A Concise Total Synthesis of (±)-1-Epiaustraline

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Supplementary Information

(±)-3,4-Dihydroxy-pyrrolidine-1, 2, 5-tricarboxylic acid *tert*-butyl ester dimethyl ester (**11**).

To alkene **8** (4.97 g, 17.4 mmol) in CH₂Cl₂ (500 mL) were added Me₃NO·2H₂O (5.93 g, 52.2 mmol) and osmium tetroxide (223 mg, 0.87 mmol). The reaction mixture was stirred at ambient temperature for 24 h. Saturated Na₂SO₃ (30 mL) was then added to the reaction mixture and stirred for a further 0.5 h and then evaporated to dryness in *vacuo*. The product was purified by flash column chromatography (eluting with 100% Et₂O) to afford the diol **11** (5.32 g, 95%) as a clear oil.

$\nu_{\max}/\text{cm}^{-1}$: 3444 (br OH), 2977 (CH) and 1714 (C=O).

(Doubling of ¹H and ¹³C NMR resonances due to Boc rotamers).

δ_{H} (400 Hz; CDCl₃); 4.59-4.47 (3H, m, CHOH, CHOH and CHCO₂Me), 4.39 (2H, d, *J* 1.5, CHCO₂Me), 3.75 and 3.74 (3H, s x 2, OMe), 3.70 (3H, s, OMe), 1.34 and 1.33 (9H, s x 2, C(Me)₃).

δ_{C} (100 Hz; CDCl₃); 173.2, 170.6, 170.4, 153.4, 81.6, 75.2, 74.2, 71.2, 70.4, 66.6, 65.9, 62.1, 61.6, 53.0, 52.7, 52.5 and 28.1.

HRMS (ES⁻) for C₁₃H₂₀NO₈ requires 318.1189. Found 318.1184.

(±)-2,2-Dimethyl-tetrahydro-[1,3]dioxolo[4,5-c]pyrrole-4,5,6- tricarboxylic acid *tert*-butyl ester dimethyl ester (**12**).

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To diol **11** (5.5 g, 17.2 mmol) in acetone (560 mL) was added 2,2-dimethoxy propane (112 mL) and *p*-TsOH (155 mg, 1 mmol). The reaction mixture was stirred at 35 °C for 24 h. Et₃N (1 mL) was added to the mixture and then evaporated to dryness. The crude product was purified by flash column chromatography (eluting with 50% Et₂O in petroleum spirit) to afford **12** (5.8 g, 94%) as a white solid.

Mp; 121-123 °C.

$\nu_{\max}/\text{cm}^{-1}$; 2980 (CH), 1751 (C=O) and 1711 (C=O)

(Doubling of ¹H and ¹³C NMR resonances due to Boc rotamers).

δ_{H} (400 Hz; CDCl₃); 4.94 and 4.92 (1H, dd x 2, *J* 6.5, 4.0 and *J'* 6.3, 4.0 Me₂OCH), 4.67 and 4.66 (1H, dd x 2, *J* 6.1, 1.0 and *J'* 6.1, 1.3, Me₂OCH), 4.63 (1H, dd, *J* 4.3 and 3.3, CHCO₂Me), 4.58 and 4.56 (1H, d x 2, *J* 7.6 and *J'* 1.0, CHCO₂Me), 3.73 and 3.72 (3H, s x 2, OMe), 3.71 and 3.70 (3H, s x 2, OMe), 1.41 and 1.40 (3H, s x 2, CMeMe), 1.35 (9H, s x 2, C(Me)₃) and 1.25 (3H, s, × CMeMe).

δ_{C} (100 Hz; CDCl₃); 171.0, 170.8, 168.6, 168.0, 154.0, 153.9, 113.6, 113.5, 82.2, 81.3, 81.3, 79.3, 78.1, 65.4, 65.1, 64.8, 64.6, 52.6, 52.4, 51.9, 51.8, 28.0, 25.5 and 24.7.

MS (ES⁺) 360 (MH⁺, 25%), 304 (25) and 260 (100).

HRMS (ES⁺) for C₁₆H₂₆NO₈ requires 360.1658. Found 360.1659.

