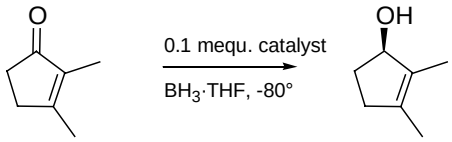
Efficient synthesis of the D-ring fragment of cobyric acid

Johann Mulzer* and Doris Riether

General Experimental

All reactions were carried out under an atmosphere of dry argon. Tetrahydrofuran (THF) was dried over KOH and distilled from potassium metal under an atmosphere of argon. Dichloromethane (methylene chloride) was passed through a column of basic aluminum oxide and then distilled from P_2O_5. Flash column chromatography was carried out using the solvent system indicated and silica gel 60 230-400 mesh.

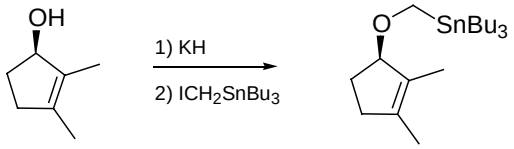
(1*R*)-2,3-Dimethyl-cyclopent-2-enol (9)



Ketone **10** (5 g, 50 mmol) in dry THF (10 ml) was added dropwise to a solution of oxazaborolidine catalyst (*S*)-B-*n*Bu (0.2 N, 37.5 ml, 7.5 mmol) and BH_3·THF (1 N, 32.5 ml) in dry THF (12 ml) at -100 °C and the reaction mixture was kept in a -80 °C freezer for seven days. Then it was quenched with water (3 ml) and the mixture poured in brine (3 ml). After washing the organic layer with NaOH (0.5 M, 2 x 5 ml), the combined aqueous solutions were extracted with diethyl ether (5 x 20 ml) and the combined organic solutions were dried over magnesium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (pentane/diethyl ether = 10:1) to yield **9** (5.4 g, 48.5 mmol, 97 %) as colorless liquid.
The enantiomeric excess was monitored by HPLC-analysis of the p-nitrobenzoic acid derivative of **9** (Chiralpak AS 0.46 cm x 25 cm, 0.2 % *i*-propanol/hexane, 1.5 ml/min, 20 °C, UV = 254 nm, r_f = 8.7 min, 9.9 min).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.58 (s, br, 1H), 2.39 (m, 1H), 2.25 (m, 1H), 2.18 – 2.10 (m, 1H), 1.65 (m, 6H), 1.63 (m, 1H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 136.2, 133.5, 81.9, 35.7, 33.0, 14.6, 11.4; **MS (EI, 70 eV, 30 °C):** *m/z* = 112.0 (10%, M^+), 96.9 (100%, M^+-CH_3), 78.9 (48%), 76.9 (28%), 69.0 (16%), 67.0 (21%); **HRMS (EI, 70 eV, 30 °C):** calc.: *m/z* = 112.0888 (M^+); found: *m/z* = 112.0891 ± 0.0006 (M^+); **IR (neat):** ν_{max} = 3356 (br), 2926, 2855, 1448, 1381, 1334, 1107, 990, 890, 739, 610; $[\alpha]_D^{20}$ = + 60.6° (c = 1.07, $CHCl_3$).

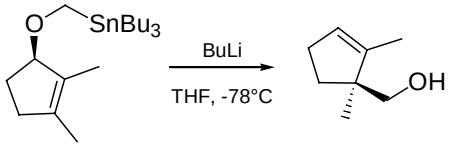
((1*R*)-Tributyl-(2,3-dimethyl-cyclopent-2-enyloxymethyl)-stannane (11)



KH (30% in mineral oil, 18.5 g, 138 mmol) was suspended in dry THF (170 ml) and DMF (50 ml) at 0 °C. Alcohol **9** (5.2 g, 46 mmol) in dry THF (25 ml) was added dropwise and the reaction mixture was stirred for one hour. Then it was treated with ICH_2SnBu_3 (30 g, 69 mmol) and stirred for two hours. After quenching the reaction carefully with ice, the aqueous solution was extracted with diethyl ether (20 ml) and the combined organic solutions were dried over magnesium sulfate. The solvents were removed under vacuum and the residue was purified by flash chromatography (hexane/ethyl acetate = 80:1) to yield **11** (16.7 g, 40.1 mmol, 87%) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.15 (s, br, 1H), 3.77 (d, *J* = 10.4 Hz, 1H), 3.54 (d, *J* = 10.4 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.17 – 2.09 (m, 1H), 2.04 (m, 1H), 1.69 (ddd, *J* = 17.8 Hz, 8.8 Hz, 4.2 Hz, 1H), 1.64 (s, 3H), 1.61 (s, 3H), 1.55 – 1.48 (m, 6H), 1.30 (sext, *J* = 7.4 Hz, 6H), 0.89 (t, *J* = 7.3 Hz, 9H), 0.92 – 0.88 (m, 6H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 135.7, 131.8, 92.2, 57.9, 35.7, 29.2, 27.7, 27.3, 14.1, 13.7, 11.4, 8.9; **MS (EI, 70 eV, 20 °C):** *m/z* = 359.1 (3%, M^+-Bu), 295.2 (18%), 293.1 (24%), 292.1, (17%), 291.1 (96%), 290.1 (36%), 289.1 (76%), 288.1 (28%), 287.1 (41%), 239.1 (16%), 237.1 (18.3), 236.1 (10%), 235.1 (86%), 234.1 (32%), 233.1 (67%), 232.1 (25%), 231.1 (36%), 181.1 (20%), 183.1 (26%), 179.0 (100%), 178.0 (34%), 177.1 (96%), 176.0 (37%), 175.1 (68%), 173.0 (14%); **HRMS (EI, 70 eV, 20 °C):** calc.: *m/z* = 359.1399 (M^+-Bu); found: *m/z* = 359.1406 ± 0.0018 (M^+-Bu); **IR (neat):** ν_{max} = 2957, 2925, 2870, 2853, 1684, 1457, 1377, 1343, 1182, 1104, 1069, 1044, 960, 913, 874, 742, 662, 610; $[\alpha]_D^{20}$ = + 5.0° (c = 1.00, MeOH).

