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Enantioselective synthesis of a potential key intermediate for the total synthesis of fumagillin

Marisa Ciampini,[a] Patrick Perlmutter[a,*] and Keith Watson[b]

[a]*School of Chemistry, Monash University, PO Box 23, Clayton, Victoria 3800, Australia*
[b]*Biota Holdings Inc., Monash University, Clayton, Victoria 3800, Australia*

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Abstract—Key intermediate, **7**, of a projected total synthesis of the anti-angiogenesis compound *Fumagillin* **1** and the semi-synthetic analogue *TNP-470* **2**, has been prepared in enantiomerically pure form by employing an early nucleophilic addition ring closure [NARC] sequence to construct the cyclohexene backbone.

1. Introduction

Angiogenesis is the process by which new blood cells are formed.[1–4] Normally this process is regulated, however cancer describes a range of diseases in which abnormal cells proliferate and spread out of control. Surgery, radiotherapy, chemotherapy, hormonal therapy, immunotherapy, laser therapy and oral drugs can now treat cancer, alone or in combination.[5] There are several compounds, which show inhibition of angiogenesis, which include fumagillin[6] **1**, TNP-470[7] **2** a synthetic derivative of fumagillin, ovalicin[8] **3**, RK-850[9] **4**, as well as 5-dimethyovalicin[10] **5** (Fig. 1). To date, seven syntheses of fumagillin **1** and fumagillol **6**, the saponification product of **1** have been reported.[11–17]

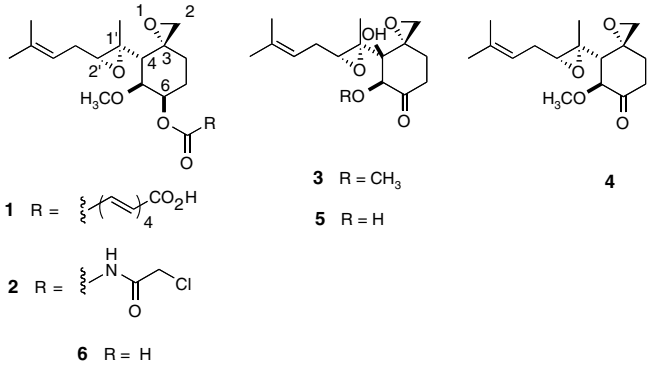

Figure 1. Fumagillin and related analogues.

2. Results and discussion

Due to the continuing importance of an anti-cancer drug, we have chosen to develop a flexible route for the synthesis of fumagillin **1** as well as new analogues. Our retrosynthesis, outlined in Figure 2, produced keto-acetonide **7** as a key target. The inclusion of a ketone at C1′ (fumagillin numbering) was seen as important given the recent evidence that C1′ planar fumagillin analogues, such as oximes, also exhibit potent anti-tumour activity[18] as well as being angiogenesis inhibitors.[19] Thus the development of a practical synthesis of **7** is the focus of this paper.

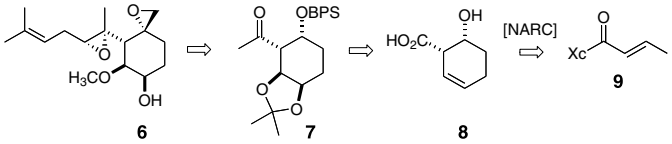

Figure 2.

A central issue in this synthetic problem is the enantioselective construction of a cyclohexane bearing four contiguous stereogenic centres.[20] It was envisaged that this could be achieved by diastereoselective dihydroxylation[21] of a cyclohexene such as **8**. In turn, **8** might be prepared using a simple 'NARC'[22] sequence beginning with crotonyl sultam[23] **9**.

* Corresponding author. Tel.: +61 3 9905 4522; fax: +61 3 9905 4597; e-mail: patrick.perlmutter@sci.monash.edu.au

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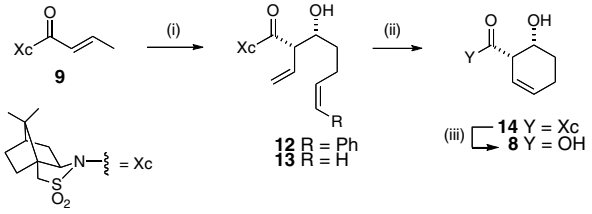
The successful execution of these ideas is outlined in this paper.

Hence the Z-boron enolate of **9** (formed by γ-deprotonation) reacted exclusively at the α-carbon[24] with aldehydes 5-phenyl-4-pentenal **10** or 4-pentanal **11** to give the corresponding *syn* aldol adducts **12** and **13** in excellent yields (Scheme 1).



Scheme 1. Reagents and conditions: (i) (a) Et_2BOTf, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, (b) **10** or **11**; (ii) $(Cy_3P)_2(Cl)_2Ru{=}CHPh$ (cat.), CH_2Cl_2; (iii) H_2O_2, LiOH.

Surprisingly, ring closing metathesis of **12** failed. Fortunately no such problems were encountered with diene **13**, which closed smoothly under standard Grubbs' RCM conditions.[25] The X-ray crystal structure of **14** is shown in Figure 3. Hydrolysis of **14** provided enantiomerically pure cyclohexene **8** in 63% yield from **9**.

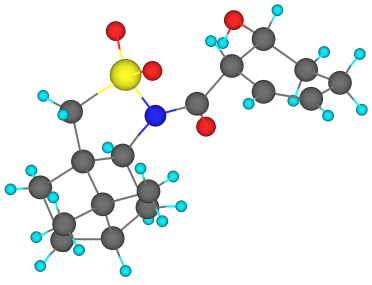
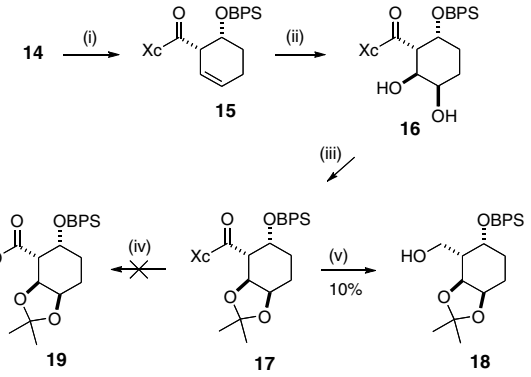


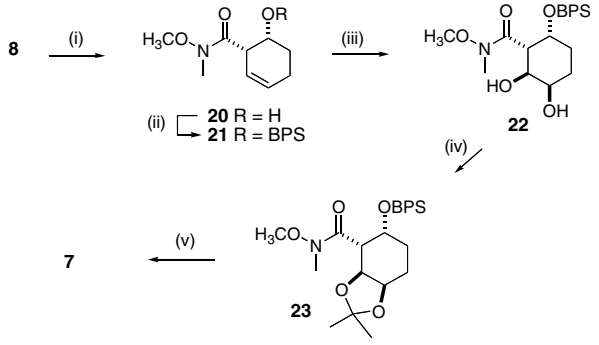
Figure 3. X-ray crystal structure of RCM product **14**.

