Carbohydrate Research, 65 (1978) 35–45

SYNTHESIS OF METHYL 4-AMINO-2,4,6-TRIDEOXY-3-*O*-METHYL-L-*arabino*-HEXOPYRANOSIDES (METHYL α- AND β-L-HOLANTOSAMINIDE) AND OF METHYL 4-AMINO-2,4,6-TRIDEOXY-3-*O*-METHYL-α-L-*lyxo*-HEXOPYRANOSIDE (METHYL α-L-3-EPIHOLANTOSAMINIDE)

CLAUDE MONNERET, CHRISTIANE CONREUR, AND QUI KHUONG-HUU
Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette (France)
(Received May 20th, 1977; accepted for publication, July 19th, 1977)

ABSTRACT

Methyl 4-amino-2,4,6-trideoxy-3-*O*-methyl-β-L-*arabino*-hexopyranoside was synthesized in eight steps, in 40% overall yield, from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside. The inversion of configuration at C-5 was achieved through 5,6-unsaturated methyl 2,6-dideoxy-3-*O*-methyl-α-D-*erythro*-hex-5-enopyranoside, followed by stereospecific reduction to give methyl β-L-diginoside. Treatment of methyl 2,6-dideoxy-3-*O*-*p*-tolylsulfonyl-α-L-*arabino*-hexopyranoside with sodium methoxide afforded stereoselectively the 3-*O*-methyl derivative, which was converted into a mixture of methyl α-L-holantosamine and its 4-amino-L-*lyxo* epimer. The latter compound was also synthesized stereospecifically *via* the 4-azido derivative.

INTRODUCTION

Holarosine A [3β-(4-amino-2,4,6-trideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)oxy-14β-hydroxy-5β,17α-card-20(22)-enolide] and holantosines C and D have been isolated from the leaves of *Holarrhena antidysenterica*[1]. The three compounds are α-glycosides of a new aminodeoxy sugar, L-holantosamine or 4-amino-4-deoxyoleandrose, the aglycon being holantogenin for the first compound and anhydroholantogenin[2] for the two last-named compounds. The β- and α-methyl glycosides of *N*-acetyl-L-holantosamine (**13** and **28**) were obtained by hydrolysis of these aminodeoxyglycosteroids. The relative configuration of the aminodeoxy sugar moiety was established by ^{1}H-n.m.r. at 220 MHz with irradiation. The absolute configuration was deduced from the same spectrum, particularly from the small splitting of the anomeric proton. It is well known[3] that, in the case of the α-L series of natural glycosides, the steroid moiety is preferentially in the axial position and, consequently, the anomeric proton is equatorial.

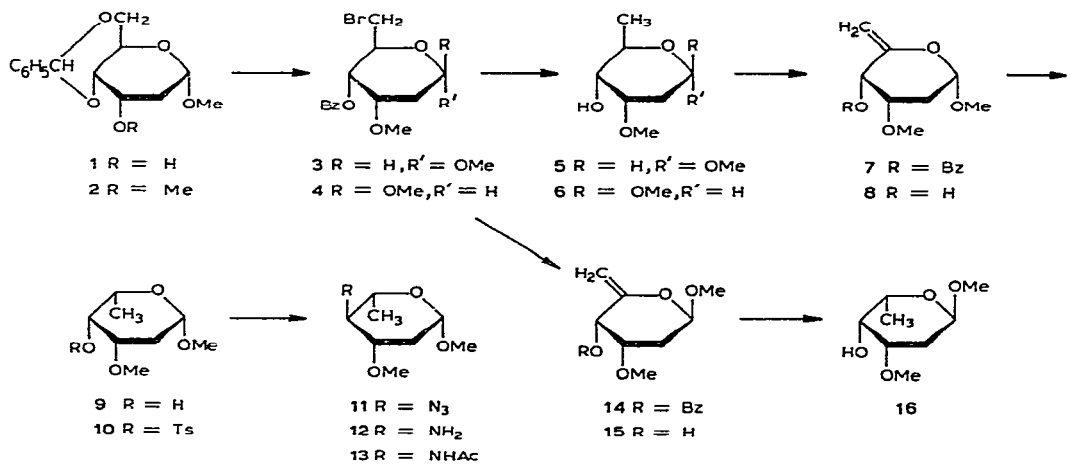
We report here the synthesis of methyl 4-amino-2,4,6-trideoxy-3-*O*-methyl-β- and -α-L-*arabino*-hexopyranosides (**12** and **27**) and of methyl 4-amino-2,4,6-trideoxy-

3-*O*-methyl-α-L-*lyxo*-hexopyranoside (**25**). This work is a part of a program designed to afford a convenient synthesis of 3-amino-2,4,6-trideoxyhexopyranoses in order to provide new sugars to couple with such aglycons as daunomycinone[4]. Replacement of the daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) sugar moiety of daunomycin and adriamycin[4] has already been reported with such closely related sugars as ristosamine[5] (3-amino-2,3,6-trideoxy-L-*ribo*-hexose), acosamine[6] (3-amino-2,3,6-trideoxy-L-*arabino*-hexose), 3-amino-2,3-dideoxy-L-*lyxo*-hexose[7], and 3-amino-2,3,4,6-tetradeoxy-L-*threo*-hexose (4-deoxydaunosamine)[8]. Recently, the synthesis of ristosamine[9] and acosamine[10] has been published, thereby making these sugars available for coupling reactions with the aglycons of adriamycin and daunomycin. In contrast, few investigations of the biological activity of new analogs possessing a sugar moiety having the amino group at C-4 rather than C-3 have been published[11].

