Synthesis of Carbocyclic *C*-Nucleoside Analogues from 8,9,10-Trinorborn-5-en-2-ol

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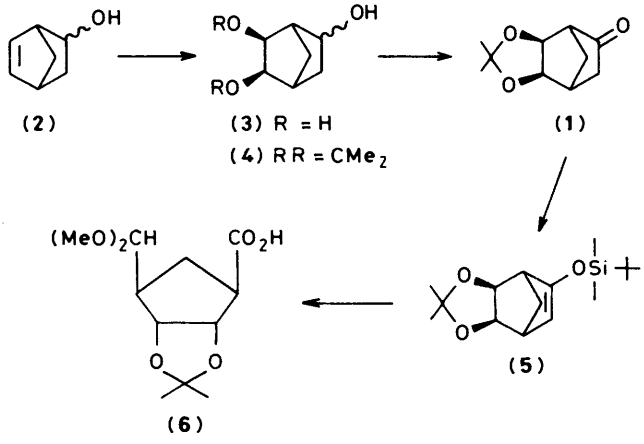
The protected cyclopentanecarboxylic acids (**6**) and (**14**), obtained from 8,9,10-trinorborn-5-en-2-ol, are useful intermediates for the synthesis of carbocyclic ribo- and 2′-deoxyribo-*C*-nucleoside analogues. This is exemplified by their conversion into the imidazo[1,5-*a*]pyridine carbocyclic *C*-nucleosides (**18**) and (**22**).

Recent reports of the antiviral activity of certain carbocyclic nucleosides have stimulated interest in the synthesis of further analogues in this series. For example, cyclaradine (carbocyclic ara-A) inhibits the replication of herpes simplex virus (HSV) types 1 and 2 and its 5′-methoxyacetate prodrug exhibits significant efficacy in the treatment of genital herpes in guinea-pigs.[1] Carbocyclic 5-halogeno-2′-deoxyuridines also possess good activity *in vitro* against HSV-1 and HSV-2,[2] while carbocyclic 3-deaza-adenosine exhibits a broad spectrum of antiviral activity.[3]

To date there have been few examples of carbocyclic *C*-nucleosides,[4,5] and existing routes to this class of compound are not directed to analogues incorporating a bicyclic heterocycle. Furthermore, syntheses of carbocyclic 2′-deoxyribonucleosides have suffered from the need to separate regioisomers at some stage of the synthetic sequence.[5,6] We now describe a convenient and flexible synthesis of carbocyclic ribo-*C*-nucleosides and their corresponding 2′-deoxy derivatives which circumvents the problem of regioselectivity.

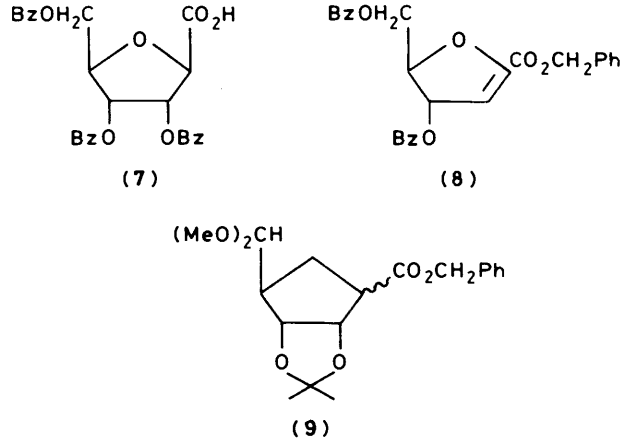
The previously unreported bicyclic ketone (**1**) served as a useful starting point. Its synthesis was effected in 75% yield from 8,9,10-trinorborn-5-en-2-ol (**2**) *via cis*-hydroxylation with osmium tetraoxide and trimethylamine *N*-oxide followed by acetonide formation, and finally oxidation of the alcohol (**4**) with pyridinium dichromate (PDC) on silica gel.* Silyl enol ether formation under conditions analogous to those used by Clark and Heathcock[7] gave the t-butyldimethylsilyl enol ether (**5**) which, on ozonolysis with dimethyl sulphide work-up followed by treatment with acidic methanol, afforded the dimethyl acetal acid (**6**) in 60% yield (Scheme 1).

Although treatment of 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allonic acid (**7**) with 2-chloro-1-methylpyridinium iodide[8] and benzyl alcohol in the presence of triethylamine caused elimination to give the unsaturated ester (**8**),[9] under the same conditions the carboxylic acid (**6**) merely underwent esterification and epimerisation to afford the esters (**9**). However, an excess of lithium di-isopropylamine (LDA) in tetrahydrofuran (THF) effected elimination of the isopropylidene group to form the dianion (**10**) which was quenched with methoxymethyl chloride to give the unsaturated ester (**11**) in 92% yield. The ^{1}H n.m.r.



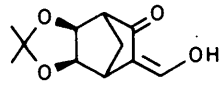
Scheme 1.

spectrum of this product suggested the presence of some of the isomeric conjugated ester (**12**), resulting from allylic deprotonation, but this was of no consequence to the subsequent steps of the synthesis (Scheme 2). Thus, hydrogenation of this mixture followed by mild base hydrolysis of the resultant methoxymethyl ester (**13**) gave the key intermediate acid (**14**) as a 1:1 mixture of α and β epimers.

