Preparation of Neplanocin-A from D-Ribose and by a Chemoenzymic Method

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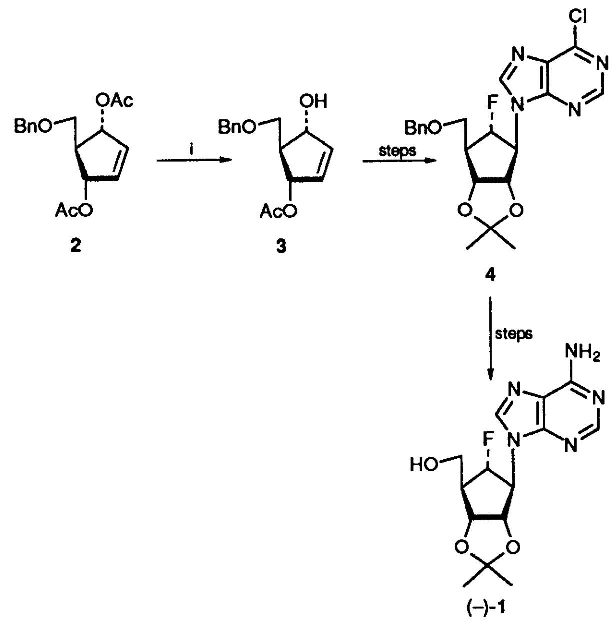
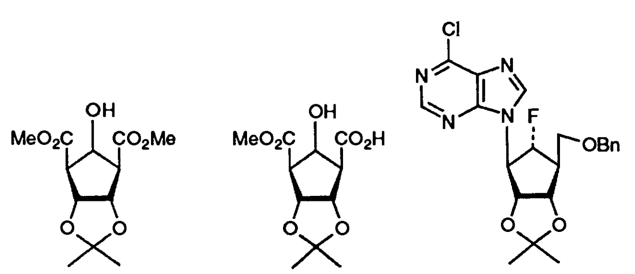
The carboxylic acid **6** was converted into the amine **13** *en route* to neplanocin-A **9**. The same enantiomer of the amine **13** was made from D-ribose in a 13-step synthesis.

Some time ago we reported the enantioselective synthesis of the fluorine-containing carbocyclic nucleoside (−)-**1**.[1] The route involved the enzyme-catalysed hydrolysis of the *meso*-diester **2** to give the acetate **3** and then a number of steps *via* the acetonide **4** (Scheme 1).



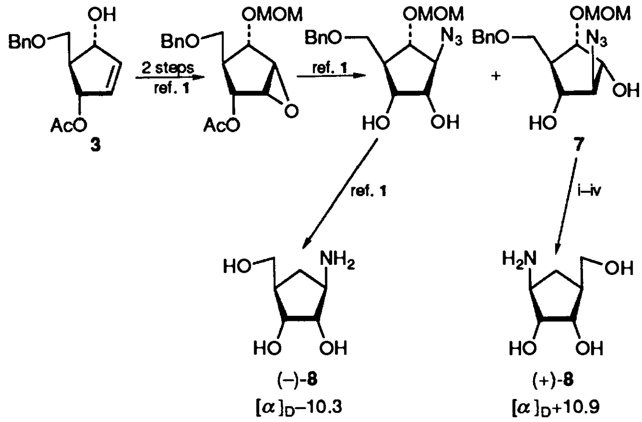
Scheme 1 *Reagents and conditions:* i, chymotrypsin or porcine pancreatic lipase, pH 7 phosphate buffer

In the same paper[1] it was concluded that hydrolysis of the diester **5** by using pig liver esterase afforded the carboxylic acid **6**; this acid was converted into the compound *ent*-**4**.[1]



5 **6** *ent*-**4**

Later, in the light of papers contradicting our assignments for both enzyme-catalysed reactions,[2] we became extremely concerned that we had misassigned the absolute configurations of enantiomers (+)-**4** and (−)-**4**. However, we later confirmed our assignment of the absolute configuration of the alcohol **3** by converting it into compounds (+)-**8** and (−)-**8** (Scheme 2);[3] the enantiomer (−)-**8** had been made previously by Ohno[4] and Martin.[5] It is noteworthy that the arrangement of the substituents within compound **7** were confirmed by NMR spectroscopy which showed that the hydroxy groups were attached to non-contiguous carbon atoms.