RESULTS AND DISCUSSION

Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**1**) was prepared from methyl α-D-glucoside in four steps[12,13]. Methylation of the free HO-4 was achieved, either with dimethyl sulfate[14] or with methyl iodide and sodium hydride[15], to afford **2** in 95% yield. Treatment of **2** by the general procedure of Hanessian[16] led only to **3** in an 80% yield or to a mixture of **3** and **4** according to the experimental procedure during extraction (see Experimental section). The structures of both anomers **3** and **4** were established by means of elementary analysis, and i.r. and n.m.r. spectrometry (see Tables I and II). Anomerization may also occur when **3** is kept at room temperature, or even at 0° for a long time. Reduction of **3** and **4** with lithium aluminum hydride afforded the known[17] methyl α- (**5**) and β-D-cymaroside (**6**), respectively.

Dehydrobromination of **3** with silver fluoride[18], according to the procedure used by Horton and Weckerle[19] in the synthesis of daunosamine, gave, in 80% yield

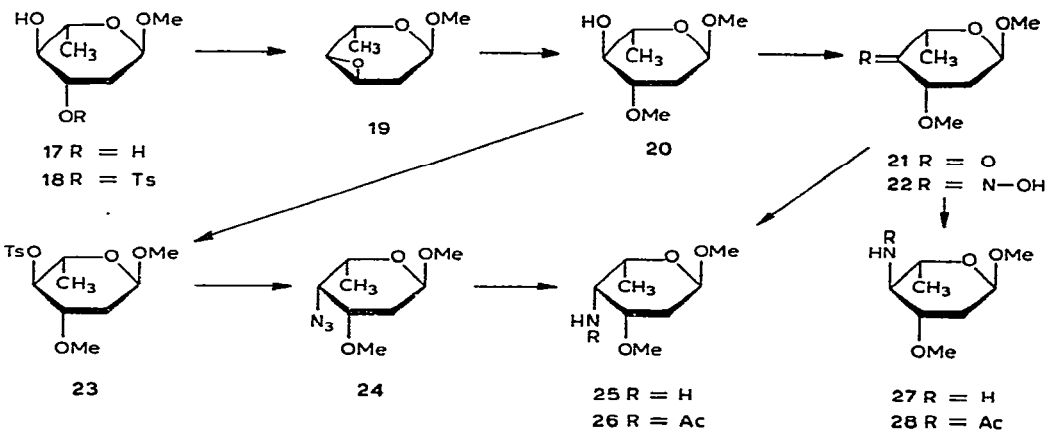


after purification, the 5,6-unsaturated derivative **7**. *O*-Deacylation of **7** by catalytic transesterification afforded quantitatively **8**, which was hydrogenated in the presence of palladium-on-barium sulfate to give stereospecifically syrupy methyl 2,6-dideoxy-3-*O*-methyl-β-L-*lyxo*-hexopyranoside (**9**, methyl β-L-diginoside). The structure of **9** was supported by analytical and physical data (see Tables I and II). Acid hydrolysis gave a free sugar, identified as L-diginose[20]. An amino group was introduced on C-4 by means of the three following steps. Tosylation of the hydroxyl group of **9** gave **10** in 65% yield, and the azidodeoxyglycoside **11** was obtained quantitatively by azidolysis in *N,N*-dimethylformamide at 100° for 18 h. Catalytic hydrogenation in methanol in the presence of palladium-on-charcoal afforded methyl 4-amino-2,4,6-trideoxy-3-*O*-methyl-β-L-*arabino*-hexopyranoside (**12**), the *N*-acetyl derivative (**13**) of which was identical with an authentic sample of the methyl β-glycoside of *N*-acetyl-L-holantosamine[1].

The sequence of dehydrobromination and *O*-deacylation was also applied to the β anomer **4** to give **15**. A stereospecific hydrogenation of **15** was not observed, unlike the case of **8**, and two compounds (**6** and **16**) were obtained in the ratio 3:1. The orientation of the anomeric methoxyl group influenced the stereochemistry of the hydrogenation of the 5,6-unsaturated glycoside. This result is in agreement with previous results on the hydrogenation of 5-enopyranosides in the D-*xylo* series where the α-anomeric methyl group was shown to be the dominating influence for the specific formation of β-L-*ido* derivatives[21].

The structures of **6** and **16** were established to belong to the D and L series, respectively, and to be methyl 2,6-dideoxy-3-*O*-methyl-β-D-*ribo*-hexopyranoside or methyl β-D-cymaroside (**6**) and methyl 2,6-dideoxy-3-*O*-methyl-α-L-*lyxo*-hexopyranoside or methyl α-L-diginoside (**16**), respectively. The difference between the molecular rotations of **5** and **6** was in good agreement with the literature data[22]. As in the case of **9**, the hydrolysis of **16** gave L-diginose[20].