[(1*S*)-1,2-dimethyl-cyclopent-2-enyl]-methanol (8)



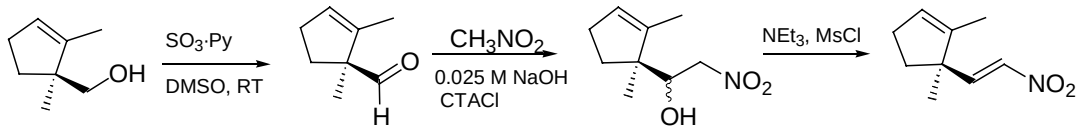
Stannane **11** (7.0 g, 16.9 mmol) was dissolved in dry THF (40 ml) and cooled to -100 °C. A solution of *n*-BuLi in hexane (20.3 ml, 2.5 M) was added slowly and the reaction mixture was stirred for two hours. Then it was allowed to warm to -50 °C where it was stirred for another three hours. After quenching with saturated aqueous ammonium chloride solution (5 ml), it was diluted with diethyl ether (40 ml). The aqueous solution was extracted with diethyl ether (2 x 10 ml), the combined organic solutions were dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography (pentane/diethyl ether = 7:1) to yield **8** (1.17 g, 9.3 mmol, 55 %) as a colorless liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.47 (d, *J* = 1.5 Hz, 1H), 3.48 (dd, *J* = 10.6 Hz, 3.3 Hz, 1H), 3.34 (dd, *J* = 10.5 Hz, 8.0 Hz, 1H), 2.26 – 2.20 (m, 2H), 2.03 (ddd, *J* = 13.0 Hz, 7.8

Hz, 5.9 Hz, 1H), 1.63 (m, 1H), 1.62 (dd, *J* = 3.8 Hz, 2.3 Hz, 3H), 1.26 (dd_{br}, *J* = 3.5 Hz, 7.8 Hz, OH), 0.99 (s, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 142.7, 127.2, 68.7, 51.6, 34.8, 29.6, 21.5, 12.3; **MS (EI, 70 eV, 20 °C):** *m/z* = 126.1 (7%, M^+), 96.0 (12%), 95.0 (100%), 83.8 (13%), 79.0 (11%), 67.0 (26%), 55.0 (16%); **HRMS (EI, 70 eV, 20 °C):** calc.: *m/z* = 126.1047 (M^+); found: *m/z* = 126.1049 ± 0.0006 (M^+); **IR (neat):** ν_{max} = 3385, 2934, 2865, 1654, 1560, 1448, 1380, 1107, 1045, 1019, 874, 738, 610; $[\alpha]_D^{20}$ = -20.8° (c = 0.90, $CHCl_3$).

(5*R*)-1,5-Dimethyl-5-[(*E*)-2-nitro-vinyl]-cyclopentene (7)

(1*S*)-1,2-dimethyl-cyclopent-2-enecarbaldehyde (**12**)



To a solution of alcohol **8** (300 mg, 2.4 mmol) in dimethyl sulfoxide (10 ml) and methylene chloride (10 ml) was added NEt_3 (713 mg, 7.1 mmol) at 0 °C. It was then treated with SO_3·Py (1.21 g, 7.1 mmol) in dimethyl sulfoxide (10 ml), and the reaction mixture was stirred for one hour at room temperature. Then the reaction was quenched with ice water (10 ml), the aqueous solution was extracted with diethyl ether/hexane (1:1, 3 x 20 ml) and the combined organic solutions were washed with water (5 ml) and dried over magnesium sulfate. After the solvents were removed, (1*S*)-1,2-dimethyl-cyclopent-2-enecarbaldehyde (**12**) was subsequently used for the next step without further purification.

1-[(1*S*)-1,2-Dimethyl-cyclopent-2-enyl]-2-nitroethanol

At room temperature hexacetyltetramethylammonium chloride (82 mg, 0.24 mmol, 0.1mequ) was added to a stirred mixture of (1*S*)-1,2-dimethylcyclopente-2-necarbaldehyde (**12**) (crude product), aqueous NaOH (15 ml, 0.025 M) and nitromethane (610 mg, 10.0 mmol) and the reaction mixture was stirred for 8 – 10 hours. Then the solution was saturated with sodium chloride, and extracted with diethyl ether (8 x 10 ml). The organic solutions were combined, dried over magnesium sulfate and concentrated *in vacuo*. The alcohol (284 mg, 1.5 mmol, 64 % over two steps), a pale yellow liquid, was used in the next step without further purification (diastereomeric ration = 1.6 : 1).

