TPAP-Catalyzed Direct Oxidation of Primary Alcohols to Carboxylic Acids through Stabilized Aldehyde-Hydrates

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Supporting Information

Materials and Methods

All reagents were used as purchased from commercial suppliers. Solvents were purified by conventional methods prior to use. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F254 TLC aluminium sheets and visualised with vanillin [vanillin (1 g), concd. H_2SO_4 (10 ml), AcOH (20 ml) ethanol (170 ml)], ceric ammonium molybdate [phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot 2H_2O$ (10 g), concd. H_2SO_4 (60 ml), H_2O (940 ml)] or bromocresol green [bromocresol green (40 mg), ethanol (100 ml), addition of 0.1 M NaOH until the solution turns blue) or by gas chromatography.

Chromatographic purification was performed as flash chromatography on Fluka silica gel 60 (particle size 0.040–0.063 mm).

Yields refer to chromatographically purified and spectroscopically pure compounds.

NMR spectra were recorded on a Bruker AC 500 (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C acquisitions), a Varian Mercury plus 400 (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C acquisitions), and a Varian Mercury plus 300 (operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C acquisitions). Chemical shifts δ are reported in ppm with the solvent resonance as the internal standard: chloroform-d_1: 7.26 (^{1}H-NMR), 77.16 (^{13}C-NMR); methanol-d_4: 3.31 (^{1}H-NMR), 49.00 (^{13}C-NMR). Coupling constants *J* are given in Hertz (Hz). Multiplicities are classified as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, and combinations thereof, or m = multiplet or bs = broad signal.

High resolution mass spectra were obtained on a Bruker Daltonics ESI-FT-ICR-MS APEX II, a Varian Ionspec QFT-7 with a Waters Micromass Z-Spray ESI-source or an Agilent 6210 ESI-

TOF. EI mass spectra were obtained on an Agilent 6890N Network GC System with a 5975B VL MSD mass detector (temperature of the MS source: 230°C).

IR spectra were obtained on an ATI/MATTSON Genesis FTIR as KBr disk. Absorbance frequencies $\tilde{\nu}$ are reported in reciprocal centimeters (cm^{-1}).

Analytical gas chromatography was performed on a Varian CP-3800 with a flame ionization detector (FID) and a Varian autosampler (CP-8400) using a capillary column (WCOT Fused Silica 15 m x 0.25 mm, 0.25 µm CP-SIL 5CB) and nitrogen as carrier gas. Chiral gas chromatography was performed on the same instrument equipped with a chiral column (CP-Chirasil-Dex CB; 25 m x 0.25 mm, 0.25 µm).

Melting points were measured on a Boetius-micro hot stage and are uncorrected.

Optical rotation data was obtained with a Schmidt+Haensch Polartronic MHZ-8 at 589 nm using a 50 mm or 100 mm path-length cell in the solvent and concentration indicated.

All compounds were named according to IUPAC rules. For simplicity, the numbering of the carbon atoms of a given structure does not follow IUPAC rules.

Preparation of tetra-*n*-propylammonium perruthenate (TPAP)[1]

Sodium carbonate (19.08 g, 180 mmol, 30 equiv.) and sodium bromate (36.21 g, 240 mmol, 40 equiv.) are dissolved in 240 ml of water. $RuCl_3 \cdot nH_2O$ (1.62 g, 6.0 mmol, 1.0 equiv.) in 30 ml of water is added. The mixture is stirred at room temperature for two hours. Then, tetra-*n*-propylammonium hydroxide solution (25% in H_2O, 4.88 g, 6.0 mmol, 1.0 equiv.) is added. A dark green precipitate forms which is extracted into dichloromethane (4 x 300 ml). The combined organic phases are dried over anhydrous $MgSO_4$ and filtered. Most of the solvent is evaporated. To the remaining solution (ca. 50-100 ml) tetrachloromethane is added until a dark green precipitate forms. The precipitate is filtered off and dried *in vacuo*. 1.80 g (5.12 mmol, 85%) of TPAP are obtained as dark green crystals.

HRMS (pos. ESI-FTICR): for $C_{12}H_{28}N^+$, calculated: m/z = 186.2216, found: m/z = 168.2210;
(neg. ESI-FTICR): for RuO_4^-, calculated: m/z = 165.8846, found: m/z = 165.8846 ; UV-VIS: λ_{max} (CH_2Cl_2) = 317, 385 nm.

[1] (a) Bailey, A. L.; Griffith, W. L.; Mostafa, S. I.; Sherwood, P. A. *Inorg. Chem.* **1993**, *32*, 268–271. (b) Farmer, V.; Welton, T. *Green Chem.* **1993**, *4*, 97–102.

General procedure for the TPAP-oxidation of primary alcohols to carboxylic acids

Representative Procedure: 0.50 mmol (1.0 equiv.) of the alcohol and *N*-methyl morpholine *N*-oxide (NMO) monohydrate (676 mg, 5.0 mmol, 10.0 equiv.) are dissolved in 2 ml of acetonitrile.[2] TPAP (10 mol%, 18 mg) is added and the mixture is stirred at room temperature. On completion the reaction is quenched with an excess of 2-propanol.

Work-up A: The solvent is evaporated and the residue is filtered over a pad of silica using ethyl acetate containing 1% of acetic acid. The filtrate is concentrated *in vacuo* and the crude product is subjected to column chromatography with the appropriate solvent (containing 1% of acetic acid). Alternatively, the residue obtained after concentrating the reaction mixture can also directly be subjected to column chromatography.

Work-up B (very polar compounds): Water is added (~ 1 ml) and the pH adjusted to 2–3 by addition of saturated $NaHSO_4$-solution (sensitive substrates may require a higher pH). The aqueous phase is extracted with diethyl ether (3x). The organic phase is dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue is subjected to purification in the appropriate way to afford the carboxylic acid.

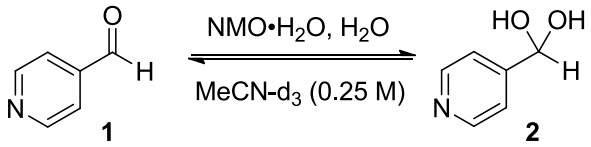
Work up C (benzoic acid derivatives): 2 ml of water are added and the pH of the solution is adjusted to 8–9 using 6 N KOH-solution. The mixture is washed twice with 10 ml of diethyl ether. The aqueous phase is then acidified with saturated $NaHSO_4$-solution and then extracted three times with 10 ml of diethyl ether. The combined organic phases of the acidic extraction are dried over $MgSO_4$, filtered, and evaporated *in vacuo* yielding the benzoic acid derivative in analytically pure form.