Several approaches for the conversion of **14** into **7** were explored. Initially **14** was protected as its BPS ether **15** (Scheme 2). Dihydroxylation then gave a single diastereomer, *cis*-diol **16**, but in moderate yield under standard conditions[21] ($K_2OsO_4{\cdot}H_2O$) employing a 1:1 mixture of DMF and *t*-BuOH as solvent. Moving to a solvent consisting of a 3:1 mixture of *t*-BuOH and water gave an improved yield of 90%. Many attempts were made to chemically manipulate **16** and its corresponding acetonide[26] **17** (formed quantitatively from diol **16** using 2,2-dimethoxypropane/camphorsulfonic acid). However, only treatment of **17** with lithium aluminium hydride gave any new product, alcohol **18**, but in very low yield.

Due to the problems encountered, dihydroxylation was delayed until the acyl sultam manipulations had first been completed. Thus **8** was converted into protected Weinreb amide[27] **21** by successive treatment with $CH_3O(CH_3)NH/Al(CH_3)_3$ and BPSCl/Et_3N. Dihydroxylation of **21** again occurred solely from the β-face (as drawn in Scheme 3) giving the new *cis*-diol **22** in 97% yield.



Scheme 2. Reagents and conditions: (i) BPSCl, imidazole, DMAP (cat.) DMF, rt; (ii) $K_2OsO_4{\cdot}H_2O$, *t*-BuOH/H_2O (3:1); (iii) $(CH_3O)_2C(CH_3)_2$, CSA (cat.); (iv) H_2O_2, LiOH; (v) $LiAlH_4$.



Scheme 3. Reagents and conditions: (i) $CH_3O(CH_3)NH$, WSC hydrochloride; (ii) BPSCl, Im., DMAP (cat.) DMF, rt; (iii) $K_2OsO_4{\cdot}H_2O$, *t*-BuOH/H_2O (3:1); (iv) $(CH_3O)_2C(CH_3)_2$, CSA (cat.); (v) CH_3Li.

cis-Diol **22** could then be converted into the target molecule **7** by first protecting the diol as its acetonide, followed by treatment with methyllithium.

The X-ray crystal structure of **7** is shown in Figure 4. The conversion of **7** into fumagillin **1** will be reported in due course.

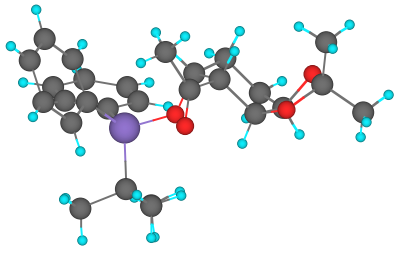


Figure 4. X-ray crystal structure of target molecule **7**.

3. Conclusion

A concise, eight-step enantioselective synthesis of a key precursor in our projected synthesis of *fumagillol* **6** and its derivatives has been developed. Important steps involve

syn-selective aldol followed by ring closing metathesis and a completely facial-selective *cis*-dihydroxylation.

4. Experimental

Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. Elemental microanalyses were performed by Chemical & Micro Analysis Services, Victoria or the University of Otago, New Zealand. Optical rotations were recorded at the sodium doublet on a Perkin Elmer 141 Polarimeter. Infrared spectra were recorded on a Perkin Elmer 1600 Series Fourier Transform spectrometer. Infrared band intensities of each frequency of absorption are expressed as s (strong), w (weak) or b (broad). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker M 300 spectrometer and the chemical shifts recorded on the δ scale in parts per million (ppm). Deuteriochloroform ($CDCl_3$) was used as the internal standard. Mass Spectrometries were performed in methanol on a Micromass Platform QMS spectrometer. High resolution mass spectra were recorded on a Bruker BioApex 47e FTMS. The principal ion peaks (m/z) are reported along with their intensities (in parentheses), expressed as a percentage of the base peak (100%). M^+ refers to the molecular ion. X-ray crystallography was performed either on a Nonius Kappa CCD or a Nicolet R3m/V diffractometer.

4.1. (4*Z*)-5-Phenyl-4-pentenal 10

To a chilled solution (0–5 °C) of (3-ethoxycarbonylprop-1-yl)triphenylphosphonium bromide (10.27 g, 0.02 mol) in THF (70 ml), $NaN(TMS)_2$ (1 M, 25.0 ml, 25 mmol) was added and stirred for 30 min. A solution of freshly distilled benzaldehyde (2.8 ml, 0.03 mol) in THF (7 ml) was then added and after 3 h was quenched with water (20 ml) and poured into an ethyl acetate/water mixture (200/180 ml). The organic phase was extracted and the aqueous layer re-extracted with ethyl acetate (200 ml). The organic extracts were combined, dried over $MgSO_4$ and reduced in vacuo. The crude product was purified using flash column chromatography (SiO_2, 15:1 light petroleum/ethyl acetate) to yield ethyl (4*Z*)-5-phenyl-4-pentenoate as a colourless oil (3.28 g, 71%). Found 205.123. $C_{13}H_6O_2(H^+)$ requires 205.123. IR (CH_2Cl_2): 3510m, 3153w, 3086m, 3063m, 2893m, 2964m, 2929m, 2856m, 2739w, 2361w, 2342w, 2254m, 1728s, 1704s, 1599m, 1585m, 1494m, 1448m, 1419m, 1375s, 1350m, 1270m, 1204m, 1182m, 1169m, 1110w, 1097m, 1072w, 1056m, 1028m, 912s, 828w, 738s, 701m cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J 7.17 Hz, 3H, CH_3CH_2); 2.38–2.45 (m, 2H, CH_2, H4); 2.60–2.68 (m, 2H, CH_2, H3); 4.11 (q, J 7.17 Hz, 2H, OCH_2CH_3); 5.61 (dt, J 11.75, 7.17 Hz, 1H, CH, H2); 6.44 (br d, J 11.60 Hz, 1H, H1); 7.17–7.34 (m, 5ArH). ^{13}C NMR ($CDCl_3$): δ 14.23, CH_3; 24.07, CH_2; 60.36, CH_2; 125.38, CH, C2; 126.56, 128.03, 128.52, 129.92, ArCH (C2′, C3′, C4′, C5′); 134.27, CH, C1; 136.99, ArC, C1′; 172.76, CO.

To a cooled solution (−78 °C) of the above ester (3.00 g, 14.7 mmol) in toluene (60 ml), DIBAL-H (1.5 M solution in toluene, 15.6 ml, 23.5 mmol) was added. After completion of the reaction (TLC, 2 h), a 1:1 mixture of acetone/water (24 ml total) was added and the reaction allowed to warm up to room temperature. It was poured into ethyl acetate/water (200 ml total), extracted and the organic phase washed with water (80 ml), dried over $MgSO_4$ and reduced in vacuo to give title compound **7** (2.34 g, 99%) as a colourless oil, which was used without purification. IR (CH_2Cl_2): 3068m, 3050m, 3023s, 3006s, 2928s, 1957m, 1885w, 1721m, 1684m, 1600m, 1574w, 1444s, 1447s, 1409m, 1358w, 1333w, 1202w, 1177w, 1137s, 1072s, 1028s, 968m, 916m, 787m, 688s, 668m cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.51–5.58 (m, 2H, CH_2, H4); 2.59–2.74 (m, 2H, CH_2, H3); 5.60 (dt, J 11.60, 11.67 Hz, 1H, H2); 6.47 (br d, J 11.60 Hz, 1H, H1); 7.24–7.26 (m, 5ArH; 9.75, t, J 1.45 Hz, 1H, CHO).

