

## Supplementary information

### Enantioselective Formal Total Synthesis of Roseophilin

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**General methods and materials.** Unless otherwise noted materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran and diethyl ether were freshly distilled from sodium/benzophenone. Dichloromethane was freshly distilled from calcium hydride. Acetonitrile, *N,N*-dimethylformamide and toluene were distilled from calcium hydride and stored over molecular sieves. Petroleum ether (bp 60-80 °C) was distilled before use. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Hexamethylphosphoramide was distilled and stored over molecular sieves. Methanol was distilled from magnesium and stored over molecular sieves. 2-[*N,N*-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine was Kugelrohr distilled before use and stored at 0 °C under an atmosphere of nitrogen. All reactions were stirred under an inert atmosphere of dry nitrogen unless otherwise indicated. During workup where drying of the organic solutions is indicated Na<sub>2</sub>SO<sub>4</sub> was used with subsequent filtration. Column chromatography was performed using Acros Chimica silica gel (0.030-0.075 mm).

Infrared spectra were recorded from CHCl<sub>3</sub> solutions using a Bruker IFS 28 spectrophotometer and absorptions are reported in units of cm<sup>-1</sup>. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker ARX 400 (400 MHz) or a Varian Inova-500 (500 MHz). Spectra are reported in units of ppm on the  $\delta$  scale relative to an internal standard of residual chloroform (7.27 ppm for <sup>1</sup>H-NMR and 77.0 for <sup>13</sup>C-NMR). *J* values are in Hertz. Carbon resonances were detected by using attached proton test (ATP). Mass spectra and accurate mass determinations were measured on a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system, with data reported as *m/z* (relative intensity). Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim a. d. Ruhr, Germany. Melting points are uncorrected.

#### **(3a*R*,6a*R*)-6-(1,3-dioxolan-2-yl)-1-(toluene-4-sulfonyl)-1,3,3a,6a-tetrahydro-**

**cyclopenta[b]pyrrol-2-one 7.** To a solution of ketone **2**<sup>1</sup> (50 mg, 172  $\mu$ mol) in dichloromethane (2 ml) at -78 °C was added 1,2-bis(trimethoxysilyl)ethane (63  $\mu$ l, 258  $\mu$ mol) and trimethylsilyl trifluoromethanesulfonate (3  $\mu$ l, 17.2  $\mu$ mol) and the solution was stored in the freezer (-20 °C)

<sup>1</sup> Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.*, **1998**, *63*, 220.

overnight. The reaction was directly poured into a vigorously stirred saturated aqueous solution of sodium bicarbonate (10 ml). The mixture was then extracted with dichloromethane (3 x 10 ml). The combined organic phases were dried and concentrated. Column chromatography (2:1 ethyl acetate/petroleum ether) afforded protected ketone **7** (47 mg, 82%) as a white solid: mp 218 °C (EtOAc);  $[\alpha]_D +59.0$  (c 1.0, CHCl<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  2977, 2900, 1733; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.92 (2H, d, *J* 8.1), 7.28 (2H, d, *J* 8.1), 5.96 (1H, dd, *J* 5.7, 2.4), 5.72 (1H, d, *J* 5.7), 4.64 (1H, d, *J* 8.0), 4.14-4.25 (2H, m), 3.91-4.04 (2H, m), 3.32-3.38 (1H, m), 2.56 (1H, dd, *J* 18.1, 10.7), 2.39 (3H, s), 2.22 (1H, dd, *J* 18.1, 6.4); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.7, 144.8, 136.0, 136.0, 131.7, 129.2, 128.4, 116.0, 67.4, 66.2, 65.5, 38.8, 36.6, 21.5; *m/z* (EI) 335 (M<sup>+</sup>, 23%), 180 (100), 125 (65) (Found M<sup>+</sup>: 335.0833. Calc. for C<sub>16</sub>H<sub>17</sub>NO<sub>5</sub>S: 335.0827) (Found: C, 57.21; H, 5.15; N, 4.11; S, 9.42. Calc. for C<sub>16</sub>H<sub>17</sub>NO<sub>5</sub>S: C, 57.30; H, 5.11; N, 4.18; S, 9.56).

