# Total Synthesis of 4-O-Methyl-DL-lyxose and 4-Deoxy-DL-ribose. Further Evidence of the Stereoselective Hydroxylation of Double Bonds by Osmic Acid

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Methyl 4-O-methyl- $\alpha$ -DL-lyxopyranoside (6) and methyl 4-deoxy- $\beta$ -DL-*erythro*-pentopyranoside (3) were obtained in excellent yield as the sole isolable products of the reaction of osmic acid in pyridine on *cis*-2,5-dimethoxy-5,6-dihydro-2*H*-pyran (2) and 2-methoxy-5,6-dihydro-2*H*-pyran (1), respectively. Hydrolysis of 6 and 3 gave respectively 4-O-methyl-DL-lyxose (9) and 4-deoxy-DL-ribose (8).

The attack on the double bond of 1 and 2 occurs nearly completely if not exclusively from the unhindered side, remote from the substituent. These results indicate that 1 must be predominantly in the conformation in which the C-2 alkoxy group is *quasi* axial.

Le 4-O-méthyl- $\alpha$ -DL-lyxopyranoside de méthyle (6) et le déoxy-4  $\beta$ -DL-érythro-pentopyranoside de méthyle (3) ont été obtenus avec un excellent rendement et comme seuls produits de la réaction entre l'acide osmique dans la pyridine et respectivement le diméthoxy-2,5-dihydro-5,6 2*H*-pyranne-*cis* (2) et le méthoxy-2 dihydro-5,6 2*H*-pyranne (1). L'hydrolyse de 6 et de 3 conduit respectivement au 4-O-méthyl DL-lyxose (9) et au déoxy-4 DL-ribose (8).

L'attaque de la double liaison de 1 et de 2 se produit presque complètement sinon complètement par le côté le moins empêché, à savoir celui le plus éloigné du substituant. Ces résultats impliquent que 1 doit être sous une conformation dans laquelle le groupe alcoxy en position 2 est *quasi* axial.

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A recent report from this laboratory has described the stereoselective attack of osmic acid on the double bond of the bicyclo compound 1,6-anhydro-3,4-dideoxy- $\beta$ -DL-*erythro*-hex-3enopyranose to produce, after hydrolysis, both  $\alpha,\beta$ -DL-allose and  $\alpha,\beta$ -DL-galactose (1). As part of a program aimed at the total syntheses of monosaccharides, and also to determine whether the stereoselective attack by osmic acid could be extended to 2-alkoxydihydropyrans, the reaction of osmic acid on both 2-methoxy-5,6-dihydro-2*H*-pyran (1 in Scheme 1) and *cis*-2,5-dimethoxy-5,6-dihydro-2*H*-pyran (2 in Scheme 1) was investigated. This report describes the results obtained.

The reactions performed and the products obtained are summarized in Scheme 1.

By the improved procedure (2), the reaction of osmic acid with 1 gave a nearly quantitative yield of crude material whose 100 MHz p.m.r. spectrum showed the presence of only one anomeric proton signal. Distillation of this crude material provided methyl 4-deoxy- $\beta$ -DL-*erythro*-pentopyranoside (3) in 93% yield. The 100 MHz p.m.r. spectrum of 3 agreed with the structure designated. The 100 MHz p.m.r. spectrum of its diacetate 4 when analyzed with the aid of double irradiation, fully confirmed that the configuration and conformation was that indicated by 4. Hydrolysis of 3 with aqueous dioxane containing sulfuric acid gave 4-deoxy-DL-ribose (8) in 77% yield. The 100 MHz p.m.r. spectrum of 8 in D<sub>2</sub>O showed at first only one anomeric proton signal as a doublet at  $\tau$  5.09 ( $J \approx 5$  Hz). When the solution had stood for a period of 24 h a second doublet appeared in the anomeric proton region at  $\tau$  5.36 ( $J \approx 1.7$  Hz) thus indicating that the  $\alpha$  anomer was now present in the ratio  $\beta$ : $\alpha = 1.0:0.42$  as shown by the integrated areas of the signals.