4.2. (2*S*)-*N*-[(2*S*,3*R*,7*Z*)-2-(Ethenyl)-3-(hydroxy)-7-phenyl-6-heptenoyl]bornane-10,2-sultam 12

Freshly distilled triflic acid (156 μl, 1.76 mmol) was added to triethylborane (1.76 ml, 1.76 mmol), which was vigorously stirred, under a flow of N_2. It was allowed to stir for 0.5 h after which time the reaction became a homogeneous yellow solution. If not, the reaction was stirred at 40 °C for 0.5 h to help initiate the reaction. The reaction was cooled to 0 °C and a solution of acyl sultam **6** (520 mg, 0.88 mmol) in CH_2Cl_2 (4.2 ml) was added and the resulting mixture stirred for 10 min. *N*,*N*-Diisopropyl(ethyl)amine (323 μl, 1.85 mmol) was then added dropwise while maintaining the internal temperature at 0 °C. The reaction was stirred for 0.5 h after which time it was cooled to −78 °C and a solution of **7** (282 mg, 1.76 mmol) in CH_2Cl_2 (2 ml) was added. After stirring at −78 °C for 2 h, aqueous phosphate buffer (pH 7, 4 ml) was added and the mixture allowed to warm to room temperature and then poured into Et_2O (20 ml). The aqueous phase was washed with Et_2O (2 × 15 ml). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo to afford a yellow solid. The crude product was purified by flash column chromatography (SiO_2, 5:1 light petroleum/ethyl acetate) to firstly give a 3:1 (291 mg, 56%, R_f 0.53) inseparable mixture of unreacted **6** and its isomerised product followed by title compound **12** (152 mg, 39%, R_f 0.17) as a colourless oil. IR (CH_2Cl_2): 3510m, 3086w, 3046w, 3006m, 2959s, 2925s, 2885m, 2845m, 1684m, 1634m, 1600w, 1494m, 1456m, 1443m, 1412m, 1376m, 1334s, 1267m, 1236m, 1214s, 1166m, 1135s, 1117m, 1063m, 992m, 929w, 878w, 765m, 668w cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 1H, CH_3, H8 or H9); 1.09 (s, 1H, CH_3, H8 or H9); 1.27–1.43 (m, 2H and 1.51–1.61, m, 1H and 1.65–1.77, m, 2H and 1.85–2.02, m, 4H, total 9H, 1(CH), H4 and 4(CH_2), H3, H5, H6, H16); 2.38–2.53 (m, 2H, CH_2, H17; 3.26, br s, 1H, OH); 3.45, 3.48 (ABq, J 13.81 Hz, 2H, CH_2, H10); 3.74 (dd, J 8.70, 3.51 Hz, 1H, CHN, H2) 3.89 (t, J 6.18 Hz, 1H, CH, H12) 4.03–4.09 (m, 1H, CH, H15); 5.33–5.41 (m, 2H, CH_2, H14); 5.62–5.71 (m, 1H, H18); 5.92 (qd, J 17.40, 9.92, 8.70 Hz, 1H, H13); 6.41–6.49 (m, 1H, H19); 7.18–7.42 (m, 5ArH). ^{13}C NMR ($CDCl_3$): δ 19.90, CH_3, C8 or C9; 20.75, CH_3, C8 or C9; 24.93, CH_2, C17; 26.42, CH_2, C5; 32.82, CH_2, C6; 34.34, CH_2, C16; 38.15, CH_2, C3; 44.63, CH, C4; 47.70, $C(CH_3)_2$, C7; 48.35, C, C1; 53.10, CH_2, C10; 54.62, CH, C12; 64.85, CH, C2; 70.39, CH, C15;

121.44, CH_2, C14; 126.31, CH, C18; 127.96, ArCH (C2′, C6′ or C3′, C5′); 128.60, ArCH (C2′, C6′ or C3′, C5′); 129.12, ArCH (C4′); 130.66, CH, C13; 131.86, CH, C19; 137.35, ArC (C1′); 173.08, CO, C11. MS: 444.3 ($[M+H]^+$, 20%), 466.2 ($[M+Na]^+$, 100). HRMS calcd for $C_{25}H_{33}NO_4S(H^+)$ requires 444.221, found 444.220. $C_{25}H_{33}NO_4S(Na^+)$ requires 466.203, found 466.201. Anal. Calcd (443.2): C, 67.69; H, 7.50; N, 3.16. Found: C, 67.79; H, 7.35; N, 3.22. $[\alpha]_D^{25} = +12.5$ (*c* 2, $CHCl_3$).

4.3. (+)-(2*S*)-*N*-[(2*S*,3*R*)-2-(Ethenyl)-3-(hydroxy)-6-hepteno-yl]bornane-10,2-sultam 13

In a manner similar to that for **12**, aldol addition of acyl sultam **9** (320 mg, 1.13 mmol) with 4-pentenal **11** (124 mg, 1.47 mmol) afforded, upon work-up, a yellow solid. Purification by flash column chromatography (SiO_2, 4:1 light petroleum/ethyl acetate) gave title compound **13** (393 mg, 87%, R_f 0.31 in 3:1 light petroleum/ethyl acetate), as colourless crystals (mp 140–141 °C). IR (CH_2Cl_2): 3519m, 3072m, 2961s, 2890s, 1728m, 1682s, 1640s, 1478m, 2961s, 2890s, 1728m, 1682s, 1640s, 1478m, 1456m, 1415m, 1376m, 1334s, 1267s, 1237s, 1215s, 1166s, 1135s, 1064m, 994m, 924w, 877w, 824w, 764w, 738m, 703m cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.95 (s, 1H, CH_3, H8 or H9); 1.08 (s, 1H, CH_3, H8 or H9); 1.15–2.31 (m, 11H, 5(CH_2) H16, H17, H6, H5, H3 and 1(CH), H4); 3.31 (br s, 1H, OH); 3.45, 3.48 (ABq, *J* 13.81 Hz, 2H, CH_2, H10); 3.73 (dd, *J* 3.51, 8.70 Hz, 1H, CHN, H2); 3.89 (br t, *J* 6.26 Hz, 1H, CH, H12); 3.98–4.05 (m, 1H, CH, H15); 4.94 (dp, *J* 10.22, 2.14,1.98 Hz, 1H, CH of CH_2; H19a); 5.03 (dq, *J* 3.51, 1.68 Hz, 1H, CH of CH_2, H19b); 5.31–5.41 (m, 2H, CH_2, H14); 5.80, ddt (*J* 17.90, 14.70, 10.38 Hz, 1H, H18); 5.91 (qd, *J*10.07, 8.70 Hz, 1H, H13). ^{13}C NMR ($CDCl_3$): δ 19.91, CH_3, C8 or C9; 20.75, CH_3, C8 or C9; 26.45, CH_2, C5; 29.81, CH_2, C17; 32.83, CH_2, C6; 32.23, CH_2, C16; 38.16, CH_2, C3; 44.64, CH, C4; 47.72, $C(CH_3)_2$, C7; 48.36, C, C1; 53.11, CH_2, C10; 54.35, CH, C12; 64.87, CHN, C2; 70.19, CH, C15; 114.75, CH_2, C19; 121.39, CH_2, C14; 130.60, CH, C18; 137.93, CH, C13; 173.25, CO, C11. MS: 390.3 ($[M+Na]^+$, 80%), 757.3 ($[2M+Na]^+$, 100). HRMS calcd for $C_{19}H_{29}NO_4S(H^+)$ requires 368.190, found 368.190. $C_{19}H_{29}NO_4S(Na^+)$ requires 390.172, found 390.172. Anal. Calcd (367.2): C, 65.10; H, 7.95; N, 3.81. Found: C, 65.60; H, 8.18; N, 3.73. $[\alpha]_D^{24} = +95.35$ (*c* 1.3, $CHCl_3$).

