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THE SYNTHESIS OF D-ARCANOSE*

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ABSTRACT

Oxidation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside (**3**) with ruthenium tetroxide gave the 3-ketone **4** in high yield Treatment of ketone **4** with methylmagnesium iodide gave predominantly methyl 4,6-*O*-benzylidene-2-deoxy-3-*C*-methyl-α-D-*xylo*-hexopyranoside (**5**), which was converted into the 3-*O*-methyl derivative (**6**) The reaction of compound **6** with *N*-bromosuccinimide afforded methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-D-*xylo*-hexopyranoside (**7**) in high yield Compound **7** was converted, by catalytic debenzoylation and reductive debromination, into methyl α-D-arcanoside (**9**). Acid-catalyzed hydrolysis of glycoside **9** gave D-arcanose (**10**) Configurational studies support the 2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-*xylo*-hexose structure for arcanose

INTRODUCTION

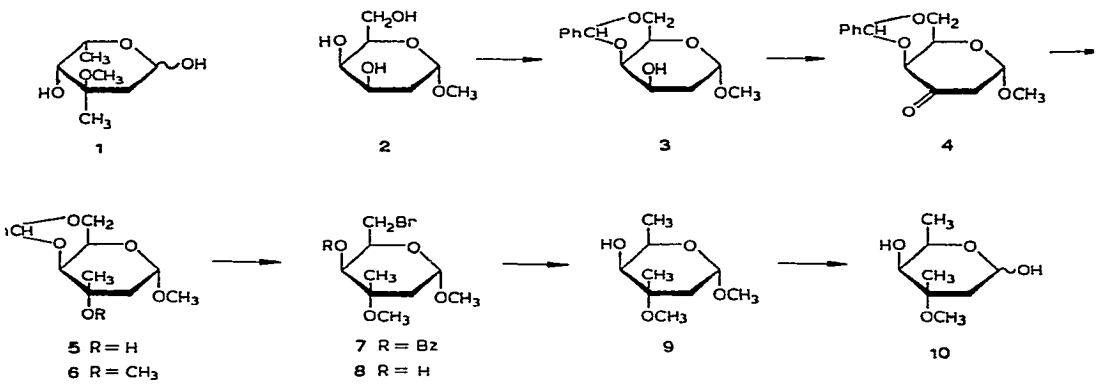
Lankamycin, a relatively new medium-spectrum antibiotic, active against gram-positive bacteria, is produced, together with another antibiotic, lankacidin, by *Streptomyces violaceoniger*[2], a micro-organism isolated from a sample of soil in Ceylon Acid hydrolysis of lankamycin, which belongs to the macrolide group[2], gives two sugar components, namely, lankavose (4,6-dideoxy-3-*O*-methyl-D-*xylo*-hexose), and the 4-*O*-acetyl derivative of a new branched-chain sugar, arcanose[3,4] By a combination of n m r and degradative studies, the 2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-L-*xylo*-hexose structure **1** was proposed for arcanose The structure was supported further by conversion[5] of L-arcanose into the diastereoisomer, L-cladinose, by a simple oxidation–reduction process at C-4

RESULTS AND DISCUSSION

In continuation of our syntheses of branched-chain sugars, we have now prepared D-arcanose by a route similar to that employed[6] in the synthesis of L-mycarose (2,6-dideoxy-3-*C*-methyl-L-*ribo*-hexose) and L-cladinose (2,6-dideoxy-3-*C*-methyl-3-

*For a preliminary communication, see Ref 1

O-methyl-L-*ribo*-hexose) Configurational investigations have led to the assignment of a D-*xylo* configuration to the hexose, in agreement with that assigned previously[5].