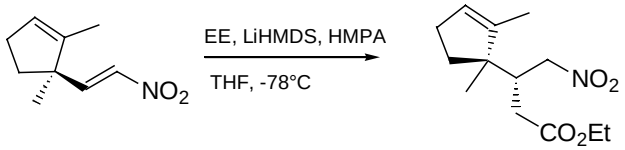
Mixture of diastereomeres: **^{1}H-NMR ($CDCl_3$, 400 MHz):** δ [ppm] = 5.52 (q_{br}, *J* = 1.2 Hz, 1H), 5.43 (q_{br}, *J* = 1.2 Hz, 2H), 4.41 – 4.29 (m, 2H), 4.41 – 4.29 (m, 3H), 2.24 – 2.18 (m, 1H), 2.13 – 2.04 (m, 1H), 2.01 – 1.91 (m, 1H), 1.64 (qu, *J* = 1.9 Hz, 1H), 1.61 (qu, *J* = 1.9, 2H), 1.58 – 1.49 (m, 1H), 1.13 (s, 2H), 1.02 (s, 1H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** major: δ [ppm] = 142.5, 128.1, 78.7, 73.9, 32.0, 29.7, 23.2, 13.0; minor: δ [ppm] = 142.5, 127.4, 78.4, 73.0, 31.9, 29.8, 22.6, 12.6; **MS (EI, 70 eV, 40 °C):** *m/z* = 167.1 (2%, M^+-H_2O), 105.0 (3%), 96.0 (9%), 95.0 (100%), 79.0 (17%), 77.0 (17%), 67.0 (32%); **IR (neat):** ν_{max} = 3538, 3037, 2960, 2855, 1556, 1444, 1382, 1282, 1203, 1101, 1069, 1024, 877, 1101, 1069, 1024, 877, 803, 669, 613.

(5*R*)-1,5-Dimethyl-5-[(*E*)-2-nitro-vinyl]-cyclopentene (**7**)

The crude alcohol (170 mg, 0.92 mmol) was dissolved in ethyl acetate (15 ml) and cooled to 0 °C. Freshly distilled NEt_3 (567 mg, 5.49 mmol), and methanesulfonyl chloride (0.42 ml, 5.49 mmol) were added, slowly. After the reaction mixture was stirred for four hours at 0 °C, the reaction was quenched with saturated aqueous sodium carbonate solution (3 ml), the aqueous solution was extracted with ethyl acetate (3 x 10 ml), the combined organic solutions dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate = 10:1) to yield **7** (135 mg, 0.81 mmol, 88 %) as a pale yellow liquid.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 7.22 (d, *J* = 13.6 Hz, 1H), 6.88 (d, *J* = 13.6 Hz, 1H), 5.52 (d_{br}, *J* = 1.8 Hz, 1H), 2.31 (tdd, *J* = 8.0 Hz, 6.0 Hz, 2.2 Hz, 2H), 2.04 (td, *J* = 12.9 Hz, 6.3 Hz, 1H), 1.84 (td, *J* = 13.1 Hz, 8.0 Hz, 1H), 1.60 (dd, *J* = 3.8 Hz, 2.3 Hz, 3H), 1.24 (s, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 148.4, 142.2, 127.6, 39.0, 29.7, 29.4, 22.6, 12.7; **MS (EI, 70 eV, 50 °C):** *m/z* = 167.1 (3%, M^+), 121.1 (22%), 106.0 (19%), 105.0 (100%), 95.0 (41%), 93.0 (43%), 91.0 (55%), 80.0 (12%), 79.0 (50%), 78.0 (21%), 77.0 (51%), 67.0 (30%), 65.0 (22%); **HRMS (EI, 70 eV, 50 °C):** calc.: *m/z* = 167.0946 (M^+); found: *m/z* = 167.0949 ± 0.0008 (M^+); **IR (neat):** ν_{max} = 2927, 2854, 1638, 1526, 1457, 1350, 1108, 969, 900, 816, 738, 610; $[\alpha]_D^{20}$ = -151.0° (c = 0.97; $CHCl_3$).

(3*R*)-3-[(1*R*)-1,2-Dimethyl-cyclopent-2-enyl]-4-nitro-butyric acid ethyl ester (13)

