Asymmetric Synthesis of Substituted Homotropinones from *N*-Sulfinyl β-Amino Ketone Ketals. (-)-Euphococcinine and (-)-Adaline

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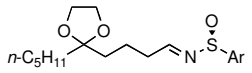
Experimental

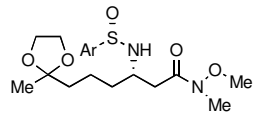
General Information: All reagents were used as received unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM), and toluene were purified by filtration on a Glass Contour Seca solvent purification system. Unless otherwise mentioned, all reactions were carried under argon atmosphere. Column chromatography was performed on silica gel, Merck grade 60 (230-400 mesh). TLC plates were visualized with UV, in an iodine chamber, or with phosphomolybdic acid, unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500, a Bruker 400 and Varian 300 MHz NMR spectrometers. Diastereomeric ratios (drs) are determined by the integration of H_4 and NH proton in the ^{1}H NMR spectra.

Comment [FD1]:

(*S*)-(+)-*N*-[5,5-(Ethylenedioxy)hexanylidene]-*p*-toluenesulfinamide (4) was prepared according to the literature procedure.[1]



(*S*)-(+)-*N*-[4-(2-Pentyl-1,3-dioxolan-2-yl)hexanylidene]-*p*-toluenesulfinamide (5). In an oven-dried, 50 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed 4-(2-pentyl-1,3-dioxolan-2-yl)butanal (**v**, see below for the synthesis of this ketal aldehyde) (1.310 g, 6.1 mmol) and (*S*)-(+)-*p*-toluenesulfinamide (1.138 g, 7.3 mmol) in dry DCM (12 mL). The reaction mixture was stirred for 15 min at rt and $Ti(OEt)_4$ (9.0 mL, 42.8 mmol) was added *via* syringe. The reaction mixture was stirred at rt for 24 h, diluted with DCM (20 mL), cooled to 0 °C, and then quenched with ice water (2 mL). After stirring for 10 min, the solids were filtered through Celite and the filter cake was washed with DCM (20 mL). The organic phase was washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (10-20% EtOAc/hexanes) afforded 0.245 g (19%) of starting material and 1.192 g (56%) of an oil at R_f = 0.30 (EtOAc/hexanes, 1:4); $[\alpha]^{20}_D$ +207.1 (*c* 0.86, $CHCl_3$); IR (neat) 1621 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.19 (t, *J* = 4.7 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 3.86 (m, 4H), 2.47 (m, 2H), 2.36 (s, 3H), 1.59 (m, 6H), 1.26 (m, 6H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.7, 141.7, 141.4, 129.6, 124.4, 111.3, 64.8, 37.0, 36.1, 35.8, 32.0, 23.4, 22.5, 21.3, 19.6, 13.9. HRMS calcd for $C_{19}H_{30}NO_3S$ (M + H) 352.1941. Found 352.1948.



Typical procedure for the preparation of *N*-sulfinyl β-amino Weinreb amides. (*S*$_S$,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-7,7 (ethylenedioxy)octamide (7). In a 100 mL, flame-dried, single-neck round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed KHMDS (5.41 ml of a 0.5 M solution in toluene, 2.708 mmol, Aldrich) in Et_2O (30 mL) under argon. The solution was cooled to -78 °C and *N*-methoxy-*N*-methyl acetamide (0.270 mL, 2.539 mmol, Aldrich) was added dropwise, and the solution was stirred at this temperature for 1 h. At this time, a pre-cooled solution of sulfinimine (+)-**4** (0.500 g, 1.693 mmol) in Et_2O (12.5 mL) was added *via* cannula, the solution was stirred