NMR-Experiments (sample preparation):
26 µl (1.0 equiv., 0.25 mmol) of 4-pyridinecarboxaldehyde are dissolved in 1.0 ml of deuterated solvent. NMO monohydrate (338 mg, 2.5 mmol, 10.0 equiv.) or distilled water (45 µl, 2.5 mmol) are added. The mixture is shaken vigorously. 0.7 ml of the solution (or the supernatant solution in case of incomplete dissolution of NMO) are filled into an NMR tube.

[2] Identical results are obtained when the reaction is carried out under a N_2-atmosphere using dry acetonitrile.

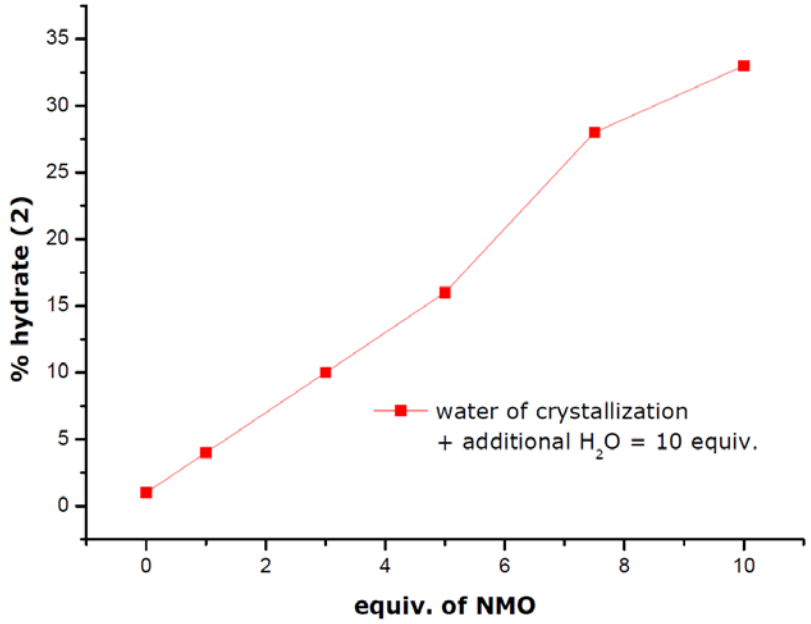
Additional NMR-Experiments

Additional NMR-Experiments were conducted in which varying amounts of NMO·H_2O were added to a 0.25 M solution of **1** in MeCN-d_3 while the amount of water was kept constant (10 equiv.). The fraction of **2** was found to grow with increasing amounts of NMO·H_2O. Figure S-1 reveals this relationship to be roughly linear.



Entry	NMO·H_2O [equiv.]	H_2O [equiv.]	Aldehyde (1)/Hydrate (2)[a]
1	10	-	67:33
2	7.5	2.5	72:28
3	5	5	84:16
4	3	7	90:10
5	1	9	96:4
6	0	10	99:1

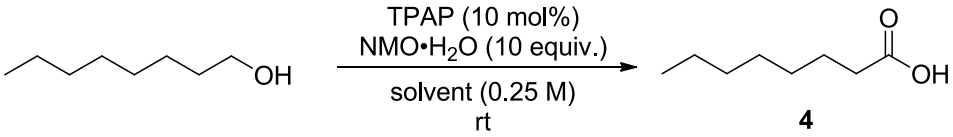
Table S-1: Hydrate stabilization depending on the amount of NMO·H_2O present. a) Determined by ^{1}H-NMR using the signals at 10.05 ppm (formyl proton of 1) and 5.91 ppm (α-proton of 2).



Fiqure S-1: Hydrate stabilization depending on the amount of NMO·H_2O present.

Complete Solvent Screening

The role of the solvent in the direct oxidation process was investigated (Table S-2). Best results were obtained when the reaction was performed in MeCN or acetone with 10 equivalents of NMO·H_2O. Similarly high yields were obtained when DCM or DMF were used. The yields were low when the reaction was conducted in solvents in which NMO·H_2O or more importantly TPAP are poorly soluble.

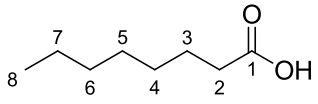


4

entry	solvent	conversion of sm	yield acid [%][a]
1	DCM	complete	91
2	MeCN	complete	94
3	DMF	complete	89
4	acetone	complete	94
5	*n*-hexane	incomplete	28
6	THF	incomplete	85
7	Et_2O	incomplete	12
8	EtOAc	incomplete	56
9	toluene	incomplete	38

Table S-2: a) Isolated yield after 24 h. sm = starting material.

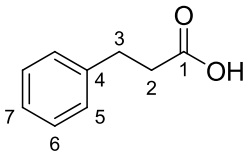
Octanoic Acid (4)[3]



Reaction time: 1 h; work-up A; column chromatography: ethyl acetate/*n*-hexane 1:4 (1% AcOH); yield: 94%; colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 11.37 (bs, 1H, OH), 2.35 (t, 2H *J* = 7.5 Hz, H-2), 1.63 (m, 2H, H-3), 1.31 (m, 8H, H-7, H-6, H-5, H-4), 0.88 (m, 3H, H-8) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 180.4 (C-1), 34.2 (C-2), 31.8, 29.2, 29.1, 24.8, 22.7 (C-7, C-6, C-5, C-4, C-3), 14.2 (C-8) ppm; MS (EI): m/z = 144 (0.4%, $[M]^+$), 127 (0.6%, $[M - OH]^+$), 115 (6%, $[M - C_2H_5]^+$), 101 (18%, $[M - C_3H_7]^+$); FTIR (film): $\tilde{\nu}$ = 2928, 2857, 1711, 1384, 1284, 1233, 1108, 939, 825, 725 cm^{-1}.

3-Phenylpropionic Acid (5)[4]

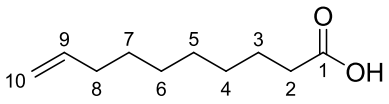


Reaction time: 1 h; work-up A; column chromatography: ethyl acetate (1% AcOH); yield: 92%; colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ =10.36 (bs, 1H, OH), 7.28 (m, 5H, Ph), 2.99 (t, 2H, *J* = 7.8 Hz, H-3), 2.71 (t, 2H, *J* = 7.8 Hz, H-2) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 179.4 (C-1), 140.3 (C-4), 128.7 (C-6), 128.4 (C-5), 126.5 (C-7), 35.8 (C-2), 30.7 (C-3) ppm; MS (neg. ESI-TOF): m/z = 149 (100%, $[M - H]^-$), 105 (7%, $[M - CHO_2]^-$); FTIR (KBr): $\tilde{\nu}$ = 3029, 1707, 1603, 1584, 1496, 1454, 1288, 1218, 1001, 931, 700, 531 cm^{-1}; HRMS (neg. ESI-TOF): for $C_9H_9O_2^-$ ($[M - H]^-$), calculated: m/z = 149.0608; found: m/z =149.0608; mp: 44–46 °C (Lit.[4] 46 °C).