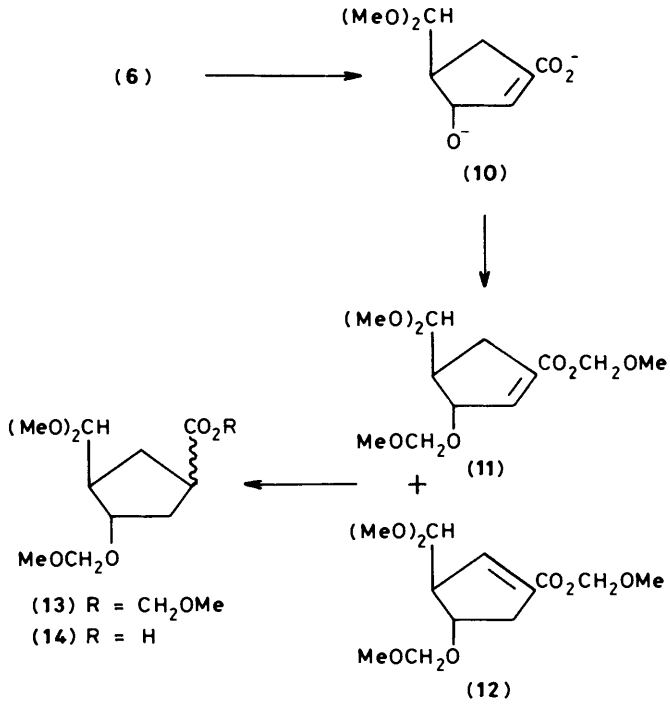


The advantage of this synthetic pathway is that only the 2′-deoxy carbocyclic nucleoside precursor is produced, rather than a mixture of 2′- and 3′-deoxy precursors as synthesized pre-

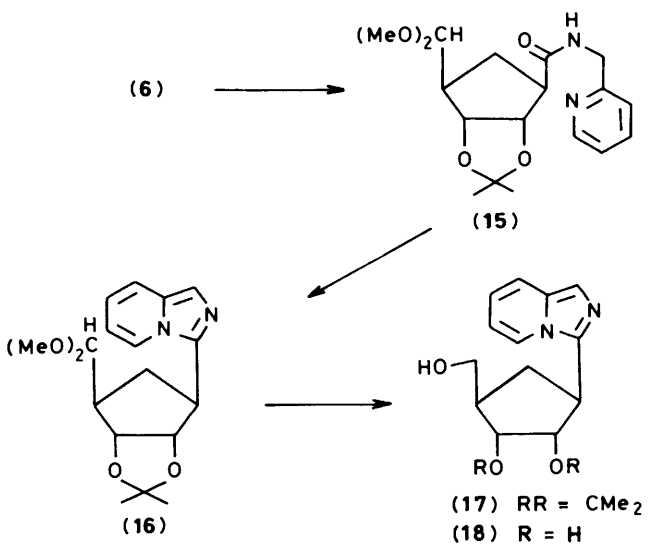
* After our synthesis and use of ketone (**1**), Saksena and Ganguly reported its preparation from 8,9,10-trinorborn-5-en-2-ol and further transformation into several carbocyclic *C*-nucleosides *via* the hydroxymethylene derivative (i).[4]



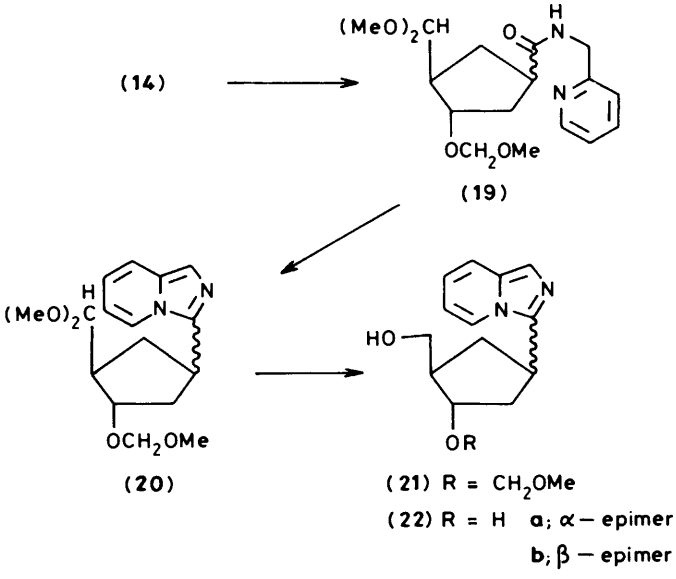
(i)



Scheme 2.



Scheme 3.



Scheme 4.

viously.[5,6] Although the hydrogenation was non-sterospecific this was not considered detrimental to the overall scheme since (a) the possibility exists to direct the hydrogenation into the α-face using the free-3-hydroxy group, and (b) we were also interested in the biological acitivity of the α-epimers.[10]

Two potentially versatile intermediate acids (**6**) and (**14**) are thus available for conversion into a range of carbocyclic nucleoside analogues. As examples, novel carbocyclic *C*-nucleosides based on the imidazo[1,5-*a*]pyridine ring system have been synthesized. Coupling of compound (**6**) with 2-(aminomethyl)pyridine in the presence of dicyclohexylcarbodi-imide (DCC) furnished the amide (**15**) which cleanly cyclised to the imidazopyridine (**16**) on treatment with phosphoryl trichloride in 1,2-dichloroethane. Selective cleavage of the dimethyl acetal was smoothly accomplished with toluene-*p*-sulphonic acid (PTSA) in acetone, and sodium borohydride reduction of the resultant aldehyde gave the alcohol (**17**). Finally, hydrolysis of the isopropylidene protecting group provided the imidazo-[1,5-*a*]pyridine carbocyclic nucleoside (**18**) in 8% overall yield from 8,9,10-trinorborn-5-en-2-ol (Scheme 3).