Methyl 2-deoxy-α-D-*lyxo*-hexopyranoside[7] (**2**) was converted into the 4,6-*O*-benzylidene derivative **3** by using copper sulfate as catalyst Oxidation of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*lyxo*-hexopyranoside (**3**) with a mixture of ruthenium dioxide and potassium metaperiodate in chloroform, in the presence of potassium carbonate[8], occurred readily to give methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-hexopyranosid-3-ulose (**4**) in 89% yield The modified procedure for ruthenium tetroxide oxidation is a significant improvement over that published earlier[9], by which the hexopyranosid-3-ulose **4** was prepared from compound **3** in 47% yield Compound **4** in benzene was treated then with methylmagnesium iodide in ether at 0° The addition appeared to be highly stereoselective, giving predominantly one compound (**5**), which was separated by column chromatography from a trace of another product (presumably the alternative addition product) which migrated at a lower rate on a thin-layer chromatogram Grignard reagents are known to attack ketones preferentially from the least-hindered side of the molecule[10] A consideration of the conformation of compound **4** (Fig 1) suggests that attack by the Grignard reagent from the side resulting in the formation of the axial alcohol (route *a*) would be sterically more favorable than attack from the side resulting in the formation of the equatorial alcohol (route *b*) In route *b*, considerable steric interaction would be expected between the attacking species and the axial methoxyl group at C-1 Treatment of compound **5** with methyl sulfate and sodium hydroxide in tetrahydrofuran gave the 3-*O*-methyl derivative **6** in high yield.

Recently, Hanessian[11] reported a novel ring-opening of benzylidene acetals of sugars by *N*-bromosuccinimide to give, in the case of 4,6-*O*-benzylidene derivatives, the corresponding 6-bromo-4-benzoates Treatment of compound **6** with 1.1 equivalents of *N*-bromosuccinimide in boiling carbon tetrachloride, in the presence of an excess of barium carbonate, afforded an almost quantitative yield of methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-D-*xylo*-hexopyranoside (**7**) After 15 min, examination of the reaction mixture by thin-layer chromatography

showed that the starting material had all reacted Removal of the benzoyl group at C-4 by catalytic hydrolysis, followed by debromination with lithium aluminum hydride, gave crystalline methyl 2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-D-*xylo*-hexopyranoside (**9**) Acid-catalyzed hydrolysis [Rexyn-101 (H^+) ion-exchange resin] of the glycoside **9** afforded crystalline D-arcanose (**10**), whose physical constants were

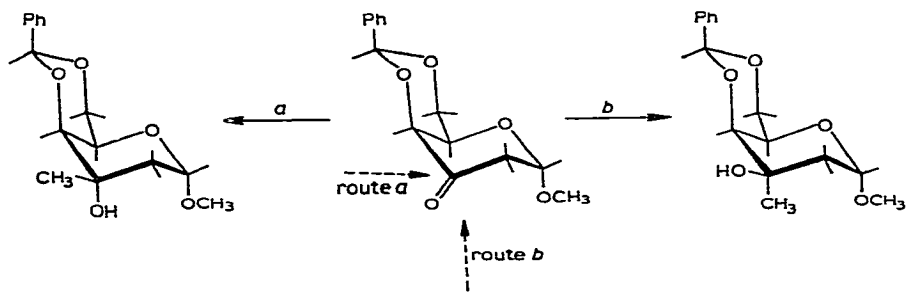


Fig 1 Addition of methylmagnesium iodide to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*threo*-hexopyranosid-3-ulose (**4**)

in good agreement with those reported for L-arcanose[3] The infrared and n m r spectra of **10** were identical with those of authentic L-arcanose, and the two compounds were indistinguishable by paper and thin-layer chromatography.

The n m r spectrum of glycoside **9** in chloroform-*d* showed two different *C*-methyl signals A singlet at τ 8 80 was assigned to the C-3 methyl group The C-5 methyl signal is observed as a doublet also centered at τ 8 80 (*J* 7 Hz) An equatorial C-5 methyl has been reported[12] previously to give a signal at τ 8 76–8 84 With acetyl chloride–dimethylaniline[13]*, compound **5** gave a syrupy acetate whose n m r spectrum showed an acetyl signal at τ 8 02 Tertiary acetoxy groups possessing the axial orientation in a number of cyclanols have been reported[14] recently to give n.m r signals in the region τ 7 93–8 04 With compound **5** in the *C1* (D) conformation, the n m r data support the previously assigned *xylo* configuration for arcanose[5] Further evidence for the axial orientation of the hydroxyl group at C-3 in compound **5**, and hence for the D-*xylo*-configuration for the compound, was obtained by application of the method of Overend *et al*[15] for the assignment of configuration to branched-chain sugars The infrared spectrum of compound **5** in carbon tetrachloride ($c < 0$ 005M) showed strong absorption at 3520 cm^{-1}, which was indicative of 1,3-diaxial, hydrogen-bonded interaction. Such interaction would arise if compound **5** had the *xylo* (but not the *lyxo*) configuration

