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SYNTHESIS OF EVERNINOSE, A NON-REDUCING DISACCHARIDE COMPONENT OF THE ORTHOSOMYCIN-TYPE OLIGOSACCHARIDE ANTIBIOTICS*

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ABSTRACT

Glycosylation of 3,4-di-*O*-benzyl-2-*O*-methyl-L-lyxopyranose (**1**) with 3,4-di-*O*-benzyl-2,6-di-*O*-methyl-α-D-mannopyranosyl chloride afforded a mixture of the α,α- (**12**) and α,β-disaccharide derivative (**10**). Reaction of **1** with 3,4-di-*O*-benzyl-2,6-di-*O*-methyl-α-D-mannopyranosyl trichloroacetimidate gave **10** exclusively. *O*-Debenzylation of **12** and **10** gave everninose and isoeverninose, respectively. The ^{1}H- and ^{13}C-n.m.r. spectra were assigned on the basis of 2D homo- and heteronuclear correlation experiments.

INTRODUCTION

The members of the orthosomycin family of oligosaccharide antibiotics, such as flambamycin, everninomicins, avilamycins, and curamycin-A, contain a common non-reducing disaccharide moiety[1–4]. The isolation of this disaccharide was reported first by Herzog *et al.*[5], and the structure and absolute chemistry were determined by Ganguly *et al.*[6] as 2-*O*-methyl-α-L-lyxopyranosyl 2,6-di-*O*-methyl-β-D-mannopyranoside and it was named everninose. We now report on the synthesis of everninose and its α,α-isomer which we have named isoeverninose.

RESULTS AND DISCUSSION

3,4-Di-*O*-benzyl-2-*O*-methyl-L-lyxopyranose[7] (**1**) was selected as the glycosyl acceptor, which in solution exists mainly in the α form. The preparation of a β-mannosidic linkage is a difficult task in synthetic carbohydrate chemistry[8], since neither the neighbouring-group participation procedure nor the *in situ* anomerisation method can be utilised. However, α-D-mannopyranosyl halides with a non-participating group at position 2 are excellent glycosyl donors[9] and gave β-mannopyranosyl derivatives when the reactions were carried out in the presence of in-

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3 $R^1 = OMe, R^2 = R^6 = H, R^4 = Bzl$
4 $R^1 = OMe, R^2 = R^4 = H, R^6 = Bzl$
5 $R^1 = OMe, R^2 = R^6 = Me, R^4 = Bzl$
6 $R^1 = OAc, R^2 = R^6 = Me, R^4 = Bzl$
7 $R^1 = Cl, R^2 = R^6 = Me, R^4 = Bzl$
8 $R^1 = OH, R^2 = R^5 = Me, R^4 = Bzl$
9 $R^1 = O-C(=NH)-CCl_3, R^2 = R^6 = Me, R^4 = Bzl$

soluble or immobilised silver salts, such as silver silicate[9], silver zeolite[10], or thallium zeolite[11]. In the absence of Lewis acids, the method can be used also to generate 1,2-*trans*-gluco- and -galacto-pyranosidic linkages.

3,4-Di-*O*-benzyl-2,6-di-*O*-methyl-α-D-mannopyranosyl chloride (**7**) was selected therefore as the glycosyl donor and was prepared as follows. Hydrogenolysis of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[12] (**2**) gave mainly methyl 3,4-di-*O*-benzyl-α-D-mannopyranoside (**3**) together with some methyl 3,6-di-*O*-benzyl-α-D-mannopyranoside (**4**). Methylation[13] of **3** and acetolysis[14] of the product **5** gave the 1-acetate **6** of **8**. Treatment of **6** with dichloromethyl methyl ether then gave **7**[15].

Glycosylation of **1** was performed under standard conditions by reaction with 1 mol of **7** in dry dichloromethane with silver zeolite[10] as the promoter and molecular sieves to remove water. After one day at room temperature, the reaction was complete and the two products were separated by column chromatography on silica gel. The slower migrating, minor product, 3,4-di-*O*-benzyl-2-*O*-methyl-α-L-lyxopyranosyl 3,4-di-*O*-benzyl-2,6-di-*O*-methyl-α-D-mannopyranoside (**10**, 16%), was isolated in homogeneous form but the major product, the desired β-D-*manno*-isomer **12**, was slightly contaminated. However, after catalytic hydrogenolysis of **12**, pure crystalline everninose (**13**) was obtained, the ^{1}H- and ^{13}C-n.m.r. spectra of which clearly showed that the two monosaccharide units had different anomeric configurations.