Subjecting the acid (**14**) to a similar set of transformations gave the imidazo[1,5-*a*]pyridine carbocyclic 2′-deoxyribonucleosides (**22**) in 7% overall yield (Scheme 4). Separation of the epimers was achieved by column chromatography and the assignment of their configuration was made on the basis of ^{1}H n.m.r. spectroscopy.[11]

Experimental

General.—M.p.s were measured on an electrothermal m.p. apparatus and are uncorrected. Mass spectra and accurate masses were recorded on a Kratos-A.E.I.MS30 spectrometer with a Digispec DS50 data system. Ion fragments were recorded as percentages of the base peak (100%). ^{1}H N.m.r. spectra were recorded on three different instruments: at 60 MHz on a Perkin-Elmer R12 spectrometer; at 100 MHz on a Varian Associates XL-100/12 spectrometer; and at 250 MHz on a Bruker WM250, with tetramethylsilane (TMS) as a standard. I.r. spectra were recorded on either a Perkin-Elmer 298 or a Perkin-Elmer 157G spectrophotometer and u.v. spectra on a Unicam SP800 spectrophotometer. Microanalyses were performed by the Analytical Chemistry Department, Glaxo Group Research, Ware.

Analytical t.l.c. was carried out on glass plates precoated with Macherey Nagel silica gel G $25W_{254}$. Flash column chromatography was carried out on either Macherey Nagel silica gel 60 (230—400 mesh) or Merck silica gel 9385 (230—400 mesh) and short-path column chromatography was performed on Merck silica gel 7729.

THF and ether were dried by distillation from sodium and benzophenone, and other solvents were dried by reported methods.[12] Butyl-lithium was used as a solution in hexane as supplied by Pfizer Ltd., or Aldrich. LDA was prepared as required by the reaction of equimolar quantities of di-isopropylamine and butyl-lithium at −70 °C under nitrogen in dry

THF unless otherwise stated. Light petroleum refers to the fraction boiling in the range 40—60 °C.

Throughout the Experimental section the following simplification (Figure) has often been used to present the n.m.r. data, even when this numbering scheme differs from that implied in the systematic name given. All of the carbocyclic 2′-deoxyribo-

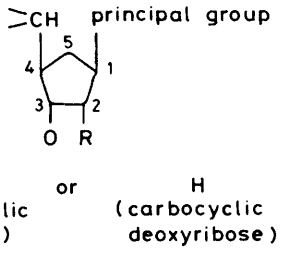


Figure.

nucleosides and precursors are an epimeric mixture, so in many cases two n.m.r. shifts are given for one proton. All compounds are racemic.

5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]*heptan*-2-*ol* (**4**) *from* 8,9,10-*Trinorborn*-5-*en*-2-*ol* (**2**).—To 8,9,10-trinorborn-5-en-2-ol (**2**) (24 g, 0.218 mol) and trimethylamine *N*-oxide (33 g, 0.297 mol) in freshly distilled t-butyl alcohol (440 ml), water (132 ml), and pyridine (17.4 ml) was added a freshly prepared solution of osmium tetraoxide in t-butyl alcohol (0.5% w/v; 17.4 ml, 87 mg). The solution was refluxed for 3 h and cooled, 20% aq. sodium metabisulphite (174 ml) was added dropwise quickly, followed by 2M-hydrochloric acid (250 ml), and the t-butyl alcohol was then removed under reduced pressure. Acetone (200 ml) was added, the mixture was stirred for 1 h, and the acetone was removed. Ethyl acetate (100 ml) was added and both layers were filtered through Celite. The aqueous layer was continuously extracted with ethyl acetate for 3 days; the ethyl acetate layer was dried ($MgSO_4$) and the solvent was removed to give a light brown viscous oil [a mixture of alcohols (**3**) and (**4**)]. This was taken up in a mixture of acetone (400 ml) and 2,2-dimethoxypropane (75 ml) with Dowex 50G-X8 cation-exchange resin (5 g) and stirred at room temperature for 4 h. The solution was filtered, concentrated, and taken up in ether (350 ml) and the ether layer was washed successively with water (50 ml) and saturated aq. sodium hydrogen carbonate (50 ml). The ether phase was dried ($MgSO_4$) and the solvent was removed to give a pale brown viscous oil (33.5 g, 84%). Separation of the two isomers was accomplished by flash column chromatography with ethyl acetate–light petroleum (1:1) as eluant; $\nu_{max.}$($CHBr_3$) 3 590 (OH) and 1 380 and 1 370 cm^{-1}; δ_H (250 MHz; $CDCl_3$) (*endo*-OH) 0.77 (1 H, dt, *J* 13.5, 3.5, and 3.5 Hz, C*H*COH), 1.10 (1 H, m), 1.32 (3 H, s, Me), 1.45 (3 H, s, Me), 1.66 (1 H, m), 1.98 (1 H, ddd, *J* 13.5, 10, and 5 Hz, C*H*COH), 2.21 (1 H, d), 2.36 (1 H, d), 3.18 (1 H, br s, OH), 4.15 (1 H, br d, CHO), 4.24 (1 H, d, br t, *J* 10, 4.5, and 3.5 Hz, C*H*OH), and 4.64 (1 H, br d, CHO); δ_H (250 MHz; $CDCl_3$) (*exo*-OH) 1.2—1.75 (3 H, m), 1.28 (3 H, s, Me), 1.44 (3 H, s, Me), 2.25 (4 H, m), 3.68 (1 H, br d, *J* 7 Hz, C*H*OH), and 3.94 (2 H, br s, 2 × CHO); *m/z* 169 ($M^+ - CH_3$, 100%), 109 (77), and 81 (79).