The 3-*p*-toluenesulfonate **18** was prepared according to the method of Marsh *et al.*[23] and Sztarickskai *et al.*[24] in their respective synthesis of daunosamine and



ristosamine. Reaction of **18** with methanolic sodium methoxide gave the epoxide[9,23] **19**, which under more drastic conditions afforded with high stereoselectivity (88% yield) the 3-*O*-methyl sugar **20**, namely methyl α-L-oleandroside[25]. Compound **20** could be obtained from **18** without isolation of the epoxide **19**. Oxidation of **20** with pyridinium chlorochromate[26] afforded the keto sugar **21** in 50% yield. No better yield was observed with such other methods, such as dimethyl sulfoxide and dicyclohexylcarbodiimide[27], or ruthenium oxide[28]. Oximation[29] of **21** gave, in 90% yield, the crystalline oxime **22** which was reduced with lithium aluminum hydride, followed by acetylation in methanol, to afford in 50% yield a mixture containing approximately equal amounts of the L-*arabino* methyl α-glycoside **28** and of the corresponding L-*lyxo* compound **26**. The latter compound was obtained stereospecifically as methyl α-L-glycoside from **20**. Tosylation of **20** led to **23** in 90% yield, and azidolysis in hexamethylphosphoramide at 100° gave the azido compound **24** (85% yield). Catalytic hydrogenation of this compound in methanol in the presence of 10% palladium-on-charcoal afforded quantitatively the L-*lyxo* derivative **25**, further transformed into the *N*-acetyl derivative **26**. The structure of this compound was supported by analytical and spectral data (see Tables I and II), and by comparison with an authentic sample[1].

EXPERIMENTAL

General methods. — Melting points were determined with a Büchi apparatus and are uncorrected. A Perkin–Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r. spectra were recorded with a Perkin–Elmer Model 257. N.m.r. spectra were recorded at 60 Mz with a Varian A-60 or at 90 Mz with a Brucker HX 90E spectrometer; chemical shifts are given in p.p.m. and tetramethylsilane was the internal standard (δ 0,00); spin-coupling values are given in Hz (see Tables I and II). Microanalyses were performed by the Service Central de Microanalyse du C.N.R.S. Kieselgel G (type 60, Merck) activated at 120° was the support for t.l.c. with the following solvents (v/v): *A*, 7:1 cyclohexane–ethyl acetate; *B*, 1:1:1 pentane–ethyl acetate–dichloromethane; *C*, 2:1:1 cyclohexane–ethyl acetate–dichloromethane; *D*, 19:1 dichloromethane–methanol; *E*, 9:1 dichloromethane–methanol.

Methyl 4,6-O-benzylidene-2-deoxy-3-O-methyl-α-D-ribo-hexopyranoside (**2**). — See ref. 2 or the following procedure: To a solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside[12] (**1**, 2.4 g, 14 mmol) in *N*,*N*-dimethylformamide (3 ml) were added successively sodium hydride (1 g) and, after cooling to 0°, methyl iodide (3 ml, 48 mmol). The mixture was stirred overnight, and the excess of sodium hydride destroyed by adding a few drops of methanol. Extraction with 1:1 (v/v) benzene–ether afforded, after repeated washing with water and evaporation of the solvent *in vacuo*, crystalline **2** (2.3 g, yield 98%), m.p. 99°, $[\alpha]_D^{20}$ +125° (*c* 1, chloroform).

Methyl 4-O-benzoyl-2,6-dideoxy-3-O-methyl-α-D-ribo-hexopyranoside (**3**). — To a solution of **2** (6.6 g, 23 mmol) in dry carbon tetrachloride (300 ml) were added

TABLE I

^{1}H-N.M.R. SPECTRAL DATA AT 60 MHz FOR COMPOUNDS 2–4, 6–7, 9–16, 18–26, AND 28

Compound[a]	*Chemical shifts* (δ)[b]							
	H-1 ($J_{1,2a}$)	*H-2a* ($J_{2a,2e}$)	*H-2e* ($J_{1,2e}$)	*H-3* ($J_{2a,3}$)	*H-4* ($J_{3,4}$)	*H-5* ($J_{4,5}$)	*H-6* ($J_{5,6}$)	OCH_3
2	4.63 (5)	1.78m (15)	2.20m (1)	← 4.0–4.60m → (5)		← 3.50–3.80m →		3.33, 3.48
3	4.81 (4)	1.93m (15)	2.30m (2)	3.95m (4)	5.10dd (3.5)	4.61m (9.5)		3.40, 3.45
4	4.81 (9)	1.77m (14)	2.27m (2.5)	3.95m (3)	5.10dd (2.5)	← 4.10–4.50m → (9)		3.41, 3.60
6	4.56 (9)	1.51m (14)	2.25m (3)	(3)	3.21dd (3)	(9)	1.28d (6.5)	3.43, 3.45
7	4.61 (5)	2.10m (8)	2.27m (5)	(1)	5.78d (2.5)		4.73, 4.78	3.36, 3.52
9	4.22 (10)	← 1.60–2.35m →	(3)	4.45–4.80m			1.33d (6.5)	3.33, 3.40
10	4.38 (9)	1.63m (14)	1.95m (2.8)	(9)	4.86d (2.5)	3.61q (1)	1.28d (6.5)	3.23, 3.47
11	4.33 (10)	1.44m (12.5)	2.37m (2)	←——2.80–3.50m —— (10)			1.37d (5.5)	3.45, 3.50
12[c]	4.36 (10)		(2)				1.31d (6)	3.38, 3.50
13	4.39 (9.3)		(2)				1.26d (6)	3.33, 3.50
14[c]	5.04 (1)	2.29m (14)	2.04m (1)	3.89m (11)	5,94m (3.2)		4.78	3.39, 3.43
15	4.85 (3)	2.23m (14)	1.96m (3)	(11)	4.32d (3)		4.58, 4.62	3.35 (6H)
16	4.78 (2)	← 1.75–2.30m →	(2)	←——3.30–4.0m —— (11)			1.30d (6.5)	3.30, 3.37
18	4.70 (2)	← 1.40–2.30m →	(2)	4.60–5.0m	← 3.10–3.80m → (11)		1.28d (6.5)	3.28
19	4.66 (3)	← 1.35–2.30m →	(3)	3.22m (11)	3.0d (11)	4.16q (11)	1.40d (6.5)	3.36
20	4.73 (3.5)	1.50m (13)	2.27m (1.5)	(11)	3.09m (9)	(9)	1.30d (6.5)	3.30, 3.36
21	4.78 (3)	2.03m (13)	2.53m (1)	4.16dd (11)		4.30q (11)	1.30d (6.5)	3.35, 3.38
22	4.85 (5)	1.86m (14)	2.41m (5)	4.41dd (5)		4.95q (5)	1.47d (6.5)	3.25, 3.40
23[c]	4.73 (4)	1.57m (13)	2.22m (1.5)	(11)	4.24m (9)	3.77m (9)	1.32d (6)	3.35, 3.39
24	4.80dd (2.5)	← 1.50–2.50m →	(2.5)	←——3.60–4.10m —— (13)		(1)	1.28d (6)	3.0
25[c]	4.56dd (1.5)	← 1.40–2.00m →	(1.5)	← 3.00–3.65m →		3.95m (2)	1.26d (6.5)	3.35, 3.38
26[c]	4.77dd (3.5)	1.62m (13.5)	1.95m (1)	3.69m (12)	4.41dd (3.5)	3.95m (1.5)	1.16d (6)	3.32, 3.37
28	4.81dd (4.5)		(1.5)				1.26d (6)	3.32 (6H)

