Acta Chemica Scandinavica B 29 (1975) 507—512

Synthesis of Methyl 2,6-Dideoxy-3-*C*-methyl-α-L-*xylo*-hexopyranoside ("Methyl α-Axenoside")

PER J. GAREGG and THOMAS NORBERG

Department of Organic Chemistry, Arrhenius Laboratory, University of Stockholm, S-104 05 Stockholm, Sweden

The synthesis of methyl 2,6-dideoxy-3-*C*-methyl-α-L-*xylo*-hexopyranoside and of the corresponding free sugar is described. The physical constants agree with those previously reported for methyl α-axenoside and axenose, respectively.

In 1973, Arcamone and co-workers described the isolation of a new branched sugar, axenose, from hydrolysates of axenomycin B, one of three antibiotics produced by *Streptomyces lysandri n.sp.* The sugar was obtained in crystalline form, as were the derived methyl α- and β-glycopyranosides and identified as 2,6-dideoxy-3-*C*-methyl-L-*xylo*-hexose.[1]

In the present paper we describe the synthesis of this sugar and its methyl α-L-glycopyranoside. The physical constants of the synthetic products confirm the structural assignment of axenose. Korte, Claussen and Snatzke have reported the synthesis of racemic 2,6-dideoxy-3-*C*-methyl-DL-*xylo*-hexose.[2] Howarth, Szarek and Jones have reported the synthesis of 2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-D-*xylo*-hexose (D-arcanose) thereby confirming the structure of the naturally occurring, corresponding L-enantiomer.[3] However, neither D-axenose nor its glycosides were synthesised at that time, since axenose was yet to be discovered in Nature. In designing the present synthesis, we preferred to start from L-fucose, which is more readily available than L-galactose, the required starting material for making axenose using a similar synthetic pathway to that described for the synthesis of D-arcanose.

L-Fucose was converted into 3,4-di-*O*-acetyl-L-fucal.[4,5] This glycal, upon treatment with acidic methanol afforded an anomeric mixture which was separated by column chromatography on silica gel. Deacetylation of each of the pure anomers of methyl 3,4-di-*O*-acetyl-2,6-dideoxy-L-*lyxo*-hexopyranoside afforded the crystalline glycosides Ia and Ib. Methyl 2,6-dideoxy-α-L-*lyxo*-hexopyranoside (Ia) was obtained in 51 % yield from 3,4-di-*O*-acetyl-L-fucal. Our constants for this compound (m.p. 58 – 59 °C, $[\alpha]_D^{20}$ −173°, chloroform) do not agree with those described by Brimacombe and Portsmouth [6] for the D-enantiomer (m.p. 70 – 72 °C, $[\alpha]_D^{16}$ +122°, chloroform) and the reason for this is not clear. The glycoside Ia was benzoylated in the 3-position in 64 % yield by treatment with benzoyl chloride and pyridine in chloroform at −5 to −10 °C. Surprisingly, partial benzoylation with *N*-benzoylimidazole in chloroform using the method described by Chittenden,[7] gave almost equal amounts of the 3- and 4-benzoates of Ia. This difference may indicate a difference in conformational equilibrium of Ia in the two experiments (−5 to −10 °C as compared to 62 °C using *N*-benzoylimidazole). The 3-*O*-benzoyl derivative II was characterized by NMR. The position of the benzoyl group is verified by the H-3 octet having the highest chemical shift (δ) of all the ring protons, as expected for a hydrogen atom attached to a benzoyloxy carbon. The spectral assignments were corroborated by spin decoupling experiments (Table 1). The 3-benzoyl derivative II was benzylated with benzyl trifluoromethanesulfonate as devised by Lemieux and Kondo.[8] The product III was debenzoylated to give the 4-benzyl ether IV in 58 %

Table 1. First-order chemical shifts and coupling constants of Ia-VIII (60 MHz NMR) Solvents: For sext, sextet; oct,

