Supplementary Material (ESI) for Chemical Communications

Application of Furyl-Stabilized Sulfur Ylides to a Concise Synthesis of 8a-*epi*-Swainsonine

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Supporting Information

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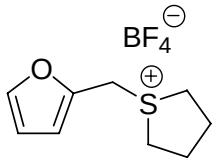
General

All reactions were performed in dry glassware under an inert atmosphere of nitrogen unless indicated otherwise. Reactions mixtures were stirred magnetically. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula into the reaction vessels through rubber septa. Yields quoted refer to isolated yields unless otherwise stated. Chromatography: Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254}, 230-400 mesh). TLC was performed on aluminium-backed silica plates (60 F_{254}, 0.2 mm) which were developed using standard visualising agents: UV fluorescence (254 and 366 nm), phosphomolybdic acid/Δ, *para*-anisaldehyde/Δ, potassium permanganate/Δ, and ninhydrin/Δ. Melting points were determined on a Kofler hot stage microscope, and are uncorrected. Infrared spectra were recorded neat on a Perkin-Elmer Spectrum One FT-IR spectrometer. Only selected absorbencies (υ_{max}) are reported in wavenumbers (cm^{-1}). ^{1}H NMR spectra were recorded at 270 MHz on a Jeol Delta GX/270 spectrometer, or at 400 MHz on Jeol Delta GX/400 or Jeol ECP/400 spectrometers. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to internal tetramethylsilane (TMS), and coupling constants (*J* values) are reported to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 101 MHz on Jeol DeltaGX/400 or Jeol ECP/400 spectrometers, separately. Chemical shifts (δ_C) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak and are assigned as C, CH, CH_2, CH_3. Low resolution EI and CI mass spectra (*m/z*) were recorded on a Micromass Analytical Autospec spectrometer with only molecular ions M^+ and major peaks being reported with intensities quoted as percentages of the base peak. High-resolution EI and CI mass spectra were recorded on a Micromass Analytical Autospec spectrometer. Low and high resolution ESI mass spectra were recorded on a 7 Tesla Apex 4 Bruker Daltonics spectrometer, with samples run at 0.1 mg/mL in 50/50 CH_2Cl_2/MeOH. GC-MS were performed using an Agilent 6890 apparatus and the following conditions, column: HP190915-433 HP-5MS (5%-Phenyl)-methylpolysiloxane, capillary 30m × 0.25mm × 0.25mm nominal, carrier gas: helium 1 ml/min (constant flow mode), injector: 250 ºC (splitless mode), detector: Agilent MSD 5973 (EI mode), oven: 70 ºC (3 min), 15 ºC/min (15.3 min), 300 ºC (8 min). Elemental analysis was performed on a Carlo Erba EA1108 or a Perkin Elmer 2400 CHN elemental

analyser. Optical rotations were recorded on an ADP220 Bellingham & Stanley polarimeter, concentrations (*c*) are reported in g of substance dissolved per 100 ml of solvent. All chemicals were purchased from Aldrich, Fluka, Lancaster or Strem. Anhydrous THF, CH_2Cl_2, hexane, Et_2O, acetonitrile and toluene were obtained from a purification column composed of activated alumina (A-2). For toluene, hexane, and CH_2Cl_2 a supported copper catalyst (Q-5 reagent) was also employed. Other anhydrous solvents were used as obtained from Aldrich, Lancaster or Fluka, and dried for 24 h over activated 4 Å MS.

1. Synthesis of Sulfonium Salts

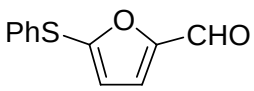
1-(2-Furylmethyl)tetrahydrothiophenium tetrafluoroborate.



2c

Aqueous hexafluoroboric acid (48% by weight, 0.92 g, 5.0 mmol) was slowly added to tetrahydrothiophene (0.44 ml, 5.0 mmol) in 3 ml of Et_2O at 0 °C. The mixture was then slowly transferred to a solution of furfuryl alcohol (0.54 g, 5.5 mmol) and tetrahydrothiophene (0.44 ml, 5.0 mmol) in 10 ml of Et_2O at 0 °C. After 1 h, the reaction mixture was dissolved in 10 ml of dichloromethane, dried over magnesium sulfate, filtered and concentrated under vacuum. Flash column chromatography, eluting with 1:9 MeOH-CH_2Cl_2, gave the sulfonium salt (0.13 g, 10%) as green cubes (very unstable compound that decomposes quickly at room temperature), R_f(MeOH-CH_2Cl_2, 1:9) 0.40; δ_H(400 MHz, d_6-DMSO) 1.88-1.98 (2H, m, 2CH*H*CH_2S), 2.02-2.13 (2H, m, 2C*H*HCH$_2$S), 3.35 (2H, pent, *J* 6.0 Hz, 2CH$_2$C*H*HS), 3.52 (2H, pent, *J* 6.0 Hz, 2CH$_2$CH*H*S), 4.70 (2H, s, CCH$_2$S), 6.57 (1H, d, *J* 3.4 Hz, furyl*H*), 6.76 (1H, dd, *J* 3.4 Hz, 1.0 Hz, furyl*H*), 7.83 (1H, d, *J* 1.0 Hz, furyl*H*); δ_C(100 MHz, d_6-DMSO) 28.4 (CH_2), 38.4 (CH_2), 42.8 (CH_2), 112.0 (CH), 113.9 (CH), 142.6 (CH), 145.8 (C).

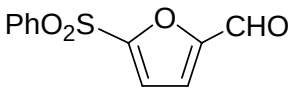
5-(Phenylsulfonyl)-2-furaldehyde.



Sodium pieces (6.23 g, 0.270 mol) were dropped slowly to a 500 ml round bottom flask charged with 200 ml of anhydrous methanol with a rapid stirring and a cooling ice bath. After the metal was dissolved, thiophenol (25.9 ml, 0.250 mol) was added in one portion. After 10 min the resulting solution was concentrated under vacuum to dryness, and 300 ml of anhydrous THF added. To the resulting white suspension was introduced via cannula a solution of

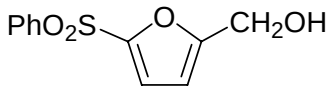
5-nitro-2-furaldehyde (31.8 g, 0.220 mol) in 200 ml of anhydrous THF, with rapid stirring and cooling ice bath. The reaction mixture was allowed to stay at room temperature for 6 h and then concentrated under vacuum. Water (1 L) was added and the suspension was extracted with CH_2Cl_2 (2×1 L), dried over anhydrous magnesium sulfate, and concentrated under vacuum. High-vacuum distillation gave the aldehyde (38.6 g, 90 %) as orange needles, bp 138-140°C (0.1 mmHg); R_f(EtOAc-petroleum, 1:9) 0.35; υ_{max} (film)/cm^{-1} 2838 and 2790 (OC-H), 1668 (C=O); δ_H(400 MHz, $CDCl_3$) 6.58 (1H, d, *J* 3.6 Hz, furyl*H*), 7.22 (1H, d, *J* 3.6 Hz, furyl*H*), 7.29-7.37 (3H, m, Ar$H^{\mathbf{meta\&para}}$), 7.38-7.45 (2H, m, Ar$H^{\mathbf{ortho}}$), 9.58 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 117.2 (CH), 121.8 (CH), 128.4 (CH), 129.6 (CH), 131.2 (CH), 131.9 (C), 154.0 (C), 154.7 (C). 177.1 (CH); *m*/*z* (EI) 204 (M^+, 100), 175 (33), 147 (95), 109 (17), 77 (38); HRMS (EI) Found: MH^+, 205.0326; $C_{11}H_9O_2S$ requires MH^+, 205.0318.

(5-Phenylsulfonyl)-2-furfuraldehyde.



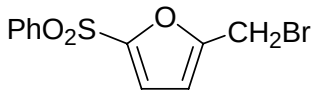
*m*CPBA (75% wt, 27.1 g, 110 mmol) was added in one portion to a solution of the aldehyde (10.2 g, 50.0 mmol) in 200 ml of CH_2Cl_2 with a cooling ice bath. The reaction mixture was then allowed to stand at room temperature for 24 hours. The resulting precipitate was filtered and the residue was washed several times with CH_2Cl_2. The filtrate was washed with saturated aqueous sodium bicarbonate solution (3 × 2 ml), dried over magnesium sulfate and concentrated under vacuum to yield the sulfonyl furfural (7.0 g, 60%) as pale yellow plates (which were directly used as the starting material for the next reduction step), mp 130-131 °C (petroleum-ether) [lit.,[248] 130 °C (petroleum)]; υ_{max} (film)/cm^{-1} 1690 (C=O), 1320 and 1150 (SO_2); δ_H(400 MHz, $CDCl_3$) 7.21 (1H, d, *J* 4.0 Hz, furyl-H), 7.30 (1H, d, *J* 4.0 Hz, furyl-H), 7.62-7.70 (3H, m, Ar$H^{\mathbf{para/meta}}$), 8.07 (2H, m, Ar$H^{\mathbf{ortho}}$), 9.82 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 118.1 (CH), 128.5 (CH), 129.8 (CH), 130.2 (CH), 131.9 (C), 134.5 (CH), 158.0 (C), 158.7 (C). 178.2 (CH); *m*/*z* (EI) 236 (M^+, 28), 125 (100), 97 (37), 77 (64); HRMS (ESI) Found: M+Na^+, 259.0044; $C_{11}H_8O_4S$ requires M+Na^+, 259.0036.

[5-(Phenylsulfonyl)-2-furyl]methanol.



*m*CPBA (75% wt, 100 g, 400 mmol) was added slowly to a solution of the aldehyde (37.0 g, 180 mmol) in 800 ml of CH_2Cl_2 at 0 °C. The reaction mixture was stirred at room temperature for 20 h. The resulting suspension was filtered and the residue was washed several times with CH_2Cl_2. The filtrate was washed subsequently with aqueous sodium metabisulphite (200 ml), aqueous bicarbonate (200 ml), and brine (200 ml) before dried over magnesium sulfate. After filtration and concentration, the crude product was purified by flash column chromatography, eluting with 1:1 EtOAc-petroleum, to give the alcohol (38.6 g, 90%) as pale yellow needles, mp 141-143°C (HOAc); R_f(EtOAc-petroleum, 1:1) 0.41; υ_{max} (film)/cm^{-1} 3427 (OH), 2940 (ArCH), 1328 and 1172 (SO_2); δ_H(400 MHz, $CDCl_3$) 4.61 (2H, s, CH_2), 6.42 (1H, d, *J* 3.5 Hz, furyl*H*), 7.17 (1H, d, *J* 3.5 Hz, furyl*H*), 7.52-7.68 (3H, m, Ar$H^{\mathbf{para/meta}}$), 7.98-8.01 (2H, m, Ar$H^{\mathbf{ortho}}$); δ_C(100 MHz, d_6-DMSO) 57.4 (CH_2), 109.2 (CH), 118.4 (CH), 127.8 (CH), 129.3 (CH), 133.8 (CH), 139.8 (C), 149.0 (C), 159.8 (C); *m*/*z* (EI) 238 (M^+, 100), 125 (93), 97 (77), 77 (80); HRMS (ESI) Found: M+Na^+, 261.0199; $C_{11}H_{10}O_4S$ requires M+Na^+, 261.0192.

