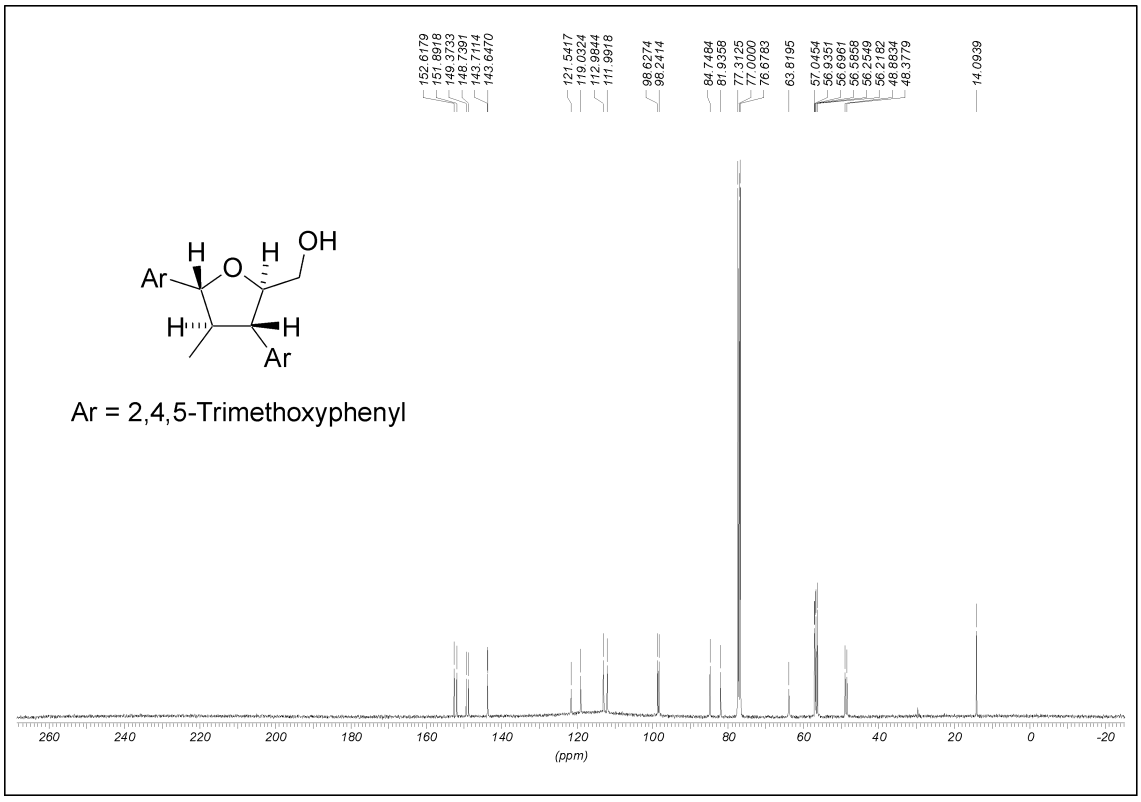

Figure S8. ^{13}C-NMR spectrum (100 MHz) of tetrahydrofurylmethanol **10h**.

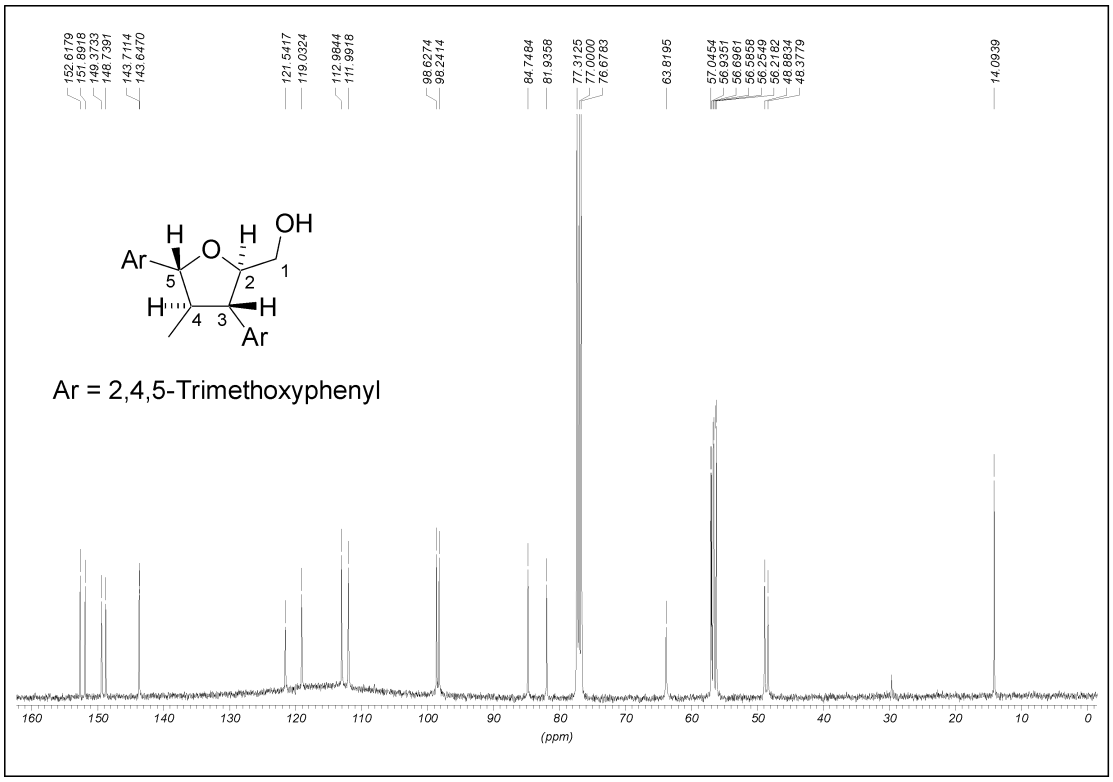

Figure S9. Zoom into the ^{13}C-NMR spectrum (100 MHz) of tetrahydrofuran **10h**.

