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Note

Branched-chain sugars

Part I. An alternative synthesis of 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-D-allopyranose

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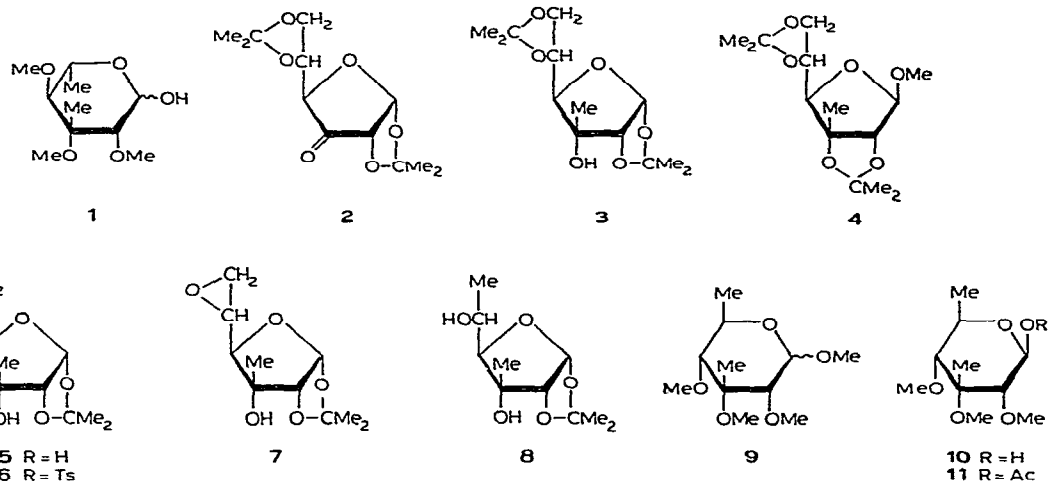
A number of unusual, branched-chain sugars are found as components of natural substances, and a recent review[1] has outlined both the occurrence and general approaches to the synthesis of these sugars Investigations in our laboratories have been concerned with a general approach to the synthesis of such methylated 6-deoxy-3-*C*-methylaldohexoses as nogalose[2] (6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-L-mannohexose, **1**) and vinelose[3] [a 6-deoxy-3-*C*-methyl-2-*O*-methyl-L-(altro, galacto, or talo)aldohexose] Nogalose is a constituent sugar of the anthracyclinone antibiotic nogalamycin[2], while vinelose has been isolated from *Azotobacter vinelandii* as a cytidine diphosphate derivative[3]

There appeared to be considerable advantages in approaching the synthesis of such methylated, branched-chain sugars from 1,2 5,6-di-*O*-isopropylidenehexofuranos-3-uloses (such as **2**), which have become available through the application of new oxidative procedures[4]. One obvious advantage is that the stereochemistry of Grignard adducts formed from such diacetalated ketones can be predicted by assuming that the reagent approaches from the sterically favoured *exo*-direction with respect to the trioxabicyclo[3 3 0]octane ring system As will be demonstrated below, an unequivocal assignment of stereochemistry to Grignard adducts presents no great problem Moreover, the versatility of this approach is enhanced by recent methods[5] that yield branched-chain derivatives epimeric with those obtained by normal Grignard addition Finally, the ease of removal of the 5,6-isopropylidene group from the Grignard adducts (*e g* **3**) not only allows for the ready introduction of a 6-deoxy function, but also provides for configurational changes at C-5 (*i e*, transformation from the D to the L series, and *vice versa*) and other synthetic manipulations A number of these ideas have been tested in the following synthesis of 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-D-allopyranose (**10**), for which an alternative synthesis has been described already[6], and are currently being applied to a synthesis of D-nogalose

The reaction of 1,2 5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose[7] (**2**) with methylmagnesium iodide in ethyl ether gave a good yield of a crystalline adduct that was characterized as 1,2 5,6-di-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose



