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PREPARATIVE SYNTHESIS OF 3-AMINO-2,3,6-TRIDEOXY-L-*xylo*-HEXOPYRANOSE DERIVATIVES

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ABSTRACT

Starting from methyl 2,6-dideoxy-β-L-*lyxo*-hexopyranoside (**1**), several derivatives of the title sugar were prepared by a sequence of high-yielding steps. Selective tosylation of the 3-hydroxyl group in **1** gave the 3-*p*-toluenesulfonate, further characterized as its 4-acetate and 4-benzoate. Treatment of these protected sulfonates with sodium azide afforded the respective 3-azido derivatives **6** and **7**, having the required L-*xylo* stereochemistry. Catalytic hydrogenation of **6** with concomitant *N*-acetylation led to methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-L-*xylo*-hexopyranoside, which was readily converted into the *O*-deacetylated derivative **9**. Alternatively, and more conveniently, compounds **6** and **7** were first saponified to give the crystalline 3-azide, which then was converted, by reduction with hydrogen, into crystalline methyl 3-amino-2,3,6-trideoxy-β-L-*xylo*-hexopyranoside (**12**). *N*-Substitution of **12** provided the crystalline methyl glycosides **9** (*N*-acetyl) and **14** (*N*-trifluoroacetyl), both of which could be converted by mild, acid hydrolysis into the crystalline reducing sugars **10** (from **9**) and **15** (from **14**), as their α-L anomers; these target compounds were obtained from **1** in 17 and 20% overall yields, respectively.

INTRODUCTION

During the past several years, a number of syntheses have been reported* for 3-amino-2,3,6-trideoxyhexoses (or derivatives thereof) having the (D or L) *lyxo*[2a,3], *ribo*[2a,4a,5], and *arabino*[2] stereochemistry, the growing interest in these compounds stemming from their frequent occurrence in Nature as components of antibiotics. The (D or L)-*xylo* isomer, however, has not thus far been reported in Nature, nor was its synthesis achieved until recently. Work from this laboratory first described[1] the preparation of several derivatives of 3-amino-2,3,6-trideoxy-L-*xylo*-hexose; the starting point was a sugar of the D series which, late in the sequence, was subjected to the now well-established[2a,6,7] elimination–hydrogenation procedure to generate the terminal *C*-methyl group with concomitant stereochemical inversion at C-5. A preparation of methyl 3-amino-2,3,6-trideoxy-β-L-*xylo*-hexopyranoside, following the same synthetic

*For references up to 1977, see ref. 1.

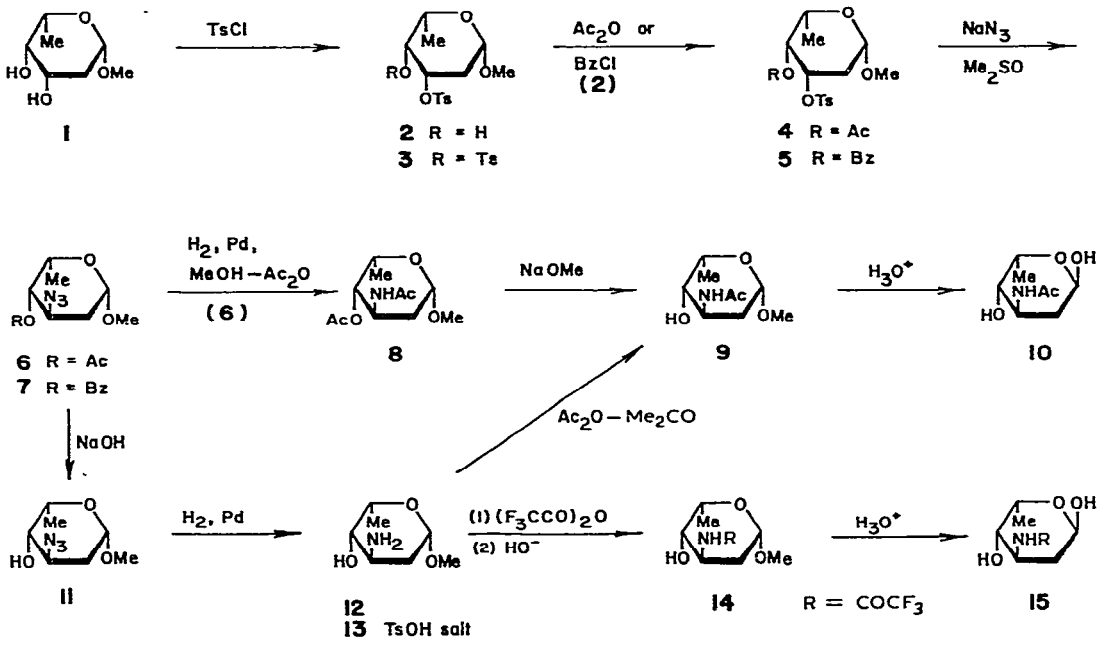
strategem, was reported[2a] independently. More recently, Bognár and co-workers applied[4a] an oxidation–nonstereospecific-reduction sequence to an L-*ribo* precursor, whereas Arcamone *et al.*[4b] employed a nucleophilic displacement reaction to gain access to an L-*xylo* isomer.