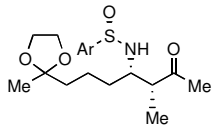
for 2 h, and quenched at -78 °C by addition of saturated aqueous NH_4Cl (20 mL). After warming to rt the solution was poured into H_2O (20 mL) and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc/hexanes, 4:1) gave 0.493 g (73%) of a clear viscous oil at R_f = 0.22 (EtOAc); 96:4 ratio of inseparable diastereoisomers; $[\alpha]^{20}_D$ +91.2 (*c* 1.04, $CHCl_3$); IR (neat) 3227, 1649 cm^{-1}; major diastereoisomer ^1H NMR ($CDCl_3$) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 4.95 (d, *J* = 9.2 Hz, 1H), 3.93 (m, 4H), 3.69 (m, 1H), 3.65 (s, 3H), 3.14 (s, 3H), 2.78 (m, 2H), 2.40 (s, 3H), 1.63 (m, 6H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.2, 142.7, 141.0, 129.4, 125.5, 109.9, 64.6, 61.2, 53.1, 38.6, 37.5, 35.7, 31.8, 23.7, 21.2, 20.7. HRMS calcd for $C_{19}H_{30}N_2O_5NaS$ (M + Na) 421.1768. Found 421.1772.

(*S*S,2*R*,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*,2-dimethyl-7,7-(ethylenedioxy)octamide (8). In a 25 mL, flame-dried, single-neck round-bottomed flask equipped with a magnetic stirring bar, and rubber septum was placed LiHMDS (3.15 mL, 3.148 mmol, 1.0 M solution in THF, Aldrich) under argon. A solution of *N*-methoxy-*N*-methylpropylamide (0.369 g, 3.148 mmol) in THF (6 mL) was added at -78 °C *via* cannula, and the solution was stirred for 2 h at this temperature. To the reaction mixture was added a pre-cooled solution of sulfinimine (+)-**4** (0.465 g, 1.574 mmol) in THF (12 mL), the reaction was monitored for completion by TLC (typically less than 30 min), and quenched with sat. aqueous NH_4Cl (6 mL) at -78 °C. After warming to rt the solution was poured into H_2O (6 mL), extracted with EtOAc (3 x 30 mL), the combined organic phases were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc/hexanes, 4:1) gave 0.493 g (76%) of a clear viscous oil at R_f = 0.31 (EtOAc); 93:7 ratio of inseparable diastereoisomers; $[\alpha]^{20}_D$ +66.7 (*c* 1.20, $CHCl_3$); IR (neat) 1653 cm^{-1}; major diastereoisomer ^1H NMR ($CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.46 (d, *J* = 7.7 Hz, 1H), 3.92 (m, 4H), 3. 66 (s, 3H), 3.49 (m, 1H), 3.16 (m, 1H), 3.11 (s, 3H), 2.38 (s, 3H), 1.63 (m, 6H), 1.31 (s, 3H), 1.14 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.5, 142.8, 141.1, 129.4, 125.5, 109.9, 64.6, 61.4, 57.6, 39.3, 38.6, 32.8, 32.0, 23.8, 21.3, 20.7, 13.1. HRMS calcd for $C_{20}H_{33}N_2O_5S$ (M + H) 413.2105. Found 413.2097.

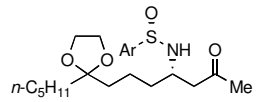
(*S*S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-3-amino-*N*-methoxy-*N*-methyl-6-(2-pentyl-1,3-dioxolan-2-yl)hexanamide (9). Flash chromatography (EtOAc/hexanes, 4:1) gave 0.753 g (71%) of a clear viscous oil at R_f = 0.45 (EtOAc); 95:5 ratio of inseparable diastereoisomers; $[\alpha]^{20}_D$ +81.2 (*c* 1.10, $CHCl_3$); IR (neat) 3472, 1658 cm^{-1}; major diastereoisomer ^1H NMR ($CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 4.94 (d, *J* = 9.1 Hz, 1H), 3.88 (s, 4H), 3.64 (m, 1H), 3.60 (s, 3H), 3.09 (s, 3H), 2.73 (m, 2H), 2.34 (s, 3H), 1.55 (m, 8H), 1.25 (m, 6H), 0.83 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 142.6, 140.9, 129.3, 125.4, 111.5, 64.8, 61.1, 53.1, 37.4 (br), 37.0, 36.4, 35.7, 32.0, 31.7 (br), 23.4, 22.5, 21.2, 20.4, 13.9. HRMS calcd for $C_{23}H_{38}N_2O_5NaS$ (M + Na) 477.2394. Found 477.2383.