[3] Rawlings, B. J.; Reese, P. B.; Ramer S. E.; Vedras, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3382–3390.
[4] Luca, L. D.; Giacomelli, G.; Masala S.; Porcheddu, A. *J. Org. Chem*. **2003**, *68*, 4999–5001.

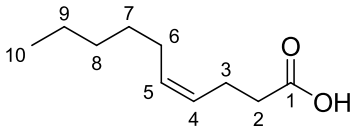
9-Decenoic Acid (6)[5]



Reaction time: 1 h; work-up A; column chromatography: ethyl acetate/*n*-hexane 1:8 (1% AcOH); yield: 89%; colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 11.32 (bs, 1H, OH), 5.81 (ddt, 1H, *J* = 16.9, 10.2, 6.7 Hz, H-9), 5.0 (m, 1H, H-10a), 4.94 (m, 1H, H-10b), 2.34 (t, 2H, *J* = 7.6 Hz, H-2), 2.03 (m, 2H, H-8), 1.63 (m, 2H, H-3), 1.33 (m, 8H, H-7, H-6, H-5, H-4) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 180.7 (C-1), 139.2 (C-9), 114.3 (C-10), 34.2 (C-2), 33.9 (C-8), 29.2, 29.1, 29.0, 28.9 (C-7, C-6, C-5, C-4), 24.7 (C-3) ppm; MS (neg. ESI-TOF): m/z = 339 (72%, $[2M - H]^-$),169 (100%, $[M - H]^-$); FTIR (film): $\tilde{\nu}$ = 2928, 2856, 1710, 1641, 1414, 1385, 1285, 1115, 994, 910, 725, 636 cm^{-1}; HRMS (ESI-TOF): for $C_{10}H_{17}O_2^-$ ($[M - H]^-$), calculated: m/z = 169.1234, found: m/z = 169.1238.

(*Z*)-Dec-4-enoic Acid (7)[6]

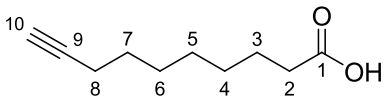


Reaction time: 3 h; work-up A; column chromatography: ethyl acetate/*n*-hexane 1:8 (1% AcOH); yield: 86%; colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 10.94 (bs, 1H, OH), 5.44 (m, 1H, H-4), 5.33 (m, 1H, H-5), 2.37 (m, 4H, H-6, H-3), 2.04 (m, 2H, H-2), 1.30 (m, 6H, H-9, H-8, H-7), 0.89 (t, 3H *J* = 6.8 Hz, H-10) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 180.0 (C-1), 132.1, 127.0 (C-5, C-4), 34.4 (C-2), 31.6, 29.4, 27.3, 22.7, 22.7 (C-9, C-8, C-7, C-6, C-3), 14.2 (C-10) ppm; MS (EI): m/z = 170 (7%, $[M]^+$), 134 (9%), 123 (41%), 110 (92%), 96 (56%), 84 (64%), 81 (95%), 67 (100%), 55 (100%); FTIR (film): $\tilde{\nu}$ = 3010, 2958, 2927, 2858, 1712, 1383, 1283, 1211, 1120, 938, 825, 727 cm^{-1}.

[5] Bartra M.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 5132–5138.
[6] Burke, C. P.; Shi, Y. *Org. Lett.* **2009**, *11*, 5150–5153.

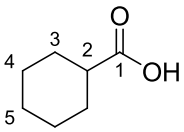
Dec-9-ynoic Acid (8)[7]



Reaction time: 50 min; work-up A; column chromatography: ethyl acetate/*n*-hexane 1:8 (1% AcOH); yield: 87%; colorless oil.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 10.96 (bs, 1H, OH), 2.30 (t, 2H, *J* = 7.5 Hz, H-2), 2.13 (dt, 2H, *J* = 7.1, 2.7 Hz, H-8), 1.90 (t, 1H, *J* = 2.7 Hz, H-10), 1.58 (m, 2H, H-3), 1.47 (m, 2H, H-7), 1.35 (m, 2H, H-6), 1.29 (m, 4H, H-5, H-4) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 180.0 (C-1), 84.6 (C-9), 68.3 (C-10), 34.1 (C-2), 28.9, 28.7, 28.5, 28.4 (C-7, C-6, C-5, C-4), 24.6 (C-3), 18.4 (C-8) ppm; MS (ESI-TOF) m/z = 167 (100%, $[M - H]^-$); FTIR (film): $\tilde{\nu}$ = 3297, 2935, 2859, 2117, 1709, 1432, 1385, 1249, 1096, 940, 725, 637 cm^{-1}; HRMS (ESI-TOF): for $C_{10}H_{15}O_2^-$ ($[M - H]^-$), calculated: m/z = 167.1072, found: m/z = 167.1073.

Cyclohexanecarboxylic Acid (9)[8]

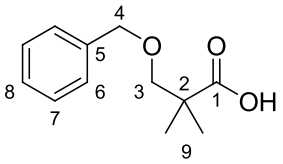


Reaction time: 4 h; work-up A; column chromatography: ethyl acetate/*n*-hexane 1:4 (1% AcOH); yield: 91%; colorless solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 11.02 (bs, 1H, OH), 2.29 (ddd, 1H, *J* = 11.2, 3.7, 3,7 Hz, H-2), 1.89 (m, 2H, H-3b), 1.71 (m, 2H, H-4b), 1.59 (m, 1H, H-5b), 1.41 (m, 2H, H-3a), 1.22 (m, 3H, H-4a, H-5a) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 182.8 (C-1), 43.0 (C-2), 28.8 (C-3), 25.8 (C-5), 25.4 (C-4) ppm; MS (neg. ESI-TOF): m/z = 127 (100%, $[M - H]^-$), 255 (31%, $[2M - H]^-$); FTIR (film, CCl_4) $\tilde{\nu}$ = 2935, 2857, 2670, 1703, 1538, 1452, 1417, 1312, 1260, 1214, 1183, 1136, 1076, 1021, 944, 895, 841, 825, 789, 684, 531 cm^{-1}; HRMS (neg. ESI-TOF): for $C_7H_{11}O_2^-$ ($[M - H]^-$), calculated: m/z = 127.0765, found: m/z = 127.0766; mp: 28–30 °C (Lit.[8] 27–29 °C).

[7] Hansen T. V.; Stenstrom, Y. *Synth. Commun.* **2000**, *30*, 2549–2557.
[8] Webb K. S.; Ruszkay, S. J. *Tetrahedron* **1998**, *54*, 401–410.