Although the synthetic procedure described in the preceding paper[1] was satisfactory for securing initial quantities of the desired title sugar, as required for coupling to daunomycinone to furnish[8] the 3′-epimer (and its β anomer) of the antitumor agent daunorubicin, it proved to have too many limitations in a scaled-up version. In particular, the hydrogenation step required extensive chromatographic purification of the product-mixture and therefore, an alternative and more-efficient synthesis of 3-amino-2,3,6-trideoxy-L-*xylo*-hexose was developed and is reported herein.

RESULTS AND DISCUSSION

The point of departure was methyl 2,6-dideoxy-β-L-*lyxo*-hexopyranoside (**1**), readily obtained[7] in five steps (46% overall yield) from methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside which, in turn, is most conveniently prepared from either methyl α-D-glucopyranoside[9] or methyl α-D-mannopyranoside[10]. Such other conceivable routes to the starting methyl glycoside **1** as the glycal method[11], or the two-step methoxymercuration–demercuration conversion[12] of 1,5-anhydro-2,6-dideoxy-L-*lyxo*-hex-1-enitol (L-fucal), or the Koenigs–Knorr glycosidation of the corresponding, peracetylated 1-halide[13], are less preferable, because these routes tend to yield mixtures of α and β anomers that necessitate tedious separation.

Selective tosylation of **1** with one molar equivalent of *p*-toluenesulfonyl chloride in pyridine under rigorously anhydrous conditions afforded the 3-*p*-toluenesulfonate



2 in theoretical yield, whereas an excess of the reagent converted **1**, as expected, into the disulfonate **3**. Preliminary results with the α anomer[11] of **1** indicate[14] that selective tosylation likewise occurs exclusively at the equatorially disposed, 3-hydroxyl group (*versus* the axial 4-OH), in line with the results of similar acetylation[15] and benzoylation[11] experiments. In contrast, the α-L-*arabino* analog of **1**, in which two equatorially attached hydroxyl groups compete for the reagent, displays poor selectivity upon partial tosylation[4].

Identification of **2** as the 3-sulfonate was based, in particular, on the analysis of ^{1}H-n.m.r. data (see Table I; most of the assignments were confirmed by double-irradiation experiments) of **2** as compared with those of the sulfonate **3**, the 4-acetate **4**, and the 4-benzoate **5**. For example, after the hydroxyl proton had been exchanged by deuterium, the broadened, multiline pattern for H-4 in **2** collapsed to a doublet (small coupling of H-4 with H-3; negligible coupling with H-5), and upon acylation (tosylation, acetylation, or benzoylation), the H-4 signal shifted characteristically downfield. Furthermore, the presence of only *one* acetyl signal in the spectrum of the initially isolated **4** attested to the regiospecific monotosylation leading to **2**.

Sodium azide in *N*,*N*-dimethylformamide or dimethyl sulfoxide did not effect straightforward transformation of the sulfonate **2**; at lower temperatures (<80°), no reaction was evident, and more-vigorous conditions led to extensive decomposition, as manifested by the dark color of the mixture and the low yield (~30%) of desired displacement-product (**11**). Consequently, fully protected derivatives better compatible with the conditions required for the azide exchange were examined. Accordingly, the 4-*O*-acetyl (**4**) and 4-*O*-benzoyl (**5**) derivatives of **2** were prepared; compound **4** was obtained crystalline in 72% yield from **2**, and compound **5** was isolated in 71% yield as an amorphous solid. Both esters were characterized by elemental analysis and by their spectral characteristics.

When the sulfonates **4** and **5** were subjected to reaction with sodium azide in dimethyl sulfoxide, the respective azides **6** and **7** were obtained as distillable syrups in excellent yields (75% for pure **6**; theoretical yield for crude **7**). The β-L-*xylo* stereochemistry for these compounds was substantiated from their 100-MHz, ^{1}H-n.m.r. spectra (see Table I), which were essentially of first order. The spectra displayed, in particular, a well-resolved, doubled doublet (splittings of ~8 and ~3.5 Hz) for the consequently axially disposed H-4, and a 4-line pattern for H-3 which, by analysis of the coupling constants (~3.5 Hz) for $J_{2e,3}$, $J_{2a,3}$, and $J_{3,4}$, established without doubt the equatorial disposition for H-3.