**(3a*R*,4*R*,6*aR*)-4-Isopropyl-6,6-dimethoxy-1-(toluene-4-sulfonyl)-hexahydro-**

**cyclopenta[*b*]pyrrol-2-one 10.** A solution of ketone **9**<sup>1</sup> (1.00 g, 2.98 mmol), trimethyl orthoformate (978  $\mu$ l, 8.94 mmol) and *p*-toluenesulfonic acid (28 mg, 149  $\mu$ mol) in methanol (15 ml) was stirred at 70 °C for 2 h. The reaction mixture was allowed to cool to room temperature. Diethyl ether (40 ml) was added and the solution was washed with saturated aqueous sodium bicarbonate solution (10 ml), water (10 ml) and brine (10 ml). The organic phase was dried and concentrated. Column chromatography (1:4 ethyl acetate/petroleum ether) afforded dimethyl acetal **10** (1.10 g, 97%) as a colourless oil:  $[\alpha]_D +49.3$  (c 1.7, CHCl<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  2959, 2870, 1740; <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  8.38 (2H, d, *J* 8.3), 6.82 (2H, d, *J* 8.3), 4.51 (1H, d, *J* 9.6), 3.28 (3H, s), 2.84 (3H, s), 2.12 (1H, dd, *J* 17.7, 10.8), 1.89 (1H, dd, *J* 17.7, 8.7), 1.86 (3H, s), 1.74-1.65 (1H, m), 1.52 (1H, dd, *J* 13.3, 7.1), 1.31 (1H, dd, *J* 13.3, 8.3), 1.14-1.02 (1H, m), 0.90-0.80 (1H, m), 0.64 (3H, d, *J* 6.6), 0.54 (3H, d, *J* 6.6); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  174.3, 144.5, 135.9, 129.1, 128.9, 107.6, 65.4, 51.3, 49.4, 49.2, 40.8, 38.1, 34.8, 32.4, 21.6, 22.0, 20.7.

**(3a*S*,4*R*,6*aR*)-4-Isopropyl-6,6-dimethoxy-1-(toluene-4-sulfonyl)-1,3a,4,5,6,6a-hexahydro-**

**cyclopenta[*b*]pyrrole-2-carboxylic acid methyl ester 11.** To a solution of lactam **10** (873 mg, 2.29 mmol) in tetrahydrofuran (15 ml) at -78 °C was added dropwise potassium bis(trimethylsilyl)amide (0.5 M in toluene, 6.87 ml, 3.43 mmol) and the solution was stirred at -78 °C for 1 h. A solution of 2-[*N,N*-bis(trifluormethylsulfonyl)amino]-5-chloropyridine (1.35 g, 3.43 mmol) and

hexamethylphosphoramide (597  $\mu$ l, 3.43 mmol) in tetrahydrofuran (5 ml) was then added dropwise. The mixture was stirred at -78 °C for 1 h and warmed to 0 °C over 1 h. The reaction was quenched with saturated aqueous ammonium chloride solution and allowed to warm to room temperature. Ethyl acetate (30 ml) was added and the solution was washed with water (10 ml), saturated aqueous sodium bicarbonate solution (10 ml), water (10 ml) and brine (10 ml). The organic phase was dried and concentrated to yield the crude triflate **5**.

A solution of the crude triflate **5** (~2.29 mmol), triphenylarsine (281 mg, 916  $\mu$ mol), tris(dibenzylideneacetone)dipalladium(0) (210 mg, 229  $\mu$ mol), lithium chloride (291 mg, 6.87 mmol), triethylamine (964 ml, 6.87 mmol) and methanol (3.72 ml, 96.6 mmol) in acetonitrile (20 ml) was stirred under 20 atm of carbon monoxide at 50 °C for 1 h. Diethyl ether (30 ml) was added and the mixture was filtered through a plug of silica. The filtrate was concentrated and purified by column chromatography (1:9 to 1:4 ethyl acetate/petroleum ether) affording ester **11** (688 mg, 71%) as a colourless oil:  $[\alpha]_D$  +88.6 (c 1.3,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2957, 1731, 1598;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 (2H, d, *J* 8.3), 7.30 (2H, d, *J* 8.3), 6.09 (1H, d, *J* 2.2), 4.33 (1H, d, *J* 9.5), 3.85 (3H, s), 3.38 (3H, s), 3.31 (3H, s), 2.49-2.48 (1H, m), 2.43 (3H, s), 1.92 (1H, dd, *J* 12.7, 6.4), 1.43-1.30 (2H, m), 1.25 (1H, t, *J* 12.3), 0.78 (6H, d, *J* 6.6);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  162.8, 144.0, 136.1, 133.5, 132.9, 129.3, 128.4, 108.5, 71.7, 52.3, 51.2, 50.0, 49.0, 47.4, 36.3, 33.1, 21.6, 20.8, 20.8; *m/z* (FAB+) 446 ( $\text{M}+\text{Na}^+$ , 40%), 392 (85), 350 (38), 295 (25), 268 (100) (Found  $\text{M}+\text{H}^+$ : 424.1742. Calc. for  $\text{C}_{21}\text{H}_{30}\text{NO}_6\text{S}$ : 424.3097).

**(3aS,4*R*,6*aR*)-[4-isopropyl-6,6-dimethoxy-1-(toluene-4-sulfonyl)-1,3*a*,4,5,6,6*a*-hexahydro-cyclopenta[*b*]pyrrol-2-yl]-methanol 12.** To a stirred solution of ester **11** (736 mg, 1.74 mmol) in tetrahydrofuran (10 ml) at -78 °C was added dropwise diisobutylaluminium hydride (1.5 M in toluene, 4.63 ml, 6.95 mmol). The solution was warmed to 0 °C over 1 h and further stirred at this temperature for 1 h. The reaction was quenched by careful dropwise addition of a saturated aqueous sodium sulfate solution. After warming to room temperature ethyl acetate (15 ml) was added and the mixture was stirred for 2 h at room temperature, upon which a white precipitate appeared. The solution was dried, filtered through celite and concentrated. Column chromatography (1:3 ethyl acetate/petroleum ether) afforded alcohol **12** (536 mg, 78%) as a white solid: mp 109.5 °C ( $\text{EtOAc}$ );  $[\alpha]_D$  +241.9 (c 1.2,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  3456, 2959, 1598;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.70 (2H, d, *J* 8.2), 7.29 (2H, d, *J* 8.2), 5.23 (1H, s), 4.49-4.43 (1H, m), 4.32 (1H, dd, *J* 14.0, 7.6), 4.22 (1H, d, *J*

