Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2403-2406, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00297-2

Syntheses of Pseudo-α-L-fucopyranose and Pseudo-6-deoxy-β-D-altropyranose from ((5*S*,6*R*)-5,6-Dihydroxy-1,3-cyclohexadienyl)methanenitrile.

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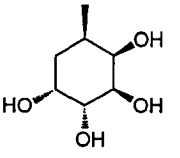
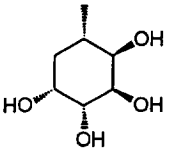
Abstract: Pseudo-α-L-fucopyranose **1** and pseudo-6-deoxy-β-D-altropyranose **2** have been synthesised from ((5*S*,6*R*)-5,6-dihydroxy-1,3-cyclohexadienyl)methanenitrile **3**.

Pseudo-sugars are carbocyclic analogues of cyclic monosaccharides in which the ring oxygen is replaced by a methylene group.[1] Owing to the structural resemblance to natural cyclic monosaccharides, pseudo-sugars were thought to be recognised by enzymes or biological systems, and thus to have biological activity.[1] From the point of view of the potential pharmaceutical properties, they have been of considerable synthetic interest[2] since the first synthesis 1966.[1]

We now wish to report the syntheses of pseudo-α-L-fucopyranose **1** and pseudo-6-deoxy-β-D-altropyranose **2** from *cis*-dihydrodiol **3**. This readily available and relatively stable homochiral diol was produced by biotransformation of cyanobenzene using a recombinant toluene dioxygenase expressed in *Escherichia coli* JM109(pDTG601).[3] In 1992, Cai *et al.* reported the synthesis of **1** in eleven steps using L-fucose as the starting material.[4] In the same year, **1** and **2** were also synthesised by Redlick *et al.* in seven steps from D-mannose.[5] Recently Carless et.al. have described the synthesis of **1** from (1*S*, 2*R*)-3-methyl-3,5-cyclohexadiene-1,2-diol.[6] Motivated by the utilisation of *cis*-dihydrodiol as a homochiral synthon, we aimed to provide an alternative route to **1** and **2** using cyano-*cis*-dihydrodiol **3** as starting material.

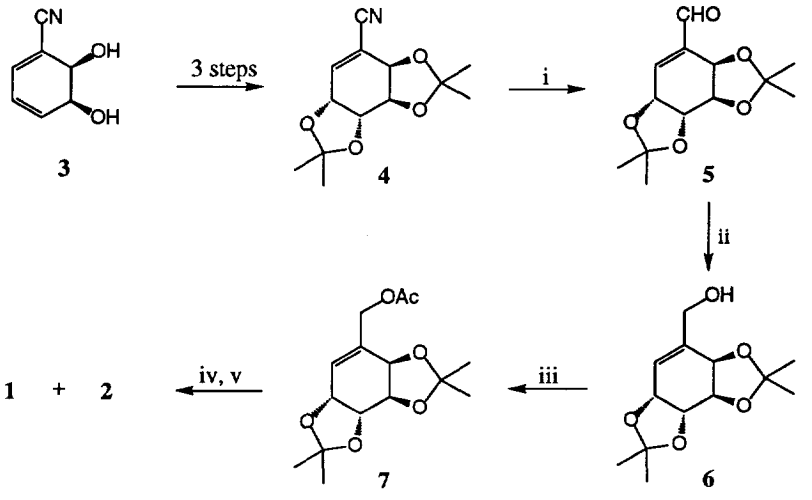


1



2

Our synthesis is shown in the Scheme below. Aldehyde **5** was prepared in four steps from the cyano-diol **3**.[3] DIBAL reduction of the nitrile **4** provided the α,β-unsaturated aldehyde **5** in 52 % yield.[7] The aldehyde **5** was reduced to allylic alcohol **6** in 82 % yield. This was converted into acetate **7** in 90 % yield. Hydrogenation of the acetate **7** over palladium on charcoal proceeded with simultaneous hydrogenolsis of the allylic acetate function and saturation of the double bond. Acid catalysed deprotection of the product yielded pseudo-α-L-fucopyranose **1** and pseudo-6-deoxy-β-D-altropyranose **2**, each in 40 % yield.



Scheme. Reagents: i, DIBAL; ii, DIBAL; iii, Ac_2O/pyridine; iv, Pd/C, H_2; v, H_2O/MeOH/H^+

The syntheses described above illustrate the simple and efficient syntheses of pseudo-α-L-fucopyranose **1** and pseudo-6-deoxy-β-D-altropyranose **2** in eight steps, using the microbial metabolite **3** as a homochiral starting material. Although this route is slightly longer than that from (1*S*, 2*R*)-3-methyl-3,5-cyclohexadiene-1,2-diol ("toluene-*cis*-diol"),[6] it has the advantage that the starting material is considerably more stable than "toluene *cis*-diol" which shows a marked propensity to undergo dehydration to the phenol.