Catalytic hydrogenation of the azide **6**, under hydrogen at 1 atm. pressure, in a mixture of methanol and acetic anhydride and in the presence of palladium-on-carbon, furnished the 3-acetamido derivative **8**, which had been prepared before[1] in this laboratory by an independent and stereochemically definitive route. In the present instance, the product crystallized spontaneously following chromatographic purification, and was otherwise identical, in all respects, with the former sample.

Mild, acid hydrolysis of the previously described[1] methyl glycoside **9** (obtained from **8** in 78% yield by Zemplén transesterification) furnished the reducing sugar **10**,

TABLE I

^{1}H-N.M.R.-SPECTRAL DATA[a] FOR THE METHYL GLYCOSIDES **2–9**, **11**, **12**, AND **14**

Compound	*Chemical shifts (δ)[b] (First-order couplings, Hz, in parentheses)*										
	H-1 ($J_{1,2a}$)	*H-2e* ($J_{1,2e}$)	*H-2a* ($J_{2a,3}$)	*H-3* ($J_{2e,3}$)	*H-4* ($J_{3,4}$)	*H-5* ($J_{4,5}$)	*H-6* ($J_{5,6}$)	*NH-3* ($J_{3,NH}$)	*OMe-1*	*OR-4* ($J_{4,OH}$)	*Others*[c]
2	4.28 dd (8.0)	← 2.11–1.76 m → (4.0)		4.59 m	3.69 m (3.0)	3.45 q (< 1)	1.25 d (7.2)	—	3.40 s	2.60 bs	7.80 d, 7.30 d; 2.38 s (8.0) (tosyl)
3	4.21 dd (8.3)	← 1.95–1.60 m → (3.8)	(11.0)	4.54 m_8 (5.8)	4.73 bd (3.3)	3.50 q (~1)	1.16 d (6.5)	—	3.29 s	← 7.75–7.56 and 7.25–7.11 m; → 2.31 s, 2.29 s (tosyl)	
4[d]	3.95 dd (6.9)	← 2.25–1.92 m → (4.8)	(10.0)	4.67 m_8	5.08 dd (3.5)	3.06 dq (1.2)	0.97 d (6.6)	—	3.22 s	1.68 s	7.81 d, 6.93 d; 1.98 s (8.0) (tosyl)
5[d]	3.98 m	← 2.30–2.05 m →		4.80 m	5.36 dd (3.4)	3.11 dq (1.2)	0.98 d (6.5)	—	3.24 s	8.02 m, 7.06 m	7.77 d, 6.81 d; 1.89 s (8.0) (tosyl)
6[d]	4.32 dd (7.5)	← 1.95–1.36 m → (3.8)	(3.8)	3.45 m_4 (3.8)	4.41 dd (3.8)	3.65 dq (2.0)	0.91 d (6.5)	—	3.15 s	1.59 s	
7[d]	4.51 dd (8.2)	← 1.98–1.50 m → (3.0)	(3.5)	3.59 m_4 (3.5)	4.79 dd (3.7)	3.84 dq (1.8)	1.07 d (6.4)	—	3.31 s	8.04 m, 7.11 m	
8	4.72 dd (7.4)	← 2.20–1.65 m → (3.3)		4.13 m	4.81 dd (4.0)	4.08 dq (2.2)	1.18 d (6.3)	7.73 d (7.7)	3.45 s	2.08 s	1.99 s (NAc)
9[e,f]	4.64 dd (8.5)	← 2.05–1.52 m → (3.0)		4.02 m	3.27 m	3.80 dq (2.0)	1.15 d (6.2)	7.82 d (7.3)	3.38 s	4.70 bs	1.88 s (NAc)
11[e,f]	4.50 dd (8.5)	1.66 m_6 (2.6)	1.93 ddd (3.8)	3.95 m_4 (3.5)	3.32 m (3.8)	3.79 dq (2.0)	1.19 d (6.6)	—	3.37 s	5.09 d (6.9)	
12[f]	4.65 dd (8.2)	1.55 m_6 (3.0)	1.90 ddd (4.0)	3.35 m (3.5)	3.18 m (3.8)	4.00 dq (2.0)	1.18 d (6.6)	2.60 bs	3.45 s	3.50 bs	
14[e]	4.44 dd (6.8)	← 1.86–1.30 m → (3.2)		3.79 m	3.22 m	3.60 dq (2.4)	1.16 d (6.4)	8.86 d (7.0)	3.12 s	4.76 d (5.7)	

[a]100-MHz, continuous-wave spectra in chloroform-*d*, unless otherwise stated. [b]Signal multiplicities: b, broadened; d, doublet; m, multiplet; m_x, x-line pattern; q, quartet; s, singlet; and t, triplet. [c]Assignments in parentheses. [d]In benzene-d_6. [e]In 3:1 dimethyl sulfoxide-d_6–chloroform-*d*. [f]$J_{2e,2a}$ = 13.6 Hz.

which crystallized in the α-L anomeric form, as indicated by its upward mutarotation.

