

# Synthesis of the Himandrine Skeleton

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Melting points were recorded on a reichert hot-stage, and are uncorrected. Microanalyses were carried out by the Australian National University Analytical Services Unit, Canberra.

Low resolution EI mass spectra (70 eV) and high resolution accurate mass measurements were recorded on a VG Micromass 7070F double focussing mass spectrometer. The molecular ion ( $M^+$ ), if present, and intense lower mass ions are reported. The data is presented in the following format m/z value (relative intensity as a percentage of base peak).

Infrared spectra were recorded on a Perkin-Elmer 683 Infrared spectrophotometer as a thin film on NaCl disks, unless otherwise stated.

$^1\text{H}$ -NMR spectra were recorded on the following instruments: Varian Gemini 300 and Varian Mercury 300 at 300 MHz and Varian Inova 500 at 500 MHz.  $^{13}\text{C}$ -NMR spectra were recorded as attached proton test (APT) spectra (unless otherwise stated) on the following instruments: Varian Gemini 300 at 75.5 MHz and Varian Inova 500 at 125 MHz. Chemical shifts are reported as  $\delta$  values in parts per million. The internal reference for all  $^1\text{H}$  spectra recorded in  $\text{CDCl}_3$  was the residual peak of  $\text{CHCl}_3$  (7.26 ppm). For  $^1\text{H}$  spectra recorded in  $d_6$ -acetone the residual peak of  $d_5$ -acetone (2.05 ppm) was used as the internal reference. The internal reference for all  $^{13}\text{C}$  spectra recorded in  $\text{CDCl}_3$  was the central peak of  $\text{CDCl}_3$  (77.0 ppm). For  $^{13}\text{C}$  spectra recorded in  $d_6$ -acetone and  $\text{CD}_3\text{OD}$  the spectra were not referenced.

Two dimensional NMR experiments were carried out using the following instruments: Varian Mercury 300 and Varian Inova 500. The pulse sequences used were

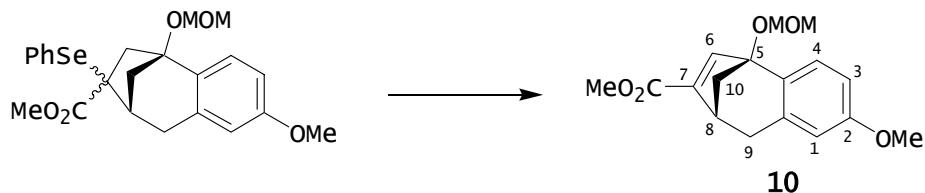
homonuclear ( $^1\text{H}/^1\text{H}$ ) correlation spectroscopy (COSY), gradient double quantum filtered homonuclear ( $^1\text{H}/^1\text{H}$ ) correlation spectroscopy (gDQCOSY), heteronuclear ( $^{13}\text{C}/^1\text{H}$ ) multiple bond correlation spectroscopy (HMBC), heteronuclear ( $^{13}\text{C}/^1\text{H}$ ) multiple quantum correlation spectroscopy (HMQC) and phase sensitive Nuclear Overhauser and exchange spectroscopy (PS- $^1\text{H}/^1\text{H}$ -NOESY).

Flash chromatography was conducted using either 'Merck Kieselgel 60' or 'Aluminium oxide activity grade 1' as the absorbent and analytical reagent grade (AR) solvent as indicated.

All reagents were used as supplied by Aldrich Chemical Company unless otherwise stated. THF,  $\text{Et}_2\text{O}$  and benzene were purified by distillation from sodium metal and benzophenone. DCM,  $^i\text{Pr}_2\text{NEt}$  ane  $\text{NEt}_3$  were purified by distillation from  $\text{CaH}_2$ . DMF and DMSO were dried over 4 $\text{\AA}$  molecular sieves before use.

All reactions were performed under a dry nitrogen atmosphere and reaction temperature refers to the external bath temperature, unless otherwise stated. All organic extracts were dried with anhydrous magnesium sulfate. After filtration of solutions from the drying agent the bulk of the solvent was removed on a Buchi rotary evaporator with a water aspirator. Samples were then subjected to high vacuum to remove any remaining solvent.

*(5SR,8SR)-2-Methoxy-5-(methoxymethoxy)-8,9-dihydro-5,8-methano-5*H*-benzocycloheptene-7-carboxylic acid methyl ester (10)*



The phenylselenium adduct **22** (5.8 g, 19.1 mmol) was taken up in DCM and cooled to  $-78^{\circ}\text{C}$ . MCPBA (9.6 g, 39 mmol) was crushed to a powder and added as a solid, then the reaction was stirred at  $-78^{\circ}\text{C}$  for 0.5 hour, during which time a thick white precipitate formed. Diisopropylamine (10 mL, 71 mmol) was added and the reaction was warmed to reflux for 10 min. The DCM was removed *in vacuo* affording a brown oil which was directly purified by flash chromatography (silica, petrol/EtOAc 5:1) to give the title compound as a transparent oil (5.7 g, 98%)

**$^1\text{H NMR}$**  (300 MHz)  $\delta$  7.40 (d,  $J$  8.4 Hz, 1H, H<sub>4</sub>), 6.98 (s, 1H, H<sub>6</sub>), 6.70 (dd,  $J$  8.4 & 2.7 Hz, 1H, H<sub>3</sub>), 6.12 (d,  $J$  2.1 Hz, 1H, H<sub>1</sub>), 4.94 (d,  $J$  7.2 Hz, 1H), 4.86 (d,  $J$  6.9 Hz, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 3.48 (s, 3H), 3.41 (m, 1H, H<sub>8</sub>), 3.07 (dd,  $J$  17.1 & 4.5 Hz, 1H, H<sub>9</sub>), 2.72 (d,  $J$  17.7 Hz, 1H, H<sub>9</sub>), 2.66 (dd,  $J$  10.2 & 5.5, 1H, H<sub>10</sub>), 2.05 (d,  $J$  10.2 Hz, 1H, H<sub>10</sub>)

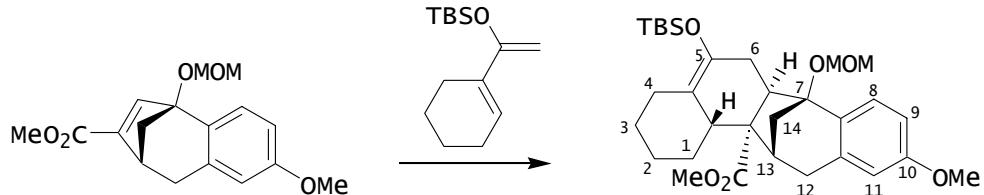
**$^{13}\text{C NMR}$**  (75 MHz)  $\delta$  164.8 (COCH<sub>3</sub>), 159.2 (C<sub>1</sub>), 150.6 (C<sub>6</sub>), 135.3 (C<sub>4</sub>), 133.8 (C<sub>7</sub>), 132.6 (C<sub>3</sub>), 123.1 (C<sub>5</sub>), 115.2 (C<sub>2</sub>), 110.7 (C<sub>6</sub>), 92.3 (CH<sub>2</sub>), 86.5 (C<sub>5</sub>), 55.6 (ArOCH<sub>3</sub>), 55.2 (CH<sub>2</sub>OCH<sub>3</sub>), 51.6 (CO<sub>2</sub>CH<sub>3</sub>), 44.6 (C<sub>10</sub>), 37.9 (C<sub>8</sub>), 31.0 (C<sub>9</sub>)

**IR**  $\nu_{\text{max}}$  1716, 1608, 1577, 1493, 1436, 1280, 1259, 1037 cm<sup>-1</sup>

**Mass Spectrum** (70 eV)  $m/z$  304.1 (M<sup>+</sup>, 19%), 271.2 (10%), 259.1 (16%), 231.1 (68%), 217.1 (100%), 199.1 (20%), 185.1 (53%), 171.1 (45%), 158.1 (83%)

**HRMS** Found: M<sup>+</sup>, 304.1309. calcd for C<sub>17</sub>H<sub>20</sub>O<sub>5</sub> M<sup>+</sup>, 304.1311

(6a*RS*,7*RS*,13*RS*,13a*RS*,13b*SR*)-2,3,4,6,6a,7,12,13,13a,13b-Decahydro-5-tert-butyldimethylsilyloxy-10-methoxy-7-(methoxymethoxy)-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2*a*]-naphthalene-13a-carboxylic acid methyl ester ({pdo65, #50})



The unsaturated methyl ester **10** (4.50 g, 14.8 mmol) and diene **7** (5.30 g, 22.0 mmol) were placed in a 50ml round bottom flask and diluted with 5 mL of 1,2-dichloroethane. The mixture was heated at 90 °C for 3 days. The solvent was removed *in vacuo* to yield a brown oil which was directly subjected to flash chromatography (silica, petrol/EtOAc, 7:1) giving the Diels-Alder adduct as a pale yellow oil, (5.0 g, 62%) along with recovered **10** (2.0 g, 25%).

**<sup>1</sup>H NMR** (300 MHz) δ 7.17 (d, J 8.4 Hz, 1H, H<sub>8</sub>), 6.66 (dd, J 2.7 & 8.4 Hz, 1H, H<sub>9</sub>), 6.53 (d, J 2.4 Hz, 1H, H<sub>11</sub>), 4.74 (d, J 7.2 Hz, 1H), 4.66 (d, J 6.9 Hz, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 3.43 (s, 3H), 3.16 (d, J 18 Hz, 1H), 2.95 (dd, J 18 & 6 Hz, 1H), 2.78 (m, 1H), 1.20 – 2.60 (m-br, 14 H), 0.95 (s, 9H), 0.16 (s, 3H), 0.10 (s, 3H).