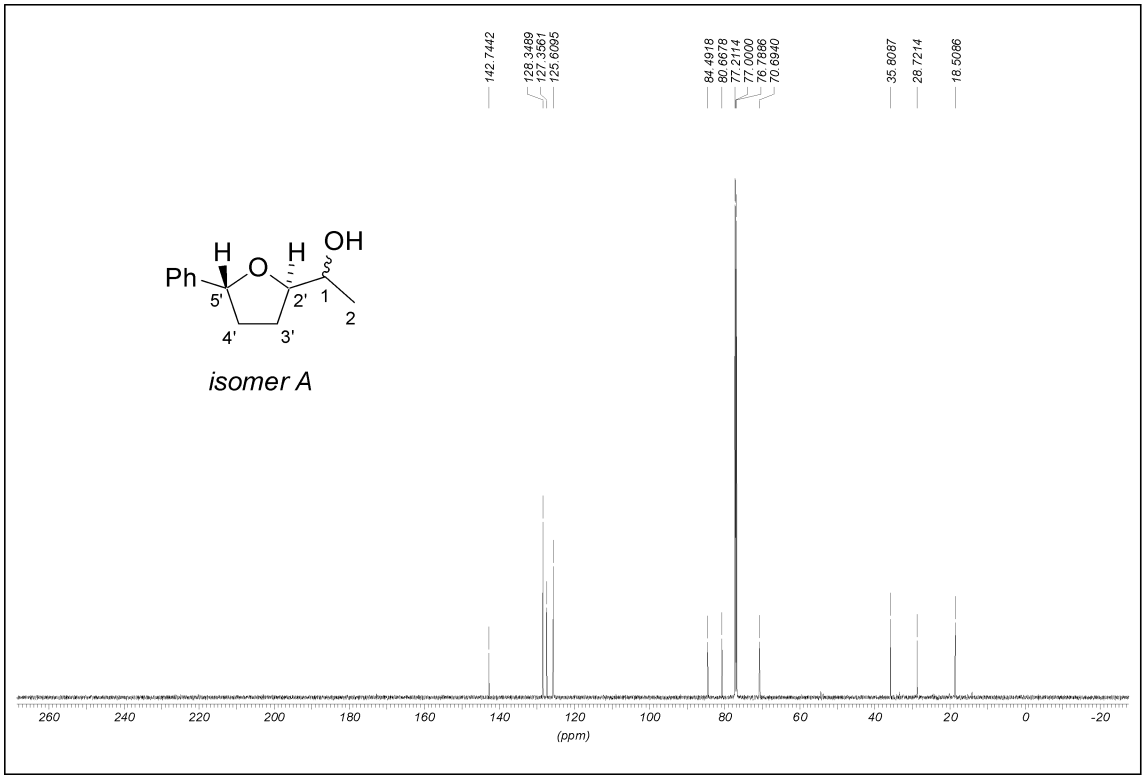

Figure S10. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran *trans*-**10i** (isomer A).

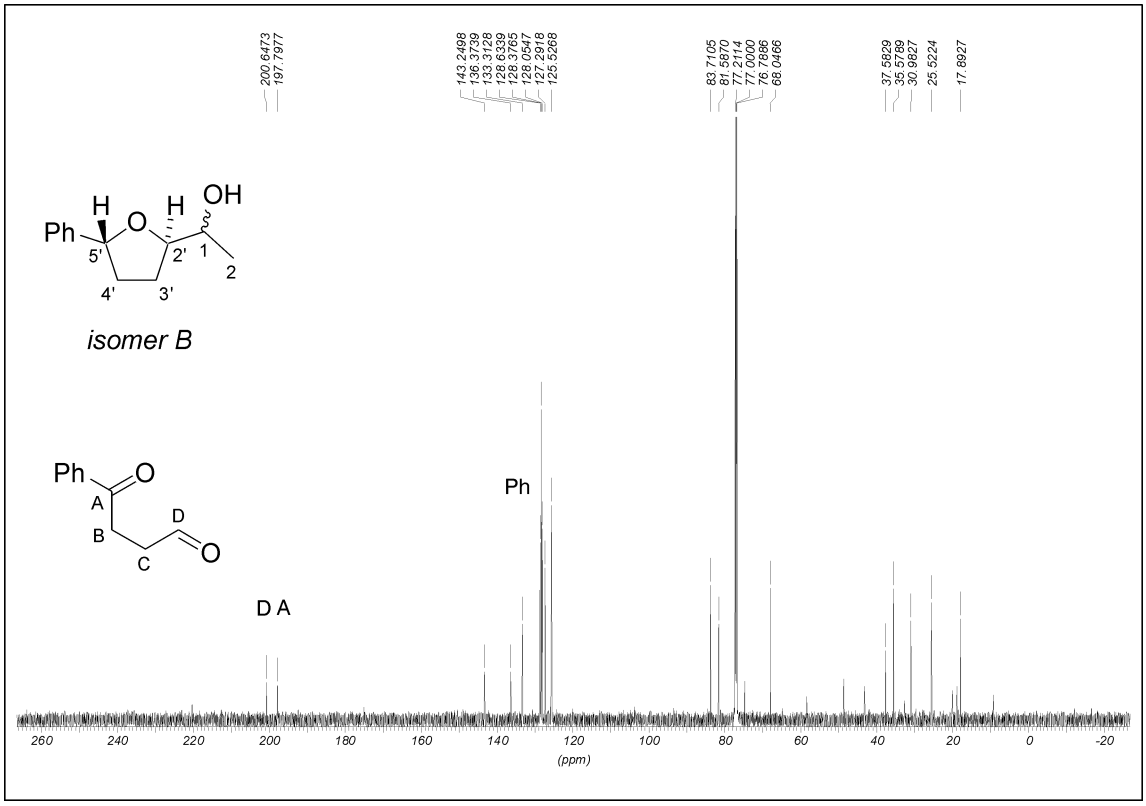

Figure S11. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran *trans*-**10i** (isomer B).