Hydrogenation of the fully protected azido sugars **6** or **7** in the absence of an acetylating agent (as used in the preparation of **8**) led to mixtures, rather than to a unique product. This complication is attributed to the presence of the 4-ester groups in **6** and **7**, which had dramatically improved the outcome of the azide-displacement reaction but which now complicated the hydrogenation step, presumably because of *O*→*N*-acyl migration[5]. Accordingly, the crystalline, deprotected 3-azido glycoside **11** was prepared (80% yield from **6**, 86% from **7**), and this readily underwent hydrogenation to afford crystalline methyl 3-amino-2,3,6-trideoxy-β-L-*xylo*-hexopyranoside (**12**) in 73% yield. The physical constants of, and the ^{1}H-n.m.r. data (see Table I) for, **12** are in good agreement with literature values[2a] for this compound as prepared by simultaneous hydrogenation of an azide group and an exocyclic, double bond.

Additional evidence for the identity of **12** was provided by its conversion into the acetamido glycoside **9**, the *p*-toluenesulfonate salt **13**, and the trifluoroacetamido derivative **14**. The last, which was prepared by use of trifluoroacetic anhydride in dichloromethane, and subsequent treatment with weak, aqueous base, was then hydrolyzed with dilute acetic acid to afford the reducing sugar **15**. Compound **15**, which crystallized in the α-L anomeric form, as evidenced by its upward mutarotation, is a suitable intermediate for the preparation of novel anthracycline glycosides possessing the L-*xylo* configuration for the amino sugar residue. Detailed characterization and biological evaluation of these glycosides will be reported separately[8].

EXPERIMENTAL

General methods. — Solvents were evaporated under diminished pressure at bath temperatures below 50°. T.l.c. was performed on precoated plates of Silica Gel 60 (E. Merck, Darmstadt); zones were detected by u.v. light, and by spraying with sulfuric acid and subsequently heating. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. I.r. spectra were recorded with a Perkin–Elmer Model 457 grating i.r. spectrophotometer (potassium bromide pellets, or films on sodium chloride discs). ^{1}H-N.m.r. spectra were recorded at 100 MHz with a Varian HA-100 spectrometer; chemical shifts refer to an internal standard of tetramethylsilane (δ = 0.00) and are listed, together with spin-coupling values (Hz), in Table I. Mass spectra were recorded with an AEI MS-9 double-focusing, high-resolution spectrometer (ionizing and accelerating potentials, 70 eV and 8 kV). Microanalyses were performed by W. N. Rond. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest); double numbers indicate approximately equal intensities.

Selective tosylation of **1**: *methyl 2,6-dideoxy-3-*O*-tosyl-β-*L*-lyxo-hexopyranoside* (**2**). — *p*-Toluenesulfonyl chloride (7.0 g, 36.7 mmol) was added to a cooled (0°)

solution of methyl 2,6-dideoxy-β-L-*lyxo*-hexopyranoside[7,11] (**1**; 6.0 g, 37.0 mmol) in dry pyridine (75 mL), and the mixture was kept for 3 days at 0°. The solution was then poured onto ice–water (500 mL) with vigorous stirring, and the product was extracted with dichloromethane (three 100-mL portions). The dried (magnesium sulfate) extract was evaporated, to afford the title compound **2** as a chromatographically homogeneous syrup; yield 11.5 g (98%), $[\alpha]_D^{23}$ −14.9° (*c* 1.5, chloroform); ν_{max}^{film} 3500 (OH), 1600 and 1498 cm^{-1} (aryl).

Anal. Calc. for $C_{14}H_{20}O_6S$ (316.38): C, 53.15; H, 6.37. Found: C, 53.46; H, 6.60.

Exhaustive tosylation of **1**: *methyl 2,6-dideoxy-3,4-di-*O*-tosyl-*β*-*L*-lyxo-hexopyranoside* (**3**). — *p*-Toluenesulfonyl chloride (840 mg, 4.4 mmol) was added to a solution of the methyl glycoside **1** (178 mg, 1.1 mmol) in pyridine (30 mL). After 10 days at 25° and 6 h at 80°, t.l.c. (3:2 toluene–ethyl acetate) indicated complete conversion of **1** into one major (R_F 0.61) and one minor product (R_F 0.44; mobility identical with that of **2**). The solution was poured onto ice–water (300 mL) with stirring, and the product was extracted with dichloromethane (three 50-mL portions). Evaporation of the dried (magnesium sulfate) extract afforded a syrupy residue that was subjected to column chromatography on silica gel with the t.l.c. solvent-system as the eluant. Isolation of the faster-migrating component afforded crystalline **3**; yield 360 mg (70%). For analytical purposes, a portion was recrystallized from isopropyl ether; m.p. 81–86° (dec.), $[\alpha]_D^{26}$ −28.8° (*c* 0.8, chloroform); X-ray powder diffraction data: 8.84 s (3), 7.53 m, 6.88 s, 6.21 s (2), 5.43 w, 4.73 vs (1), 4.54 m, 4.21 m, 4.08 m, 3.91 m, and 3.76 s.

