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Note

A stereospecific synthesis of evalose, a constituent of orthosomycin antibiotics

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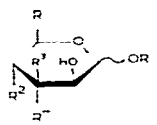
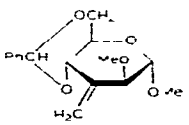
The branched-chain carbohydrate evalose (**1**), a constituent of the orthosomycin antibiotics everninomicin B[1] and flambamycin[2], has been synthesised[3] The key step of the synthesis, namely, peroxy-acid oxidation of methyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-methyl-3-*C*-methylene-α-D-*arabino*-hexopyranoside (**2**) afforded mainly the spiro-epoxide **3** having the D-*manno* configuration[4] which was subsequently transformed by known methods into **1**



1 R = R^4 = Me R^2 = R^3 = OH
7 R = CH_2OBz R^2 = OH R^3 = OBz R^4 = H
14 R = R^3 = Me R^2 = NHMe R^4 = OH



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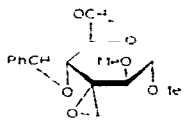

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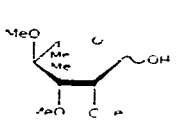

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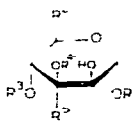
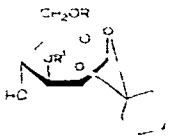
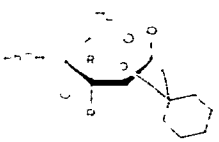


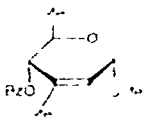
5 R = Allyl R^2 = CH_2CH R^3 = R^4 = R^5 = H
6 R = Allyl R^2 = CH_2OBz R^3 = R^5 = H R^4 = Bz
16 R = R^2 = R^5 = Me R^3 = Bz R^4 = H
17 R = R^2 = R^5 = Me R^3 = R^4 = H



8 R = Bz
9 R = H



10 R = Me
11 R = O
12 R = H
13 R = Me



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Our first approach to the synthesis of evalose was based on that used for nogalose[5] (**4**), which is a related, branched-chain carbohydrate constituent of the antibiotic nogalamycin[6]

Treatment of allyl α-D-mannopyranoside (**5**) with 2.2 equiv of benzoyl chloride

at −40° in pyridine gave, after chromatography, 50% of the 3,6-dibenzoate **6**. Deallylation of **6**, using 10% palladium-on-carbon in ethanol–acetic acid–water (2 1 1) at 80° for 2 days, gave 76% of syrupy 3,6-di-*O*-benzoyl-D-mannose (**7**). A 1,2-*O*-cyclohexylidene protecting-group was then introduced on the β side of the molecule, by heating a solution of **7** in *N*,*N*-dimethylformamide containing 1,1-dimethoxycyclohexane and toluene-*p*-sulfonic acid. 68% of the 1,2-*O*-cyclohexylidene derivative **8** was subsequently isolated. Saponification of **8** with methanolic sodium methoxide afforded 85% of syrupy 1,2-*O*-cyclohexylidene-β-D-mannopyranose (**9**). Treatment of **9** with α,α-dimethoxytoluene in *N*,*N*-dimethylformamide containing toluene-*p*-sulfonic acid gave 65% of 4,6-*O*-benzylidene-1,2-*O*-cyclohexylidene-β-D-mannopyranose (**10**). Oxidation of **10** with methyl sulfoxide–acetic anhydride furnished 89% of syrupy 4,6-*O*-benzylidene-1,2-*O*-cyclohexylidene-β-D-*arabino*-hexopyranos-3-ulose (**11**).

Unfortunately, the 1,2-*O*-cyclohexylidene group in **11** does not sterically hinder attack by methylmagnesium iodide, which gave a 1 1 mixture of the tertiary alcohols **12** and **13**. The configuration of the asymmetric centres in **12** is the same as that in evalose (**1**) and the conversion **12** → **1** is straightforward. The absence of stereoselectivity in the crucial Grignard reaction led to the consideration of a better strategy for the synthesis of evalose.