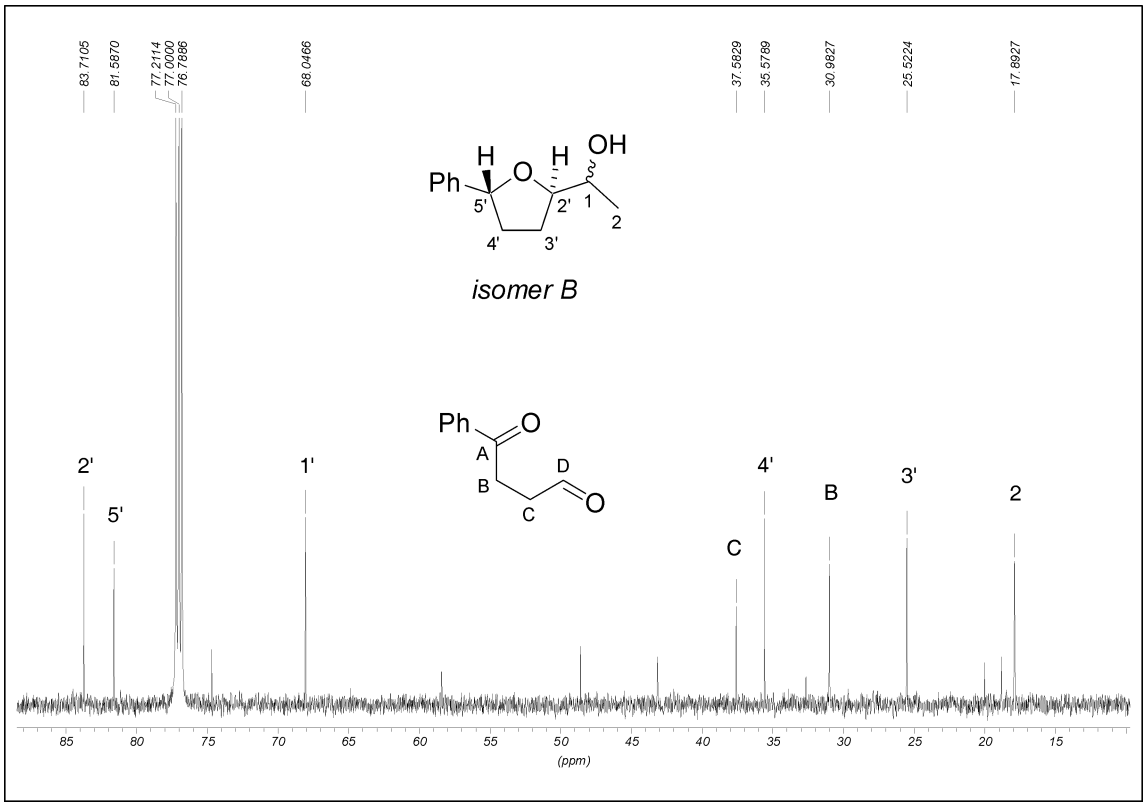

Figure S12. Zoom into the ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran *trans*-**10i** (isomer B).

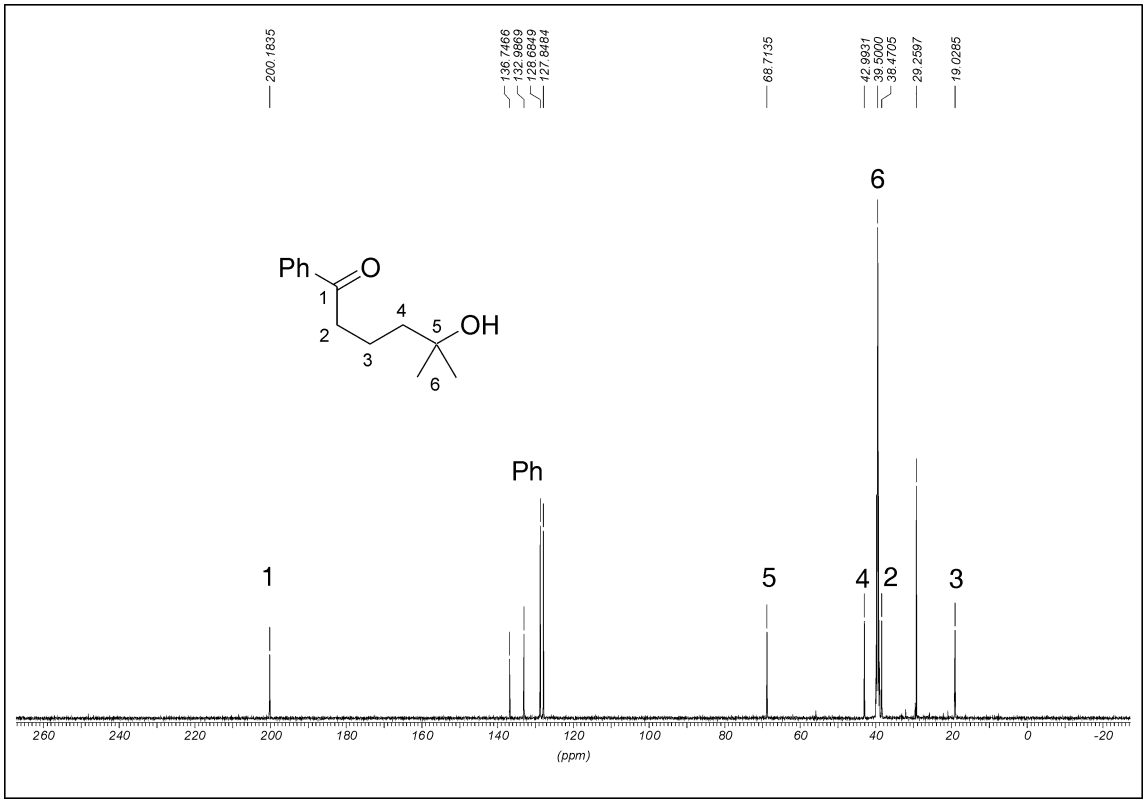

Figure S13. ^{13}C-NMR spectrum (100 MHz) of hydroxyketone **22**.