Substance	Chemical shifts (δ) downfield from TMS and multiplicity								
	H-1	H-2	H-2′	H-3	H-4	H-5	H-6	$OCOCH_3$	OCH_3
Ia 3,4-acetate [a]	4.87t	1.8–2.2m	1.8–2.2m	5.2–5.5m	5.1–5.3m	4.03q	1.13d	1.97s 2.15s	3.33s
Ia	4.87t	1.83±0.02m	1.83±0.02m	3.6–4.3m	3.6–4.3m	3.6–4.3 m	1.22d	–	3.35s
II [b]	4.83q	1.9–2.45m	1.9–2.45m	5.40 oct	3.92d	3.97q	1.27d	–	3.35s
III	4.92q	2.17m or 2.40m	2.40m or 2.17m	5.52 oct	3.80d	4.02q	1.23d	–	3.35s
IV	~4.75	1.87±0.02m	1.87±0.02m	3.8–4.2m	3.48d	3.92q	1.25d	–	3.28s
V	5.08q	3.14q	2.37sext	–	3.47t	4.13oct	1.32d	–	3.33s
VIa	4.82q	2.05q	1.58sext	–	3.03	4.28q	1.23d	–	3.35s
VIb	4.7	1.7–1.9m	1.7–1.9m	–	3.10	3.98 oct	1.28d	–	3.28s
VIIa	4.82q	1.4–2.2m	1.4–2.2m	–	3.13s	4.35q	1.25d	–	3.38s
VIIb	4.77q	1.7–2.0m	1.7–2.0m	–	3.20s	4.00q	1.28d	–	3.33s
VIII	7.39d	5.43q	–	–	3.55q	4.48 oct	1.48d	–	

[a] Confirmed by adding $Eu(DPM)_3$. [b] Confirmed by spin decoupling experiments.

yield from II. Ruthenium tetroxide oxidation [9] of IV afforded the 3-ulose derivative V in 97 % yield. Treatment of V with methylmagnesium iodide gave two main products, (yield 75 %) VIa and VIb in a ratio of 1:2.4. These were hydrogenated to give VIIa and VIIb, respectively. The stereochemical arrangement of these products at C-3 was demonstrated by strong intramolecular hydrogen bonding (C-3 OH to OCH_3) of VIIa and by the change in optical rotation of VIIa and VIIb upon the addition of cuprammonium hydroxide ("Cupra B"),[10] which caused a shift in molecular rotation at 436 nm of +1746° for VIIb (*lyxo* configuration). The corresponding shift for VIIa (*xylo* configuration) was +32°. The glycoside VIIa has physical constants identical to those of methyl α-axenoside.[1] Furthermore, hydrolysis of VIIa affords the corresponding free sugar with physical constants in agreement with those previously reported for the natural sugar.[1]

The reaction of the uloside V with methylmagnesium iodide thus gave a mixture of two products, the predominant one having the *lyxo*-configuration (VIb). This is in contradistinction to the results obtained when methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-hexopyranosid-3-ulose was similarly treated to give the corresponding 3-*C*-methyl-*xylo*-hexoside [3] in high yield. This difference probably reflects the stereochemical rigidity conferred by the 4,6-*O*-benzylidene group in the latter derivative. The NMR parameters for V are indicative of a skew-boat conformation or a dynamic conformational equilibrium averaging this conformation. In this conformation (Scheme 1) attack from either side of the pyranose ring is about equally hindered.

In preliminary experiments, treatment of V with the 1,3-dithiane anion [11] gave products having both the *xylo* and the *lyxo* configuration in a ratio of 1:1. The overall yield of VIa was, however, not improved and this route offers little, if any, advantage over the one shown in Scheme 1. Treatment of V with methyllithium afforded an olefinic product with NMR parameters suggesting structure VIII.

substance Ia D_2O, for all others $CDCl_3$. Observed multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; octet; m, multiplet.