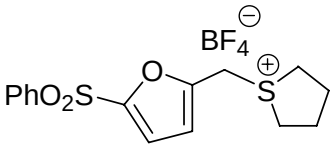
2-(Bromomethyl)-5-(phenylsulfonyl)furan.



Dimethyl sulfide (15.5 g, 249 mmol) was added dropwise to a cooled suspension of *N*-bromosuccinimide (37.0 g, 207 mmol) in 500 ml of CH_2Cl_2 at 0 °C. After 10 min a solution of the alcohol (33.0 g, 138 mmol) in 300 ml of CH_2Cl_2 was introduced via cannula. The reaction mixture was then allowed to stand at room temperature for 6 h before concentrated to dryness. The residue was dissolved in Et_2O (1 L) and washed with water (200 ml) and brine (200 ml). After drying over anhydrous sodium sulfate and concentrating under vacuum, the crude product was purified by flash column chromatography, eluting with 3:7

EtOAc-petroleum, to give the *bromide* (37.0 g, 90%) as light yellow cubes, mp 74-75 °C dec. (Et_2O), R_f(EtOAc-petroleum, 1:4) 0.30; υ_{max} (film)/cm^{-1} 3048 (ArCH), 1326 and 1168 (SO_2); δ_H(400 MHz, $CDCl_3$) 4.39 (2H, s, CH_2), 6.48 (1H, d, *J* 3.5 Hz, furyl*H*), 7.13 (1H, d, *J* 3.5 Hz, furyl*H*), 7.52-7.70 (3H, m, Ar$H^{\mathbf{para/meta}}$), 8.00 (2H, m, Ar$H^{\mathbf{ortho}}$); δ_C(100 MHz, $CDCl_3$), 21.3 (CH_2), 111.1 (CH), 118.4 (CH), 127.8 (CH), 129.4 (CH), 133.9 (CH), 139.6 (C), 149.9 (C), 155.6 (C); *m*/*z* (EI) 302 (M^+, Br^{81}, 6), 300 (M^+, Br^{79}, 6), 221 (61), 125 (100); HRMS (ESI) Found: MH^+, Br^{79}, 300.9538; $M+H^+$, Br^{81}, 302.9518; $M+Na^+$, Br^{79}, 322.9357; $M+Na^+$, Br^{81}, 324.9336; $C_{11}H_9BrO_3S$ requires MH^+, Br^{79}, 300.9529; MH^+, Br^{81}, 302.9508; $M+Na^+$, Br^{79}, 322.9357; $M+Na^+$, Br^{81}, 324.9328.

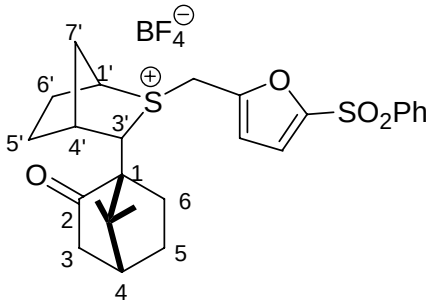
1-{[(5-Phenylsulfonyl)-2-furyl]methyl}tetrahydrothiophenium tetrafluoroborate.



2d

The bromide (9.00 g, 30.0 mmol) was dissolved in 15 ml of CH_2Cl_2 in a 100 ml round bottom flask. To the organic solution were added tetrahydrothiophene (15.80 ml, 180.0 mmol) and a saturated aqueous solution of sodium tetrafluoroborate (5.0 g, 45.0 mmol). The resulting biphasic mixture was stirred vigorously at room temperature for 7 d before concentrating under vacuum to dryness. Water (100 ml) was added and the solid was filtered and washed with a small amount of water before dissolving in acetone (100 ml). Recrystallisation gave the *sulfonium salt* (11.1 g, 93 %) as colorless cubes, mp 161-163 °C (acetone); R_f(MeOH-CH_2Cl_2, 1:10) 0.33; υ_{max} (film)/cm^{-1} 2935, 1337 and 1172 (SO_2), 1055; δ_H(400 MHz, d_6-DMSO) 1.70-1.82 (2H, m, 2CH*H*CH_2S), 1.95-2.07 (2H, m, 2C*H*HCH_2S), 3.27 (2H, pent, *J* 6.4 Hz, 2CH_2CH*H*S), 3.45 (2H, pent, *J* 6.4 Hz, 2CH_2C*H*HS), 4.74 (2H, s, ArCH_2S), 7.00 (1H, d, *J* 3.5 Hz, furyl*H*), 7.52 (1H, d, *J* 3.5 Hz, furyl*H*), 7.76-7.81 (3H, m, Ar$H^{\mathbf{para/meta}}$), 7.96-7.98 (2H, m, Ar$H^{\mathbf{ortho}}$); δ_C(100 MHz, d_6-DMSO) 28.6 (CH_2), 38.2 (CH_2), 43.6 (CH_2), 116.3 (CH), 119.9 (CH), 128.0 (CH), 130.6 (CH), 135.3 (CH), 139.5 (C), 149.7 (C), 151.1 (C); *m*/*z* (CI) 309 (M-BF_4^+, 2%), 251 (7), 223 (62), 89 (100); Found: C, 45.9; H, 4.37; $C_{15}H_{17}BF_4O_3S_2$ requires C, 45.5; H, 4.29.

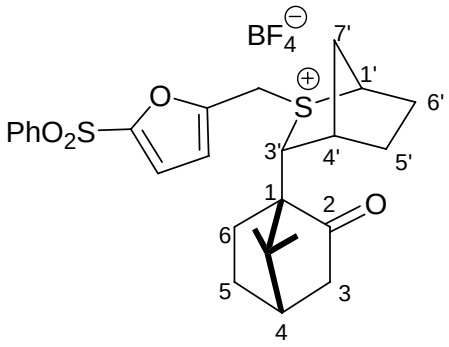
(1*S*,3*S*,4*R*)-2-{[(5-Phenylsulfonyl)-2-furyl]methyl}-3-[(1*S*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane tetrafluoroborate.



(+)-2e

A solution of the bromide (0.75 g, 2.5 mmol) and the corresponding chiral sulfide (0.13 g, 0.50 mmol) in 1 ml of CH_2Cl_2 was added to a saturated aqueous solution of sodium tetrafluoroborate (0.33 g, 3.0 mmol). The resulting biphasic mixture was stirred vigorously at room temperature for 14 d before diluted with CH_2Cl_2 (10 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 ml), and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. Flash column chromatography, eluting with 1:19 MeOH-CH_2Cl_2, gave the *sulfonium salt* (0.24 g, 89%) as white plates, mp 96-98 °C (EtOH); υ_{max} (film)/cm^{-1} 2954, 1735 (C=O), 1330 and 1173 (SO_2), 1047; R_f(MeOH-CH_2Cl_2, 1:19) 0.21; δ_H(400 MHz, $CDCl_3$) 0.89 (1H, m, CH*H*), 1.07 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.52-1.70 (3H, m, C^{5}H$_2$, C^{4}H), 1.76 (1H, br. s, C*H*H), 1.86 (1H, d, *J* 19.0 Hz, C^{3}H*H*), 2.03-2.11 (1H, m, CH*H*), 2.11-2.19 (3H, m, 3C*H*H), 2.20 (1H, d, *J* 13.2Hz, C$^{7'}$H*H*), 2.50 (1H, ddd, *J* 19.0Hz, 4.4Hz and 3.3Hz, C^{3}*H*H), 2.67 (1H, d, *J* 13.2 Hz, C$^{7'}$*H*H), 3.16 (1H, br. s, C$^{4'}$H), 4.22 (1H, d, *J* 1.8Hz, C$^{1'}$H), 4.46 (1H, d, *J* 4.8Hz, C$^{3'}$H), 4.58 (1H, d, *J* 14.7Hz, CH*H*Ar), 4.67 (1H, d, *J* 14.7Hz, C*H*HAr), 6.99 (1H, d, *J* 3.3 Hz, furyl*H*), 7.10 (1H, d, *J* 3.3 Hz, furyl*H*), 7.58-7.71 (3H, m, Ar*H*$^{meta/para}$), 7.98-8.01 (2H, m, Ar*H*^{ortho}); δ_C(100 MHz, $CDCl_3$) 19.1 (CH_3), 21.9 (CH_3), 24.4 (CH_2), 26.6 (CH_2), 26.8 (CH_2), 33.0 (CH_2), 40.0 (CH_2), 41.6 (CH_2), 43.6 (CH), 44.0 (CH_2), 45.2 (CH), 50.0 (C), 60.0 (CH), 60.2 (C), 69.7 (CH), 116.0 (CH), 118.5 (CH), 128.1 (2CH), 129.7 (2CH), 134.3 (CH), 139.4 (C), 147.6 (C), 152.1 (C), 215.3 (C); *m*/*z* (ESI) 471 (M-BF_4^+, 100%), 217 (70); Found: C, 55.6; H, 5.48; $C_{26}H_{31}BF_4O_4S_2$ requires C, 55.9; H, 5.56; α_D^{23} -80.0 (*c* 0.250 in $CHCl_3$).

(1*R*,3*R*,4*S*)-2-{[(5-Phenylsulfonyl)-2-furyl]methyl}-3-[(1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl]-2-thioniabicyclo[2.2.1]heptane tetrafluoroborate.

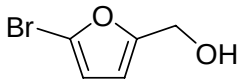


(-)-2e

A solution of the bromide (0.75 g, 2.5 mmol) and the corresponding chiral sulfide (0.13 g, 0.50 mmol) in 1 ml of CH_2Cl_2 was added to a saturated aqueous solution of sodium tetrafluoroborate (0.33 g, 3.0 mmol). The resulting biphasic mixture was stirred vigorously at room temperature for 14 d before diluted with CH_2Cl_2 (10 ml). The aqueous phase was extracted with CH_2Cl_2 (3 × 5 ml), and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. Flash column chromatography, eluting with 1:19 MeOH-CH_2Cl_2, gave the *sulfonium salt* (0.27 g, 91%) as white plates, mp 97-98 °C (EtOH); υ_{max} (film)/cm^{-1} 2955, 1735 (C=O), 1330 and 1173 (SO_2), 1047; R_f(MeOH-CH_2Cl_2, 1:19) 0.21; δ_H(400 MHz, $CDCl_3$) 0.89 (1H, m, CH*H*), 1.07 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.52-1.70 (3H, m, C^{5}H$_2$, C^{4}H), 1.76 (1H, br. s, C*H*H), 1.86 (1H, d, *J* 19.0 Hz, C^{3}H*H*), 2.03-2.11 (1H, m, CH*H*), 2.11-2.19 (3H, m, 3C*H*H), 2.20 (1H, d, *J* 13.2Hz, C$^{7'}$H*H*), 2.50 (1H, ddd, *J* 19.0Hz, 4.4Hz and 3.3Hz, C^{3}*H*H), 2.67 (1H, d, *J* 13.2 Hz, C$^{7'}$*H*H), 3.16 (1H, br. s, C$^{4'}$H), 4.22 (1H, d, *J* 1.8Hz, C$^{1'}$H), 4.46 (1H, d, *J* 4.8Hz, C$^{3'}$H), 4.58 (1H, d, *J* 14.7Hz, CH*H*Ar), 4.67 (1H, d, *J* 14.7Hz, C*H*HAr), 6.99 (1H, d, *J* 3.3 Hz, furyl*H*), 7.10 (1H, d, *J* 3.3 Hz, furyl*H*), 7.58-7.71 (3H, m, Ar*H*$^{meta/para}$), 7.98-8.01 (2H, m, Ar*H*^{ortho}); δ_C(100 MHz, $CDCl_3$) 19.1 (CH_3), 21.9 (CH_3), 24.4 (CH_2), 26.6 (CH_2), 26.8 (CH_2), 33.0 (CH_2), 40.0 (CH_2), 41.6 (CH_2), 43.6 (CH), 44.0 (CH_2), 45.2 (CH), 50.0 (C), 60.0 (CH), 60.2 (C), 69.7 (CH), 116.0 (CH), 118.5 (CH), 128.1 (2CH), 129.7 (2CH), 134.3 (CH), 139.4 (C), 147.6 (C), 152.1 (C), 215.3 (C); *m*/*z* (ESI) 471 (M-BF_4^+, 100%), 217 (60); Found: C, 55.5; H, 5.49; $C_{26}H_{31}BF_4O_4S_2$ requires C, 55.9;

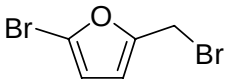
H, 5.56; α_D^{23} +80.0 (*c* 0.250 in $CHCl_3$).