6 Quantitative Analysis of Reaction Water

6.1 General remarks. Hydranal® reagents for the volumetric Karl Fischer titration were purchased from Riedel-deHaën. Hydranal® Composite 1 Karl Fischer reagent was used as titrating reagent. Methanol-free solution Hydranal® CompoSolver E was used as working medium in the titration cell.

6.2 General procedure. A Schlenk-type flask was charged with a solution of alkenol **9a** (142.2 mg, 1 mmol) or **9b** (162.2 mg, 1 mmol) and complex **6** (55.3 mg, 0.10 mmol) in *i*PrOH (8 mL). The solution was stirred for 2.5–3 hours under 3 or 1.5 bar of O_2 at 60 °C. The solutions were immediately cooled to 20 °C (*solution A*). Identical reactions were performed in the absence of alkenols **9a**–**b** (*solution B*) for correcting H_2O-values associated with the oxidative cyclization to those from background H_2O levels.

The following sequence of titrations was performed to determine reaction water originated from oxidative cyclizations: (i) Titer determination was performed using Apura® H_2O standard (5 mg mL^{-1}, 1 mL) (ii) H_2O content of the solvent (2-propanol, 2 mL) was quantified, (iii) H_2O content of a solution of **9a** or **9b** in 2-propanol (2 mL) was determined (iii) H_2O content of *solution B* (1 mL) was checked, and finally (iv) the H_2O level of *solution A* (1 mL) was determined. All samples were measured twice.

7 Quantitative Acetone Analysis

7.1 General remarks. Acetone was determined using the 2,4-dinitrophenylhydrazine (DNPH) derivatization method. All blanks and samples were prepared according to a modified literature procedure.[5] In a typical run, an aliquot (100 μL) of the solution to analyze was added to a solution of 2,4-dinitrophenylhydrazine (3.28×10^{-3} M) and 5 drops of 1 M perchloric acid in CH_3CN (total volume of 25 mL). The solution was vigorously agitated and then allowed to rest for 30 min at 20 °C. The retrieval rate of acetone under such conditions was 98 % ± 4 %, as determined in an independent study.

7.2 HPLC Analysis. The eluent was formed from (A) CH_3CN p.a. and (B) destilled water using the following program: 30 % (A) to 55 % (A) in 11 min, isocratic at 55 % (A) for 4 min, 55 % (A) to 70 % (A) in 1 min, isocratic at 70 % (A) for 9 min, 70 % (A) to 30 % (A) in 1 min and isocratic at 30 % (A) for 9 min. A flow rate of 1.5 mL min^{-1} was applied. The column (Delta Bond (AK), *Keystone Scientific*, Inc., 4.6 mm × 150 mm length, particle size 5 μm, pore size 300 Å) and the pre-concentration column (Delta Bond (AK), *Keystone Scientific*, Inc., 4.0 mm × 10 mm length) were kept at

22–24 °C. Injection volumes were set to 20 µl. Detection was achieved using an L-4250 (*Merck*) UV/Vis absorption detector operating at 365 nm.

The following solutions were analyzed for the determination of acetone originated from oxidative cyclizations: (i) acetone 2,4-dinitrophenylhydrazone as standard (ii) solvent (2-propanol), (iii) solution of **9a** or **9b** in 2-propanol and (iii) *solution B* (see 6.2) as blanks, and finally (iv) *solution A* (see 6.2).

8 General Procedure for Determining Enantiomeric Purity of Substituted Tetrahydrofur-2-ylmethanol

Triethylamine (~ 1 mmol) was added in an atmosphere of N_2 to a solution of 2-chloro-(4*R*,5*R*)-bis-(ethyloxycarbonyl)-1,3,2-dioxaphospholane (~ 1 mmol) in anhydrous THF (4 mL).[6] The mixture was stirred for 15 min at 20 °C. Neat tetrahydrofurylmethanol **10** (250–500 µmol) was added and stirring of the mixture was continued for 5 min. The solids were removed by filtration and the solution (300 µl) was transferred via syringe into a NMR tube. $CDCl_3$ (100 µl) was added and the sample was analyzed by ^{31}P-NMR spectroscopy (242.9 MHz).

9 Aerobic Oxidation of 1-Phenylpent-4-en-1-ol (9b) in 2-Propanol-d_8

Alkenol **9b** (164.4 mg, 1.01 mmol) and cobalt(II) complex **6** (56.5 mg, 102 µmol, 0.10 equivalents) were dissolved in 2-propanol-d_8 (6 mL) and stirred for 2 h at 75 °C in an atmosphere of O_2/N_2 = 1/1 (*v*/*v*). The reaction mixture was worked up as described in the general procedure in the associated manuscript. **5-Methyl-2-phenyltetrahydrofuran** (**11b**). Yield: 29.7 mg (18 %, deuteration grade 50 %), R_f 0.52 [SiO_2, Et_2O/pentane = 1/6 (*v*/*v*)], colorless oil, $C_{11}H_{14}O$ (162.23) and $C_{11}H_{13}DO$ (163.23). δ_H (600 MHz, $CDCl_3$) 1.30 (1 H, dd, *J* 6.1, 1.9, CH_2D), 1.31 (1 H, dd, *J* 6.1, 1.9, CH_2D), 1.32 (3 H, d, *J* 6.1, Me), 1.62 (2 × 1 H, ddt, J_d 12.1, 10.0, J_t 7.8, 4-H), 1.88 (2 × 1 H, ddt, J_d 12.3, 10.0, J_t 7.9, 4-H), 2.16 (2 × 1 H, m_c, 3-H), 2.39 (2 × 1 H, m_c, 3-H), 4.32–4.39 (2 × 1 H, m, 5-H), 5.04 (2 × 1 H, dd, *J* 8.1, 6.6, 2-H), 7.22–7.26 (2 × 1 H, m, Ph), 7.30–7.36 (2 × 4 H, m, Ph). δ_C (150 MHz, $CDCl_3$) 21.2 (t, CH_2D), 21.5 (Me), 34.2 and 34.3 (C4), 35.6 (C3), 2 × 75.9 (C5), 80.2 (C2), 125.5, 127.0, 128.3, 144.0 (Ph); *m*/*z* (EI, 70 eV) 163 (46) and 162 (M^+, 69 %), 147 (8), 129 (7), 117 (59), 105 (100), 91 (41), 77 (48), 56 (37).