				Coupling constants (Hz)									
CCH_3	$PhCH_2$	OH	Aromatic	$J_{1,2}$	$J_{1,2'}$	$J_{2,2'}$	$J_{2,3}$	$J_{2',3}$	$J_{2',4}$(?)	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
–	–	–	–	2.5	2.5				–	–		<1	6.5
–	–		–	2.5	2.5				–	–			6.5
–	–	2.27s	7.1–7.5m	2 or	3.5 or		6 or	11.5 or	–	–	3	<1	6.5
			7.8–8.1m	3.5	2		11.5	6					
–	4.7m		7.1–7.5m	1.5 or	4 or		5 or	11 or	–	–	3	<1	6.5
			7.9–8.1m	4	1.5		11	5					
–	~4.75 ABq		7.2–7.7m								3	<1	6.5
–	4.38d 4.61d $J_{H,H}$12		7.33	4.5	1.5	14	–	–	1.5	0	–	2	6.5
1.25s	4.67s	4.25s	7.35	4	1.5	14	–	–	1.5	0	–	<1	6.5
1.38s	4.7s	2.53s	7.35				–	–	–		–	1	6.5
1.23s	–	2.4,3.9 broad s	–	4	1.5				–	–	–	<1	6.5
1.38s	–	3.0 broad s	–	4	2	–	–	–	–	–	–	<1	6.5
	4.53d 4.83d $J_{H,H}$12		7.37	6	–	–	–	–	–	1.5	–	2	6.5

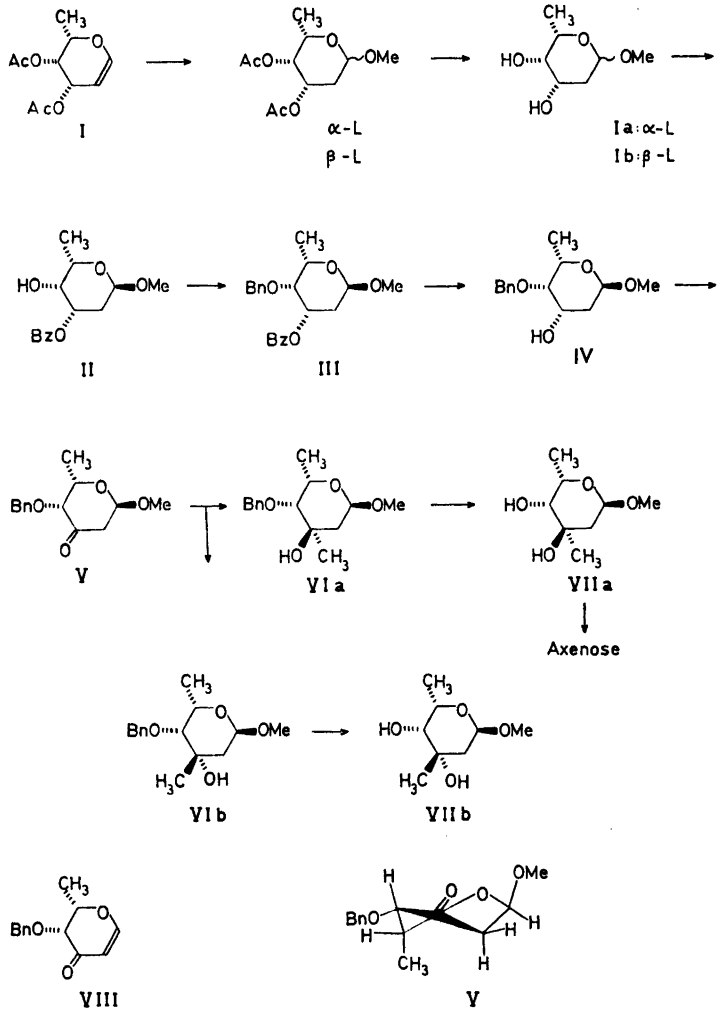
EXPERIMENTAL

General methods were the same as those described in a recent paper.[5] Column chromatography was performed on Silica Gel 60 (230–400 mesh, Merck).