(5-Bromo-furan-2-yl)-methanol.



A solution of sodium borohydride (0.59 g, 16 mmol) in 15 ml of water was slowly introduced to a 250 ml round flask charged with a solution of 5-bromo-2-furfural (8.2 g, 47 mmol) in 80 ml of ethanol with an external ice bath. The reaction mixture was warmed to room temperature and vigorously stirred for 3 h before concentrating to dryness. The residue was dissolved in EtOAc (500 ml) and washed subsequently with water (100 ml), brine (100 ml), and dried over magnesium sulfate. Filtration and concentration afforded the crude product (7.3 g, approx. 95% purity, 84% yield) as a colorless oil, δ_H(400 MHz, $CDCl_3$) 2.92 (1H, br. s, OH), 4.50 (2H, s, CH_2), 6.23 (2H, br. s, furylH); δ_C(100 MHz, $CDCl_3$) 57.0 (CH_2), 110.5 (CH), 112.0 (CH), 121.8 (C), 156.2 (C). (This compound is not stable at room temperature and decomposes rapidly.)

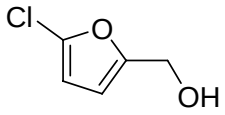
2-Bromo-5-bromomethyl-furan



Dimethyl sulfide (6.1 ml, 81 mmol) was added dropwise to a stirred suspension of *N*-bromosuccinimide (12 g, 68 mmol) in 250 ml of CH_2Cl_2 at 0 °C. After 10 min a solution of alcohol (7.3 g, 41 mmol) in 50 ml of CH_2Cl_2 was introduced via cannula. The reaction mixture was then allowed to reach room temperature and stirred for 6 h before concentrating to dryness. The residue was dissolved in Et_2O (700 ml), washed with water (2 × 80 ml) and brine (3 × 80 ml), and dried over magnesium sulfate. After evaporation under vacuum, the crude product was purified by distillation under reduced pressure to afford the *bromide* (5.4 g, approx. 95% purity, 55% yield) as a light green liquid, bp 93-95 °C (approx. 25 mmHg); δ_H(400 MHz, $CDCl_3$) 4.31 (2H, s, CH_2), 6.27 (2H, br. s, furylH); δ_C(100 MHz, $CDCl_3$) 22.8 (CH_2), 112.4

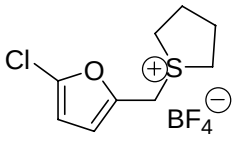
(CH), 112.8 (CH), 123.0 (C), 152.1 (C). (This compound is not stable at room temperature and was used in the next step immediately after distillation.)

5-Chloro-2-furfuryl alcohol.



A solution of sodium borohydride (96 mg, 2.5 mmol) in 3 ml of water was slowly introduced to a 25 ml round flask charged with a solution of 5-chloro-2-furfural (1.0 g, 7.5 mmol) in 10 ml of ethanol with an external ice bath. The reaction mixture was warmed to room temperature and vigorously stirred for 3 h before concentrating to dryness. The residue was dissolved in EtOAc (100 ml) and washed subsequently with water (20 ml), brine (20 ml), and dried over magnesium sulfate. Filtration and concentration afforded the crude *alcohol* (0.98 g, approx. 90% purity, 89% yield) as a colorless oil, δ_H (400 MHz, $CDCl_3$) 1.92 (1H, br. s, OH), 4.54 (2H, s, CH_2), 6.11 (1H, d, *J* 3.4 Hz, furyl*H*), 6.29 (1H, d, *J* 3.4 Hz, furyl*H*); δ_C(100 MHz, $CDCl_3$) 52.0 (CH_2), 108.7 (CH), 113.8 (CH), 122.0 (C), 153.2 (C). (This compound is not stable at room temperature and decomposes rapidly.)

1-[(5-Chloro-2-furyl)methyl] tetrahydrothiophenium tetrafluoroborate.



2g

Tetrafluoroboric acid (54% w in ether, 0.27 g, 1.00 mmol) was slowly added to tetrahydrothiophene (0.35 ml, 4.0 mmol) in 1 ml of Et_2O at 0 °C. The mixture was then slowly transferred to a vigorously stirred solution of 5-chloro-2-furfuryl alcohol (0.13 g, 1.0 mmol) and tetrahydrothiophene (0.17 ml, 2.0 mmol) in 2 ml of ether at 0 °C. After vigorously stirring for 45 min at room temperature, the precipitate was filtered and cautiously washed with dry

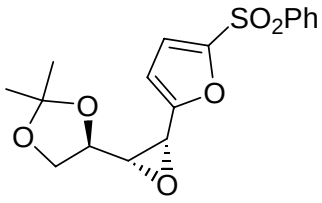
ether (5 × 1 ml) to give the *sulfonium salt* as a pale white powder (0.26 g, 82%). Recrystallisation of the crude product from Et_2O-CH_2Cl_2 gave pure **2g** as bright cyan needles, mp 94-95 °C (CH_2Cl_2-Et_2O); R_f(CH_2Cl_2-CH_3OH, 1:19) 0.13; υ_{max} (film)/cm^{-1} 3027, 2964, 1509, 1412, 1055; δ_H(400 MHz, $CDCl_3$) 2.02-2.14 (2H, m, 2CH*H*CH_2S), 2.22-2.32 (2H, m, 2C*H*HCH_2S), 3.51 (2H, pent., *J* 6.5 Hz, CH_2CH*H*S), 3.68 (2H, pent., *J* 6.5 Hz, CH_2C*H*HS), 6.25 (1H, d, *J* 3.4 Hz, furyl*H*), 6.86 (1H, d, *J* 3.4 Hz, furyl*H*); δ_C(100 MHz, $CDCl_3$) 28.8 (CH_2), 38.7 (CH_2), 42.5 (CH_2), 108.8 (CH), 118.0 (CH), 139.6 (C), 141.2 (C); *m*/*z* (ESI) 203 (M-BF_4^+), 493 (2M-BF_4^+); HRMS (EMS) Found: M-BF_4^+, 203.0302; $C_9H_{12}OSClBF_4$ requires M-BF_4^+, 203.0292.

2. Catalytic and stoichiometric epoxidation

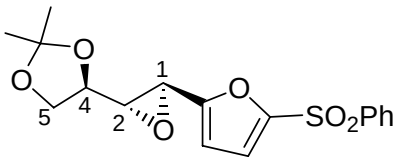
General Procedure for Epoxidation at Low Temperature

The base (0.50 mmol) was slowly added to a solution (or suspension) of the sulfonium salt (0.55 mmol) in anhydrous solvent (0.7 ml) at the desired reaction temperature. After stirring for 10–15 min a solution of the aldehyde (0.50 mmol) in anhydrous solvent (1.0 ml) was added dropwise. The reaction mixture was stirred at the desired temperature until the reaction was shown to be complete by TLC. After addition of water (20 ml), the organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 20 ml). The organic phases were combined, dried over magnesium sulfate, filtered and concentrated under vacuum. Purification by column chromatography yielded the epoxide as a mixture of *trans*- and *cis*-diastereomers.

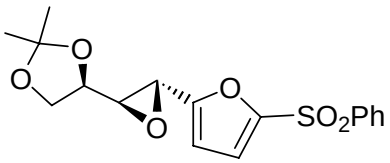
1-[5-(Phenylsulfonyl)-2-furyl]-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]oxirane.



11a



11b



11c

The mixture of two *trans*-epoxides (1*S*,2*R*)-1-[5-(phenylsulfonyl)-2-furyl]-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]oxirane (**11b**) and (1*R*,2*S*)-1-[5-(phenylsulfonyl)-2-furyl]-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]oxirane (**11c**) were obtained as a pale yellow oil, R_f(EtOAc-petroleum, 3:7) 0.33; υ_{max} (neat)/cm^{-1} 2988, 1330, 1245, 1142; δ_H(400 MHz, $CDCl_3$) **11b**: 1.36 (3H, s, CH_3), 1.44 (3H, s, CH_3), 3.44 (1H, dd, *J* 5.6 Hz, 2.0 Hz, C^2H), 3.82 (1H, d, *J* 2.0 Hz, C^1H), 3.96 (1H, dd, *J* 8.3 Hz, 5.6 Hz, C^5H*H*), 4.01 (1H, dt, *J* 6.3 Hz, 5.6 Hz, C^4H), 4.16 (1H, dd, *J* 8.3 Hz, 6.3 Hz, C^5*H*H), 6.47-6.49 (1H, m, furyl*H*), 7.16-7.18 (1H, m, furyl*H*), 7.53-7.66 (3H, m, Ar$H^{meta\&para}$), 7.97-8.01 (2H, m, ArH^{ortho}); **11c**: 1.40 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.44 (1H, dd, *J* 5.6 Hz, 2.0 Hz, C^2H), 3.90 (1H, d, *J* 2.0 Hz, C^1H), 3.92 (1H, dd, *J* 8.3 Hz, 6.3 Hz, C^5H*H*), 4.15 (1H, dd, *J* 8.3 Hz, 6.3 Hz, C^5*H*H), 4.23 (1H, td, *J* 6.3 Hz, 5.6 Hz, C^4H), 6.47-6.49 (1H, m, furyl*H*), 7.16-7.18 (1H, m, furyl*H*), 7.53-7.66 (3H, m, Ar$H^{meta\&para}$), 7.97-8.01 (2H, m, ArH^{ortho}); δ_C (100 MHz, $CDCl_3$) **11b**: 25.2 (CH_3), 26.5 (CH_3), 50.2 (CH),

59.9 (CH), 66.7 (CH_2), 75.0 (CH), 110.3 (C), 110.7 (CH), 118.3 (CH), 128.0 (C), 129.4 (C), 133.9 (CH), 139.9 (CH), 150.1 (CH), 155.4 (CH); **11c**: 25.6 (CH_3), 26.1 (CH_3), 48.7 (CH), 59.4 (CH), 66.0 (CH_2), 73.9 (CH), 110.3 (C), 110.6 (CH), 118.3 (CH), 128.0 (C), 129.4 (C), 133.9 (CH), 139.8 (CH), 150.1 (CH), 155.5s (CH); *m*/*z* (CI) 351 (MH^+, 3 %), 237 (44), 125 (100), 101 (95).