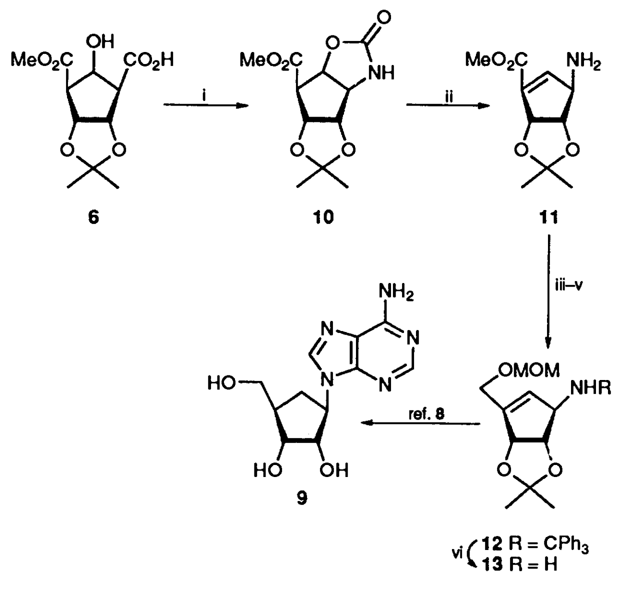
Scheme 2 *Reagents and conditions:* i, BBr_3; ii, Me_2CO, H^+; iii, $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 0 °C; then LiI, DMF; iv, Bu_3SnH, benzene, reflux; v, 80% AcOH; vi, Na, liq. NH_3. $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.

Having established the validity of our initial structural assignments for the alcohol **3** and the acid **6**, it seemed sensible to establish that the acid **6** was, indeed, a viable synthon for the preparation of optically active naturally occurring carbocyclic nucleosides. Herein we report a new route to neplanocin-A **9** from the acid **6**; the absolute configuration of a key intermediate in this new route was verified by using an independent pathway starting from D-ribose.

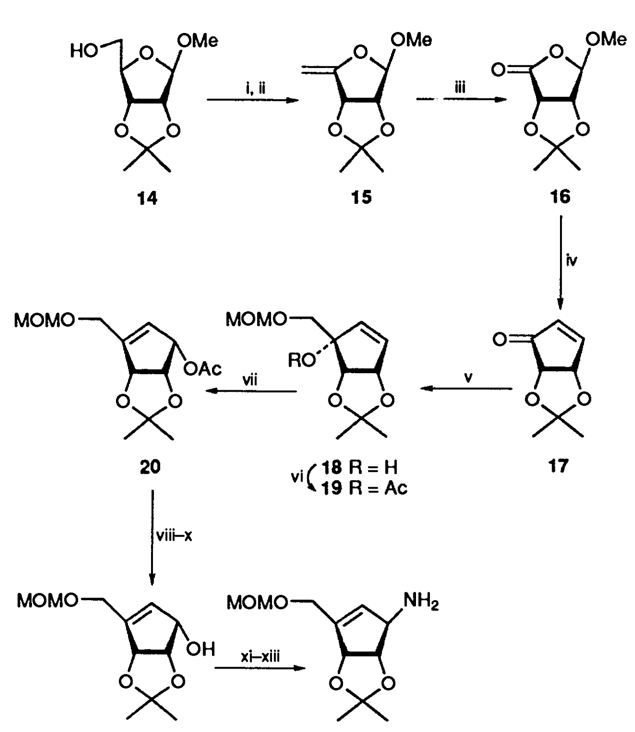
Results and Discussion

The acid **6** was subjected to conditions aimed to promote a Curtius rearrangement (Scheme 3). However, the normal course of the reaction was frustrated by the trapping of the intermediate isocyanate by the neighbouring hydroxy group, which led to the isolation of the oxazolidinone **10** in good yield (Scheme 3). Treatment of this compound with base led to the α,β-unsaturated ester **11** *via* abstraction of a proton and elimination of carbon dioxide. Following tritylation of the amine **11**, selective reduction of the ester to the corresponding alcohol was cleanly effected with diisobutylaluminium hydride (DIBAL-H) and the resultant allylic alcohol was converted into the methoxymethyl derivative **12**. Detritylation of compound **12** with mild acid liberated the free amine **13** ($[\alpha]_D$ −34.4, $[\alpha]_D$ −37.1)[4] which was converted into neplanocin-A under prescribed conditions.[4]

Further confirmation of the absolute configuration of the key intermediate **13** was accomplished by establishing a complementary route to the compound from D-ribose (Scheme 4). Protected D-ribose **14**[6] was converted into the lactone **16** *via*