(3) This identity was established by treating **3** with acidified methanol–acetone for several days at room temperature, when one of the products isolated, after chromatography on silica gel, was methyl 2,3 5,6-di-*O*-isopropylidene-3-*C*-methyl-*β*-D-allofuranoside (**4**)*. N m r spectroscopy (see Experimental for details) revealed the gross structural features of **4**, and the presence of a furanoid ring was indicated by the appearance of a significant peak at *m/e* 101 ($C_5H_9O_2$) in the mass spectrum, the *m/e* 101 peak is characteristic[8] of 2,3 5,6- and 1,2 5,6-di-*O*-isopropylidenehexofuranoses since it arises from rupture of the C-4 to C-5 bond Accepting that a furanoid ring is present and that no epimerization has taken place, then **4** is the only reasonable structure that can accommodate two isopropylidene groups and a methoxyl group, the latter group must be present at C-1 in the *β*-D configuration, since the H-1 signal appears as a singlet at τ 5 15 in the n.m r. spectrum[9] The D-*allo* configuration of **3** is to be expected on the basis of our introductory remarks and is in keeping with the configuration of the products obtained[10] by the reaction of a variety of Grignard reagents with 1,2 5,6-di-*O*-cyclohexylidene-α-D-*ribo*-hexofuranos-3-ulose

Partial hydrolysis of **3** with 75% acetic acid afforded a crystalline triol **5**, which gave 1,2-*O*-isopropylidene-3-*C*-methyl-6-*O*-tosyl-α-D-allofuranose (**6**) on treatment with a molar proportion of tosyl chloride in pyridine Although a formal proof of structure of the sulphonate **6** was not carried out, there can be little doubt as to its structure since primary hydroxyl groups are known[11] to esterify in similar situations much more readily than secondary hydroxyl groups Brief treatment of the sulphonate **6** with methanolic sodium methoxide at −25° yielded the anhydro sugar **7**, which, with lithium aluminium hydride, gave 6-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**8**) Acid-catalysed methanolysis of the acetal **8**, followed by

*Although compound **4** is only a minor product of this reaction, it proved most amenable to structural elucidation The other reaction products are currently under investigation, but none showed the introduction of a methoxyl group It is notable that the proportion of products formed depended critically on the reaction conditions

methylation[12], gave a separable mixture of the anomeric methyl 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-D-allopyranosides (**9**) N m r spectroscopy showed that the β anomer ($J_{1,2}$ 8 Hz) of **9** preponderated ($\beta:\alpha$ ~2 5 1) in the mixture, and there appeared to be little or no furanoside present Acid hydrolysis of the glycoside **9** to give 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-D-allopyranose (**10**) formally completed the synthesis The free sugar was characterized as the crystalline 1-acetate **11**, whose physical properties were in complete accord with those previously reported[6]

EXPERIMENTAL

Thin-layer chromatography (t l c) was performed on Kieselgel G, and detection was effected with vanillin–sulphuric acid[13] N m r spectra were routinely measured with a Perkin–Elmer R-10 spectrometer for solutions in deuteriochloroform and were compatible with the assigned structures Optical rotations were measured at ambient temperature with a Perkin–Elmer 141 automatic polarimeter Light petroleum refers to the fraction having b p. 40–60°

1,2 5,6-Di-O-isopropylidene-3-C-methyl-α-D-allofuranose (**3**) — To a solution of methylmagnesium iodide [prepared from magnesium (12 2 g) and methyl iodide (63 ml)] in ether (300 ml) was gradually added a solution of the ketone **2**[7] (50 2 g) in ether (500 ml), whereafter the solution was heated under reflux for 3 h After decomposition of the excess of the Grignard reagent with water, the ethereal solution was dried ($MgSO_4$) and concentrated to a solid residue (30 3 g) Recrystallisation from ether–light petroleum gave **3**, m p 105–107°, $[\alpha]_D$ +22° (*c* 1, chloroform) (Found C, 56 8; H, 7 8 $C_{13}H_{22}O_6$ calc C, 56 9, H, 8 0%) N m r data τ 4 25 (*d*, 1 proton, $J_{1,2}$ 4 Hz, H-1); 5 80 (*d*, 1 proton, $J_{2,1}$ 4 Hz, H-2), 8 40 (*s*, 3 protons, C-3–Me); and 8 54, 8 64, and 8 75 (*s*, 12 protons, intensity ratio 1 2 1, $2CMe_2$)