4.4. (+)-(2*S*)-*N*-[(1*R*,2*S*)-1-Hydroxy-3-cyclohexen-2-carbonyl]bornane-10,2-sultam 14

Grubbs' catalyst (231 mg, 0.27 mmol), in degassed CH_2Cl_2 (50 ml), was added to a solution of **13** (2.00 g, 5.44 mmol) in degassed CH_2Cl_2 (450 ml) under a flow of argon and the resulting solution was stirred at room temperature for 24 h. The solvent was removed in vacuo and the crude material was purified by column chromatography (SiO_2, 4:1 light petroleum/ethyl acetate) to give title compound **13** (1.62 g, 88%, R_f 0.16) as colourless crystals (mp 139–140.5 °C). IR (CH_2Cl_2): 3526s, 3053s, 3024s, 2981s, 2880s, 3841s, 1686s, 1478m, 1456m, 1429m, 1410m, 1391m, 1377m, 1332s, 1267s, 1237s, 1213s, 1165m, 1134s, 1122m, 1078m, 1064s, 991m, 977m, 953w, 893m, 871w, 856m, 805w, 765m, 737s, 703m cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.97 (s, 1H, CH_3, H8 or H9); 1.18 (s, 1H, CH_3, H8 or H9); 1.21–2.54 (m, 11H, 5(CH_2), H16, H15, H6, H5, H3 and 1(CH), H4); 3.45 (d, *J* 3.51 Hz, 1H, OH); 3.49, 3.52 (ABq, *J* 13.88 Hz, 2H, CH_2, H10); 3.86–3.96 (m, 2H, 2(CH), H2, H12); 4.12–4.20 (m, CH, H17); 5.54 (dp, *J* 5.80, 2.14 Hz, 1H, CH, H14); 5.92 (dq, *J* 5.95, 3.36 Hz, 1H, CH, H13). ^{13}C NMR ($CDCl_3$): δ 19.21, CH_3, C8 or C9; 20.96, CH_3, C8 or C9; 22.83, CH_2, C15; 26.45, CH_2, C5; 27.06, CH_2, C16; 32.88, CH_2, C6; 38.39, CH_2, C3; 44.63, CH, C4; 46.87, CH, C12; 47.77, $C(CH_3)_2$, C7; 48.27, C, C1; 53.19, CH_2, C10; 65.33, CHN, C2; 66.52, CH, C17; 120.97, CH, C14; 130.89, CH, C13; 172.62, CO, C11. MS: 340.3 ($[M+H]^+$, 5%), 362.2 ($[M+Na]^+$, 100), 701.4 ($[2M+Na]^+$, 90). HRMS calcd for $C_{17}H_{25}NO_4S(H^+)$ requires 340.158, found 340.159. $C_{17}H_{25}NO_4S(Na^+)$ requires 362.140, found 362.140. Anal. Calcd (339.2): C, 60.15; H, 7.94; N, 4.13; S, 9.45. Found: C, 59.94; H, 7.94; N, 4.07; S, 9.25. $[\alpha]_D^{24} = +270.0$ (*c* 0.7, $CHCl_3$).

4.5. (+)-(1*S*,2*R*)-2-Hydroxy-5-cyclohexenecarboxylic acid 8

Hydrogen peroxide (0.51 ml, 30% solution, 4.50 mmol) was added to a chilled (0 °C) solution of **14** (318 mg, 0.94 mmol) in THF/H_2O (6:1, total 21 ml). This was followed by incremental addition of lithium hydroxide (51.0 mg, 1.22 mmol). The reaction was warmed to room temperature overnight, quenched with $Na_2SO_3{\cdot}7H_2O$ (940 mg, 9.4 ml H_2O) and CH_2Cl_2 (15 ml) added. The aqueous phase was washed with CH_2Cl_2 (2 × 10 ml). The organics were combined, dried over $MgSO_4$ and reduced under vacuum to yield a quantitative recovery of camphorsultam (203 mg). The aqueous layer was acidified with 1 M HCl and extracted with ethyl acetate (5 × 10 ml). The organics were combined, dried over $MgSO_4$ and reduced in vacuo to give title compound **8** (110 mg, 82%) as an orange oil (R_f 0.44 in ethyl acetate), which was used without further purification. IR (CH_2Cl_2): 3442m, 3339m, 3055s, 2987m, 2899m, 2306m, 1711s, 1431m, 1422s, 1265s, 1087m, 1070m, 1034m, 982w, 936w, 896m, 865w, 643m, 738s, 704s cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.73–1.82, m, 1H, CH of CH_2, H4 or H5; 1.93–1.21, m, 2H, H4 or H5; 2.22–2.30, m, 1H, CH of CH_2, H4 or H5; 3.33, br s, 1H, CH, H1; 4.28, br s, 1H, CH, H6; 5.70, br d, *J* 10.07 Hz, 1H, CH, H3; 5.87, qd, *J* 10.07, 2.43 Hz, 1H, CH, H2, 6.83; br s, 2H, 2(OH). ^{13}C NMR ($CDCl_3$): δ 21.88, CH_2, C4; 27.70, CH_2, C5; 38.73, CH, C1; 66.43, CH, C6; 121.15, CH, C3; 129.58, CH, C2; 167.66, CO. MS: 142.7 ($[M]^+$, 5%), 164.8 ($[M+Na]^+$, 100). HRMS calcd for $C_7H_{10}O_3(Na^+)$ requires 165.053, found 165.052. Anal. Calcd (142.1): C, 59.14; H, 7.09. Found: C, 58.58; H, 6.87. $[\alpha]_D^{22} = +95.45$ (*c* 4, $CHCl_3$).