Scheme 3 *Reagents and conditions:* i, $(PhO)_2P(O)N_3$, THF, DMAP; ii, KF, $MeC_6H_4SO_2F$, pyridine, THF; iii, Ph_3CCl, Et_3N, DMAP, DMF; iv, DIBAL-H, toluene, −78 °C; v, $MeOCH_2Cl$, Pr^i_2NEt, CH_2Cl_2; vi, 1-hydroxybenzotriazole, CF_3CH_2OH



Scheme 4 *Reagents and conditions:* i, I_2, imidazole, Ph_3P; ii, DBU, benzene, reflux; iii, OsO_4, $NaIO_4$, aq. THF; iv, $(MeO)_2P(O)Me$, BuLi, −78 °C; v, Bu_3SnCH_2OMOM, BuLi, −78 °C; vi, Ac_2O, pyridine, DMAP, CH_2Cl_2; vii, $PdCl_2(MeCN)_2$, benzoquinone, THF; viii, K_2CO_3, MeOH; ix, PCC, CH_2Cl_2; x, $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH; xi, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; xii, NaN_3, acetone, 15-C-5; xiii, Ph_3P, aq. THF, reflux

the enol ether **15**, using an improved procedure from that previously reported.[7] Although yields of the lactone were generally in the 60–65% range, the subsequent cyclisation to the enantiomerically pure cyclopentenone **17**[7] proved to be capricious, occurring to the extent of 38% at best.

Following work described by Johnson and Medich[8] the enone **17** was converted into the known alcohol **18**. Acetylation afforded the ester **19** which, on palladium-catalysed allylic rearrangement, yielded the acetate **20**. Examination of the ^1H NMR spectrum of the acetate **20** revealed the presence of a minor contaminant, which could not be removed by silica chromatography. It was therefore necessary to introduce an oxidation–reduction sequence to obtain the alcohol **21** in pure form (Scheme 4). The optical rotation of alcohol **21** ($[\alpha]_D$ +46) was higher than the value quoted in the literature[9] ($[\alpha]_D$ +36) but all other data correlated exactly. Final formation of the desired neplanocin A intermediate was achieved *via* a three-step sequence which yielded the amine **13** in 89% overall yield. The physical data for the latter compound correlated with those previously obtained (*e.g.*, $[\alpha]_D$ −32) and confirmed our initial assignments.

Experimental

General.—All reactions were conducted under an atmosphere of nitrogen or argon. All reagents were obtained from commercial suppliers and were used as supplied unless otherwise noted. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Anhydrous dichloromethane was obtained by distillation from calcium hydride. Light petroleum (60–80 °C) and ethyl acetate were distilled prior to use. Flash chromatography was performed using silica gel 60H Merck 7385. TLC was performed on Merck 60F-254 (0.25 mm thickness) glass-backed plates and visualised with UV light (254 nm), *p*-anisaldehyde, phosphomolybdic acid, ninhydrin (all as acidic solutions in ethanol), or potassium permanganate (as a basic, aqueous solution). M.p.s were measured with an 'Electrothermal' capillary melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 881 Grating Fourier-Transform Infrared spectrophotometer. The spectra were recorded as solutions or films on sodium chloride plates (for oils) or as potassium bromide discs (for solids). Optical rotations were performed on an Optical Activity Ltd., AA-1000 polarimeter. $[\alpha]_D$ Values are given in units of 10^{-1} deg cm^2 g^{-1}. ^1H and ^{13}C NMR spectra were recorded on either a Bruker AM-250 instrument (at 250 and 62.9 MHz) or a Bruker AC-300 instrument (at 300 or 75.5 MHz). Chemical shifts are reported in p.p.m. relative to tetramethylsilane as internal standard, and the coupling constants are quoted in Hz. For ^{13}C NMR the carbon-substitution patterns were assigned using the DEPT technique. Mass spectra were run at the Department of Chemistry, University of Exeter using a Kratos Profile HV-3 high-resolution instrument and at the SERC Mass Spectrometry Centre, Swansea using a VG ZAB-E high-resolution instrument.