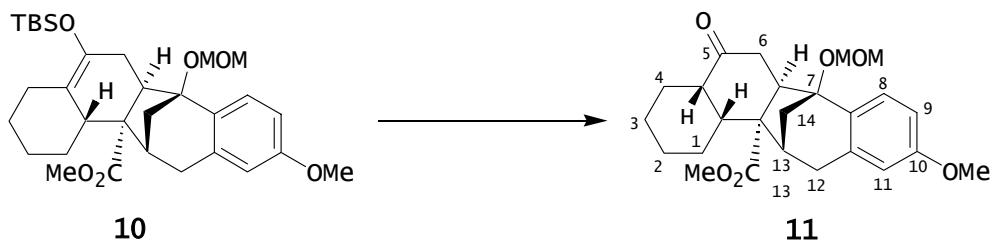
**<sup>13</sup>C NMR** (75 MHz) δ 174.2 (C), 158.0 (C), 142.3 (C), 138.6 (C), 136.3 (C), 122.7 (CH), 114.7 (C), 113.5 (CH), 111.3 (CH), 92.9 (CH<sub>2</sub>), 84.0 (C), 59.3 (C), 55.6 (CH<sub>3</sub>), 55.1 (CH<sub>3</sub>), 54.4 (CH), 51.1 (CH<sub>3</sub>), 46.3 (CH), 42.5 (CH), 37.5 (CH<sub>2</sub>), 34.8 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 25.8 (SiC(CH<sub>3</sub>)<sub>3</sub>), 23.9 (CH<sub>2</sub>), 23.21 (CH<sub>2</sub>), 23.20 (CH<sub>2</sub>), 18.1 (SiC(CH<sub>3</sub>)<sub>3</sub>), -3.6 & -4.0 (SiCH<sub>3</sub>).

**IR**  $\nu_{\text{max}}$  2931, 2856, 1725, 1684, 1608, 1495 cm<sup>-1</sup>

**Mass Spectrum** (70 eV) m/z 542.2 (M<sup>+</sup>, 60%), 497.2 (13%), 304.1 (29%), 259.1 (21%), 182.1 (100%),

**HRMS** Found: M<sup>+</sup>, 542.3061. calcd for C<sub>31</sub>H<sub>46</sub>O<sub>6</sub>Si M<sup>+</sup>, 542.3064.

(4a*RS*,6a*RS*,7*RS*,13*SR*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-(methoxymethoxy)-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carboxylic acid methyl ester (**11**)



The TBS-enol ether **24** (6.2 g, 11.4 mmol) was taken up in a premixed 3:1:1 solution of acetic acid, THF and water at room temperature; the mixture was stirred for 0.5 h after which time the majority of the solvent was removed *in vacuo*. The remaining oil was partitioned between EtOAc (50 mL) and 3M NaOH (50 mL). The product was extracted with EtOAc (3 x 30 mL) and the pooled organic fractions washed with brine and dried over MgSO<sub>4</sub> to give a colourless oil. This product was then purified by flash chromatography (silica, petrol/EtOAc 3:1) to yield the title ketone as a pleasant smelling transparent oil, (4.89 g, 98 %).

**<sup>1</sup>H NMR** (300 MHz) δ 7.22 (d, J 8.7 Hz, 1H, H<sub>8</sub>), 6.71 (dd, J 2.1 & 8.4 Hz, H<sub>9</sub>), 6.49 (d, J 2.1 Hz, H<sub>11</sub>), 4.69 (d, J 7.2 Hz, 1H), 4.58 (d, J 7.2 Hz, 1H), 3.74 (s, 3H), 3.43 (s, 3H), 0.90 3.40 (m-br, 21H).

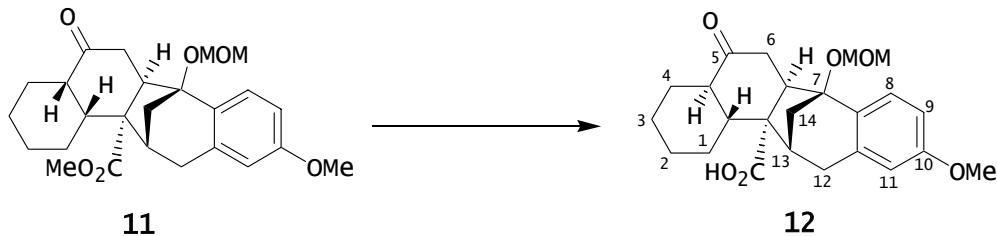
**<sup>13</sup>C NMR** (75 MHz) δ 214.1 (C), 174.6 (C), 158.5 (C), 136.5 (C), 135.3 (C), 124.7 (CH), 112.9 (CH), 112.1 (CH), 92.7 (CH<sub>2</sub>), 84.2 (C), 56.1 (CH<sub>3</sub>), 55.1 (CH<sub>3</sub>), 51.6 (CH<sub>3</sub>), 49.6 (CH), 46.0 (CH), 44.7 (CH), 44.0 (CH), 40.3 (CH<sub>2</sub>), 38.1 (CH<sub>2</sub>), 37.2 (CH<sub>2</sub>), 28.4 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 25.9 (CH<sub>2</sub>), 22.4 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2940, 1734, 1704, 1609, 1496 cm<sup>-1</sup>

**Mass Spectrum** (70 eV) *m/z* 428.2 (M<sup>+</sup>, 58%), 398.1 (8%), 383.1 (9%), 367.1 (13%), 335.1 (10%), 307.1 (8%), 279.1 (6%), 219.1 (100%)

**HRMS** Found: M<sup>+</sup>, 428.2196. calcd for C<sub>25</sub>H<sub>32</sub>O<sub>6</sub> M<sup>+</sup>, 421.2199

(4aRS,6aRS,7RS,13SR,13aRS,13bRS)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-(methoxymethoxy)-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carboxylic acid (**12**)



Propane thiolate solution was prepared as follows. Sodium hydride (2g, 50 mmol) was washed several times in dry petroleum ether and the dried residue was suspended in 25 mL of HMPA. The suspension was then degassed under high vacuum. To the stirred suspension of NaH in HMPA was added distilled *n*-propanethiol (3.8 mL, 42 mmol). Stirring was continued for 1 h by which time the mixture had become transparent. To a dry 50 mL round bottom flask, equipped with a rubber septum and containing the methyl ester **11** (6.3 g, 14.7 mmol), was added a 20 mL aliquot of the previously prepared thiolate solution. After 2 days stirring at room temperature, the reaction was quenched with water and acidified with 1M HCL. Following extraction with EtOAc (3 x 40 mL), the solvent removed *in vacuo* and the resultant oil triturated with Et<sub>2</sub>O – petroleum ether to give the title carboxylic acid as a white solid (5.9 g, 97%).

**<sup>1</sup>H NMR** (300 MHz) δ 7.15 (d, J 8.7, 1H, H<sub>8</sub>), 6.63 (dd, J 2.4 & 8.4 Hz, 1H, H<sub>9</sub>), 6.50 (d, J 2.4 Hz, 1H, H<sub>11</sub>), 4.68 (d, J 6.9 Hz, 1H), 4.58 (d, J 6.9 Hz, 1H), 3.71 (s, 3H), 3.44 (m, 1H), 3.40 (s, 3H), 3.00 (m-br, 2H), 0.90 – 2.40 (m-br, 16H).

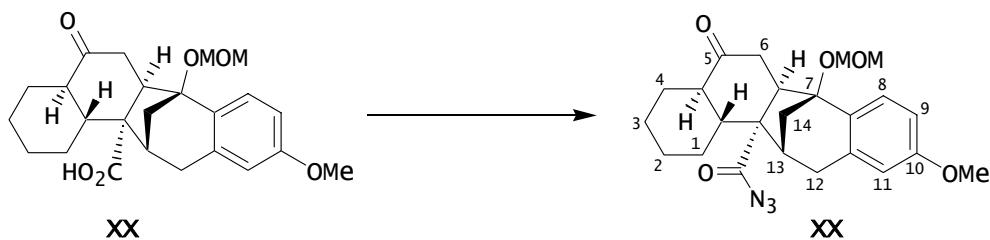
**<sup>13</sup>C NMR** (75 MHz) δ 215.4 (C), 174.3 (C), 158.4 (C), 136.5 (C), 136.4 (C), 123.8 (CH), 113.5 (CH), 111.9 (CH), 92.9 (CH<sub>2</sub>), 83.7 (C), 56.3 (CH<sub>3</sub>), 55.9 (CH<sub>3</sub>), 55.0 (CH), 52.3 (CH), 49.4 (CH), 45.4 (CH), 39.5 (CH), 38.6 (CH<sub>2</sub>), 36.2 (CH<sub>2</sub>), 34.9 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2931, 1711, 1609, 1496, 1298 cm<sup>-1</sup>

**Mass Spectrum** (70 eV) m/z 414 (M<sup>+</sup>, 1.6%), 289 (4.1%), 219 (100%), 189 (21%), 175 (31%), 160 (14%).

**HRMS** Found: M<sup>+</sup>, 414.2042, calcd for C<sub>24</sub>H<sub>30</sub>O<sub>6</sub> M<sup>+</sup>, 414.2042

(4a*RS*,6a*RS*,7*RS*,13*SR*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-(methoxymethoxy)-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbonyl azide (**25**)



Into a 100 mL 3 neck round bottom flask containing DCM (15 mL) was injected DMF (4.3 mL, 56 mmol). The mixture was cooled to 0 °C and oxalyl chloride (6.0 mL, 68 mmol) was added slowly, resulting in the formation of a white precipitate. After stirring for 1 h, the DCM was removed along with excess oxalyl chloride under reduced pressure to leave a white solid which was then diluted with THF (15 mL) and cooled to 0 °C. The carboxylic acid **12** (4.6 g, 11.2 mmol) was mixed with pyridine (8.4 mL, 112 mmol) and dissolved in 50 mL of THF; this cooled solution was added by cannula to the previously prepared DMF-oxalyl chloride adduct and the resultant mixture was stirred for 1 h. A reflux condenser was fitted to the flask and the mixture was heated under vigorous reflux for 10 min, during which time a dark brown-black colour developed. The resultant mixture was allowed to cool to room temperature, whereupon powdered sodium azide (7.3 g, 112 mmol) was added and the slurry stirred. Stirring was continued for ~5 hours, after which time water was added and the products were extracted with EtOAc (3 x 30 mL). The organic phase was washed over brine and the solvent removed *in vacuo* to afford black tar which was purified by flash chromatography (silica, petrol/EtOAc 3:1) to give the acyl azide as a yellow foam (3.8g, 77%).