Characterization of **3** — A solution of **3** (1 g) in acetone (20 ml) and 3% methanolic hydrogen chloride (20 ml) was kept for several days at room temperature, during which time t l c (light petroleum–acetone, 6 1) showed the formation of a major and several minor products. Chromatography on silica gel (elution with light petroleum–acetone, 6 1) afforded one of the minor products, which was identified as methyl 2,3 5,6-di-*O*-isopropylidene-3-*C*-methyl-β-D-allofuranoside (**4**) (60 mg, ~6%), b p 80–85°/0 3 mmHg, $[\alpha]_D$ −5° (*c* 0 6, chloroform) (Found C, 59 0, H, 8 6. $C_{14}H_{24}O_6$ calc C, 58 3, H, 8 3%) Accurate measurement of the peak of highest mass at *m/e* ($M^+ - 15$) gave a value of 273 1339, corresponding to $C_{13}H_{21}O_6$ (calc. 273.1338); another significant peak occurred at *m/e* 101 ($C_5H_9O_2$), arising from cleavage between C-4 and C-5 The n m r spectrum exhibited the following salient features τ 5 15 (*s*, 1 proton, H-1), 5 80 (*s*, 1 proton, H-2), 6 70 (*s*, 3 protons, OMe), 8 40 (*s*, 3 protons, C-3–Me), and 8 55, 8 65, and 8.72 (*s*, 12 protons, intensity ratio 1 2 1, $2CMe_2$)

1,2-O-Isopropylidene-3-C-methyl-α-D-allofuranose (**5**). — A solution of the diacetal **3** (8 7 g) in 75% acetic acid (70 ml) was set aside at room temperature for 24 h, during which time removal of the 5,6-*O*-isopropylidene group was complete.

Concentration of the solution afforded a crystalline residue (7 2 g), which, on recrystallisation, gave the monoacetal **5**, m p 132 5–133 5° (from chloroform–light petroleum), $[\alpha]_D$ +23° (*c* 0 4, chloroform) (Found· C, 51 1, H, 7 9 $C_{10}H_{18}O_6$ calc . C, 51 3, H, 7.7%) N m r data τ 4 25 (*d*, 1 proton, $J_{1,2}$ 4 Hz, H-1), 5 84 (*d*, 1 proton, $J_{2\ 1}$ 4 Hz, H-2), 8 40 (*s*, 3 protons, C-3–Me), and 8 65 and 8 67 (*s*, each 3 protons, CMe_2)

1,2-O-*Isopropylidene-3*-C-*methyl-6*-O-*toluene*-p-*sulphonyl*-α-D-*allofuranose* (**6**) — The monoacetal **5** (6 5 g) in dry pyridine (75 ml) was treated overnight at room temperature with a solution of tosyl chloride (5 8 g) in pyridine (75 ml) Work up in the usual manner gave the monosulphonate **6** (10 2 g), m p 97–97 5° (from ether), $[\alpha]_D$ +10 5° (*c* 0 8, chloroform) (Found C, 52 5, H, 6 2, S, 8 3 $C_{17}H_{24}O_8S$ calc C, 52 6, H, 6 2; S, 8 25%) N m r data τ 2 40 (*m*, 4 aromatic protons), 4 30 (*d*, 1 proton, $J_{1,2}$ 4 Hz, H-1), 7 55 (*s*, 3 protons, Ar-Me), 8 43 (*s*, 3 protons, C-3–Me), and 8 66 and 8 72 (*s*, each 3 protons, CMe_2)

6-Deoxy-1,2-O-*isopropylidene-3*-C-*methyl*-α-D-*allofuranose* (**8**) — To a solution of the 6-sulphonate **6** (10 2 g) in dry chloroform (50 ml) at −25°, an approximately molar solution of sodium methoxide in methanol (50 ml) was added, and the solution was maintained at this temperature for 30 min, t l c then showed that the reaction was complete The excess of reagent was destroyed with solid carbon dioxide, the solution was then concentrated, the residue was extracted with ether (3 × 100 ml), and the combined extracts were filtered and concentrated to yield a crystalline residue Recrystallisation from ether–light petroleum gave 5,6-anhydro-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose (**7**) (2 3 g), m p 137–137 5°, $[\alpha]_D$ +18° (*c* 1, chloroform), several failures to obtain a satisfactory elemental analysis on this compound were attributed to opening of the anhydro ring during transit The following n m r. data served to characterize the anhydro sugar τ 4 27 (*d*, 1 proton, $J_{1,2}$ 4 Hz, H-1), 5 86 (*d*, 1 proton, $J_{2\ 1}$ 4 Hz, H-2), 6 33 (*d*, 1 proton, $J_{4,5}$ 4 5 Hz, H-4), 6 95 (*m*, 1 proton, H-5), 7 22 (*m*, 2 protons, H-6,6′), 8 46 (*s*, 3 protons, C-3–Me); and 8 67 and 8 69 (*s*, each 3 protons, CMe_2)