Methyl 6,7-Isopropylidenedioxy-3-oxo-2-oxa-4-azabicyclo-[3.3.0]octane-8-carboxylate **10**.—To a stirred solution of the ester **6** (71 mg, 0.27 mmol) and 4-(dimethylamino)pyridine (DMAP) (cat.) in dry THF (2 cm^3) was added diphenyl phosphorazidate (117 mm^3, 0.54 mmol). The mixture was refluxed for 24 h whereupon more diphenyl phosphorazidate (60 mm^3) was added. After a further 24 h the solvent was removed under reduced pressure. Flash chromatography (2:1, ethyl acetate–light petroleum) of the crude residue yielded the *oxazolidinone* **10** (43 mg, 62%) as a crystalline solid, m.p. 152 °C [Found: C, 51.2; H, 5.8; N, 5.6; (M + H)$^+$, 258.0978. $C_{11}H_{15}NO_6$ requires C, 51.34; H, 5.88; N, 5.40%; (M + H), 258.0978]; $[\alpha]_D^{27}$ +83.6 (*c* 0.52, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3438 (NH), 2984, 1734 (C=O), 1404, 1378, 1218, 1166 and 1076; δ_H(250 MHz; $CDCl_3$) 6.6 (1 H, s, NH), 5.35 (1 H, dd, *J* 7.2 and 6.4, 1-H), 5.17 (1 H, dd, *J* 6.4 and 5.2, 7-H), 4.52 (1 H, d, *J* 5.2, 6-H), 4.30 (1 H, d, *J* 7.2, 5-H), 3.77 (3 H, s, OMe), 3.26 (1 H, t, *J*

6.4, 8-H) and 1.46 and 1.31 (each 3 H, s, Me_2C); δ_C(62.9 MHz; $CDCl_3$) 166.77 (C), 158.12 (C), 112.72 (C), 85.26 (CH), 82.02 (CH), 80.95 (CH), 60.12 (CH), 55.70 (CH), 52.50 (OMe), 27.70 and 25.30 (Me).

Methyl(3R,4S,5R)-3-*Amino*-4,5-*isopropylidenedioxycyclopent*-1-*enecarboxylate* **11**.—Toluene-*p*-sulfonyl fluoride (275 mg, 1.58 mmol) and pyridine (182 mm^3, 2.26 mmol) were added to a solution of the oxazolidinone **10** (193.6 mg, 0.75 mmol) in THF (5 cm^3). After 10 min potassium fluoride (52 mg, 0.90 mmol) and 18-crown-6 (3.9 mg, 0.015 mmol) were added to the reaction mixture which was then stirred at room temperature for 48 h. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (6:1; EtOAc–MeOH) to give the *amine* **11** (126.8 mg, 79%) as an oil; $[\alpha]_D^{27}$ −37.14 (*c* 0.52, $CHCl_3$); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3376 (NH), 2991, 1719 (C=O), 1634, 1437, 1375, 1221 and 1063; δ_H(250 MHz; $CDCl_3$) 6.70 (1 H, m, *J* 2.4, 1.0 and 0.5, 2-H), 5.42 (1 H, m, *J* 5.8, 1.5 and 0.5, 4-H), 4.44 (1 H, m, *J* 5.8, 0.9 and 1.0, 5-H), 4.05 (1 H, m, *J* 2.4, 1.5 and 0.9, 3-H), 3.78 (3 H, s, OMe), 1.95 (2 H, br s, NH_2) and 1.40 and 1.32 (each 3 H, s, Me_2C); δ_C(62.9 MHz; $CDCl_3$) 164.44 (C), 146.46 (CH), 136.78 (C), 111.89 (C), 87.48 (CH), 82.80 (CH), 62.40 (CH), 51.95 (OMe) and 27.18 and 25.41 (Me) [Found: $(M + H)^+$, 214.1079. $C_{10}H_{15}NO_4$ requires $(M + H)$, 214.1079].

Methyl(3R,4S,5R)-4,5-*Isopropylidenedioxy*-3-[(*triphenylmethyl*)*amino*]*cyclopent*-1-*enecarboxylate*.—A solution of triphenylmethyl chloride (191 mg, 0.68 mmol) in dimethylformamide (DMF) (600 mm^3) was added to a stirred solution of amine **11** (97.5 mg, 0.46 mmol), triethylamine (115 mm^3, 0.82 mmol) and DMAP (3 mg, 0.024 mmol) in DMF (900 mm^3). After 19 h, water (10 cm^3) was added to the reaction mixture and the aqueous layer was extracted with ethyl acetate (4 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography (5:1; light petroleum–EtOAc) of the residue gave the *tritylamine* (156.2 mg, 77%) as a foam; $[\alpha]_D^{26}$ −40.45 (*c* 1.1, $CHCl_3$); $\nu_{max}(KBr)/cm^{-1}$ 3336 (NH), 3027 (CH), 2992 (CH), 1719 (C=O) and 638; δ_H(250 MHz; $CDCl_3$) 7.5–7.3 (15 H, m, ArH), 5.55 (1 H, d, *J* 2.0, 2-H), 5.27 (1 H, dd, *J* 6.0 and 2.0, 5-H), 4.37 (1 H, d, *J* 6.0, 4-H), 3.8 (1 H, s, 3-H), 3.72 (3 H, s, CO_2Me), 1.6 (1 H, br s, NH) and 1.26 and 1.28 (each 3 H, s, Me_2C); δ_C(62.9 MHz; $CDCl_3$) 146.06 (CH), 128.65 (CH), 128.16 (CH), 126.68 (CH), 111.58 (C), 86.43 (CH), 81.98 (CH), 63.98 (CH), 51.75 (OMe) and 27.20 and 25.40 (Me) (Found: M^+, 455.2110. $C_{29}H_{29}NO_4$ requires *M*, 455.2096).