9.9), 3.43 (3H, s), 3.42 (3H, s), 2.92 (1H, dd, *J* 7.6, 6.4), 2.45-2.42 (1H, m), 2.42 (3H, s), 1.93 (1H, dd, *J* 12.3, 5.8), 1.44-1.27 (3H, m), 0.80 (3H, d, *J* 6.5), 0.78 (3H, d, *J* 6.5);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  143.9, 142.1, 133.7, 129.5, 127.5, 122.3, 108.7, 71.8, 59.3, 51.0, 50.1, 48.2, 47.7, 37.0, 32.9, 21.5, 20.8, 20.8; (Found: C, 60.65; H, 7.46; N, 3.39; S, 7.95. Calc. for  $\text{C}_{20}\text{H}_{29}\text{NO}_5\text{S}$ : C, 60.73; H, 7.39; N, 3.54; S, 8.11).

**(3a*S*,4*R*,6*aR*)-2-Iodomethyl-4-isopropyl-6,6-dimethoxy-1-(toluene-4-sulfonyl)-1,3*a*,4,5,6,6*a*-hexahydro-cyclopenta[*b*]pyrrole 13.**

To a solution of alcohol **12** (330 mg, 834  $\mu\text{mol}$ ) in diethyl ether and acetonitrile (3:2, 15 ml) at 0 °C was added sequentially triphenylphosphine (427 mg, 1.63 mmol), imidazole (122 mg, 1.79 mmol) and iodine (508 mg, 2.00 mmol) and the solution was stirred at 0 °C for 1 h. Ethyl acetate (10 ml) was added and the solution was washed with 5% aqueous sodium thiosulfate solution (15 ml), saturated aqueous copper(II) sulfate solution (15 ml) and brine (15 ml). The organic phase was dried and concentrated. Column chromatography (1:8 ethyl acetate/petroleum ether) afforded iodide **13** (405 mg, 96%) as a pale yellow solid: mp 115 °C ( $\text{EtOAc}$ );  $[\alpha]_D$  +45.7 (c 0.6,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2958, 2838, 1598;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.65-7.60 (2H, m), 7.26 (2H, d, *J* 8.0), 5.42 (1H, s), 4.53 (1H, d, *J* 10.6), 4.31 (1H, d, *J* 9.5), 4.05 (1H, d, *J* 10.6), 3.47 (3H, s), 3.37 (3H, s), 2.40 (3H, s), 2.38-2.20 (1H, m), 1.88-1.84 (1H, m) 1.39-1.23 (3H, m), 0.77 (3H, d, *J* 6.1), 0.71 (3H, d, *J* 6.1);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  143.9, 140.4, 133.4, 129.4, 127.6, 125.2, 108.4, 71.9, 50.8, 49.4, 48.4, 46.8, 35.9, 32.5, 21.5, 20.8, 20.7, -3.08; *m/z* (FAB+) 506 ( $\text{M}+\text{H}^+$ , 15%), 474 (100), 350 (95), 346 (93), 318 (75) (Found  $\text{M}+\text{H}^+$ : 506.0873. Calc. for  $\text{C}_{20}\text{H}_{29}\text{NO}_4\text{SI}$ : 506.0862).

**(3a*S*,4*R*,6*aR*)-2-Benzenesulfonylmethyl-4-isopropyl-6,6-dimethoxy-1-(toluene-4-sulfonyl)-1,3*a*,4,5,6,6*a*-hexahydro-cyclopenta[*b*]pyrrole 14.**

To a solution of iodide **13** (400 mg, 791  $\mu\text{mol}$ ) in dimethylformamide (6 ml) was added benzenesulfinic acid, sodium salt (520 mg, 3.17 mmol) and hexamethylphosphoramide (138 ml, 791  $\mu\text{mol}$ ) and the solution was stirred at 45 °C for 2 h. The reaction mixture was allowed to cool to room temperature, poured into water (10 ml) and extracted with diethyl ether (15 ml). The organic phase was then washed with water (4  $\times$  10 ml), brine, dried and concentrated. Column chromatography (1:4 ethyl acetate/petroleum ether) afforded sulfone **14** (391 mg, 95%) as a white solid: mp 122 °C ( $\text{EtOAc}$ );  $[\alpha]_D$  +131.5 (c 1.3,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2958, 1598;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05-8.03 (2H, m), 7.69-7.66 (1H, m), 7.60-7.57 (4H, m) 7.29-