(*S*S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-amino-8,8-(ethylenedioxy)-nonan-2-one (10). **Typical procedure.** In an oven-dried, 100 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (+)-**7** (0.402 g, 1.009 mmol) in

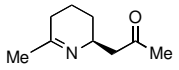
dry THF (32 mL). The solution was cooled to -78 °C, and methylmagnesium bromide (5.044 mmol, 1.68 mL of a 3.0 M solution in Et_2O, Aldrich) was added dropwise. The reaction mixture was warmed to 0 °C, stirred for 30 min, and quenched with saturated aqueous NH_4Cl (2 mL). At this time, H_2O (4 mL) was added, the aqueous layer was extracted with EtOAc (2 x10 mL), and the combined organic phases were dried ($MgSO_4$), and concentrated. Flash chromatography (EtOAc/hexanes, 4:1) gave 0.335 g (94%) of a clear oil at R_f = 0.34 (EtOAc); 25:1 ratio of inseparable diastereoisomers; $[\alpha]^{20}_D$ +57.9 (*c* 1.07, $CHCl_3$); IR (neat) 3206, 1704 cm^{-1}; major diastereoismer ^1H NMR ($CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 4.48 (d, *J* = 9.2 Hz), 3.90 (m, 4H), 3.63 (m, 1H), 2.74 (d, *J* = 5.6 Hz, 2H), 2.37 (s, 3H), 2.07 (s, 3H), 1.55 (m, 6H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 207.3, 142.4, 141.1, 129.4, 125.4, 109.8, 64.5, 52.4, 49.0, 38.5, 35.7, 30.7, 23.7, 21.2, 20.6. HRMS calcd for $C_{18}H_{27}NO_4NaS$ (M + Na) 376.1553. Found 376.1554.



(*S*S,3*R*,4*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-amino-3-methyl-8,8-(ethylenedioxy)-nonan-2-one (11). Flash chromatography (EtOAc/hexanes, 4:1) gave 93% of a clear oil at R_f = 0.50 (EtOAc); 14:1 ratio of inseparable diastereoisomers; $[\alpha]^{20}_D$ +81.4 (*c* 1.01, $CHCl_3$); IR (neat) 1707 cm^{-1}; major diastereoisomer ^1H NMR ($CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.31 (d, *J* = 8.7 Hz, 1H), 3.94 (m, 4H), 3.51 (m, 1H), 2.84 (m, 1H), 2.40 (s, 3H), 2.04 (s, 3H), 1.61 (m, 6H), 1.33 (s, 3H), 1.14 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 210.9, 142.2, 141.0, 129.2, 125.3, 109.6, 64.4, 56.8, 50.5, 38.4, 32.7, 28.9, 23.6, 21.1, 20.7, 12.2. HRMS calcd for $C_{19}H_{30}NO_4S$ (M + H) 368.1890. Found 368.1894.

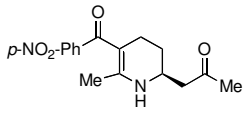


(*S*S,3*S*)-(+)-*N*-(*p*-Toluenesulfinyl)-4-amino-7-(2-pentyl-1,3-dioxolan-2-yl)heptan-2-one (12). Flash chromatography (10% EtOAc in hexanes) gave 95% of a clear oil at R_f = 0.57 (EtOAc/hexanes, 4:1); 22:1 ratio of inseparable diastereoisomers; $[\alpha]^{20}_D$ +68.2 (*c* 1.04, $CHCl_3$); IR (neat) 3468, 1712 cm^{-1}; major diastereoisomer ^1H NMR ($CDCl_3$) δ 7.51 (d, *J* = 7.5 Hz, 2H), 7.22 (d, *J* = 7.5 Hz, 2H), 4.51 (d, *J* = 9.3 Hz, 1H), 3.87 (s, 4H), 3.61 (m, 1H), 2.71 (m, 2H), 2.34 (s, 3H), 2.04 (s, 3H), 1.64-1.17 (m, 14H), 0.83 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 207.3, 142.3, 141.0, 129.3, 125.3, 111.4, 64.7, 52.3, 49.0, 37.0, 36.3, 35.7, 32.0, 30.6, 23.4, 22.5, 21.2, 20.3, 13.9. HRMS calcd for $C_{22}H_{36}NO_4S$ (M + H) 410.2360. Found 410.2362.



