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THE SYNTHESIS OF BRANCHED-CHAIN, DEOXY SUGARS BY SUGAR EPOXIDE–GRIGNARD REAGENT REACTIONS

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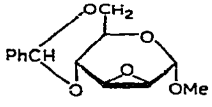
ABSTRACT

Alkylmagnesium chlorides react with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) and -α-D-allopyranoside (**2**) to give, preponderantly, 3-alkyl and 2-alkyl, branched-chain, deoxy sugars. In contrast, alkylmagnesium iodides and bromides do not give branched-chain, deoxy sugars with **1** and **2** but give, initially, halohydrins which undergo elimination and reduction with excess of Grignard reagent. Preliminary investigations of the reaction of **2** with a complex derived from alkylmagnesium iodides and tetrahydropyran indicate the formation of methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucopyranoside (**13b**) by *trans*-diequatorial opening of epoxide **2**, whereas normal Grignard reagents (alkylmagnesium iodides) react with **2** in tetrahydropyran to give the usual *trans*-diaxial product (**14b**).

INTRODUCTION

Branched-chain, deoxy sugars are formed in reactions between sugar epoxides and dialkyl(or diaryl)magnesium[1,2] or alkyl(or aryl)-lithium[3] compounds, and by less-general reactions[4] or from less readily available starting materials[5]. However, direct extension of the reported methods to the synthesis of methyl 4,6-*O*-benzylidene-2-deoxy-2-ethyl(or 3-deoxy-3-ethyl)-hexopyranosides, which were required as key intermediates for other studies, was not possible for a variety of reasons. Thus the reaction of ethyl-lithium with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**2**) was not investigated, since the reaction between **2** and methyl-lithium yields the unsaturated products **10** and **11** in addition to a low yield of methyl 4,6-*O*-benzylidene-2-deoxy-2-methyl-α-D-altropyranoside[3,4] (**15**), and a similar mixture of products has been reported[6] for the reaction between pentachlorophenyl-lithium and **2**. Although the reaction of methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) is known to give methyl 4,6-*O*-benzylidene-3-deoxy-3-methyl-α-D-altropyranoside[3], in our hands only low yields were obtained. Moreover, the reaction of **1** with ethyl-lithium yielded no 3-deoxy-3-ethyl derivatives but only a complex mixture of products including some where cleavage of the acetal ring had occurred. Also, only low yields of products have been obtained by reactions between **2** and dialkyl-[1] and diaryl-magnesium[2] compounds, and, generally, the methods used were unsatisfactory for large-scale application. Consequently, it was decided to investigate the reactions of Grignard reagents with the sugar epoxides **1** and **2** as a means of synthesis of the required, branched-chain, deoxy sugars.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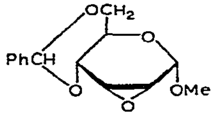
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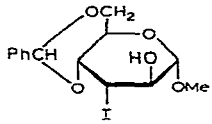
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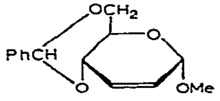
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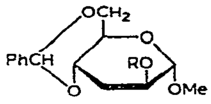
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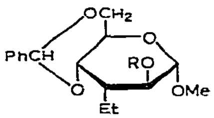
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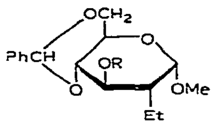
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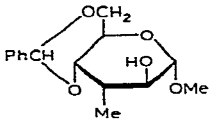
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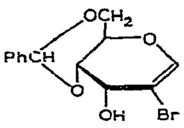
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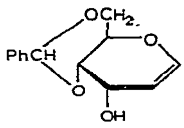
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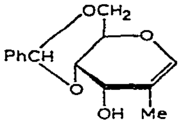
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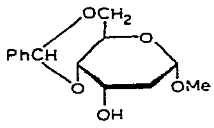
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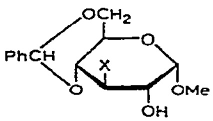
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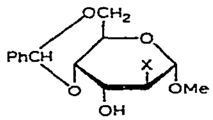
13b X = I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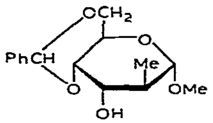
14b X = I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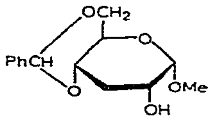
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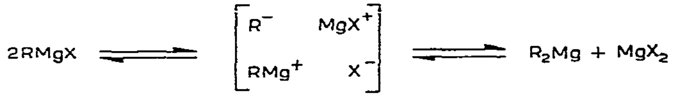
The Schlenk equilibrium (Scheme 1) has been invoked to explain the principal reactions of epoxides with Grignard reagents. Attack on the epoxide by X^- will lead to halohydrins (Route 1, Scheme 2), and attack by R^- will give *C*-alkyl derivatives (Route 2, Scheme 2). Preference for one route or the other and for attack at C-1 or C-2 depends on the reaction conditions, the nature of the Grignard reagents and R' and R'', and on the stereochemistry of the entire molecule[7]. Thus, if the expected *trans*-diaxial ring-opening[8] of the 2,3-anhydro-alloside (**2**) and -mannoside (**1**) derivatives takes place, the preponderant products from reaction of **2** with Grignard reagents will be 2-alkyl (or 2-halogeno) derivatives of methyl-4,6-*O*-benzylidene-2-deoxy-α-D-altropyranoside, and reactions between **1** and Grignard reagents will yield, preponderantly, 3-alkyl (or 3-halogeno) derivatives of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-altropyranoside. Previous investigators[9–11] of the reaction of Grignard reagents with **1** and **2** have reported only the isolation of halohydrins, and no branched-chain deoxy sugars were detected. This paper is concerned with the synthesis of branched-chain deoxy sugars by reactions of **1** and **2** with Grignard reagents.