**<sup>1</sup>H NMR** (300 MHz) δ 7.18 (d, J 8.7 Hz, 1H, H<sub>8</sub>), 6.70 (dd, J 8.7 & 2.7 Hz, 1H, H<sub>9</sub>), 6.55 (d, J 2.4 Hz, 1H, H<sub>11</sub>), 4.70 (d, J 7.2 Hz, 1H), 4.59 (d, J 6.9 Hz, 1H), 3.75 (s, 3H), 3.42 (s, 3H), 3.25 (d, J 17.7 Hz, 1H), 1.00- 3.00 (m-br, 17H).

**<sup>13</sup>C NMR** (75 MHz) δ 214.1 (C), 180.0 (C), 158.6 (C), 135.7 (C), 135.4 (C), 123.8 (CH), 113.3 (CH), 112.5 (CH), 92.9 (CH<sub>2</sub>), 83.4 (C), 58.2 (C), 56.0 (CH<sub>3</sub>), 55.1 (CH<sub>3</sub>), 52.7 (CH), 49.9 (CH), 46.3 (CH), 40.6 (CH), 38.3 (CH<sub>2</sub>), 36.4 (CH<sub>2</sub>), 34.6 (CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2941, 2135  $\nu_{\text{as}}$  (NNN), 1714, 1608, 1496, 1175  $\text{cm}^{-1}$

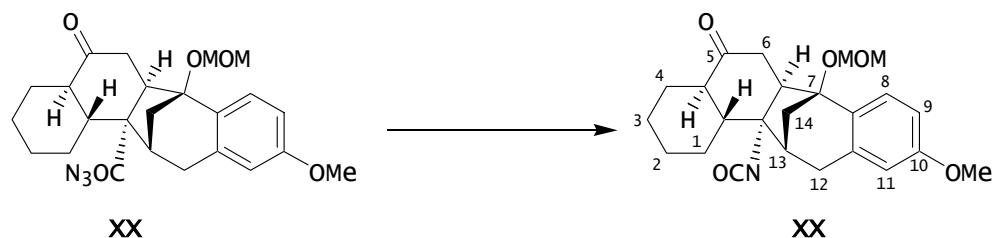
**Mass Spectrum**<sup>▲</sup> (70 eV) m/z 439 ( $\text{M}^+$ , 8%), 412 (10%), 378 (12%), 350 (16%).

**HRMS** Found:  $\text{M}^+$ , 439.2105, calcd for  $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_5$   $\text{M}^+$ , 439.2107.

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<sup>▲</sup> FAB in NOPE matrix

13a-Isocyanato-(4aSR,6aSR,7RS,13RS,13aSR,13bSR)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-dodecahydro-10-methoxy-7-methoxymethoxy-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene (**26**)



The acyl azide **25** (3.8g, 8.6 mmol) was taken up in dry toluene *ca.* 100 mL. The mixture was heated to maintain a vigorous reflux for 15 min, after which time the solvent was removed to yield the isocyanate as a yellow foam, (3.5 g,  $\sim$ 100%).

**<sup>1</sup>H NMR** (300 MHz)  $\delta$  7.22 (d, *J* 8.7 Hz, 1H, H<sub>8</sub>), 6.75 (dd, *J* 8.7 & 2.4 Hz, 1H, H<sub>9</sub>), 6.70 (d, *J* 2.7 Hz, 1H, H<sub>11</sub>), 4.74 (d, *J* 6.9 Hz, 1H), 4.59 (d, *J* 6.9 Hz, 1H), 3.79 (s, 3H), 3.41 (s, 3H), 1.00 – 3.20 (m-br, 18H).

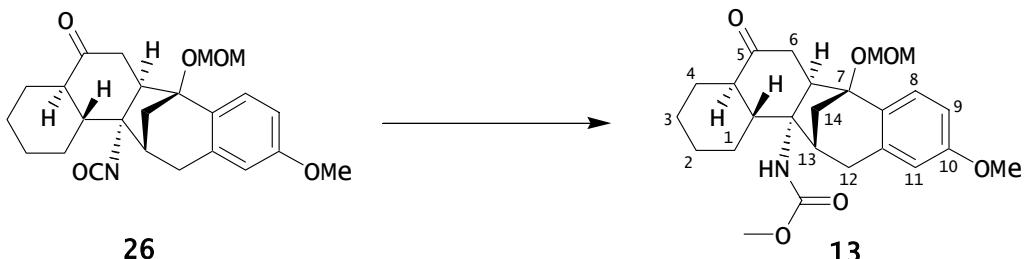
**<sup>13</sup>C NMR** (75 MHz)  $\delta$  213.4 (C), 158.9 (C), 135.8 (C), 135.6 (C), 124.1 (CH), 113.5 (CH), 112.5 (CH), 109.7 (C), 92.7 (CH<sub>2</sub>), 82.9 (C), 68.2 (C), 59.9 (CH), 56.0 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 47.8 (CH), 45.9 (CH), 41.7 (CH), 38.7 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>), 35.1 (CH<sub>2</sub>), 28.6 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2933, 2266  $\nu_{\text{as}}$  (NCO), 1712, 1609, 1495  $\text{cm}^{-1}$

**Mass Spectrum** (70 eV) m/z 411.2 (M<sup>+</sup>, 13%), 274 (7%), 219 (100%), 187 (19%), 175 (10%), 159 (17%).

**HRMS** Found: M<sup>+</sup>, 411.2043, calcd for C<sub>24</sub>H<sub>29</sub>NO<sub>5</sub> M<sup>+</sup>, 411.2046

(4a*RS*,6a*RS*,7*SR*,13*SR*,13a*RS*,13b*RS*)-2,3,4,4a,5,6,6a,7,12,13,13a,13b-Dodecahydro-10-methoxy-7-(methoxymethoxy)-5-oxo-7,13-methano-1*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-13a-carbamate methyl ester (**13**)



To a solution of isocyanate **26** (2.9 g, 7.0 mmol) in 50 mL of dry MeOH, was added a freshly prepared methanolic solution of sodium methoxide, made by dissolving sodium (0.80 g, 34 mmol) in dry methanol (*ca.* 20 mL). The suspension was briefly heated to reflux to allow the isocyanate to dissolve, whereupon the solution was allowed to cool to room temperature and stirred for *ca.* 10 h. The methanol was removed under reduced pressure, and the residue taken up in a mixture of DCM and water. The product was extracted with 3 × 50 mL of DCM, and the pooled organic fractions dried over MgSO<sub>4</sub>. The solvent was removed *in vacuo* to afford the methyl carbamate as a yellow powder, which was further purified by recrystallization from a methanol hexane solution (3.1 g, ~100%).

**<sup>1</sup>H NMR** (500 MHz) δ 7.16 (d, 8.5 Hz, 1H, H<sub>8</sub>), 6.67 (dd, J 9.0 & 2.8 Hz, 1H, H<sub>9</sub>), 6.59 (d, J 2.5 Hz, 1H, H<sub>11</sub>), 4.77 (s, 1H), 4.69 (d, J 7.5 Hz, 1H), 4.58 (d, J 7.5 Hz, 1H), 3.75 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 3.09 (dd, J 18 & 4 Hz, 1H), 3.01 (m, 1H), 2.80 (d, J 18 Hz, 1H), 2.69 (m, 1H), 2.65 (dd, J 15 & 6 Hz, 1H), 2.46 (m, 2H), 2.15 (m, 3H), 1.80 (m, 4H), 1.20 (m, 4H).

**<sup>13</sup>C NMR** (75 MHz) δ 214.4 (C), 158.5 (C), 156.3 (C), 136.6 (C), 135.2 (C), 124.0 (CH), 113.3 (CH), 111.8 (CH), 92.8 (CH<sub>2</sub>), 83.5 (C), 62.7 (C), 56.1 (CH<sub>3</sub>), 55.2 (CH<sub>3</sub>), 53.5 (CH), 52.0 (CH<sub>3</sub>), 49.2, 48.7, 41.0, 39.3, 36.2, 33.8, 30.1, 27.9, 26.5, 26.3.