Hydrogenolysis of **10** gave **11** (isoeverninose), the ^{13}C-n.m.r. spectrum of which suggested that the monosaccharide units were both α and, in order to confirm the structure, an alternative synthesis was worked out. *O*-Benzylated or *O*-glycosylated α-D-mannopyranosyl trichloroacetimidate reacted in the presence of boron trifluoride etherate to give exclusively α-D-mannopyranosyl compounds, reflecting the stronger anomeric effect. Saponification of **6** gave **8** which was treated[15] with sodium hydride and trichloroacetonitrile to give the trichloroacetimidate **9**. Mannosylation of **1** with **9** in the presence of trifluoromethanesulphonic acid gave **10** and confirmed the assumed structure.

The analysis of the n.m.r. spectra of **10**–**13** was difficult because 2-*O*-methyl-L-lyxose and 2,6-di-*O*-methyl-D-mannose belong to the same homomorphous series and, consequently, they are magnetically nearly equivalent. The α,α configuration of **10** and **11** was deduced from the $J_{C\text{-}1,H\text{-}1}$ values (170 Hz). In interpreting the COSY spectrum of **11**, the signals of H-5,5′ of the lyxopyranosyl unit and H-4 (3.576 p.p.m.) of the mannopyranosyl unit served as reference signals for determining the proton–proton connectivities. The ^{13}C-n.m.r. spectrum of **11** was assigned by the proton–carbon correlation method[17]. The resonances of H-1 for **13** were separated significantly and the $^1J_{C,H}$ values also indicated the presence of β (δ 97.11, *J* 160 Hz) and α (δ 94.68, *J* 170 Hz) units. Assignment of the proton–proton cross-peaks in the COSY spectrum of **13** showed unambiguously that the mannopyranosyl unit was β and that the lyxopyranosyl unit was α. Although there were higher-order parts in the ^{1}H-n.m.r. spectrum of everninose (H-2,3,4 of the lyxose

residue and H-5,6 of the mannose residue), the ^{13}C-n.m.r. spectrum could be interpreted by proton–carbon correlations. Thus, the C-2 carbons resonate at low field because of the MeO-2 group and that of the mannosyl unit was assigned. Likewise, of the C-4 resonances at 68.17 and 68.18 p.p.m., the latter was assigned to the mannose residue. The methylene carbons (C-5 of lyxose and C-6 of mannose) were assigned easily by the attached-proton-test at 65.34 and 72.56 p.p.m., respectively. There were three signals in the range of 71–73 p.p.m.; those at 71.07 and 73.05 p.p.m. belong to C-3 and C-5 of mannose, and that at 72.68 p.p.m. to C-3 of lyxose.

The structure of everninose is also confirmed by the synthesis now reported.

EXPERIMENTAL

Metlting points were determined on a Kofler hot-stage and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. ^{1}H-N.m.r. and the 2D spectra were obtained with a Varian XL-400 spectrometer, for solutions in $CDCl_3$ (internal Me_4Si) or D_2O (internal DSS). ^{13}C-N.m.r. spectra were obtained with a Bruker WP 200 SY (50.3 MHz) spectrometer. T.l.c. was carried out on DC-Alurolle Kieselgel 60 F_{254} (Merck) and detection by charring with sulfuric acid. Short-column chromatography was effected on Kieselgel G (Reanal).

Methyl 3,4-di-O-benzyl- (**3**) *and 3,6-di-O-benzyl-α-*D*-mannopyranoside* (**4**). — To a stirred solution of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside[12] (**2**, 1.94 g) in dichloromethane (20 mL) and ether (8 mL) were added gradually lithium aluminium hydride (0.396 g) and a solution of aluminium chloride (1.4 g) in ether (12 mL). After 6 h, t.l.c. revealed two products. Ethyl acetate (2 mL) and then water (4 mL) were added dropwise, and the mixture was diluted with dichloromethane (100 mL), washed with water (3 × 10 mL), dried (Na_2SO_4), and concentrated. Column chromatography (dichloromethane–acetone, 85:15) of the residue gave **3** (1.52 g, 78%), m.p. 83–85° (from light petroleum–ethyl acetate), $[\alpha]_D$ +55° (*c* 1, chloroform), R_F 0.28 (dichloromethane–acetone, 85:15). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.25–7.50 (m, 10 H, 2 Ph), 4.75 (d, 1 H, $J_{1,2}$ 2.5 Hz, H-1), 4.87 and 4.70 (2 d, 2 H, *J* 11.0 Hz, PhCH_2), 4.70 (s, 2 H, PhCH_2), 3.32 (s, 3 H, OMe), 2.35 and 2.75 (b, 2 H, HO-2,6).