4.6. (+)-(2*S*)-*N*-[(1*R*,2*S*)-1-(((*tert*-Butyldiphenyl)silyl)oxy)-3-cyclohexen-2-carbonyl]bornane-10,2-sultam 15

Imidazole (20.2 mg, 0.30 mmol) and BPSCl (40.8 mg, 37.0 μl) were added to a solution of **14** (310.0 mg, 0.91 mmol) in CH_2Cl_2 (2 ml) at room temperature. Following stirring overnight the reaction was quenched with water (1 ml) and then poured into Et_2O (5 ml). The aqueous

phase was washed with Et_2O (2×5 ml). The organic extracts were combined, dried ($MgSO_4$) and the solvent was removed in vacuo to afford a white solid. The crude product was purified by flash column chromatography (SiO_2, 5:1 light petroleum/ethyl acetate) to yield *the title compound* **15** (455 mg, 87%, R_f 0.55 in 8:1 light petroleum/ethyl acetate) as colourless crystals (mp 158–159 °C). IR (CH_2Cl_2): 3066m, 3046m, 2959s, 2946s, 2957s, 1707s, 1472w, 1458w, 1428m, 1391m, 1362w, 1332s, 1268s, 1236m, 1219m, 1199m, 1164m, 1133s, 1111s, 1063m, 990w, 895w, 840w, 822w, 788w, 766w, 740w, 704m cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.98 (s, 3H, CH_3, H8 or H9); 1.04 (s, 9H, 3(CH_3) –BPS; 1.09, s, 3H, CH_3, H8 or H9); 1.22–2.60 (m, 11H, 5(CH_2), H16, H15, H6, H5, H3 and 1(CH), H4); 3.49, 3.51 (ABq, *J* 13.89 Hz, 2H, CH_2, H10); 3.91–4.02 (m, 3H, 3(CH), H2, H12, H17); 5.61–5.65 (m, 1H, H14); 5.72–5.76 (m, 1H, H13); 7.32–7.46 (m, 6ArH –BPS); 7.71–7.79 (m, 4ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.24, $C(CH_3)_3$ –BPS; 19.98, CH_3, C8 or C9; 20.93, CH_3, C8 or C9; 24.92, CH_2, C15; 26.52, CH_2, C5; 26.93, $C(CH_3)_3$ –BPS; 27.32, CH_2, C16; 32.85, CH_2, C6; 38.35, CH_2, C3; 44.59, CH, C4; 47.56, CH, C12; 47.78, $C(CH_3)_3$ –BPS, C7; 48.20, C, C1; 53.13, CH_2, C10; 65.20, *C*HN, C2; 70.39, CH, C17; 122.29, CH, C14; 127.22, 127.39, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 129.23, 129.23, ArCH, 2(C4′) –BPS; 130.87, CH, C13; 133.47, 134,85, ArC, 2(C1′) –BPS; 135.87, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 169.25, CO, C11. MS: 578.4 ($[M+H]^+$, 40%), 600.4 ($[M+Na]^+$, 90). HRMS calcd for $C_{33}H_{43}NO_4SSi(Na^+)$ requires 600.258 found 600.256. Anal. Calcd (577.3): C, 68.59; H, 7.50; N, 2.42. Found: C, 68.66; H, 7.32; N, 2.53. $[\alpha]_D^{22} = +81.0$ (*c* 0.2, $CHCl_3$).

4.7. (+)-(2*S*)-*N*-[(1*R*,2*R*,3*S*,4*R*)-1-(((*tert*-Butyldiphenyl)-silyl)oxy)-3,4-(dihydroxy)cyclo-hexan-2-carbonyl]bornane-10,2-sultam 16

NMO (332 mg, 2.84 mmol) followed by $K_2OsO_4{\cdot}H_2O$ (52.2 mg, 0.142 mmol) was added to a solution of **15** (480 mg, 1.42 mmol) in a 3:1 mixture of *t*-BuOH/H_2O (12 ml total), at room temperature and allowed to stir overnight. The pale orange solution was quenched with $Na_2S_2O_3$ (1 M, 1.5 ml) and allowed to stir for an additional 0.5 h. The solution was evaporated to dryness, and an ethyl acetate (20 ml) and water (5 ml) mixture added. The aqueous phase was washed with ethyl acetate (2×20 ml). The organic extracts were combined, dried over $MgSO_4$ and the solvent was removed in vacuo to afford a yellow solid. The crude product was purified using flash column chromatography (SiO_2, 4:1 light petroleum/ethyl acetate) to yield title compound **16** (470 mg, 92%, R_f 0.14, mp 215–216 °C), as colourless crystals. IR (CH_2Cl_2): 3484s, 3073s, 3072s, 2932s, 2858, 1702m, 1472m, 1428s, 1391w, 1362w, 1332m, 1266s, 1199w, 822s, 739s, 703s cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H, CH_3, H8 or H9); 1.08 (9H, $3CH_3$ –BPS); 1.09 (s, 3H, CH_3, H8 or H9); 1.18–2.36 (m, 11H, 5(CH_2), H16, H15, H6, H5, H3 and 1(CH), H4); 3.23, 3.46 (ABq, *J* 13.73 Hz, 2H, CH_2, H10); 3.34–3.41 (m, 2H, 2(CH), H2, H12); 4.08 (br d, *J* 2.59 Hz, 1H, CH, H14); 4.54 (dd, *J* 10.07, 2.90 Hz, 1H, CH, H17); 4.82 (br s, 1H, CH, H13); 7.31–7.44 (m, 6ArH –BPS); 7.61–7.71 (m, 4ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.44, $C(CH_3)$ –BPS; 19.84, CH_3, C8 or C9; 20.97, CH_3, C8 or C9; 25.00, CH_2, C15; 26.20, CH_2, C5; 26.33, 3(CH_3) –BPS; 27.20, CH_2, C16; 32.82, CH_2, C6; 38.57, CH_2, C3; 44.64, CH, C4; 47.65, CH, C12; 48.32, $C(CH_3)_2$, C7; 50.46, CH, C17; 52.91, CH, C1; 53.02, CH_2, C10; 65.27, *C*HN, C2; 68.75, CH, C14; 68.97, CH, C13; 69.41, CH, C14; 127.35, 127.45, ArCH, 2(C2′, C6′ or C3′, C5) –BPS; 129.52, 129.57 ArCH, 2(C4′) –BPS; 134.02, 134.96, ArC, 2(C1′) –BPS; 136.24, 138.64, ArCH, 2(C2′, C6′ or C3′, C5) –BPS; 169.79, CO, C11. MS: 612.4 ($[M+H]^+$, 25%), 634.3 ($[M+Na]^+$, 100), 644.3 ($[M+MeOH(H)]^+$, 50). HRMS calcd for $C_{33}H_{45}NO_6SSi(Na^+)$ requires 634.264, found 634.262. Anal. Calcd (611.4): C, 64.78; H, 7.41; N, 2.29. Found: C, 64.57; H, 7.26; N, 2.29. $[\alpha]_D^{22} = +5.4$ (*c* 0.73, $CHCl_3$).