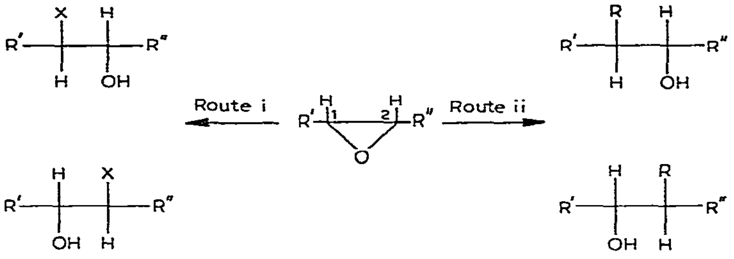
Reactions with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside

The unsaturated derivative **4**, the 3-deoxy derivative **5**, and the 3-*C*-ethyl



$$2RMgX \rightleftharpoons \begin{bmatrix} R^- & MgX^+ \\ RMg^+ & X^- \end{bmatrix} \rightleftharpoons R_2Mg + MgX_2$$

SCHEME 1



SCHEME 2

derivative **6** were isolated from the reaction of the anhydromannopyranoside derivative **1** and excess of ethylmagnesium iodide in ether. When equimolar quantities of the Grignard reagent and **1** were used, methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-α-D-altropyranoside (**3**) was the preponderant product. The unsaturated derivative **4** and the 3-deoxy derivative **5** were also the major products from the reaction of the 3-iodo-altrose derivative **3** with excess of ethylmagnesium iodide. These experiments confirm, in many respects, the results of previous work, where it was shown that the 3-iodo compound **3** undergoes reduction and elimination reactions with an excess of ethylmagnesium iodide[11]. The presence of the 3-*C*-ethyl derivative was not detected previously in reactions between **1** and ethylmagnesium iodide, but it has been shown that if magnesium iodide is precipitated form ethereal ethylmagnesium iodide with *p*-dioxane, the resulting solution, which is enriched with diethylmagnesium, then reacts with **1** to yield the 3-ethyl derivative[1] **6**.