In a synthesis[7] of the branched-chain amino sugar sibirosamine **14**, the intermediate **15** was reported to be easily accessible. Cis-hydroxylation of the double bond of **15** with osmium tetraoxide occurred exclusively from the β side of the molecule, affording syrupy methyl 4-*O*-benzoyl-6-deoxy-3-*C*-methyl-α-D-mannopyranoside (**16**), saponification of which afforded an excellent yield of methyl 6-deoxy-3-*C*-methyl-α-D-mannopyranoside (**17**, methyl α-evaloside). The physical properties[8] of methyl 6-deoxy-3-*C*-methyl-α-D-allopyranoside differ from those of **17**. A crystalline methyl glycoside of natural evalose has been reported[9], without assignment of the anomeric configuration. On the basis of its ^{13}C-n.m.r. spectrum[10] it is very likely[11] that this compound corresponds to methyl β-evaloside and is different from our synthetic product. Acid hydrolysis of **17** afforded 67% of a product which was identical with evalose (**1**).

EXPERIMENTAL

General — Solutions were concentrated under diminished pressure and extracts were dried over Na_2SO_4. Optical rotations were measured on solutions in $CHCl_3$ at room temperature. N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with Varian T-60 (^{1}H) and Bruker HX-90 F.T. spectrometers (^{13}C). Chromatography was performed on Silica Gel G (Merck). Melting points are uncorrected.

Allyl 3,6-di-O-benzoyl-α-D-mannopyranoside (**6**) — Benzoyl chloride (28.7 ml) was added slowly to a solution of allyl α-D-mannopyranoside (25 g) in pyridine (1 litre) at −40° and the mixture was allowed to attain room temperature, stored for

18 h, and then partitioned between water (3 litres) and dichloromethane (3 × 500 ml) The organic layer was dried and concentrated, and the syrupy residue was chromatographed on silica gel The major product was crystallised from chloroform–hexane, to yield **6** (23 g, 50%), m p 135–137°, $[\alpha]_D$ +51° Mass spectrum *m/z* 428 (M^+) ^{1}H-N m r data δ 7 73 and 7 16 (2 m, 10 H), 5 79, 5 13, 3 96 (3 m, 5 H, allyl group) 5 13 (m 1 H, H-3), 4 73 (bs, 1 H H-1), 4 50 (bs OH), and 3 96 (m, 2 H, H-6,6′)

Anal Calc for $C_{23}H_{24}O_8$ C, 64 48, H, 5 65 Found C, 64 64, H, 5 58

*3,6-Di-O-benzoyl-1,2-O-cyclohexylidene-β-*D*-mannopyranose* (**8**) — To a solution of **6** (1 g) in ethanol–acetic acid–water (2 1 1, 24 ml) was added 10% palladium-on-carbon (1 g) The mixture was heated at 80° for 2 days, cooled filtered through Kieselguhr, and concentrated, to give syrupy 3,6-di-*O*-benzoyl-D-mannose (**7**, 690 mg, 76%) Mass spectrum *m/z* 388 (M^+) and 371

To a solution of **7** (750 mg) in *N,N*-dimethylformamide (10 ml) were added 1,1-dimethoxycyclohexane (3 ml) and toluene-*p*-sulfonic acid (50 mg) The mixture was heated at 50–55° under diminished pressure for 24 h and then partitioned between water (100 ml) and dichloromethane (3 × 100 ml) The organic layer was dried and concentrated, and the residue was crystallised from ethyl acetate–hexane, to yield **8** (620 mg, 68%), m p 168–169° $[\alpha]_D$ −9° Mass spectrum *m/z* 468 (M^+) N m r data ^{1}H, δ 8 12 and 7 50 (2 m, 10 H), 5 38 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), 5 33 (q 1 H $J_{2,3}$ 3, $J_{3,4}$ 9 Hz, H-3), 4 56 (q, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 3 Hz, H-2), 4 23 (m, 2 H, H-6,6′) 3 66 (m 1 H, H-5), and 1 56 (m, 10 H) ^{13}C δ 97 2 (C-1), 74 1 (C-2), 76 3 (C-3) 65 1 (C-4), 73 6 (C-5), and 63 6 (C-6) + benzoate and cyclohexylidene carbons

