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Preliminary communication

Stereoselective synthesis of methyl 4-*C*-acetyl-6-deoxy-2,3-*O*-methylene-D-galactonate and -D-gluconate. Determination of the D-*galacto* configuration of methyl eurekanate by synthesis

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Oligosaccharide antibiotics, everninomicins[1] and flambamycin[2] of the orthosomycin family contain a characteristic 4-*C*-substituted 2,3-*O*-methylene-aldonolactone which is attached at a terminal position by an acetal interlinkage. The configuration of the lactone in everninomicins B and D was determined by X-ray analysis[3] and characterized as the corresponding methyl aldonate[4]. Recently, we have synthesized the methyl ester, namely, methyl 6-deoxy-4-*C*-(hydroxymethyl)-5-*O*-methyl-2,3-*O*-methylene-L-idonate (**1**) from L-arabinose[5]. As the configuration of methyl eurekanate (methyl 4-*C*-acetyl-6-deoxy-2,3-*O*-methylenehexonate) from flambamycin was ambiguous, the D-*galacto* (**2**) and D-*gluco* (**4**) diastereomers were stereoselectively synthesized from D-glucose, on the assumption that the configurations of the carbon atoms bearing the characteristic 2,3-methylenedioxy group in **1** and methyl eurekanate are the same. As a result, the configuration of methyl eurekanate has now been determined to be D-*galacto*.

Treatment with sodium hydride of benzyl 4,6-*O*-benzylidene-α-D-glucopyranoside in *N*,*N*-dimethylformamide and dichloromethane[6] and separation of the products on a column of silica gel using 8:1 hexane–ethyl acetate, gave the corresponding 2,3-*O*-methylene derivative (**5**), m.p. 107–108°, $[\alpha]_D$ +123° (*c* 1.0, $CHCl_3$), and two dimers, **6**, m.p. 111–113°, $[\alpha]_D$ +171° (*c* 0.98, $CHCl_3$), and **7**, m.p. 114–116°, $[\alpha]_D$ +196° (*c* 0.8, $CHCl_3$) in 43, 6.2, and 7.2% yield, respectively. The configurations of **6** and **7** were deduced from the methylene proton signals in their ^{1}H-n.m.r. spectra (**6**: δ 4.75 and 4.96, ABq, *J* 7.0 Hz; **7**: δ 4.70 and 4.90, each s). Partial hydrolysis of **5** with 70% acetic acid for one day at room temperature gave the *O*-de benzylidenated product **8**, m.p. 108–110°, $[\alpha]_D$ +176° (*c* 1.0, $CHCl_3$) in 64% yield. Monotosylation of **8** in pyridine with *p*-toluenesulfonyl chloride gave the 6-*O*-tosyl derivative (**9**), m.p. 80–82°, $[\alpha]_D$ +78.9° (*c* 1.2, $CHCl_3$), in 81% yield. Reduction of **9** in dimethyl sulfoxide with sodium borohydride gave the 6-deoxy derivative (**10**) as a syrup, $[\alpha]_D$ +154° (*c* 0.85, $CHCl_3$), in 81% yield. Oxidation of **10** with dimethyl sulfoxide–trifluoroacetic anhydride[7] gave a quantitative yield of benzyl 6-deoxy-2,3-*O*-methylene-α-D-*xylo*-hexopyranosid-4-ulose (**11**) as a syrup: ^{1}H-n.m.r. data ($CDCl_3$): δ ~7.38 (m, 5 H, Ph), 5.47 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.19 and 5.10 (each d, 2 H, J_{gem} 0.8 Hz, OCH_2O), 4.82

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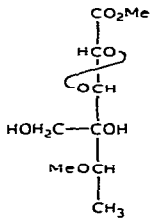
(s, 2 H, CH_2Ph), 4.70 (dd, 1 H, $J_{3,5}$ 1.0 Hz, H-3), 4.12 (dq, 1 H, $J_{5,6}$ 3.5 Hz, H-5), 3.63 (dd, 1 H, $J_{2,3}$ 10.5 Hz, H-2), and 1.35 (d, 3 H, H-6). Syrupy **11** was used for the next reaction without purification.