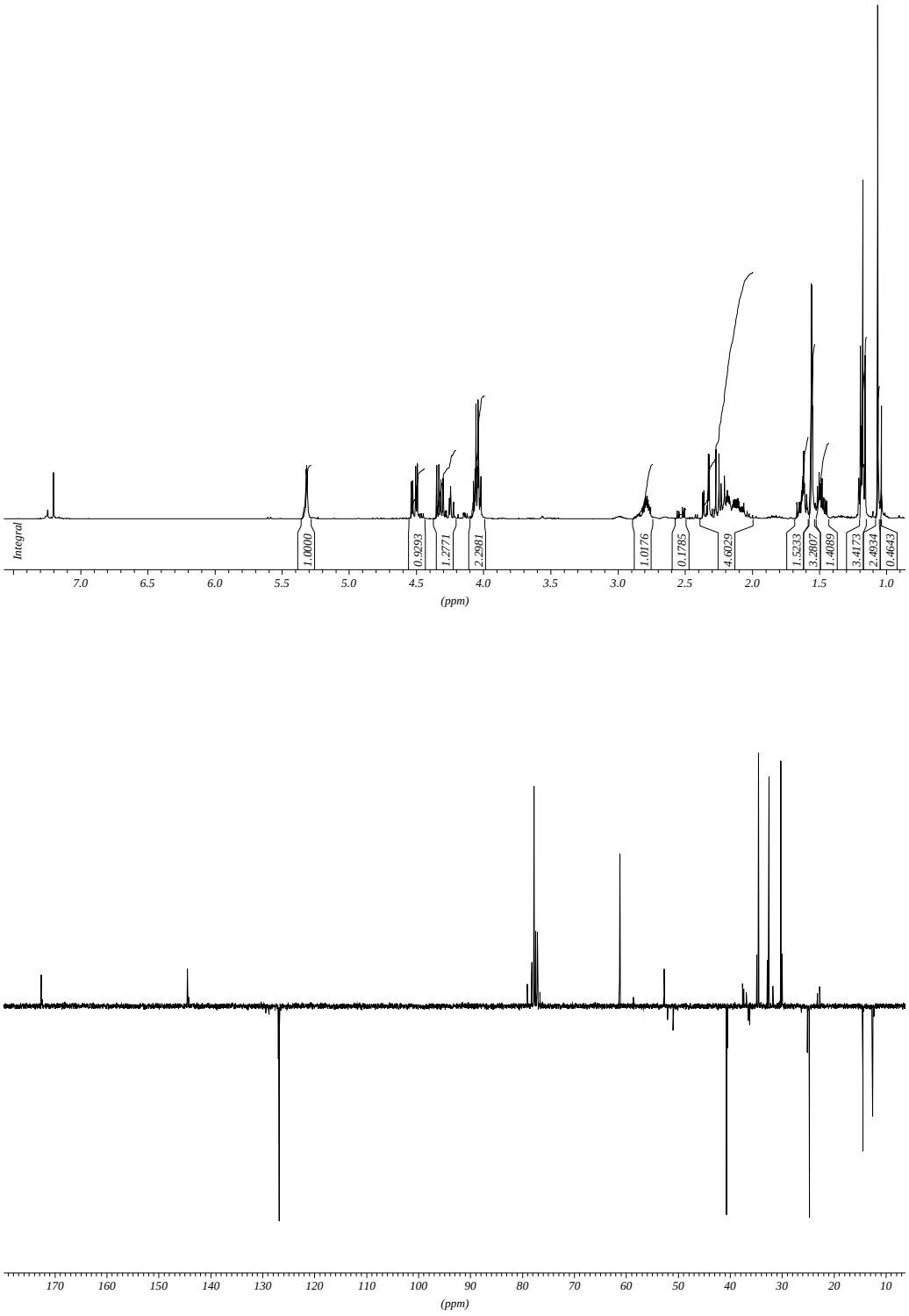


To a solution of ethyl acetate (19 mg, 0.24 mmol) in dry THF (1 ml) was added a solution of LiHMDS in THF (0.24 ml, 1 M) at -95 °C and the reaction mixture was stirred for ten minutes. Then it was treated with HMPA (128 mg, 0.72 mmol) and after 25 minutes a solution of nitro olefin **7** (40 mg, 0.24 mmol) in dry THF (0.5 ml) was added dropwise to the solution at -100 °C. The reaction mixture was stirred for 30 minutes and was then quenched with saturated aqueous ammonium chloride solution (4 ml) and diluted with diethyl ether (5 ml). The aqueous solution was extracted with diethyl ether (3 x 5 ml), and the combined organic solutions were dried over magnesium sulfate. After the solvents were removed, the residue was purified by flash chromatography (hexane/ethyl acetate = 20:1) to yield **13** (40 mg, 0.16 mmol, 69 %) as a colorless liquid (diastereomeric ratio: 86:14, detected by HPLC).

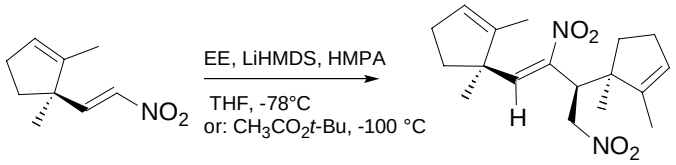
^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.38 (d_{br}, *J* = 1.5 Hz, 1H), 4.57 (dd, *J* = 12.6 Hz, *J* = 4.8 Hz, 1H), 4.38 (dd, *J* = 12.6 Hz, 6.8 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.88 – 2.81 (m, 1H), 2.40 (dd, *J* = 16.4 Hz, 3.0 Hz, 1H), 2.30 (dd, *J* = 16.6 Hz, 9.7 Hz, 1H), 2.25 – 2.12 (m, 2H), 1.69 (ddd, *J* = 13.2 Hz, 9.3 Hz, 6.3 Hz, 1H), 1.62 (q, *J* = 1.9 Hz, 3H), 1.54 (ddd, *J* = 13.5 Hz, 9.0 Hz, 4.6 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 172.2, 144.0, 126.4, 77.3, 60.8, 52.2, 40.2, 34.1, 32.1, 29.8, 24.4, 14.0, 12.2; **MS (EI, 70 eV, 40 °C):** *m/z* = 255.1 (0.2%, M^+), 220.1 (4%), 133.0 (7%), 119.0 (10%), 96.0 (12%), 95.0 (100.0%); **HRMS (EI, 70 eV, 40 °C):** calc.: *m/z* = 255.1471 (M^+); found:

m/z = 255.1467 ± 0.0013 (M^+); **IR (neat):** ν_{max} = 2962, 1733, 1556, 1444, 1379, 1298, 1180, 1107, 1027, 890, 816, 739, 610; $[\alpha]_D^{20}$ = -17.3° (c = 1.05, $CHCl_3$) (mixture of diastereomeres).