5-exo,6-exo-(*Isopropylidenedioxy*)*bicyclo*[2.2.1]*heptan*-2-*one* (**1**).—A solution of the alcohol (**4**) (36.5 g, 0.2 mol) in dichloromethane (300 ml) was added to a slurry of PDC (185 g, 0.5 mol), pyridinium trifluoroacetate (8.1 g, 0.04 mol), and silica gel (MN Kieselgel 1 600; 230—400 mesh; 370 g) in dichloromethane (800 ml). The mixture was stirred for 24 h at room temperature under nitrogen, diluted with ether (1 l), and filtered. The filtrate was washed with ether (1 l) and the solvent was removed from the combined organic layers to give an off-white solid. This was treated with boiling pentane (350 ml) for 30 min and the mixture was filtered hot. A white solid (26 g) precipitated out on cooling and was filtered off. The filtrate was concentrated to give more solid which was recrystallised from pentane to give clear platelets of the ketone (**1**) (6.2 g, total yield 89%), m.p. 74—75 °C (lit.,[4] 74—76 °C) (Found: C, 65.8; H, 7.8. Calc. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74%); $\nu_{max.}$($CHCl_3$) 1 755 (CO) and 1 385 and 1 375 cm^{-1} (CMe_2); δ_H (250 MHz; $CDCl_3$) 1.34 (3 H, s, Me), 1.5 (3 H, s, Me), 1.62—1.72 (2 H, m), 2.0—2.2 (2 H, m), 2.72 (2 H, m), 4.28 (1 H, d, CHO), and 4.34 (1 H, d, CHO); δ_H (250 MHz; C_6D_6) 1.05 (1 H, m), 1.45 (1 H, dd) 1.1 (1 H, dd), 1.07 (3 H, s, Me), 1.37 (3 H, s, Me), 1.93 (1 H, br d), 2.18 (1 H, br d), 2.58 (1 H, br s), 3.68 (1 H, d, CHO), and 3.89 (1 H, d, CHO); δ_C (62.9 MHz; $CDCl_3$) 24.1 (CH_3), 25.3 (CH_2), 31.1 (CH_2), 39.3 (CH_2), 39.5 (CH), 55.3 (CH), 76.9 (CH), 81.2 (CH), 111.2 (C), and 214.1 p.p.m. (CO); *m/z* 167 (M^+ − Me, 64%), 125 (36), 107 (34), 79 (69), 55 (66), and 43 (100).

2-*Dimethyl*(*t-butyl*)*silyloxy*-5-exo,6-exo-(*isopropylidenedioxy*)*bicyclo*[2.2.1]*hept*-2-*ene* (**5**).—To a solution of LDA (144 mmol) in THF (120 ml) at −70 °C under nitrogen was added a solution of the ketone (**4**) (22.08 g, 120 mmol) in THF (50 ml) and the mixture was stirred at −70 °C for 45 min. Hexamethylphosphoric triamide (18 ml) was added followed by dimethyl (t-butyl) silyl chloride (19.8 g, 132 mmol) in pentane (15 ml). The temperature was allowed to rise slowly to room temperature and the solution was then diluted with pentane (300 ml) and washed with water (150, then 45 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed to give a brown liquid. Distillation afforded a pale yellow liquid (28 g, 80%), b.p. 88—92 °C at 0.02—0.05 mmHg; $\nu_{max.}$ (liquid film) 1 620 (C=C), 1 380 and 1 370, and 835 cm^{-1} (C=C–H); δ_H (250 MHz; $CDCl_3$) 0.16 (3 H, s, SiMe), 0.18 (3 H, s, SiMe), 0.94 (9 H, s, $SiBu^t$), 1.39 (3 H, s Me), 1.49 (3 H, s, Me), 1.80 (1 H, d, *J* 6 Hz, CH), 1.95 (1 H, d, *J* 6 Hz, CH), 2.45 (1 H, s), 2.67 (1 H, br s), 4.35 (1 H, d, *J* 5 Hz, CHO), 4.46 (1 H, d, *J* 5 Hz, CHO), and 4.64 (1 H, d, *J* 3 Hz, HC=C).

4β-*Dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentane*-1β-*carboxylic Acid* (**6**).—Ozonised oxygen was bubbled through a solution of the silyl enol ether (**5**) (26 g, 87 mmol) in a mixture of dry methanol (250 ml) and dichloromethane (75 ml) at −78 °C until a blue colour was evident. Methyl sulphide (18 ml, 15.2 g, 0.25 mol) was added and the temperature was allowed to rise slowly to ambient. The solvent was removed, and the residue was taken up in 2,2-dimethoxypropane (250 ml) containing methanol (10.5 ml) and the solution was cooled to 2 °C. Dowex 50G-X8 cation-exchange resin (12 g) was added, and the suspension was stirred at 2 °C for 9 days, then filtered and concentrated. Flash column chromatography of the residue with 4% methanol in dichloromethane as eluant afforded the pure *acid* (**6**) (17.3 g, 76%) as a white solid. Recrystallisation from ether–pentane gave an analytically pure sample, m.p. 82—83.5 °C (Found: C, 55.0; H, 7.8. $C_{12}H_{20}O_6$ requires C, 55.37; H, 7.75%); $\nu_{max.}$($CHBr_3$) 3 480 (OH), 2 500—3 300 (OH), 2 830, 1 740 and 1 710 (CO_2H), and 1 385 and 1 375 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.32 (3 H, s, Me), 1.5 (3 H, s, Me), 1.94 (1 H, dt, 5-H), 2.3 (1 H, dt, 5-H), 2.46 (1 H, dq, 4-H), 2.92 (1 H, dt, *J* 4.5 and 8 Hz, 1-H), 3.37 [6 H, s, $(OMe)_2$], 4.25 [1 H, d, C*H*$(OMe)_2$], 4.58 (1 H, dd, 3-H), 4.86 (1 H, dd, 2-H), and 8—10 (1 H, br s, CO_2H).