The only one *cis*-epoxide (1*R*,2*R*)-1-[5-(phenylsulfonyl)-2-furyl]-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]oxirane (**11a**) was obtained as a pale yellow oil, R_f(EtOAc-petroleum, 3:7) 0.34; υ_{max} (neat)/cm^{-1} 2988, 1330, 1245, 1142; δ_H(400 MHz, $CDCl_3$) 1.25 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.27 (1H, dd, *J* 8.1 Hz, 4.0 Hz, C^2H), 3.83 (1H, ddd, *J* 8.1 Hz, 6.3 Hz and 4.9 Hz, C^4H), 4.01 (1H, d, *J* 4.0 Hz, C^1H), 4.05 (1H, dd, *J* 8.8 Hz and 4.9 Hz, C^5HH), 4.12 (1H, dd, *J* 6.3 Hz and 8.8 Hz, C^5HH), 6.43-6.49 (1H, m, furyl*H*), 7.17-7.18 (1H, m, furyl*H*), 7.53-7.66 (3H, m, Ar$H^{meta\&para}$), 7.99-8.01 (2H, m, ArH^{ortho}); δ_C(100 MHz, $CDCl_3$) 25.0 (CH_3), 26.8 (CH_3), 50.9 (CH), 59.0 (CH), 67.8 (CH_2), 72.5 (CH), 110.0 (C), 111.1 (CH), 118.0 (CH), 127.9 (C), 129.3 (C), 133.8 (CH), 139.7 (CH), 150.1 (CH), 154.2 (CH); *m*/*z* (CI) 351 (MH^+, 6 %), 291 (19), 125 (14), 101 (100); HRMS (EI) Found: M^+, 350.0823; $C_{17}H_{18}SO_6$ requires M^+, 350.3826; α_D^{25} +37.5 (*c* 0.630 in $CHCl_3$).

Sulfur ylide	Base	Yield[b]	diastereoselectivity dr[c] (**a**:**b**:**c**)
(-)-**2a**	EtP_2	56 %	78: 1:21
2d	EtP_2	58 %	6:83:11
2d	KHMDS	82 %	6:83:11
(+)-**2e**	EtP_2	49 %	14:53:33
(-)-**2e**	EtP_2	52 %	6:42:52

a: Reactions were carried out in CH_2Cl_2 at – 78 °C;
b: Isolated yields;
c: Diastereomer ratios were determined by analysis of NMR spectrum.

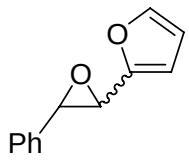
Table 1 Epoxidation of (+)-Glyceraldehyde with Sulfur Ylides

General Procedure for Epoxidation under Catalytic Conditions

To a 5 ml round bottom flask equipped with a nitrogen balloon and a stirring bar was added sequentially: tetrahydrothiophene (5.8 μl, 20 mol%), anhydrous acetonitrile (1.0 ml), rhodium(II) acetate dimer (1.5 mg, 1 mol%), benzyl triethylammonium chloride (7.5 mg, 10

mol%), tosylhydrazone sodium salt **10** (0.50 mmol, 1.5 equiv), and the desired aldehyde (0.33 mmol, 1.0 equiv). The reaction mixture was stirred vigorously at room temperature for 10 min, and then at 40 °C for 24 h. The reaction was quenched by the addition of water (0.5 ml) and ethyl acetate (0.5 ml). The aqueous layer was washed with ethyl acetate (2 × 0.5 ml) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated under vacuum. The crude product was analyzed by ^{1}H NMR to determine the diastereomeric ratio and then purified by flash column chromatography to afford the corresponding epoxide.

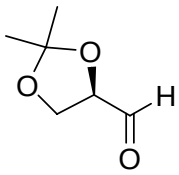
2-(3-Phenyl-oxiranyl)-furan.



According to the general procedure above, benzaldehyde (53 mg, 0.5 mmol) was converted to 2-(3-phenyl-oxiranyl)-furan (75 mg, 82%) as a mixture of *trans*- and *cis*-epoxide as a pale yellow oil, R_f(10% EtOAc-petroleum on Al_2O_3) 0.69; δ_H(400 MHz, $CDCl_3$) *trans*-isomers: 3.81 (1H, d, *J* 2.0 Hz, C*H*), 4.35 (1H, d, *J* 2.0 Hz, C*H*), 6.32 (1H, dd, *J* 3.4 Hz, 2.0 Hz, furyl*H*), 6.41 (1H, d, *J* 3.4 Hz, furyl*H*), 7.25-7.60 (6H, m, Ar*H* and furyl*H*); *cis*-isomers: 4.18 (1H, d, *J* 4.0 Hz, C*H*), 4.31 (1H, *J* 4.0 Hz, C*H*), 6.36 (1H, dd, *J* 3.4 Hz, 2.0 Hz, furyl*H*), 6.45 (1H, d, *J* 3.4 Hz, furyl*H*), 7.25-7.60 (6H, m, Ar*H* and furyl*H*); δ_C(100 MHz, $CDCl_3$) 55.8 (CH), 60.4 (CH), 109.5 (CH), 111.8 (CH), 125.3 (CH), 128.7 (CH), 128.8 (CH), 135.7 (C), 144.3 (CH), 152.0 (C).

3. Completion of synthesis

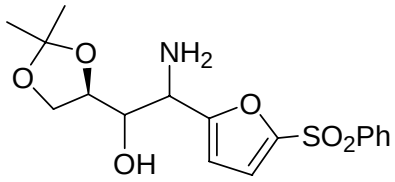
(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde.



3

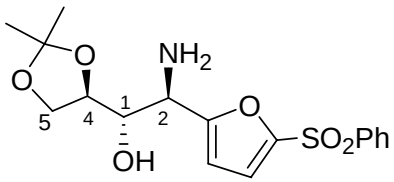
The mannitol diacetonide (4.00 g, 15.3 mmol) was dissolved in 40 ml of dichloromethane. Saturated aqueous sodium bicarbonate (1.6 ml) was then added while maintaining the temperature below 25 °C. Sodium periodate (6.00 g, 28.0 mmol) was slowly introduced over a period of 20 min with a strong stirring. After 6 hours, magnesium sulfate (4.0 g) was added and after 10 min, the mixture was filtered. The solvent was evaporated and the residue was purified by distillation under reduced pressure to give the glyceraldehyde (3.18 g, 80%) as a colorless oil; υ_{max} (neat)/cm^{-1} 2990, 2945, 2890, 1730, 1375, 1250, 1215; δ_H(400 MHz, $CDCl_3$) 1.36 (3H, s, CH_3), 1.42 (3H, s, CH_3), 4.11-4.18 (2H, C*H*$_2$CH), 4.36-4.43 (1H, C*H*CH$_2$), 9.70 (1H, d, *J* 2.0 Hz, CHO); δ_C(100 MHz, $CDCl_3$) 24.5 (CH_3), 26.0 (CH_3), 65.8 (CH_2), 80.1 (CH), 110.9 (C), 202.2 (CH); $[\alpha]^{24}_D$ +75.0 (*c* 1.38 in $CHCl_3$). (Note: this compound tends to polymerise at room temperature, and has to be freshly distilled before use.)

2-Amino-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[5-(phenylsulfonyl)furan-2-yl] ethanol.



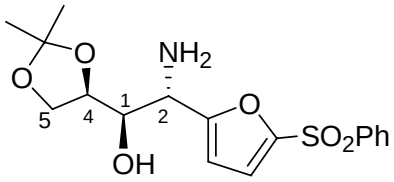
The epoxide (a mixture of two *trans*- diastereomers **11b** and **11c** from the epoxidation reaction, dr ~ 7:1) (4.50 g, 12.8 mmol) was dissolved in 125 ml of methanol in a 500 ml round bottom flask. Concentrated aq. ammonia (35%, 125 ml) was then slowly introduced into the epoxide solution. The resultant yellow solution was stirred vigorously at room temperature for 24 h at

which time the starting material was completely consumed according to TLC analysis. Evaporation of the excess ammonia and the solvent afforded the crude *amino alcohol* (4.4 g, >95% purity, 90% yield) as a mixture of two *trans*-diastereomers (dr ~ 7:1) as white plates.



b

Flash column chromatography of the crude product, eluting with 1:19 MeOH-CH_2Cl_2, gave pure (1*S*,2*R*)-2-amino-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[5-(phenyl sulfonyl)furan-2-yl]ethanol (*trans*-diastereomer **b**, 3.30 g, 79%) as colorless needles: mp 143-145 °C (Et_2O); R_f(MeOH-CH_2Cl_2 1:19) 0.30; υ_{max} (film)/cm^{-1} 3382 and 3312 (NH, OH), 1326 and 1142 (SO_2); δ_H(400 MHz, $CDCl_3$) 1.27 (3H, s, CH_3), 1.31 (3H, s, CH_3), 2.06 (2H, br. s, NH_2), 3.76-3.89 (4H, $C^{\mathbf{1}}H$, $C^{\mathbf{4}}H$ and $C^{\mathbf{5}}H_2$), 4.22 (1H, d, *J* 3.9 Hz, $C^{\mathbf{2}}H$), 6.41 (1H, dd, *J* 3.4 Hz and 0.7 Hz, furyl*H*), 7.16 (1H, d, *J* 3.7 Hz, furyl*H*), 7.51-7.64 (3H, m, $ArH^{\mathbf{ortho\&para}}$), 7.98-8.01 (2H, m, $ArH^{\mathbf{meta}}$); δ_C(100 MHz, $CDCl_3$) 25.1 (CH_3), 26.5 (CH_3), 52.0 (CH), 66.1 (CH_2), 74.1 (CH), 75.7 (CH), 108.9 (CH), 118.4 (CH), 127.8 (CH), 129.3 (CH), 133.7 (CH), 140.2 (C), 148.6 (C), 160.8 (C); *m*/*z* (CI) 368 (MH^+, 58 %), 310 (100), 101 (80); Found: C, 55.6; H, 5.72; N, 3.8; $C_{17}H_{21}NO_6S$ requires C, 55.6; H, 5.62; N, 3.7; $[\alpha]^{23}_D$ -21.3 (*c* 0.308 in $CHCl_3$).