EXPERIMENTAL

General methods — Solutions were concentrated below 50° under diminished pressure Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Optical rotations were measured with a Bendix ETL-NPL

*We thank Professor F W Lichtenthaler for suggesting the acetylation procedure

automatic polarimeter, Type 143A, at 20 ±2° Infrared spectra were measured on a Beckman-IR5A spectrophotometer. N m r. spectra were determined at 60 MHz in chloroform-*d* with tetramethylsilane as internal standard Thin-layer chromatography (t l c) was performed, unless otherwise stated, with Silica Gel G as the adsorbent, and 2 3 ethyl acetate–petroleum ether (b p 60–80°) as the developing solvent The developed plates were air-dried, sprayed with 5% ethanolic sulfuric acid, and heated at about 150°. Paper chromatography was carried out by the descending method on Whatman No 1 filter paper in the following solvent systems butyl alcohol saturated with water (*A*), 6 4 3 butyl alcohol–pyridine–water (*B*); 3 1·1 butyl alcohol–ethanol–water (*C*) Sugars were detected[16] by spraying the chromatograms with a 1 1 mixture of vanillin (1% in ethanol) and perchloric acid (3% in water), and heating for 2 min

Methyl 4,6-O-benzylidene-2-deoxy-α-D-lyxo-hexopyranoside (**3**) — Methyl 2-deoxy-α-D-*lyxo*-hexopyranoside[7] (4 g) was stirred with freshly distilled benzaldehyde (15 ml) and anhydrous copper sulfate until t l c revealed no starting material (24 h) Addition of water and petroleum ether to the mixture gave a crystalline solid which was removed by filtration Recrystallization from methanol–water gave compound **3** as needles, yield 4 8 g (80%), m p 184–185°, $[\alpha]_D$ +104° (*c* 0 3, ethanol), lit[7], m p 178–179°, $[\alpha]_D^{20}$ +106° (*c* 0 62, chloroform)

Methyl 4,6-O-benzylidene-2-deoxy-α-D-threo-hexopyranosid-3-ulose (**4**) — Compound **3** (4 g) was stirred with a mixture of potassium metaperiodate (3 34 g, 2 equiv), ruthenium dioxide (0 10 g), and potassium carbonate in ethanol-free chloroform (20 ml) and water (20 ml) T l c did not show any starting material after 5 h Propyl alcohol (1 ml) was added, and the mixture was stirred for 15 min to destroy excess of ruthenium tetroxide The mixture was filtered through Celite, and the aqueous layer was extracted with chloroform (2 × 25 ml) The extracts were combined, dried ($MgSO_4$), and concentrated to give a crystalline product which was recrystallized from isopropyl alcohol, yield 3 5 g (89%), m p 134–135°, $[\alpha]_D$ +154° (*c* 0 7, chloroform), λ_{max}^{Nujol} 5 8 μm (C=O), lit[9], m p 132–133°, $[\alpha]_D$ +150° (chloroform)

Methyl 4,6-O-benzylidene-2-deoxy-3-C-methyl-α-D-xylo-hexopyranoside (**5**). — A solution of ketone **4** (3 g) in dry benzene (50 ml) was added dropwise to a stirred solution of methylmagnesium iodide [prepared from magnesium (4 3 g) and methyl iodide (14 6 ml)] in ether (200 ml) at 0° After being kept at room temperature overnight, the reaction mixture was poured into ice–water (500 ml), and the aqueous layer was extracted with chloroform Concentration of the dried extracts yielded a viscous syrup (3 1 g) T l c revealed the presence of a major component, R_F 0 43, and a trace of another component, R_F 0 14 Fractionation on silica gel (200 g), with 2 3 ethyl acetate–petroleum ether (b p 60–80°) as eluent, gave the major component **5** as a syrup, yield 2 8 g (91%), b p 135–140°/0 03 mm, $[\alpha]_D$ +159° (*c* 1 1, chloroform), λ_{max}^{film} 2 85 (OH), 14 4 μm (Ph), n m r data τ 2 32–2 8 (5-proton multiplet, Ph), τ 4 54 (1-proton singlet, benzylidene-methine H), τ 5 18 (1-proton multiplet, H-1), τ 6 75 (3-proton singlet, OMe), τ 7 8–8 2 (1-proton quartet, H-2 *eq*), τ 8 25–8.64 (1-proton quartet, H-2 *ax*), τ 8 8 (3-proton singlet, C-3 Me)