Methoxymethyl 4β-*Dimethoxymethyl*-3α-(*methoxymethoxy*)*cyclopent*-1-*ene*-1-*carboxylate* (**11**).—To a solution of di-isopropylamine (28.8 ml, 20.8 g, 0.206 mol) in THF (300 ml) under

nitrogen at −60 °C was added butyl-lithium (135 ml, 0.203 mol) dropwise, and the resulting solution was stirred at this temperature for 30 min. A solution of the acid (**6**) (12.6 g, 0.048 mol) in THF (200 ml) was added dropwise and the temperature was then allowed to rise to ambient. (A white solid precipitated out and then partly dissolved.) After the mixture had been stirred for 90 min at room temperature, 85% methoxymethyl chloride (24 ml) was added. (The solid soon completely dissolved.) The mixture was stirred overnight, and was then concentrated to remove THF and the residue was taken up in ether (300 ml). The ether layer was washed successively with water (50 ml), saturated aq. ammonium chloride (30 ml), and saturated aq. sodium hydrogen carbonate (50 ml), and was then dried ($MgSO_4$). Evaporation of the solvent afforded a deep red liquid (17.6 g) which was sufficiently pure for use in the next step. Purification of the crude product by flash column chromatography with 25% ethyl acetate in light petroleum as eluant gave the pure methoxymethyl ester (**11**) (90% yield), $\nu_{max.}$ (liquid film) 1 720 (CO_2R) and 1 640 cm^{-1} (C=C); δ_H (100 MHz; $CDCl_3$) 2.35—2.9 (3 H, m), 3.41 (9 H, s, 3 × OMe), 3.5 (3 H, s, OMe), 4.34 [1 H, d, $CH(OMe)_2$], 4.66—4.84 (3 H, m), 5.33 (2 H, br s, CH_2OMe), and 7.95 (1 H, m, HC≡C); *m/z* 259 (M^+ − OMe, 0.2%), 258 (*M* − MeOH, 0.8), 75 (100), and 45 (90).

Methoxymethyl 3β-*Dimethoxymethyl*-4α-(*methoxymethoxy*)-*cyclopentane*-1-*carboxylate* (**13**).—The crude unsaturated esters (**11**) and (**12**) (17.6 g) and 5% Pd–C (5.5 g) were stirred in ethanol (300 ml) under hydrogen for 4 h and the mixture was then filtered. The charcoal residue was washed with ethanol (300 ml) and the solvent was removed from the combined ethanol layers to give a red oil (16 g) which was used without further purification in the next stage. [Hydrogenation of pure unsaturated ester afforded the pure saturated ester (**13**) in 92% yield]; $\nu_{max.}$(CCl_4) 2 830 and 1 745 cm^{-1} (CO_2R); δ_H (60 MHz; $CDCl_3$) 1.7—3.0 (6 H, m), 3.4 and 3.45 (12 H, 2 × s, 4 × OMe), 4.0—4.3 (2 H, m), 4.65 (2 H, s, OCH_2OMe), and 5.3 (2 H, s, CO_2CH_2OMe); *m/z* 292 (M^+, 0.2%), 261 (*M* − OMe, 1.6), 260 (*M* − MeOH, 0.3), 199 (16), and 75 (100).

3β-*Dimethoxymethyl*-4α-(*methoxymethoxy*)*cyclopentane*-1-*carboxylic Acid* (**14**).—To a solution of the crude ester (**13**) (16 g) in methanol (100 ml) and water (200 ml) was added potassium carbonate (40 g) and the mixture was stirred overnight. G.l.c. (SE30, 165 °C) showed no starting material remaining, so the solution was washed with dichloromethane (100, then 50 ml). The aqueous phase was acidified with 2M-hydrochloric acid (~320 ml) and extracted with dichloromethane (3 × 300 ml). The organic layer was dried ($MgSO_4$) and concentrated to give a pale brown viscous liquid [8.2 g, 68% from the acid (**6**)], $\nu_{max.}$(CCl_4) 2 830 and 1 710 cm^{-1} (CO_2H); δ_H (250 MHz; $CDCl_3$) 1.6—2.5 (5 H, m), 2.82 and 3.0 (1 H, 2 × m, $CHCO_2$), 3.35 (9 H, s, 3 × OMe), 4.04 and 4.13 (1 H, 2 × m, CHO), 4.23 [1 H, 2 × d, $CH(OMe)_2$], 4.65 (2 H, m, CH_2O), and 7.0—9.0 (1 H, br s, CO_2H); *m/z* 217 (M^+, 0.1%), 155 (11), and 75 (100).