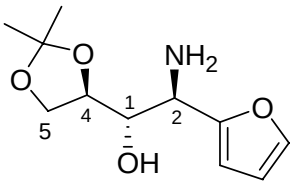


c

(1*R*,2*S*)-2-amino-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-[5-(phenylsulfonyl)furan-2-yl]ethanol (*trans*-diastereomer **c**, 0.45 g, 11%) was obtained as colorless needles, mp 107-109 °C (Et_2O); R_f(MeOH-CH_2Cl_2 1:19) 0.33; υ_{max} (film)/cm^{-1} 3365 and 3304 (NH, OH), 1319 and 1148 (SO_2); δ_H(400 MHz, $CDCl_3$) 1.20 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.61 (2H, br. s, NH_2),

3.62 (1H, dd, *J* 5.9 Hz, 4.0 Hz, C*H*OH), 3.63 (1H, dd, *J* 8.3 Hz, 6.8 Hz, C^{5}H*H*), 3.79 (1H, dd, *J* 8.3 Hz, 6.8 Hz, C^{5}*H*H), 3.87 (1H, dt, *J* 6.8 Hz, 4.0 Hz, C^{4}H), 3.98 (1H, d, *J* 5.9 Hz, C^{2}H), 6.34 (1H, d, *J* 3.4 Hz, furyl*H*), 7.10 (1H, d, *J* 3.4Hz, furyl*H*), 7.45-7.58 (3H, m, Ar$H^{\mathbf{ortho\&para}}$), 7.89-7.94 (2H, m, Ar$H^{\mathbf{meta}}$); δ_C(100 MHz, $CDCl_3$) 25.3 (CH_3), 26.3 (CH_3), 53.1 (CH), 66.2 (CH_2), 72.2 (CH), 75.4 (CH), 108.3 (CH), 109.8 (C), 118.5 (CH), 127.7 (2CH), 129.3 (2CH), 133.7 (CH), 140.0 (C), 148.0 (C), 162.0 (C); *m*/*z* (ESI) 368 (MH^+), 390 ($M+Na^+$); HRMS (ESI) Found: MH^+, 368.1172; $C_{17}H_{21}NO_6S$ requires MH^+, 368.1162; $[\alpha]^{23}_D$ -58.6 (*c* 0.625 in $CHCl_3$).

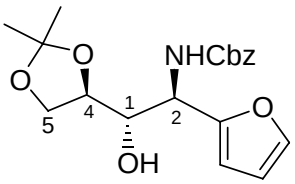
(1*S*,2*R*)-2-Amino-2-(furan-2-yl)-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]ethanol.



6b

Pieces of sodium (0.710 g, 30.5 mmol) were slowly dropped into 5 ml of mercury under a nitrogen atmosphere in a Schlenk flask (severe exothermic reaction). To the formed sodium amalgam (cooled to room temperature) were introduced 20 ml of anhydrous methanol, potassium hydrogen phosphate (5.3 g, 30.5 mmol), and a solution of the trans amino alcohol (diastereomer **b**, 2.8 g, 7.6 mmol) in 80 ml of anhydrous methanol. After 20 min, the white suspension was taken out by syringe, passed through celite, and concentrated under vacuum to afford a white solid, which was redissolved in water (80 ml) and extracted with CH_2Cl_2 (5 × 80 ml). The organic solution was dried over magnesium sulfate, filtered and concentrated under vacuum to give the *amino alcohol* (1.60 g, 92%) as colorless needles, mp 93-95 °C (CH_2Cl_2); R_f(MeOH-CH_2Cl_2, 1:9) 0.23; υ_{max} (film)/cm^{-1} 3373, 3311, 3113; δ_H(400 MHz, $CDCl_3$) 1.25 (3H, s, CH_3), 1.35 (3H, s, CH_3), 2.08 (2H, br. s, NH_2), 3.72-3.91 (4H, C^{1}H, C^{4}H and C$^{5}H_2$), 4.16 (1H, d, *J* 3.9 Hz, C^{2}H), 6.21 (1H, dd, *J* 3.2 Hz and 0.5 Hz, furyl*H*), 6.28 (1H, dd, *J* 3.2 Hz and 1.9 Hz, furyl*H*), 7.32 (1H, dd, *J* 1.9 Hz and 0.5 Hz, furyl*H*); δ_C(100 MHz, $CDCl_3$) 27.6 (CH_3), 29.1 (CH_3), 51.7 (C), 54.1 (CH), 68.7 (CH_2), 77.0 (CH), 78.8 (CH), 109.5 (CH), 111.4 (C), 112.7 (CH), 144.3 (CH); *m*/*z* (CI) 368 (MH^+, 58%), 310 (100), 101 (80); Found: C, 58.0; H, 7.52; N, 6.1; $C_{11}H_{17}NO_4$ requires C, 58.1; H, 7.54; N, 6.2; $[\alpha]^{23}_D$ -13.2 (*c* 0.385 in $CHCl_3$).

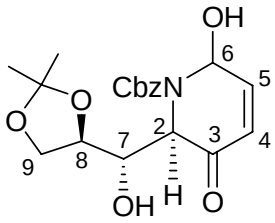
(1*S*,2*R*)-2-[(Benzyloxy)carbonyl]amino-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(2-furyl) ethanol.



12

A solution of amine **6b** (1.60 g, 7.05 mmol) in 70 ml of CH_2Cl_2 and an aqueous solution of sodium carbonate (1.50 g, 14.0 mmol) in 40 ml of water were mixed in a 250 ml round bottom flask and stirred vigorously with an ice-bath. A solution of Benzyl chloroformate (1.20 ml, 7.76 mmol) in 50 ml of CH_2Cl_2 was then introduced into the mixture via cannula. After 20 min, water (150 ml) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 × 150 ml). The combined organic extracts were washed with brine (30 ml), dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography, eluting with 2:3 EtOAc-petroleum, to give the amine-protected *alcohol* (2.47 g, 98%) as a colorless oil, R_f(EtOAc-petroleum, 3:7) 0.23; υ_{max} (film)/cm^{-1} 3416, 3065, 2892, 1694 (C=O), 1215 (COC); δ_H(400 MHz, $CDCl_3$) 1.36 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.36 (1H, d, *J* 7.1 Hz, OH), 2.88 (1H, d, *J* 6.9 Hz, NH), 3.81 (1H, br. t, *J* 6.9 Hz, C^{2}H), 3.85-3.96 (3H, m, C^{4}H and C$^{5}H_2$), 5.06 (1H, td, *J* 7.1 Hz, 3.6 Hz, C^{1}H), 5.08 (1H, d, *J* 12.2 Hz, CH*H*Ph), 5.13 (1H, d, *J* 12.2 Hz, C*H*HPh), 6.36 (2H, br. s, furyl*H*), 7.30-7.40 (6H, m, PhH and furyl*H*); δ_C(100 MHz, $CDCl_3$) 25.1 (CH_3), 26.8 (CH_3), 51.0 (CH), 66.1 (CH_2), 67.1 (CH_2), 74.4 (CH), 76.0 (CH), 108.7 (CH), 109.4 (C), 110.5 (CH), 128.1 (C), 128.2 (CH), 128.4 (CH), 128.6 (CH), 136.1 (C), 142.4 (CH), 150.9 (C); *m*/*z* (ESI) 384 (M+Na^+, 60%), 745 (2M+Na^+, 100%); HRMS (ESI) Found: M+Na^+, 384.1423; $C_{19}H_{23}NO_6$ requires M+Na^+, 384.1418; $[\alpha]^{23}_D$ +50.2 (*c* 0.918 in $CHCl_3$).

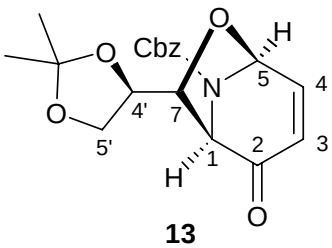
(*R*)-2-{(*S*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-hydroxy-methyl}-6-hydroxy-3-oxo-3,6-dihydro-2H-pyridine-1-carboxylic acid benzyl ester.



7b

Anhydrous *m*CPBA (95% purity, 1.60 g, 8.35 mmol) was added in small portions to a solution of protected amino alcohol **12** (2.50 g, 6.92 mmol) in 250 ml of anhydrous CH_2Cl_2 at room temperature. The reaction mixture was vigorously stirred for 20 h, at which time TLC showed complete consumption of the starting material. Anhydrous triethylamine (1.12 ml) was slowly introduced into the resultant suspension before it was concentrated cautiously under vacuum. Flash column chromatography, eluting with EtOAc-Petroleum (1:1), gave the *pyridinone* (1.88 g, 72%) as a white solid as a mixture of two diastereomers (**a**:**b** ~ 1:2), R_f(EtOAc-petroleum, 1:1) 0.30; υ_{max} (film)/cm^{-1} 3373 (OH), 1680 (CO); δ_H(400 MHz, $CDCl_3$) 1.25$^{\mathbf{a}}$ (3H, s, CH_3), 1.36$^{\mathbf{a}}$ (3H, s, CH_3), 1.36$^{\mathbf{b}}$ (3H, s, CH_3), 1.42$^{\mathbf{b}}$ (3H, s, CH_3), 3.74$^{\mathbf{a}}$ (1H, dd, *J* 8.8 Hz, 1.7 Hz, C$^{\mathbf{7}}$H), 3.88-4.00$^{\mathbf{a+b}}$ (2H×2, C$^{\mathbf{9}}$H$_2$), 4.12$^{\mathbf{b}}$ (1H, dd, *J* 8.8 Hz, 1.7 Hz, C$^{\mathbf{7}}$H), 4.08-4.14$^{\mathbf{a}}$ (1H, m, C$^{\mathbf{8}}$H), 4.18-4.24$^{\mathbf{b}}$ (1H, m, C$^{\mathbf{8}}$H), 5.02$^{\mathbf{b}}$ (1H, d, *J* 1.7 Hz, C$^{\mathbf{2}}$H), 5.06$^{\mathbf{a}}$ (1H, d, *J* 1.7 Hz, C$^{\mathbf{2}}$H), 5.13$^{\mathbf{a}}$ (1H, d, *J* 12.2 Hz, CH*H*Ph), 5.25$^{\mathbf{b}}$ (1H, d, *J* 12.2 Hz, CH*H*Ph), 5.31$^{\mathbf{a}}$ (1H, d, *J* 12.2 Hz, C*H*HPh), 5.33$^{\mathbf{b}}$ (1H, d, *J* 12.2 Hz, C*H*HPh), 6.10$^{\mathbf{b}}$ (1H, d, *J* 4.9 Hz, C$^{\mathbf{6}}$H), 6.21$^{\mathbf{b}}$ (1H, d, *J* 10.5 Hz, C$^{\mathbf{4}}$H), 6.25$^{\mathbf{a}}$ (1H, d, *J* 4.9 Hz, C$^{\mathbf{6}}$H), 6.28$^{\mathbf{a}}$ (1H, d, *J* 10.5 Hz, C$^{\mathbf{4}}$H), 6.90$^{\mathbf{b}}$ (1H, dd, *J* 10.5 Hz, 4.9 Hz, C$^{\mathbf{5}}$H), 6.93$^{\mathbf{a}}$ (1H, dd, *J* 10.5 Hz, 4.9 Hz, C$^{\mathbf{5}}$H), 7.33-7.45$^{\mathbf{a+b}}$ (5H×2, m, ArH); δ_C(100 MHz, $CDCl_3$) diastereomer **a**: 24.8 (CH_3), 26.6 (CH_3), 61.6 (CH), 67.0 (CH_2), 68.3 (CH_2), 70.3 (CH), 74.2 (CH), 75.8 (CH), 109.4 (C), 128.1 (CH), 128.4 (CH), 128.5 (CH), 129.8 (CH), 134.9 (C), 143.4 (CH), 155.0 (C), 192.6 (C); diastereomer **b**: 25.0 (CH_3), 26.5 (CH_3), 62.5 (CH), 66.3 (CH_2), 68.3 (CH_2), 70.8 (CH), 75.1 (CH), 75.4 (CH), 109.7 (C), 128.1 (CH), 128.4 (CH), 128.5 (CH), 129.7 (CH), 135.3 (C), 144.0 (CH), 155.0 (C), 192.6 (C); *m*/*z* (ESI) 400 (M+Na^+, 100%), 239 (64); HRMS (ESI) Found: M+Na^+, 400.1372; $C_{19}H_{23}NO_7$ requires M+Na^+, 400.1367).