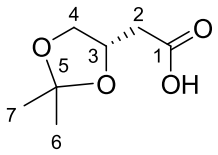
3-(Benzyloxy)-2,2-dimethylpropionic Acid (10)[9]



Reaction time: 4 h; work-up A; column chromatography: *n*-hexane/ethyl acetate 1:2 (1% AcOH); yield: 84%; colorless solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.31 (m, 5H, Ph), 4.57 (s, 2H, H-4), 3.48 (s, 2H, H-3), 1.24 (s, 6H, H-9) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 182.5 (C-1), 138.2 (C-5), 128.5 (C-7), 127.8 (C-8), 127.6 (C-6), 76.7 (C-3), 73.6 (C-4), 43.6 (C-2), 22.5 (C-9) ppm; MS (neg. ESI-TOF): m/z = 253 (11%, $[M + CO_2H]^-$) 207 (100%, $[M - H]^-$); FTIR (KBr): $\tilde{\nu}$ = 2983, 1704, 1453, 1317, 1273, 1253, 1115, 1028, 938, 737, 714, 696, 553 cm^{-1}; HRMS (neg. ESI-TOF): for $C_{12}H_{15}O_3^-$ ($[M - H]^-$), calculated: m/z = 207.1027, found: m/z = 207.1023; mp: 61–63°C (Lit.[9] 62.1–63.8 °C).

(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acetic Acid (11)[10]

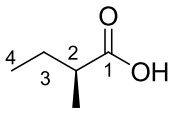


Reaction time: 4 h; work-up B; no column chromatography; yield: 74 %; colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 9.29 (bs, 1H, OH), 4.45 (p, 1H, *J* = 6.5 *Hz*, H-3), 4.13 (dd, 1H, *J* = 8.4, 6.0 Hz, H-4b), 3.63 (dd, 1H, *J* = 8.4, 6.2 Hz, H-4a), 2.71 (dd, 1H, *J* = 16.2, 6.7 Hz, H-2b), 2.53 (dd, 1H, *J* = 16.2, 6.8 Hz, 1H, H-2a), 1.39, 1.32 (2s, 3H each, H-7, H-6) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 176.0 (C-1), 110.0 (C-5), 71.9 (C-3), 69.1 (C-4), 38.8 (C-2), 26.9, 25.5 (C-7, C-6) ppm; MS (EI) m/z = 145 (23%, $[M - CH_3]^+$), 115 (2%, $[M - CO_2H]^+$), 101 (3%, $[M - C_2H_3O_2]^+$), 85 (100%, $[M - C_3H_7O_2]^+$); FTIR (film): $\tilde{\nu}$ = 3250, 2988, 1714, 1383, 1064, 967, 826, 792, 651, 629, 515 cm^{-1}; $[\alpha]_D$ = 9.5° (*c* = 4.3, $CHCl_3$) [Lit.[10] 5.8° (*c* = 4.3, $CHCl_3$)].

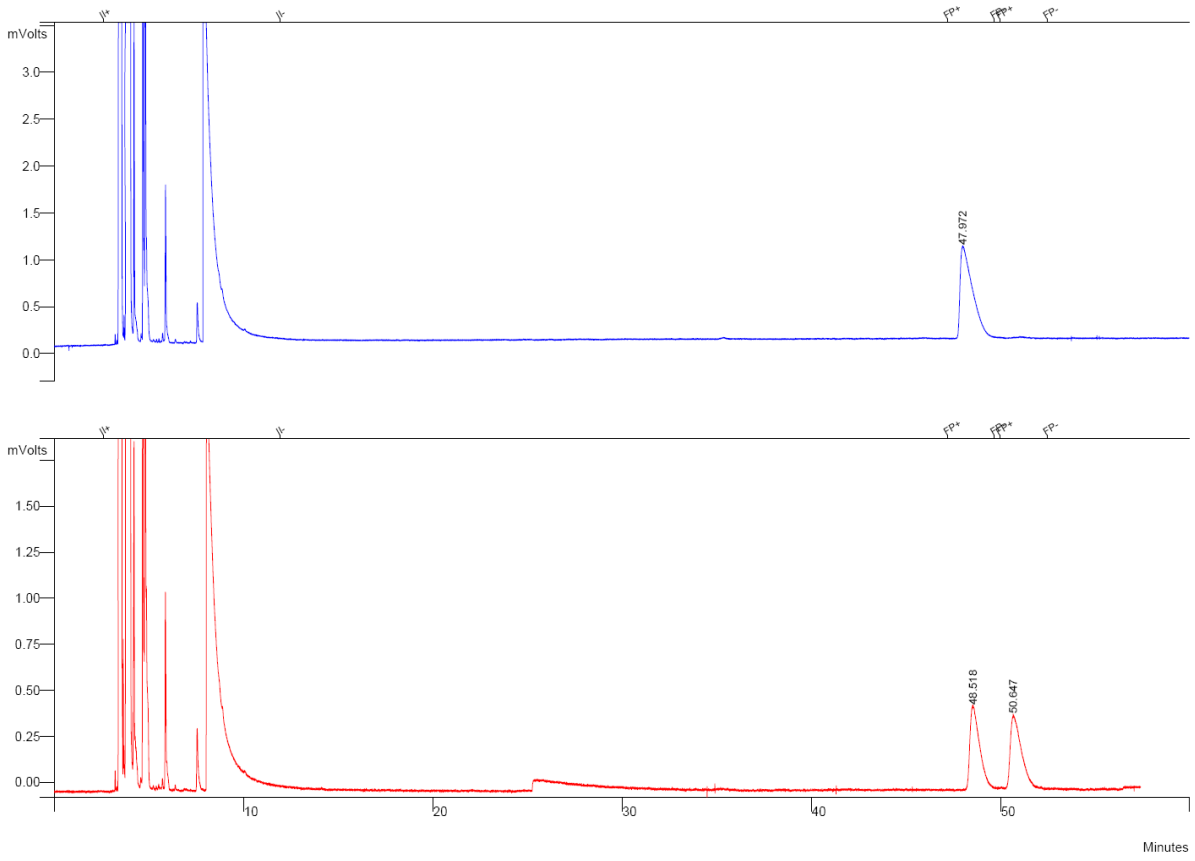
[9] Iliev, B.; Linden, A.; Heimgartner, H.; *Helv. Chim. Acta.* **2003**, *86*, 3215–3234.
[10] Wee, A. G. H.; McLeod, D. *Heterocycles* **2000**, *53*, 637–656.

(*S*)-2-Methylbutanoic Acid (12)[11]



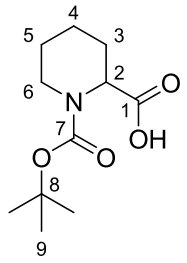
The reaction was followed by GC-FID. The conversion was 100%. The *ee* was determined by chiral GC-FID after 3 h. The racemic sample was obtained by TPAP-oxidation of *DL*-2-methylbutanol. Due to the volatility of the compound isolation was not attempted. Formation of the acid was confirmed by ^{1}H- and ^{13}C-NMR-spectra of the crude product after aqueous work-up (B): ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 10.28 (m, 1H, OH), 2.40 (dq, 1H, *J* = 7.0, 7.0 Hz, H-2), 1.70 (m, 1H, H-3b), 1.50 (m, 1H, H-3a), 1.17 (d, 3H, *J* = 7.0 Hz, H-5), 0.94 (t, 3H, *J* = 7.5 Hz, H-4) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 183.5 (C-1), 41.0 (C-2), 26.7 (C-3), 16.5 (C-5), 11.7 (C-4) ppm.