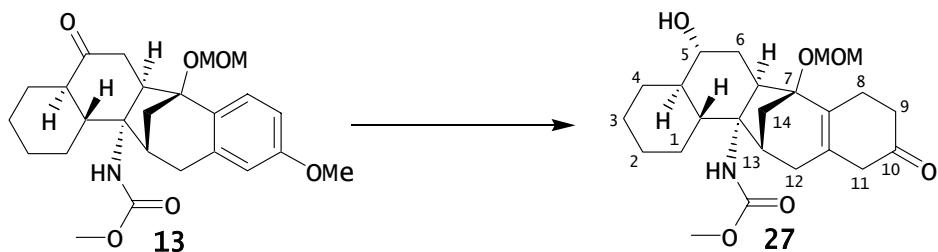
**IR**  $\nu_{\text{max}}$  3379, 3305, 2931, 1730, 1516, 1029 cm<sup>-1</sup>

**Mass Spectrum** (70 eV) m/z 443 (M<sup>+</sup>, 1.9%), 323 (1.1%), 219 (100%), 187 (22%), 159 (11%).

**HRMS** Found: M<sup>+</sup>, 443.2308. calcd for C<sub>25</sub>H<sub>33</sub>NO<sub>6</sub> M<sup>+</sup>, 443.2308.

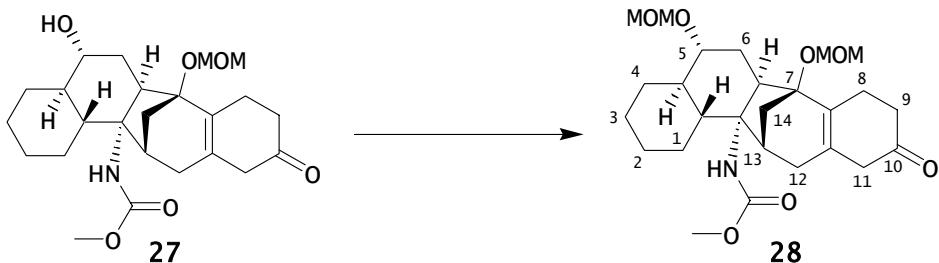
**Elemental Analysis** Found: C, 67.65; H, 7.76; N, 2.98. C<sub>25</sub>H<sub>39</sub>NO<sub>7</sub> Requires: C, 67.70; H, 7.50; N, 3.16.

(4aRS,5RS,6aRS,7SR,13SR,13aRS,13bRS)-1,2,3,4,4a,5,6,6a,7,8,9,11,12,13,13a,13b-Hexadecahydro-7-(methoxymethoxy)-5-hydroxy-7,13-methano-10H-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-10-one-13a-carbamate methyl ester (**27**)



Isocyanate **13** (2.06 g, 4.64 mmol) was loaded into a 500 mL 3-neck round bottom flask equipped with a stirrer bar, rubber septum and a dry ice condenser, which was attached to a well-ventilated nitrogen manifold. The flask containing the isocyanate was charged with 30 mL of anhydrous THF. Sodium dried ammonia, was distilled into the stirred suspension until the 500 ml flask was approximately  $\frac{1}{2}$  full. Methanol (5 mL, 120 mmol) was added via syringe followed by continuous addition of small flat pieces of lithium metal, addition of lithium metal (*ca.* 0.5 g, 72 mmol) was continued until the blue colour of solvated electrons persisted for at least 1 min. The ammonia was allowed to evaporate overnight, whereupon the residue was taken up in a solution of 4:2:1-AcOH/THF/H<sub>2</sub>O, the mixture was stirred for 1 h before the majority of solvent was removed *in vacuo*. The acidic residue was taken up in 3M NaOH and extracted with 3 x mL portions of EtOAc, washed with brine and dried over MgSO<sub>4</sub>. The crude material was used in the next step without purification.

(4a*RS*,5*RS*,6*aRS*,7*SR*,13*SR*,13a*RS*,13b*RS*)-5,7-Bis-(methoxymethoxy)-1,2,3,4,4a,5,6,6a,7,9,10,11,12,13,13a,13b-hexadecahydro-7,11-methano-8*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalene-10-one-13a-carbamic acid methyl ester (**28**)



The crude secondary alcohol **27** (1.9 g, 4.5 mmol) from the Birch reduction, was taken up in 100 mL of dry DCM. DIPEA (1.4 mL, 11 mmol) and DMAP (219 mg, 1.8 mmol) were added at room temperature. Neat MOMCl (1.9 mL, 23 mmol) was added to the stirred solution at 0 °C while the reaction was gradually allowed to return to room temperature over 10 h. The residual MOMCl was quenched by the addition of 10 ml of 1M NaOH, which was stirred for 30 min after which time the reaction was diluted with cold 1M HCl and extracted with 3 × 20 mL of DCM, the organic fractions were pooled, dried over MgSO<sub>4</sub>, and the solvent removed *in vacuo*. The crude product was purified using flash chromatography, (silica petrol/EtOAc 2:1) to yield the pure β,γ-enone as a white foam (2.1 g, 85%).

**<sup>1</sup>H NMR** (300 MHz) δ 4.63, (s, 1H, NH), 4.59 (d, J 6.6 Hz, 1H), 4.52 (d, J 6.6 Hz, 1H), 3.58 (s, 3H CO<sub>2</sub>CH<sub>3</sub>), 3.52 (s, 1H), 3.37 (s, 3H), 3.36 (s, 3H), 2.96 (m, 1H), 2.69 (s-br, 2H), 1.00 – 2.50 (m-br, 21H).

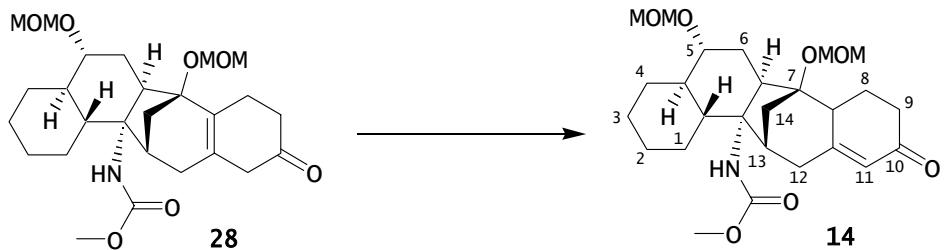
**<sup>13</sup>C NMR** (75 MHz) δ. 210.7 (C), 156.4 (C), 138.4 (C), 127.6 (C), 94.7 (CH<sub>2</sub>), 93.2 (CH<sub>2</sub>), 82.9 (C), 77.1 (C), 65.1 (C), 55.7 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 54.7 (CH), 51.7 (CH<sub>3</sub>), 46.9 (CH), 43.1 (CH<sub>2</sub>), 42.4 (CH), 39.2 (CH<sub>2</sub>), 38.0 (CH), 37.8 (CH<sub>2</sub>), 35.0 (CH<sub>2</sub>), 33.9 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 23.9 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2930, 2852, 1732, 1716, 1513, 1031 cm<sup>-1</sup>

**Mass Spectrum** (70 eV) m/z 477(M<sup>+</sup>, 10%), 415 (55%), 370 (20%), 340 (30%), 295 (30%).

**HRMS** Found: M<sup>+</sup>, 477.2736 calcd for C<sub>26</sub>H<sub>39</sub>NO<sub>7</sub>M<sup>+</sup>, 477.2727

(4aRS,5RS,6aRS,7RS,7aRS,13SR,13aRS,13bRS)-5,7-Bis-(methoxymethoxy)-1,2,3,4,4a,5,6,6a,7,7a,8,9,12,13,13a,13b-hexadecahydro-7,13-methano-10H-benzo[4,5]cyclohepta[1,2-*a*]-naphthalen-10-one-13a-carbamic acid methyl ester (**14**)



The  $\beta,\gamma$ -enone **28** (210 mg, 427  $\mu$ mol) was dissolved in  $\text{CHCl}_3$ , the mixture was cooled to 0  $^{\circ}\text{C}$  before a small quantity of anhydrous  $\text{HCl}$  was injected through a rubber septum from a cylinder. The mixture was stirred for 30 seconds, before the solvent was removed *in vacuo*. The crude mixture was purified using silica flash chromatography, (pet-spirits/EtOAc 1:1) giving the title compound as a white foam (140 mg, 67%) along with unreacted starting material (42 mg, 20%).

**$^1\text{H NMR}$**  (400 MHz)  $\delta$  5.93 (s, 1H,  $\text{H}_{11}$ ), 5.60 (s, 1H, NH), 4.80 (d,  $J$  6.9 Hz, 1H), 4.72 (d,  $J$  6.9 Hz, 1H), 4.66 (d,  $J$  6.9 Hz, 1H), 4.62 (d,  $J$  6.9 Hz, 1H), 3.59 (s, 3H), 3.52 (m, 1H,  $\text{H}_5$ ), 3.42 (s, 3H), 3.52 (s, 3H), 3.08 (m, 1H,  $\text{H}_{7a}$ ), 2.93 (m, 1H,  $\text{H}_{13}$ ), 2.70 (d,  $J$  16.8 Hz, 1H,  $\text{H}_{12}$ ).

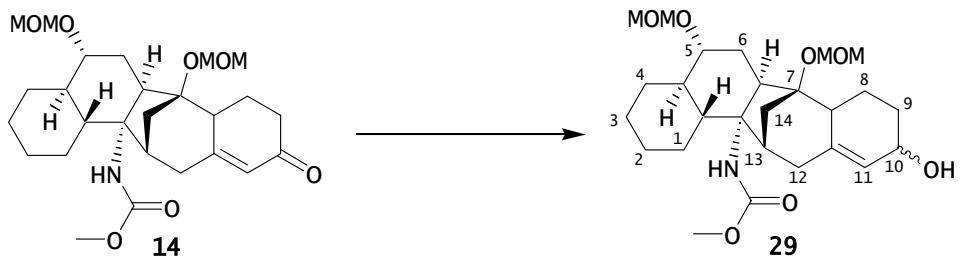
**$^{13}\text{C NMR}$**  (75 MHz)  $\delta$  199.4 (C), 164.8 (C), 156.4 (C), 127.6 (CH), 94.9 ( $\text{CH}_2$ ), 92.2 ( $\text{CH}_2$ ), 83.8 (C), 77.5 (CH), 64.3 (C), 56.1 ( $\text{CH}_3$ ), 55.7 ( $\text{CH}_3$ ), 51.7 ( $\text{CH}_3$ ), 48.2 (CH), 46.8 (CH), 45.8 (CH), 42.4 (CH), 40.6 ( $\text{CH}_2$ ), 38.6 ( $\text{CH}_2$ ), 37.6 (CH), 36.3 ( $\text{CH}_2$ ), 33.3 ( $\text{CH}_2$ ), 27.9 ( $\text{CH}_2$ ), 27.2 ( $\text{CH}_2$ ), 26.7 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_2$ ), 22.1 ( $\text{CH}_2$ ).