[a]In chloroform-*d*. [b]First order couplings, Hz, in parentheses. Signal multiplicities: d, doublet; m, multiplet; s, singlet; q, quadruplet. [c]90-MHz spectrum.

TABLE II

^{13}C-N.M.R. SPECTRAL DATA FOR COMPOUNDS **5**, **6**, **9**, **11–13**, **20**, AND **24–26**

Compound[a]	*Chemical shifts (p.p.m.)*[b]						
	C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OCH_3-1 and -3*
5	97.3	31.0	75.5[c]	72.2[c]	64.4	17.9	55.4/56.9
6	98.7	33.4	78.6[c]	77.2[c]	72.0	18.2	56.3/57.0
9	101.0	31.4	78.0	70.5[c]	67.1[c]	17.7	55.7/56.3
11	100.7	36.1	80.0	67.7[c]	70.7[c]	18.7	56.5/56.5
12	100.9	35.3	81.0	58.4	73.2	18.2	56.1/56.4
13	100.6	36.0	77.0[c]	56.9	75.6[c]	18.2	55.6/56.4
17	98.3	37.2	68.7[c]	77.5	67.5[c]	17.7	54.5
20	98.4	33.9	78.4[c]	75.9[c]	67.4	17.8	54.6/56.4
25	98.8	29.4	75.5	51.0	65.6	17.4	54.7/55.4
26	98.6	31.6	73.4	48.6	64.9	17.2	54.9/56.1
24	98.7	30.4	75.6	62.4[c]	64.7[c]	17.9	54.9/55.9

[a]Spectrum recorded at room temperature in chloroform-*d* solution on a Bruker HX-90E, Fourier-transform spectrometer at 22.63 MHz. [b]From external tetramethylsilane peak. [c]Assignments can be inversed on a same horizontal line.

N-bromosuccinimide (4.8 g, 27 mmol) and barium carbonate (8 g). The mixture was boiled under reflux for 2 h and, after cooling, filtered. The clear filtrate was diluted with dichloromethane (200 ml) and washed successively with water, aqueous sodium hydrogencarbonate, dried (sodium sulfate), and concentrated to a volume of ~10 ml. This solution was applied to a column of Florisil (200 g) with dichloromethane as eluent. In the first fractions (1, 2, and 3) (450 ml each), elution gave pure **3** (yield 7 g, 83%); an analytical sample was recrystallized from cyclohexane, m.p. 67°, $[\alpha]_D^{20}$ +137° (*c* 1, chloroform); ν_{max}^{Nujol} 1735 cm^{-1} (CO ester).

Anal. Calc. for $C_{15}H_{19}BrO_5$ (359.05): C, 50.17; H, 5.29; Br, 22.25; O, 22.28. Found: C, 49.87; H, 5.29; Br, 22.26; O, 22.18.

*Methyl 4-O-benzoyl-2,6-dideoxy-3-O-methyl-β-*D-ribo-*hexopyranoside* (**4**). — Compound **2** (2.9 g, 10 mmol) was treated as just described but, after filtration, the filtrate was evaporated to dryness *in vacuo*. During this operation a spot(R_F 0.4) supplementary to that of **3** (R_F 0.3) appeared on t.l.c. (solvent *A*). Extraction with dichloromethane as described for **3** afforded a syrup (3 g, 80%). Separation of the two products by chromatography on Kieselgel H (type 60, Merck; 150 g; column of 40 mm diameter; solvent *A*; 20-ml fractions) gave **4** in fractions 35–110 (1.8 g) and in fractions 137–200 **3** (0.9 g). A sample of **4** was recrystallized from cyclohexane, m.p. 65°, $[\alpha]_D^{20}$ +2° (*c* 1,2, chloroform); ν_{max}^{Nujol} 1735 cm^{-1} (CO ester).