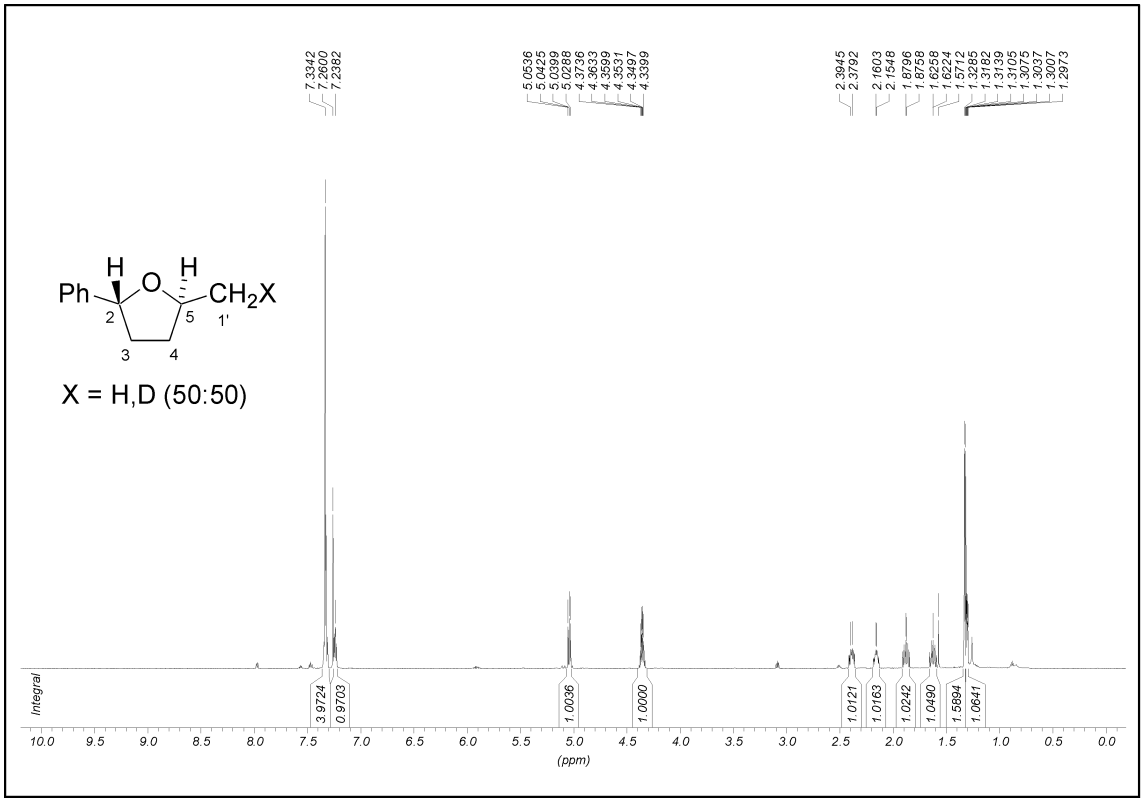

Figure S14. ^{1}H-NMR spectrum (600 MHz) of tetrahydrofuran **11b** obtained from aerobic oxidation of alkenol **9b** in 2-propanol-d_8.