Anal. Calc. for $C_{15}H_{20}O_5$. C, 64 3, H, 7 2 Found C, 63 9, H, 7 6

Methyl 4,6-O-benzylidene-2-deoxy-3-C-methyl-3-O-methyl-α-D-xylo-hexopyranoside (**6**) — Methyl sulfate (25 ml) was added dropwise to a slurry of compound **5** (2 38 g) and finely powdered sodium hydroxide (5 g) in tetrahydrofuran (50 ml) After the mixture had been stirred for 24 h at room temperature, it contained the 3-*O*-methyl derivative **6** and a small amount of unchanged starting material Fractionation of the syrupy product on silica gel, with 1 4 ethyl acetate–petroleum ether (b p 60–80°) as eluent, gave compound **6** as a syrup, yield 1 96 g (82%), which crystallized on standing in a refrigerator, m p 38–39°, $[\alpha]_D$ +119° (*c* 0 8, chloroform), R_F 0 52 (t l c), λ_{max}^{KBr} 14 2 μm (Ph), no absorption attributable to OH, n m r data τ 2 32–2 8 (5-proton multiplet, Ph), τ 4 5 (1-proton singlet, benzylidene-methine H), τ 5 25 (1-proton multiplet, H-1), τ 6 72, 6 78 (3-proton singlets, C-1 OMe and C-3 OMe), τ 8 84 (3-proton singlet, C-3 Me)

Anal Calc for $C_{16}H_{22}O_5$ C, 65 3, H, 7 5 Found C, 65 4, H, 7 6

Methyl 4-O-benzoyl-6-bromo-2,6-dideoxy-3-C-methyl-3-O-methyl-α-D-xylo-hexopyranoside (**7**) — A solution of compound **6** (964 mg) and *N*-bromosuccinimide (643 mg) in dry carbon tetrachloride (34 ml) containing barium carbonate (3 34 g) was heated for 15 min at reflux temperature T l c showed that the starting material had all reacted The reaction mixture was filtered, and the filtrate was washed with sodium hydrogen carbonate solution and water, and concentrated to yield a syrup, which was chromatographed on silica gel, with 1 4 ethyl acetate–petroleum ether (b p 60–80°) as eluent Compound 7 was obtained as a syrup, yield 1 12 g (91%), $[\alpha]_D$ +134° (*c* 0 9, chloroform), R_F 0 75 (t l c), λ_{max}^{film} 5 8 (OBz), 6 21, 14 0 μm (Ph), n m r data τ 1 8–2 0, 2 3–2 55 (multiplets, 5 protons, Ph), τ 5 1 (1-proton multiplet, H-1), τ 6 53, 6 68 (3-proton singlets, C-1 OMe and C-3 OMe), τ 8 86 (3-proton singlet, C-3 Me)

Anal Calc for $C_{16}H_{21}BrO_5$ C, 51 5; H, 5 6, Br, 21 4 Found C, 51 5, H, 5 6, Br, 21 5

Methyl 6-bromo-2,6-dideoxy-3-C-methyl-3-O-methyl-α-D-xylo-hexopyranoside (**8**) — A solution of compound 7 (1 02 g) in dry methanol (15 ml) in which sodium (~ 0 1 g) had been dissolved was left for 4 h at room temperature The debenzoylated compound **8** was isolated in the usual manner [yield 0 61 g (86%)], and recrystallized from pentane to give needles, m p 62–63°, $[\alpha]_D$ +134° (*c* 0 7, chloroform), R_F 0 49 (t l c); λ_{max}^{KBr} 2 9 μm (OH), no absorption attributable to OBz, n m r data, τ 6 58, 6 75 (3-proton singlets, C-1 OMe and C-3 OMe), τ 8 8 (3-proton singlet, C-3 Me)