{(3R,4S,5R)-4,5-*Isopropylidenedioxy*-3-[*triphenylmethyl*)-*amino*]*cyclopent*-1-*enyl*}*methanol*.—To a stirred solution of the above compound (159 mg, 0.36 mmol) in toluene (2 cm^3) at −78 °C was added DIBAL-H [(720 mm^3, 0.72 mmol) as a 1 mol dm^{-3} solution in toluene] during 15 min. After 4.5 h, excess of methanol was added and the mixture was warmed to room temperature. On warming, a gel precipitated out which was removed by filtration and washed with ethyl acetate. The filtrate was concentrated and the residue was purified by flash chromatography (2:1; light petroleum–EtOAc) to give the *alcohol* (117 mg, 76%) as a foam; $[\alpha]_D^{24}$ −30.4 (*c* 0.46, $CHCl_3$); $\nu_{max}(KBr)/cm^{-1}$ 3448 (NH, OH), 3060, 1656, 1448, 1373, 1208, 1072 and 705; δ_H(250 MHz; $CDCl_3$) 7.6–7.3 (15 H, m, ArH), 5.08 (1 H, d, *J* 5.5, 5-H), 4.57 (1 H, s, 2-H), 4.32 (1 H, d, *J* 5.5, 4-H), 4.12 (2 H, s, CH_2OH), 3.73 (1 H, s, 3-H), 1.7 (1 H, br s, NH), 1.2 and 1.1 (each 3 H, s, Me_2C); δ_C(62.9 MHz; $CDCl_3$) 146.42 (CH), 143.84 (C), 129.75 (CH), 128.76 (CH), 128.03 (CH), 126.49 (CH), 111.16 (C), 86.66 (CH), 83.59 (CH), 71.67 (C), 63.56 (CH), 60.30 (CH_2) and 27.37 and 25.66 (Me) [Found: $(M + H)^+$, 428.2226. $C_{28}H_{29}NO_3$ requires $(M + H)$, 428.2226].

(3R,4S,5R)-4,5-*Isopropylidenedioxy*-1-{[(*methoxy*)*methoxy*]*methyl*}-3-[(*triphenylmethyl*)*amino*]*cyclopentene* **12**.—Chloromethyl methyl ether (41 mm^3, 0.54 mmol) was added to a stirred solution of the above alcohol (115.9 mg, 0.27 mmol) and *N*,*N*-diisopropylethylamine (95 mm^3, 0.54 mmol) in dichloromethane (1 cm^3) at 0 °C and the mixture was warmed to room temperature. After 15 h, ice was added, the two layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography gave the *amine* **12** (123.7 mg, 97%) as an oil; $[\alpha]_D^{25}$ −33.79 (*c* 0.58, $CHCl_3$); $\nu_{max}(KBr)/cm^{-1}$ 3327 (NH), 2936, 1725, 1451, 1149, 1052 and 704; δ_H(250 MHz; $CDCl_3$) 8.8 (6 H, m, ArH), 8.4 (9 H, m, ArH), 5.81 (1 H, d, *J* 5.5, 5-H), 5.31 (1 H, s, 2-H), 5.23 (2 H, s, OCH_2O), 4.86 (1 H, d, *J* 5.5, 4-H), 4.57 (2 H, s, CH_2OCH_2), 4.23 (1 H, s, 3-H), 3.73 (3 H, s, OMe), 1.76 (1 H, s, NH) and 1.26 and 1.24 (each 3 H, s, Me_2C) [Found: M^+, 471.2390. $C_{30}H_{33}NO_4$ requires *M*, 471.2409].