Anal. Calc. for $C_{15}H_{19}BrO_5$ (359.05): C, 50.17; H, 5.29; Br, 22.25; O, 22.28. Found: C, 50.33; H, 5.35; Br, 22.42; O, 22.33.

*Methyl 2,6-dideoxy-3-O-methyl-α-*D-ribo-*hexopyranoside* (*methyl α-*D-*cymaroside*) (**5**). — To a solution of **3** (400 mg, 1.1 mmol) in tetrahydrofuran (50 ml) was added lithium aluminum hydride (400 mg). After being stirred overnight at room

temperature, the mixture was diluted with ether, and the excess of reducing agent was eliminated by careful addition of saturated sodium sulfate. After filtration, evaporation of the solvent *in vacuo* gave **5** (195 mg), m.p. 35°; $[\alpha]_D^{20}$ +205° (*c* 1, methanol); lit.[17] m.p. 32–35°, $[\alpha]_D^{27}$ +212°, $[M]_D^{27}$ +373°.

*Methyl 2,6-dideoxy-3-O-methyl-β-*D-ribo-*hexopyranoside* (*methyl β-*D-*cymaroside*) (**6**). — Compound **6** was obtained from **4** in a way similar to that described for **5**, m.p. 30°, $[\alpha]_D^{20}$ +7° (*c* 1, methanol), $[M]_D^{20}$ +12°; $[M]_D$ of **5** − $[M]_D$ of **6** = +360°.

Anal. Calc. for $C_8H_{16}O_4$ (176.21): C, 54.53; H, 9.15; O, 36.32. Found: C, 54.65; H, 9.32; O, 36.48.

*Methyl 4-O-benzoyl-2,6-dideoxy-3-O-methyl-α-*D-erythro-*hex-5-enopyranoside* (**7**). — A mixture of **3** (7 g, 20 mmol) and dry silver fluoride (8 g, 34 mmol) in dry pyridine (40 ml) was treated according to the procedure of Horton and Weckerle[19] to give **7** (4.48 g, yield 80%) as a syrup homogeneous on t.l.c. (solvent *A*); $[\alpha]_D^{20}$ +84° (*c* 1.26, chloroform); ν_{max}^{film} 1710 cm^{-1} (CO ester).

Anal. Calc. for $C_{15}H_{18}O_5$ (278.29): C, 64.73; H, 6.52; O, 28.75. Found: C, 64.46; H, 6.55; O, 28.60.

*Methyl 2,6-dideoxy-3-O-methyl-α-*D-erythro-*hex-5-enopyranoside* (**8**). — A solution of **7** (4 g, 14.3 mmol) in absolute methanol (30 ml) was treated with M sodium methoxide (0.5 ml) and processed as described by Horton and Weckerle[19] to give a syrup (1.25 g, yield 98%) that was not purified but immediately hydrogenated.

*Methyl 2,6-dideoxy-3-O-methyl-β-*L-lyxo-*hexopyranoside* (*methyl β-*L-*diginoside*) (**9**). — A solution of **8** (1 g, 5.7 mmol) in methanol (15 ml) was hydrogenated in the presence of 10% palladium-on-barium sulfate (200 mg) at atmospheric pressure. After 3 h, the catalyst was filtered off and the methanol evaporated *in vacuo* to give **9** (0.99 g, 99%) as a syrup homogeneous on t.l.c. (solvent *B*). A sample was distilled *in vacuo* (0.5 torr) at 60°, $[\alpha]_D^{20}$ +40° (*c* 0.35, chloroform), $[M]_D^{20}$ +78°; ν_{max}^{film} 3460 cm^{-1} (OH).

Anal. Calc. for $C_8H_{15}O_4$ (176.21): C, 54.53; H, 9.15; O, 36.32. Found: C, 54.25; H, 9.30; O, 36.43.

*Methyl 2,6-dideoxy-3-O-methyl-4-O-tosyl-β-*L-lyxo-*hexopyranoside* (**10**). — To a solution of **9** (2 g, 11 mmol) in dry pyridine (10 ml) was added *p*-toluenesulfonyl chloride (3 g, 15 mmol), and the mixture was kept for 2 days at room temperature. After addition of crushed ice, the mixture was extracted with dichloromethane. The organic layer was washed with M aqueous sulfuric acid (2 × 20 ml) and with a saturated aqueous solution of sodium hydrogencarbonate. Evaporation *in vacuo* afforded crystalline **10** (2.6 g). Filtration through a column of Florisil (52 g) with dichloromethane as solvent gave pure **10** (2.4 g, 65%), which was recrystallized from ether, m.p. 66–68°, $[\alpha]_D^{20}$ −8° (*c* 1, chloroform).

Anal. Calc. for $C_{15}H_{22}O_6S$ (330.33): C, 54.54; H, 6.71; O, 29.06. Found: C, 54.41; H, 6.66; O, 28.79.