Benzyl 4β-*Dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)-*cyclopentane*-1-*carboxylate* (**9**).—To a solution of the acid (**6**) (330 mg, 1.27 mmol) in dry acetonitrile (10 ml) was added 2-chloro-1-methylpyridinium iodide (664 mg, 2.6 mmol) and the mixture was stirred under nitrogen for 20 min. Triethylamine (0.54 ml, 0.39 g, 3.9 mmol) was added, the mixture was stirred for 90 min, and a solution of benzyl alcohol (206 mg, 1.9 mmol) in acetonitrile (4 ml) was added. The solution was stirred for 15 h and concentrated, the residue was taken up in ether, and the solution was filtered. The organic layer was washed with 0.5M-hydrochloric acid, dried ($MgSO_4$), and the solvent was removed to give a brown oil. Flash column chromatography with 20% ethyl acetate in hexane as eluant afforded an epimeric mixture of the benzyl esters, from which the two pure epimers were obtained (total yield 75%); $\nu_{max.}$ (liquid film) 2 830, 1 730 (CO_2R), 1 380 and 1 370 [$(OMe)_2$], and 750 and 699 cm^{-1} (Ph); δ_H (250 MHz; $CDCl_3$) (α-epimer) 1.31 (3 H, s, Me), 1.43 (3 H, s, Me), 1.9—2.0 (2 H, m, 5-H_2), 2.22 (1 H, dtd, *J* 10, 9, and 5 Hz, 4-H), 2.97 (1 H, br t, *J* 4.5 Hz, 1-H), 3.27 (3 H, s, OMe), 3.38 (3 H, s, OMe), 4.50 [1 H, d, *J* 9 Hz, $CH(OMe)_2$], 4.63 (1 H, t, *J* 5 Hz, 2-H), 4.88 (1 H, d, *J* 5 Hz, 3-H), 5.13 (2 H, s, CH_2Ph), and 7.4 (5 H, s, Ph); δ_H (250 MHz; $CDCl_3$) (β-epimer) 1.32 (3 H, s, Me), 1.49 (3 H, s, Me), 1.92 (1 H, dt, 5-H), 2.3 (1 H, dt, 5-H), 2.46 (1 H, m, 4-H), 2.95 (1 H, m, 1-H), 3.34 (6 H, s, 2 × OMe), 4.22 [1 H, d, $CH(OMe)_2$], 4.55 (1 H, dd, 3-H), 4.88 (1 H, dd, 2-H), 5.15 (2 H, s, CH_2Ph), and 7.35 (5 H, s, Ph); *m/z* 350 (M^+, 0.1%), 335 (6.3), 91 (84), and 75 (100).

N-(2-*Pyridylmethyl*)-4β-*dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentane*-1β-*carboxamide* (**15**).—To a solution of the acid (**6**) (1.2 g, 4.62 mmol) in dry dichloromethane (75 ml) was added a solution of 2-(aminomethyl)pyridine (0.56 g, 5.18 mmol) in dichloromethane (6 ml) followed by DCC (0.98 g, 4.75 mmol). The resulting solution was stirred under nitrogen for 1 h, then filtered to remove dicyclohexylurea, and the solvent was removed. Flash column chromatography of the residue with 50% ethyl acetate–light petroleum followed by 5% methanol in ethyl acetate as eluant afforded the pure *amide* (**15**) (920 mg, 57%) as a brown solid (Found: C, 61.3; H, 7.3; N, 8.0. $C_{18}H_{26}N_2O_5$ requires C, 61.7; H, 7.48; N, 7.99%); $\nu_{max.}$($CHBr_3$) 3 420 (NH), 2 835 [$CH(OMe)_2$], 1 670 and 1 515 (CONH), and 753 cm^{-1} (pyr); δ_H (250 MHz; $CDCl_3$) 1.33 (3 H, s, Me), 1.53 (3 H, s, Me), 1.95 (1 H, ddd, *J* 14, 12, and 11 Hz, 5-H_β), 2.19 (1 H, ddd, *J* 14, 7, and 6.5 Hz, 5-H_α), 2.46 (1 H, ddt, *J* 12, 7, and 4 Hz, 4-H), 2.79 (1 H, dt, *J* 11 and 6.5 Hz, 1-H), 3.4 (3 H, s, OMe), 3.45 (3 H, s, OMe), 4.31 [1 H, d, $CH(OMe)_2$], 4.53 (1 H, dd, *J* 6.5 and 4 Hz, 3-H), 4.45—4.7 (2 H, 2 × dd, CH_2NH), 4.73 (1 H, t, *J* 6.5 Hz, 2-H), 6.9 (1 H, br t, CH_2NH), 7.20 (1 H, t), 7.27 (1 H, d), 7.66 (1 H, td), and 8.54 (1 H, d).

3-[4β-*Dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentan*-1β-yl]*imidazo*[1,5-a]*pyridine* (**16**).—To a solution of the amide (**15**) (0.92 g, 2.63 mmol) in dry 1,2-dichloroethane (60 ml) were added pyridine (4 ml) and phosphoryl trichloride (1.4 ml, 2.3 g, 15 mmol). The resulting solution was gently refluxed under nitrogen for 1 h, the solvent was removed, and the residue was partitioned between ethyl acetate (30 ml) and saturated aq. sodium hydrogen carbonate (15 ml). The aqueous layer was washed with ethyl acetate (2 × 15 ml) and the combined organic layers were washed with a little saturated aq. sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and concentrated to give a brown viscous oil, which was purified by flash column chromatography with ethyl acetate as eluant to afford the pure imidazopyridine (**16**) (365 mg, 41%), $\nu_{max.}$($CHBr_3$) 2 830 and 1 060 cm^{-1} (C–O); δ_H (250 MHz; $CDCl_3$) 1.33 (3 H, s, Me), 1.61 (3 H, s, Me), 2.2—2.5 (2 H, m, 5-H_2), 2.6 (1 H, m, 4-H), 3.35 (3 H, s, OMe), 3.42 (3 H, s, OMe), 3.55 (1 H, dt, 1-H), 4.33 [1 H, d, $CH(OMe)_2$], 4.67 (1 H, dd, 3-H), 4.80 (1 H, t, 2-H), 6.58 (1 H, t), 6.69 (1 H, dd), 7.34 (1 H, s), 7.40 (1 H, d), and 8.04 (1 H, d); *m/z* 332 (M^+, 11%), 317 (11), 144 (58), 85 (69), and 83 (100).