(1R,4R,5S)-4,5-*Isopropylidenedioxy*-3-{[(*methoxy*)*methoxy*]-*methyl*}*cyclopent*-2-*enamine* **13**.—A solution of the amine **12** (54.8 mg, 0.12 mmol) in trifluoroethanol (200 mm^3) was added to a stirred solution of 1-hydroxybenzotriazole (18 mg, 0.14 mmol) in trifluoroethanol (500 mm^3). After 3 h the reaction mixture was neutralised with saturated aq. potassium carbonate and the aqueous layers were extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography (5:1; $CHCl_3$–MeOH) gave the amine **13** (17.7 mg, 67%) as an oil; $[\alpha]_D^{22}$ −34.4 (*c* 0.61, $CHCl_3$); $\nu_{max}(neat)/cm^{-1}$ 3371 (NH_2), 2934, 1589, 1455, 1374, 1149 and 1053; δ_H(250 MHz; $CDCl_3$) 5.71 (1 H, br s, 2-H), 5.18 (1 H, d, *J* 5.5, 4-H), 4.68 (2 H, s, OCH_2O), 4.38 (1 H, d, *J* 5.5, 5-H), 4.23 (1 H, d, *J* 14, C*H*HOCH$_2$), 4.14 (1 H, d, *J* 14, CH*H*OCH$_2$), 3.95 (1 H, br s, 1-H), 3.38 (3 H, s, OMe), 1.57 (2 H, br s, NH_2) and 1.38 and 1.33 (3 H, s, Me_2C).

Methyl 5-*Deoxy*-2,3-O-*isopropylidene*-β-D-erythro-*pent*-4-*enofuranoside* **15**.—Iodine (40.14 g, 157 mmol) was added in portions to a stirred solution of the protected ribose **14** (22.24 g, 108 mmol), imidazole (11.13 g, 163 mmol) and triphenylphosphine (41.48 g, 157 mmol) in diethyl ether–acetonitrile (3:1) (500 cm^3). The mixture was stirred for 12 h before being filtered through Celite and then concentrated under reduced pressure. The residue was extracted with light petroleum (2 × 500 cm^3 then 10 × 100 cm^3). Concentration of the extracts gave the crude iodide. This was redissolved in dry benzene (250 cm^3) and diazabicycloundecene (DBU) (25 cm^3) was added. The mixture was heated to reflux for 12 h before being allowed to cool to room temperature, and was then filtered through Celite. The filtrate was concentrated and the residue was dissolved in diethyl ether (400 cm^3); the solution was washed with water (3 × 200 cm^3), dried ($MgSO_4$), and finally concentrated to furnish a yellow oil. Distillation at 0.3 mmHg (40–42 °C) gave the *enol ether* **15** as an oil (15.91 g, 78%); $[\alpha]_D^{27}$ +60.2 (*c* 1.22, $CHCl_3$); $\nu_{max}(neat)/cm^{-1}$ 2993 and 2941 (CH), 1665, 1453, 1373, 1155, 1046, 932 and 831; δ_H(300 MHz; $CDCl_3$) 5.10 (1 H, s, 1-H), 5.01 (1 H, d, *J* 6.0, =C*H*H), 4.59 (1 H, m, 2-H), 4.48 (1 H, d, *J* 6.0, =CH*H*), 4.37 (1 H, m, 3-H), 3.40 (3 H, s, OMe) and 1.46 and 1.34 (each 3 H, s, Me); δ_C(75 MHz; $CDCl_3$) 161.18, 113.12, 108.28, 88.54, 82.59, 78.61, 55.54, 26.66 and 25.59 [Found: M^+, 186.0892. $C_9H_{14}O_4$ requires *M*, 186.0892].

(2S,3R,4R)-2,3-*Isopropylidenedioxy*-4-*methoxybutyrolactone* **16**.—Sodium periodate (7.95 g, 37.0 mmol) was added in small portions over a period of 6 h to a stirred solution of enol ether **15** (3.46 g, 18.6 mmol) and osmium tetraoxide (cat.) in a mixture of THF (120 cm^3) and water (25 cm^3) at 0 °C. A further portion (2.0 g, 9.5 mmol) of sodium periodate was added and the mixture was allowed to warm to room temperature. After 1 h the mixture was filtered through Celite and poured into ethyl acetate (250 cm^3), which was washed successively with brine (3 × 100 cm^3) and water (100 cm^3), and dried ($MgSO_4$). Concentration of the solution gave a crystalline solid, which was recrystallised from diethyl ether–light petroleum to give the lactone **16** (2.80 g, 80%) as needles; ν_{max}(neat)/cm^{-1} 2996 and 2943 (CH), 1794 (CO), 1449, 1376, 1210, 1154, 1118, 1045 and 928; δ_H(300 MHz; $CDCl_3$) 5.31 (1 H, s, 4-H), 4.52 (1 H, d, *J* 2.5, 3-H), 4.79 (1 H, d, *J* 2.5, 2-H), 3.51 (3 H, s, OMe) and 1.44 and 1.37 (each 3 H, s, Me); δ_C(75 MHz; $CDCl_3$) 173.53, 114.42, 105.07, 79.27, 74.43, 57.05, 26.62 and 25.67.