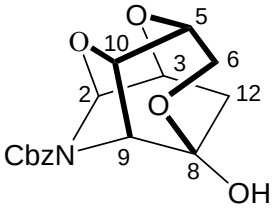
(1*R*,5*S*,7*S*)-7-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-oxo-6-oxa-8-aza-bicyclo[3.2.1]oct-3-ene-8-carboxylic acid benzyl ester.



13

A 50 ml Schlenk flask filled with 0.2 g of 4 Å molecular seives was heated at 140 ºC under high vacuum overnight. Anhydrous toluene (10 ml) and *p*-toluenesufonic acid monohydrate (7 mg, 0.04 mmol) were introduced into the Schlenk flask under a nitrogen atmosphere. The suspension was then stirred vigorously for 20 min, after which a solution of the substrate **7b** (190 mg, 0.503 mmol) in 15 ml of anhydrous toluene was slowly introduced via cannula. After 1.5 h, the reaction was quenched with 0.15 ml of triethylamine and filtered through celite. Flash chromatography (eluting with 3:7 EtOAc-petroleum) gave the *bridged ketone* (146 mg, 80%) as pale yellow oil, R_f(EtOAc-petroleum, 3:7) 0.25; υ_{max} (film)/cm^{-1} 1680 (C=O), 1278 and 1212 (NC-O), 1152, 1073, 1048; δ_H(400 MHz, $CDCl_3$) 1.20 (3H, s, CH_3), 1.32 (3H, s, CH_3), 3.63 (1H, ddd, *J* 9.5 Hz, 6.0 Hz, and 4.9 Hz, C$^{4'}$H), 3.81 (1H, dd, *J* 8.8 Hz, 4.9 Hz, C$^{5'}$H*H*), 3.92 (1H, dd, *J* 8.8 Hz, 6.0 Hz, C$^{5'}$*H*H), 3.96 (1H, dd, *J* 9.5 Hz, 5.4 Hz, C^{7}H), 5.02 (1H, d, *J* 5.4 Hz, C^{1}H), 5.07 (1H, d, *J* 12.2 Hz, C*H*HPh), 5.12 (1H, d, *J* 12.2 Hz, CH*H*Ph), 5.89 (1H, dd, *J* 4.4 Hz, 1.0 Hz, C^{5}H), 6.09 (1H, dt, *J* 9.6 Hz, 1.0 Hz, C^{3}H), 7.25-7.33 (6H, m, ArH and C^{4}H); δ_C(100 MHz, $CDCl_3$) 20.6 (CH_3), 22.2 (CH_3), 62.0 (CH), 62.9 (CH_2), 63.8 (CH_2), 69.4 (CH), 72.8 (CH), 77.0 (CH), 105.9 (C), 123.7 (CH), 124.1 (CH), 124.2 (CH), 125.5 (CH), 130.7 (C), 145.2 (CH), 148.8 (C), 187.8 (C); *m*/*z* (ESI) 382 (M+Na$^+$), 741 (M+2Na$^+$); HRMS (ESI) Found: M+Na$^+$, 382.1256; $C_{19}H_{21}NO_6$ requires M+Na$^+$, 382.1261; $[\alpha]^{23}_D$ +99.8 (*c* 0.518 in $CHCl_3$.

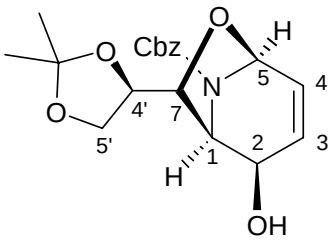
(2*S*,3*S*,5*R*,8*S*,9*R*,10*S*)-8-Hydroxy-1,4,7-trioxa-11-aza-tetracyclo[1.1.0]decane-11-carboxylic acid benzyl ester.



14

p-Toluenesufonic acid monohydrate (2.6 mg, 0.014 mmol) was added to a solution of the substrate **7b** (50 mg, 0.13 mmol) in 1 ml of toluene. After stirring at room temperature for 2 h, the reaction was quenched with triethylamine (3 μl) and the resulting solution was concentrated under vacuum. Flash chromatography (eluting with 1:1 EtOAc-petroleum) gave the *tetracycle* (16 mg, 40%) as pale yellow syrup, R_f(EtOAc-petroleum, 1:1) 0.19; υ_{max} (film)/cm^{-1} 3344 (OH), 1704 (C=O); δ_H(400 MHz, $CDCl_3$) 2.07-2.10 (2H, m, C^{12}H$_2$), 3.91 (1H, d, *J* 9.8 Hz, C^{6}H*H*), 4.05 (1H, t, *J* 4.0 Hz, C^{5}H), 4.04-4.10 (1H, m, C^{3}H), 4.27 (1H, dd, *J* 9.8 Hz, 4.0 Hz, C^{6}*H*H), 4.48 (1H, dd, *J* 6.6 Hz, 4.0 Hz, C^{10}H), 4.64 (1H, d, *J* 6.6 Hz, C^{9}H), 5.20 (2H, s, C*H*$_2$Ph), 5.87 (1H, br. s, C^{2}H), 7.34-7.43 (5H, m, ArH); δ_C(100 MHz, $CDCl_3$) 58.3 (CH), 64.8 (CH), 65.1 (CH_2), 68.0 (CH_2), 75.0 (CH), 75.2 (CH), 85.3 (CH), 90.5 (C), 128.1 (2CH), 128.4 (CH), 128.6 (2CH), 135.5 (C), 154.0 (C); *m*/*z* (ESI) 342 (M+Na$^+$), 761 (M+2Na$^+$); HRMS (ESI) Found: M+Na$^+$, 342.2998; $C_{16}H_{17}NO_6$ requires M+Na$^+$, 342.3006; $[\alpha]^{24}_D$ -50.0 (*c* 0.500 in $CHCl_3$).

(1*R*,2*S*,5*S*,7*S*)-7-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)]-2-hydroxy-6-oxa-8-aza-bicyclo[3.2.1]oct-3-ene-8-carboxylic acid benzyl ester.

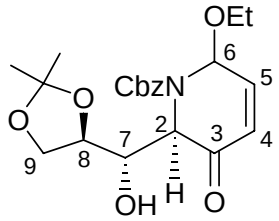


15

The substrate **13** (108 mg, 0.300 mmol) was dissolved in 1 ml of methanol and cooled at 0 °C. To this solution was added $CeCl_3 \cdot 7H_2O$ (149 mg, 0.400 mmol) and the reaction was stirred vigorously for 10 min. The resulting mixture was then warmed to room temperature, and

$NaBH_4$ (15 mg, 0.40 mmol) was added slowly in small portions over 15 min. After stirring for another 10 min, the reaction mixture was diluted with water (70 ml) and extracted with EtOAc (3 × 80 ml). The combined organic layers were dried over magnesium sulfate and concentrated under vacuum to give the crude product (112 mg, 95%) as a white syrup, R_f(EtOAc-petroleum, 2:3) 0.33; υ_{max} (film)/cm^{-1} 3434 (OH), 2985, 1709 (C=O), 1118 and 1069 (COC); δ_H(400 MHz, $CDCl_3$) 1.29 (3H, s, CH_3), 1.35 (3H, s, CH_3), 3.86 (1H, dd, *J* 8.8 Hz, 5.1 Hz, $C^{5'}H$*H*), 3.92 (1H, d, *J* 7.5 Hz, $C^{1}H$), 3.95 (1H, d, *J* 5.4 Hz, $C^{7}H$), 4.07 (1H, ddd, *J* 5.8 Hz, 5.4 Hz, and 5.1 Hz, $C^{4'}H$), 4.13 (1H, dd, *J* 8.8 Hz, 5.8 Hz, $C^{5'}$*H*H), 4.84 (1H, d, *J* 7.5 Hz, $C^{2}H$), 5.10 (2H, s, C*H*$_2$Ph), 5.61 (1H, d, *J* 3.9 Hz, $C^{5}H$), 5.80 (1H, d, *J* 10.0 Hz, $C^{3}H$), 5.85 (1H, dd, *J* 10.0 Hz, 3.9 Hz, $C^{4}H$), 7.24-7.33 (5H, m, ArH); δ_C(100 MHz, $CDCl_3$) 25.2 (CH_3), 26.6 (CH_3), 60.0 (CH), 67.9 (CH_2), 68.6 (CH_2), 70.8 (CH), 74.7 (CH), 79.7 (CH), 81.7 (CH), 110.3 (C), 127.7 (CH), 128.1 (CH), 128.4 (CH), 128.6 (CH), 133.6 (CH), 135.7 (C), 154.0 (C); *m*/*z* (ESI) 384 ($M+Na^+$); HRMS (ESI) Found: $M+Na^+$, 382.1429; $C_{19}H_{23}NO_6$ requires $M+Na^+$, 384.1418; $[\alpha]^{23}_D$ -50.0 (*c* 0.900 in $CHCl_3$).

(*R*)-2-{(*S*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-hydroxy-methyl}-6-ethoxy-3-oxo-3,6-dihydro-2H-pyridine-1-carboxylic acid benzyl ester.

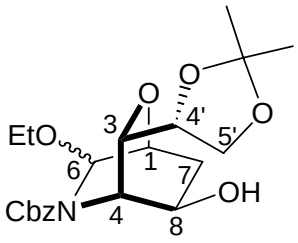


16

To a suspension of 4 Å molecular sieves (32 mg) in 2 ml of THF at 0 °C were sequentially added **7b** (0.30 g, 0.80 mmol), triethylorthoformate (0.33 ml, 2.0 mmol) and $BF_3{\cdot}Et_2O$ (20 µl, 0.16 mmol). The resulting reaction mixture was stirred at 0 °C for 3 h, after which 10 ml of water was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 ml). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluting with 3:7 EtOAc-petroleum) to afford

