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A SYNTHESIS OF METHYL D-ALDGAROSIDE B

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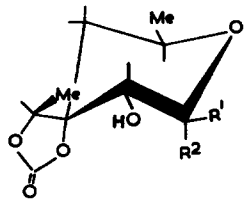
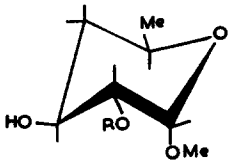
Methanolysis of the neutral, macrolide antibiotic aldgamycin E (from Streptomyces lavendulae[1]) yields the anomeric methyl D-aldgarosides A(α-anomer) (1) and B(β-anomer) (2) among the sugar components.[2] Initial studies on these branched-chain sugar cyclic carbonates established their gross structural features, but the configuration of the C-(1-hydroxyethyl) chain-branch was not assigned. Recent synthetic studies[3] have established the (S)-configuration of the chain-branch. We have reached the same conclusion, and presently report part of our studies that culminated in a synthesis of methyl D-aldgaroside B (2). The described route was chosen so as to allow a reasonable degree of stereochemical control in introducing the new asymmetric centres.

The starting material for the synthesis was methyl 4,6-dideoxy-α-D-xylo-hexopyranoside (3), which was readily prepared[4] in two steps from methyl α-D-glucopyranoside. Treatment of (3) with N-benzoylimidazole[5] in boiling chloroform gave principally the 2-benzoate (4), m.p. 107-108° (from light petroleum), $[\alpha]_D$ + 153° (c 2.8 in $CHCl_3$). The site of benzoylation was revealed by the next step in the sequence, which afforded methyl 2-O-benzoyl-4,6-dideoxy-α-D-erythro-hexopyranosid-3-ulose (5), $[\alpha]_D$ + 66° (c 1.8 in $CHCl_3$), following oxidation of (4) with ruthenium tetroxide in carbon tetrachloride.[6] The n.m.r. spectrum ($CDCl_3$) of the hexopyranosidulose (5) showed the anomeric proton as a doublet ($J_{1,2}$ 4Hz) at δ4.76 mutually coupled to the doublet of H-2 at δ4.47; these assignments were confirmed by spin-decoupling experiments.

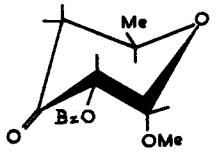
Treatment of (5) with an excess of vinylmagnesium bromide in ether gave, with concomitant debenzoylation, methyl 4,6-dideoxy-3-C-vinyl-α-D-ribo-hexopyranoside (6) (81%), $[\alpha]_D$ + 109° (c 1.2 in $CHCl_3$). The configuration of the new asymmetric centre at C-3 of (6) was established by catalytic hydrogenation to the C-ethyl derivative (7), $[\alpha]_D$ + 92.5° (c 0.7 in $CHCl_3$), whose c.d. spectrum in Cupra A solution exhibited a



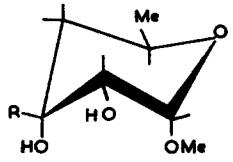
(1) R^1=H, R^2=OMe
(2) R^1=OMe, R^2=H



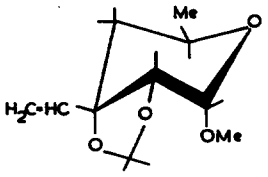
(3) R=H
(4) R=Bz



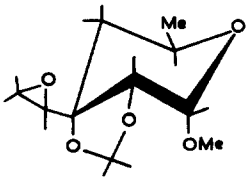
(5)



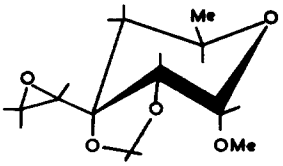
(6) R=CH=CH$_2$
(7) R=Et



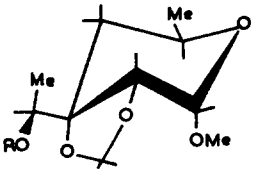
(8)



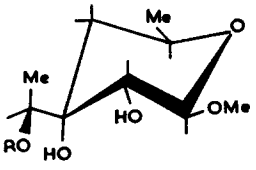
(9)



(10)



(11) R=H
(12) R=CO·OCH$_2$CCl$_3$



(13) R=CO·OCH$_2$CCl$_3$
(14) R=H

negative Cotton effect indicative[7] of a positive dehedral angle between the hydroxyl groups at C-2 and C-3.

The C-vinylglycoside (6) was then treated with 2,2-dimethoxypropane[8] in the presence of toluene-p-sulphonic acid to give the 2,3-O-isopropylidene derivative (8), b.p. 62-64° (bath) at 12mmHg, $[\alpha]_D$ + 72° (c 3 in $CHCl_3$). It was hoped that the fused pyranose-dioxolane ring-system would serve two purposes in connection with the next step in the synthetic sequence, which involved peroxyacid oxidation of the double bond. First, it should ensure that the reagent's approach from the endo-direction with respect to the fused-ring system is impeded. Second, that the double bond is orientated so as to minimize non-bonded interactions between it and the dioxolane ring. Examination of molecular models showed that formation of the (S)-epoxide should then be favoured. We were pleased to find that treatment of (8) with m-chloroperbenzoic acid in methylene chloride gave a 3:1 mixture (g.l.c. examination) of the two epoxides, which

were obtained pure following chromatography on silica gel. On the basis of the foregoing discussion, the major epoxide (9), b.p. 45-50°(bath) at 0.3mmHg, $[\alpha]_D$ + 54° (c 1.2 in $CHCl_3$), was assigned the (S)-configuration, and the minor epoxide (10), m.p. 67-69° (from ether), $[\alpha]_D$ + 60° (c 2.7 in $CHCl_3$), the (R)-configuration.

Reductive ring-opening of the major epoxide (9) with lithium aluminium hydride in ether furnished methyl 4,6-dideoxy-3-C-(1'-(S)hydroxyethyl)-2,3-O-isopropylidene-α-D-ribo-hexopyranoside (11), m.p. 66-68° (from ether), $[\alpha]_D$ + 71° (c 1.3 in $CHCl_3$). The branched-chain glycoside (11) was converted[9] into the 1'-O-(2,2,2-trichloroethoxycarbonyl) derivative (12), m.p. 97-98°, $[\alpha]_D$ + 25° (c 1.1 in $CHCl_3$), which on methanolysis, followed by chromatography on silica gel, furnished methyl β-D-aldgaroside B (2), m.p. 175-177° (from methylene chloride-ether), $[\alpha]_D$ - 40 ± 2° (c 1 in MeOH) [lit., m.p. 175-177°, $[\alpha]_D$ - 41 ± 3° (c 1 in MeOH) (ref. 2); m.p. 178-180°, $[\alpha]_D$ - 43.5° (MeOH) (ref. 3)]. The deacetonated β-glycoside (13) resulting from methanolysis was presumably cyclized to yield to 1',3-cyclic carbonate during the isolation or chromatographic procedures used. Alternatively, methanolysis of (11) gave, after chromatography, the decarbonated form (14), $[\alpha]_D$ - 46° (c 1.3 in $CHCl_3$), of methyl β-D-aldgaroside B, which preferentially furnished (2) (80%), with physical constants identical to those found previously, following reaction with phosgene in pyridine. The n.m.r. spectra ($CDCl_3$) of synthetic and naturally derived methyl β-D-aldgaroside B were indistinguishable.

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