Anal Calc for $C_{26}H_{28}O_8$ C, 66 65, H, 6 02 Found C, 66 69, H, 6 20

*4,6-O-Benzylidene-1,2-O-cyclohexylidene-β-*D*-mannopyranose* (**10**) — A solution of **8** (370 mg) in methanolic 0 1M sodium methoxide (20 ml) was stored at room temperature for 3 h and then neutralised with Amberlite MB-3 (H^+) resin Concentration gave chromatographically homogeneous, syrupy 1 2-*O*-cyclohexylidene-*β*-D-mannopyranose (**9**, 176 mg, 85%) ^{1}H-N m r data δ 5 11 (d, 1 H, $J_{1,2}$ 2 Hz H-1) 4 35 (q, 1 H, $J_{1,2}$ 2, $J_{2,3}$ 4 Hz H-2), 3 88 (m, 3 H, H-3,4,5), and 1 60 (m, 10 H)

To a solution of **9** (950 mg) in *N,N*-dimethylformamide (16 ml) were added *α,α*-dimethoxytoluene (3 ml) and toluene-*p*-sulfonic acid (100 mg) The mixture was heated at 50–55° under diminished pressure for 3 h and then partitioned between water (100 ml) and dichloromethane (3 × 80 ml) Concentration of the organic layer and crystallisation of the residue from ethyl acetate–hexane yielded **10** (800 mg 65%), m p 172–173°, $[\alpha]_D$ −58° N m r data ^{1}H, δ 7 40 (m, 5 H) 5 57 (s, H-7), 5 31 (d, $J_{1,2}$ 2 5 Hz, H-1), 4 38 (q, $J_{1,2}$ 2 5, $J_{2,3}$ 5 Hz, H-2) 4 31 (q $J_{2,3}$ 5 $J_{3,4}$ 10 Hz H-3), 4 06 (m, H-6e and OH) 3 90 (q $J_{6a,6e} = J_{6a,5}$ = 10 Hz, H-6a), 3 74 (t, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 3 36 (m, H-5), and 1 62 (m, 10 H) ^{13}C, δ 97 4 (C-1), 78 0 (C-2), 69 6 (C-3), 78 7 (C-4), 65 2 (C-5), and 68 7 (C-6) + benzylidene and cyclohexylidene carbons

Anal Calc for $C_{19}H_{24}O_6$ C, 65 50, H, 6 94 Found C, 65 79, H, 7 04

*4,6-O-Benzylidene-1,2-O-cyclohexylidene-β-*D*-mannopyranos-3-ulose* (**11**) — A solution of **10** (280 mg) in methyl sulfoxide (7 ml) and acetic anhydride (4 ml) was

stored for 24 h at room temperature, and then partitioned between water (100 ml) and dichloromethane (3 × 100 ml) The combined organic layers were concentrated, to give **11** (250 mg, 89%) ^{1}H-N m r data δ 7 37 (m 5 H), 5 64 (s, H-7), 5 54 (bs, H-1), 4 79 (d, $J_{4,5}$ 10 Hz, H-4), 4 48 (m H-6e), 4 34 (bs, H-2), 3 91 (m, H-6a), 3 67 (m, H-5), and 1 64 (m, 10 H)

*4,6-O-Benzylidene-1,2-O-cyclohexylidene-3-C-methyl-β-*D*-manno-* (**12**) *and -altro-pyranose* (**13**) — To a solution of **11** (170 mg) in tetrahydrofuran (50 ml) was added, under nitrogen at −20°, a solution in tetrahydrofuran (50 ml) of methylmagnesium iodide prepared from magnesium (360 mg) and methyl iodide (6 3 ml). The mixture was allowed to attain room temperature slowly After 24 h, cold, saturated, aqueous ammonium chloride was added, the solvent was evaporated, and the residue was partitioned between water and dichloromethane Concentration of the organic layer yielded a 1 · 1 mixture of **12** and **13**, as judged by the ^{1}H-n m r spectrum of the residue δ 5 62 and 5 58 (s H-7 of **12** and **13**), and 5 40 and 5 34 (d, $J_{1,2}$ 2 Hz, H-1 of **12** and **13**)