4.8. (+)-(2*S*)-*N*-[(3a*S*,4*S*,5*R*,7a*R*)-2,2-Dimethyl-5-(((*tert*-butyldiphenyl)silyl)oxy)hexahydro[1,3]benzodioxol-4-carbonyl]bornane-10,2-sultam 17

2,2-Dimethoxypropane (80.4 μl, 0.65 mmol) followed by camphorsulfonic acid (2.0 mg, 0.0082 mmol) was added to a solution of **16** (50 mg, 0.082 mmol) in acetone (0.5 ml), which contained 4 Å molecular sieves at room temperature. After completion of the reaction (TLC 1 h), NEt_3 (0.1 ml) was added. Stirring for a further 15 min was followed by evaporation under vacuum. Water (1 ml) and Et_2O (5 ml) were added and the aqueous phase was further washed with Et_2O (3×5 ml). The organic extracts were combined, dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified using flash column chromatography (SiO_2, 4:1 light petroleum/ethyl acetate) to yield title compound **17**, as colourless crystals (50 mg, 94%, R_f 0.75, mp 203–205 °C). IR (CH_2Cl_2): 3077w, 3049w, 2946s, 2932s, 2890m, 2857m, 1698s, 1459w, 1471w, 1428m, 1407w, 1392m, 1330s, 1265m, 1234m, 1213s, 1164m, 1134m, 1112s, 1067s, 1047s, 1000w, 982w, 874w, 860w, 824w, 799w, 767w, 735m, 703s cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.92 (s, 3H, CH_3, H8 or H9); 1.08 (s, 9H, 3(CH_3) –BPS); 1.11 (3H, CH_3, H8 or H9); 1.32 (3H, CH_3, $C(CH_3)_2$); 1.44 (3H, CH_3, $C(CH_3)_2$); 1.56–2.18 (m, 11H, 5(CH_2), H16, H15, H6, H5, H3 and 1(CH), H4); 3.16 (d, *J* 9.46 Hz, 1H, CH, H12); 3.36, 3.43 (ABq, *J* 13.51 Hz, 2H, CH_2, H10); 3.42 (t, *J* 6.33 Hz, 1H, CH, H2); 4.36 (br s, 1H, CH, H14); 4.84 (br s, 1H, CH, H17); 4.92 (dd, *J* 9.38, 4.60 Hz, 1H, CH, H13); 7.32–7.43 (m, 6H, 6ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.51, $C(CH_3)$ –BPS; 19.94, CH_3, C8 or C9; 20.82, CH_3, C8 or C9; 21.02, CH_2, C15; 26.51, CH_2, C5; 26.62, CH_3, $C(CH_3)_2$; 26.96, CH_2, C16; 27.27, 3(CH_3) –BPS; 27.83, CH_3 ($CH_3)_2$; 32.79, CH_2, C6; 38.54, CH_2, C3; 44.57, CH, C4; 47.73, $C(CH_3)_2$, C7; 48.39, C, C1; 51.15, CH, C12; 52.98, CH_2, C10; 65.27, *C*HN, C2; 68.46, CH, C17; 72.76, CH, C14; 74.94, CH, C13; 108.11, $C(CH_3)_2$; 127.13, 127.26, ArCH, 2(C2′, C6′ or C3′, C5) –BPS; 129.29, 129.35, ArCH, 2(C4′) –BPS; 133.61, 134.69, ArC, 2(C1′) –BPS; 135.92, 136.45, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 169.33, CO, C11. MS: 652.3 ($[M+H]^+$, 100%), 674.2 ($[M+Na]^+$, 28). HRMS calcd for $C_{36}H_{49}NO_6SSi(Na^+)$ requires 674.295, found 674.294. Anal. Calcd (651.3): C, 66.32; H, 7.58; N, 2.15. Found: C, 66.47; H, 7.34; N, 2.12. $[\alpha]_D^{24} = +8.2$ (*c* 1, $CHCl_3$).

4.9. (3a*S*,4*R*,5*R*,7a*R*)-2,2-Dimethyl-4-(hydroxymethyl)-5-(((*tert*-butyldiphenyl)silyl)oxy)hexahydro[1,3]benzodioxole 18

$LiAlH_4$ (7.3 mg, 0.193 mmol) was added to a solution of **17** (60 mg, 0.09 mmol) in CH_2Cl_2 (1 ml) at 0 °C. After stirring for 4 h at room temperature, TLC indicated the presence of unreacted starting material. Therefore, extra $LiAlH_4$ (15 mg, 0.4 mmol) was added at room temperature and the mixture left to stir overnight. Addition of a mixture of $Na_2S_2O_6{\cdot}10H_2O$ (10 mg) in water (1 ml) was followed by washing with CH_2Cl_2 (3×5 ml). The organics were combined, dried over $MgSO_4$ and reduced in vacuo. The crude reaction mixture was purified by column chromatography (SiO_2, 4:1 light petroleum/ethyl acetate) to give firstly BPSOH (20 mg), followed by title compound **18** (9 mg, 10%), isolated as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H, 3(CH_3) –BPS); 1.35 (s, 3H, CH_3, C(CH_3)$_2$); 1.45 (s, 3H, CH_3, C(CH_3)$_2$); 1.51–1.57 (m, 2H, H1, H2 or H3); 1.61–1.69 (m, 1H, H1, H2 or H3); 1.90–1.96 (m, 1H, H1, H2 or H3); 2.14–2.27 (m, 1H, H1, H2 or H3); 3.43 (dd (ABX), J_{7a-7e} 10.76 Hz, J_{7a-6} 7.10 Hz, 1H CH of CH_2, H7); 3.75 (dd (ABX), J_{7a-7e} 10.76 Hz, J_{7e-6} 6.49 Hz, 1H, CH of CH_2, H7); 4.13–4.18 (m, 2H, 2(CH), H4, H5); 4.30–4.34 (m, 1H, CH, H6; 4.81, br d, *J*4.42 Hz, 1H, OH); 7.35–7.48 (m, 6ArH –BPS); 7.60–7.68 (m, 4ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.83, *C*(CH_3)$_3$ –BPS; 21.85, CH_2, C4; 26.85, CH_3, C(*C*H_3)$_2$; 27.39, CH_2, C5; 27.50, CH_3, 3(CH_3) –BPS; 28.82, CH_3, C(*C*H_3)$_2$; 46.94, CH, C1; 63.97, CH_2, C7; 69.06, CH, C6; 73.28, CH, C3; 76.86, CH, C2; 108.40, C, *C*(CH_3)$_2$; 127.86, 128.01, ArCH, 2(C2′, C4′ or C3′, C5′) –BPS; 130.10, 130.17, ArCH, 2(C4′) –BPS; 133.54, 134.05, ArC, 2(C1′) –BPS; 136.07, 136.09, ArCH, 2(C2′, C4′ or C3′, C5′) –BPS. MS: 441.2 ([M+H]$^+$, 15%), 463.2 ([M+Na]$^+$, 100). HRMS calcd for $C_{26}H_{36}O_4Si(Na^+)$ requires 463.228, found 463.228.