(±)-6-(*tert*-Butyl-dimethyl-silyloxymethyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-4,5-dicarboxylic acid 5-*tert*-butyl ester 4-methyl ester (**15**).

a) NaBH₄ (1.5 g, 40 mmol) was added to a mixture of acetonide **12** (5.57 g, 15.5 mmol), LiCl (1.70 g, 40 mmol), EtOH (150 mL) and THF (120 mL) at ambient temperature. The mixture was stirred for 24 h at ambient temperature and saturated NH₄Cl aq. (50 mL) was added. Stirring was continued for 30 min before AcOH was added until pH = 7 was obtained. Evaporation of the organic solvents and extraction of the aqueous layer with EtOAc (300 mL x 2) followed by drying (MgSO₄) and evaporation of EtOAc under reduced pressure gave crude alcohol (6.0 g) that was used in the next step without purification.

b) To a mixture of crude alcohol (6.0 g, from part a) in DMF (4 mL) at ambient temperature was sequentially added imidazole (2.45 g, 36 mmol) and TBSCl (4.07 g, 27 mmol). The mixture was stirred for 24 h after which more TBSCl (4.20 g) and imidazole (2.0 g) were added and stirred for a further 9 h. Saturated NH₄Cl aq. (30 mL) was added and the aqueous layer was extracted with Et₂O (100 mL x 2). The organic layer was dried (MgSO₄) and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5% Et₂O in petroleum spirit) to afford **15** (5.89 g, 85% over two steps) as a white solid.

Mp; 79-81 °C.

$\nu_{\max}/\text{cm}^{-1}$; 2954 (CH), 2932 (CH), 1768 (C=O) and 1704 (C=O).

(Doubling of ^1H and ^{13}C NMR resonances due to Boc rotamers).

δ_{H} (400 Hz; CDCl_3); 4.90-4.84 (1H, m, Me_2OCH), 4.66 and 4.65 (1H, d x 2, J 5.8 and J' 6.1, CHCO_2Me), 4.49 and 4.44 (1H, d x 2, J 8.1 and J' 7.8, Me_2OCH), 4.28-4.25 and 4.16-4.14 (1H, m, NCH), 4.10 and 3.88 (1H, dd x 2, J 2.0 and 10.4 J' 2.5 and 10.4, SiOCHH), 3.72 (3H, s, COMe), 3.62 and 3.57 (1H, dd x 2, J 1.8 and 10.4 J' 1.5 and 10.4, SiOCHH), 1.43 and 1.37 (9H, s, CMe_3), 1.42 and 1.40 (3H, s, CMe), 1.28 (3H, s, CMe), 0.86 and 0.85 (9H, s, SiCMe_3) and 0.03, 0.01, 0.00 (6H, SiMe_2).

δ_{C} (100 Hz; CDCl_3); 169.4, 168.5, 153.7, 153.3, 112.2, 83.3, 82.4, 80.4, 79.6, 78.4, 63.9, 63.6, 63.4, 62.1, 51.7, 51.6, 28.4, 28.1, 25.8, 25.3, 24.6, 24.5, 18.1, -5.5, -5.6 and -5.7.

MS (ES^+) 446 (MH^+ , 25%), 468 (45) and 913 (100).

HRMS (ES^+) for $\text{C}_{21}\text{H}_{40}\text{NO}_7\text{Si}$ requires 446.2574. Found 446.2581.

($\pm$)-4(*tert*-Butyl-dimethyl-silyloxymethyl)-6-formyl-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester (**13**).

Dibal-H (18 mL of 1.5 M in toluene, 27 mmol) was slowly added to a solution of ester **15** (4.0 g, 9.0 mmol) in CH_2Cl_2 (50 mL) at $-60\text{ }^\circ\text{C}$ over 15 min. The mixture was stirred at $-60\text{ }^\circ\text{C}$ for 3 h after which MeOH (10 mL) was slowly added over 20 min. Saturated NH_4Cl aq. (20 mL) was then added to the mixture and the resulting gel was filtered through a pad of celite and the celite was washed several times with CH_2Cl_2 .

The filtrate was evaporated under reduced pressure and the product was purified by flash column chromatography (eluting with 5% EtOAc in petroleum spirit) to afford **13** (3.63 g, 97%) as a clear oil.

$\nu_{\max}/\text{cm}^{-1}$; 2929, 2858 (CH), 1738 (C=O), 1732 (C=O), 1694 (C=O) and 1682 (C=O).

(Doubling of ^1H and ^{13}C NMR resonances due to Boc rotamers).

δ_{H} (400 Hz; CDCl_3); 9.28 and 9.24 (1H, d x 2, J 3.8 and J' 3.8, HCO), 4.91-4.85 (1H, m, Me_2OCH), 4.69 and 4.68 (1H, d x 2, J 5.2 and J' 5.8, COCH), 4.22-4.20, 4.15-4.05 and 3.87-3.81 (4H, m, Me_3OCH , SiOCH_2 and NCH), 3.63 and 3.60 (1H, dd x 2, J 10.4, 1.8, and J' 10.5, 1.5, NCH), 1.42 and 1.40 (3H, s x 2, CMe), 1.43 and 1.36 (9H, s x 2, CMe_3), 1.25 (3H, s, CMe), 0.84 and 0.83 (9H, s x 2, $\text{SiC}(\text{Me})_3$), -0.01 (3H, s, SiMe) and -0.02 (3H, s, SiMe).