The observation that the 3-ethyl derivative **6** was formed by reaction of ethylmagnesium iodide and **1** prompted an investigation of the reaction between **1** and ethylmagnesium chloride. Chloride ion is known to be a considerably weaker nucleophile than iodide ion, and it is known that the order of reactivity of **1** with magnesium halides decreases in the order I>Br>Cl. In fact, it has been reported[12] that, in ether, **1** is not affected by magnesium chloride, but since similar results were reported for magnesium bromide and iodide, the results are either suspect or the formation of halohydrins from epoxides and Grignard reagents cannot be explained simply on the basis of the Schlenk equilibrium. It has also been reported[4] that **1**, although reacting with lithium iodide, does not react with lithium bromide or chloride. When **1** was treated with excess of ethylmagnesium chloride in ether and the products were separated chromatographically, a 54% yield of methyl 4,6-*O*-benzylidene-3-deoxy-3-ethyl-α-D-altropyranoside (**6**) was obtained, together with smaller yields of the unsaturated compound **4** (7%), the 3-deoxymannose derivative **5** (7%), and methyl 4,6-*O*-benzylidene-2-deoxy-2-ethyl-α-D-glucopyranoside **7** (4%). Formation of **4** and

5 indicates initial formation of *ca.* 14% of the 3-chloro analogue of **3**. In subsequent experiments, yields of up to 70% of **6** were isolated by direct crystallisation from the mixed reaction-products, although sometimes co-crystallisation of the 3-deoxy derivative **5** occurred. Previous chemical studies[1] have indicated that **6** is a 3-deoxy-3-ethyl derivative, and the configuration at C-2 and C-3 was assigned on the grounds that *trans*-diaxial opening of the epoxide would take place. The n.m.r. spectra of **6** and **7** and their acetates are consistent with the assigned structures.

The reaction between **1** and methylmagnesium chloride in ether also provides a convenient method for the synthesis of methyl 4,6-*O*-benzylidene-3-deoxy-3-methyl-α-D-altropyranoside (**8**). The yield of **8** was 62%, together with smaller amounts of the 3-deoxy derivative **5** (5%) and the 2,3-ene **4** (17%). This yield of **8** compares with that (77%) obtained[3] by reaction of **1** with methyl-lithium prepared from methyl iodide. However, in our hands, only a 19% yield of **8** was obtained from the reaction of **1** with methyl-lithium from methyl iodide, and only a 12% yield when the methyl-lithium was prepared from methyl bromide; unidentified products were isolated which lacked a benzylidene group.

In the reactions between **1** and ethylmagnesium iodide or ethylmagnesium chloride, the elimination product **4** and the reduction product **5** were formed in similar yields. In the reaction between **1** and methylmagnesium chloride, however, the elimination product **4** preponderated, and only a small amount of the reduction product **5** was formed. This is in accord with expectations[13].

Reactions with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside

Studies of reactions of the allopyranoside derivative **2** and Grignard reagents are complicated by the fact that **2** is only sparingly soluble in ethereal solvents. To minimise solubility problems, tetrahydropyran was previously used[9,10] as solvent. In this solvent, ethylmagnesium iodide (or bromide) and magnesium iodide (or bromide) reacted with **2** to give the 2-halohydrins (**14** and **14a**), but use of methylmagnesium iodide afforded a high yield of methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucopyranoside (**13b**). In an attempt to clarify this anomaly and in order to assess the possibility of preparing branched-chain deoxy sugars from **2** by the Grignard reaction, the use of tetrahydropyran and other solvents has been investigated.