Anal. Calc. for $C_{21}H_{26}O_8S_2$ (470.56): C, 53.60; H, 5.57; S, 13.63. Found: C, 53.49; H, 5.60; S, 13.56.

*Methyl 4-*O*-acetyl-2,6-dideoxy-3-*O*-tosyl-*β*-*L*-lyxo-hexopyranoside* (**4**). — Treatment of the crude monosulfonate **2** (11.5 g, 36.4 mmol) with 1:2 acetic anhydride–pyridine (75 mL) for 20 h at 25° afforded, after conventional processing, the crude, crystalline title-compound **4** (12.07 g, 93%), which was recrystallized from isopropyl alcohol; yield 9.36 g (72%), m.p. 82–85° (dec.), $[\alpha]_D^{24}$ −4.0° (*c* 1.3, chloroform) and −13.1° (*c* 1.4, methanol); ν_{max}^{KBr} 1750 (ester C=O), 1605 and 1500 cm^{-1} (aryl); X-ray powder diffraction data: 12.44 s (3), 10.21 s (2), 6.39 vw, 6.06 s, 5.38 m, 5.12 s, 4.89 m, 4.68 m, 4.31 s, 4.03 vs (1), and 3.87 s.

Anal. Calc. for $C_{16}H_{22}O_7S$ (358.41): C, 53.62; H, 6.19. Found: C, 53.68; H, 6.04.

*Methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-tosyl-*β*-*L*-lyxo-hexopyranoside* (**5**). — Benzoylation of the crude monosulfonate **2** (600 mg, 1.9 mmol) in pyridine (15 mL) with benzoyl chloride (3 mL, 25.8 mmol) for 20 h at 25° furnished, after conventional processing, the 4-benzoate **5** as a chromatographically homogeneous, amorphous solid; yield 570 mg (71%), $[\alpha]_D^{24}$ −39.2° (*c* 0.7, chloroform) and −36.8° (*c* 1.1, methanol); ν_{max}^{film} 1725 (ester C=O), 1602 and 1587 cm^{-1} (aryl).

Anal. Calc. for $C_{21}H_{24}O_7S$ (420.49): C, 59.99; H, 5.75; S, 7.63. Found: C, 60.20; H, 5.74; S, 7.51.

*Methyl 4-*O*-acetyl-3-azido-2,3,6-trideoxy-*β*-*L*-xylo-hexopyranoside* (**6**). — A suspension of the 3-sulfonate **4** (9.34 g, 26.1 mmol) and sodium azide (9 g, 138.4

mmol) in dimethyl sulfoxide (100 mL) was stirred vigorously for 7 h at 130–140°, after which time, t.l.c. (4:1 ether–petroleum ether) revealed only traces of unchanged **4**. The mixture was poured onto ice–water (800 mL) with stirring, and the product was extracted with ether (three 150-mL portions). The combined extracts were washed with water, dried (magnesium sulfate), and evaporated. The resulting, brownish syrup was distilled *in vacuo* (20 mtorr, bath temp. 100–120°), to give **6** as a colorless, chromatographically homogeneous syrup; yield 4.47 g (75%), $[\alpha]_D^{26}$ −0.6° (*c* 1.3, chloroform) and +2.2° (*c* 2.1, methanol); ν_{max}^{film} 2110 (azide) and 1745 cm^{-1} (ester C=O); *m/e* (rel. intensity): 229 (0.05, M^+), 228 (0.4, M − 1), 198 (0.8, M − MeO·), 187 (0.1, M − $H_2C{=}C{=}O$ or $\cdot N_3$), 186 (0.8, M − HN_3), and 127 (10, 187 − HOAc; m* at 70.4, calc. for 229→127: 70.43).

Anal. Calc. for $C_9H_{15}N_3O_4$ (229.24): C, 47.16; H, 6.60; N, 18.33. Found: C, 46.57; H, 6.33; N, 18.04.