4.10. (+)-(1*S*,2*R*)-2-(Hydroxy)-5-cyclohexenecarboxylic acid (*N*-methoxy-*N*-methyl)amide 20

N,*O*-Dimethylhydroxylamine hydrochloride (38 mg, 0.51 mmol), followed by *N*-methylmorpholine (40 mg, 43 μl, 0.51 mmol) was added to a cooled (0 °C) solution of **8** (54 mg, 0.39 mmol) in CH_2Cl_2 (1 ml). *N*-(3-Dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (75 mg, 0.51 mmol) was added incrementally and allowed to stir at this temperature for 2 h. The reaction was quenched with 1 M HCl (1.5 ml), extracted and the aqueous phase re-extracted with CH_2Cl_2 (2 ml). The organics were combined, washed with satd $NaHCO_3$ (2 ml) and the aqueous phase was washed with CH_2Cl_2 (2 ml). The organics were combined, dried over $MgSO_4$ and reduced in vacuo to give title compound **20** (50 mg, 77%). IR (CH_2Cl_2): 3428s, 3054s, 2926s, 2850s, 1654s, 1642s, 1458m, 1439m, 1423m, 1388m, 1318w, 1266s, 1192w, 1179w, 1112w, 1073w, 1034w, 1012w, 895w, 739s, 704m, 673m cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.70–1.77 (m, 1H, CH of CH_2, H4 or H5); 1.99–2.15 (m, 2H, CH_2, H4 or H5); 2.24–2.34 (m, 1H, CH of CH_2, H4 or H5); 3.16 (br s, 1H, OH); 3.21 (s, 3H, NCH_3); 3.61–3.70 (m, 1H, CH, H1); 3.73 (s, 3H, OCH_3); 4.09–4.14 (m, 1H, CH, H6); 5.52 (br dd, *J* 10.07, 2.45 Hz, 1H, CH, H3); 5.88 (bqd, *J* 6.28, 2.45 Hz, 1H, CH, H2). ^{13}C NMR ($CDCl_3$): δ 22.15, CH_2, C4; 27.81, CH_2, C5; 42.27, CH, C1; 61.37, CH_3, NCH_3, OCH_3; 66.36, CH, C6; 121.35, CH, C3; 130.01, CH, C2; 174.18, CO. MS: 185.8 ([M+H]$^+$, 20%), 207.9 ([M+Na]$^+$, 100). HRMS calcd for $C_9H_{15}NO_3(Na^+)$ requires 208.095, found 208.095. $[\alpha]_D^{23} = +108.9$ (*c* 7.5, $CHCl_3$).

4.11. (+)-(1*S*,2*R*)-2-(((*tert*-Butyldiphenyl)silyl)oxy)-5-cyclohexenecarboxylic acid (*N*-methoxy-*N*-methyl)amide 21

Alcohol **20** (415 mg, 2.25 mmol) was silylated in a manner similar to that for **15**. The crude product was purified *via* column chromatography (SiO_2, 6:1 light petroleum/ethyl acetate), to give title compound **21** (650 mg, 68%, R_f 0.22, in 10:1 in light petroleum/ethyl acetate) as a colourless oil. IR (CH_2Cl_2): 3071m, 3046m, 2931w, 2895m, 2857s, 1642m, 1472m, 1428s, 1390w, 1363w, 1113s, 1008w, 821m, 740m, 701s cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (1.04, s, 9H, 3(CH_3) –BPS); 1.60 (pd, *J* 9.08, 3.13 Hz, 1H, CH of CH_2, H4 or H5); 1.77–1.87 (m, 1H, CH of CH_2, H4 or H5); 2.14 (br dd, *J* 18.47, 2.90 Hz, 1H, CH of CH_2, H4 or H5); 2.29–2.44 (m, 1H, H4 or H5); 3.20 (s, 3H, NCH_3); 3.61 (3H, OCH_3); 3.81 (br s, 1H, CH, H1); 4.15 (dq, *J* 5.73 3.74 Hz, 1H, CH, H6); 5.45–5.50 (m, 1H, CH, H3); 5.80–5.83 (m, 1H, CH, H2); 7.34–7.45 (m, 6ArH –BPS); 7.69–7.71 (m, 4ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.25, *C*(CH_3)$_3$ –BPS; 24.28, CH_2, C4; 26.92 (*C*H_3) –BPS; 27.13, CH_2, C5; 42.38, CH, C1; 61.25, NCH_3, OCH_3; 70.44, CH, C6; 122.65, CH, C3; 127.29, 127.30, ArCH, 2(C2′, C6′ or C3′, C6′) –BPS; 129.36, ArCH, 2(C4′) –BPS; 130.02, CH, C2; 133.95, 134.49, ArC, 2(C1′) –BPS; 135.75, 135.77, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 172.70, CO. MS: 424.2 ([M+H]$^+$, 25%), 446.2 ([M+Na]$^+$, 85). HRMS calcd for $C_{25}H_{33}NO_3Si(Na^+)$ requires 446.213, found 446.212. Anal. Calcd (423.2): C, 70.88; H, 7.85; N, 3.31. Found: C, 70.89; H, 7.84; N, 3.27. $[\alpha]_D^{23} = +83.6$ (*c* 1.95, $CHCl_3$).

4.12. (−)-(1*S*,2*S*,3*R*,6*R*)-2,3-(Dihydroxy)-6-(((*tert*-butyldiphenyl)silyl)oxy)cyclohexane-carboxylic acid (*N*-methoxy-*N*-methyl)amide 22

Alkene **21** (163 mg, 0.38 mmol), dissolved in *t*-BuOH (1.8 ml), DMF (1.8 ml), was dihydroxylated in a manner similar to that for diol **16**. After work-up title compound **22** was isolated as a colourless oil (170 mg, 97%, R_f 0.10 in 2:1 light petroleum/ethyl acetate). Recrystallisation from light petroleum/ CH_2Cl_2 gave title compound **22** as colourless crystals (mp 50–51 °C). IR (CH_2Cl_2): 3440s, 3053s, 2933s, 2858s, 1963w, 1895w, 1750w, 1737m, 1644s, 1590m, 1428m, 1391m, 1266s, 1193m, 1112m, 1050m, 965m, 928w, 895w, 863w, 823m, 739s, 704s cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, 3(CH_3) –BPS); 1.54–1.72 (m, 2H, CH_2, H5); 1.90–2.20 (m, 2H, CH_2, H4); 3.00 (br s, 1H, CH, H1); 3.04 (s, 3H, NCH_3); 3.47 (s, 3H, OCH_3); 4.18 (q, *J* 2.29 Hz, 1H, CH, H6); 4.57 (dd, *J* 10.48, 2.83 Hz, 1H, CH, H2); 4.61 (br s, 1H, CH, H3); 4.61 (br s, OH, 7.32, m, 6ArH –BPS); 7.59–7.63 (m, 4ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.47, *C*(CH_3)$_2$; 24.65, CH_2, C4; 26.52, CH_2, C5; 27.04, CH_3, 3(CH_3) –BPS; 48.15, CH, C1; 60.87, CH_3, OCH_3 and NCH_3; 67.95, CH, C6; 68.73, CH, C3; 69.71, CH, C2; 127.30, 127.34, ArCH, 2(C2′,

C6′ or C3′, C5′) –BPS; 129.48, ArCH, 2(C4′) –BPS; 133.43, 134.29, ArC, 2(C1′) –BPS; 135.79, 136.05, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 172.45, CO. MS: 458.4 ($[M+H]^+$, 100%), 480.3 ($[M+Na]^+$, 80). HRMS calcd for $C_{25}H_{35}NO_5Si(H^+)$ requires 458.236, found 458.241. $C_{25}H_{35}NO_5Si(Na^+)$ requires 480.215, found 480.220. Anal. Calcd (457.2): C, 65.61; H, 7.71; N 3.06, 7. Found: C, 65.60; H, 7.80; N, 3.01. $[\alpha]_D^{24} = -17.95$ (*c* 2, $CHCl_3$).