From the reaction between **2** and excess of ethylmagnesium bromide in tetrahydrofuran, the products **9**, **10**, **12**, and **13a** were isolated. The 3-bromo-3-deoxy derivative (**13a**), isolated in a yield of 6%, was tentatively identified by comparison of its n.m.r. spectrum with that of the corresponding, known 3-deoxy-3-iodoglucose derivative (**13b**). The 1,2-ene **10** and the 2-deoxy derivative **12** were also formed by treatment of methyl 4,6-*O*-benzylidene-2-deoxy-2-bromo-α-D-altropyranoside (prepared by treatment of **2** with an equimolar quantity of ethylmagnesium bromide) with ethylmagnesium bromide, ethylmagnesium iodide, or methylmagnesium iodide, although with methylmagnesium iodide the ratio of the elimination product (**10**) to the reduction product (**12**) was increased.

The structure of the bromo-olefin **9** is tentative and was assigned on the basis of analytical data, chromatographic properties, and n.m.r. data. Compound **9** showed a low-field proton signal at 6.64 p.p.m. which was not coupled to any other proton and thus was fully consistent with H-1 in the structure assigned. The crude acetate from **9** also had a low-field proton signal and also showed a distinct signal at 5.83 p.p.m. which was assigned to H-3 and was basically a doublet complicated by virtual, long-range coupling with H-4 and H-5. The $J_{3,4}$ coupling of 3.2 Hz was similar to that[14] for compound **10**. The mechanism of formation of the bromo-olefin **9** is presumably similar to that suggested[4] for the formation of **11**. However, the conditions for this formation appear to be very critical, since usually only trace quantities were produced and isolation from compound **14a** was not achieved.

The reactions of **2** with methyl- and ethyl-magnesium iodide gave similar products to the reactions of ethylmagnesium bromide and **2** in both ether and tetrahydrofuran, with the unsaturated compound **10** and the 2-deoxy derivative **12** as major products. In no case was there evidence for the formation of branched-chain sugar derivatives. A compound having chromatographic properties similar to the bromo-olefin **9**, and thus possibly the corresponding iodo-olefin, was detected in some reactions, but was not isolated in sufficient quantity for identification purposes. Since it is clear that the olefin **10** and the 2-deoxy derivative **12** are derived from **14** by elimination and reduction, respectively, the experiments described indicate that the Grignard reagents, including methylmagnesium iodide, react quite normally with **2** to afford the 2-halogeno derivative (**14**) as the initial, major product.

Similarly, the normal, *trans*-diaxial ring-opening occurred when **2** was treated with excess of methylmagnesium chloride in ether. The reaction was relatively slow, however, and in addition to the unsaturated compound **10** (46%) and the 2-deoxy derivative **12** (11%), an appreciable quantity (31%) of methyl 4,6-*O*-benzylidene-2-deoxy-2-methyl-α-D-altropyranoside (**15**) was produced. In contrast to the reaction between **15** and methyl-lithium[4], there was no evidence for the formation of the unsaturated product **11** from the reaction between **15** and excess of methylmagnesium chloride or methylmagnesium iodide. The formation of **15** from **2** and methylmagnesium chloride, and the formation of **6**, **7**, and **8** from alkylmagnesium chlorides and **1** suggests that the reaction of sugar epoxides with alkyl(or aryl)magnesium chlorides may be a convenient, general method for the preparation of branched-chain, deoxy sugars.