*Methyl 3-azido-4-*O*-benzoyl-2,3,6-trideoxy-β-*L-xylo-*hexopyranoside* (**7**). — By the procedure described in the preceding experiment for the acetyl analog **4**, the benzoylated 3-sulfonate **5** (280 mg, 0.67 mmol) in dimethyl sulfoxide (10 mL) was treated with sodium azide (320 mg, 4.9 mmol) to afford the syrupy 3-azide **7**, pure enough for most purposes; yield 200 mg (theoretical). A small portion was distilled *in vacuo* (30 mtorr, bath temp. 135–140°); $[\alpha]_D^{27}$ −55.5° (*c* 0.3, chloroform); ν_{max}^{film} 2110 (azide), 1725 (ester C=O), 1605 and 1590 cm^{-1} (monosubstituted phenyl); *m/e* (rel. intensity): 291 (0.03, M^+), 260 (0.1, M − MeO·), 247 (0.03, M − MeCHO), 233 (0.1, M − $CH_2{=}CH$-OMe), 189 (4, 233 − MeCHO), and 137 (0.4, M − MeOH − BzOH).

Anal. Calc. for $C_{14}H_{17}N_3O_4$ (291.31): C, 57.72; H, 5.88; N, 14.42. Found: C, 57.93; H, 5.63; N, 14.26.

*Methyl 3-acetamido-4-*O*-acetyl-2,3,6-trideoxy-β-*L-xylo-*hexopyranoside* (**8**). — The 3-azide **6** (200 mg, 0.87 mmol), dissolved in methanol (10 mL) and acetic anhydride (0.5 mL, 5.3 mmol), was hydrogenated under atmospheric pressure in the presence of 10% palladium-on-carbon (40 mg) for 2 h at 25°. Removal of the catalyst, followed by evaporation of the filtrate, afforded a semi-crystalline residue that was subjected to column chromatography on silica gel with 8:1 ethyl acetate–ethanol as the eluant. A fast-moving (R_F 0.65), minor component that was visible on t.l.c. plates under u.v. light, but did not char after spraying with sulfuric acid and subsequently heating, was not further investigated. The major component (R_F 0.34), however, was identified as the β-L-*xylo* glycoside **8** by comparison (t.l.c., i.r. and n.m.r. spectroscopy, and mass spectrometry) with an authentic[1] sample; yield 120 mg (56%). After recrystallization from ether, **8** had m.p. 102–103°, $[\alpha]_D^{28}$ +41.1° (*c* 0.3, chloroform) (lit.[1] syrup, $[\alpha]_D$ +41.7° in chloroform and[2a] m.p. 101–102°, $[\alpha]_D$ +43° in chloroform).

Anal. Calc. for $C_{11}H_{19}NO_5$ (245.28): C, 53.87; H, 7.81; N, 5.71. Found: C, 53.48; H, 7.89; N, 5.77.

*Methyl 3-acetamido-2,3,6-trideoxy-β-*L-xylo-*hexopyranoside* (**9**). — *A. From the peracetate* **8**. Catalytic transesterification of **8** (100 mg, 0.41 mmol) in abs.

methanol (3 mL) with M sodium methoxide (50 μL) afforded, after recrystallization from ethanol–ether, analytically pure **9** indistinguishable (by t.l.c., i.r. and n.m.r. spectroscopy, mass spectrometry, and X-ray powder diffraction data) from an authentic sample[1]; yield 65 mg (78%), m.p. 138–139°, $[\alpha]_D^{25}$ +35.8° (*c* 0.4, methanol) (lit.[1] m.p. 136–138°, $[\alpha]_D$ +41.4° in methanol and[2a] m.p. 137–138°, $[\alpha]_D$ +43° in methanol).

Anal. Calc. for $C_9H_{17}NO_4$ (203.24): C, 53.19; H, 8.43; N, 6.89. Found: C, 52.93; H, 8.45; N, 6.81.

B. From the amine **12**. The unprotected glycoside **12** (380 mg, 2.36 mmol) in acetone (25 mL) was treated with acetic anhydride (2 mL, 21.2 mmol) for 20 h at 25°, after which time, t.l.c. (2:3 benzene–acetone) showed the reaction to be complete. Evaporation of the solvent, and recrystallization of the residue from ethanol–ether, furnished pure **9**, which was identical in all respects with the foregoing sample; yield 370 mg (77%).