Chromatograms of the enantiomerically pure acid **12** (top) and the racemic sample (bottom):



[11] Santangelo, E. M.; Zarbin, P. H. G.; Cass, Q. B.; Ferreira, J. T. B.; Corrêa, A. G. *Synth. Commun.* **2001**, *31*, 3685–3698.

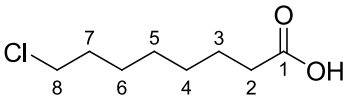
1-(*tert*-Butoxycarbonyl)piperidine-2-carboxylic Acid (15)[12]



Reaction time: 3h; work-up B; no column chromatography; yield: 98%; colorless solid.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 9.51 (bs, 1H, OH), 4.84 (m, 1H, H-2), 3.95 (m, 1H, H-6b), 2.93 (m, 1H, H-6a), 2.15 (m, 1H, H-3b), 1.68 (m, 3H, H-5b, H-4b, H-3a), 1.45 (s, 9H, H-9), 1.36 (m, 2H, H-5a, H-4a) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 178.4, 178.0 (C-1), 156.4, 155.8 (C-7), 80.5 (C-8), 54.9, 53.8 (C-2), 42.3, 41.3 (C-6), 28.5 (C-9), 26.7 (C-3), 24.8 (C-5), 21.0 (C-4) ppm; MS (ESI-TOF): m/z = 268 (14%, $[M + K]^+$), 252 (100%, $[M + Na]^+$); FTIR (KBr): $\tilde{\nu}$ = 2968, 2585, 1754, 1628, 1545, 1479, 1439, 1372, 1336, 1317, 1279, 1256, 1201, 1161, 1142, 1092, 1040, 1002, 929, 864, 773, 736, 594, 576, 547 cm^{-1}; HRMS (ESI-TOF): for $C_{11}H_{19}NaO_4^+$ ($[M + Na]^+$), calculated: m/z = 252.1206, found: m/z = 252.1211; mp: 131–134 °C (Lit.[12] 130–131 °C).

8-Chlorooctanoic Acid (13) [13]



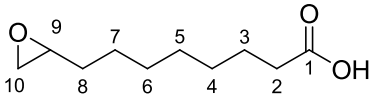
Reaction time: 3h; work-up A; column chromatography: ethyl acetate/*n*-hexane 1:4 (1% AcOH); yield: 86%; colorless solid.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 11.09 (bs, 1H, OH), 3.50 (t, 2H, *J* = 6.7 Hz, H-8), 2.33 (t, 2H, *J* = 7.5 Hz, H-2), 1.74 (dt, 2H, *J* = 14.5, 6.7 Hz, H-7), 1.61 (dt, 2H, *J* = 14.7, 7.5 Hz, H-3), 1.40 (m, 2H, H-6), 1.32 (m, 4H, H-5, H-4) ppm; ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 180.5 (C-1), 45.1 (C-8), 34.1 (C-2), 32.6 (C-7), 28.9, 28.6, 26.7 (C-6, C-5, C-4), 24.6 (C-3) ppm; MS (neg. ESI-TOF): m/z = 177 (100%, $[M - H]^-$); FTIR (film): $\tilde{\nu}$ = 2936, 2859, 1708, 1384, 1285, 1260, 1223, 1094, 937,

[12] Heller B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J.; Holzgrabe, U.; Heller E.; G. Oehme, *J. Org. Chem*. **2002**, *67*, 4414–4422.
[13] Olomucki, M. *Bull. Soc. Chim. Fr*. **1963**, 2067–2074.

825, 724, 652 cm^{-1}; HRMS (neg. ESI-TOF): for $C_8H_{14}ClO_2$ ($[M - H]^-$), calculated: m/z = 177.0682, found: m/z = 177.0681; mp: 31–34 °C (Lit.[13] 32–33 °C).

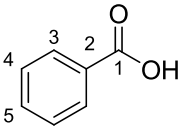
6-(Oxiran-2-yl)hexanoic acid (14)[14]



Reaction time: 3 h; work-up A; ethyl acetate/*n*-hexane 1:1 (1% AcOH); yield: 99%; colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 10.11 (bs, 1H, OH), 2.87 (m, 1H, H-9), 2.71 (dd, 1H, *J* = 5.0, 4.1 Hz, H-10a), 2.43 (dd, 1H, *J* = 5.0, 2.8 Hz, H-10b), 2.29 (t, 2H, *J* = 7.5 Hz, H-2), 1.59 (m, 2H, H-3), 1.45 (m, 4H, H-8, H-7), 1.26 (m, 6H, H-6, H-5, H-4) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 179.7 (C-1), 52.6 (C-9), 47.2 (C-10), 34.1 (C-2), 32.4 (C-8), 29.3, 29.2, 29.0 (C-6, C-5, C-4), 26.0 (C-7), 24.7 (C-3) ppm; MS (EI) m/z = 168 (< 1%, $[M - H_2O]^+$), 143 (< 1%, $[M - C_2H_3O]^+$), 125 (3%, $[M - H_2O - C_2H_3O]^+$], 115 (1%, $[M - C_4H_7O]^+$), 85 (9%, $[M - C_5H_9O_2]^+$), 73 (16%, $[M - C_6H_{11}O_2]^+$), 71 (100%, $[M - C_6H_{11}O_2]^+$), 57 (16%, $[M - C_7H_{13}O_2]^+$); FTIR (film) $\tilde{\nu}$ = 2927, 2856, 1711, 1631, 1551, 1386, 1279, 1110, 852, 726, 616, 465 cm^{-1}.

Benzoic Acid (16)[15]



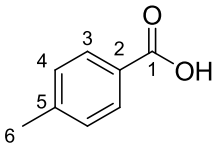
Reaction time: 3 h; work-up C; no column chromatography; yield: 70%; colorless solid.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 11.43 (bs, 1H, OH), 8.14 (m, 2H, H-3), 7.63 (m, 1H, H-5), 7.49 (m, 2H, H-4) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 172.6 (C-1), 134.0 (C-5), 130.4 (C-2), 129.5 (C-3), 128.6 (C-4) ppm; MS (EI) m/z = 122 (72%, $[M]^+$), 105 (100%, $[M - OH]^+$), 77 (87%, $[M - CO_2H]^+$), 51 (54%, $[C_4H_3]^+$); FTIR (KBr): $\tilde{\nu}$ = 3072, 3006, 2835, 2675, 2560, 1686, 1602, 1583,

[14] Takemoto, T.; Yasuda, K.; Ley, S. V. *Synlett* **2001**, 1555–1556.
[15] Minoura, Y.; Tsuboi, S. *J. Org. Chem*. **1972**, *37*, 2064–2069.