the *pyridinone* (0.24 g, 77%) as pale yellow oil as a mixture of two diastereomers (**a**:**b** ~ 1:2), R_f(EtOAc-petroleum, 3:7) 0.33; υ_{max} (film)/cm^{-1} 1685 (C=O), 1215 (COC); δ_H(400 MHz, $CDCl_3$) 1.14$^{\mathbf{b}}$ (3H, s, CH_3), 1.22$^{\mathbf{a+b}}$ (3H, *J* 7.3 Hz, CH_2CH_3), 1.27$^{\mathbf{b}}$ (3H, s, CH_3), 1.33$^{\mathbf{a}}$ (3H, s, CH_3), 1.48$^{\mathbf{a}}$ (3H, s, CH_3), 3.55$^{\mathbf{a+b}}$ (1H×2, d, *J* 8.6 Hz, C$^{\mathbf{7}}$H), 3.78$^{\mathbf{a}}$ (2H, q, *J* 7.3 Hz, CH_2CH_3), 3.82$^{\mathbf{b}}$ (2H, q, *J* 7.3 Hz, CH_2CH_3), 3.91$^{\mathbf{a+b}}$ (1H×2, dd, *J* 8.4 Hz, 3.4 Hz, C$^{\mathbf{9}}$H*H*), 3.98$^{\mathbf{a+b}}$ (1H×2, dd, *J* 8.4 Hz, 5.9 Hz, C$^{\mathbf{9}}$*H*H), 3.99-4.07$^{\mathbf{a+b}}$ (1H×2, m, C$^{\mathbf{8}}$H), 5.05$^{\mathbf{a+b}}$ (1H×2, d, *J* 12.2 Hz, C*H*HPh), 5.11$^{\mathbf{a+b}}$ (1H×2, s, C$^{\mathbf{2}}$H), 5.20$^{\mathbf{a+b}}$ (1H×2, d, *J* 12.2 Hz, CH*H*Ph), 5.83$^{\mathbf{a}}$ (1H, d, *J* 4.9 Hz, C$^{\mathbf{6}}$H), 6.03$^{\mathbf{b}}$ (1H, d, *J* 4.9 Hz, C$^{\mathbf{6}}$H), 6.13$^{\mathbf{a+b}}$ (1H×2, d, *J* 10.0 Hz, C$^{\mathbf{4}}$H), 6.75$^{\mathbf{a}}$ (1H, dd, *J* 10.0 Hz, 4.9 Hz, C$^{\mathbf{5}}$H), 6.83$^{\mathbf{b}}$ (1H, dd, *J* 10.0 Hz, 4.9 Hz, C$^{\mathbf{5}}$H), 7.23-7.36$^{\mathbf{a+b}}$ (5H×2, m, ArH); δ_C(100 MHz, $CDCl_3$) 17.9 (CH_3), 27.6 (CH_3), 29.5 (CH_3), 64.3 (CH), 68.7 (CH_2), 69.8 (CH_2), 71.1 (CH_2), 77.0 (CH), 78.4 (CH), 79.9 (CH), 112.2 (C), 130.9 (CH), 131.0 (CH), 131.1 (CH), 132.8 (CH), 137.9 (CH), 144.3 (CH), 158.0 (C), 195.4 (C); *m*/*z* (ESI) 428 (M+Na$^+$), 460 (100); HRMS (ESI) Found: M+Na$^+$, 428.1670; $C_{21}H_{27}NO_7$ requires M+Na$^+$, 428.1680.

(1*S*,3*S*,4*S*,8*R*)-3-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-ethoxy-8-hydroxy-2-oxa-5-aza-bicyclo[2.2.2]octane-5-carboxylic acid benzyl ester.

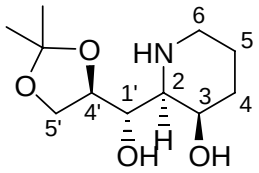


18

A solution of the substrate **16** (81 mg, 0.20 mmol) in 2 ml of methanol was cooled at -78 ºC and $CeCl_3 \cdot 7H_2O$ (38 mg, 0.11 mmol) was added with strong stirring. After 30 min, $NaBH_4$ (8 mg, 0.2 mmol) was added in small portions. The reaction mixture was vigorously stirred for 3 h before concentrating under vacuum. The residue was dissolved in isopropanol (3 ml), filtered through celite and concentrated under vacuum. Flash column chromatography, eluting with 2:3 EtOAc-petroleum, gave the *alcohol* (38 mg, 47%) as a pale yellow oil as a mixture of two diastereomers (**a**:**b** ~ 2:3); R_f(EtOAc-petroleum, 2:3) 0.29; υ_{max} (film)/cm^{-1} 3419 (OH), 1699 (C=O), 1100; δ_H(400 MHz, $CDCl_3$) 1.16$^{\mathbf{a}}$ (3H, t, *J* 7.0 Hz, CH_2CH_3), 1.26$^{\mathbf{b}}$ (3H, t, *J* 7.0 Hz,

C*H*$_2$CH$_3$), 1.28[b] (3H, s, CH$_3$), 1.31[a] (3H, s, CH$_3$), 1.34[b] (3H, s, CH$_3$), 1.49[a] (3H, s, CH$_3$); 2.05[a+b] (1H×2, dt, *J* 13.7 Hz, 3.9 Hz, C^{7}H*H*), 2.10-2.22 (1H×2, C^7*H*H), 3.48[a] (2H, q, *J* 7.0 Hz, C*H*$_2$CH$_3$), 3.57[b] (2H, q, *J* 7.0 Hz, C*H*$_2$CH$_3$), 3.71[a] (1H, d, *J* 5.0 Hz, C^{6}H), 3.76[b] (1H, d, *J* 5.0 Hz, C^{6}H), 3.83-4.02[a+b] (3H×2, C^{8}H & C$^{5'}$H$_2$), 4.04-4.14[a+b] (1H×2, C^{3}H), 4.17-4.28[a+b] (1H×2, C^{1}H), 4.28-4.37[a+b] (1H×2, C^{4}H), 4.42-4.53[a+b] (1H×2, m, C$^{4'}$H), 5.13[a+b] (1H×2, d, *J* 12.2 Hz, CH*H*Ph), 5.28[a+b] (1H×2, d, *J* 12.2 Hz, C*H*HPh), 7.33-7.45[a+b] (5H×2, m, PhH); δ_C(100 MHz, $CDCl_3$) 15.0 (CH_3), 24.8 (CH_3), 26.5 (CH_3), 53.7 (CH), 56.8 (CH), 64.6 (CH_2), 65.4 (CH_2), 65.6 (CH), 66.0 (CH_2), 68.3 (CH_2), 73.0 (CH), 77.3 (CH), 81.4 (CH), 108.9 (C), 128.2 (CH), 128.5 (CH), 128.8 (CH), 136.1 (C), 156.4 (C); *m*/*z* (ESI) 430 (M+Na$^+$); HRMS (ESI) Found: M+Na$^+$, 430.1833; $C_{21}H_{29}NO_7$ requires M+Na$^+$, 430.1836.

(2*S*,3*R*)-2-{(*S*)-[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-hydroxymethyl}-piperidin-3-ol.

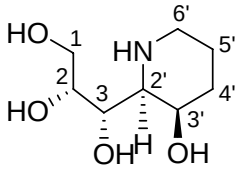


19

A 10 ml flask was charged with the substrate **15** (110 mg, 0.304 mmol), methanol (2.5 ml), and 10% palladium on carbon (14 mg, 0.014 mmol). The headspace was flushed with hydrogen gas and a hydrogen balloon was attached to the flask via a septum. The mixture was stirred for 12 h at which time the starting material was absent by TLC analysis. Filtration through celite and concentration under vacuum afforded the crude product, which was purified by flash column chromatography, eluting with 2:10:88 NH_4OH-MeOH-CH_2Cl_2, to give the *amine* (46 mg, 67%) as white needles, mp 155-156 °C (MeOH-$CHCl_3$-Et_2O); R_f(NH_4OH-MeOH-CH_2Cl_2, 2:10:88) 0.25; υ_{max} (film)/cm^{-1} 3252 (OH), 2985 and 2935 (NH), 1210; δ_H(400 MHz, $CDCl_3$) 1.29 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.37 (1H, m, C^{4}H*H*), 1.53 (1H, tq, *J* 13.2 Hz, 2.2 Hz, C^{5}H*H*), 1.75 (1H, qt, *J* 13.2 Hz, 4.2 Hz, C^5*H*H), 1.85 (1H, m, C^4*H*H), 2.61 (1H, td, *J* 12.8 Hz, 3.0 Hz, C^{6}H*H*), 2.67 (1H, dd, *J* 5.1 Hz, 1.2 Hz, C^{2}H), 3.03 (1H, br. d, *J* 12.8 Hz, C^6*H*H), 3.52 (1H, dd, *J* 8.1 Hz, 5.1 Hz, C^{3}H), 3.89-3.95 (1H, C$^{1'}$H), 4.04-4.11 (3H, C$^{4'}$H & C$^{5'}$H$_2$); δ_C(100 MHz, $CDCl_3$) 19.6 (CH_2), 25.3 (CH_3), 26.7 (CH_3), 30.9 (CH_2), 46.3 (CH_2), 60.4 (CH), 64.7 (CH), 67.7 (CH_2), 73.6 (CH), 76.0 (CH), 109.9 (CH); *m*/*z* (ESI) 232 (MH$^+$); HRMS (ESI) Found:

MH^+, 232.1550; $C_{11}H_{22}NO_4$ requires MH^+, 232.1543; $[\alpha]^{23}_D$ -13.3 (*c* 0.450 in MeOH).

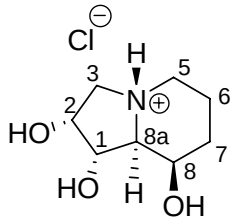
(2*S*,3*S*,2'*S*,3'*R*)-1-(3'-Hydroxy-piperidin-2'-yl)-propane-1,2,3-triol.



8b

Tosic acid monohydrate (70 mg, 0.37 mmol) was added to a solution of free amine **19** (78 mg, 0.33 mmol) in 2 ml of methanol. After vigorous stirring at room temperature for 12 h the mixture was concentrated to dryness and was rinsed subsequently with dry ether (2 ml), dry THF (2 ml), and $CHCl_3$ (2 ml). After drying under vacuum the white solid was deposited on Dowex 50W×8 (H^+ form, 10 g, 200-400 mesh) and washed subsequently with H_2O (50 ml), MeOH (50 ml), and 5N $NH_3 \cdot H_2O$ (100 ml). The solution from the last wash was evaporated and lyophilised to give a slightly yellow foam, which was decolorised by by active charcoal (H_2O) to give the pure *piperidine* (60 mg, 93%) as a white foam, mp 178 °C dec. (MeOH-$CHCl_3$); R_f(NH_4OH-MeOH-CH_2Cl_2, 1:3:6) 0.33; υ_{max} (film)/cm^{-1} 3700-3100, 1070, 1020; δ_H(400 MHz, CD_3OD) 1.48 (1H, br. d, *J* 12.2 Hz, C$^{4'}$H*H*), 1.67 (1H, m, C$^{5'}$H*H*), 1.85-2.00 (2H, m, C$^{4'}$*H*H & C$^{5'}$*H*H), 2.80 (1H, td, *J* 13.0 Hz, 3.0 Hz, C$^{6'}$H*H*), 2.96 (1H, dd, *J* 5.9 Hz, 1.5 Hz, C$^{2'}$H), 3.16 (1H, br. d, *J* 13.0 Hz, C$^{6'}$*H*H), 3.59-3.70 (3H, C$^{3'}$H & C^{1}H*H* & C^{2}H), 3.74 (1H, dd, *J* 5.9 Hz, 2.4 Hz, C^{3}H), 4.21 (1H, br. s, C^{1}*H*H); δ_C(100 MHz, CD_3OD) 22.5 (CH_2), 34.1 (CH_2), 48.5 (CH_2), 63.9 (CH), 67.0 (CH), 67.1 (CH_2), 74.4 (CH), 77.5 (CH); *m*/*z* (CI) 192 (MH^+, 59), 176 (3), 172 (3), 130 (9), 100 (100); found: C, 50.3; H, 8.91, N, 7.39; $C_8H_{17}NO_4$ requires C, 50.5; H, 8.83, N, 7.47); $[\alpha]^{23}_D$ -11.8 (*c* 1.23 in MeOH).