7.27 (2H, m), 5.54 (1H, s), 4.72 (1H, d, *J* 15.6), 4.18 (1H, d, *J* 15.6), 4.16 (1H, d, *J* 9.3), 3.40 (3H, s), 3.21 (3H, s), 2.43 (3H, s), 2.33-2.32 (1H, m), 1.89-1.88 (1H, m) 1.35-1.25 (3H, m), 0.80 (3H, d, *J* 5.9), 0.74 (3H, d, *J* 5.9); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 144.2, 139.4, 133.7, 132.9, 130.6, 129.6, 129.0, 128.6, 128.0, 127.9, 108.5, 71.1, 55.7, 50.7, 49.3, 48.9, 47.3, 35.6, 32.4, 21.6, 20.9, 20.9; (Found: C, 60.15; H, 6.48; N, 2.61; S, 12.26. Calc. for C<sub>26</sub>H<sub>33</sub>NO<sub>6</sub>S<sub>2</sub>: C, 60.09; H, 6.40; N, 2.70; S, 12.34).

**(1'S,3aS,4R,6aR)-2-(1-Benzenesulfonyl-hept-6-enyl)-4-isopropyl-6,6-dimethoxy-1-(toluene-4-sulfonyl)-1,3a,4,5,6,6a-hexahydro-cyclopenta[b]pyrrole 15.** To a solution of sulfone **14** (408 mg, 785 μmol) in tetrahydrofuran (8 ml) at -78 °C was added dropwise *n*-butyllithium (1.6 M in hexanes, 540 μl, 864 μmol) and the solution was stirred at -78 °C for 1 h. Hexamethylphosphoramide (273 μl, 1.57 mmol) was added, followed immediately by the addition of 6-bromo-1-hexene (210 μl, 1.57 mmol). The reaction mixture was stirred for 1 h at -78 °C and then allowed to warm to -40 °C over 1 h. Saturated aqueous ammonium chloride solution was added to quench the reaction and the mixture was allowed to warm to room temperature. Diethyl ether (15 ml) was added, the solution was washed with water (15 ml), and the aqueous phase was extracted with diethyl ether (2 × 15 ml). The combined organic phases were dried and concentrated. Column chromatography (1:7 ethyl acetate/petroleum ether) afforded alkylated sulfone **15** (305 mg, 65%) as a colourless oil: [α]<sub>D</sub> +62.0 (c 1.0, CHCl<sub>3</sub>);  $\nu_{\text{max}}$ /cm<sup>-1</sup> 3068, 2957, 1640, 1597; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.02-8.00 (2H, m), 7.73-7.67 (3H, m), 7.63-7.59 (2H, m), 7.26-7.23 (2H, m), 5.84 (1H, d, *J* 1.6), 5.71 (1H, ddt, *J* 16.9, 10.2, 6.7), 5.01-5.98 (1H, m), 4.93-4.86 (2H, m), 4.01 (1H, d, *J* 9.1), 3.47 (3H, s), 3.19 (3H, s), 2.41 (3H, s), 2.23-2.21 (1H, m), 1.99-1.83 (5H, m), 1.75-1.67 (1H, m), 1.45-1.20 (6H, m), 0.77 (3H, d, *J* 6.1), 0.74 (3H, d, *J* 6.1); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 143.9, 139.0, 138.5, 136.7, 133.6, 132.8, 129.3, 129.1, 128.7, 128.5, 124.9, 114.3, 108.4, 70.4, 63.2, 50.5, 48.5, 46.5, 35.0, 33.2, 32.0, 31.7, 28.5, 25.5, 21.5, 20.8, 20.6; *m/z* (FAB+) 602 (M+H<sup>+</sup>, 15%), 570 (70), 446 (80), 428 (45), 290 (100), 154 (100) (Found M+H<sup>+</sup>: 602.2643. Calc. for C<sub>32</sub>H<sub>44</sub>NO<sub>6</sub>S<sub>2</sub>: 602.2610).

**(1'S,3aS,4R,6aR)-2-(1-Benzenesulfonyl-hept-6-enyl)-4-isopropyl-1-(toluene-4-sulfonyl)-3a,4,5,6a-tetrahydro-1H-cyclopenta[b]pyrrol-6-one 16.** To a solution of alkylated sulfone **15** (289 mg, 480 μmol) in acetone (5 ml) was added hydrochloric acid (2 M, 1 ml) and the solution was stirred at 50 °C for 4 h. The reaction mixture was allowed to cool to room temperature. Diethyl ether