*Methyl 4-azido-2,4,6-trideoxy-3-O-methyl-β-*L-arabino-*hexopyranoside* (**11**). — A solution of **10** (1.17 g, 3.55 mmol) in *N*,*N*-dimethylformamide (15 ml) was heated overnight at 100° with sodium azide (0.9 g, 16 mmol). T.l.c. (solvent *C*) indicated that

no starting material remained. After addition of water, the solution was extracted with 1:1 (v/v) benzene–ether. The extract was washed with water (5 × 10 ml), dried (sodium sulfate), and evaporated *in vacuo* to give crystalline **11** (700 mg, 99%) which was recrystallized from cyclohexane, m.p. 68–69°, $[\alpha]_D^{20}$ +5° (*c* 1.5, chloroform); ν_{max}^{Nujol} 2100 cm^{-1} (azide).

Anal. Calc. for $C_8H_{15}NO_3$ (201.22): C, 47.75; H, 7.51; N, 20.88; O, 23.85. Found: C, 47.82; H, 7.45; N, 21.02; O, 23.90.

*Methyl 4-amino-2,4,6-trideoxy-3-O-methyl-β-*L-arabino-*hexopyranoside* (**12**). — A solution of **11** (200 mg, 1 mmol) in methanol (20 ml) was hydrogenated in the presence of 10% palladium-on-charcoal (100 mg) at atmospheric pressure, overnight. The catalyst was filtered off, and the filtrate concentrated to a syrup (200 mg, 100%) homogeneous on t.l.c. (solvent *D*), $[\alpha]_D^{20}$ +87° (*c* 2, chloroform).

Anal. Calc. for $C_8H_{17}NO_3$ (177.22): C, 54.83; H, 9.78; N, 7.99; O, 27.39. Found: C, 54.77; H, 9.86; N, 8.17; O, 27.12.

*Methyl 4-acetamido-2,4,6-trideoxy-3-O-methyl-β-*L-arabino-*hexopyranoside* (**13**). — To a solution of **12** (200 mg, 0.92 mmol) in dry methanol (20 ml) was added acetic anhydride (0.5 ml). After being stirred overnight at room temperature the solution was evaporated *in vacuo* to give **13** (205 mg), m.p. 227–229°, $[\alpha]_D^{20}$ +50° (*c* 0.8, chloroform) {lit.[1] m.p. 212°, $[\alpha]_D^{20}$ +41° (*c* 1, chloroform)}; ^1H- and ^{13}C-n.m.r. identical to those of the natural compound.

*Methyl 4-O-benzoyl-2,6-dideoxy-3-O-methyl-β-*D-erythro-*hex-5-enopyranoside* (**14**). — A mixture of **4** (1.6 g, 4.4 mmol) and dry silver fluoride (1.45 g, 6 mmol) in dry pyridine (10 ml) was treated according to the procedure of Horton and Weckerle[19] to afford **14** (1 g, 80%) as a syrup homogeneous on t.l.c. (solvent *A*), $[\alpha]_D^{20}$ −61.5° (*c* 2, chloroform); ν_{max}^{film} 1725 (CO ester), 1670 (C=C), 1600 and 1590 cm^{-1} (Ar).

Anal. Calc. for $C_{15}H_{18}O_5$ (278.29): C, 64.73; H, 6.52; O, 28.75. Found: C, 64.78; H, 6.77; O, 28.39.

*Methyl 2,6-dideoxy-3-O-methyl-β-*D-erythro-*hex-5-enopyranoside* (**15**). — Compound **14** (716 mg, 2.6 mmol) gave **15** (440 mg, 98%) as described for the preparation of **6**. This compound was not purified but immediatly hydrogenated.

*Methyl 2,6-dideoxy-3-O-methyl-α-*L-lyxo-*hexopyranoside* (*methyl α-*L-*diginoside*) (**16**). — A solution of **15** (2 g, 10.4 mmol) in methanol (30 ml) was hydrogenated as described for **8**. The crude product (1.7 g) showed two spots on t.l.c. (solvent *E*). Chromatography on silica gel (100–200 mesh) afforded **6** (680 mg) in the first fraction, a mixture of **6** and **16** in the following fractions (280 mg, ratio 1:1), and then **16** as a pure compound (140 mg) in the last fractions. Purification of fractions 2 and 3 (280 mg) by preparative chromatography gave additional pure **6** (140 mg, total yield 820 mg, 75%) and **16** (140 mg, total yield 280 mg, 25%) as a syrup, $[\alpha]_D^{20}$ −70° (*c* 0.5, chloroform), $[M]_D^{20}$ −123°, $[M]_D$ of **9** − $[M]_D$ of **16** = +201°.

Anal. Calc. for $C_8H_{16}O_4$ (176.21): C, 54.53; H, 9.15; O, 36.32. Found: C, 54.62; H, 9.22; O, 36.42.

*Methyl 2,6-dideoxy-3-O-methyl-α-*L-arabino-*hexopyranoside* (*methyl α-*L-*oleandroside*) (**20**). — (*a*) *From* **18**. A solution of **18** (950 mg, 2.84 mmol) was heated

under reflux overnight with sodium methoxide in absolute methanol (1 g of sodium in 60 ml of methanol). After filtration through Amberlite IR 120(H^+) ion-exchange resin, addition of sodium hydrogencarbonate and filtration, the solvent was evaporated and the residue dissolved in dichloromethane. Evaporation after filtration gave **18** as a syrup (204 mg, 88%), homogeneous on t.l.c. (solvent *C*), $[\alpha]_D^{20}$ −100° (*c* 1, chloroform); lit.[25] $[\alpha]_D^{24}$ −105° (chloroform).