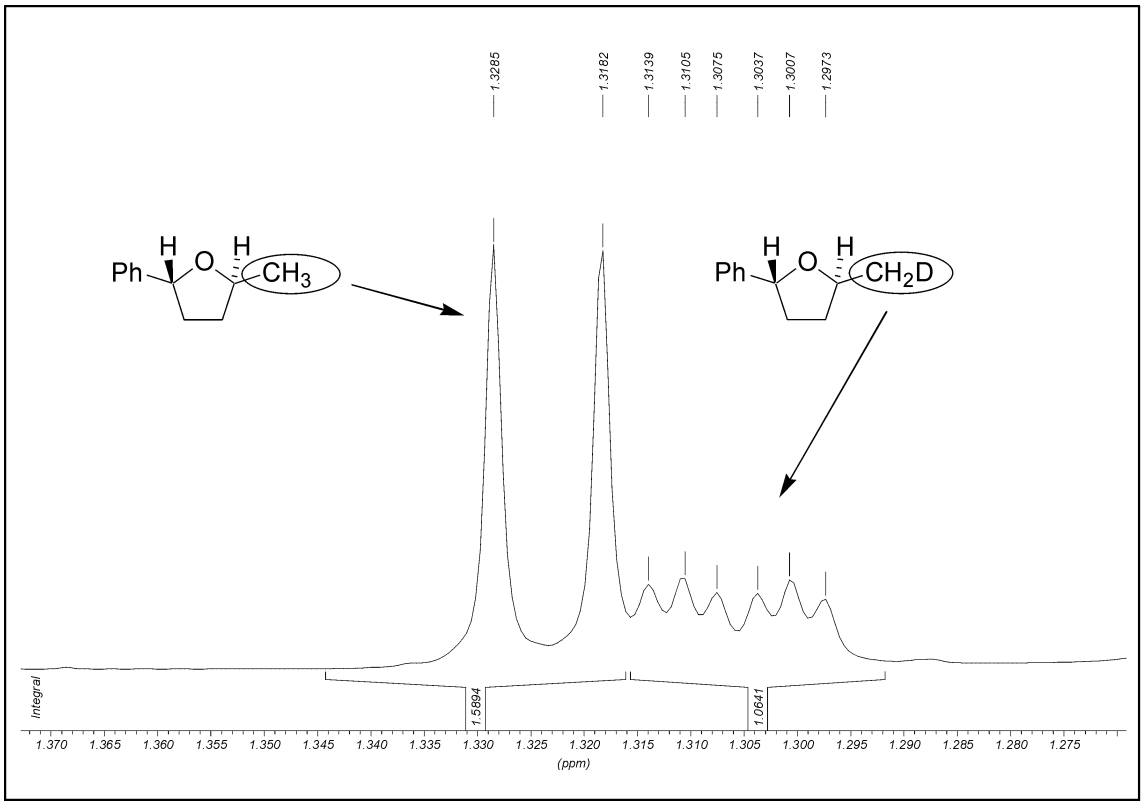

Figure S15. ^{1}H-NMR spectrum (600 MHz) of tetrahydrofuran **11b** obtained from aerobic oxidation of alkenol **9b** in 2-propanol-d_8 showing part of the aliphatic region.

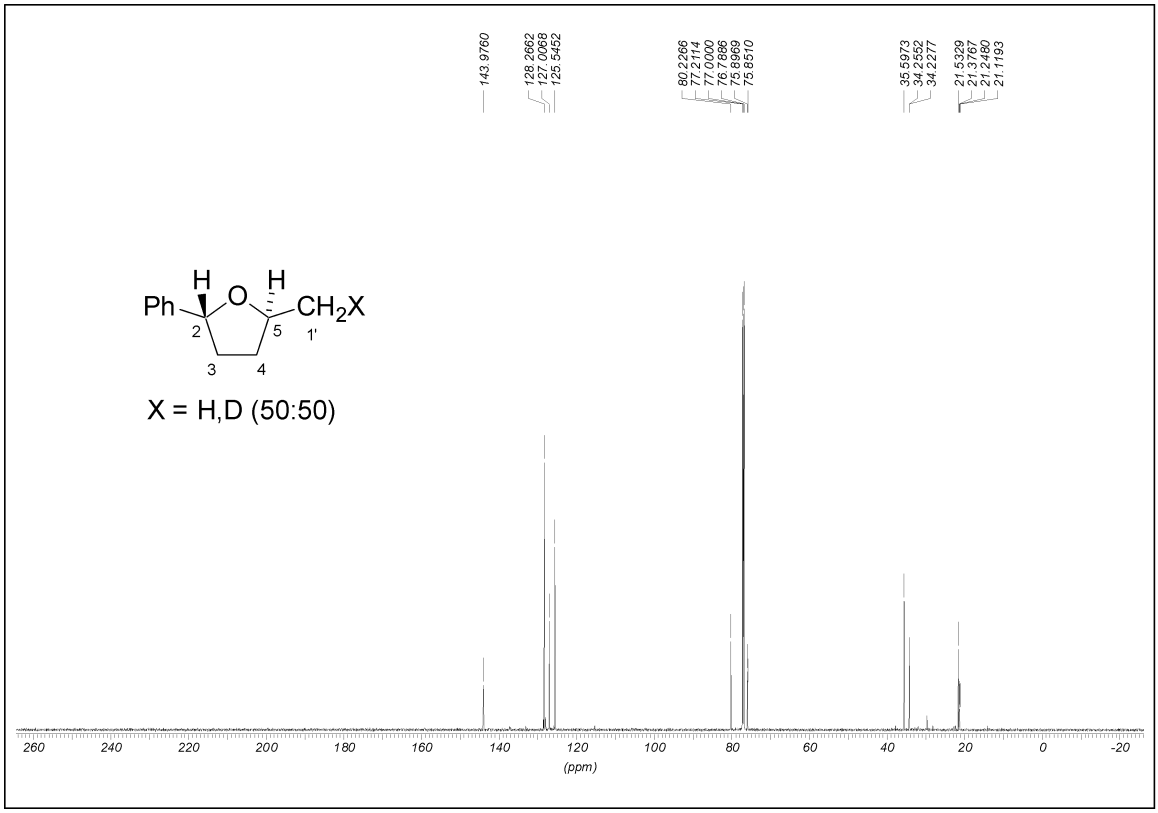

Figure S16. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran **11b** obtained from aerobic oxidation of alkenol **9b** in 2-propanol-d_8.