(20 ml) was added, the solution was washed with water (10 ml), saturated aqueous sodium bicarbonate solution (10 ml) and brine (10 ml). The organic phase was dried and concentrated. Column chromatography (1:6 ethyl acetate/petroleum ether) afforded ketone **16** (265mg, 99%) as a colourless oil:  $[\alpha]_D +28.9$  (c 1.2,  $\text{CHCl}_3$ );  $\nu_{\text{max}}/\text{cm}^{-1}$  2960, 2872, 1757, 1639, 1597;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98-7.96 (2H, m), 7.81 (2H, d,  $J$  8.3), 7.71-7.67 (1H, m), 7.61-7.57 (2H, m), 7.28 (2H, d,  $J$  8.1), 5.85 (1H, d,  $J$  1.8), 5.67 (1H, ddt,  $J$  16.9, 10.2, 6.7), 4.93-4.85 (3H, m) 4.06 (1H, d,  $J$  8.7), 2.83-2.81 (1H, m), 2.41 (3H, s), 2.15 (2H, d,  $J$  7.1), 1.95-1.85 (3H, m), 1.83-1.71 (1H, m), 1.70-1.62 (1H, m), 1.57-1.47 (1H, m), 1.40-1.10 (4H, m), 0.78 (3H, d,  $J$  5.6), 0.76 (3H, d,  $J$  5.6);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  212.8, 144.5, 138.4, 138.3, 137.8, 133.9, 133.7, 129.7, 129.3, 128.8, 128.3, 122.1, 114.6, 66.5, 62.4, 45.6, 44.2, 38.9, 33.0, 32.8, 32.4, 28.2, 24.9, 21.6, 19.7, 19.7;  $m/z$  (FAB+) 556 ( $\text{M}+\text{H}^+$ , 20%), 414 (25), 344 (33), 260 (43), 69 (100) (Found  $\text{M}+\text{H}^+$ : 556.2202. Calc. for  $\text{C}_{30}\text{H}_{38}\text{NO}_5\text{S}_2$ : 556.2191).

**(1'S,3aR,4R,5R and 5S,6aR)-2-(1-Benzenesulfonyl-hept-6-enyl)-5-bromo-4-isopropyl-1-(toluene-4-sulfonyl)-3a,4,5,6a-tetrahydro-1*H*-cyclopenta[*b*]pyrrol-6-one 17.** To a solution of ketone **16** (85 mg, 153  $\mu\text{mol}$ ) in ethyl acetate (2 ml) at 50 °C was added copper(II) bromide (75 mg, 333  $\mu\text{mol}$ ) and the suspension was stirred vigorously at this temperature for 2 h. After ~10 min a bright green colour was visible and this persisted until the reaction was complete by TLC. The warm reaction mixture was filtered through celite to remove copper(I) bromide. Ethyl acetate (15 ml) was added and the solution was washed with water (10 ml). The aqueous layer was separated and extracted with ethyl acetate ( $2 \times 10$  ml). The combined organic phases were dried and concentrated. Column chromatography (1:7 ethyl acetate/petroleum ether) afforded bromide **17** (89 mg, 92%) as a white solid and as a 1:1 mixture of diastereoisomers:  $\nu_{\text{max}}/\text{cm}^{-1}$  2961, 1769;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01-7.98 (2H, m), 7.94-7.90 (2H, m), 7.73-7.70 (1H, m), 7.63-7.60 (2H, m), 7.38-7.34 (2H, m), 5.91 (0.5H, s), 5.85 (0.5H, s), 5.74-5.66 (1H, m), 4.98 (0.5H, dd,  $J$  9.5, 4.4), 4.96-4.88 (3H, m), 4.33 (0.5H, d,  $J$  9.0), 4.21 (0.5H, d,  $J$  6.3), 4.11 (0.5H, d,  $J$  4.9), 3.03-3.00 (0.5H, m), 2.91-2.89 (0.5H, m), 2.45 (3H, s), 2.24-2.21 (0.5H, m), 1.96-1.13 (9.5H, m), 1.03 (1.5H, d,  $J$  6.6), 0.96 (1.5H, d,  $J$  6.6), 0.93 (1.5H, d,  $J$  6.6), 0.86 (1.5H, d,  $J$  6.6);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  202.9, 144.8, 144.7, 138.5, 138.4, 138.3, 138.3, 138.0, 137.3, 134.1, 134.0, 134.0, 133.5, 129.9, 129.9, 129.3, 129.3, 128.8, 128.8, 128.5, 128.4, 121.5, 119.4, 114.6, 114.5, 65.3, 63.9, 62.3, 62.0, 54.5, 53.1, 51.7, 46.4, 44.0, 43.3, 33.1, 32.9, 32.7, 32.5, 32.0, 31.4, 28.3, 28.1, 25.2, 24.9, 21.7, 21.7, 20.8, 19.9, 19.7, 18.4;

*m/z* (FAB+) 634 (M+H<sup>+</sup>, 35%), 316 (60), 136 (75), 97 (100) (Found M+H<sup>+</sup>: 634.1301. Calc. for C<sub>30</sub>H<sub>37</sub>NO<sub>5</sub>S<sub>2</sub>Br: 634.1297).