Methyl 2,6-dideoxy-α-L-lyxo-hexopyranoside (Ia). 3,4-Di-*O*-acetyl-1,2,6-trideoxy-L-*lyxo*-hex-1-enopyranose ("di-*O*-acetyl-L-fucal") (4.80 g)[4,5] was dissolved in analytical grade methanol (200 ml). Acetyl chloride (1.94 ml) was added to provide approximately 0.5 % hydrochloric acid. After standing at room temperature overnight, the mixture was neutralized with silver carbonate (10 g), filtered and concentrated.[12] The mixture was reacetylated with pyridine and acetic anhydride (2:1) at room temperature overnight, concentrated and repeatedly co-distilled with toluene, yielding a syrup (5.70 g) which (TLC, toluene-ethyl acetate, 4:1) contained one major (R_F ~0.45) and two minor components (slightly lower R_F). GLC (150 °C) showed the presence of three components whose peak areas gave a ratio of 77:10:13. Chromatography using a column of silica gel (250 g) eluted with toluene, followed by a gradient containing up to 20 % ethyl acetate in toluene gave first the main fraction (3,4-acetate of Ia) (3.20 g) as a colourless syrup, a second component (0.28 g, β anomer) and a fraction (0.35 g) which was not characterized. Deacetylation of the major component with 3 % ammoniacal methanol (100 ml) at room temperature overnight and concentration afforded chromatographically pure, crystalline Ia (1.95 g) which, after recrystallization from diisopropyl ether had m.p. 58–59 °C, $[\alpha]_D$ −173° (*c* 0.5, chloroform) (Found: C 51.8; H 8.7. $C_7H_{14}O_4$ requires: C 51.8; H 8.7).

Similar deacetylation and work-up of the second component (methyl 3,4-di-*O*-acetyl-2,6-dideoxy-β-L-*lyxo*-hexopyranoside, Ib, 0.28 g) gave chromatographically pure crystals (0.15 g) which on recrystallization from di-isopropyl ether gave methyl 2,6-dideoxy-β-L-*lyxo*-hexopyranoside m.p. 108–109 °C, $[\alpha]_D$ +48° (*c* 0.5, chloroform). (Found: C 51.7; H 8.8. $C_7H_{14}O_4$ requires: C 51.8; H 8.7).

Methyl 3-O-benzoyl-2,6-dideoxy-α-L-lyxo-hexopyranoside (II). Methyl 2,6-dideoxy-α-L-*lyxo*-hexopyranoside (Ia) (3.55 g) was dissolved in dry chloroform (20 ml). Benzoyl chloride (3.08 g), dissolved in dry chloroform (20 ml) containing pyridine (10 ml) was added dropwise while the reaction mixture was maintained at −5 to −10 °C. After standing overnight at 0 °C and then for a further 24 h at room temperature, TLC (toluene-ethyl acetate, 3:2) showed the presence of II (major spot, R_F about 0.6) in addition to minor amounts of the dibenzoate, 4-benzoate, and starting material. The mixture was diluted with chloroform (100 ml) and the solution shaken sequentially with



Scheme 1. Bz = Ph – CO, Bn = Ph – CH_2.

water, ice-cold 2 M sulfuric acid, saturated aqueous sodium hydrogen carbonate, and water. The chloroform solution was dried over magnesium sulfate, filtered and concentrated giving a syrup, from which pure II (3.75 g) was obtained by crystallization from diethyl ether-hexane, m.p. 88–89 °C, $[\alpha]_D$ –156° (*c* 0.5, chloroform). (Found: C 63.1; H 6.7. $C_{14}H_{18}O_5$ requires: C 63.1; H 6.8).

*Methyl 4-O-benzyl-2,6-dideoxy-α-*L*-lyxo-hexopyranoside (IV).* A solution of the above monobenzoate II (3.21 g) and 2,6-lutidine (1.94 g) in dry chloroform (10 ml) was added dropwise, to a stirred solution (–60 °C) of benzyl trifluoromethanesulfonate prepared as described by Lemieux and Kondo [8] from benzyl alcohol (3.93 g), 2,6-lutidine (3.89 g), and trifluoromethanesulfonic anhydride (10.24 g) in chloroform (30 ml). After 48 h at –60 to –70 °C, more 2,6-lutidine (1.94 g) was added and the mixture poured into ice-cold, saturated aqueous sodium hydrogen carbonate (200 ml). The mixture was extracted with chloroform; the combined chloroform phases were shaken with, in turn, ice-cold 2 M sulfuric acid, aqueous sodium hydrogen carbonate and then water. The chloroform solution was then dried over magnesium sulfate, filtered and concentrated to a syrup containing one major product in addition to some unreacted II which had a lower mobility on TLC (toluene-ethyl acetate, 8:2). An aliquot of this syrup was purified by TLC (above solvent) to give a substance which gave an NMR spectrum (including decoupling experiments)