1496, 1454, 1425, 1327, 1292, 1185, 1128, 1101, 1073, 1027, 934, 809, 707, 684, 667, 552 cm^{-1}; mp: 122–124 °C (Lit.[15] 122–124 °C).

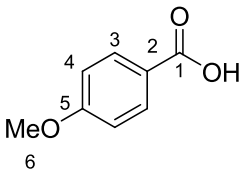
_p_-Methylbenzoic Acid (17)[16]



Reaction time: 3 h; work-up C; no column chromatography; yield: 26%; colorless solid.

^{1}H-NMR (300 MHz, CD_3OD) δ = 7.90 (m, 2H, H-3), 7.27 (m, 2H, H-4), 2.40 (s, 3H, H-6) ppm; ^{13}C-NMR (75 MHz, CD_3OD) δ = 170.0 (C-1), 145.1 (C-5), 130.8 (C-3), 130.1 (C-4), 129.1 (C-2), 21.6 (C-6) ppm; MS (neg. ESI): m/z = 135 (100%, $[M - H]^-$), 293 (38%, $[2(M - H) + Na^+]^-$); FTIR (KBr): $\tilde{\nu}$ = 3500, 2975, 1806, 1677, 1611, 1576, 1322, 1285, 1180, 1117, 961, 947, 754, 688, 541, 468 cm^{-1}; mp: 181–183 °C (Lit.[16] 180–182 °C).

_p_-Methoxybenzoic Acid (18)[17]

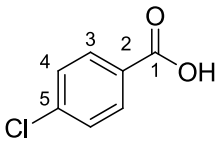


Reaction time: 20 h; work-up C; no column chromatography; yield: 32%; colorless solid.

^{1}H-NMR (400 MHz, CD_3OD) δ = 7.96 (m, 2H, H-3), 6.96 (m, 2H, H-4), 3.84 (s, 3H, H-6) ppm; ^{13}C-NMR (100 MHz, CD_3OD) δ = 169.8 (C-1), 165.0 (C-5), 132.8 (C-3), 124.0 (C-2), 114.7 (C-4), 55.9 (C-6) ppm; MS (EI): m/z = 152 (85%, $[M]^+$), 135 (100%, $[M - OH]^+$), 107 (15%, $[M - CO_2H]^+$), 77 (41%, $[C_6H_5]^+$); FTIR (KBr): $\tilde{\nu}$ = 3027, 2940, 2557, 1923, 1682, 1577, 1466, 1366, 1304, 1261, 1168, 1107, 1045, 918, 813, 707, 609, 503 cm^{-1}; mp: 181–185 °C (Lit.[17] 182–184 °C).

[16] Huang, N.; Xu, L. *Synth. Commun.* **1990**, *20*, 1563–1567.
[17] Trisler, J. C.; Cheng J. D.; Freasier, B. F. *J. Org. Chem*. **1970**, *35*, 2693–2695.

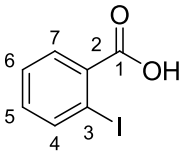
***p*-Chlorobenzoic Acid (19)**[18]



Reaction time: 90 min; work-up C; no column chromatography; yield: 95%; colorless solid.

^{1}H-NMR (300 MHz, CD_3OD) δ = 7.99 (m, 2H, H-3), 7.47 (m, 2H, H-4) ppm; ^{13}C-NMR (75 MHz, CD_3OD) δ = 168.7 (C-1), 140.2 (C-5), 132.3 (C-3), 130.7 (C-2), 129.7 (C-4) ppm; MS (neg. ESI-FTICR): m/z = 333 (27%, $[2(M - H) + Na^+]^-$), 155 ($[M - H]^-$, 100%), 111 (3%, $[M - CO_2H]^-$); FTIR (KBr): $\tilde{\nu}$ = 3500, 3094, 2223, 2067, 1682, 1591, 1574, 1371, 1295, 1092, 1015, 853, 762, 545, 471 cm^{-1}; mp: 239–242 °C (Lit.[18] 240–242 °C).

***o*-Iodobenzoic Acid (20)**[19]

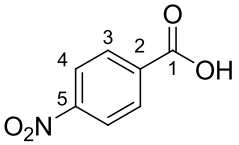


Reaction time: 20 h; work-up C; no column chromatography; yield: 94%; colorless solid.

^{1}H-NMR (400 MHz, CD_3OD) δ = 8.00 (dd, 1H, *J* = 7.9, 1.1 Hz, H-4), 7.78 (dd, 1H, *J* = 7.8, 1.7 Hz, H-7), 7.44 (m, 1H, H-6), 7.18 (m, 1H, H-5) ppm; ^{13}C-NMR (100 MHz, CD_3OD) δ = 170.1 (C-1), 142.3 (C-4), 137.8 (C-2), 133.4 (C-5), 131.6 (C-7), 129.0 (C-6), 94.1 (C-3) ppm; MS (neg. ESI-FTICR): m/z = 517 (7%, $[2(M - H) + Na^+]^-$), 266 ($[M - H]^-$, 100%), 127 (11%, $[M - CO_2H]^-$); FTIR (KBr): $\tilde{\nu}$ = 2232, 2071, 1681, 1581, 1560, 1465, 1428, 1343, 1296, 1265, 1166, 1147, 1109, 1059, 1048, 1014, 955, 880, 797, 739, 676, 660, 633, 545 cm^{-1}; mp: 161–164 °C (Lit.[19] 162–163 °C).

[18] Farah, B. S.; Gilbert, E. E.; Jones, E. S.; Otto, J. A. *J. Org. Chem*. **1965**, *30*, 1006–1007.
[19] Jílek, J. O.; Seidlová, V.; Svátek, E.; Protiva, M. *Monatsh. Chem.* **1965**, *95*, 182–207.

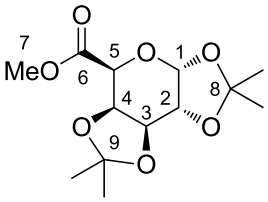
***p*-Nitrobenzoic Acid (21)**[20]



Reaction time: 3 h, work-up C; no column chromatography; yield: 91%; colorless solid.

^{1}H-NMR (300 MHz, CD_3OD) δ = 8.21 (m, 4H) ppm; ^{13}C-NMR (75 MHz, CD_3OD) = 166.8 (C-1), 150.7 (C-5), 136.6 (C-2), 131.2 (C-3), 123.6 (C-4) ppm; MS (neg. ESI-FTICR): m/z = 355 (24%, $[2(M - H) + Na^+]^-$), 166 ($[M-H]^-$, 100%), 122 (21%, $[M - CO_2H]^-$); FTIR (KBr): $\tilde{\nu}$ = 3063, 2670, 1692, 1607, 1541, 1430, 1351, 1312, 1279, 1108, 878, 860, 800, 716, 507 cm^{-1}; mp: 238–241 °C (Lit.[20] 240–241 °C).