**(1'S,3aS,4R,5S,6aR)-5-Allyl-2-(1-benzenesulfonyl-hept-6-enyl)-4-isopropyl-1-(toluene-4-sulfonyl)-3a,4,5,6a-tetrahydro-1*H*-cyclopenta[*b*]pyrrol-6-one 4.** A solution of bromide **17** (108 mg, 170  $\mu$ mol), allyltributyltin (211  $\mu$ l, 681  $\mu$ mol) and 2,2'-azobisisobutyronitrile (3 mg, 17.0  $\mu$ mol) in toluene (2 ml) was degassed by bubbling through a stream of argon for 20 min. The mixture was then stirred at 100 °C for 3 h. The reaction mixture was allowed to cool to room temperature and was concentrated. Column chromatography (1:8 ethyl acetate/petroleum ether) afforded allylated product **4** (53 mg, 52%) as a colourless oil:  $[\alpha]_D$  +36.9 (c 0.65, CHCl<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  2927, 1755, 1642; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.00-7.98 (2H, m), 7.88 (2H, d, *J* 8.3), 7.72-7.68 (1H, m), 7.63-7.60 (2H, m), 7.32 (2H, d, *J* 8.1), 5.81 (1H, d, *J* 1.8), 5.71 (1H, ddt, *J* 16.9, 10.3, 6.7), 5.67-5.59 (1H, m), 5.05-5.01 (2H, m), 4.93-4.87 (3H, m), 4.21 (1H, d, *J* 8.9), 2.75-2.73 (1H, m), 2.44 (3H, s), 2.36-2.32 (1H, m), 2.17-2.10 (2H, m), 2.08-1.88 (2H, m), 1.83-1.56 (4H, m), 1.40-1.10 (4H, m), 0.83 (3H, d, *J* 6.8), 0.77 (3H, d, *J* 6.8); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  214.7, 144.5, 138.5, 138.5, 137.9, 134.9, 134.3, 133.9, 129.8, 129.3, 128.8, 128.3, 122.4, 117.7, 114.5, 68.0, 62.4, 48.2, 46.9, 42.8, 34.4, 33.1, 32.8, 31.7, 28.4, 25.1, 21.6, 19.9, 18.3; *m/z* (FAB+) 596 (M+H<sup>+</sup>, 77%), 454 (92), 300 (75), 162 (100), 91 (92) (Found M+H<sup>+</sup>: 596.2492. Calc. for C<sub>33</sub>H<sub>42</sub>NO<sub>5</sub>S<sub>2</sub>: 596.2504).

**(1'S,3aS,4R,5S,6aR)-2-(1-Benzenesulfonyl-hexyl)-4-isopropyl-5-propyl-1-(toluene-4-sulfonyl)-3a,4,5,6a-tetrahydro-1*H*-cyclopenta[*b*]pyrrol-6-one 18.** To a solution of allyl ketone **4** (4 mg, 6.71  $\mu$ mol) in ethyl acetate (1 ml) was added platinum(IV) oxide (0.8 mg, 3.36  $\mu$ mol) and the mixture was vigorously stirred at room temperature under an hydrogen atmosphere. After 1 h the hydrogen balloon was removed, the reaction vessel was flushed with nitrogen and the reaction mixture was filtered through celite. The filtrate was concentrated and purified by column chromatography (1:7, ethyl acetate/petroleum ether), affording hydrogenated product **18** (3 mg, 75%) as a colourless oil:  $[\alpha]_D$  +36.5 (c 0.2, CHCl<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  2958, 2928, 2871, 1750; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.00-7.98 (2H, m), 7.89 (2H, d, *J* 8.3), 7.72-7.68 (1H, m), 7.63-7.59 (2H, m), 7.32 (2H, d, *J* 8.0), 5.83 (1H, d, *J* 1.7), 4.89 (1H, dd, *J* 9.5, 3.7), 4.16 (1H, d, *J* 8.8), 2.74 (1H, d, *J* 8.8), 2.44 (3H, s), 2.04-2.00 (1H, m), 1.80-1.67 (3H, m), 1.65-1.51 (2H, m), 1.41-1.08 (11H, m), 0.87 (3H, d, *J* 7.1), 0.82 (3H, d, *J* 6.7), 0.82 (3H, d, *J* 7.0), 0.77 (3H, d, *J* 7.0); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  215.9, 144.4, 138.5,

137.9, 134.4, 133.9, 129.8, 129.3, 128.8, 128.3, 122.6, 68.0, 62.5, 49.5, 47.4, 43.1, 33.2, 33.0, 32.0, 31.2, 28.9, 25.6, 22.5, 21.6, 20.6, 19.9, 18.4, 14.0, 14.0;  $m/z$  (FAB+) 600 ( $M+H^+$ , 60%), 458 (90), 318 (65), 304 (60), 164 (100) (Found  $M+H^+$ : 600.2781. Calc. for  $C_{33}H_{46}NO_5S_2$ : 600.2817).