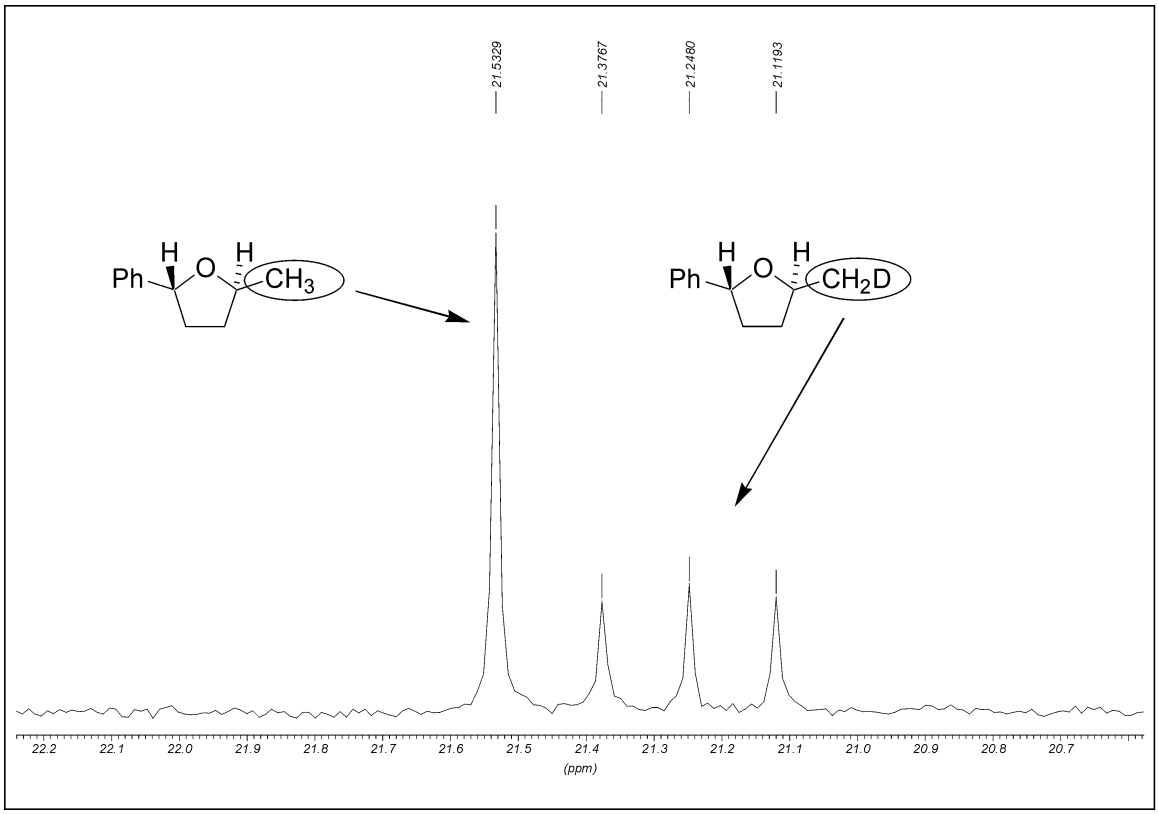

Figure S17. ^{13}C-NMR spectrum (150 MHz) of tetrahydrofuran **11b** obtained from aerobic oxidation of alkenol **9b** in 2-propanol-d_8 showing part of the aliphatic region.

10 Products of Cobalt Complex Desintegration in the Absence of Alkenols

2-Propanol (10 mL) was purged with a stream of N_2. Complex **6** (552.0 mg, 1 mmol) was dissolved into the deaerated solvent. The solution was allowed to stir at 22 °C in an O_2-atmosphere provided by a burette. After 138 h 3.21 mmol O_2 were taken up. The solution was analyzed as described in chapters 6 and 7 to give 3.21 mmol acetone and 3.20 mmol H_2O. The remaining solution was worked up according to the general procedure for cobalt-catalyzed oxidations described in the associated manuscript. The residual oil was purified by column chromatography [SiO_2, acetone/pentane = 1:8 (*v*/*v*)] to give 4-isopropoxy-1,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octan-2-one (84.5 mg, 0.37 mmol) and 3-oxa-1,8,8-trimethylbicyclo[3.2.1]octane-2,4-dione[7] (15.0 mg, 0.08 mmol). A control experiment indicated no volumetric change in the O_2 burette upon stirring of similarly deaerated 2-propanol over a period of 72 h at 22 °C.

4-Isopropoxy-1,8,8-trimethyl-3-oxa-bycyclo[3.2.1]octan-2-one. Yield: 84.5 mg (0.37 mmol, *dr* = 50:50) from **6** (552.0 mg, 1.00 mmol), R_f 0.53 [SiO_2, acetone/pentane = 1:8 (*v*/*v*)], colorless solid, $C_{13}H_{22}O_3$ (226.31). δ_H (600 MHz; $CDCl_3$) 0.91 (3 H, s, Me), 0.95 (3 H, s, Me), 1.07 (3 H, s, Me), 1.12–1.17 (2 × 3 H, m, OCH-Me), 1.14 (3 H, s, Me), 1.15 (3 H, s, Me), 1.16 (3 H, s, Me), 1.21 (3 H, d, *J* 6.2, OCH-Me), 1.24 (3 H, d, *J* 6.2, OCH-Me), 1.52–2.29 (2 × 5 H, m, 5-H, 6-H, 7-H), 4.03 (1 H, sept, *J* 6.2, OCH), 4.10 (1 H, sept, *J* 6.2, OCH), 5.15 (1 H, s, 4-H), 5.41 (1 H, d, *J* 2.9, 4-H), δ_C (150 MHz; $CDCl_3$) 14.1 (Me), 18.8 (CH_2), 19.6, 21.2, 21.3, 21.6, 22.6, 23.3, 23.5 (7 × Me), 25.2 (CH_2), 25.7 (2 × Me), 34.4, 34.9 (2 × CH_2), 42.3 and 42.9 (C8), 48.7 and 49.7 (C5), 52.5 and 53.3 (C1), 70.7 and 70.9 (OCH), 100.9 and 105.8 (C4), 176.4 and 176.7 (C2). *m*/*z* (EI, 70 eV) 225 (M^+–H, 1 %), 138 (8), 122 (20), 109 (6), 99 (41), 95 (24), 69 (21), 57 (100).