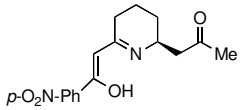
1-((*S*)-(-)-2,3,4,5-Tetrahydro-6-methylpyridin-2-yl)propan-2-one (13). In an oven-dried, 100 mL round-bottom flask equipped with a magnetic stirring bar, and rubber septum was placed amino ketone (+)-**10** (0.185 g, 0.523 mmol) in THF (26 mL) and MeOH (26 mL). The solution was cooled to 0 °C, and 3 N aqueous HCl was added slowly. The reaction mixture was warmed to rt, stirred for 15 h, concentrated, and the residue was dissolved in DCM (50 mL). The pH of the solution was adjusted to 8 by using saturated aqueous $NaHCO_3$, the phases were separated, and the aqueous phase was extracted with DCM (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (1% MeOH in DCM) gave 0.069 g (86%) of a clear oil at R_f = 0.23 (5% MeOH in DCM); $[\alpha]^{20}_D$ -41.9 (*c* 0.83 , $CHCl_3$); IR (neat) 1715, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (m, 1H), 2.76 (dd, *J* = 16.2, 6.0 Hz, 1H), 2.44 (dd, *J* = 16.0, 7.8 Hz, 1H), 2.15 (s, 3H), 2.05 (m, 2H), 1.86 (d, *J* = 1.9, 3H), 1.72 (m, 2H), 1.56 (m, 1H), 1.06

(m, 1H); ^{13}C NMR ($CDCl_3$) δ 208.1, 168.3, 54.2, 51.4, 30.7, 29.9, 27.4, 27.0, 18.6. HRMS calcd for $C_9H_{16}NO$ (M + H) 154.1226. Found 154.1231.

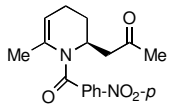


1-((*S*)-(+)-5-(*p*-Nitrobenzoyl)-1,2,3,4-tetrahydro-6-methylpyridin-2-yl)propan-2-one (14). In an oven-dried, 10 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed *p*-nitrobenzoyl chloride (0.021 g, 0.115 mmol) and DMAP (0.015 g, 0.125 mmol) in dry DCM (1.5 mL). The reaction mixture was cooled to 0 °C and a solution of (-)-**13** (0.016 g, 0.104 mmol) in dry DCM (1 mL) was added slowly at 0 °C. After stirring at 0 °C for 2 h, the solution was concentrated. Chromatography (EtOAc/hexanes/Et_3N, 80:20:1) gave 0.017 g (54%) of an orange solid (+)-**14** at R_f = 0.23 (EtOAc/hexanes/ Et_3N, 8:2:1 drop) and 0.013 g (41%) of orange colored oil (*S*)-(+)-**15** at R_f = 0.37 (EtOAc/hexanes/ Et_3N, 8:2:1 drop).

For (+)-**14**: Mp 159-160 °C; $[\alpha]^{20}_D$ +110.1 (*c* 1.02, $CHCl_3$); IR (neat) 3325, 1714 cm^{-1}; The NH proton in (+)-**14** at δ 5.40 disappeared on addition of D_2O; ^{1}H NMR (CD_2Cl_2) δ 8.20 (m, 2H), 7.54 (m, 2H), 5.40 (br s, 1H), 3.79 (m, 1H), 2.66 (m, 2H), 2.32 (m, 2H), 2.17 (s, 3H), 2.03 (s, 3H), 1.82 (m, 1H), 1.54 (m, 1H); ^{13}C NMR (CD_2Cl_2) δ 208.5, 192.2, 156.4, 150.9, 148.4, 128.5, 123.9, 102.1, 49.4, 47.8, 30.8, 27.5, 23.5, 23.3. HRMS calcd for $C_{16}H_{19}N_2O_4$ (M + H) 303.1339. Found 303.1341.