(3a*R*,5*S*,5a*R*,8a*S*,8b*R*)-methyl-2,2,7,7-tetramethyltetrahydro-3a*H*-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-carboxylate (22)[21]

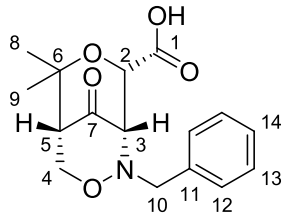


Reaction time: 2 h, work-up B; esterification of the crude product with $TMSCHN_2$; column chromatography: ethyl acetate/*n*-hexane 1:2; yield: 66%; colorless oil.

^{1}H-NMR (300 MHz, $CDCl_3$):δ = 5.60 (d, 1H, *J* = 5.0 Hz, H-1), 4.61 (dd, 1H, *J* = 7.7, 2.6 Hz, H-3), 4.52 (dd, 1H, *J* = 7.7, 2.3 Hz, H-4), 4.39 (d, 1H, *J* = 2.3 Hz, H-5), 4.32 (dd, 1H, *J* = 5.0, 2.6 Hz, H-2), 3.76 (s, 3H, H-7), 1.47 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.28 (s, 6H, 2 CH_3) ppm.^{13}C-NMR (75 MHz, $CDCl_3$):δ = 168.7 (C-6), 110.1 (C-8), 109.0 (C-9), 96.6 (C-1), 72.1 (C-4), 70.7 (C-3), 70.3 (C-2), 68.5 (C-5), 52.4 (C-7), 26.0 (CH_3), 25.9 (CH_3), 24.8 (CH_3), 24.7 (CH_3) ppm. MS (pos. ESI-FTICR) m/z = 327 (10% ($[M + K]^+$), 311 (11%, $[M + Na]^+$), 306 (74%, $[M + H_2O]^+$], 289 (100%, $[M - H]^+$). FTIR (film): $\tilde{\nu}$ = 3626, 3542, 3436, 2936, 1732, 1633, 1436, 1385, 1030, 929, 904, 875, 855, 839, 797, 756, 700, 648, 581, 540, 513, 448, 425 cm^{-1}. $[\alpha]_D$ = -92.0° (*c* = 1.0, $CHCl_3$), [Lit. -92.5°(*c* = 1.0, $CHCl_3$)].

[20] Roberts, D. D. *J. Org. Chem*. **1976**, *41*, 486–489.
[21] Lichtenthaler, F. W; Jarglis, P.; Lorenz, K. *Synthesis* **1988**, 790–792.

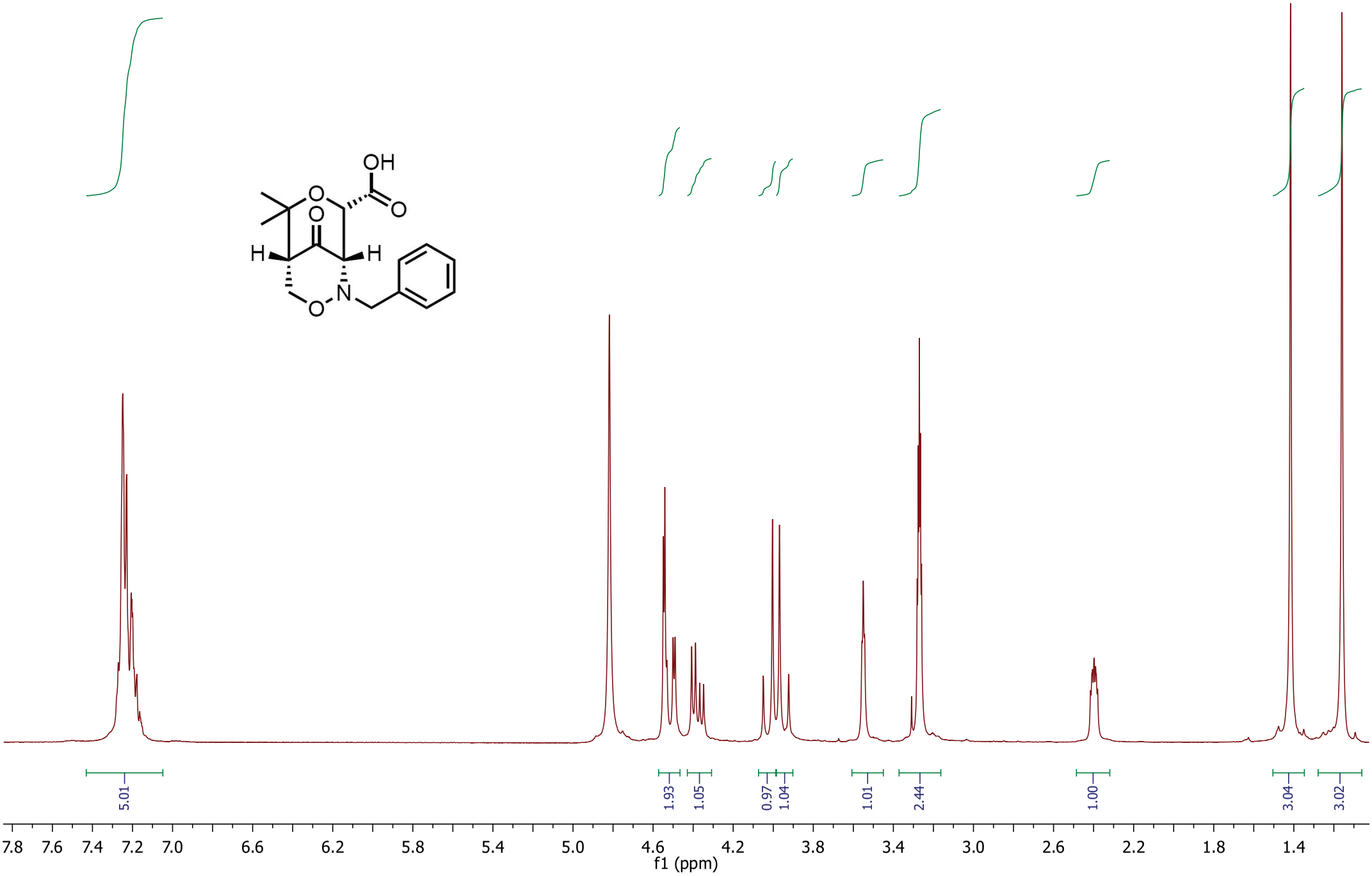
(1*S*,5*S*,8*S*)-2-Benzyl-6,6-dimethyl-9-oxo-3-oxa-2-azabicyclo[3.3.1]nonane-8-carboxylic acid (23)