3-[4β-*Hydroxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentan*-1β-*yl*]*imidazo*[1,5-a]*pyridine* (**17**).—To a solution of the fully protected imidazopyridine (**16**) (100 mg, 0.30 mmol) in AnalaR acetone (5 ml) was added PTSA monohydrate (150 mg, 0.79 mmol) and the mixture was stirred at room temperature under nitrogen for 2.5 h. Solid sodium hydrogen carbonate (0.8 g) was added and after 15 min the suspension was filtered and the residue washed well with acetone. The acetone layer was

concentrated, the residue was taken up in dichloromethane (15 ml), and the organic layer was washed with saturated aq. sodium hydrogen carbonate (10 ml). The aqueous layer was back-extracted with dichloromethane (2 × 10 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was removed to give a brown viscous oil (85 mg, 99%). T.l.c. (ethyl acetate, u.v. or 2,4-dinitrophenylhydrazine) suggested the presence of essentially one product with small amounts of impurities.

To a solution of the crude aldehyde (85 mg, 0.3 mmol) in ethanol (4 ml) at 0 °C was added sodium borohydride (150 mg, 4 mmol). After the mixture had been stirred for 1 h at room temperature, 0.5M-hydrochloric acid was added dropwise (to pH 5), and the solution was extracted with dichloromethane (3 × 10 ml). The organic phase was dried ($MgSO_4$) and the solvent was removed to give a pale yellow viscous oil (75 mg, 88%). Flash column chromatography with 6% methanol in dichloromethane as eluant afforded the pure product (**17**) as an oily foam (Found: M^+, 288.1469. $C_{16}H_{20}N_2O_3$ requires M, 288.1474); δ_H (100 MHz; $CDCl_3$) 1.33 (3 H, s, Me), 1.49 (3 H, s, Me), 2.5—2.7 (3 H, m, 4-H and 5-H_2), 3.3—3.9 (3 H, m, CH_2OH and 1-H), 4.6 (2 H, m, 2- and 3-H), 6.5—6.8 (2 H, m), 7.3 (1 H, s), 7.4 (1 H, m), and 7.96 (1 H, d); m/z 288 (M^+, 45%), 273 (16), and 144 (imidazopyridine + C_2H_3, 100).

3-[2α,3α-*Dihydroxy*-4β-(*hydroxymethyl*)*cyclopentan*-1β-*yl*]-*imidazo*[1,5-a]*pyridine* (**18**).—The crude alcohol (**17**) (75 mg, 0.26 mmol) was stirred in ethanol (0.5 ml), water (0.5 ml), and trifluoroacetic acid (0.4 ml) at room temperature for 2 h. The solvent was removed below 40 °C under reduced pressure with ethanol as the chaser, and the residue was purified by flash column chromatography with 15% methanol in dichloromethane as eluant. This afforded the pure nucleoside (**18**) (55 mg, 85%) as an off-white solid after trituration with ether (Found: M^+, 248.1382. $C_{13}H_{16}N_2O_3$ requires M, 248.1403); δ_H [250 MHz; $(CD_3)_2SO$–$CDCl_3$] 1.8—2.2 (3 H, m, 4-H and 5-H_2), 3.4—3.6 (3 H, m, CH_2OH and 1-H), 3.78 (1 H, m, 2-H), 3.97 (1 H, dd, 3-H), 4.5—4.9 (1 H, br s, OH), 6.63 (1 H, dd), 6.73 (1 H, dd), 7.3 (1 H, s), 7.51 (1 H, d), and 8.28 (1 H, d); m/z 248 (M^+, 48%), 231 (11), 145 (imidazopyridine + C_2H_4, 100), 144 (22), and 119 (imidazopyridine, 8).

N-2-(*Pyridylmethyl*)-3β-*dimethoxymethyl*-4α-(*methoxymethoxy*)*cyclopentane*-1-*carboxamide* (**19**).—To a solution of the deoxy acid (**14**) (1.6 g, 6.45 mmol) in dry dichloromethane (50 ml) was added a solution of 2-(aminomethyl)pyridine (0.79 g, 7.3 mmol) in dichloromethane (10 ml) followed by DCC (1.38 g, 6.68 mmol). The solution was stirred under nitrogen for 90 min, filtered, and the solvent was removed. Flash column chromatography of the residue with 5% methanol in dichloromethane as eluant gave the pure amide (**19**) (1.6 g, 73%) as an oily solid, which was shown to be an epimeric mixture by n.m.r. spectrometry; $\nu_{max.}$($CHCl_3$) 3 390 and 3 420 (NH), 1 665 (CONH), 1 600 and 1 580 (aromatic), and 1 515 cm^{-1} (CONH and aromatic); δ_H (250 MHz; $CDCl_3$) 1.7—2.5 (5 H, m), 2.76 and 2.91 (1 H, m, CH–C=O), 3.40 (9 H, s, 3 × OMe), 4.07 and 4.17 (1 H, 2 × br q, CHO), 4.2—4.3 [1 H, 2 × d, CH(OMe)$_2$], 4.56 (2 H, d, CH_2N), 4.66 (2 H, m, OCH_2O), 6.87 and 7.00 (1 H, br s, NH), 7.2—7.3 (2 H, m), 7.68 (1 H, m), and 8.53 (1 H, 2 × d); m/z 338 (M^+, 3%), 323 (21), 307 (11), 306 (7), 261 (100), 245 (78), and 135 (65).