**IR**  $\nu_{\text{max}}$  2929, 1729, 1669, 1515, 1253, 1100  $\text{cm}^{-1}$

**Mass Spectrum** (70 eV)  $m/z$  477.1 ( $\text{M}^+$ , 15%), 415.1 (30%), 371.0 (51%), 340.1 (22%), 83.9 (100%).

**HRMS** Found:  $\text{M}^+$ , 477.2726 calcd for  $\text{C}_{26}\text{H}_{39}\text{NO}_7\text{M}^+$ , 477.2727

(4a*RS*,5*RS*,6*RS*,7*RS*,7a*RS*,13*SR*,13a*RS*,13b*RS*)-5,7-Bis-(methoxymethoxy)-1,2,3,4,4a,5,6,6a,7,7a,8,9,12,13,13a,13b-hexadecahydro-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalen-10-ole-13a-carbamic acid methyl ester (**29**)



To a stirred solution of the  $\alpha,\beta$ -enone **14** (1.35 g, 2.83 mmol) in dry THF at 0 °C was added a 0.5 M solution of 9-BBN in THF (10.7 mL, 5.37 mmol). Stirring was continued until all of the  $\alpha\beta$ -enone (as judged by TLC) had been consumed. Excess 9-BBN was quenched by the addition of MeOH (2.0 mL, 48 mmol), and the mixture was further diluted with 1 M NaOH (18 mL, 18 mmol) along with 30% w/w  $\text{H}_2\text{O}_2$  (1.5 mL, 13 mmol). A condenser was fitted to the flask and the mixture was stirred at 60°C for 20 min. The mixture was diluted with *ca.* 50 mL of  $\text{H}_2\text{O}$  and extracted with 3  $\times$  50 mL of EtOAc, the combined organic layers were washed with brine and dried over  $\text{MgSO}_4$ . After removal of the solvent *in vacuo* the crude product could be purified using flash chromatography, (silica, petrol/EtOAc – 3:4) to give the title alcohol as a colourless oil (1.03 g 87 %).

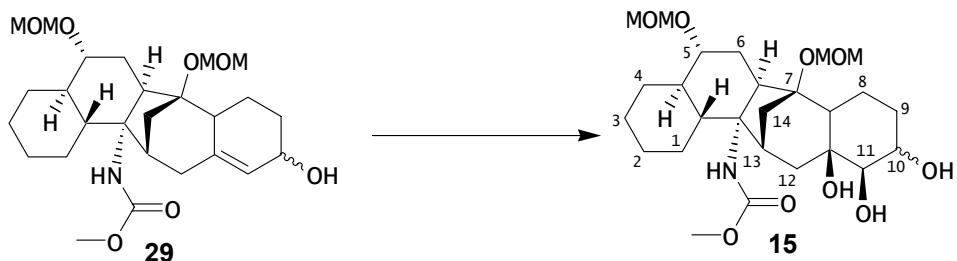
**$^1\text{H NMR}$**  (300 MHz)  $\delta$  5.49 (m, 1H), 4.77 (m, 1H), 4.63 (m, 4H), 4.21 (m, 1H), 3.59 (s, 3H), 3.47 (m, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 2.88 (m, 1H), 2.58 (m, 1H), 2.4 – 1 (m-br, 21H)

**$^{13}\text{C NMR}$**  (75 MHz)  $\delta$ . 156.0 (C), 139.7 (C), 128.0 (CH), 95.0 ( $\text{CH}_2$ ), 91.9 ( $\text{CH}_2$ ), 78.2 (CH), 72.1, 67.6, 64.2, 55.9, 55.7, 55.6, 51.7, 47.3, 46.6, 46.0, 42.5, 41.5, 37.9, 37.6, 34.7, 33.5, 31.7, 31.1, 28.1, 27.4, 26.8, 25.5, 22.7, 22.1, 21.5.

**IR**  $\nu_{\text{max}}$  2929, 1715, 1519, 1032  $\text{cm}^{-1}$

**Mass Spectrum** (70 eV) m/z 479 ( $\text{M}^+$ , 11%), 461 (10%), 446 (2%), 418 (11%), 399 (20%).

(4a*RS*,5*RS*,6*RS*,7*RS*,7a*RS*,11*RS*,11a*SR*,13*SR*,13a*RS*,13b*RS*)-5,7-Bis-(methoxymethoxy)-1,2,3,4,4a,5,6,6a,7,7a,8,9,12,13,13a,13b-hexadecahydro-7,13-methano-10*H*-benzo[4,5]cyclohepta[1,2-*a*]-naphthalen-10,11,11a-triol-13a-carbamic acid methyl ester (**15**)

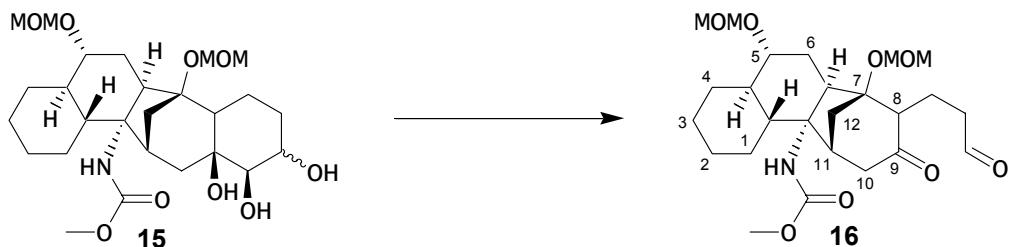


A 250 ml round bottom flask was charged with a THF (100 mL) solution of allylic alcohol **29** (740 mg, 1.54 mmol) and pyridine (2.0 mL 25 mmol). To this stirred solution was added solid 70% w/w OsO<sub>4</sub> (613 mg, 1.69 mmol) at room temperature. Stirring was continued until the starting material was no longer visible using TLC. After consumption of starting material (*ca.* 18 hours) the reaction was quenched by the addition of an aqueous solution of NaHSO<sub>3</sub> (0.70 g, 6.7 mmol), which was stirred at room temperature for 2 hours. The mixture was diluted with brine and extracted with 3 x 40 mL of EtOAc, the combined organic layers were pooled, dried over MgSO<sub>4</sub>, and the solvent removed *in vacuo* to yield the title compound as a brown oil. The material was not purified, but used crude in the following ring-opening step<sup>8</sup>.

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<sup>8</sup> Characterisation of the triol was not undertaken due to the highly polar nature of the molecule and the fact that a 1:1 mixture of diastereoisomers were present.

(4a*RS*,5*RS*,6*aRS*,7*SR*,8*RS*,11*RS*,11*aRS*,11*bRS*)-5,7-Bis-(methoxymethoxy)-8-(3-oxo-propyl)-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-tetradecahydro-7,11-methano-9*H*-cyclohepta[*a*]naphthalen-9-one-11*a* carbamic acid methyl ester (**16**)



To a stirred solution of the crude triol **15** (790 mg, 1.54 mmol) in MeOH (*ca.* 80 mL) at 0 °C was added solid Pb(OAc)<sub>4</sub> (591 mg, 3.08 mmol). The mixture immediately turned a green colour and was stirred for 1 h, after which time TLC indicated the absence of starting material. A 30 mL aliquot of saturated NaHCO<sub>3</sub> was added and the organic solvent was evaporated leaving a solid brown suspension which was immediately extracted with 3 × 50 mL portions of EtOAc, the combined organic layers were washed with brine and dried over MgSO<sub>4</sub>, and the solvent was removed *in vacuo* to yield the title compound as a brown oil. The crude product was used in the next reaction without purification<sup>3</sup>.

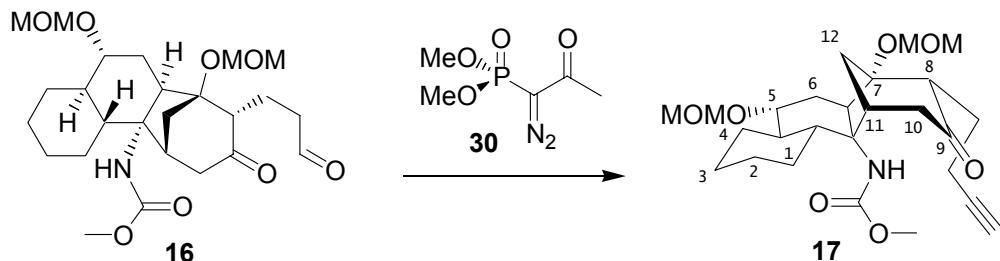
<sup>1</sup>**H NMR** (300 MHz) δ 9.75 (s, 1H), 5.60 (s, 1H), 4.70 (m, 4H), 3.57 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.20 – 0.90 (m-br, 24 H)

<sup>13</sup>**C NMR** (75 MHz) δ 210.4 (C), 202.2 (C), 156.2 (C), 95.0 (CH<sub>2</sub>), 92.8 (CH<sub>2</sub>), 83.5 (C), 76.7 (CH), 64.8 (C), 59.8, 56.6, 54.7 (CH<sub>3</sub>), 55.5 (CH<sub>3</sub>), 51.8 (CH<sub>3</sub>), 46.1, 45.6, 43.3, 42.6, 41.0, 36.3, 33.5, 28.1, 27.4, 26.8, 25.3, 15.7.

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<sup>3</sup> Silica flash chromatography was found to give exceptionally low overall yields, moreover upon standing the purity of the aldehyde rapidly deteriorated. For the latter reason a partial characterisation is presented.