Anal. Calc. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.38; H, 7.05.

Syrupy **4** (0.27 g, 13.9%) was isolated also and had $[\alpha]_D$ +29° (*c* 0.7, chloroform), R_F 0.74. ^{1}H-N.m.r. data ($CDCl_3$): δ 7.2–7.5 (m, 10 H, 2 Ph), 4.80 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 4.75 and 4.65 (2 d, 2 H, *J* 12.0 Hz, PhCH_2), 4.62 (s, 2 H, PhCH_2), 3.40 (s, 3 H, OMe), 2.6 and 2.4 (b, 2 H, HO-2,4).

Anal. Calc. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.33; H, 6.98.

*Methyl 3,4-di-O-benzyl-2,6-di-O-methyl-α-*D*-mannopyranoside* (**5**). — To a vigorously stirred solution of **3** (2.5 g) in methyl sulfoxide (8 mL) were added powdered potassium hydroxide (2.24 g) and methyl iodide (1.23 mL). Stirring was continued for 3 h at room temperature, and the mixture was then diluted with dichloromethane (250 mL), filtered, washed with water (4 × 30 mL), dried

(Na_2SO_4), and concentrated to give syrupy **5** (2.4 g, 92%), $[\alpha]_D$ +53° (*c* 1.3, chloroform), R_F 0.80 (dichloromethane–acetone, 85:15). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.25–7.50 (m, 10 H, 2 Ph), 4.95 and 4.60 (2 d, 2 H, *J* 11.0 Hz, PhCH_2), 4.80 (d, 1 H, $J_{1,2}$ 2.0 Hz, H-1), 4.72 (s, 2 H, PhCH_2), 3.50, 3.38, and 3.35 (3 s, 9 H, 3 OMe).

Anal. Calc. for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.66; H, 7.47.

*3,4-Di-O-benzyl-2,6-di-O-methyl-α-*D*-mannopyranosyl chloride* (**7**). — A stirred solution of **5** (3.65 g) in glacial acetic acid (40 mL) and acetic anhydride (40 mL) was treated at 0° with conc. sulphuric acid (1.72 mL). After stirring for 1 h at 0°, the mixture was poured into ice–water (200 mL) containing 10% of sodium hydrogencarbonate. The mixture was kept for 1 h at room temperature and then extracted with dichloromethane (4 × 100 mL), and the combined extracts were washed with water (5 × 40 mL), dried (Na_2SO_4), and concentrated. Column chromatography of the residue gave syrupy **6** (2.59 g, 66.3%), $[\alpha]_D$ +61° (*c* 1.1, chloroform), R_F 0.51 (light petroleum–ethyl acetate, 6:4). ^{1}H-N.m.r. data ($CDCl_3$): δ 7.25–7.50 (m, 10 H, 2 Ph), 6.42 (d, $J_{1\alpha,2}$ 2.0 Hz, H-1α), 5.12 (b, H-1β), 4.95 and 4.60 (2 d, 2 H, *J* 10.5 Hz, PhCH_2), 4.72 (s, 2 H, PhCH_2), 3.37, 3.36, 3.55, and 3.52 (4 s, 6 H, 2 MeO), 2.05–2.10 (m, 3 H, Ac).

A solution of **6** (1.50 g) in dichloromethane (26 mL) was stirred with fused 4 Å molecular sieve (260 mg) for 5 min under argon. After the addition of fused zinc chloride (26 mg) and dichloromethyl methyl ether (2 mL), stirring was continued for 1 h at −10°. The mixture was then filtered and concentrated at 30° (bath) to give syrupy **7** (1.35 g, 95.2%), $[\alpha]_D$ +66° (*c* 1.7, chloroform), R_F 0.62 (dichloromethane–ethyl acetate, 9:1). ^{1}H-N.m.r. data ($CDCl_3$): δ 6.15 (d, 1 H, $J_{1,2}$ 1.8 Hz, H-1), 3.47 and 3.35 (2 s, 6 H, 2 OMe).