Anal Calc for $C_9H_{17}O_4Br$ C, 40 2, H, 6 3, Br, 29 8 Found C, 40 4, H, 6 5, Br, 30 0

Methyl 2,6-dideoxy-3-C-methyl-3-O-methyl-α-D-xylo-hexopyranoside (*methyl α-D-arcanoside*) (**9**) — Compound **8** (540 mg) and lithium aluminum hydride (500 mg) in dry ether were heated for 3 h at reflux temperature The reduced product was isolated in the usual manner, and recrystallized from pentane to give compound **9** as needles, yield 237 mg (62%), m p 93–94°, $[\alpha]_D$ +167° (*c* 0 7, chloroform), R_F 0 21 (t l c), λ_{max}^{KBr} 2 9 μm (OH), n m r data τ 5 35 (1-proton multiplet, H-1), τ 6 69,

6 79 (3-proton singlets, C-1 OMe and C-3 OMe), τ 8 8 (3-proton singlet, C-3 Me), τ 8 8 (3-proton doublet, J 6 5 Hz, C-5 Me)

Anal Calc for $C_9H_{18}O_4$ C, 56 8, H, 9 5 Found C, 56 6, H, 9 3

*2,6-Dideoxy-3-C-methyl-3-O-methyl-*D-xylo-*hexose* (D-*arcanose*) (**10**) — Methyl α-D-arcanoside (**9**) (177 mg) in water (2 5 ml) was stirred with Rexyn-101 resin (H^+) for 4 h The filtered solution was passed through a small column of Duolite A-4 resin (OH^-) to remove any trace of acid Concentration of the solution gave a colorless syrup which crystallized on trituration with ether Recrystallization from ethyl acetate–petroleum ether (b p 60–80°) gave D-arcanose (**10**) as prisms, yield 55 mg (31%), m p 101–102°, $[\alpha]_D$ +19 8° (*c* 1 0, ethanol), λ_{max}^{KBr} 2 93 μm (OH), n m r data τ 6 81 (3-proton singlet, C-3 OMe) τ 8 78 (3-proton singlet, C-3 Me), τ 8 78 (3-proton doublet, J 6 5 Hz, C-5 Me), lit [3] for L-arcanose, m p 96–98°, $[\alpha]_D$ −19 2° (*c* 4 6, ethanol) The infrared and n m r spectra of the synthetic product were identical with those of authentic L-arcanose The two compounds were indistinguishable by paper chromatography and had R_{Rha} 3 1 (solvent *A*), 1.42 (solvent *B*), and 1 98 (solvent *C*)

Anal Calc for $C_8H_{16}O_4$ C, 54 5, H, 9 1 Found C, 54 7, H, 9 1

*Methyl 3-O-acetyl-4,6-O-benzylidene-2-deoxy-3-C-methyl-*α-D-xylo-*hexopyranoside* — To a solution of compound **5** (190 mg) in *N,N*-dimethylaniline (0 41 ml) was added acetyl chloride (0 1 ml), and the mixture was left at room temperature for 1 h and then heated on a steam bath for 4 h The reaction mixture was poured into water and extracted with chloroform The extracts were washed with 6N sulfuric acid, sodium hydrogen carbonate solution, and water, and concentrated to yield a syrup (190 mg), which was chromatographed on silica gel with 2 3 ethyl acetate–petroleum ether (b p 60–80°) as eluent The 3-*O*-acetyl derivative was isolated as a syrup, R_F 0 75 (t l c), ν_{max}^{film} 5 75 (OAc), 13 3, 14 4 μm (Ph), n m r. data τ 2 4–2 8 (5-proton multiplet, Ph), τ 4 41 (1-proton singlet, benzylidene-methine H), τ 6 65 (3-proton singlet, C-1 OMe), τ 8 02 (3-proton singlet, OAc), τ 8 40 (3-proton singlet, C-3 Me)

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