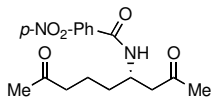


1-((*S*)-(-)-2,3,4,5-Tetrahydro-6-((*Z*)-2-hydroxy-2-(4-nitrophenyl)vinyl)pyridin-2-yl)propan-2-one (15). $[\alpha]^{20}_D$ -49.0 (*c* 1.12 , $CHCl_3$); IR (neat) 1713, 1590 cm^{-1}; The enolic proton disappeared upon the addition of D_2O; ^{1}H NMR (CD_2Cl_2) δ 11.9 (br s, 1H), 8.20 (m, 2H), 7.97 (m, 2H), 5.58 (s, 1H), 3.92 (m, 1H), 2.75 (d, *J* = 6.7 Hz, 2H), 2.51 (dd, *J* = 7.4, 5.1 Hz, 2 H), 2.20 (s, 3H), 2.00 (m, 1H), 1.84 (m, 1H), 1.72 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (CD_2Cl_2) δ 206.8, 183.9, 167.1, 149.2, 146.8, 128.2, 123.8, 91.1, 50.4, 47.9, 30.7, 29.5, 28.6, 18.9. HRMS calcd for $C_{16}H_{19}N_2O_4$ (M + H) 303.1339. Found 303.1340.



(*S*)-(-)-*N*-(*p*-Nitrobenzoyl)-2,3,4-trihydro-6-methylpyridin-2-yl)propan-2-one (16). In an oven-dried, 10 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed (-)-**13** (0.019 g, 0.124 mmol) in dry DCM (2 mL) and cooled to 0 °C. At this time NEt_3 (0.021 mL, 0.149 mmol) and *p*-nitrobenzoyl chloride (0.025 g, 0.136 mmol) in dry DCM (1 mL) were added slowly at 0 °C. After stirring at this temperature for 2 h, the solution was concentrated to give an oil. Chromatography (EtOAc/hexanes 2:1) gave 0.025 g (67%) of an orange oil consisting of (*S*)-(-)-**16** at R_f = 0.59 (EtOAc/hexanes, 3:2) and 0.009 g (23%) of an off-white solid (*S*)-(-)-**17** at R_f = 0.19 (EtOAc/hexanes, 3:2).

For (-)-**16**: $[\alpha]^{20}_D$ -181.6 (*c* 0.73, $CHCl_3$); IR (neat) 1712, 1633, 1601cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.25 (m, 2H), 7.68 (m, 2H), 5.17 (br, 1H), 4.95 (br, 1H), 2.74 (dd, *J* = 15.7, 6.8 Hz, 1H), 2.68 (dd, *J* = 15.7, 7.6 Hz, 1H), 2.24 (s, 3H), 2.18 (m, 1H), 2.12 (m, 1H), 1.98 (m, 1H), 1.85 (m, 1H), 1.63 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 206.4, 167.8, 148.7, 143.2, 132.6, 128.6, 123.7, 115.2, 49.1, 43.8, 30.4, 26.3, 23.1, 19.6. HRMS calcd for $C_{16}H_{19}N_2O_4$ (M + H) 303.1339. Found 303.1345.

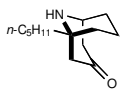


(*S*)-(-)-*N*-(*p*-Nitrobenzoyl)-4-aminononane-2,8-dione (17). Mp 118-119 °C; $[\alpha]^{20}_D$ -23.1 (*c* 0.30, $CHCl_3$); IR (neat) 3300, 1712, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.28 (m, 2H), 7.97 (m, 2H), 7.31 (d,

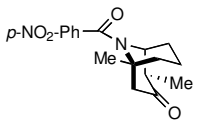
J = 8.0 Hz, 1H, NH), 4.34 (m, 1H), 2.92 (dd, J =17.6, 4.2 Hz, 1H), 2.75 (dd, J =17.5, 5.7 Hz, 1H), 2.51 (m, 2H), 2.20 (s, 3H), 2.14 (s, 3H), 1.64 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 208.9, 208.7, 164.9, 149.6, 139.9, 128.2, 123.8, 46.9, 46.3, 42.7, 33.0, 30.9, 30.1, 19.9. HRMS calcd for $C_{16}H_{21}N_2O_5$ (M + H) 321.1445. Found 321.1447.