δ_{C} (100 Hz; CDCl_3); 198.6, 198.2, 154.3, 153.3, 111.9, 83.2, 82.3, 81.5, 81.3, 81.0, 80.2, 69.0, 64.7, 64.5, 63.4, 62.2, 28.3, 28.1, 25.8, 25.7, 24.0, 18.0, -5.6 and -5.7.

MS (ES^+) 316 ($\text{M} + \text{H}^+ - \text{Boc}$, 100%), 360 (100) and 416 ($\text{M} + \text{H}^+$, 25).

HRMS (ES^+) for $\text{C}_{20}\text{H}_{38}\text{NO}_6\text{Si}$ requires 416.2468. Found 416.2470.

(±)-4(*tert*-Butyl-dimethyl-silyloxymethyl)-6-(1-hydroxy-allyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylic acid *tert*-butyl ester (**14**)

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To a solution of aldehyde **13** (570 mg, 1.37 mmol) in THF (100 mL) at ambient temperature was added vinylmagnesium bromide (4.1 mL of 1M in THF, 4.1 mmol).

The reaction mixture was stirred for 10 min. and saturated NH_4Cl aq. (20 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (100 x 3). The organic layer was dried (MgSO_4) and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5% EtOAc in petroleum spirit) to afford **14** (553 mg, 91%) as a clear oil.

$\nu_{\text{max}}/\text{cm}^{-1}$; 3373 (br OH), 2932 (CH) and 1682 (C=O).

(Doubling of ^1H and ^{13}C NMR resonances due to Boc rotamers).

δ_{H} (400 Hz; CDCl_3); 6.37 (1H, br s, OH), 6.16 (1H, ddd, J 4.9 10.6 and 16.3, $\text{CH}=\text{CHH}$), 5.53 (1H, d, J 17.2, $\text{CH}=\text{CHH}$), 5.20 (1H, d, J 10.6, $\text{CH}=\text{CHH}$), 4.89-4.70 and 4.63-4.52 (3H, m x 2, $=\text{CCHOH}$, Me_2OCH , SiOCHH), 4.20-4.09 and 4.00-3.92 (1H, m x 2, Me_2OCH), 3.73-3.64 (2H, m, NCH, SiOCHH), 3.58 (1H, dd, J 3.7, 7.9, NCH), 1.44 (9H, s, CMe_3), 1.42 (3H, s, CMeMe), 1.28 (3H, s, CMeMe), 0.86 (9H, s, SiCMe_3) and 0.02 (6H, s, SiMe_2).

δ_{C} (100 Hz; CDCl_3); 155.5, 137.3, 116.1, 111.1, 81.2, 80.8, 79.6, 70.1, 69.6, 67.0, 63.0, 28.4, 26.6, 25.8, 25.0, 18.1, -5.5 and -5.6.

MS (ES^+) 344 ($\text{M} + \text{H}^+ - \text{Boc}$, 80%), 388 (65) and 444 ($\text{M} + \text{H}^+$, 100).

HRMS (ES^+) for $\text{C}_{22}\text{H}_{42}\text{NO}_6\text{Si}$ requires 444.2781. Found 444.2786.

(±)-3-((*tert*-Butyl-dimethyl-silyloxy)-3-[6-((*tert*-butyl-dimethyl-silyloxymethyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-*c*]pyrrol-4-yl]-propan-1-ol (21b).

To a solution of **14** (340 mg, 0.77 mmol) in CH_2Cl_2 (5 mL) and 2,6-lutidine (410 μL) at -78°C was added TBSOTf (810 μL). The reaction mixture was slowly warmed to

ambient temperature over 1 h and stirred for 24 h. Saturated NH_4Cl aq. (3 mL) was added and the aqueous layer was extracted with EtOAc (10 mL x 2). The organic layer was dried (MgSO_4) and evaporated under *vacuo* to remove the organic solvent and 2,6-lutidine. The crude product was dissolved in THF (2 mL) and $\text{BH}_3\cdot\text{THF}$ (2.3 mL of 1 M in THF, 2.3 mmol) was added. The reaction mixture was stirred at ambient temperature overnight. Aqueous NaOH (3 M, 3 mL) was added to the reaction mixture followed by H_2O_2 (30%, 3 mL). Stirring was continued for a further 1 h before EtOAc (50 mL) was added. The layers were separated and the aqueous layer was extracted with EtOAc (50 mL x 2). The organic layer was dried (MgSO_4) and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 10-20% EtOAc in petroleum spirit) to afford **21** (223 mg, 61%) as a 7:1 mixture of diastereomers (**21b:21a**).