*3-Acetamido-2,3,6-trideoxy-α-*L*-xylo-hexose* (**10**). — A solution of the glycoside **9** (125 mg, 0.62 mmol) in aqueous acetic acid (10%, 6 mL) was boiled under reflux for 1 h, whereupon t.l.c. (2:3 benzene–acetone) indicated that hydrolysis was complete. Evaporation of the solvent gave a solid residue that was recrystallized from ethyl acetate–hexane to afford pure **10**; yield 82 mg (70%), m.p. 119–121°, $[\alpha]_D^{29}$ −39.7 (initial, extrapolated) →−31.1 (4 min) →−27.9 (6 min) →−24.1 (9 min) →−19.6 (15 min) →−14.5 (30 min) →−11.5° (1 h, equil.; *c* 0.7, methanol); *m/e* (rel. intensity): 189 (M^+, absent), 153 (5, M − 2 H_2O), 144 (6, M − H· − MeCHO), 127 (5, 144 − ·OH), and 101 (4, M − 2 MeCHO); X-ray powder diffraction data: 9.66 m, 6.96 s (3), 5.92 vs (1,1), 5.15 vs (1,1), 5.03 w, 4.64 m, 4.48 m, 4.26 s (2), and 3.84 m.

Anal. Calc. for $C_8H_{15}NO_4$ (189.21): C, 50.78; H, 7.99; N, 7.40. Found: C, 50.54; H, 7.74; N, 7.19.

*Methyl 3-azido-2,3,6-trideoxy-β-*L*-xylo-hexopyranoside* (**11**). — Saponification of the 4-acetate **6** (4.13 g, 18.0 mmol) was effected by aqueous M sodium hydroxide (35 mL) in methanol (35 mL). After 18 h at 25°, the product was extracted with dichloromethane (two 80-mL portions), and the extracts were combined, washed with water, dried (magnesium sulfate), and evaporated, to afford crude **11**. Sublimation (20 torr, 50°) furnished analytically pure **11**; yield 2.69 g (80%), m.p. 69–71° (subl.), $[\alpha]_D^{25}$ −3.3° (*c* 0.6, chloroform) and +9.4° (*c* 0.8, methanol); ν_{max}^{KBr} 3420 (broad, OH) and 2105 cm^{-1} (azide); *m/e* (rel. intensity): 186 (1.4, M − 1), 156 (4, M − MeO·), 145 (7, M − ·N_3), 113 (9, M − MeO· − HN_3), and 58 (100, $H_2C{=}CH\text{-}OMe^{+}$); X-ray powder diffraction data: 11.18 w, 9.82 w, 6.55 m, 6.10 m, 5.15 s (2), 4.89 m, 4.48 w, 4.30 w, 4.09 s (3), and 3.84 s (1).

Anal. Calc. for $C_7H_{13}N_3O_3$ (187.20): C, 44.91; H, 7.00; N, 22.45. Found: C, 45.05; H, 7.01; N, 22.34.

Alternatively, saponification of the 4-benzoate **7** (1.46 g, 5.00 mmol) with aqueous M sodium hydroxide (20 mL) in methanol (20 mL) afforded, after the same

processing, 800 mg (86%) of crude **11**, indistinguishable from the sample prepared from **6**.

*Methyl 3-amino-2,3,6-trideoxy-β-*L-xylo-*hexopyranoside* (**12**). — Catalytic hydrogenation of the azide **11** (2.49 g, 13.3 mmol) in methanol (65 mL) under hydrogen at atmospheric pressure in the presence of 10% palladium-on-carbon (150 mg) for 6 h at 25° furnished the amine **12**. The catalyst was removed, and the residue obtained after evaporation of the filtrate was recrystallized from ether, to afford pure **12**; yield 1.57 g (73%), m.p. 98–100°, $[\alpha]_D^{27}$ +76.8° (*c* 0.5, chloroform); ν_{max}^{KBr} 3440, 3300 (OH, NH), and 1590 cm^{-1} (NH); *m/e* (rel. intensity): 161 (0.1, $M^{+\cdot}$), 144 (3, M — ·OH), 130 (5, M — MeO·), 103 (2, M — $H_2C{=}CH{-}OMe$), 59 (100, 103 — MeCHO), and 58 (60, $H_2C{=}CH{-}OMe^{+\cdot}$); X-ray powder diffraction data: 10.33 s (3,3), 5.79 s (2), 5.45 m, 5.05 s (3,3), 4.12 vs (1), 3.64 m, 3.48 m, 3.33 m, 3.09 w, and 2.95 m.

Anal. Calc. for $C_7H_{15}NO_3$ (161.20): C, 52.16; H, 9.38; N, 8.69. Found: C, 52.17; H, 9.28; N, 8.52.

This compound, prepared by simultaneous hydrogenation of an exocyclic double bond and an azide group, has been reported[2a] to have m.p. 96–97°, $[\alpha]_D$ +79° in chloroform.