(1S,4S,5S)-4,5-*Isopropylidenedioxy*-1-{[(*methoxy*)*methoxy*]-*methyl*}*cyclopent*-2-*enyl Acetate* **19**.—Acetic anhydride (4.0 cm^3) was added to a stirred solution of alcohol **18** (1.851 g, 8.0 mmol), pyridine (5 cm^3) and DMAP (cat.) in dichloromethane (25 cm^3). After 16 h the mixture was diluted with dichloromethane (200 cm^3) and washed with water (3 × 50 cm^3), dried ($MgSO_4$), and concentrated under reduced pressure. After the removal of excess of pyridine by azeotropic distillation with toluene (3 × 50 cm^3), the residue was purified by flash chromatography (1:4; ethyl acetate–light petroleum) to give the *acetate* **19** (2.032 g, 93%) as an oil; $[\alpha]_D^{23}$ +110.3 (*c* 0.22, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2940 (CH) and 1746 (CO); δ_H(300 MHz; $CDCl_3$) 6.00 (2 H, s, 2-H and 3-H), 5.05 and 4.76 (2 × 1 H, 2 d, *J* 5.5, 4- and 5-H), 4.57 and 4.55 (AB q, *J* 6.0, OCH_2O), 3.92 and 3.81 (AB q, *J* 10.0, CH_2OCH_2OMe), 3.31 (3 H, s, OMe), 2.07 (3 H, s, OAc), 1.37 (3 H, s, Me) and 1.36 (3 H, s, Me); δ_C(75 MHz; $CDCl_3$) 169.92 (CO), 134.24 (=CH), 133.55 (=CH), 112.13 (C), 96.62 (CH_2), 88.57 (C), 83.72 (CH), 80.58 (CH), 69.22 (CH_2), 55.32 (OMe), 27.57 (Me), 26.95 (Me), 21.49 (Me) [Found: $(M + H)^+$, 273.1338. $C_{13}H_{21}O_6$ requires (*M* + H), 273.1338].

(1S,4R,5S)-4,5-*Isopropylidenedioxy*-3-{[(*methoxy*)*methoxy*]-*methyl*}*cyclopent*-2-*enyl Acetate* **20**.—A solution of the acetate **19** (2.032 g, 7.5 mmol), palladium(II) chloride bisacetonitrile complex (cat.) and benzoquinone (0.3 g, 2.8 mmol) in THF (30 cm^3) was heated to reflux under nitrogen for 8 h. After cooling to room temperature the mixture was concentrated under reduced pressure to yield an orange oil. Flash chromatography (1:9; acetone–light petroleum) gave the acetate **20** (1.596 g, 78%) as an oil. Examination of the ^1H NMR spectrum revealed the presence of a minor impurity. The acetate was not purified but was subjected to the following series of reactions.

(1S,4R,5S)-4,5-*Isopropylidenedioxy*-3-{[(*methoxy*)*methoxy*]-*methyl*}*cyclopent*-2-*enol* **21**.—To a solution of the acetate **20** (1.596 g, 5.9 mmol) in methanol (40 cm^3) was added anhydrous potassium carbonate (2.0 g, 14.50 mmol). After 1 h the mixture was diluted with ethyl acetate (100 cm^3) and filtered through silica gel; evaporation of the solvent and flash chromatography (1:3, ethyl acetate–light petroleum) gave the 1*S*-alcohol (1.341 g, 99%) as an oil.

To a stirred solution of the alcohol (1.341 g, 5.8 mmol) in CH_2Cl_2 (25 cm^3) were added silica gel (5 g) and pyridinium chlorochromate (PCC) (2.0 g, 9.3 mmol). After 16 h the mixture was filtered through a pad of silica gel and concentrated under reduced pressure. Flash chromatography (1:9; ethyl acetate–light petroleum) gave the enone (1.194 g, 90%) as an oil.