Acknowledgement

We thank Dr J.J. Hastings for NMR spectra, Mr I. Katyal for mass spectra and Dr G.M. Whited, Genencor International, Inc., 180 Kimball Way, South San Francisco, California 94080, USA, for a gift of the diol **3**.

Experimental

General — ^1H NMR spectra were recorded on Bruker AC-400 or 250 MHz spectrometers. ^{13}C NMR spectra were determined at 62.9 MHz on the Bruker AC-250 spectrometer. Optical rotations were determined using an AA-1000 polarimeter (Optical Activity Ltd) with a 2 dm cell. Optical rotations are given in units of 10^{-1} deg cm^2 g^{-1}. MS spectra were recorded with a Kratos MS80 spectrometer. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected.

(1*R*, 4*R*, 8*R*, 9*R*)-2-Hydroxymethyl-6, 6, 11, 11-tetramethyl-5, 7, 10, 12-tetraoxabicyclo[7.3.0.0^{9,1}]dodec-2-ene 6.

To a solution of aldehyde **5**[3] (0.80 g, 3.15 mmol) in dry THF (40 ml) under nitrogen at 0 °C was added DIBAL (1 M in hexane, 10 ml, 10 mmol). The solution was stirred at 0 °C for two hours, then methanol (15 ml) and HCl (1 N, 20 ml) were added. The resulting mixture was stirred at 0 °C for 15 minutes and extracted with diethyl ether (4 x 40 ml). The organic phase was washed with saturated $NaHCO_3$ (20 ml), dried ($MgSO_4$) and

evaporated under reduced pressure. The residue was subjected to flash chromatography (diethyl ether) to give **6** as a clear liquid (R_f (diethyl ether) 0.65, 0.29 g, 82 %); (Found $[M + H]^+$: 257.1389. $C_{13}H_{21}O_5$ requires 257.1389); $[\alpha]_D^{23}$ +24.5 (c 0.14 in $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 1.34 (3 H, s, Me), 1.36 (3 H, s, Me), 1.37 (3 H, s, Me), 1.38 (3 H, s, Me), 2.01 (1 H, br s, OH), 4.21 (1 H, d, *J* 13.66 Hz, CH_2OH), 4.28 (1 H, d, *J* 13.66 Hz, CH_2OH), 4.58 (4 H, m, H-1, H-4, H-8, H-9), 5.69 (1 H, br s, H-3); δ_C (62.9 MHz; $CDCl_3$) 26.14 (Me), 26.26 (Me), 27.55 (Me), 27.86 (Me), 64.36 (CH-O), 70.62 (CH-O), 71.31 (CH-O), 73.07 (CH-O), 73.23 (CH-O), 109.05 (O-C-O), 109.29 (O-C-O), 122.65 (C=C), 135.89 (C=C); *m/z* (relative abundance) (CI) 257 ($[M + H]^+$, 55 %), 241 (40), 216 (25), 199 (100), 123 (40).

(1*R*, 4*R*, 8*R*, 9*R*)-2-Acetoxymethyl-6, 6, 11, 11-tetramethyl-5, 7, 10, 12-tetraoxabicyclo[7.3.0.0^{9,1}]dodec-2-ene 7.

Alcohol **6** (2.8 g, 11 mmol) was dissolved in pyridine (6 ml) and acetic anhydride (6 ml). The mixture was allowed to stand at room temperature for 1 day. It was concentrated under reduced pressure and the residue was diluted with ethyl acetate (150 ml). The solution was washed with 1N HCl (3 x 20 ml), saturated $NaHCO_3$ (3 x 20 ml), water (20 ml), brine (20 ml). It was dried ($MgSO_4$) and evaporated under reduced pressure to give a brown liquid. Purification of the liquid by flash chromatography (dichloromethane/diethyl ether, 1 : 1, v/v) afforded **7** as a clear liquid (R_f (dichloromethane/diethyl ether) 0.73, 2.96 g, 90 %); (Found $[M + NH_4]^+$: 316.1760. $C_{15}H_{26}NO_6$ requires 316.1760); $[\alpha]_D^{25}$ +45.7 (c 0.55 in $CHCl_3$); ν_{max}/cm^{-1} 2987, 2936, 2896, 1745 (C=O); δ_H (250 MHz; $CDCl_3$) 1.34 (6 H, s, 2 Me), 1.36 (3 H, s, Me), 1.37 (3 H, s, CH_3), 2.08 (3 H, s, OAc), 4.58 (4 H, m, H-8, H-9, C*H*$_2$OAc), 4.60 (2 H, m, H-4, H-1), 5.68 (1 H, br s, H-3); δ_C (62.9 MHz; $CDCl_3$) 20.74 (Me), 26.28 (Me), 26.40 (Me), 27.52 (Me), 27.72 (Me), 64.01 (CH-O), 70.32 (CH-O), 70.52 (CH-O), 72.95 (CH-O), 73.04 (CH-O), 109.23 (O-C-O), 109.38 (O-C-O), 124.22 (C=C), 132.19 (C=C), 170.42 (C=O); *m/z* (relative abundance) (CI) 316 ($[M + NH_4]^+$, 12 %), 241 (100), 183 (5), 52 (12).