Reactions in tetrahydropyran

In the reactions between the allopyranoside derivative **2** and excess of Grignard reagents, where there was no requirement to isolate the 2-deoxy-2-halogeno derivatives (**14**), it was convenient to add powdered **2** portionwise to the Grignard solution when an immediate reaction took place, and **2** dissolved with rapid formation of **10** and **12**. However, **2** is only sparingly soluble in ether, and it is therefore very difficult to obtain **14** in high yield, since the reaction of suspensions of **2** with equimolar quantities of Grignard reagents results in the formation of **10** and **12** with much unreacted starting-material (**2**). For these reasons, tetrahydropyran (in which **2** is reasonably soluble) was chosen for reactions of **2** with equimolar quantities of Grignard reagents[10], and the surprising result was reported[9,10] that the reaction with methylmagnesium iodide afforded high yields of methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucopyranoside (**13b**). When powdered **2** was added to freshly prepared solutions of excess of ethylmagnesium iodide and methylmagnesium iodide in tetrahydropyran, the reactions were normal, and the preponderant products were the unsaturated compound **10** and the deoxy derivative **12**, with only trace amounts of the 3-iodo derivative **13b**. Under these conditions, samples of the alkylmagnesium iodide–tetrahydropyran reagent react vigorously with water, both before and after addition of **2**. Richards and co-workers[9,10] chose to add a dilute solution of **2** in tetrahydropyran to the alkylmagnesium iodide–tetrahydropyran reagent. Under similar conditions (it was not possible to repeat the reaction of **2** with the methylmagnesium iodide–tetrahydropyran reagent, since in the experiments described the quantities used and yields obtained are not consistent), it was possible to obtain variable, but in some cases high, yields of the 3-iodo derivative **13b** from the reaction of **2** with both the ethyl- and methyl-magnesium iodide–tetrahydropyran reagents. An alternative procedure for forming **13b** was then investigated. It was observed that tetrahydropyran* (or some impurity therein) reacts vigorously with freshly prepared Grignard reagents, and consequently the alkylmagnesium iodide–tetrahydropyran reagents were first "aged" by addition of more tetrahydropyran. When a sample of the solution no longer reacted vigorously with water, powdered **2** was added. Under these conditions, good yields of **13b** were obtained from both ethyl- and methylmagnesium iodide–tetrahydropyran reagents. The precise nature of the reaction of the "aged" alkylmagnesium iodide with the allose derivative **2** to give diequatorial opening of the epoxide is currently under investigation, and the generality of the reagent to other epoxides is being explored. Definite evidence that **13b** is not formed by a normal Grignard reagent is provided by the absence of methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (**16**) in the reaction mixture. In the presence of excess of ethylmagnesium iodide or methylmagnesium iodide, the iodo derivative **13b** is reduced to the deoxy derivative **16**. In contrast to the reaction of the diaxial halohydrin **3**, where both elimination and reduction occur, only reduction of **13b** by excess Grignard reagent takes place. In the presence of a catalytic amount of ferric chloride, reduction of **13b** by ethylmagnesium iodide is rapid and quantitative and is recommended as a practical procedure for reducing equatorial halides to deoxy derivatives.

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography was performed on microscope slides coated with Silica Gel G (Merck), and column chromatography was performed with Silica Gel (Merck) of particle size 0.05–0.2 mm. The chromatoplates were developed with 50% sulphuric acid and/or iodine vapour. For the Gri-

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*Tetrahydropyran (B.D.H.) was dried over molecular sieves.

gnard reactions, ether was dried over sodium wire, and tetrahydrofuran and tetrahydropyran were dried over molecular sieves (Type 3A. B.D.H.). N.m.r. spectra were measured with a JEOL-JNM-4H-100 n.m.r. spectrometer at 100 MHz with deuteriochloroform as solvent and with tetramethylsilane as an internal standard. Only distinctive n.m.r. data are reported. Chemical shifts are expressed as δ values in p.p.m., and coupling constants are in Hz. Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (**2**) and methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (**1**) were prepared by literature procedures[15,16]. Grignard reagents were prepared in the usual way[7], with initiation by iodine where necessary. The formation of methylmagnesium chloride was very slow, and the reaction of methyl chloride (4 ml) with magnesium took 3–4 h. Reactions were monitored by sampling the Grignard mixtures into water, extracting with ether, and examining the ether extract by t.l.c. Unless stated otherwise, a ten-fold excess of Grignard reagent was used.