Sodium borohydride (237 mg, 6.3 mmol) was added in small portions to a stirred solution of the enone (1.194 g, 5.2 mmol) and cerium(III) chloride heptahydrate (3.28 g, 8.8 mmol) in methanol (35 cm^3). The mixture was stirred at room temperature for 30 min before being poured into ethyl acetate (250 cm^3) and washed with brine (3 × 100 cm^3). The organic fraction was dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography of the residue (1:4; ethyl acetate–light petroleum) gave the *alcohol* **21** (1.026 g, 85%) as an oil (Found: C, 57.1; H, 7.8. $C_{11}H_{18}O_5$ requires C, 57.36; H, 7.88%); $[\alpha]_D^{28}$ +46.5 (*c* 1.72, $CHCl_3$) (lit.,[9] $[\alpha]_D^{26}$ +36.8); ν_{max}(neat)/cm^{-1} 3493 (OH), 2990 and 2938 (CH), 1457, 1381, 1239, 1151 and 1049; δ_H(300 MHz; $CDCl_3$) 5.75 (1 H, m, 2-H), 4.95 (1 H, d, *J* 5.5, 4-H), 4.74 (1 H, t, *J* 5.5, 5-H), 4.64 (2 H, s, OCH_2O), 4.54 (1 H, m, 1-H), 4.06–4.25 (2 H, m, CH_2OCH_2OMe), 3.36 (3 H, s, OMe), 2.7 (1 H, br s, OH), 1.40 (3 H, s, Me) and 1.38 (3 H, s, Me); δ_C(75 MHz; $CDCl_3$) 142.37 (C), 131.34 (CH), 112.55 (C), 96.09 (CH_2), 82.94 (CH), 77.84 (CH), 73.30 (CH), 63.26 (CH_2), 55.29 (Me), 27.60 (Me) and 26.62 (Me) [Found: $(M + NH_4)^+$, 248.1498. $C_{11}H_{22}NO_5$ $(M + NH_4)^+$ requires *m*/*z*, 248.1498].

(1R,4R,5S)-4,5-*Isopropylidenedioxy*-3-{[(*methoxy*)*methoxy*]-*methyl*}*cyclopent*-2-*enamine* (*Alternative Preparation*) **13**.—A solution of the alcohol **21** (508 mg, 2.2 mmol) and triethylamine (2 cm^3, 15.1 mmol) in CH_2Cl_2 (30 cm^3) was cooled to 0 °C and methanesulfonyl chloride (0.5 cm^3, 6.4 mmol) was added dropwise. After 15 min the mixture was poured into dichloromethane (150 cm^3), washed with water (3 × 50 cm^3), and dried ($MgSO_4$). Concentration under reduced pressure gave the crude unstable mesyl ester (738 mg), which was immediately redissolved in acetone (30 cm^3) containing 15-crown-5 (0.5 cm^3). Sodium azide (2.0 g, 30.8 mmol) was added and the mixture was heated to reflux for 5 h. After the mixture had cooled to room temperature, ethyl acetate–light petroleum (1:1) (100 cm^3) was added and the mixture was filtered through a short pad of silica. Concentration of the filtrate gave the crude azide (710 mg).

Triphenylphosphine (1.45 g, 5.5 mmol) was added to a stirred solution of the crude azide in THF (25 cm^3)–water (1 cm^3). The mixture was heated to reflux for 2 h before being allowed to cool to room temperature. The solvent was then removed under reduced pressure and the residue was subjected to flash chromatography (9:1; $CHCl_3$–MeOH) to give the *amine* **13** (451 mg, 89%) as an oil; $[\alpha]_D^{28}$ −32.0 (*c* 0.66, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3376 (NH_2), 2990 and 2934 (CH), 1599, 1458, 1377, 1151 and 1056; δ_H(300 MHz; $CDCl_3$) 5.71 (1 H, br s, 2-H), 5.18 (1 H, d, *J* 5.5, 4-H), 4.66 (2 H, s, OCH_2O), 4.38 (1 H, d, *J* 5.5, 5-H), 4.22 (1 H, d, *J* 14, $CHHOCH_2OMe$), 4.14 (1 H, d, *J* 14, $CHHOCH_2OMe$), 3.94 (1 H, br s, 1-H), 3.37 (3 H, s, OMe), 1.60 (2 H, br s, NH_2), 1.37 and 1.33 (each 3 H, s, Me_2C); δ_C(75 MHz; $CDCl_3$) 143.02, 130.94, 111.37, 96.09, 87.75, 83.74, 63.70, 61.94, 55.32, 27.40 and 25.91 (Me, Me_2C) [Found: $(MH)^+$, 230.1392. $C_{11}H_{20}NO_4$ $(MH)^+$ requires *m*/*z*, 230.1392].

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