(1*R*, 2*R*, 3*R*, 4*R*, 5*R*)-5-Methylcyclohexane-1, 2, 3, 4-tetraol 1 and (1*R*, 2*R*, 3*R*, 4*R*, 5*S*)-5-methylcyclohexane-1, 2, 3, 4-tetraol 2.

Palladium over activated carbon (0.20 g, of 10 %) was added to a solution of acetate **7** (0.6 g, 2.01 mmol) in ethanol (50 ml). The mixture was hydrogenated at 30 p.s.i. with shaking at room temperature for 7 hours. The mixture was then filtered through a pad of celite and the filtrate was evaporated under reduced pressure to give a yellow liquid. Column chromatography of the liquid on silica gel with petroleum ether 40-60 °C/diethyl ether (100 : 5, v/v) as eluent yielded two oily liquids: first fraction (0.19 g), second fraction (0.25 g). The first fraction was dissolved in methanol (4 ml) and water (4 ml). Conc. HCl (3 drops) was added and the resulting mixture was allowed to stand at room temperature for 2 days. It was evaporated under reduced pressure and freeze dried to give **1** as a crystalline solid (0.13 g, 40 %). Using the same deprotecting procedure, **2** was obtained as a white solid (0.13 g, 40 %); **1**, m.p. 115-117 °C (from ethyl acetate) (lit.,[5] 115 °C) (Found $[M + NH_4]^+$: 180.1236. $C_7H_{18}NO_4$ requires 180.1236); $[\alpha]_D^{23}$ -55.8 (c 0.21 in ethanol) (lit.,[5] $[\alpha]_D^{20}$ -58); δ_H (400 MHz; D_2O) 0.89 (3 H, d, *J* 6.95 Hz, Me), 1.51 (2 H, m, H-6), 1.90 (1 H, m, H-5), 3.59 (1 H, dd, *J* 2.91, 10.28 Hz, H-2), 3.66 (1 H, dd, *J* 2.91, 10.28 Hz, H-3), 3.78 (1 H, dd, *J* 2.91, 2.68 Hz, H-4), 3.97 (1 H, m, H-1); δ_C (62.9 MHz; D_2O) 17.33 (Me), 29.41, 33.23, 70.38 (CH-O), 71.65 (CH-O), 72.18 (CH-O), 75.03 (CH-O); *m/z* (relative abundance) (CI) 180 ($[M + NH_4]^+$, 25 %), 124 (15 %), 97 (10), 84 (22), 55 (15), 35.3 (100); **2**, m.p. 170-172 °C (from ethyl acetate) (lit.,[5] 178 °C) (Found $[M + NH_4]^+$: 180.1236. $C_7H_{18}NO_4$ requires 180.1236); $[\alpha]_D^{24}$ +45 (c 0.24 in ethanol) (lit.,[5] $[\alpha]_D^{20}$ +41); δ_H (400 MHz; D_2O) 0.93 (3 H, d, *J* 6.53 Hz, Me), 1.34 (1 H, m,

H-6), 1.64 (1 H, m, H-6), 1.75 (1 H, m, H-5), 3.38 (1 H, dd *J* 2.77, 10.73 Hz, H-4), 3.88-3.92 (3 H, m, H-3, H-2, H-1); δ_C (62.9 MHz; D_2O) 18.50 (Me), 31.09, 34.64, 67.89 (CH-O), 73.57 (CH-O), 73.71 (CH-O), 73.77 (CH-O); *m/z* (relative abundance) (CI) 180 ($[M + NH_4]^+$, 100 %), 171 (10 %), 160 (12), 146 (12).

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(*Received in UK* 28 *May* 1996)