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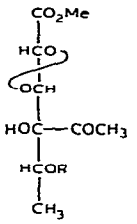
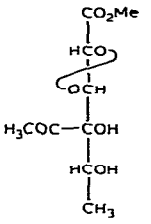


2 R = H
3 R = Ac



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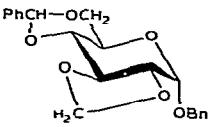
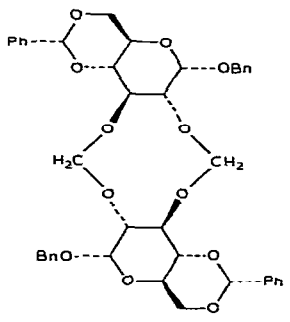


5 Ph = C_6H_5
Bn = $C_6H_5CH_2$



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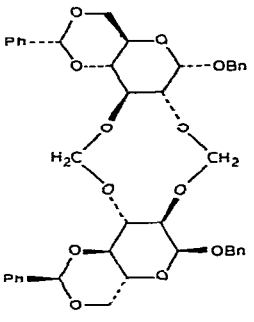

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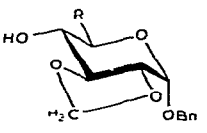
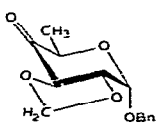
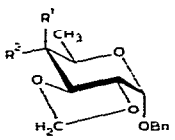


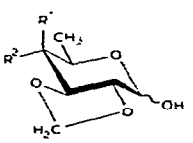
8 R = CH_2OH
9 R = CH_2OTs
10 R = Me



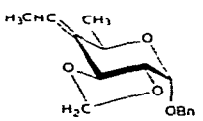
11



12 R' = OH, R^2 = $-CH=CH_3$
13 R' = OH, R^2 = 
14 R' = OH, R^2 = $-CH-CH_2$ (O)
15 R' = OH, R^2 = $-CHOHCH_3$
16 R' = OH, R^2 = $-COCH_3$
17 R' = $-CHOHCH_3$, R^2 = OH
18 R' = $-COCH_3$, R^2 = OH



19 R' = OH, R^2 = $-COCH_3$
20 R' = $-COCH_3$, R^2 = OH



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Reaction of **11** with vinylmagnesium bromide in oxolane (tetrahydrofuran) at room temperature, and separation of the products on a column of silica gel with 4:1 hexane–ethyl acetate, gave benzyl 6-deoxy-2,3-*O*-methylene-4-*C*-vinyl-α-D-galactopyranoside (**12**) as a syrup, $[\alpha]_D$ +141° (*c* 6.8, $CHCl_3$), and the 4-epimer of **12** as a syrup, $[\alpha]_D$ +167° (*c* 2.3, $CHCl_3$) in the ratio of 15.9:1 in 55.4% yield. These configurations were deduced from the chemical shifts of the α-carbon atoms in the vinyl groups: ^{13}C-n.m.r. data, **12**, 137.6; 4-epimer, 132.7 p.p.m. (ref. 8). A similar reaction of **11** with 2-lithio-2-methyl-1,3-dithiane[9] gave, exclusively, the corresponding D-*galacto* derivative (**13**) as a syrup in 40% yield, $[\alpha]_D$ + 116° (*c* 0.8, $CHCl_3$); ^{13}C-n.m.r. of C-2 of the 1,3-dithianyl group: 58.36 p.p.m. (ref. 10). Epoxidation of **12** with *m*-chloroperoxybenzoic acid in 1,2-dichloroethane at 80° gave a mixture of the corresponding (*S*)- and (*R*)-epoxides (**14**) in 46% yield; this was converted into the 4-*C*-acetyl derivative (**16**), a syrup, {$[\alpha]_D$ +135.9° (*c* 1.3, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.50–7.26 (m, 5 H, Ph), 5.36 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.14 and 5.04 (each d, 2 H, J_{gem} 1.0 Hz, OCH_2O), 4.78 and 4.74 (ABq, 2 H, *J* 12.0 Hz, CH_2Ph), 4.31 (d, 1 H, $J_{2,3}$ 10.0 Hz, H-3), 4.04 (q, 1 H, $J_{5,6}$ 6.0 Hz, H-5), 3.87 (dd, 1 H, H-2), 3.87 (s, 1 H, OH), 2.26 (s, 3 H, $COCH_3$), and 0.98 (d, 3 H, H-6)}, *via* the corresponding diols* (**15**) in 55% overall yield, by successive reduction with lithium aluminum hydride and oxidation with *N*-chlorosuccinimide and dimethyl sulfide[11]. Compound **16** was also obtained, in 50% yield, from **13** by treatment with mercuric oxide and mercuric chloride in aqueous methanol. Hydrogenation of **16** in the presence of palladium-on-charcoal gave the free sugar (**19**) as a syrup, $[\alpha]_D$ −45.2 → −48.5° (*c* 1.5, EtOH; 8 h), in 96% yield.