The reaction of osmic acid with 2 gave a nearly quantitative yield of crude material which showed only two spots on a t.l.c., one barely discernible. Distillation of this crude substance gave methyl 4-O-methyl- $\alpha$ -DL-lyxopyranoside (6) in 84% yield as the sole insoluble product. The i.r. spectrum of 6 in carbon tetrachloride showed a narrow band at 3600 cm<sup>-1</sup> and a broad absorption band, 3260–3540 cm<sup>-1</sup>. An extensively diluted solution gave an i.r. spectrum with only one narrow band at 3590 cm<sup>-1</sup>, indicative of the absence of intramolecular hydrogen bonding. The 100 MHz p.m.r. spectrum of 6 in pyridine-d<sub>5</sub> showed the anomeric proton signal as a doublet ( $J \approx 2.8$  Hz) centered at  $\tau$  5.05 in agreement with the configura-

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tion and conformation shown by **6**. Spin decoupling experiments provided no further corroboration of the structure proposed. However, the 100 MHz p.m.r. spectrum of the crystalline di-O-acetyl derivative 7 agreed with the proposed structure and spin decoupling experiments corroborated that 7 was in fact methyl 2,3-di-Oacetyl-4-O-methyl- $\alpha$ -DL-lyxopyranoside.

Hydrolysis of 6 with aqueous dioxane containing sulfuric acid afforded 4-O-methyl-DLlyxose 9 as a viscous sirup in 75% yield. The 100 MHz p.m.r. spectrum of 9 in D<sub>2</sub>O, after it had stood at room temperature for 16 h, showed two anomeric proton signals as doublets at  $\tau$  4.72 ( $J \approx 5$  Hz) and 4.83 ( $J \approx 1.5$  Hz) in the area ratio of 1.0:0.37, indicative of a mixture of the  $\beta$ and  $\alpha$  anomers respectively. Final corroboration that 9 was indeed the structure indicated was obtained by the observation that the 100 MHz p.m.r. spectrum of 9 in D<sub>2</sub>O was identical to that of authentic 4-O-methyl-D-lyxose.

It is clear that for both 1 and 2, the attack by osmic acid on the double bond occurs nearly if not completely exclusively from the side remote from the substituent at C-2 and -4 and thus provides further evidence that the preferred direction of attack by osmic acid on a double bond of this six-membered ring structure is determined by steric factors. In this respect it is similar to the effect of substituents in directing the attack of peroxy acids on the double bond of 3-substituted cyclohexenes (3). This steric effect is readily discerned in either of the conformations a and b of

compound 2 (Scheme 1). However, only in conformation a does compound 1 show such steric opposition by the C-2 methoxy group to the approach of osmic acid to the double bond on the same side of the ring occupied by the substituent. In conformation 1b, the double bond of compound 1 is readily accessible from either side of the ring. The fact that such a high proportion (84% at least) is obtained of the product resulting from attack of the double bond trans to the C-2 methoxy group indicates that compound 1 must prefer to a very large degree the conformation a in which the C-2 methoxy group is in the quasi axial orientation. It is well known that 2-alkoxytetrahydropyrans prefer that chair conformation in which the alkoxy group is axial. This phenomenon is known as the "anomeric effect" (4-6). This phenomenon is thought to be due to the polar character of the C2-OCH3 bond and the  $C_6 - O_1$  or  $C_2 - O_1$  bond of the 2-alkoxytetrahydropyran ring system (6-9). The similarity in these structural features of compound 1 leads to the reasonable assumption that the anomeric effect should be operative here also and thus conformer a would be preferred to conformer b. The great preponderance of attack by osmic acid on the side of the double bond remote from the C-2 methoxy group lends further support for this view.