*Methyl 3-amino-2,3,6-trideoxy-β-*L-xylo-*hexopyranoside* p-*toluenesulfonate* (**13**). — To a cooled (0°) solution of the unprotected amine **12** (73 mg, 0.45 mmol) in methanol (5 mL) was added *p*-toluenesulfonic acid monohydrate (128 mg, 0.67 mmol). After 15 min at 25°, ~3 mL of the solvent was evaporated off, and ether (25 mL) was added to the concentrate (~2 mL) to precipitate the product; yield 98 mg (65%), m.p. 80–83° (somewhat dependent on the rate of heating), $[\alpha]_D^{29}$ +25.2° (*c* 0.3, chloroform); ν_{max}^{KBr} 3400 (OH), 1625 and 1525 (amine salt), and 1215, 1180, 1130, and 1040 cm^{-1} (aromatic sulfonate); X-ray powder diffraction data: 11.18 vs (1), 7.19 vw, 5.79 s (3,3), 5.27 s (3,3), 4.82 s (2), 4.49 m, 4.24 w, 4.06 w, and 3.88 m.

Anal. Calc. for $C_{14}H_{23}NO_6S$ (333.41): C, 50.44; H, 6.95; N, 4.20; S, 9.62. Found: C, 50.43; H, 6.88; N, 4.08; S, 9.38.

*Methyl 2,3,6-trideoxy-3-(trifluoroacetamido)-β-*L-xylo-*hexopyranoside* (**14**). — To a solution of the unprotected glycoside **12** (306 mg, 1.9 mmol) in dichloromethane (20 mL) was added trifluoroacetic anhydride (1 mL, 7.0 mmol). After 15 min at 0° and 3 h at 25°, the clear solution was evaporated, and toluene (two 30-mL portions) was added to, and evaporated from, the residue. The remaining, pale-yellow syrup was dissolved in ethyl acetate (12 mL), saturated, aqueous sodium hydrogencarbonate (10 mL) was added, and the mixture was vigorously stirred for 20 h at 25°. The organic layer was separated, and the aqueous phase was extracted with ethyl acetate (two 20-mL portions). The organic solutions were combined, washed with water, dried (sodium sulfate), and evaporated, to afford crystalline **14**; yield 423 mg (87%). For analytical purposes, a sample was recrystallized from acetone–hexane; m.p. 175–177°, $[\alpha]_D^{28}$ +39.2° (*c* 0.3, methanol); ν_{max}^{KBr} 3440, 3300 (OH, NH), 1695 and 1565 cm^{-1} (amide); *m/e* (rel. intensity): 256 (0.3, M — 1), 226 (37, M — MeO·), 225 (65, M — MeOH), 213 (3, M — MeCHO), 207 (3, 225 — H_2O), 192 (14, 207 — Me·),

113 (24, $F_3CCONH_2^+$ or 226 — F_3CCONH_2), and 69 (29, CF_3^+); X-ray powder diffraction data: 10.10 w, 9.25 w, 5.66 m, 5.30 s (2), 5.12 w, 4.38 vs (1), 3.74 m, 3.53 m, and 3.43 s (3).

Anal. Calc. for $C_9H_{14}F_3NO_4$ (257.21): C, 42.03; H, 5.49; N, 5.45. Found: C, 41.97; H, 5.54; N, 5.70.

*2,3,6-Trideoxy-3-(trifluoroacetamido)-α-*L*-xylo-hexose* (**15**). — A solution of the methyl glycoside **14** (144 mg, 0.56 mmol) in aqueous acetic acid (10%, 8 mL) was heated for 1 h at 100°, after which time t.l.c. (2:3 toluene–ethyl acetate) showed hydrolysis to be complete. The solvent was evaporated off, and the solid residue was recrystallized from acetone–hexane, to give pure **15**; yield 100 mg (73%), m.p. 114–116°, $[\alpha]_D^{28}$ −15.7 (initial, extrapolated) →−13.3 (3.5 min) →−12.0 (5.5 min) →−10.9 (8 min) →−7.3 (30 min) →−5.4° (1 h, equil.; *c* 0.8, methanol); ν_{max}^{KBr} 3520, 3310 (OH, NH), 1725 and 1550 cm^{-1} (amide); *m/e* (rel. intensity): 243 (M^+, absent), 225 (2.2, M − H_2O), 207 (3.3, M − 2 H_2O), 199 (2, M − MeCHO), 155 (25, M − 2 MeCHO), 130 (3, M − F_3CCONH_2), and 113 (5, $F_3CCONH_2^+$ or 113 − ·OH); X-ray powder diffraction data: 9.45 w, 7.02 w, 5.94 s (3), 5.37 m, 5.03 vs (1,1) 4.90 w, 4.70 s (2), 4.42 vs (1,1), 3.92 m, 3.64 s, and 3.54 s.

Anal. Calc. for $C_8H_{12}F_3NO_4$ (243.19): C, 39.51; H, 4.97; N, 5.76. Found: C, 39.32; H, 4.69; N, 5.74.

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