On the other hand, reaction of **11** with 1.5 molar equivalents of ethyltriphenylphosphonium bromide and butyllithium in ether gave a 1:1.6 mixture of the (*E*)- and (*Z*)-4-*C*-ethylidene derivatives (**21**) in 65% yield. Compound **21** was exclusively converted into the corresponding 4-*C*-acetyl derivative (**18**) having the D-*gluco* configuration[12] {m.p. 88–89°, $[\alpha]_D$ +152.7° (*c* 2.6, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.50–7.30 (m, 5 H, Ph), 5.40 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.10 and 5.05 (each d, 2 H, J_{gem} 1.0 Hz, OCH_2O), 4.77 and 4.70 (ABq , 2 H, *J* 12.3 Hz, CH_2Ph), 4.24 (s, 1 H, OH), 4.10 (d, 1 H, $J_{2,3}$ 10.0 Hz, H-3), 3.95 (dd, 1 H, H-2), 3.79 (q, 1 H, $J_{5,6}$ 7.0 Hz, H-5), 2.26 (s, 3 H, $COCH_3$), and 1.07 (d, 3 H, H-6)} *via* the corresponding diols* (**17**), in 50% overall yield, by oxidation with 4-methylmorpholine *N*-oxide and a catalytic amount of osmium tetraoxide, followed by oxidation as already described. Hydrogenation of **18** in the presence of palladium-on-charcoal gave the corresponding, free sugar (**20**) as a syrup in 96% yield, $[\alpha]_D$ −12.1 → −15.3° (*c* 1.7, EtOH; 8 h).

Thus obtained, **19** and **20** were oxidized with bromine in the presence of barium carbonate in water, and the resulting barium aldonates were treated with Amberlite IR-120 ion-exchange resin in methanol, to give the corresponding methyl aldonate; **2**, $[\alpha]_D$ −52.1° (*c* 0.6, EtOH), and **4**, $[\alpha]_D$ −39.8° (*c* 0.8, EtOH), as syrups, in 37 and 36% yield, respectively. It was found that the ^{1}H- and ^{13}C-n.m.r. parameters of **2** were completely identical with those reported[2] for methyl eurekanate, $[\alpha]_D$ −55.2° (EtOH). Moreover, the ^{1}H-n.m.r. parameters of the monoacetate (**3**; m.p. 85–86°) of **2**, obtained

*For the examination of stereoselectivities in the reactions used, the (*S*)- and (*R*)-1-hydroxyethyl derivatives were separated. The results will be reported elsewhere.

by the usual acetylation of 2 with acetic anhydride in pyridine, were identical with those reported for methyl eurekanate monoacetate, m.p. 87°, and no depression of the melting point was observed on admixture of 2 with an authentic sample. From these results, the configuration of methyl eurekanate was determined to be D-*galacto***.

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**According to information from Prof. W. Keller-Schierlein of the Eidgenössische Technische Hochschule, Zurich, he determined the D-*galacto* configuration of methyl eurekanate monoacetate by X-ray analysis; paper submitted to *Helv. Chim. Acta*.