## Experimental

Boiling points and melting points are uncorrected. The b.p. of the viscous sirup was obtained in a sublimation apparatus. The lower end of this apparatus was dipped into an oil bath and slowly heated. When the sirup started to deposit on the cold finger, the bath temperature was recorded as the b.p.

Elemental analyses were made by Mrs. Darlene Mahlow and Mrs. Andrea Dunn of this Department.

The 60 MHz p.m.r. spectra were made by Mr. R. Swindlehurst on a Varian A-60 spectrometer at  $35 \pm 1^{\circ}$ . The 100 MHz p.m.r. spectra and spin decoupling experiments were done by Mr. Glen Bigam and associates of this Department, using a Varian HR-100 MHz instrument at  $33 \pm 1^{\circ}$ . Unless otherwise specified, deuteriochloroform was the solvent used, with tetramethylsilane as internal or external reference. The couplings reported have been estimated from the spacings on the spectrum and are therefore approximate values.

The t.l.c. was done with Silica Gel G (E. Merck and Co.) as adsorbent. Iodine vapor was used to detect the spots.

Solvents were removed by rotary evaporator under vacuum unless otherwise stated.

#### Methyl 4-O-Methyl- $\alpha$ -DL-lyxopyranoside (6)

Osmium tetroxide (1.0 g, 3.39 mmol) in 4 ml of dry pyridine (2) was added to a solution of 0.563 g (3.90 mmol) of cis-2,5-dimethoxy-5,6-dihydro-2H-pyran (2) (10) in 9 ml of pyridine at room temperature. The solution was stirred for 20 h at room temperature and then treated with a solution of 1.8 g of sodium bisulfite in a mixture of 20 ml of pyridine and 30 ml of water and then stirred for an additional 4 h. The orange solution was extracted with methylene chloride ( $6 \times 25$  ml) and the extract dried  $(K_2CO_3)$  and filtered. The drying agent was washed with methylene chloride. The combined methylene chloride solutions were freed from solvent at room temperature under vacuum and gave 0.65 g of a sirup which showed two spots on a t.l.c. (solvent, 10% methanol in chloroform). Distillation at 70° at 0.05 mm gave 0.51 g (73%) of 6 as a colorless sirup.

Anal. Calcd. for  $C_7H_{14}O_5$ : C, 47.19; H, 7.92. Found: C, 46.99; H, 7.72.

The aqueous portion left after methylene chloride extraction was further extracted continuously for 48 h with methylene chloride and provided, after purification, 80 mg (11.4%) more of 6. The t.l.c. of this pure material showed only one spot.

The i.r. spectrum in carbon tetrachloride showed a narrow band at 3600 (OH) and a broad band at 3260–3540 cm<sup>-1</sup> (bonded OH). In highly dilute solution only one narrow band at 3590 cm<sup>-1</sup> occurred (unbonded OH). The 100 MHz p.m.r. spectrum in pyridine- $d_5$  showed a

doublet ( $J \sim 2.8$  Hz) at  $\tau$  5.05.

## Methyl 2,3-Di-O-acetyl-4-O-methyl-α-DL-lyxopyranoside (7)

A solution of 6 (0.51 g, 2.86 mmol) in 2.5 ml of dry pyridine and 2.5 ml of acetic anhydride was warmed for 0.5 h at 60° and then stirred overnight at room temperature. The bulk of the pyridine and excess acetic anhydride was removed by fractional distillation under vacuum (5-6 mm) at room temperature. The residual liquid in 10 ml of chloroform was treated with 10 ml of cold 3N aqueous ammonium hydroxide and the resulting solution

then extracted with chloroform (5  $\times$  25 ml). The chloroform extract was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and freed from solvent. The residual sirup crystallized from chloroformhexane; yield, 515 mg (69%), m.p. 79–82°, raised to 81–82.5° by two recrystallizations.