*Methyl 4-O-benzoyl-6-deoxy-3-C-methyl-α-*D*-mannopyranoside* (**16**) — Methyl 4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-α-D-*erythro*-hex-2-enopyranoside[7] (**15**, 90 mg) was added to pyridine (3 ml) containing osmium tetraoxide (75 mg), and the mixture was stored at room temperature for 2 h A solution of sodium bisulfite (1 2 ml), water (2.5 ml), and pyridine (1.7 ml) was then added with stirring and, after 1 h, the mixture was partitioned between water and dichloromethane The organic layer was concentrated, to yield syrupy **16** (100 mg, 98%), $[\alpha]_D$ +81° ^{1}H-N m r data δ 7 83 and 7 26 (m, 5 H), 5 00 (d, $J_{4,5}$ 10 Hz, H-4), 4 70 (d, $J_{1,2}$ 2 Hz, H-1), 3 90 (m, H-5), 3 53 (bs H-2 and OH), 3 33 (s, OMe), 1 40 (s, Me-3), and 1 26 (d, $J_{5,6}$ 6 Hz, Me-5)

*Methyl 6-deoxy-3-C-methyl-α-*D*-mannopyranoside* (**17**) — A solution of **16** (115 mg) in methanolic 0 1M sodium methoxide (10 ml) was stored at room temperature for 3 h, and then neutralised with Amberlite MB-3 (HO^-) resin Concentration of the solution gave methyl α-evaloside (**17**, 70 mg, 94%), m p 122° (from ether–hexane), $[\alpha]_D$ +54° Mass spectrum *m/z* 192 (M^+) ^{1}H-N m r data δ 4 63 (bs, H-1), 3 33 (s, OMe), and 1 30 (s, Me-3)

Anal Calc for $C_8H_{16}O_5$ C, 49.99, H, 8 39. Found C, 49 76, H, 8 29

*6-Deoxy-3-C-methyl-*D*-mannose* (evalose, **1**) — To a solution of **17** (70 mg) in tetrahydrofuran (1 ml) was added 2M hydrochloric acid (2 ml), and the mixture was boiled under reflux for 3 h, neutralised with barium carbonate, filtered through Kieselguhr, and concentrated, to give **1** as a colorless oil (43 mg, 67%), $[\alpha]_D$ −7° (ethanol), lit [8] $[\alpha]_D$ −4 9° (ethanol)

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REFERENCES

1 A K Ganguly and A K Saksena, *Chem Commun*, (1973) 531–532
2 W D Ollis, C Smith, and D E Wright, *Chem Commun*, (1974) 881–882
3 J Yoshimura, N Hong and K Sato, *Chem Lett* (1979) 1263–1264
4 J Yoshimura, K Sato, and M Funabashi *Bull Chem Soc Jpn*, 52 (1979) 2630–2634
5 L Valente, A Olesker, R Rabanal L E S Barata, G Lukacs and T T Thang, *Tetrahedron Lett* (1979) 1153–1156
6 P F Wiley R B Kelly, E L Caron V H Wiley J H Johnson F A MacKellar and S A Mizsak, *J Am Chem Soc*, 99 (1977) 542–549
7 I Dyong and G Schulte, *Tetrahedron Lett*, (1980) 603–606
8 G B Howarth, W A Szarek and J K N Jones *Can J Chem*, 46 (1968) 3691–3694
9 W D Ollis, C Smith, and D E Wright *Tetrahedron* 35 (1979) 105–127
10 W D Ollis, I O Sutherland B F Taylor C Smith and D E Wright, *Tetrahedron* 35 (1979) 993–1001
11 S Omura A Nakagawa, A Neszmelyi S D Gero A-M Sepulchre, F Piriou and G Lukacs, *J Am Chem Soc*, 97 (1975) 4001–4009