^{1}H- and ^{13}C-NMR of **13** as a mixture of diastereomeres:



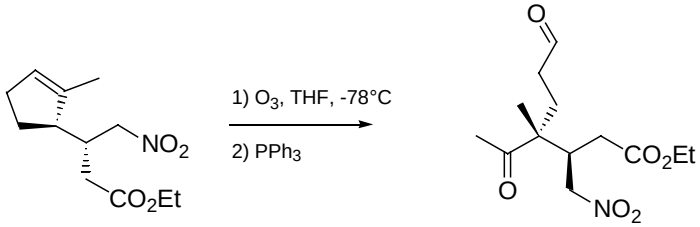
(5*R*)-5-{(1*Z*,3*S*)-3-[(1*R*)-1,2-dimethylcyclopent-2-en-1-yl]-2,4-dinitrobut-1-enyl}-1,5-dimethylcyclopent-1-ene (14)



The same procedure was carried out as for the synthesis of **7**: The reaction was performed at –78 °C instead of –100 °C or CH_3CO_2t-Bu was used instead of EE.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 5.65 (s, 1H), 5.38 (d, *J* = 1,7 Hz, 1H), 5.34 (d, *J* = 1.72 Hz, 1H), 4.86 (dd, *J* = 11.0 Hz, 13.2 Hz, 1H), 4.63 (dd, *J* = 4.1 Hz, 13.2 Hz, 1H), 3.52 (dd, *J* = 11.2 Hz, 4.3 Hz, 1H), 2.26 – 2.15 (m, 3H), 2.08 (m, 1H), 1.89 (m, 2H), 1.63 (q, *J* = 2.0 Hz, 3H), 1.59 (q, *J* = 2.1 Hz, 3H), 1.56 (m, 1H), 1.26 (m, 1H), 1.13 (s, 3H), 1.12 (s, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 146.5, 143.7, 142.4, 138.5, 128.0, 126.1, 75.7, 51.9, 49.7, 38.7, 33.7, 30.1, 29.7, 25.9, 24.3, 23.4, 12.9, 12.6; **MS (EI, 70 eV, 40 °C):** *m/z* = 335.1 (25%, M+H$^+$), 334.1 (100%, M$^+$); **IR (Si-Pellet):** $\tilde{\upsilon}_{max}$ = 2962, 1556, 1444, 1379, 1298, 1180, 1107, 1027, 890, 816, 739, 610.

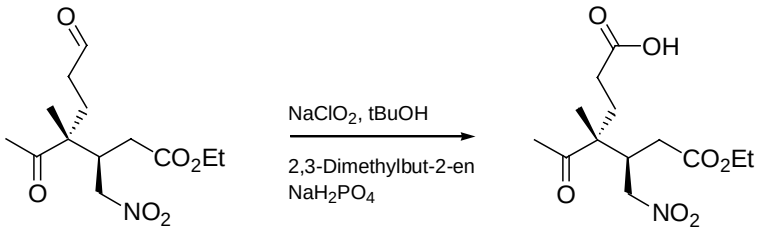
(3*R*,4*R*)-4-Acetyl-4-methyl-3-nitromethyl-7-oxo-heptanoic acid ethyl ester (6)



Ester **13** (40 mg, 0.16 mmol) was dissolved in methylene chloride and methanol (20 ml, 20:1) and cooled to –78 °C. Ozone was bubbled through the solution until it turned pale blue. After PPh_3 (123 mg, 0.47 mmol) was added, the reaction mixture was allowed to warm to room temperature over night. Then the solvent was removed and the residue purified by flash chromatography (hexane/ethyl acetate = 5:1 -> 1:1) to yield **6** (40 mg, 10.14 mmol, 87 %) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 9.73 (s, 1H), 4.38 (m, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.19 (ddd, *J* = 4.4 Hz, 7.6 Hz, 11.9 Hz, 1H), 2.47 (dd, *J* = 4.6 Hz, 16.4 Hz, 1H), 2.42 (m, 2H), 2.36 (dd, *J* = 8.0 Hz, 16.6 Hz, 1H), 2.19 (s, 3H), 1.97 (ddd, *J* = 5.8 Hz, 9.4 Hz, 14.9 Hz, 1H), 1.70 (ddd, *J* = 5.9 Hz, 9.6 Hz, 14.7 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.14 (s, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 210.9, 200.2, 171.4, 77.1, 61.2, 52.6, 38.4, 38.5, 33.7, 26.8, 26.0, 18.3, 14.0; **MS (EI, 70 eV, 90 °C):** *m/z* = 242.1 (2%, M$^+$-C_2H_5O), 197.1 (2%), 169.1 (3%), 151.0 (12%), 123.1 (11%), 109.0 (20%), 105.0 (15%), 95.0 (19%), 93.0 (12%), 83.0 (12%), 81.0 (21%), 69.0 (12%), 67.0 (11%); **HRMS (EI, 70 eV, 90 °C):** calc.: *m/z* = 242.1028 (M$^+$-C_2H_5O); found: *m/z* = 242.1034 ± 0.0012 (M$^+$-C_2H_5O); **IR (neat):** ν_{max} = 2984, 2732, 1726, 1702, 1555, 1422, 1380, 1301, 1181, 1108, 1026, 884, 738, 610.

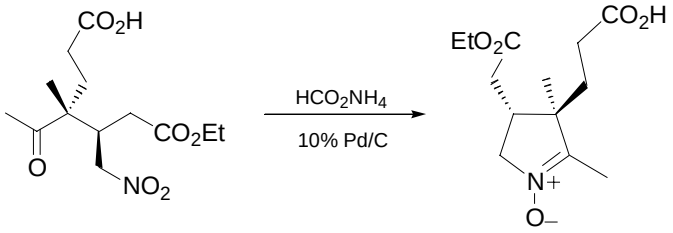
(3*R*,4*R*)-4-Acetyl-4-methyl-3-nitromethyl-heptanedioic acid ethyl ester (17)



$NaClO_2$ (110 mg) and NaH_2PO_4 (110 mg) were dissolved in water (2 ml) and added dropwise to a solution of aldehyde **6** (75 mg, 0.26 mmol) in *t*-BuOH (10 ml) and 2,3-dimethyl-2-but-2-en (10 ml). After the reaction mixture was stirred for one hour the reaction was quenched with saturated aqueous ammonium chloride solution (10 ml). The aqueous layer was extracted with methylene chloride (5 x 10 ml), the organic solutions were combined, dried over magnesium sulfate and the solvents removed under vacuum. The residue was purified by flash chromatography (hexane/ethyl acetate = 1:1) to yield **17** (58 mg, 0.19 mmol, 74 %) as a colorless oil.