Anal. Calc. for $C_8H_{16}O_4$ (176.21): C, 54.53; H, 9.15; O, 36.32. Found: C, 54.67; H, 9.23; O, 36.33.

(*b*) *From* **19**. A sample of **19** was treated as just described to give pure **20** (85 mg).

*Methyl 2,6-dideoxy-3-*O*-methyl-α-*L*-*threo*-hexopyranosid-4-ulose* (**21**). — To a solution of **20** (100 mg, 0.56 mmol) in dry dichloromethane (5 ml) was added pyridinium chlorochromate[26] (150 mg, 0.7 mmol), and the mixture was kept at room temperature with stirring for 24 h. Extraction with ether afforded pure **21** (70 mg), $[\alpha]_D^{20}$ −245° (*c* 3,3, chloroform); ν_{max}^{film} 1740 cm^{-1} (CO).

Anal. Calc. for $C_8H_{14}O_4$ (174.19): C, 55.16; H, 8.10; O, 36.74. Found: C, 55.22; H, 8.04; O, 36.57.

*Methyl 2,6-dideoxy-3-*O*-methyl-α-*L*-*threo*-hexopyranosid-4-ulose oxime* (**22**). — The ketone **21** (174 mg, 1 mmol) was oximated by the procedure described by Beynon *et al.*[29] to afford crystalline **22** (170 mg, 90%), m.p. 105–110°, $[\alpha]_D^{20}$ −193° (*c* 1.22, chloroform); ν_{max}^{Nujol} 3360 (OH) and 1670 cm^{-1} (C=N).

Anal. Calc. for $C_8H_{15}NO_4$ (189.21): C, 50.78; H, 7.99; N, 7.40. Found: C, 51.01; H, 8.03; N, 7.28.

*Methyl 4-acetamido-2,4,6-trideoxy-3-*O*-methyl-α-*L*-arabino-* (**28**) *and-* α-L-lyxo-*hexopyranoside* (**26**). — To a solution of **22** (133 mg, 0.7 mmol) in dry tetrahydrofuran (30 ml) was added lithium aluminum hydride (140 mg) at 0°. After stirring of the suspension overnight at room temperature, the excess of reducing agent was removed by cautious addition of a saturated, aqueous solution of sodium sulfate. The residue obtained after evaporation *in vacuo* was dissolved in pyridine (2 ml) and acetic anhydride (1 ml) with stirring. After 10 h, t.l.c. showed two spots (solvent *E*). Preparative chromatography afforded pure **26** (35 mg, see further for description) and a compound (36 mg) identified by (i.r., n.m.r., and t.l.c.) as the methyl α-L-glycoside of *N*-acetylholantosamine[1] (**28**).

*Methyl 2,6-dideoxy-3-*O*-methyl-4-*O*-tosyl-α-*L*-arabino-hexopyranoside* (**23**). — A solution of **20** (736 mg, 4.18 mmol) in dry pyridine (10 ml) was treated with *p*-toluenesulfonyl chloride (1.5 g, 7.19 mmol) and kept for 24 h at room temperature. After extraction as described for **10**, a syrup homogeneous on t.l.c. (solvent *D*) was obtained (1.23 g, 90%), $[\alpha]_D^{20}$ −76° (*c* 1, chloroform); ν_{max}^{film} 1600 cm^{-1} (Ar).

Anal. Calc. for $C_{15}H_{22}O_6S$ (330.33): C, 54.54; H, 6.71; O, 29.06; S, 9.68. Found: C, 54.66; H, 6.85; O, 29.02; S, 9.57.

*Methyl 4-azido-2,4,6-trideoxy-3*O*-methyl-α-*L*-lyxo-hexopyranoside* (**24**). — A solution of **23** (377 mg, 1.15 mmol)- in hexamethylphosphorictriamide (10 ml) was

heated overnight at 100° with sodium azide (165 mg, 3 mmol). T.l.c. (solvent *D*) indicated that no starting material remained. After addition of water, extraction was achieved as for **11** and gave pure **24** (200 mg, 85%), $[\alpha]_D^{20}$ +4° (*c* 1, chloroform); ν_{max}^{film} 2100 cm^{-1} (azide).

Anal. Calc. $C_8H_{15}N_3O_3$ (201.22): C, 47.75; H, 7.51; N, 20.88. Found: C, 47.89; H, 7.63; N, 20.65.

*Methyl 4-amino-2,4,6-trideoxy-3-*O*-methyl-α-*L*-lyxo-hexopyranoside* (**25**). — A solution of **24** (450 mg, 2.24 mmol) in methanol (25 ml) was hydrogenated in the presence of 10% palladium-on-charcoal (200 mg) at atmospheric pressure. After 18 h, the catalyst was filtered off and the solvent evaporated to give **25** as a syrup, $[\alpha]_D^{20}$ −165° (*c* 1.7, chloroform).

Anal. Calc. for $C_8H_{17}NO_3$ (175.22): C, 54.83; H, 9.78; N, 7.99; O, 27.39. Found: C, 54.49; H, 9.58; N, 7.72; O, 27.61.

*Methyl 4-acetamido-2,4,6-trideoxy-3-*O*-methyl-α-*L*-lyxo-hexopyranoside* (**26**). — Acetylation of **25** (100 mg, 0.6 mmol) in methanol (5 ml) with acetic anhydride (0.5 ml) gave pure (t.l.c. solvent *D*) crystalline **26** (113 mg) which was recrystallized from cyclohexane, m.p. 122–124°, $[\alpha]_D^{20}$ −170° (*c* 1, chloroform).