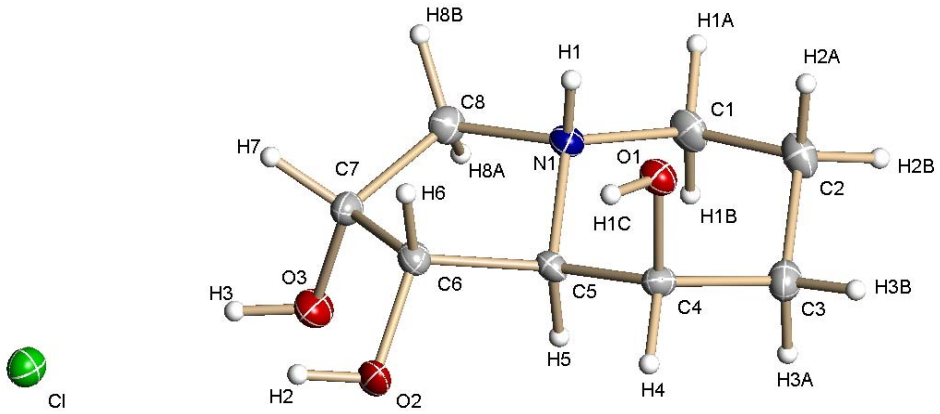
(1*S*,2*S*,8*S*,8a*R*)-Octahydro-1,2,8-indolizinetriol (8a-*epi*-swainsonine) hydrochloric salt.



20

To a solution of piperidine **8b** (58 mg, 0.30 mmol) in 2 ml of anhydrous DMF were added subsequently triphenylphosphine (158 mg, 0.60 mmol), anhydrous carbon tetrachloride (0.058 ml, 0.60 mmol), and anhydrous triethylamine (0.083 ml, 0.60 mmol). The solution was vigorously stirred at room temperature for 2 h and then quenched with methanol (3 ml). After 30 min, the mixture was concentrated under vacuum and chromatographed on silica gel, eluting with 2:10:88 MeOH-$CHCl_3$-Et_2O, to afford a pale yellow solid (40 mg, 80%), which upon recrystallisation ($CHCl_3$-MeOH-Et_2O) gave *8a-epi-swainsonine hydrochloric salt* as colorless needles, mp 202-204 °C dec. (MeOH-$CHCl_3$-Et_2O); R_f(NH_4OH-MeOH-CH_2Cl_2, 2:10:88) 0.21; υ_{max} (film)/cm^{-1} 3670-3370, 3345, 3311, 2547, 1077, 1108; δ_H(400 MHz, D_2O) 1.56-1.71 (2H, m, C^{6}H*H* & C^{7}H*H*), 1.76-1.91 (2H, m, C^{6}*H*H & C^{7}*H*H), 2.83 (1H, dd, *J* 12.7 Hz, 3.6 Hz, C^{3}H*H*), 2.86 (1H, dd, *J* 12.2 Hz, 3.2 Hz, C^{5}H*H*), 3.06 (1H, br. d, *J* 10.3 Hz, C^{8a}H), 3.39 (1H, br. d, *J* 12.2 Hz, C^{5}*H*H), 3.79 (1H, dd, *J* 12.7 Hz, 6.6 Hz, C^{3}*H*H), 3.97 (1H, dd, *J* 10.3 Hz, 6.1 Hz, C^{1}H), 4.20 (1H, td, *J* 6.6 Hz, 3.6 Hz, C^{2}H), 4.21 (1H, br. d, *J* 2.4 Hz, C^{8}H); δ_C(100 MHz, D_2O) 17.8 (CH_2), 28.3 (CH_2), 52.9 (CH_2), 58.9 (CH_2), 61.5 (CH), 65.9 (CH), 68.3 (CH), 68.4 (CH); *m*/*z* (ESI) 174 (M-Cl^+), 196 (M-HCl+Na^+); HRMS (ESI) Found: M-Cl^+, 174.1131, $C_8H_{16}NO_3Cl$ requires M-Cl^+, 174.1125); $[\alpha]^{23}_D$ -22.7 (*c* 0.440 in MeOH).

4. X-ray structure of 8a-*epi*-swainsonine



Crystallographic data are presented in the Tables below. A single crystal of **8a-epi-swainsonine** was coated in perfluoropolyether oil and mounted on a glass fibre. X-ray measurements were made using a Bruker-AXS Proteum CCD area-detector diffractometer with Cu-K_α radiation (λ = 1.5418 Å).[1] Intensities were integrated[2] from several series of exposures, each exposure covering 0.3° in ω, and the total data set being almost a sphere. Absorption corrections were applied, based on multiple and symmetry- equivalent measurements.[3] The structure was solved by direct methods and refined by least squares on weighted F^2 values for all reflections (see Table 1).[4] All non-hydrogen atoms were assigned anisotropic displacement parameters and refined without positional constraints. Hydrogen atom H1 was located in the electron density difference map and its position was refined with an N-H distance restraint of 0.88(3) Å. The positions of the hydroxyl hydrogen atoms were assigned by a rotating group refinement with fixed, idealised O-H distances. All other hydrogen atoms were constrained to ideal geometries. All hydrogen atoms were assigned isotropic displacement parameters equal to 1.5 times (hydroxyl hydrogen atoms) or 1.2 times (all other hydrogen atoms) that of their parent atom. Refinement proceeded smoothly to give the residuals shown in Table 1. Complex neutral-atom scattering factors were used.[5]

References

1. *SMART diffractometer control software version5.628*, Bruker AXS Inc., Madison, WI, 1997-2002.
2. *SAINT integration software version 7.06A*, Bruker AXS Inc., Madison,WI, 1997-2003.
3. G. M. Sheldrick. *SADABS version 2.05*, University of Göttingen: Germany, 2003.
4. *SHELXTL program system version 6.14*, Bruker-AXS Inc., Madison, WI, 2000-2003.
5. *International Tables for Crystallography*, Kluwer, Dordrecht, 1992, vol. C.

Table 1. Crystal data and structure refinement for **8a-epi-swainsonine**.

Identification code	108	
Empirical formula		
Formula weight	209.67	
Temperature	100 K	
Wavelength	1.5418 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 8.3941(3) Å	α = 90°
	b = 9.4475(3) Å	β = 90°
	c = 12.0154(4) Å	γ = 90°
Volume	952.86(6) Å^3	
Z	4	
Density (calculated)	1.462 Mg/m^3	
Absorption coefficient	3.381 mm^{-1}	
F(000)	448	
Crystal size	0.24 x 0.13 x 0.08 mm	
θ range for data collection	5.96 to 69.95°	
Index ranges	-10<=h<=10, -11<=k<=11, -14<=l<=14	
Reflections collected	7381	
Independent reflections	1766 [R_{int} = 0.0319]	
Completeness to θ = 69.95°	98.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.766 and 0.604	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1766 / 1 / 121	
Goodness-of-fit on F^2	S = 1.051	
R indices [for 1718reflections with I>2σ(I)]	R_1 = 0.0318, wR_2 = 0.0816	
R indices (for all 1766 data)	R_1 = 0.0326, wR_2 = 0.0823	
Weighting scheme	$w^{-1} = \sigma^2(F_o^2) + (aP)^2 + (bP)$,	
	where $P = [\max(F_o^2, 0) + 2F_c^2]/3$	
	a = 0.0429, b = 0.6223	
Absolute structure (Flack) parameter	0.038(19)	
Largest diff. peak and hole	0.724 and -0.702 eÅ^{-3}	

Table 2. Bond lengths [Å] and angles [°] for **8a-epi-swainsonine**.

C(1)-N(1)	1.496(3)
C(1)-C(2)	1.524(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.528(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.525(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-O(1)	1.426(3)
C(4)-C(5)	1.524(3)
C(4)-H(4)	1.0000
C(5)-N(1)	1.498(3)
C(5)-C(6)	1.520(3)
C(5)-H(5)	1.0000
C(6)-O(2)	1.404(3)
C(6)-C(7)	1.554(3)
C(6)-H(6)	1.0000
C(7)-O(3)	1.396(2)
C(7)-C(8)	1.532(3)
C(7)-H(7)	1.0000
C(8)-N(1)	1.512(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
N(1)-H(1)	0.862(16)
O(1)-H(1C)	0.8400
O(2)-H(2)	0.8400
O(3)-H(3)	0.8400
N(1)-C(1)-C(2)	109.33(18)
N(1)-C(1)-H(1A)	109.8
C(2)-C(1)-H(1A)	109.8
N(1)-C(1)-H(1B)	109.8
C(2)-C(1)-H(1B)	109.8
H(1A)-C(1)-H(1B)	108.3
C(1)-C(2)-C(3)	112.31(19)
C(1)-C(2)-H(2A)	109.1

C(3)-C(2)-H(2A)	109.1
C(1)-C(2)-H(2B)	109.1
C(3)-C(2)-H(2B)	109.1
H(2A)-C(2)-H(2B)	107.9
C(4)-C(3)-C(2)	110.23(19)
C(4)-C(3)-H(3A)	109.6
C(2)-C(3)-H(3A)	109.6
C(4)-C(3)-H(3B)	109.6
C(2)-C(3)-H(3B)	109.6
H(3A)-C(3)-H(3B)	108.1
O(1)-C(4)-C(5)	110.08(17)
O(1)-C(4)-C(3)	108.47(17)
C(5)-C(4)-C(3)	108.29(17)
O(1)-C(4)-H(4)	110.0
C(5)-C(4)-H(4)	110.0
C(3)-C(4)-H(4)	110.0
N(1)-C(5)-C(6)	101.02(17)
N(1)-C(5)-C(4)	108.92(17)
C(6)-C(5)-C(4)	121.03(17)
N(1)-C(5)-H(5)	108.4
C(6)-C(5)-H(5)	108.4
C(4)-C(5)-H(5)	108.4
O(2)-C(6)-C(5)	109.44(18)
O(2)-C(6)-C(7)	115.87(17)
C(5)-C(6)-C(7)	102.13(17)
O(2)-C(6)-H(6)	109.7
C(5)-C(6)-H(6)	109.7
C(7)-C(6)-H(6)	109.7
O(3)-C(7)-C(8)	108.83(17)
O(3)-C(7)-C(6)	111.79(17)
C(8)-C(7)-C(6)	104.25(17)
O(3)-C(7)-H(7)	110.6
C(8)-C(7)-H(7)	110.6
C(6)-C(7)-H(7)	110.6
N(1)-C(8)-C(7)	105.72(16)
N(1)-C(8)-H(8A)	110.6
C(7)-C(8)-H(8A)	110.6
N(1)-C(8)-H(8B)	110.6
C(7)-C(8)-H(8B)	110.6
H(8A)-C(8)-H(8B)	108.7

C(1)-N(1)-C(5)	113.10(17)
C(1)-N(1)-C(8)	115.95(16)
C(5)-N(1)-C(8)	105.13(16)
C(1)-N(1)-H(1)	103.9(16)
C(5)-N(1)-H(1)	109.9(16)
C(8)-N(1)-H(1)	108.8(16)
C(4)-O(1)-H(1C)	109.5
C(6)-O(2)-H(2)	109.5
C(7)-O(3)-H(3)	109.5