**(1*R*,4*S*,12*S*,13*S*,14*S*,*E* and *Z*)-4-Benzenesulfonyl-13-isopropyl-2-(toluene-4-sulfonyl)-2-aza-tricyclo[10.2.1.1<sup>3,14</sup>]hexadeca-3(16),9-dien-15-one 19.** A solution of triene **4** (100 mg, 168  $\mu$ mol) in dichloromethane (168 ml) was degassed by bubbling through a stream of argon for 20 min.  $(Cy_3P)_2Cl_2Ru=CHPh$  (14 mg, 16.8  $\mu$ mol) was added and the reaction mixture was stirred at 40 °C for 16 h. After cooling to room temperature air was bubbled through the solution for 5 min. The crude reaction mixture was concentrated and purified by column chromatography (1:7 ethyl acetate/petroleum ether) affording ring-closed product **19** (87 mg, 91%) as a white solid and as a 3:1 mixture of double bond isomers:  $\nu_{max}/cm^{-1}$  2925, 1747; <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.03-7.98 (4H, m), 7.72-7.67 (1H, m), 7.63-7.58 (2H, m), 7.36-7.29 (2H, m), 5.96 (0.75H, d, *J* 1.7), 5.79 (0.25H, d, *J* 1.8), 5.55-5.50 (0.75H, m), 5.33-5.21 (1H, m), 5.18-5.08 (0.25H, m), 4.85 (0.75H, dd, *J* 11.9, 2.8), 4.79 (0.25H, dd, *J* 11.5, 2.6), 4.09 (0.25H, d, *J* 8.8), 3.99 (0.75H, d, *J* 7.8), 2.88-2.84 (1H, m), 2.75-2.68 (0.25H, m), 2.45 (3H, s), 2.31-1.09 (10.75H, m), 0.97-0.80 (2H, m), 0.84 (0.75H, d, *J* 6.7), 0.83 (0.75H, d, *J* 6.7), 0.75 (2.25H, d, *J* 6.8), 0.75 (2.25H, d, *J* 6.8); <sup>13</sup>C NMR (125 MHz,  $CDCl_3$ )  $\delta$  215.9, 144.5, 144.4, 138.8, 138.3, 138.2, 138.2, 135.0, 134.6, 134.1, 134.0, 133.8, 129.9, 129.8, 129.7, 129.3, 129.3, 128.9, 128.8, 128.6, 128.5, 127.2, 125.0, 123.1, 121.8, 68.7, 67.6, 65.8, 63.1, 63.0, 50.9, 47.7, 47.6, 47.1, 45.0, 43.8, 33.8, 33.1, 32.8, 32.7, 32.1, 31.9, 29.3, 27.1, 25.2, 24.1, 22.3, 22.1, 21.8, 21.6, 19.5, 19.4, 19.3, 19.1;  $m/z$  (FAB+) 568 ( $M+H^+$ , 20%), 426 (25), 154 (100), 136 (97), 91 (75) (Found  $M+H^+$ : 568.2186. Calc. for  $C_{31}H_{38}NO_5S_2$ : 568.2191).

**(4*S*,12*S*,13*S*,*E* and *Z*)-4-Benzenesulfonyl-13-isopropyl-2-aza-tricyclo[10.2.1.1<sup>3,14</sup>]hexadeca-1(14),3(16),9-trien-15-one 20.** To a solution of macrocycle **19** (55 mg, 75.7  $\mu$ mol) in tetrahydrofuran (2 ml) at -78 °C was added dropwise sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 227  $\mu$ l, 227  $\mu$ mol). The reaction was stirred for 10 min at -78 °C and then allowed to warm to -30 °C over 30 min and stirred at this temperature for 6 h. Saturated aqueous ammonium chloride solution was added to quench the reaction and the mixture was allowed to warm to room temperature. Ethyl acetate (15 ml) was added, the solution was washed with water (10 ml), and the aqueous phase was extracted with ethyl acetate (2  $\times$  15 ml). The combined organic phases were dried

and concentrated. Column chromatography (1:3 ethyl acetate/petroleum ether) afforded pyrrole **20** (22 mg, 71%) as a white solid and as a 3:1 mixture of double bond isomers:  $\nu_{\text{max}}/\text{cm}^{-1}$  3158, 2925, 2869, 1660;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  11.76 (0.75H, br s), 11.53 (0.25H, br s), 7.91-7.88 (2H, m), 7.60-7.53 (1H, m), 7.48-7.43 (2H, m), 6.48 (0.75H, d,  $J$  1.4), 6.28 (0.25H, d,  $J$  1.4), 5.25-5.18 (0.75H, m), 5.08-5.02 (0.75H, m), 4.96-4.85 (0.5H, m), 4.60-4.56 (1H, m), 2.85-2.81 (0.75H, m), 2.76-2.72 (1H, m), 2.59 (0.25H, d,  $J$  6.6), 2.55-2.49 (0.75H, m), 2.42-2.32 (2.25H, m), 1.92-1.61 (3H, m), 1.46-0.57 (5H, m), 1.03 (0.75, d,  $J$  6.6), 1.01 (2.25H, d,  $J$  6.6), 0.87 (0.75H, d,  $J$  6.6), 0.83 (2.25H, d,  $J$  6.6);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  195.2, 194.5, 157.4, 157.0, 140.3, 139.1, 138.1, 138.1, 134.4, 134.3, 133.8, 133.6, 132.4, 129.0, 129.0, 128.8, 125.2, 124.0, 110.4, 109.7, 64.8, 64.5, 59.0, 57.3, 49.2, 48.0, 35.1, 33.2, 32.6, 30.7, 30.5, 30.0, 28.4, 27.9, 27.8, 24.8, 23.7, 21.7, 21.5, 20.0, 19.9;  $m/z$  (FAB+) 412 ( $\text{M}+\text{H}^+$ , 15%), 393 (30), 349 (40), 305 (40), 154 (100), 136 (95) (Found  $\text{M}+\text{H}^+$ : 412.1957. Calc. for  $\text{C}_{24}\text{H}_{30}\text{NO}_3\text{S}$ : 412.1946).