(1*R*,5*S*)-(-)-1-Methyl-9-azabicyclo[3.3.1]nonan-3-one (2) from (-)-13. In an oven-dried, 25 mL round-bottom flask equipped with a magnetic stirring bar and rubber septum was placed (-)-**13** (0.0220 g, 0.144 mmol) in EtOH (5 mL) and AcOH (5 mL). To the reaction mixture was added NH_4OAc (0.2770 g, 3.590 mmol) and the solution was stirred at 75 °C (oil bath) for 36 h. The reaction mixture was cooled to rt and concentrated to removed EtOH and DCM (10 mL) was added. The solution was washed with saturated aqueous Na_2CO_3 until the aqueous phase reached pH 8. The organic phase was separated, the aqueous phase was extracted with DCM (2 x10 mL), and the combined organic phases were dried ($MgSO_4$), and concentrated. Flash chromatography (5% MeOH/DCM) gave 0.0205 g (93%) of (1*R*,5*S*)-(-)-**2** as an off-white solid.

From *N*-sulfinyl β-amino ketal (+)-10. **Typical procedure.** In an oven-dried, 50 mL round-bottom flask equipped with a magnetic stirring bar and rubber septum was placed (+)-**10** (0.105 g, 0.297 mmol) in EtOH (13 mL) and AcOH (13 mL). To the reaction mixture was added NH_4OAc (0.573 g, 7.426 mmol) and the solution was stirred at 75 °C (oil bath) for 36 h. The reaction mixture was cooled to rt and concentrated to removed EtOH and DCM (75 mL) was added. The solution was washed with saturated aqueous Na_2CO_3 until the aqueous phase reached pH 8. The organic phase was separated, the aqueous phase was extracted with DCM (2 x 25 mL), and the combined organic phases were dried ($MgSO_4$), and concentrated. Flash chromatography (5% MeOH/DCM) gave 0.041 g (90%), R_f = 0.18 (5% MeOH in DCM) of an off-white low melting solid, mp 31-32 °C, [lit.[2] mp 32 °C]; $[\alpha]^{20}_D$ -6.4 (*c* 0.83, MeOH); [lit[2] $[\alpha]^{20}_D$ -6.5 (*c* 1.80, MeOH)]. Spectral properties were identical to literature values.[2]

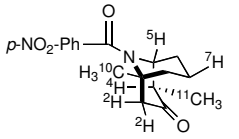


(1*R*,5*S*)-(-)-Adaline (3). Flash chromatography (1-2% MeOH in DCM) gave 0.051 g (85%) as an oil at R_f = 0.30 (4% MeOH in DCM), $[\alpha]^{20}_D$ -12.6 (*c* 0.85, $CHCl_3$) [lit.[3] $[\alpha]^{20}_D$ -13 ($CHCl_3$)]. Spectral data were identical to literature values.[2]



(1*R*,4*R*,5*S*)-(-)-*N*-(*p*-Nitrobenzoyl)-1,4-dimethyl-9-azabicyclo[3.3.1]nonan-3-one (19). Flash chromatography (5% MeOH/DCM) gave homotropinone **18** with an unknown impurity, which was converted into its *N*-*p*-nitrobenzoate amide for purification. In an oven-dried, 10 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed crude **18** in dry DCM (3 mL). The reaction mixture was cooled to 0 °C and Et_3N (0.2 mL, 1.429 mmol) was added followed by a solution of *p*-nitrobenzoyl chloride (0.058 g, 0.314 mmol) in dry DCM (3 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for 4 h at rt and concentrated. Chromatography (EtOAc/hexanes, 2:3) gave 0.074 g (82%) of an off-white solid mp 152-153 °C, at R_f = 0.56 (EtOAc/hexanes, 2:3); $[\alpha]^{20}_D$ -11.2 (*c* 1.11, $CHCl_3$); IR (neat) 1714, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.28 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 4.00 (m, 1H), 2.93 (d, J = 16.0, 1H), 2.47 (m, 1H), 2.41 (d, J = 16.0 Hz, 1H), 1.93 (m, 1H), 1.80 (m, 1H), 1.72 (s, 3H), 1.65 (m, 3H), 1.39 (m, 1H), 0.95(d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 209.8, 171.7, 148.9, 143.4, 128.3, 124.1, 59.3, 58.7, 51.6, 47.2, 39.1,