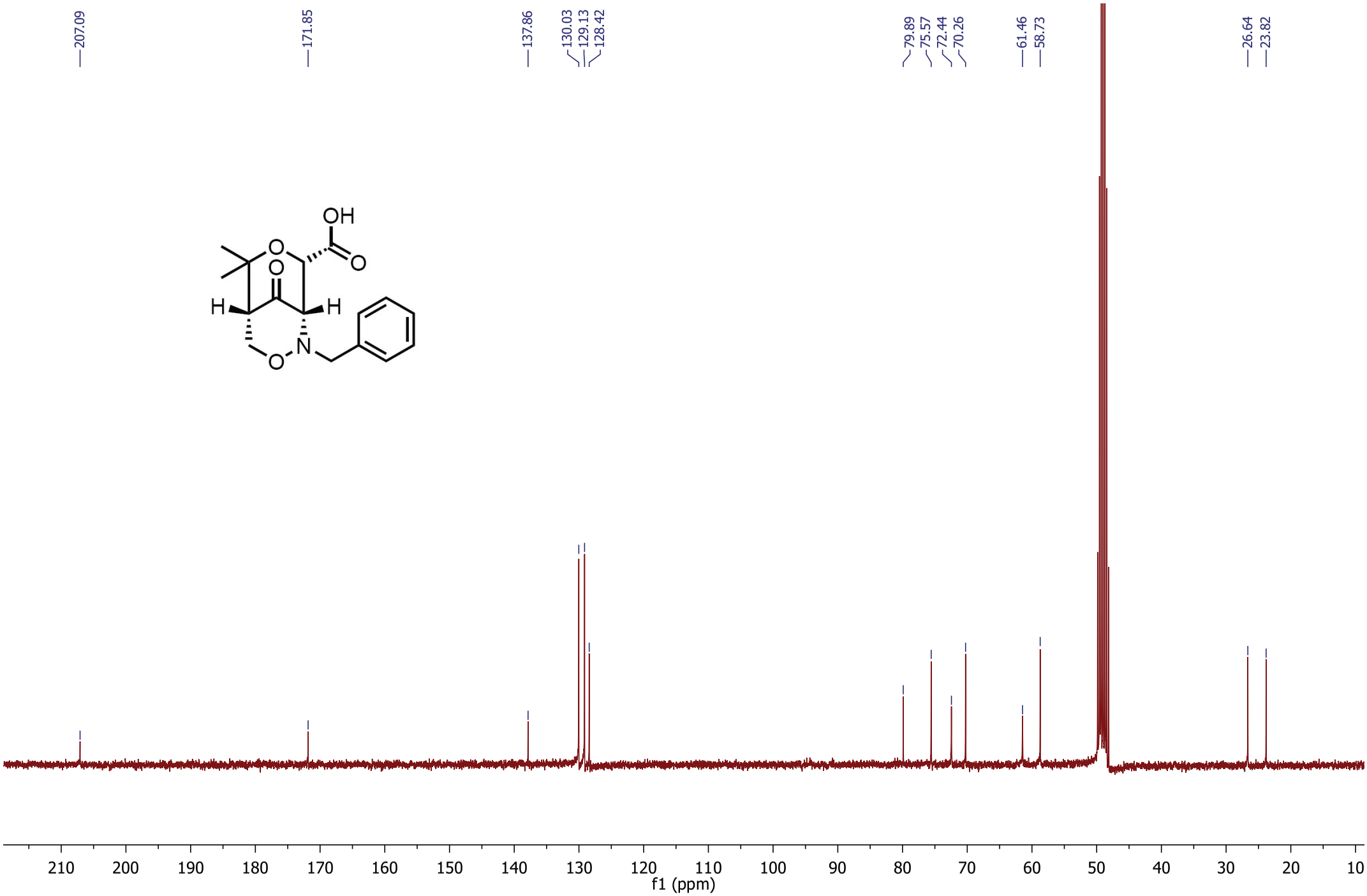
Reaction time: 3 h, work-up C; no column chromatography; yield: 58% after recrystallization; colorless solid.

^{1}H-NMR (300 MHz, CD_3OD): δ = 7.21 (m, 5H, Ph), 4.58 (d, 1H, *J* = 2.0 Hz, H-2), 4.56 (dd, 1H, *J* = 12.1, 3.0 Hz, H-4b), 4.38 (dd, 1H, *J* = 12.1, 5.6 Hz, H-4a), 4.03 (d, 1H, *J* = 13.8 Hz, H-10b), 3.95 (d, 1H, *J* = 13.8 Hz, H-10a), 3.55 (dd, *J* = 2.0, 2.0 Hz, H-3), 2.40 (ddd, 1H, *J* = 5.6, 3.0, 2.0 Hz, H-5), 1.45 (s, 3H, H-9), 1.16 (s, 3H, H-8) ppm; ^{13}C-NMR (300 MHz, CD_3OD): δ = 207.1 (C-7), 171.9 (C-1), 137.9 (C-11), 130.0 (C-12), 129.1 (C-13), 128.4 (C-14), 79.9 (C-6), 75.6 (C-2), 72.5 (C-3), 70.3 (C-4), 61.5 (C-10), 58.9 (C-5), 26.6 (C-9), 23.8 (C-8) ppm; MS (pos. ESI-FTICR): m/z = 633 (67%, $[2M + Na]^+$), 328 (100%, $[M + Na]^+$), 306 (8%, $[M + H]^+$); FTIR (KBr): $\tilde{\nu}$ = 3465, 2985, 2360, 2341, 1737, 1709, 1635, 1455, 1357, 1236, 1204, 1153, 1102, 1039, 982, 882, 839, 819, 768, 735, 699, 669, 537, 455, 433 cm^{-1}; HRMS (pos. ESI-FTICR): For $C_{16}H_{20}NO_5^+$ ($[M + H)^+$) calculated: m/z = 306.1336, found: m/z = 306.1336; mp: 186–188 °C, $[\alpha]_D$ = 61.0° (*c* = 0.2, $CHCl_3$).

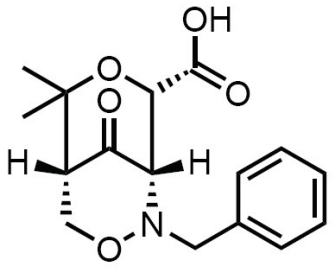
^{1}H-NMR of compound **23**



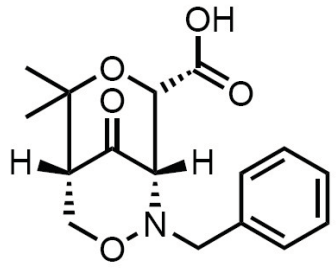
^{13}C-NMR of compound **23**



COSY of compound **23**



HSQC of compound **23**



HMBC of compound **23**