Data for major diastereomer **21b**.

$\nu_{\text{max}}/\text{cm}^{-1}$; 3466 and 3188 (br OH and NH), 2930 and 2857 (CH)

δ_{H} (400 Hz; CDCl_3); 5.20 (1H, br s, NH), 4.86 (1H, dd, J 5.5 and 6.0, Me_2COCH), 4.74 (1H, dd, J 2.1 and 6.2, Me_2COCH), 4.46-4.41 (1H, m, SiOCH), 4.25 (1H, dd, J 3.6, 11.1, SiOCHH), 3.94 (1H, dd, J 5.2, 11.1, SiOCHH), 3.81-3.77 (2H, m, CH_2OH), 3.43-3.38 (1H, m, NCH), 3.28-3.23 (1H, m, NCH), 2.15-1.97 (2H, m, CH_2), 1.97 (1H, br s, OH), 1.51 (3H, s, CMeMe), 1.32 (3H, s, CMeMe), 0.91 (9H, s, SiCMe_3), 0.90 (9H, s, SiCMe_3), 0.14 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.10 (3H, s, SiMe) and 0.09 (3H, s, SiMe).

δ_{C} (100 Hz; CDCl_3); 111.8, 80.4, 79.9, 69.1, 68.8, 67.9, 59.9, 59.8, 35.7, 25.9, 25.8, 18.4, 18.0, 15.2, -4.5, -5.4 and -5.5.

m/z (ESI) 476 ($\text{M} + \text{H}^+$, 100%), 460 (10) and 346 (20)

HRMS Found $\text{M} + \text{H}^+$, 476.3235. $\text{C}_{23}\text{H}_{50}\text{NO}_5\text{Si}_2$ requires 476.3228.

(±)-1-Epiaustraline (3)

a) To a solution of alcohol **21** (35 mg, 0.074 mmol) in CH₂Cl₂ and Et₃N (22 mg, 0.22 mmol) at 0 °C was added MeSO₂Cl (25 mg, 0.22 mmol). The mixture was stirred at 0 °C for 10 min and then warmed to ambient temperature. Stirring was continued for a further 1 h and the solvent was evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 10% EtOAc in petroleum spirit) to afford **22** (24 mg, 71%) as a clear oil.

b) TFA (0.4 mL) was added to a mixture of **22** (20 mg, 0.044 mmol) and H₂O (0.6 mL) at ambient temperature. The reaction mixture was stirred overnight. Aqueous NH₃ (25%, 2 mL) was slowly added to the mixture until pH was greater than 7. The solvent was evaporated under reduced pressure and the product was purified by flash column chromatography (eluting first with 2:1 CHCl₃:MeOH, then 1:1 CHCl₃:MeOH and finally 5:4:1 CHCl₃:MeOH:25% NH₄OH) to afford 1-epiaustraline (7.5 mg, 84%) as a clear oil. Both ¹H and ¹³C NMR matched that of natural 1-epiaustraline.¹

δ_H(500 Hz; H₂O); 4.42 (1H, q, *J* 4.7, CH-7), 4.25 (1H, t, *J* 4.9, CH-1), 3.76 (1H, dd, *J* 4.6 and 9.0, CH-2), 3.65 (1H, dd, *J* 4.0 and 11.6, CH-8), 3.48 (1H, dd, *J* 6.7 and 11.6, CH-8), 3.29 (1H, t, *J* 5.2, CH-7a), 3.00 (1H, ddd, *J* 4.2, 7.2 and 10.8, CH-5), 2.85 (1H, ddd, *J* 4.0, 6.7 and 9.0, CH-3), 2.75 (1H, td, *J* 6.7 and 10.0, CH-5) and 1.91-1.77 (2H, m, CH-6).

δ_C(125 Hz; H₂O); 75.2, 73.7, 72.7, 70.7, 66.7, 63.5, 52.7 and 35.9.

HRMS Found *M* + H⁺, 190.1084. C₈H₁₅NO₄ requires 190.1079.

Natural 1-epiaustraline

Synthetic 1-epiaustraline

Reference

1. Denmark S. E.; Cottell J. J. *J. Org. Chem.* **2001**, *66*, 4276.