*Reaction of ethylmagnesium iodide with methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside* (**1**). — The mannopyranoside derivative **1** (1.2 g) was added to an excess of ethylmagnesium iodide in ether, and the solution was boiled under reflux and monitored by t.l.c. (benzene–ether, 1:1). When no starting material remained, the reaction mixture was worked up in the usual manner, and the three major products were isolated by chromatography over silica gel. In order of elution were obtained: (*a*) methyl 4,6-*O*-benzylidene-α-D-*erythro*-hex-2-enopyranoside (**4**) (0.3 g, 27%), m.p. 119°, $[\alpha]_D^{20}$ +129° (*c* 2, chloroform); lit.[14], m.p. 119.5°, $[\alpha]_D^{25}$ +129°; (*b*) methyl 4,6-*O*-benzylidene-3-deoxy-3-ethyl-α-D-altropyranoside (**6**) (0.17 g, 13%), m.p. 98–99°, $[\alpha]_D^{20}$ +110° (*c* 1.1, chloroform); lit.[1], m.p. 97–98°, $[\alpha]_D^{16}$ +113°; compound **6** afforded a crystalline acetate (**6a**), m.p. 65°, $[\alpha]_D^{20}$ +78.5° (*c* 1, chloroform) (Found: C, 64.0; H, 7.1. $C_{18}H_{24}O_6$ calc.: C, 64.3; H, 7.2%); n.m.r. data: H-1 was at 4.55 and H-2 at 5.03 p.p.m. ($J_{1,2}$ 1, and $J_{2,3}$ 1.2 Hz); (*c*) methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*arabino*-hexopyranoside[17] (**5**) (0.4 g, 33%), m.p. 111–112°. This compound was indistinguishable from a sample prepared by reduction of the anhydro-mannoside derivative **1** with lithium aluminium hydride. Compound **5** afforded a crystalline toluene-*p*-sulphonate[17] (**5a**), m.p. 123–124°.

Reaction of ethylmagnesium chloride with **1**. — The anhydro sugar **1** (4.2 g) was added to an excess of ethylmagnesium chloride in ether, and the solution was boiled under reflux until no starting material remained (t.l.c.; ether–light petroleum, 1:1). The mixture was worked up in the usual way, and four products were separated by column chromatography over silica gel. In order of elution were obtained: (*a*) compound **4**, (0.3 g, 7.5%); (*b*) methyl 4,6-*O*-benzylidene-2-deoxy-2-ethyl-α-D-glucopyranoside (**7**) (0.18 g, 4%), m.p. 162–163° (from ethanol), $[\alpha]_D^{20}$ +111° (*c* 2, chloroform) (Found: C, 65.6; H, 7.5. $C_{16}H_{22}O_5$ calc.: C, 65.3; H, 7.5%); n.m.r. data (δ): H-1, 4.67 ($J_{1,2}$ 3.3 Hz); H-3,4,5,6,6′, 3.5–4.4; benzylic H, 5.52; OMe, 3.35; compound **7** afforded a crystalline acetate (**7a**), m.p. 129–130° (from ethanol), $[\alpha]_D^{21}$ +115° (*c* 1, chloroform) (Found: C, 63.8; H, 7.1. $C_{18}H_{24}O_6$ calc.: C, 64.3; H, 7.2%); n.m.r. data (δ): H-3, 5.30 ($J_{2,3}$ 9, $J_{3,4}$ 10 Hz); H-1, 4.73 ($J_{1,2}$ 3.2 Hz); H-4,5,6,6′, 3.45–4.10; OMe, 3.36; OAc, 2.06; (*c*) compound **6** (2.5 g, 54%); (*d*) compound **5** (0.3 g, 7%).

Reaction of methylmagnesium chloride with **1**. — The anhydro sugar **1** (1 g) was added to a suspension of the Grignard reagent prepared from methyl chloride (4 ml) and magnesium in ether (100 ml), and the mixture was boiled under reflux until no anhydro sugar **1** remained (t.l.c.; benzene–ether, 1:1). The products were resolved by column chromatography over silica gel to yield in order of elution: (*a*) compound **4** (0.16 g, 17%); (*b*) methyl 4,6-*O*-benzylidene-3-deoxy-3-methyl-α-D-altropyranoside[3,4] (**8**) (0.65 g, 62%), m.p. 115° (from ether–light petroleum), $[\alpha]_D^{20}$ +121° (*c* 2, chloroform); lit.[3], m.p. 114.5–116°, $[\alpha]_D^{20}$ +115.9° (ethanol); (*c*) compound **5** (0.05 g, 5%).