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 8.76 (s_{br}, 1H), 4.39 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.19 (m, 1H), 2.49 (dd, *J* = 16.4 Hz, 4.6 Hz, 1H), 2.38 (dd, *J* = 16.6 Hz, 8.0 Hz, 1H), 2.28 (m, 2H), 2.22 (s, 3H), 2.04 (ddd, *J* = 14.3 Hz, 9.1 Hz, 6.8 Hz, 1H), 1.72 (ddd, *J* = 14.3 Hz, 9.5 Hz, 6.7 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.17 (s, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 210.9, 177.9, 171.4, 76.9, 61.3, 52.7, 38.6, 33.7, 29.8, 28.5, 26.0, 18.1, 14.0; **MS (EI, 70 eV, 150 °C):** *m/z* = 258.1 (5%, M^+-C_2H_5O), 167.1 (15%), 139.0 (13%), 121.1 (30%), 109.0 (14%), 99.0 (16%), 97.0 (16%), 95.0 (12%), 93.0 (26%), 85.0 (11%), 55.0 (21%), 43.0 (100%); **HRMS (EI, 70 eV, 150 °C):** calc.: *m/z* = 258.0978 (M^+-C_2H_5O); found: *m/z* = 258.0972 ± 0.0013 (M^+-C_2H_5O); **IR (neat):** ν_{max} = 2934, 1734, 1702, 1554, 1380, 1107, 879, 816, 738, 610; $[\alpha]_D^{20}$ = +12.6° (c = 1.70, $CHCl_3$) (mixture of diastereomeres).

(3*R*,4*R*)-3-(4-Ethoxycarbonylmethyl-2,3-dimethyl-1-oxy-4,5-dihydro-3H-pyrrol-3-yl)-propionic acid (19)

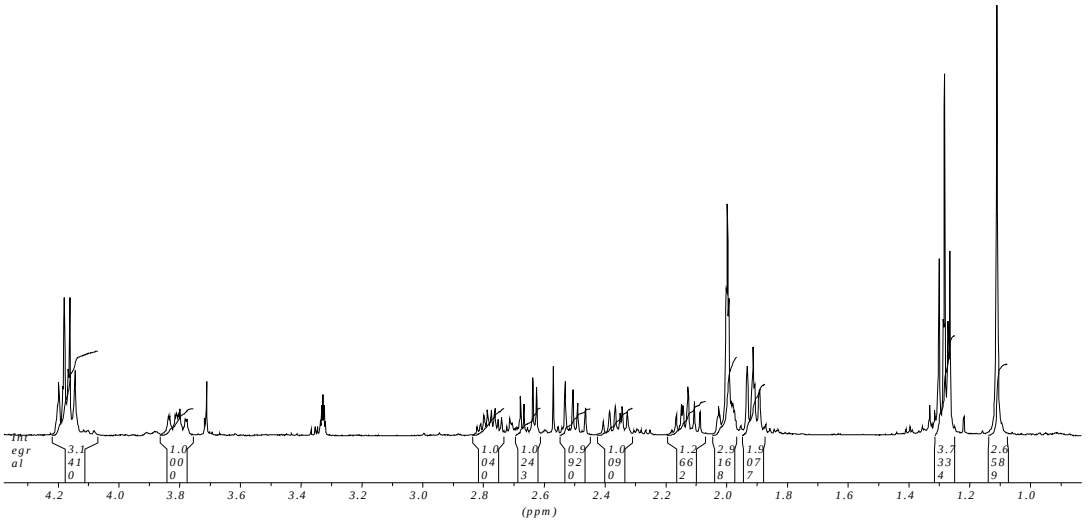


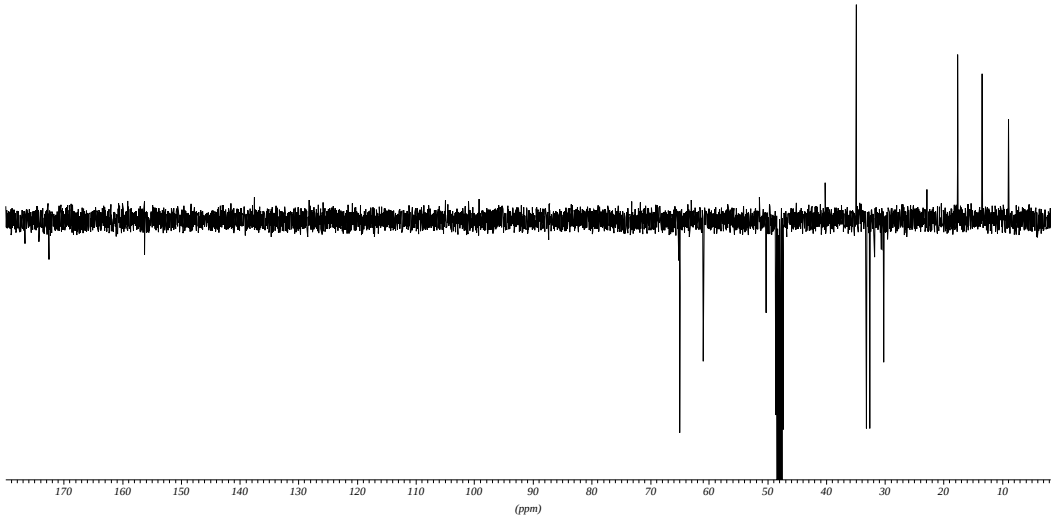
To a solution of **17** (44 mg, 0.073 mmol) in dry methanol (2 ml) were added ammonium formate (126 mg, 2 mmol) and Pd/C (10%, 15 mg). The reaction mixture was stirred overnight at room temperature. Then it was filtered through a pad of Celite, which was thoroughly washed with methanol. The solvent was removed under vacuum to yield **19** (32 mg, 0.063 mmol, 87 %) as colorless oil without further purification.