(4a*RS*,5*RS*,6*RS*,7*SR*,8*RS*,11*RS*,11a*RS*,11b*RS*)-5,7-Bis-(methoxymethoxy)-8-But-3-ynyl-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-tetradecahydro-7,11-methano-9*H*-cyclohepta [*a*]naphthalen-9-one-11a carbamic acid methyl ester (**17**)



To a stirred solution of the crude keto aldehyde (359 mg, 745  $\mu$ mol) in dry methanol (*ca.* 30 mL) at 0  $^{\circ}$ C was added anhydrous  $K_2CO_3$  (206 mg, 1.49 mmol) and the diazophosphonate **30** (171 mg, 892  $\mu$ mol). The mixture was allowed to gradually warm to room temperature while stirring was continued until no further change could be observed by TLC (*ca.* 4 h). The methanol was removed *in vacuo* and the resultant oil was taken up in EtOAc (50 mL) and saturated  $NaHCO_3$ . The product was extracted with 3  $\times$  40 mL of EtOAc, and the pooled organic fractions were washed with brine, dried over  $MgSO_4$  and the solvent removed *in vacuo* to give an opaque oil. Flash chromatography (silica, petrol/EtOAc 3:2) on the crude residue gave the title compound as a colourless oil, which crystallized upon standing (159 mg, 44%). Recrystallization from pentane chloroform afforded white needles m.p. 234-235  $^{\circ}$ C.

**$^1H$  NMR** (300 MHz)  $\delta$  5.60 (s, NH), 4.90 (d, *J* 6.9 Hz, 1H), 4.67 (d, *J* 7.2 Hz, 1H), 4.61 (d, *J* 6.9 Hz, 1H), 4.58 (d, *J* 6.9 Hz, 1H), 3.57 (s, 3H), 3.49 (br. s, 1H), 3.42 (s, 3H), 3.34 (s, 3H), 3.12 (m, 1H), 2.85 (d, *J* 8.7 Hz, 1H), 2.73 (br. d, 1H), 1.00 – 2.40 (m-br, 21H).

**$^{13}C$  NMR** (75 MHz)  $\delta$  210.4 (C<sub>6</sub>), 156.2 (C), 94.9 (CH<sub>2</sub>), 92.0 (CH<sub>2</sub>), 84.5 (C), 83.2 (C), 77.3 (CH<sub>2</sub>), 68.7 (CH), 64.7 (C<sub>11a</sub>), 59.4 (C<sub>5</sub>), 56.2 (CH<sub>3</sub>), 55.7 (CH<sub>3</sub>), 51.8 (CH<sub>3</sub>), 48.1 (C<sub>6a</sub>), 46.0 (C<sub>11b</sub>), 45.5 (C<sub>10</sub>), 42.5 (C<sub>4a</sub>), 41.2 (CH<sub>2</sub>), 36.3 (C<sub>11</sub>), 33.4 (C<sub>4</sub>), 28.0 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 25.1 (C<sub>6</sub>), 21.8 (CH<sub>2</sub>), 17.7 (CH<sub>2</sub>).

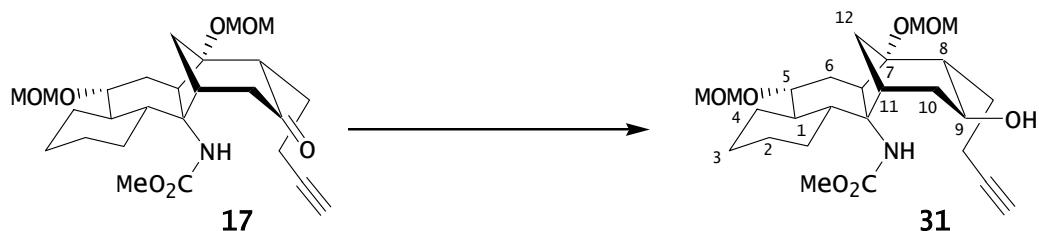
**IR**  $\nu_{\text{max}}$  3379, 3305, 2931, 1730, 1516, 1029  $\text{cm}^{-1}$

**Mass Spectrum** (70 eV) m/z 477 (M<sup>+</sup>, 7%), 415 (34%), 370 (77%), 332 (100%).

**HRMS** Found: M<sup>+</sup>, 477.2723. calcd for C<sub>26</sub>H<sub>39</sub>NO<sub>7</sub> M<sup>+</sup>, 477.2726

**Elemental Analysis** Found: C, 65.48; H, 7.74; N, 2.84.  $C_{26}H_{39}NO_7$  Requires: C, 65.39; H, 8.23; N, 2.93.

(4a*RS*,5*RS*,6*RS*,7*SR*,8*SR*,9*SR*,11*RS*,11a*RS*,11b*RS*)-5,7-Bis(methoxymethoxy)-8-(but-3-enyl)-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-tetradecahydro-7,11-methano-9*H*-cyclohepta[*a*]naphthalen-9-ol-11a carbamic acid methyl ester (**31**)



Ammonia (*ca.* 40 mL) was distilled into a 100 mL 3 neck round bottomed flask containing the keto-alkyne **17** (181 mg, 379  $\mu$ mol). Methanol was syringed in to the flask (0.5 mL, 12 mmol). Several small pieces of lithium metal were added such that the blue colour of solvated electrons persisted for approximately 30 seconds, after which time, ammonium chloride was added in to quench the excess metal if required. The ammonia was left to evaporate and the dry residue was taken up in water and ethyl acetate, and then extracted with 3  $\times$  30 mL of EtOAc. The organic layer was washed with brine, dried over  $\text{MgSO}_4$  and the solvent removed *in vacuo* to yield the title compound as a colourless oil (165 mg, 90%)<sup>9</sup>.

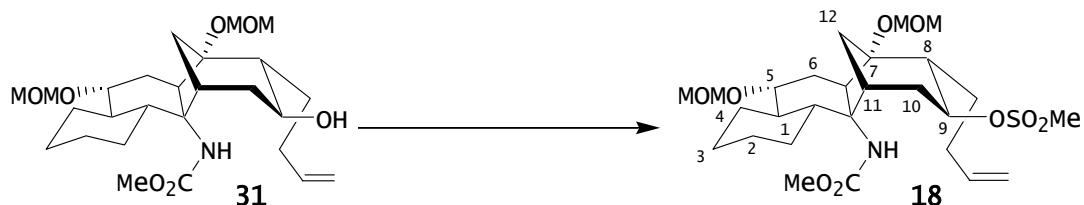
**$^1\text{H NMR}$**  (300 MHz)  $\delta$  5.83 (m, 1H), 5.60 (s, 1H), 4.98 (m, 2H), 4.76 (d, *J* 6.9 Hz, 1H), 4.66 (s, 2H), 4.56 (d, *J* 6.9 Hz), 3.80 (m, 1H), 3.59 (s, 3H), 3.52 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 2.87 (m, 1H), 1.00 – 2.40 (m-br, 26H).

**$^{13}\text{C NMR}$**  (75 MHz)  $\delta$  156.2 (C), 139.4 (CH), 114.3 (CH<sub>2</sub>), 95.0 (CH<sub>2</sub>), 92.0 (CH<sub>2</sub>), 83.7 (C), 77.8 (CH), 74.2 (CH), 64.2 (C), 55.9 (CH<sub>3</sub>), 55.7 (CH<sub>3</sub>), 52.4 (CH), 51.7 (CH<sub>3</sub>), 47.6 (CH), 46.4 (CH), 42.7 (CH), 41.3 (CH<sub>2</sub>), 38.8 (CH<sub>2</sub>), 36.7 (CH), 33.8 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 28.4 (CH<sub>2</sub>), 28.2 (CH<sub>2</sub>), 27.4 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2928, 1733, 1514, 1447, 1248  $\text{cm}^{-1}$

<sup>9</sup> Mass spectroscopic data unavailable due to the facile in-flight elimination of the alcohol moiety.

(4a*RS*,5*RS*,6*RS*,7*SR*,8*SR*,9*SR*,11*RS*,11a*RS*,11b*RS*)-8-But-3-enyl-9-methanesulfonyl-1,2,3,4,4a,5,6,6a,7,8,10,11,11a,11b-tetradecahydro-5,7-bis-(methoxymethoxy)-7,11-methano-9*H*-cyclohepta[a]naphthalene-11*a* carbamic acid methyl ester (**18**)



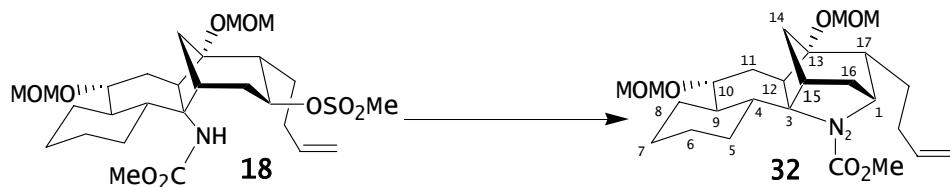
Alcohol **31** (201 mg, 417  $\mu$ mol) and triethylamine (1.5 mL, 18 mmol) were dissolved in 30 mL of DCM, and methanesulfonyl chloride (0.1 mL, 1.2 mmol) was added via syringe to the stirred solution at 0  $^{\circ}$ C. Upon consumption of the starting alcohol (as monitored by TLC) the reaction was quenched by the addition of 50 mL of water. The product was extracted with 3  $\times$  30 mL of DCM, and the combined organic layers were pooled and dried over  $\text{MgSO}_4$ . Evaporation of the solvent gave a brown solid that after purification by flash chromatography, (silica, petrol/EtOAc 1:1) afforded the title compound as a colourless oil (218 mg, 93%).