Anal. Calc. for $C_{22}H_{27}ClO_5$: C, 64.94; H, 6.69. Found: C, 65.00; H, 6.67.

Glycosylation of **1** *with* **7**. — A solution of **1** (1.10 g) in dichloromethane (10 mL) was stirred with fused 4 Å molecular sieve (220 mg) for 5 min and then silver zeolite (6.0 g) was added. A solution of **7** (1.35 g) in dichloromethane (10 mL) was stirred for 5 min with fused 4 Å molecular sieve (200 mg) and then added to the above solution. The mixture was stirred for 24 h in the dark under argon and t.l.c. then showed the disappearance of **1** and **7**. The mixture was then concentrated. Column chromatography (hexane–ethyl acetate, 1:1) of the residue gave syrupy **10** (370 mg, 16%), R_F 0.37, and impure syrupy 3,4-di-*O*-benzyl-2-*O*-methyl-α-L-lyxopyranosyl 3,4-di-*O*-benzyl-2,6-di-*O*-methyl-β-D-mannopyranoside (**12**; 720 mg, 32%), R_F 0.48.

Anal. Calc. for $C_{42}H_{50}O_{10}$: C, 70.57; H, 7.05. Found: C, 70.50; H, 7.07.

A mixture of **10** (270 mg), aqueous 96% ethanol (36 mL), glacial acetic acid (10 mL), and 10% Pd/C (250 mg) was hydrogenated for 48 h, then filtered, and concentrated. Column chromatography of the residue gave 2-*O*-methyl-α-L-lyxopyranosyl 2,6-di-*O*-methyl-α-D-mannopyranoside (**11**, isoeverninose), as a foam (100 mg, 75%), $[\alpha]_D$ +17° (*c* 0.8, methanol), R_F 0.20 (acetone).

Anal. Calc. for $C_{14}H_{26}O_{10}$: C, 47.45; H, 7.40. Found: C, 47.42; H, 7.45.

In a similar manner, **12** (720 mg) was hydrogenolysed for 24 h. Column

TABLE I

^{1}H-N.M.R. DATA FOR **11** AND **13**

		Chemical shifts (δ)						
	Unit	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6(5')*	*H-6'*
11	lyxose	5.165	3.589	3.867	3.832	3.804	3.545	
	mannose	5.229	3.640	3.867	3.576	3.822	3.703	3.640
13	lyxose	5.297	←3.70–3.76→			3.980	3.268	
	mannose	4.959	3.636	3.859	3.578	3.74–3.83		3.631

		Coupling constants (Hz)						
	Unit	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,6}$	$J_{6,6'(5,5')}$
11	lyxose	2.9	3.4	9.8	4.8	10.0		12.5
	mannose	1.9	3.9	10.0	9.8	2.2	6.2	11.3
13	lyxose	1.7			4.8	8.4		11.7
	mannose	1.5	3.7	9.8	10.0		6.6	10.8

TABLE II

^{13}C-N.M.R. CHEMICAL SHIFT DATA FOR **11** AND **13**

	Unit	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*
11	lyxose	101.09	82.70	73.14[a]	69.85	66.58	
	mannose	100.52	83.00	72.92[a]	70.05	75.47	74.44
13	lyxose	94.68	80.11	72.68	68.17	65.34	
	mannose	97.11	80.93	71.07	68.18	73.05	72.56

[a]The chemical shifts of the H-3 resonances are identical, and hence the assignments of the C-3 resonances are exchangeable.

chromatography (dichloromethane–methanol, 8:2) of the product gave 2-*O*-methyl-α-L-lyxopyranosyl 2,6-di-*O*-methyl-β-D-mannopyranoside (everninose, **13**; 190 mg, 53.4%), m.p. 199–200°, $[\alpha]_D$ −73° (*c* 6.4, water) {lit.[6] m.p. 200–201°, $[\alpha]_D$ −74.1° (water)}, R_F 0.5 (dichloromethane–methanol, 8:2).

Anal. Found: C, 47.40; H, 7.43.