^{1}H-NMR (CD_3OD, 400 MHz): δ [ppm] = 4.19 (q, *J* = 7.2 Hz, 2H), 4.17 (m, 1H), 3.83 (ddd, *J* = 13.6 Hz, 8.9 Hz, 2.0 Hz, 1H), 2.80 (ddd, *J* = 18.9 Hz, 8.8 Hz, 4.7 Hz, 1H), 2.67 (dd, *J* = 4.6 Hz, 16.4 Hz, 1H), 2.52 (dd, *J* = 10.1 Hz, 16.4 Hz, 1H), 2.39 (ddd, *J* = 6.8 Hz, 16.0 Hz, 9.2 Hz, 1H), 2.15 (ddd, *J* = 15.5 Hz, 8.8 Hz, 7.0 Hz, 1H), 2.02 (t, *J* = 1.8 Hz, 3H), 1.93 (m, 2H), 1.30

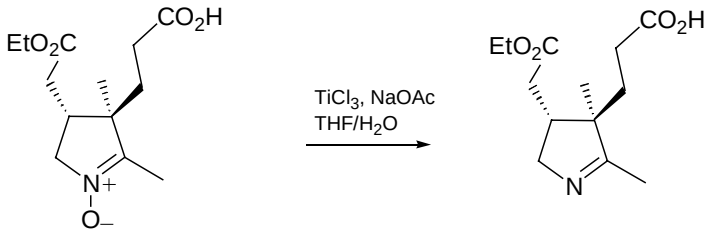
(t, *J* = 7.2 Hz, 3H), 1.13 (s, 3H); **^{13}C-NMR (CD_3OD, 100.6 MHz):** δ [ppm] = 177.6, 173.6, 157.2, 66.2, 62.0, 51.3, 36.2, 34.2, 33.6, 31.2, 18.6, 14.5, 10.0; **MS (MALDI, 5787 mV, 10% TFA/MeOH):** *m/z* = 294.3 (20%, $M+Na^+$), 295.3 (12%, $M+Na+H^+$), 272.2 ($M+H^+$, 62%), 271.3 (100%, M^+), 255.3 (19%, $M-O^+$); **MS (EI, 70 eV, 200 °C):** *m/z* = 272.2 (15%, $M+H^+$), 271.2 (11%, M^+), 227.1 (12%, $M^+-C_2H_5O$), 201.1 (16%), 200.1 (62%), 199.1 (100%); **IR (neat):** ν_{max} = 3168, 2970, 1729, 1632, 1566, 1399, 1303, 1197, 1123, 1025, 903, 817, 738, 610; $[\alpha]_D^{20}$ = + 39.7° (c = 1.6, MeOH) (mixture of diastereomeres)