3-[3β-*Dimethoxymethyl*-4α-(*methoxymethoxy*)*cyclopentan*-1-*yl*]*imidazo*[1,5-a]*pyridine* (**20**).—To a solution of the amide (**19**) (1.5 g, 4.4 mmol) in 1,2-dichloroethane (90 ml) were added pyridine (5.9 ml) and phosphoryl trichloride (2.06 ml, 22 mmol). The solution was gently refluxed for 75 min during which time the colour became deep red. The solvent was removed and the residue was partioned between ethyl acetate and saturated aq. sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and the solvent was removed to give a deep red viscous oil (0.79 g, 55%) which was sufficiently pure for use in the next stage. A small amount was purified for analytical purposes by flash column chromatography with ethyl acetate as eluant (Found: M^+, 320.1689. $C_{17}H_{24}N_2O_4$ requires M, 320.1736); $\nu_{max.}$(CCl_4) 2 830 and 1 060 cm^{-1} (C–O); δ_H (100 MHz; $CDCl_3$) 1.8—2.7 (5 H, m), 3.4 (10 H, ms, 3 × OMe and 1-H), 4.1—4.4 [2 H, m, CH(OMe)$_2$ and 3-H], 4.72 (2 H, br s, OCH_2O), 6.6 (2 H, m), 7.3—7.5 (2 H, m), and 7.8 (1 H, t); m/z 320 (M^+, 54%), 305 (30), 289 (29), 288 (8), 243 (100), and 136 (40).

3-[3β-*Hydroxymethyl*-4α-(*methoxymethoxy*)*cyclopentan*-1-*yl*]*imidazo*[1,5-a]*pyridine* (**21**).—The imidazopyridine (**20**) (0.74 g, 2.2 mmol) was stirred with PTSA dihydrate (1.04 g, 5.4 mmol) in acetone (50 ml) at room temperature for 5 h and then saturated aq. sodium hydrogen carbonate (20 ml) and water (30 ml) were added. The solution was extracted with ethyl acetate (3 × 50 ml), and the combined extracts were washed with saturated aq. sodium hydrogen carbonate (20 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a brown viscous oil (670 mg), which was taken up in ethanol (25 ml) and sodium borohydride (500 mg, 13 mmol) was added at 0 °C. The solution was stirred at room temperature for 30 min, water (10 ml) was added, the solution was partially concentrated, and then more water (15 ml) was added. The aq. phase was extracted with ethyl acetate (3 × 25 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was removed to give a light brown viscous oil (0.54 g, 85%); δ_H (60 MHz; $CDCl_3$) 1.5—2.5 (5 H, m), 3.3 (3 H, 2 × s, OMe), 3.35—4.5 (5 H, m), 4.55 (2 H, br s, OCH_2O), 6.5 (2 H, m), 7.3—7.5 (2 H, m), and 7.7 (1 H, m); m/z 276 (M^+, 62%), 261 (2), 245 (9), 231 (69), 185 (51), 145 (100), 144 (50), 119 (37), 107 (29), and 92 (73).

3-[3α-*Hydroxy*-4β-(*hydroxymethyl*)*cyclopentan*-1-*yl*]-*imidazo*[1,5-a]*pyridine* (**22**).—To a solution of the crude alcohol (**21**) (425 mg, 1.54 mmol) in methanol (2 ml) was added 6M-hydrochloric acid (6 ml) and the mixture was stirred for 2 h at room temperature. The solution was neutralised (2M-sodium hydroxide, then sodium hydrogen carbonate) and extracted successively with dichloromethane (3 × 20 ml) and ethyl acetate (20 ml). The combined extracts were dried ($MgSO_4$) and the solvents were removed to give a brown oily solid (250 mg, 70%). Flash column chromatography afforded the two pure epimers in a *ca.* 1:1 ratio; (α)-epimer:[11] δ_H (250 MHz; $CDCl_3$) 1.82 (1 H, ddd, 5-H), 2.09 (1 H, ddd, 5-H), 2.2—2.5 (3 H, m, 2-H_2 and 4-H), 3.6—3.8 (3 H, m, CH_2OH and 1-H), 4.22 (1 H, dt, 3-H), 6.57 (1 H, dt), 6.68 (1 H, dt), 7.3 (1 H, s), 7.41 (1 H, d), and 7.7 (1 H, d); m/z 232 (M^+, 24%), 215 (3), 174 (23), 145 (87), 94 (100), 92 (41). (β)-Epimer:[11] δ_H (250 MHz; $CDCl_3$) 1.92 (1 H, m, 5-H), 2.17 (1 H, m, 2-H), 2.27 (1 H, m, 2-H), 2.28 (1 H, m, 4-H), 2.43 (1 H, m, 5-H), 3.7—3.8 (3 H, m, CH_2OH and 1-H), 4.40 (1 H, q, 3-H), 6.52 (1 H, dd), 6.65 (1 H, dd), 7.28 (1 H, s), 7.36 (1 H, d), and 7.77 (1 H, d); m/z 232 (M^+, 28%), 215 (2), 145 (100), 144 (26), 119 (22), 107 (18), and 92 (43). (For the trifluoroacetyl derivatives see accompanying paper.[11])

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