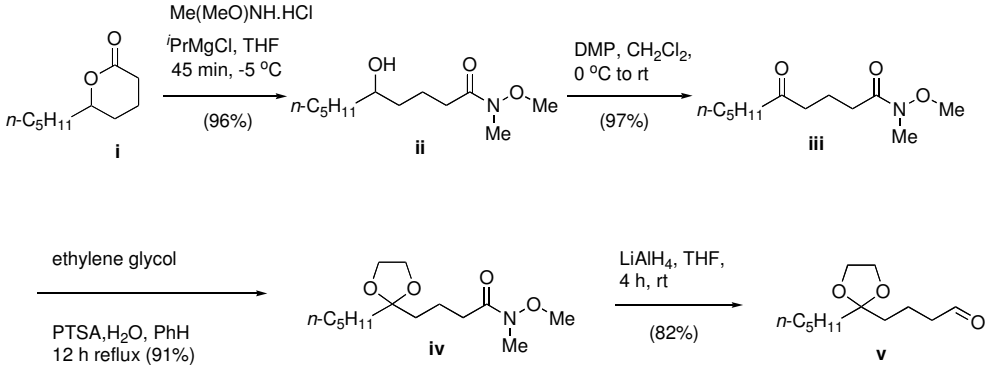
29.6, 25.3, 17.4, 11.2; HRMS calcd for $C_{17}H_{21}N_2O_4$ (M + H) 317.1501. Found 317.1509.

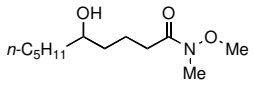


(1*R*,4*R*,5*S*)-(-)-**19**

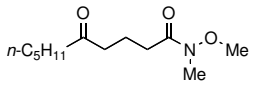
COSY and NOE studies confirm the stereochemistry at C-4 position. On irradiation of C-11 protons at δ 0.95 see C-5 proton at δ 4.00 and C-7 proton at δ 1.80. On irradiation of C-4 proton at δ 2.47 see aromatic protons at δ 7.72 and vice-versa. On irradiation of C-11 protons at δ 0.95 do not see C-2 protons at δ 2.93 and δ 2.41 and vice-versa.

4-(2-Pentyl-1,3-dioxolan-2-yl)butanal (v) was prepared according to the following scheme.



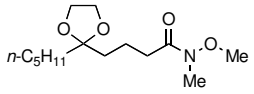


5-Hydroxy-*N*-methoxy-*N*-methyldecanamide (ii). In an oven-dried, 250 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed 5-decanolide **i** (5.00 g, 29.3 mmol, Aldrich) and Me(MeO)NH.HCl (4.44 g, 45.5 mmol, Aldrich) in dry THF (60 mL). The solution was cooled to -30 °C and ^{i}PrMgCl (88.1 mmol, 2.0 M solution in THF, Aldrich) was added slowly over 30 min *via* syringe keeping the temperature below -10 °C. The reaction mixture was maintained for 45 min at -5 °C and quenched with 20 wt% aqueous NH_4Cl. The solution was extracted with EtOAc (2 x 50 mL), the combined organic phases were dried (Na_2SO_4), and concentrated. Flash chromatography (30-40% EtOAc in hexanes) afforded 6.52 g (96%) of a colorless oil at R_f = 0.16 (EtOAc/hexanes, 2:3): IR (neat) 3435, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H), 3.50 (m, 1H), 3.10 (s, 3H), 2.59 (br, 1H), 2.38 (m, 2H), 1.67 (m, 2H), 1.37 (m, 5H), 1.22 (m, 5H), 0.80 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 70.9, 61.0, 37.2, 36.9, 32.0, 31.8, 31.4, 25.2, 22.5, 20.3, 13.9. HRMS calcd for $C_{12}H_{26}NO_3$ (M + H) 232.1907. Found 232.1911.