Reaction of methyl-lithium with **1**. — (*a*) To methyl-lithium, prepared[3] from methyl iodide, was added powdered **1** (1 g). T.l.c. (benzene–ether, 1:1) indicated the formation of a complex mixture of products from which compound **8** (0.2 g, 19%) was isolated by column chromatography over silica gel.

(*b*) To methyl-lithium, prepared from methyl bromide, was added powdered **1** (1 g). Compound **8** (0.13 g, 12%) was isolated from the reaction mixture by column chromatography over silica gel.

Reactions of Grignard reagents with methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (**2**). — (*A*) *Chromatography*. The reactions were monitored by t.l.c. with ether–light petroleum (1:1). In this solvent, approximate R_F values on microplates were: **9**, 0.7; **10**, 0.45; **14a** and **14b**, 0.4–0.5; **1** and **13b**, 0.3; **16**, 0.2; **13a** and **12**, 0.15. Where products have similar R_F values, separations were achieved by triple development of the microplate. Satisfactory separations on columns were achieved by using the same solvent system.

(*B*) *Reaction with ethylmagnesium bromide*. The powdered allopyranoside derivative **2** (3 g) was added to a solution of excess of ethylmagnesium bromide in tetrahydrofuran, and the solution was boiled under reflux until no starting material remained. Column chromatography of the products afforded: (*a*) 4,6-*O*-benzylidene-2-bromo-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (**9**, 0.27 g, 8%), m.p. 115–116° (from ethanol), $[\alpha]_D^{20}$ +12° (*c* 1, chloroform) (Found: C, 50.4; H, 4.3. $C_{13}H_{13}BrO_4$ calc.: C, 49.86; H, 4.18%); n.m.r. data(δ): H-1, 6.64; benzylic H, 5.57; H-3,4,5,6,6′, 3.5–4.5; n.m.r. data (δ) for the crude acetate of **9**: H-1, 6.75; H-3, 5.83 ($J_{2,3}$ 3.2, $J_{3,4}$ 9 Hz); benzylic H, 5.55; H-4,5,6,6′, 3.5–4.8; OAc, 2.13; (*b*) 4,6-*O*-benzylidene-1,2-dideoxy-D-*ribo*-hex-1-enopyranose (**10**, 1.2 g, 45%), m.p. 82° (from ethanol) (the m.p. and n.m.r. parameters for this compound were in agreement with the published[14] data); (*c*) methyl 4,6-*O*-benzylidene-3-bromo-3-deoxy-α-D-glucopyranoside (**13a**, 0.25 g, 6%), m.p. 169–170° (from ethanol), $[\alpha]_D^{21}$ *ca.* 0° (*c* 0.1, chloroform) (Found: C, 49.3; H, 5.0. $C_{14}H_{17}BrO_5$ calc.: C, 48.7; H, 5.0%); n.m.r. data: H-1 at 4.8 p.p.m. ($J_{1,2}$ 3.5 Hz), and the overall spectrum closely resembled that of **13b**; (*d*) methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**12**, 1.1 g, 37%), m.p. 127–128° (from ethanol); the n.m.r. spectrum of **12** was consistent with the assigned structure and indistinguishable from that of an authentic sample of **12** prepared by reduction of **2** with lithium aluminium hydride.

Similar results were obtained with ether as solvent.

When compound **2** was added to an equimolar quantity of ethylmagnesium bromide in ether or tetrahydrofuran, the principal product was methyl 4,6-*O*-benzylidene-2-bromo-2-deoxy-α-D-altropyranoside (**14a**), m.p. 119° (from ethanol); lit.[10] m.p. 117.5–118.5°. N.m.r. data: H-1 at 4.78 p.p.m. with $J_{1,2}$ <1.0 Hz, consistent with an equatorial proton at C-2.