Anal. Calc. for $C_{10}H_{19}NO_4$ (217.26): C, 55.28; H, 8.82; N, 6.45; O, 29.46. Found: C, 55.39; H, 8.66; N, 6.51; O, 29.72.

ACKNOWLEDGMENTS

The authors are deeply indebted to Dr. R. Goutarel for many helpful discussions and thank Mr. B. Septe for assistance in recording the n.m.r. spectra.

REFERENCES

1 Q. Khuong-Huu, C. Monneret, I. Kabore, P. Choay, J. M. Tekam, and R. Goutarel *Bull. Soc. Chim. Fr.*, (1971) 864–869; J. M. Tekam, Thèse Doctorat d'État, Université de Paris (Orsay), 1974.
2 M.-M. Janot, Q. Khuong-Huu, C. Monneret, I. Kabore, J. Hildesheim, S. D. Gero, and R. Goutarel, *Tetrahedron*, 26 (1970) 1695–1709.
3 T. Reichstein and E. Weiss, *Adv. Carbohydr. Chem.*, 17 (1962) 65–120.
4 A. DiMarco, F. Arcamone, and F. Zunino, in J. W. Corcoran and F. E. Hahn (Eds.), *Antibiotics*, Vol. III, Springer, 1975, pp. 101–128.
5 F. Arcamone, A. Bargiotti, G. Cassinelli, S. Penco, and S. Hanessian, *Carbohydr. Res.*, 46 (1976) C3–C5.
6 F. Arcamone, A. M. Casazza, T. Dasdia, A. Necco, P. Reggiani, and R. Supino, *J. Med. Chem.*, 19 (1976) 733–734.
7 F. Arcamone, S. Penco, S. Redaelli, and S. Hanessian, *J. Med. Chem.*, 19 (1976) 1424–1425.
8 W. W. Lee, H. Y. Wu, J. J. Marsh, Jr., C. W. Mosher, E. M. Acton, L. Goodman, and D. W. Henry, *J. Med. Chem.*, 18 (1975) 767–768.
9 S. K. Gupta, *Carbohydr. Res.*, 37 (1974) 381–383.
10 W. W. Lee, H. Y. Wu, J. E. Christensen, L. Goodman, and D. W. Henry, *J. Med. Chem.*, 18 (1975) 768–769.
11 H. Y. Wu, W. W. Lee, T. H. Smith, and D. W. Henry, *Abstr. Pap. Am. Chem. Soc. Meet.*, 172 (1976) CARB-98.
12 A. Rosenthal and P. Catsoulacos, *Can. J. Chem.*, 46 (1968) 2868–2872.
13 N. K. Richtmyer, *Methods Carbohydr. Chem.*, 1 (1962) 107–113.

14 J. HILDESHEIM, S. D. GERO, Q. KHUONG-HUU, AND C. MONNERET, *Tetrahedron Lett.*, (1969) 2849–2851.
15 J. S. BRIMACOMBE, B. D. JONES, M. STACEY, AND J. J. WILLARD, *Carbohydr. Res.*, 2 (1966) 167–169.
16 S. HANESSIAN, *Carbohydr. Res.*, 2 (1966) 86–88.
17 H. R. BOLLIGER AND P. ULRICH, *Helv. Chim. Acta*, 35 (1952) 93–98.
18 B. HELFERICH AND E. HIMMEN, *Ber.*, 61 (1928) 1825–1835; M. J. BLAIR, *Methods Carbohydr. Chem.*, 2 (1963) 415–418.
19 D. HORTON AND W. WECKERLE, *Carbohydr. Res.*, 44 (1975) 227–240.
20 O. RENKONEN, O. SCHINDLER, AND T. REICHSTEIN, *Helv. Chim. Acta*, 42 (1959) 182–200.
21 D. IKEDA, T. TSUCHIYA, AND S. UMEZAWA, *Bull. Chem. Soc. Jpn.*, 44 (1971) 2529–2537.
22 W. KLYNE, *Biochem. J.*, 47 (1950) xli; C. S. HUDSON, *Bur. Stand. (U.S.) Bull.*, 21 (1926) 241.
23 J. P. MARSH, JR., C. W. MOSHER, E. M. ACTON, AND L. GOODMAN, *Chem. Commun.*, (1967) 973–975.
24 F. SZTARICSKAI, I. PELYVÁS, R. BOGNÁR, AND G. BUJTÁS, *Tetrahedron Lett.* (1975) 1111–1114.
25 K. KOGA, S. YAMADA, M. YOH, AND T. MIZOGUCHI, *Carbohydr. Res.*, 36 (1974) C9–C11.
26 E. J. COREY AND J. W. SUGGS, *Tetrahedron Lett.*, (1975) 2647–2650.
27 K. E. PFITZNER AND J. G. MOFFATT, *J. Am. Chem. Soc.*, 85 (1963) 3027.
28 P. J. BEYNON, P. M. COLLINS, P. T. DOGANGES, AND W. G. OVEREND, *J. Chem. Soc., C*, (1966) 1131–1136.
29 P. J. BEYNON, P. M. COLLINS, AND W. G. OVEREND, *J. Chem. Soc., C*, (1969) 272–281.