**$^1\text{H NMR}$**  (300 MHz)  $\delta$  5.78 (m, 1H), 5.61 (s, 1H, NH), 4.98 (m, 2H), 4.83 (ddd, J 6.6 & 10.8 & 16.5 Hz, 1H), 4.75 (d, J 7.2 Hz, 1H), 4.68 (d, J 6.9 Hz, 1H), 4.63 (d, J 6.6 Hz, 1H), 4.56 (d, J 7.2 Hz, 1H), 3.60 (s, 3H), 3.53 (m, 1H), 3.38 (s, 6H), 2.97 (s, 3H) 2.95 (m, 1H), 2.60 (m, 5H), 2.20–1.00 (m, 17H)

**$^{13}\text{C NMR}$**  (75 MHz)  $\delta$  156.5 (C), 138.7 (CH), 114.7 (CH<sub>2</sub>), 94.8 (CH<sub>2</sub>), 92.1 (CH<sub>2</sub>), 85.7 (CH), 83.6 (C), 77.1 (CH), 64.0 (CH), 55.9 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 51.8 (CH<sub>3</sub>), 49.3 (CH), 47.7 (CH), 46.1 (CH<sub>2</sub>), 42.4 (CH), 40.8 (CH<sub>2</sub>), 39.0 (CH), 36.6 (CH), 35.6 (CH<sub>2</sub>), 33.5 (CH<sub>2</sub>), 33.1 (CH<sub>2</sub>), 31.5 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 27.2 (CH<sub>2</sub>), 25.2 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2931, 1731, 1512, 1248, 1175, 1030  $\text{cm}^{-1}$

(1*S*,3*S*,4*S*,9*S*,10*S*,12*S*,13*S*,15*R*,17*S*)-10,13-Bis-(methoxymethoxy)-17-but-3-enyl-2-aza-pentacyclo[11.3.1.0<sup>3,15</sup>,0<sup>3,12</sup>,0<sup>4,9</sup>]heptadecane-2-carboxylic acid methyl ester (**32**)



To a solution of the mesylate **18** (99 mg, 176  $\mu$ mol) in DMF (15 mL) at room temperature was added a suspension of sodium hydride (30 mg, 1.3 mmol) in a small amount of DMF (*ca.* 3 mL). The suspension was stirred for 2 hours during which time the opaque solution turned yellow. Water (*ca.* 50 mL) was carefully added and the product was extracted with 3  $\times$  30 mL of EtOAc, the combined organic layers were pooled, washed with brine and dried over  $\text{MgSO}_4$ . Evaporation of the solvent yielded the title compound as a colourless oil which could be further purified using flash chromatography (silica, petrol/EtOAc 5:1), the purified material solidified upon standing to give a white semi-crystalline material (80 mg, 97%).

**<sup>1</sup>H NMR** (300 MHz)  $\delta$  5.76 (m, 1H), 4.95 (m, 1H), 4.71 (d, *J* 7.2 Hz, 1H), 4.64 (d, *J* 7.2 Hz, 1H), 4.58 (d, *J* 7.2 Hz, 1H), 4.58 (d, *J* 6.9 Hz, 1H), 4.57 (d, *J* 7.2 Hz, 1H), 4.54 (s, 1H), 3.61 (s, 3H), 3.52 (m, 1H), 3.64 (s, 3H), 3.33 (s, 3H), 2.75 (m, 1H), 2.4 – 0.9 (m, 22H).

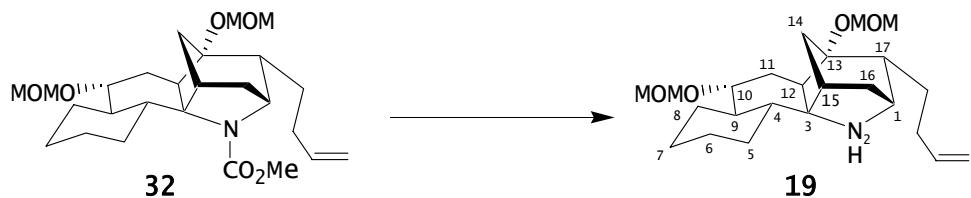
**<sup>13</sup>C NMR** (75 MHz)  $\delta$  154.5 (C), 138.5 (CH), 114.4 (CH<sub>2</sub>), 94.0 (CH<sub>2</sub>), 91.9 (CH<sub>2</sub>), 84.9 (C), 77.9 (CH), 70.3 (C), 60.0 (CH), 55.6 (CH<sub>3</sub>), 55.1 (CH<sub>3</sub>), 51.8 (CH<sub>3</sub>), 49.1 (CH), 48.5 (CH), 45.0 (CH), 43.0 (CH), 40.7 (CH<sub>2</sub>), 40.0 (CH<sub>2</sub>), 39.5 (CH), 34.6 (CH<sub>2</sub>), 31.8 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 24.5 (CH<sub>2</sub>), 24.2 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2947, 2853, 1709, 1444, 1369  $\text{cm}^{-1}$

**Mass Spectrum** (70 eV) *m/z* 463.2 ( $\text{M}^+$ , 40%), 418.2 (56%), 401.2 (100%), 357.2 (73%), 339.2 (23%), 324.1 (30%).

**HRMS** Found:  $\text{M}^+$ , 463.2936. calcd for  $\text{C}_{26}\text{H}_{41}\text{NO}_6\text{M}^+$ , 463.2934.

(1*RS*,3*RS*,4*RS*,9*RS*,10*RS*,12*RS*,13*RS*,15*SR*,17*RS*)-10,13-Bis-(methoxymethoxy)-17-but-3-enyl-2-aza-pentacyclo[11.3.1.0<sup>3,15</sup>,0<sup>3,12</sup>,0<sup>4,9</sup>]heptadecane (**19**)



Sodium hydride (400 mg, 10 mmol) was washed several times with hexane in a 3-neck 50 ml round bottom flask, and the residual solvent was removed *in vacuo*. HMPA (5.0 mL, 28 mmol) was added, and the mixture was degassed, then purged with nitrogen. To a stirred suspension of the sodium hydride in HMPA was added distilled *n*-propane thiol (0.9 mL, 9.9 mmol), and the mixture was stirred for 2 hours, and then left to stand until a transparent solution was obtained. The carbamate protected pyrrolidine **32** (48 mg, 37 mmol) was dissolved in 5 mL of the previously prepared thiolate solution, and the mixture was stirred for 2 days at room temperature. The reaction was quenched with 20 mL of water and extracted with 3 x 20 mL of EtOAc, and the solvent was removed *in vacuo* to yield a brown solid residue. Purification using flash chromatography, (alumina, isocratic elution, benzene  $\Rightarrow$  pet-spirits/EtOAc 5:1) afforded the title compound as a colourless oil (37 mg, 90 %).

**<sup>1</sup>H NMR** (300 MHz)  $\delta$  5.80 (m, 1H), 4.96 (m, 2H), 4.73 (d, *J* 7.2 Hz, 1H), 4.69 (d, *J* 6.9 Hz, 1H), 4.57 (d, *J* 7.2 Hz, 1H), 4.54 (d, *J* 6.9 Hz, 1H), 3.55 (m, 2H), 3.39 (s, 3H), 3.35 (s, 3H).

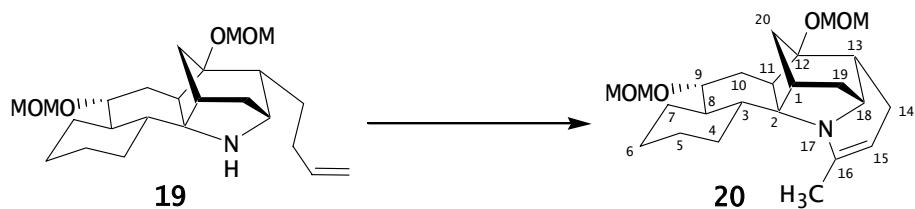
**<sup>13</sup>C NMR** (75 MHz)  $\delta$  138.8 (CH), 114.6 (CH<sub>2</sub>), 94.4 (CH<sub>2</sub>), 91.7 (CH<sub>2</sub>), 84.2 (C), 78.7 (CH), 68.8 (C), 59.3 (CH), 55.5 (CH<sub>3</sub>), 55.4 (CH<sub>3</sub>), 49.1 (CH), 46.7 (CH), 44.8 (CH), 44.2 (CH<sub>2</sub>), 41.8 (CH<sub>2</sub>), 41.7 (CH), 41.1 (CH), 34.0 (CH<sub>2</sub>), 32.6 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 26.3 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 24.1 (CH<sub>2</sub>).

**IR**  $\nu_{\text{max}}$  2930, 1640, 1444, 1038 cm<sup>-1</sup>

**Mass Spectrum** (70 eV) m/z 405.3 (M<sup>+</sup>, 70%), 360.2 (62%), 344 (100%), 312.2 (17%), 298.2 (47%), 282.2 (45%).

**HRMS** Found: M<sup>+</sup>, 405.2879. calcd for C<sub>24</sub>H<sub>39</sub>NO<sub>4</sub> M<sup>+</sup>, 405.2883.

(1*S*,2*R*,3*R*,8*R*,9*R*,11*R*,12*R*,13*R*,18*R*)-9,12-Bis(methoxymethoxy)-16-methyl-17-aza-hexacyclo[10.7.1.0<sup>2,11</sup>.0<sup>2,17</sup>.0<sup>3,8</sup>.0<sup>13,18</sup>]eicos-15-ene (**20**)



A 50 mL round bottom flask containing alkene **19** (35 mg, 86  $\mu$ mol) was charged with  $\text{PdCl}_2$  (8 mg, 43  $\mu$ mol),  $\text{nBu}_4\text{N}^+\text{Cl}^-$  (132 mg, 470  $\mu$ mol),  $\text{CuCl}$  (10 mg, 100  $\mu$ mol),  $\text{K}_2\text{CO}_3$  (30 mg, 210  $\mu$ mol) and anhydrous acetonitrile (20 mL). The mixture was stirred at 50 °C over an atmosphere of  $\text{O}_2$ . The initially pale green solution changed to an orange colour during the first 0.5 h, and stirring was continued at 50 °C for a further 10 h. The solvent was removed *in vacuo*, and the residue taken up in 10 mL of 16 M aqueous  $\text{NH}_3$ , and then extracted with 3  $\times$  20 mL of EtOAc. The organic layer was washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and the solvent was evaporated to yield the product as a brown oil. Purification by flash chromatography, (silica, petrol/EtOAc 1:1)<sup>20</sup> afforded the title compound as a colourless oil (30 mg, 85%).