consistent with the substance being methyl 4-*O*-benzyl-3-*O*-benzoyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (III). The syrup was dissolved in methanol (500 ml), barium oxide (2.0 g) was added and the mixture was refluxed for 45 min. Neutralization with solid carbon dioxide and concentation gave a syrup which was taken up in diethyl ether, filtered to remove salts and concentrated. Column chromatography on silica gel (200 g) using hexane-diethyl ether (1:9) as eluent afforded chromatographically pure crystalline IV (1.76 g). Recrystallization from diisopropyl ether-hexane gave material with m.p. 82 °C $[\alpha]_D$ −149° (*c* 0.6, chloroform). (Found: C 66.7; H 8.1. $C_{14}H_{20}O_4$ requires C 66.6; H 8.0).

*Methyl 2,6-dideoxy-3-*C*-methyl-α-*L*-*xylo*-hexopyranoside (VIIa).* The 4-*O*-benzyl ether IV (700 mg) was stirred with a mixture of potassium periodate (3.82 g), ruthenium dioxide (50 mg), and potassium carbonate (700 mg) in ethanol-free chloroform (15 ml) and water (15 ml) at room temperature. TLC (hexane-diethyl ether, 2:8) indicated that no starting material remained after 6 h; therefore, propan-2-ol (1 ml) was added and the mixture stirred at room temperature for another 15 min. Then, the mixture was filtered through Celite, the aqueous layer extracted with chloroform and the combined chloroform extracts dried over magnesium sulfate, filtered and concentrated to give syrupy V (0.67 g). The structure of V was verified by IR [strong absorption at 1730 cm^{-1} (film)] and by NMR. The ulose V (670 mg) in dry benzene (10 ml) was added dropwise to a cooled (0 °C), stirred solution of methylmagnesium iodide (prepared from magnesium (1.010 g) and iodomethane (3.44 ml) in dry diethyl ether (50 ml)). The reaction mixture was allowed to stand at room temperature overnight, poured into ice-water (100 ml) and the aqueous phase was extracted with chloroform. The combined chloroform extracts were dried over magnesium sulfate, filtered and concentrated to a syrup (0.77 g). GLC (160 °C) gave three peaks in an approximate ratio of 2:5:14. Column chromatography on silica gel (200 mg), packed in toluene and eluted with toluene containing gradually increasing concentrations of ethyl acetate (up to 40 % in toluene) gave a fast-moving, unidentified, minor fraction (40 mg) and then VIa (160 mg) as a colourless syrup. The last compound to be eluted, VIb, (380 mg) was also obtained as a colourless syrup. Debenzylation of VIa (160 mg) in absolute ethanol (25 ml) by catalytic hydrogenation at room temperature and atmospheric pressure for 3 h in the presence of a catalytic amount of 10 % palladium on charcoal, filtration and concentration afforded crystalline VIIa (100 mg), m.p. 102 – 103 °C (from di-isopropyl ether), $[\alpha]_D$ −151° (*c* 0.5, chloroform) (Arcamone and co-workers [1] give m.p. 101 – 103 °C, $[\alpha]_D$ −142° (chloroform) for methyl α-axenoside, derived from the natural sugar). IR: 3580 cm^{-1} (sharp), 3535 cm^{-1} (broad) (*c* < 0.005 M in carbon tetrachloride).

*Methyl 2,6-dideoxy-3-*C*-methyl-α-*L*-lyxo-hexopyranoside (VIIb)* The above benzyl ether VIb (380 mg) was hydrogenated as described above for IVa. Recrystallization of the product from diisopropyl ether afforded VIIb (0.198 g), m.p. 77 – 78 °C, $[\alpha]_D$ −161° (*c* 0.5 in chloroform). IR: 3575 cm^{-1} (*c* 0.005 M in carbon tetrachloride). (Found: C 54.7; H 9.2. $C_8H_{16}O_4$ requires: C 54.5; H 9.2).