The n.m.r. data for **11** and **13** are given in Tables I and II.

3,4-Di-O-benzyl-2,6-di-O-methyl-α,β-D-mannopyranose (**8**). — A solution of **6** (1.85 g) in methanol (60 mL) containing a catalytic amount of sodium methoxide was stored for 24 h at room temperature, then neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated. ^{1}H- and ^{13}C-n.m.r. measurements showed the amorphous product (1.62 g, 97%) to be an α,β-mixture of **8**, R_F 0.17 (light

petroleum–ethyl acetate, 6:4). N.m.r. data ($CDCl_3$): ^1H, δ 7.2–7.5 (m, 10 H, 2 Ph), 5.3 (d, $J_{1\alpha,2}$ 2.0 Hz, H-1α), 4.75 (b, H-1β), 4.95 and 4.57 (2 d, 2 H, J 11.0 Hz, PhCH_2), 4.70 (s, 2 H, PhCH_2), 3.47, 3.42, 3.35, 3.32 (4 s, 6 H, MeO-2,6), 2.1 (b, exchangeable with D_2O, HO-1); ^{13}C, δ 93.81 (C-1β), 92.10 (C-1α), 59.34 and 58.97 (CH_3O-2,6).

Anal. Calc. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.26. Found: C, 68.10; H, 7.30.

3,4-Di-O-benzyl-2,6-di-O-methyl-α-D-mannopyranosyl trichloroacetimidate (**9**). — To a solution of **8** (1.5 g) in dichloromethane (20 mL) were added sodium hydride (0.093 g) and then trichloroacetonitrile (1.36 mL). The mixture was stirred for 30 min under nitrogen and then filtered through Celite, the filter was washed with dichloromethane (20 mL), and the combined filtrate and washings were concentrated. Column chromatography (1:1 light petroleum–ethyl acetate + 1% of triethylamine) of the residue gave **9** (0.95 g, 46.1%), $[\alpha]_D$ +55° (*c* 0.7, chloroform), R_F 0.73 (1:1 light petroleum–ethyl acetate + 1% of triethylamine). ^1H-N.m.r. data ($CDCl_3$): δ 8.55 (s, 1 H, $\geq$C=NH), 7.2–7.5 (m, 10 H, 2 Ph), 6.32 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 4.95 and 4.65 (2 d, 2 H, J 11.0 Hz, PhCH_2), 4.80 and 4.72 (2 d, 2 H, J 12.0 Hz, PhCH_2), 3.55 and 3.37 (2 s, 6 H, MeO-2,6).

Anal. Calc. for $C_{24}H_{28}Cl_3NO_6$: C, 54.10; H, 5.30. Found: C, 54.05; H, 5.28.

3,4-Di-O-benzyl-2-O-methyl-α-L-lyxopyranosyl · 3,4-di-O-benzyl-2,6-di-O-methyl-α-D-mannopyranoside (**10**). — To a solution of **1** (0.379 g) in dichloromethane (5 mL) were added 4 Å molecular sieve (2.0 g) and a solution of **9** (0.72 g) in dichloromethane. The mixture was stirred for ~30 min under nitrogen and then a solution of trifluoromethanesulphonic acid (0.43 g) in dichloromethane (5 mL) was added. The mixture was stirred for 28 h, a few drops of triethylamine were added, the mixture was filtered, the filter was washed with dichloromethane (150 mL), and the combined filtrate and washings were concentrated. Repeated column chromatography [ether–light petroleum (9:1), then dichloromethane–ethyl acetate (9:1)] gave syrupy **10** (0.224 g, 28.5%), $[\alpha]_D$ +21° (*c* 0.8, chloroform), R_F 0.24 (ether–light petroleum, 9:1). N.m.r. data ($CDCl_3$): ^1H, δ 7.25–7.50 (m, 20 H, 4 Ph), 4.90–5.07 (m, 2 H, H-1,1'), 4.55–5.0 (m, 8 H, 4 PhCH_2), 3.47, 3.45, and 3.35 (3 s, 9 H, 3 OMe); ^{13}C, δ 98.35 and 97.66 (C-1,1'), 62.72, 59.15, and 59.00 (3 CH_3O).

Anal. Calc. for $C_{42}H_{50}O_{10}$: C, 70.57; H, 7.05. Found: C, 70.61; H, 7.00.

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