**<sup>1</sup>H NMR** (300 MHz)  $\delta$  5.41 (m, 1H), 4.74 (d, *J* 7.2 Hz, 1H), 4.68 (d, *J* 7.2 Hz, 1H), 4.62 (d, *J* 7.2 Hz, 1H), 4.45 (d, *J* 7.2 Hz, 1H), 3.47 (m, 1H), 3.38 (s, 3H), 3.35 (s, 3H), 3.21 (m, 1H), 2.68 (m, 1H), 2.30 – 0.90 (m, 23H).

**<sup>13</sup>C NMR** (75 MHz)  $\delta$  143.9 (C), 119.2 (CH), 94.4 (CH<sub>2</sub>), 92.2 (CH<sub>2</sub>), 86.0 (C), 78.7 (CH), 72.6 (C), 64.6 (CH), 55.4 (CH<sub>3</sub>), 55.3 (CH<sub>3</sub>), 47.8 (CH), 42.2 (CH), 40.6 (CH), 40.5 (CH<sub>2</sub>), 40.4 (CH), 39.6 (CH<sub>2</sub>), 38.2 (CH<sub>2</sub>), 33.9 (CH), 26.9 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 24.9 (CH<sub>3</sub>), 24.3 (CH<sub>2</sub>).

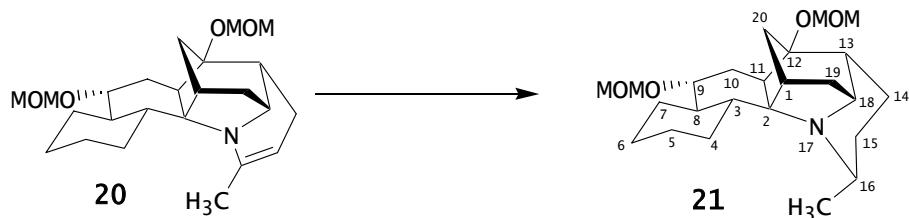
**IR**  $\nu_{\text{max}}$  2924, 1446, 1145, 1035  $\text{cm}^{-1}$

**Mass Spectrum** (70 eV) *m/z* 403 ( $\text{M}^+$ , 82%), 376 (8%), 358 (93%), 342 (100%), 326 (7%), 308 (41%), 296 (48%).

**HRMS** Found:  $\text{M}^+$ , 407.2726. calcd for  $\text{C}_{24}\text{H}_{37}\text{NO}_4\text{M}^+$ , 407.2723.

<sup>20</sup> The product could also be purified by flash chromatography on alumina, benzene  $\Rightarrow$  pet-spirits / EtOAc 5:1

(1*S*,2*R*,3*R*,8*R*,9*R*,11*R*,12*R*,13*R*,16*S*,18*R*)-9,12-Bis(methoxymethoxy)-16-methyl-17-aza-hexacyclo[10.7.1.0<sup>2,11</sup>.0<sup>2,17</sup>.0<sup>3,8</sup>.0<sup>13,18</sup>]eicosane (**21**)



Enamine **20** (28 mg, 69  $\mu$ mol) was dissolved in 1,1,1,3,3-hexafluoropropan-2-ol (3 mL) and placed in a Parr hydrogenation vessel, along with solid 5% w/w rhodium on alumina (20 mg, 10  $\mu$ mol), and the mixture was shaken for 2 hours under a 70 psi atmosphere of hydrogen. The solvent was removed *in vacuo* and the residue suspended in a mixture of 20 mL of 16 M aqueous ammonia and 20 mL of EtOAc. The mixture was extracted with 4  $\times$  20 mL of EtOAc, and the organic layers were pooled, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . Flash chromatography of the crude product (alumina, toluene  $\Rightarrow$  petrol/EtOAc, 3:1) gave the amine **21** as a colourless oil, (22 mg, 95%)

**<sup>1</sup>H NMR** (300 MHz)  $\delta$  4.74 (d, *J* 7.2 Hz, 1H), 4.72 (d, *J* 6.9 Hz, 1H), 4.63 (d, *J* 6.9 Hz, 1H), 4.59 (d, *J* 6.9 Hz, 1H), 3.48 (m-br, 1H), 3.53 (m, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 3.26 (m, 1H), 2.57 (m, 1H), 0.90 – 2.20 (m-br, 25H).

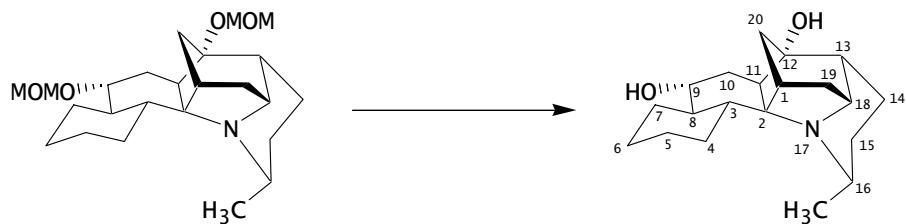
**<sup>13</sup>C NMR** (75 MHz)  $\delta$  94.4 ( $\text{CH}_2$ ), 92.0 ( $\text{CH}_2$ ), 86.1 (C), 78.2 (CH), 70.5 (C), 68.6 (CH), 55.5 ( $\text{CH}_3$ ), 55.2 ( $\text{CH}_3$ ), 54.3 (CH), 52.6 (CH), 44.6 (CH), 44.1 (CH), 41.8 (CH), 41.0 ( $\text{CH}_2$ ), 39.4 (CH), 39.3 ( $\text{CH}_2$ ), 35.0 ( $\text{CH}_2$ ), 29.1 ( $\text{CH}_2$ ), 28.0 ( $\text{CH}_2$ ), 27.0 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 24.2 ( $\text{CH}_2$ ), 23.3 ( $\text{CH}_3$ ).

**IR**  $\nu_{\text{max}}$  2926, 1480, 1452, 1128, 1044  $\text{cm}^{-1}$

**Mass Spectrum** (70 eV) *m/z* 405.6 ( $\text{M}^+$ , 1%), 391.5 (30%), 361.4 (100%), 345.4 (71%).

**HRMS** Found:  $\text{M}^+$ , 405.2878. calcd for  $\text{C}_{24}\text{H}_{39}\text{NO}_4\text{M}^+$ , 405.2879.

(1*S*,2*R*,3*R*,8*R*,9*R*,11*R*,12*R*,13*R*,16*S*,18*R*)-9,12-Bishydroxy-16-methyl-17-aza-hexacyclo[10.7.1.0<sup>2,11</sup>.0<sup>2,17</sup>.0<sup>3,8</sup>.0<sup>13,18</sup>]-eicosane (**22**)



Bis-MOM protected **21** (5.0 mg, 12  $\mu$ mol) was dissolved in a 5:1 solution of methanol / water. Pre-treated<sup>8</sup> Dowex 50W ion exchange resin was added, and the mixture was heated to reflux. After 5 hours, the reaction was cooled to room temperature, and the Dowex resin was filtered through a glass scinter and then washed with twice, with alternating 10 mL aliquots of 1M NaOH followed by MeOH. The alcohol was evaporated *in vacuo*. The resulting aqueous solution was saturated with brine and extracted with 5  $\times$  20 mL of EtOAc. The organic fractions were pooled, dried over Na<sub>2</sub>SO<sub>4</sub> and filtered into a 50 mL round bottom flask. After evaporation of the solvent the white residue on the bottom of the flash was taken up in 5  $\times$  3 mL of dry toluene, and the pooled toluene fractions were transferred to another flask. After evaporation of the toluene the remaining residue was then washed with *n*-hexane to remove the last vestiges of oil and grease. The title compound was isolated in pure form, as a white crystalline solid, (3 mg, 60%).

**<sup>1</sup>H NMR** (300 MHz)  $\delta$  4.09 (m, 1H), 3.88 (m, 1H), 3.71 (m, 1H), 3.07 (m, 1H), 2.62 (m, 1H), 2.44 (m, 2H), 2.40 – 1.00 (m, 24 H)

**<sup>13</sup>C NMR** (75 MHz)  $\delta$  82.6 (C), 75.0 (CH), 70.8 (C), 57.1 (CH), 54.0 (CH), 49.9 (CH), 46.4 (CH), 45.9 (CH<sub>2</sub>), 45.6 (CH), 45.4 (CH), 45.3 (CH), 40.5 (CH), 36.7 (CH), 30.7 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 30.1 (CH<sub>2</sub>), 28.9 (CH<sub>2</sub>), 28.4 (CH<sub>2</sub>), 25.6 (CH<sub>2</sub>), 24.0 (CH<sub>3</sub>)

**Mass Spectrum** (70 eV) m/z 317.3 (M<sup>+</sup>, 18%), 276.2 (25%), 207.2 (11%), 149.0 (41%), 111.1 (100%).

**HRMS** Found: M<sup>+</sup>, 317.2355. Calculated for C<sub>20</sub>H<sub>31</sub>NO<sub>2</sub>M<sup>+</sup>, 317.2355

<sup>8</sup> Resin was prepared by washing with 2  $\times$  50 mL of 2M NaOH followed by 2  $\times$  50 mL 2M HCl then water until pH of the eluant was neutral.