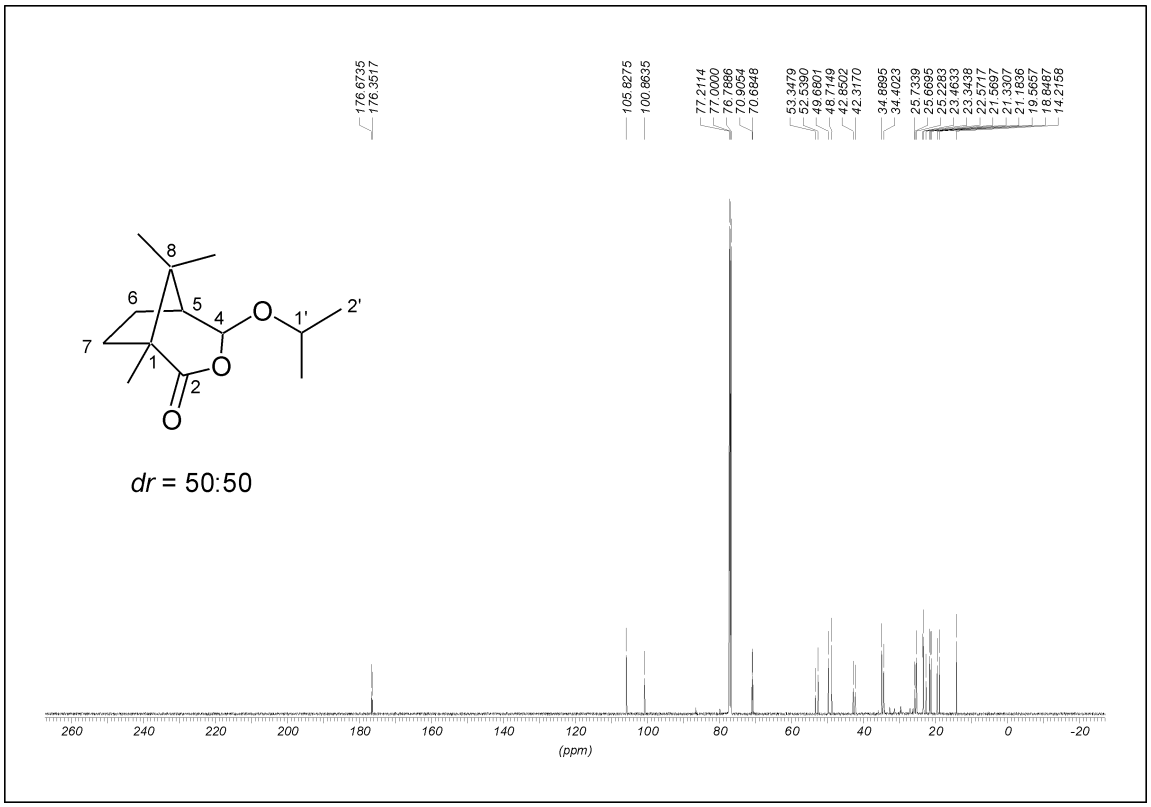

Figure S18. ^{13}C-NMR spectrum (150 MHz) 4-Isopropoxy-1,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octan-2-one.

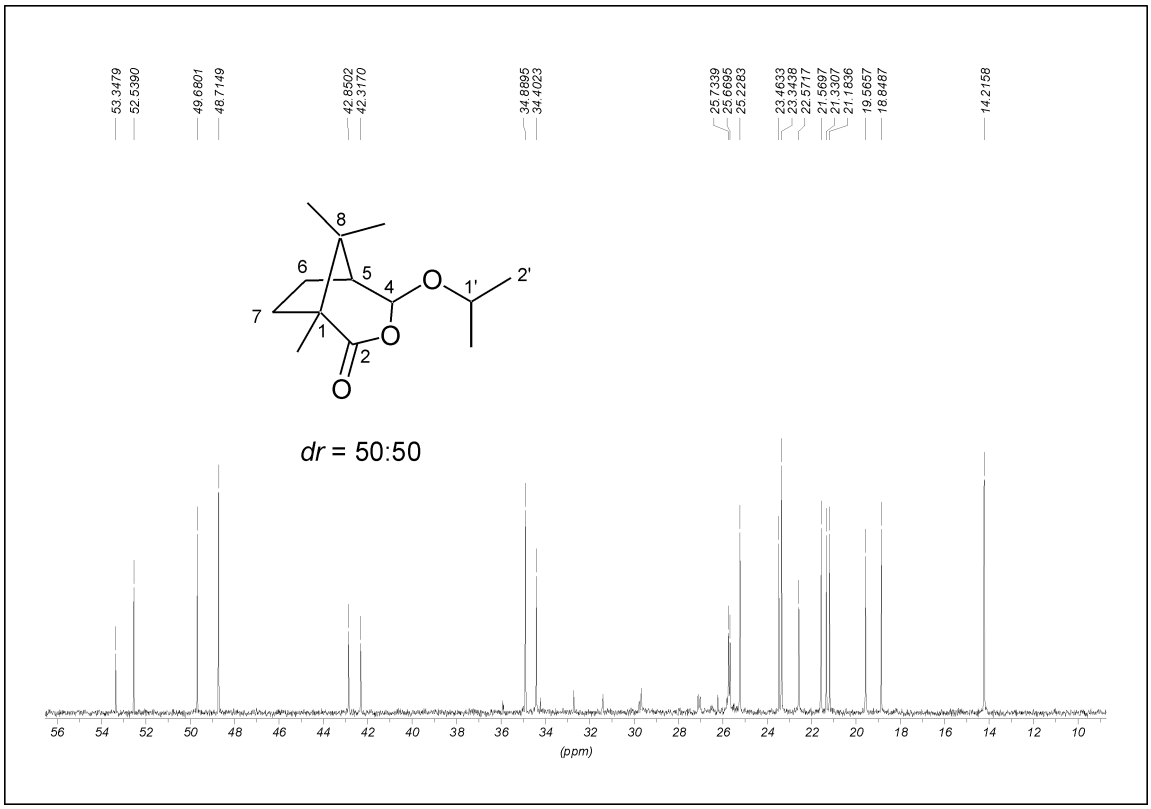

Figure S19. Zoom into the ^{13}C-NMR spectrum (150 MHz) 4-Isopropoxy-1,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octan-2-one.

11 References

1 S. Tang, R. M. Kennedy, *Tetrahedron Lett.*, 1992, **33**, 5299–5302.

2 M.-C. Benhamou, G. Etemad-Moghadam, V. Spéziale, A. Lattes, *J. Heterocycl. Chem.*, 1978, **15**, 1313–1318.

3 J. L. Princival, S. M. G. de Barros, J. V. Comasseto, A. A. Dos Santos, *Tetrahedron Lett.*, 2005, **46**, 4423–4425.

4 F. Foubelo, S. A. Saleh, M Yus, *J. Org. Chem.*, 2000, **65**, 3478–3483.

5 F. Lipari, S. J. Swarin, *J. Chrom.* 1982, **247**, 297–306.

6 J.-M. Brunel, O. Pardigon, M. Maffei, G. Buono, *Tetrahedron: Asymmetry*, 1992, **3**, 1243–1246.

7 M. G. Moloney, D. R. Paul, R. M. Thompsom, E. Wright *Tetrahedron: Asymmetry*, 1996, **7**, 2551–2562.