*2,6-Dideoxy-3-*C*-methyl-*L*-xylo-hexopyranose (axenose).* The above glycoside VIIa (28.4 mg) was hydrolyzed in 1 M aqueous hydrochloric acid at room temperature for 4 h. The solution was neutralized with silver carbonate, filtered and concentrated. TLC (ethyl acetate) showed the presence of a single component with a lower mobility than that of VIIa. Crystals (20.3 mg) were obtained from ethyl acetate. One recrystallization from ethyl acetate-hexane afforded crystals (15.3 mg) m.p. 103 – 106 °C. Further recrystallisation from the same solvents afforded material (13.1 mg), m.p. 106 – 108 °C, $[\alpha]_D$ −27° (*c* 0.32, water). Arcamone and co-workers report m.p. 111 – 112 °C, $[\alpha]_D$ −28.5° (water) for axenose.

Treatment of methyl 4-O-*benzyl-2,6-dideoxy-α-*L*-threo-hexopyranosid-3-ulose with methyllithium.* The uloside V (50 mg) was dissolved in dry diethyl ether and the solution was cooled to −20 °C. Methyllithium in diethyl ether (1 ml 1 M solution) was added at −20 °C and the solution was allowed to stand, first at this temperature for 20 min and then for a further 20 min at room temperature. Water was added and the mixture was extracted with chloroform. The combined chloroform solutions were shaken with water. Then chloroform solution was dried over magnesium sulfate, filtered and concentrated to a chromatographically homogeneous syrup (30 mg) (TLC, toluene-ethyl acetate 6:4). The NMR spectrum is consistent with the structure VIII. IR (chloroform) 1680 cm^{-1}.

Repetition of the above experiment at −78 °C and examination of the reaction mixture by TLC showed that VIII was formed together with minor amounts of VIb.

Optical rotations in cuprammonium hydroxide.[10] The optical rotations of the two glycosides VIIa and VIIb were measured at 436 nm in "Cupra B" (*c* 0.1 – 0.4) containing more than a ten-fold excess of copper. The optical rotations at the same wave-length of VIIa and VIIb in ammonium hydroxide was also determined. The results are given in the general part.

Acknowledgements. We are indebted to Professor Bengt Lindberg for his interest and to the Swedish Natural Science Research Council for financial support.

REFERENCES

1. Arcamone, F., Barbieri, G., Franceschi, G., Penco, S. and Vigevani, A. *J. Amer. Chem. Soc. 95* (1973) 2008.

2. Korte, F., Claussen, U. and Snatzke, G. *Tetrahedron 20* (1964) 1477.
3. Howarth, G. B., Szarek, W. A. and Jones, J. K. N. *Carbohyd. Res. 7* (1968) 284; *Chem. Commun.* (1968) 62.
4. Iselin, B. and Reichstein, T. *Helv. Chim. Acta 27* (1944) 1200.
5. Garegg, P. J., Lindberg, B. and Norberg, T. *Acta Chem. Scand. B 28* (1974) 1104.
6. Brimacombe, J. S. and Portsmouth, D. *Carbohyd. Res. 1* (1965) 128.
7. Chittenden, G. J. F. *Carbohyd. Res. 16* (1971) 495.
8. Lemieux, R. U. and Kondo, T. *Carbohyd. Res. 35* (1974) C 4.
9. Beynon, P. J., Collins, P. M., Doganges, P. T. and Overend, W. G. *J. Chem. Soc. C* (1966) 1131.
10. Reeves, R. E. *Methods Carbohyd. Chem. 5* (1965) 203.
11. Paulsen, H., Sinnwell, V. and Stadler, P. *Angew. Chem. Int. Ed. Engl. 11* (1972) 149.
12. Overend, W. G., Shafizadeh, F. and Stacey, M. *J. Chem. Soc.* (1951) 992.

Received December 13, 1974.