Anal. Calcd. for  $C_{11}H_{18}O_7$ : C, 50.38; H, 6.92. Found: C, 50.50; H, 6.87.

The i.r. spectrum in chloroform showed a strong band at  $1750 \text{ cm}^{-1}$  (--CO<sub>2</sub>---).

The 100 MHz p.m.r. spectrum showed the anomeric proton signal at  $\tau 5.41$  (doublet,  $J \sim 2.0$  Hz) and a multiplet (2H) at 4.79 due to H-2 and -3. Irradiation of the nucleus of H-1 at  $\tau 5.41$  resulted in loss of a small coupling in the multiplet at  $\tau 4.79$ . Double irradiation of H-1 ( $\tau 5.41$ ) and H-4 ( $\sim \tau 6.36$ ) produced an AB pattern for the signal of H-2 and -3 at  $\tau 4.79$  which appeared as a rather broad singlet. The loss of a large coupling in the signal at  $\tau 4.79$  due to this double irradiation shows that H-3 and -4 are *trans* diaxially disposed.

#### 4-O-Methyl-DL-lyxose (9)

A solution of 6 (0.1 g, 0.56 mmol) in 1.2 ml of p-dioxane and 3 ml of 1.5% aqueous sulfuric acid was refluxed for 4 h, then cooled, neutralized with barium carbonate, and filtered. The solid was washed with a 1.1 mixture of p-dioxane and water ( $4 \times 3$  ml). The combined filtrate and washings were freed from solvent and gave 80 mg of crude viscous sirup. Distillation provided 69 mg (75%) of colorless sirup boiling at 80° at 0.07 mm.

Anal. Calcd. for  $C_6H_{12}O_5$ : C, 43.90; H, 7.37. Found: C, 43.94; H, 7.45.

The 100 MHz p.m.r. spectrum (tetramethylsilane as external reference) of a solution of 9 in  $D_2O$  after standing for 16 h, showed two anomeric proton signals at  $\tau 4.72$  (doublet,  $J \sim 5$  Hz) and 4.83 (doublet,  $J \sim 1.5$  Hz) in the area ratio of 1.0:0.37. Both the 60 and 100 MHz p.m.r. spectra of 9 were identical to those of authentic 4-O-methyl-D-lyxose.

## Methyl 4-Deoxy- $\beta$ -DL-erythro-pentopyranoside (3)

The reaction of osmic acid with 1 (11) was carried out essentially as described above for the formation of 6 except that after decomposition of the osmate ester the solution was extracted continuously with methylene chloride. The extract was then worked-up as described for the isolation of 6. The crude product, obtained in almost quantitative yield, gave a 100 MHz p.m.r. spectrum whose amplified anomeric proton signal region gave only one anomeric proton signal, a doublet at  $\tau 5.40$  $(J \sim 4.0 \text{ Hz})$ . Distillation of the crude product in a sublimation apparatus afforded a colorless, viscous liquid in 93% yield, b.p. 72° at 1.5 mm. This showed a single spot on t.l.c. (5% methanol in chloroform).

Anal. Calcd. for  $C_6H_{12}O_4$ : C, 48.64; H, 8.16. Found: C, 47.92, 48.27; H, 7.85, 8.16.

An ether solution, cooled in ice, gave an hygroscopic solid, m.p.  $49-51.5^{\circ}$ .

The 100 MHz p.m.r. spectrum of the viscous oil showed the anomeric proton (H-1) signal as a doublet at  $\tau$  5.39  $(J \sim 4.0$  Hz). Irradiation of H-1 caused a collapse of the triplet (total  $J \sim 7.5$  Hz) for H-2 at  $\tau$  6.38 to a doublet  $(J \sim 3.5$  Hz). A one-proton multiplet at  $\tau$  5.97 with total width ~16 Hz remained unaffected. This, as well as its splitting pattern indicated that this multiplet at  $\tau$  5.97 was due to H-3.