4.13. (−)-(3a*S*,4*S*,5*R*,7a*R*)-5-(((*tert*-Butyldiphenyl)-silyl)oxy)-2,2-dimethylhexahydro-[1,3]benzodioxol-4-carboxylic acid (*N*-methoxy-*N*-methyl)amide 23

To a solution of **22** (666 mg, 1.57 mmol) in acetone (6 ml), which contained 4 Å molecular sieves, 2,2-dimethoxypropane (1.54 ml, 13 mmol) followed by camphor sulfonic acid (40.0 mg, 0.16 mmol) was added at room temperature. After completion of the reaction (TLC 1 h) NEt_3 (2.0 ml) was added, allowed to stir for 15 min and reduced under vacuum. A water (20 ml) and Et_2O (100 ml) mixture was added, it was extracted and the aqueous phase re-extracted with Et_2O (3×100 ml). The organic extracts were combined, dried over $MgSO_4$ and reduced under pressure. The crude product was purified using flash column chromatography (SiO_2, 2:1 light petroleum/ethyl acetate) to give **23** (764 mg, 98%, R_f 0.28 in 4:1 light petroleum/ethyl acetate) as a colourless oil, which solidified on standing. Recrystallisation from CH_2Cl_2/light petroleum gave *the title compound* **23** as colourless crystals (mp 89–90 °C). IR (CH_2Cl_2): 3072s, 3046s, 2932s, 2885s, 2858s, 1966w, 1906w, 1850w, 1736w, 1648s, 1589w, 1473m, 1428m, 1390m, 1363w, 1348w, 1266m, 1194w, 1112s, 1052s, 1027m, 1007m, 965m, 928w, 894w, 881w, 863w, 823m, 780w, 741m, 703s cm^{-1} ^1H NMR ($CDCl_3$): δ 1.05 (s, 9H, CH_3, 3(CH_3) –BPS); 1.36 (s, 3H, CH_3, C(CH_3)$_2$); 1.44 (s, 3H, CH_3, C(CH_3)$_2$); 1.81 (br dd, *J* 16.31, 3.21 Hz, 2H, CH_2, H4); 2.9–2.14 (m, 2H, CH_2, H5); 2.79 (dd, *J* 9.16, 1.68 Hz, 1H, CH, H1); 3.11 (s, 3H, NCH_3); 3.50 (s, 3H, OCH_3); 4.41 (q, *J* 6.87, 4.43 Hz, 1H, CH, H6); 4.48 (br d, *J* 1.68 Hz, 1H, CH, H3); 4.99 (dd, *J* 9.24, 4.96 Hz, 1H, CH, H2); 7.32–7.44 (m, 6ArH –BPS); 7.58–7.64 (4ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.39, $C(CH_3)_3$ –BPS; 21.36, CH_2, C4; 26.39, CH_3, 3(CH_3)$_2$; 26.89, CH_2, C5; 27.06, CH_3; 3(CH_3) –BPS; 28.75, CH_3, C(CH_3)$_2$; 48.33, CH, C1; 60.94, CH_3, NCH_3, OCH_3; 69.34, CH, C6; 72.60, CH, C3; 73.29, CH, C2; 107.52, C, $C(CH_3)_2$; 127.26, 127.35, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 129.45, ArCH, 2(C4′) –BPS; 133.26, 134.37, ArC, 2(C1′) –BPS; 135.68, 136.02, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 171.30, CO. HRMS calcd for $C_{28}H_{39}NO_5Si(H^+)$ requires 498.268, found 498.265. Anal. Calcd (497.3): C, 67.57; H, 7.90; N, 2.81. Found: C, 67.60; H, 7.86; N, 2.66. $[\alpha]_D^{24} = -84.1$ (*c* 1.00, $CHCl_3$).

4.14. (−)-(3a*S*,4*S*,5*R*,7a*R*)-4-Acetyl-5-(((*tert*-butyldiphenyl)silyl)oxy)-2,2-dimethylhexahydr-[1,3]benzodioxole 7

To a solution of **23** (90 mg, 0.18 mmol) in Et_2O (2 ml) cooled to 0 °C, freshly made methyl magnesium iodide (0.51 ml, 1.3 M, 0.66 mmol) was added. Once the addition is complete, the bath was removed and allowed to warm to room temperature overnight. The reaction was quenched with NH_4Cl aq (2 ml), extracted and the aqueous phase re-extracted with Et_2O (3×5 ml). The organics were combined, dried over $MgSO_4$ and reduced under vacuum. The crude product (90 mg) was purified *via* column chromatography (SiO_2, 6:1 light petroleum/ethyl acetate) to give title compound **7** (66 mg, 80%, R_f 0.31 in 8:1 light petroleum/ethyl acetate) as a colourless oil, which solidifies on standing. Recrystallisation from light petroleum/CH_2Cl_2 afforded colourless crystals (mp 75–76 °C). IR (CH_2Cl_2): 3076m, 3046m, 2986s, 2946s, 2931s, 2885m, 2855s, 1718s, 1472w, 1373m, 1369m, 1245m, 1217m, 1160m, 1111m, 1062s, 965w, 874w, 861w, 822m, 799w, 776w, 741m, 702s, 678m, 668s cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.03 (s, 9H, CH_3, 3(CH_3) –BPS); 1.37 (s, 3H, CH_3, C(CH_3)$_2$); 1.41–1.53 (m, 1H, CH of CH_2, H4 or H5); 1.57 (s, 3H, CH_3, C(CH_3)$_2$); 1.82–1.88 (m, 2H, CH_2, H4 or H5); 1.89 (s, 3H, CH_3, CO(CH_3)); 2.10–2.22 (m, 1H, CH of CH_2, H4 or H5); 2.47 (dd, *J* 8.85, 2.29 Hz, 1H, CH, H1); 4.39 (qd, *J* 4.58, 3.05 Hz, 1H, CH, H6); 4.46 (dt, *J* 4.43, 4.27 Hz, 1H, CH, H3); 4.82 (dd, *J* 8.93, 5.11 Hz, 1H, CH, H2); 7.34–7.46 (m, 6ArH –BPS); 7.58–7.61 (4ArH –BPS). ^{13}C NMR ($CDCl_3$): δ 19.37, $C(CH_3)_3$ –BPS; 21.67, CH_2, C4; 26.38, CH_3, C(CH_3)$_2$; 27.07, CH_3, 3(CH_3) –BPS; 27.20, CH_2, C5; 28.63, CH_3, C(CH_3); 29.48; CH_3, CO(CH_3)$_2$; 58.34, CH, C1; 69.83, CH, C6; 72.59, 2(CH), C2 and C3; 107.81, C, $C(CH_3)_2$; 127.45, 127.54, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 129.70, 129.80, ArCH, 2(C4′) –BPS; 132.68, 133.80, ArC, 2(C1′) –BPS; 135.73, 135.98, ArCH, 2(C2′, C6′ or C3′, C5′) –BPS; 206.98, CO. MS: 475.3 ($[M+Na]^+$, 100%). HRMS calcd for $C_{27}H_{36}O_4Si(Na^+)$ requires 475.228, found 475.228. $C_{27}H_{36}O_4Si(K^+)$ requires 491.202, found 491.204. Anal. Calcd for $C_{27}H_{36}O_4Si$ (452.2): C, 71.64; H, 8.02. Found: C, 71.53; H, 7.94. $[\alpha]_D^{25} = -74.9$ (*c* 1.25, $CHCl_3$).

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