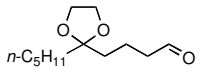


***N*-Methoxy-*N*-methyl-5-oxodecanamide (iii)**. In an oven-dried, 500 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed Dess-Martin Periodinane (DMP) (13.31 g, 31.4 mmol) in dry DCM (225 mL). The solution was cooled to 0 °C and a solution of **ii** (6.05 g, 26.2 mmol) in DCM (25 mL) was added slowly *via* syringe. The reaction mixture was warmed to rt and monitored for completion by TLC (typically 2 h). At this time the reaction was quenched with a 1:1 sat. solution of $NaHCO_3$:$Na_2S_2O_3$ (100 mL). The organic layer was separated, washed with a 1:1 sat.

solution of $NaHCO_3$:$Na_2S_2O_3$ (2 x 50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (40% EtOAc in hexanes) afforded 5.82 g (97%) as a clear viscous oil at R_f = 0.35 (EtOAc/hexanes, 2:3): IR (neat) 1711, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.60 (s, 3H), 3.09 (s, 3H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.37 (m, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.82 (m, 2H), 1.48 (m, 2H), 1.20 (m, 4H), 0.80 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 210.7, 173.8 (br), 61.0, 42.6, 41.6, 31.9, 31.2, 30.7, 23.3, 22.3, 18.5, 13.7. HRMS calcd for $C_{12}H_{24}NO_3$ (M + H) 230. 1751. Found 230.1753.



***N*-Methoxy-*N*-methyl-4-(2-pentyl-1,3-dioxolan-2-yl)butanamide (iv)**. In an oven-dried, 100 mL round-bottom flask equipped with a magnetic stirring bar was placed **iii** (5.15 g, 22.5 mmol) in benzene (50 mL), ethylene glycol (1.75 mL, 31.4 mmol) and *p*-toluenesulfonic acid (0.21 g, 1.1 mmol) were added. The reaction mixture was refluxed for 18 h with water being removed using Dean-Stark apparatus. At this time the reaction mixture was diluted with benzene (50 mL), washed with sat. aqueous $NaHCO_3$ solution (2 x 20 mL), brine (15 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (30% EtOAc in hexanes) afforded 5.58 g (91%) as a clear viscous oil at R_f = 0.36 (EtOAc/hexanes, 2:3): IR (neat) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89 (s, 4H), 3.63 (s, 3H), 3.13 (s, 3H), 2.39 (m, 2H), 1.61 (m, 6H), 1.26 (m, 6H), 0.84 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.3 (br), 111.5, 64.8, 61.1, 37.1, 36.4, 32.0, 31.8 (br), 23.4, 22.5, 18.9, 13.9. (One carbon imbedded). HRMS calcd for $C_{14}H_{28}NO_4$ (M + H) 274.2013. Found 274.2020.



4-(2-Pentyl-1,3-dioxolan-2-yl)butanal (v). In an oven-dried, 50 mL round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon inlet was placed $LiAlH_4$ (1.03 g, 27.2 mmol) in dry THF (25 mL). The solution was cooled to 0 °C and **iv** (4.95 g, 18.1 mmol) in dry THF (12 mL) was added slowly *via* syringe. The reaction mixture was warmed to rt and monitored for completion by TLC (typically 4 h). At this time the reaction was quenched with H_2O (1 mL), 10% aqueous NaOH (2 mL), and H_2O (3 mL). The solution was stirred for 1 h at rt and the precipitated salts were filtered through the Celite and the filter cake was washed with Et_2O (25 mL). Chromatography (10-15% EtOAc in hexanes) afforded 3.18 g (82%) of a colorless oil at R_f = 0.38 (EtOAc/hexanes, 1:4); IR (neat) 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.70 (t, *J* = 1.7 Hz, 1H), 3.87 (s, 4H), 2.41 (dd, *J* = 7.2, 1.7 Hz, 1H), 2.39 (dd, *J* = 7.2, 1.7 Hz, 1H), 1.58 (m, 6H), 1.25 (m, 6H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 210.7, 104.1, 64.7, 42.6, 42.1, 33.0, 31.2, 23.4, 22.3, 18.1, 13.8. HRMS calcd for $C_{12}H_{23}O_3$ (M + H) 215.1647. Found 215.1651.

References

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2. Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211.
3. Tursch, B.; Chome, C.; Braekman, J.-C.; Daloze, D. *Bull. Soc. Chim. Belg.* **1973**, *82*, 699.