#### Methyl 4-Deoxy-2,3-di-O-acetyl-β-DL-erythro-pentopyranoside (4)

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Compound 3 (0.4 g) was converted to its diacetate 4 by the same procedure used to prepare the diacetate 7 above. Crystals (505 mg, 81%) from methylene chloride – hexane, m.p.  $80-82.5^{\circ}$ , raised to  $82-83.5^{\circ}$  by two recrystallizations.

Anal. Calcd. for  $C_{10}H_{16}O_6$ : C, 51.72; H, 6.94. Found: C, 51.53; H, 6.71.

The i.r. spectrum (Nujol mull) showed a strong band at  $1750 \text{ cm}^{-1}$  (---CO<sub>2</sub>---).

The 100 MHz p.m.r. spectrum gave a triplet at  $\tau$  4.97 ( $J \sim 2.5$ -3.0 Hz) for H-2 and an eight-line multiplet for H-3 at 4.75 with total width  $\simeq$  19 Hz. Irradiation of H-1 at  $\tau$  5.36 (doublet,  $J \sim 2.5$  Hz) caused the triplet for H-2 at 4.97 to change to a doublet ( $J \sim 3.0$  Hz) thus corroborating the location of the H-2 signal. A slight sharpening of the eight-line multiplet at  $\tau$  4.75 occurred. This multiplet can be accommodated only if H-3 is axial. This information clearly confirms the structure and conformation of this diacetate as shown by 4.

## Methyl 4- Deoxy-2,3-di-O-methyl-β-DL-erythro-pentopyranoside (5)

Compound 3 was methylated by the following modification of the published general procedure (12). A solution of 3 (0.37 g, 2.5 mmol) in 5 ml of dry 1,2-dimethoxyethane (DME) was added dropwise over a period of 15 min to a stirred slurry of sodium hydride (0.15 g, 6.2 mmol) in 5 ml of dry DME containing 1 ml of methyl iodide (an excess). The mixture was stirred overnight at room temperature, then diluted with 50 ml of ether and filtered. The solvent was removed by fractional distillation. The residue was distilled in a two-bulb apparatus and gave 0.21 g (48%) of a colorless oil, b.p. 95° (oil bath temperature) at 11 mm,  $n_D^{27.5}$ , 1.4394.

Anal. Calcd. for  $C_8H_{16}O_4$ : C, 54.53; H, 9.15. Found: C, 54.68; H, 9.06.

C, 54.68; H, 9.06. The i.r. and 60 MHz p.m.r. spectra were consistent with the structure as shown by 5.

#### 4-Deoxy-DL-ribose (8)

Hydrolysis of 3 was carried out by the same procedure used above to hydrolyze 6. From 200 mg of 3 there was obtained 175 mg of crude product. Distillation in a sublimation apparatus gave 139 mg (76.8%) of a semisolid, b.p. 74-76° (oil bath temperature) at 0.09 mm. Anal. Calcd. for  $C_{5}H_{10}O_{4}$ : C, 44.77; H, 7.51. Found: C, 44.68; H, 7.57.

The i.r. spectrum (neat) showed a strong broad band at 3360 (OH) and two weak bands at 1720 (C=O) and 1650 cm<sup>-1</sup> (unknown).

The 60 MHz p.m.r. spectrum in D<sub>2</sub>O, with tetramethylsilane as external reference, was taken after the solution had stood at room temperature for a short time and showed one anomeric proton signal at  $\tau$  5.09 (doublet for H-1,  $J \simeq 5$  Hz). The spectrum, obtained this time at 42° after the solution had stood for 24 h, showed two anomeric proton signals as doublets, one at  $\tau$  5.1 and the other at 5.36. Expansion of these signals to a sweep width of 100 Hz gave  $J \simeq 5.2$  and  $J \sim 1.7$  Hz respectively with the signals in the area ratio of 1.0:0.42.

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