Reaction of **14a** in ether with ethylmagnesium bromide, ethylmagnesium iodide, or methylmagnesium iodide afforded a mixture of the 1,2-ene **10** and the 2-deoxy derivative **12**.

(*C*) *Reaction with ethylmagnesium iodide*. (*a*) *In ether*. From the reaction of **2** (2 g) with excess of ethylmagnesium iodide in ether were obtained **10** (0.7 g, 39%), **13b** (0.05 g, 1.7%), and **12** (0.7 g, 35%). (*b*) Similar results were obtained in tetrahydrofuran. *Method 1*. Powdered **2** (0.5 g) was added to an excess of ethylmagnesium iodide in dry tetrahydropyran (the Grignard reagent was prepared in the usual way, and samples reacted vigorously with water before and after addition of **2**); the solution was monitored immediately, and the major products detected and subsequently isolated were the 1,2-ene (**10**) and the 2-deoxy derivative (**12**). *Method 2*. Tetrahydropyran was added to a freshly prepared solution of ethylmagnesium iodide in tetrahydropyran. A vigorous reaction took place, and addition was continued until a permanent yellow colour was observed. At this stage, the solution did not react vigorously with water. When powdered **2** was added to this solution, and the mixture was boiled under reflux, t.l.c. showed that **10** and methyl 4,6-*O*-benzylidene-3-deoxy-3-iodo-α-D-glucopyranoside were the preponderant products.

(*D*) *Reaction with methylmagnesium iodide*. (*a*) *In ether*. The reaction of **2** (1.5 g) with excess of methylmagnesium iodide in ether afforded **10** (0.59 g, 44%), **13b** (0.1 g, 45%), and **12** (0.3 g, 20%). (*b*) *In tetrahydropyran: method 1*. With freshly prepared Grignard reagent, the preponderant products were **10** and **12**. *Method 2*. With "aged" Grignard reagent, or by adding a dilute solution of **2** in tetrahydropyran to fresh Grignard reagent, high yields (50–80%) were obtained of the highly crystalline 3-deoxy-3-iodoglucose derivative (**13b**), m.p. 193–194° (from ethanol); lit.[9], m.p. 195–196°; n.m.r. data: H-1 at 4.70 p.p.m. with $J_{1,2}$ 3.5 Hz. Compound **13b** afforded a crude acetate with H-1 at 4.80 and H-2 at 5.12 p.p.m. with $J_{1,2}$ 3.5 and $J_{2,3}$ 10.5 Hz.

When compound **13b** was boiled under reflux in ether with excess of ethylmagnesium iodide or methylmagnesium iodide, the only product was methyl 4,6-*O*-benzylidene-3-deoxy-α-D-*ribo*-hexopyranoside (**16**), m.p. 190–191° (from ethanol); lit.[17], m.p. 190–191°. N.m.r. data (δ). H-1, 4.65 ($J_{1,2}$ 3.5 Hz); H-3*e*, 2.25, and H-3*a*, 1.88 ($J_{3e,4} \approx J_{3e,2} \approx 4$ Hz, and $J_{2a,3e} \approx J_{3a,2} \approx J_{3a,4} \approx 11$ Hz). The formation of **16** took several hours with ethylmagnesium iodide and much longer with methylmagnesium iodide. When a catalytic quantity of ferric chloride was added to the Grignard reagents, reduction was instantaneous and quantitative.

(*E*) *Reaction with methylmagnesium chloride*. From the reaction between the allose derivative **2** (2.2 g) and excess of methylmagnesium chloride in ether were obtained **10** (0.9 g, 46%); unchanged **2** (0.25 g, 11%); methyl 4,6-*O*-benzylidene-2-deoxy-2-methyl-α-D-altropyranoside (**15**, 0.71 g, 31%), m.p. 110–111° (from ether–

light petroleum); lit.[4], m.p. 110–111°; the n.m.r. spectrum of **15** was indistinguishable from that published; **12** (0.25 g, 11%).

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