The anhydro sugar **7** (5 6 g) in dry ether (300 ml) was treated with lithium aluminium hydride (2 5 g) for 30 min at room temperature Ether (300 ml) was then added, followed by the dropwise addition of water to decompose the excess of reagent The filtered solution and washings were dried ($MgSO_4$) and then concentrated to a crystalline residue (3 85 g) Recrystallisation from chloroform–light petroleum gave the 6-deoxy compound **8**, m p 121–121 5°, $[\alpha]_D$ +23° (*c* 1, chloroform) (Found. C, 55 2, H, 8 4 $C_{10}H_{18}O_5$ calc C, 55 0; H, 8 3%) N m r data τ 4 28 (*d*, 1 proton, $J_{1,2}$ 4 Hz, H-1), 5 85 (*d*, 1 proton, $J_{2,1}$ 4 Hz, H-2), 8 40 (*s*, 3 protons, C-3–Me), 8 63 and 8 69 (*s*, each 3 protons, CMe_2), and 8 66 (*d*, 3 protons, $J_{5,6}$ ~7 Hz, C-5–Me)

Methyl 6-deoxy-3-C-*methyl-2,3,4-tri*-O-*methyl*-D-*allopyranoside* (**9**) — Methanolysis of the acetal **8** (1 5 g) was accomplished in refluxing, 2% methanolic hydrogen chloride (100 ml) after 1 h The solution was neutralized ($PbCO_3$) and filtered, and the filtrate was concentrated to yield a syrupy mixture of glycosides (1 32 g).

To a solution of the glycosides (1 32 g) in *N,N*-dimethylformamide (120 ml) containing sodium hydride (1.65 g), methyl iodide (10 ml) was gradually added, and the reaction mixture was stored for 2 h at room temperature Methanol was then carefully added to decompose the excess of hydride, and the solution was concentrated The residue was extracted with ether (100 ml) and, after removal of the solvent, chromatographed on silica gel (elution with light petroleum–acetone, 9 1) The first component eluted was methyl 6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-β-D-allopyranoside (**β-9**, 0 67 g), b p 75–80°/0 1 mmHg, $[\alpha]_D$ −26 5° (*c* 0 9, chloroform) (Found C, 56 8, H, 9 7 $C_{11}H_{22}O_5$ calc C, 56 4, H, 9 4%) N m r data τ 5 45 (*d*, 1 proton, $J_{1,2}$ 8 Hz, H-1), 6 52, 6 60 (*s*, 12 protons, 4OMe); 8 60 (*s*, 3 protons, C-3–Me); and 8 74 (*d*, 3 protons, $J_{5,6}$ 6 Hz, C-5–Me) Continued elution gave **α-9** (0 18 g), b p 75–80°/<0 1 mmHg, $[\alpha]_D$ +128 ±2° (*c* 1, chloroform) {*lit* [6] b p 80–85°/0 05 mmHg, $[\alpha]_D$ +131° (*c* 0 3, chloroform)}, having an n m r spectrum identical with that previously described

6-Deoxy-3-C-methyl-2,3,4-tri-O-methyl-D-allopyranose (**10**). — A mixture of the foregoing αβ-glycosides **9** (0 67 g) in ethanol (4 ml) and M sulphuric acid (12 ml) was heated for 1 h on a boiling water-bath, during which time complete hydrolysis occurred The hydrolysate was neutralized ($BaCO_3$), and the filtered solution was concentrated to a syrupy residue, which was chromatographed on silica gel (elution with light petroleum–acetone, 3 1) to remove minor impurities The free sugar **10** (0 31 g), $[\alpha]_D$ +17 5 ±3° (*c* 2 6, methanol), was obtained as a syrup, which exhibited an n m r spectrum virtually identical with that recorded for the same sugar, $[\alpha]_D$ +28° (*c* 2 6, methanol), prepared by an alternative route[6]

Acetylation of **10** (0 31 g) by the literature procedure[6] gave 1-*O*-acetyl-6-deoxy-3-*C*-methyl-2,3,4-tri-*O*-methyl-β-D-allopyranose (**11**) (0 24 g), m p 88–89° (from light petroleum–pentane), $[\alpha]_D$ −6° (*c* 1 0, ethyl acetate), *lit* [6] m p 88–89°, $[\alpha]_D$ −6° (*c* 2 3, ethyl acetate) (Found C, 55 3, H, 8 6 $C_{12}H_{22}O_6$ calc C, 55 0, H, 8 4%) The n m r spectrum of the acetate **11** was identical with that previously described.

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