**(12S,13S,E and Z)-13-Isopropyl-2-aza-tricyclo[10.2.1.1<sup>3,14</sup>]hexadeca-1(14),3(16),9-trien-15-one 21.** To a solution of sulfone **20** (18 mg, 43.7  $\mu\text{mol}$ ) and disodium hydrogen phosphate (39 mg, 219  $\mu\text{mol}$ ) in tetrahydrofuran (1 ml) and methanol (1 ml) at 0 °C was added sodium amalgam (6%, 335 mg, 875  $\mu\text{mol}$ ) and the solution was stirred at 0 °C for 3 h. The reaction mixture was decanted into water (10 ml) and extracted with ethyl acetate (15 ml). The aqueous phase was separated and extracted with ethyl acetate (2  $\times$  15 ml). The combined organic phases were dried and concentrated. Column chromatography (1:4 ethyl acetate/petroleum ether) afforded pyrrole **21** (11 mg, 90%) as a colourless oil and as a 3:1 mixture of double bond isomers:  $\nu_{\text{max}}/\text{cm}^{-1}$  3169, 2929, 1659;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.32 (0.75H, br s), 9.85 (0.25H, br s), 5.97 (0.75H, d,  $J$  1.6), 5.92 (0.25H, d,  $J$  1.6), 5.38-5.31 (0.75H, m), 5.18-5.09 (1H, m), 5.03-4.97 (0.25H, m), 2.90-2.64 (4H, m), 2.54-2.32 (2H, m), 1.84-0.59 (9H, m), 1.02 (0.75H, d,  $J$  6.7), 1.01 (2.25H, d,  $J$  6.7), 0.90 (0.75H, d,  $J$  6.7), 0.88 (2.25H, d,  $J$  6.7);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  193.6, 192.9, 157.2, 156.7, 149.3, 147.7, 134.7, 134.5, 133.7, 132.6, 125.7, 124.9, 109.0, 109.0, 59.1, 58.0, 50.0, 47.7, 35.3, 33.4, 32.8, 31.7, 31.1, 31.1, 29.4, 28.8, 28.6, 28.3, 28.1, 27.4, 25.2, 24.0, 21.7, 21.4, 20.1, 19.9;  $m/z$  (FAB+) 272 ( $\text{M}+\text{H}^+$ , 72%), 154 (100), 136 (95), 55 (97) (Found  $\text{M}+\text{H}^+$ : 272.2026. Calc. for  $\text{C}_{18}\text{H}_{26}\text{NO}$ : 272.2014).

**(12S,13S)-13-Isopropyl-2-aza-tricyclo[10.2.1.1<sup>3,14</sup>]hexadeca-1(14),3(16)-dien-15-one 1.** To a solution of pyrrole **21** (13 mg, 47.9  $\mu\text{mol}$ ) in ethyl acetate (1 ml) was added platinum(IV) oxide (3

mg, 12.0  $\mu$ mol) and the mixture was vigorously stirred at room temperature under an hydrogen atmosphere. After 2 h the hydrogen balloon was removed, the reaction vessel was flushed with nitrogen and the reaction mixture was filtered through celite. The filtrate was concentrated and purified by column chromatography (1:4, ethyl acetate/petroleum ether), affording macrocycle **1** (13 mg, 99%) as a colourless oil:  $[\alpha]_D$   $-32.0$  (c 1.0,  $\text{CHCl}_3$ );  $\nu_{\text{max}}$ /cm $^{-1}$  3161, 2927, 2854, 1656;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  9.90 (1H, br s), 5.99 (1H, d,  $J$  1.7), 2.88 (1H, dt,  $J$  13.9, 4.9), 2.77 (1H, dd,  $J$  4.9, 3.7), 2.62 (1H, d,  $J$  6.6), 2.59-2.53 (1H, m), 1.96-1.78 (4H, m), 1.39-1.23 (4H, m), 1.08-0.82 (5H, m), 1.01 (3H, d,  $J$  6.6), 0.90 (3H, d,  $J$  6.6), 0.47-0.42 (2H, m);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  193.9, 156.9, 149.7, 133.6, 107.0, 50.7, 40.2, 33.1, 32.0, 28.3, 28.3, 28.1, 27.4, 27.3, 25.5, 24.9, 21.5, 19.1;  $m/z$  (FAB+) 274 ( $\text{M}+\text{H}^+$ , 100%) (Found  $\text{M}+\text{H}^+$ : 274.2163. Calc. for  $\text{C}_{18}\text{H}_{28}\text{NO}$ : 274.2171).