^{1}H- and ^{13}C-NMR of crude **19** as a mixture of diastereomeres



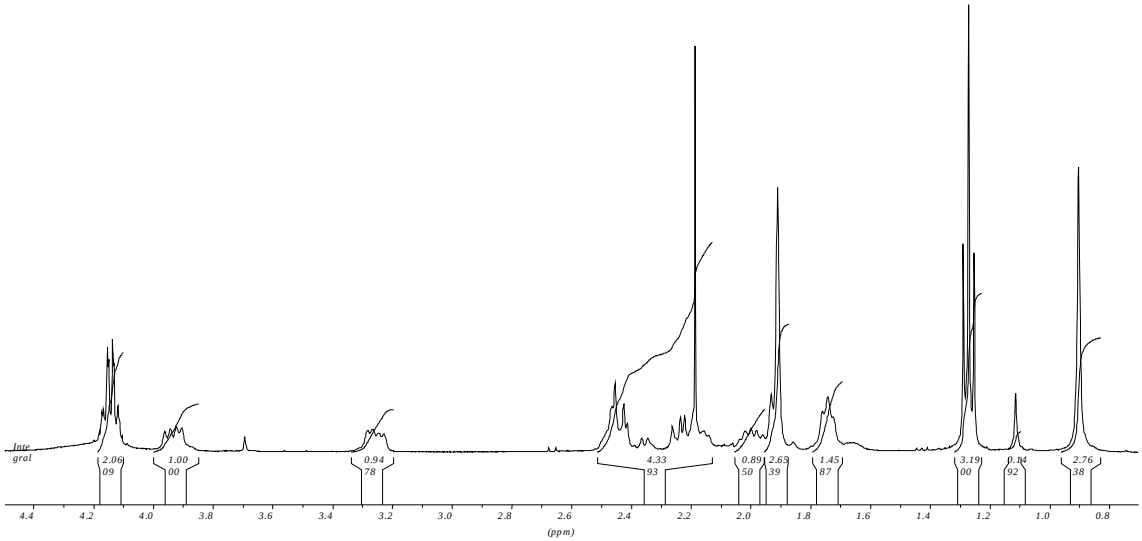


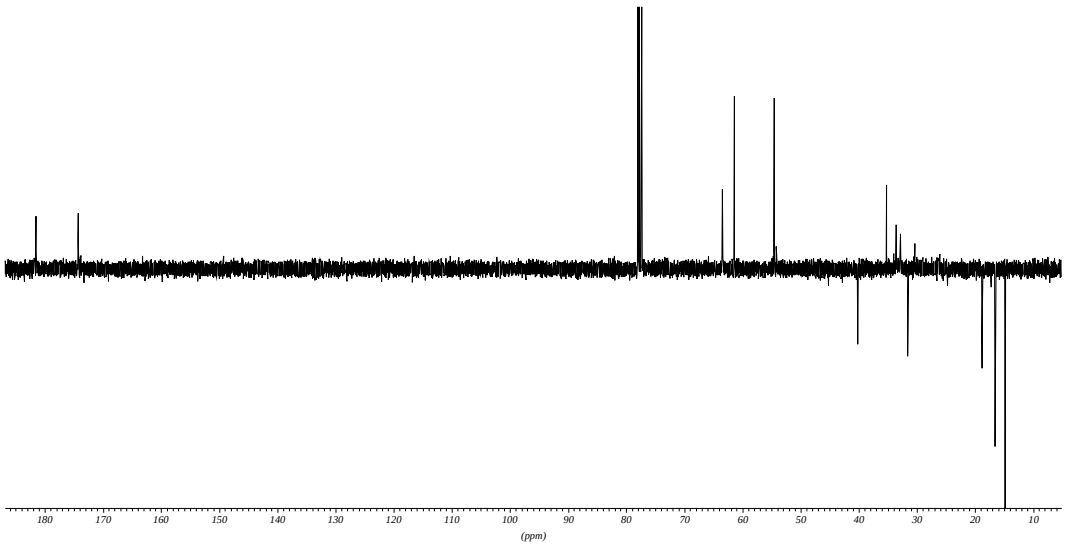
(3*R*,4*R*)- 3-(4-Ethoxycarbonylmethyl-2,3-dimethyl-4,5-dihydro-3H-pyrrol-3-yl)-propionic acid (5a)



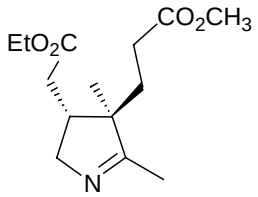
To a solution of nitrone **19** (32 mg, 0.12 mmol) in THF (2 ml) a puffered solution of $TiCl_3$ in water (0.5 M, NaOAc, 1.0 ml water) was added under inert atmosphere. The reaction mixture was stirred at room temperature for four hours and was then diluted with methylene chloride (4 ml) and filtered through a pad of Celtite. The Celite pad was washed thoroughly with methylene chloride and the organic solution was washed with saturated aqueous sodium hydrocarbonate solution (2 x 2 ml). Then the aqueous phase was re-extracted with methylene chloride (3 x 5 ml), the combined organic solutions were dried over magnesium sulfate and the solvent removed *in vacuo*. The residue was purified by flash chromatography (methylene chloride/aceton (3:1) -> methanol) to yield **5a** (20 mg, 0.78 mmol, 65 %) and the diastereomeres were separated by chiral HPLC (Chiracel (OD-H, 0.46 cm ID x 25 cm, 5 µm), 5% *i*-propanol/hexane; 1 ml/min; UV = 254 nm, RI, 7.5 min (major), 8.0 min (minor).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ [ppm] = 4.12 (q, *J* = 6.9 Hz, 2H), 3.91 (dd, *J* = 15.1 Hz, 7.5 Hz, 1H), 3.24 (dd, *J* = 15.0 Hz, 6.8 Hz, 1H), 2.42 (dd, *J* = 16.2 Hz, 4.3 Hz, 2H), 2.21, (dd, *J* = 17.1 Hz, 11.5 Hz, 1H), 2.15 (m, 1H), 1.98 (m, 1H), 1.89 (s, 3H), 1.74 (t, *J* = 7.25 Hz, 2H), 1.25 (t, *J* = 7.25 Hz, 3H), 0.88 (s, 3H); **^{13}C-NMR ($CDCl_3$, 100.6 MHz):** δ [ppm] = 180.8, 173.6, 173.1, 62.8, 60.7, 53.9, 39.5, 34.6, 32.9, 32.0, 18.1, 15.9, 14.2; **MS (EI, 70 eV, 150 °C):** *m/z* = 255.1 (2%, M^+), 210.1 (21%, M^+ C_2H_5O), 150.1 (54%), 140.1 (30%), 122.0 (37%), 55.0 (100%); **HRMS (EI, 70 eV, 120 °C):** calc.: *m/z* = 255.1471 (M^+); found: *m/z* = 255.1461 ± 0.0013 (M^+); **IR (neat):** ν_{max} = = 3168, 2970, 1729, 1632, 1566, 1399, 1303, 1197, 1123, 1025, 903, 817, 738, 610; $[\alpha]_D^{20}$ = + 49.8° (c = 0.17, $CHCl_3$).





(3*R*,4*R*)- 3-(4-Ethoxycarbonylmethyl-2,3-dimethyl-4,5-dihydro-3H-pyrrol-3-yl)-propionic acid methyl ester (5b)



To a solution of **5a** in diethyl ether was added a solution of diazo methane (1M in diethyl ether) until the solution stayed yellow. The reaction mixture was stirred for one hour before a couple drops of diluted acetic acid were added. The mixture was then washed with a saturated aqueous sodium hydrocarbonate solution, the aqueous layer washed three times with diethyl ether, dried over magnesium sulfate and the solvents removed *in vacuo*.