Carbohydrate Research, 59 (1977) 477–503

GRIGNARD ADDITION-REACTIONS TO GLYCOSULOSE DERIVATIVES*†

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(Received May 24th, 1977; accepted for publication, June 13th, 1977)

ABSTRACT

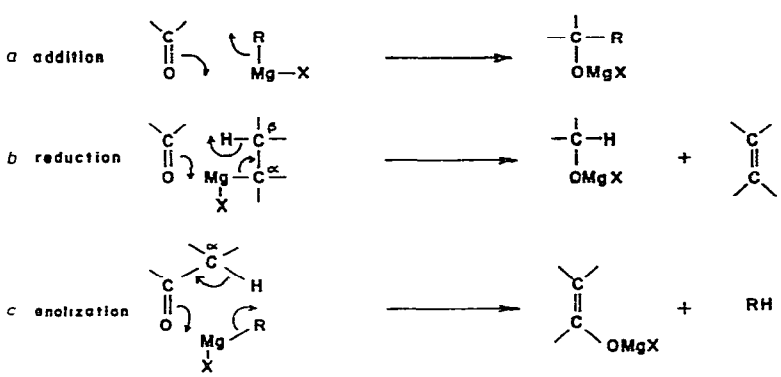
The course of Grignard addition-reactions to 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**) has been examined as a function of the nature of the reagent, the solvent, the halide, and the temperature. Ethylmagnesium bromide in ether at −14° converted **1** into 60% of the 3-*C*-ethyl-D-*allo* adduct **2**. The latter was convertible in 90% yield into the 3-benzyl ether **6**, despite the tertiary nature of the hydroxyl group. The use of tetrahydrofuran (THF) or THF–ether at higher temperatures, or of ethylmagnesium iodide, lowered the yield of **2** and gave substantial proportions of such side products as 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**), and the hydrate (**5**) of the starting ketone **1**. Phenylmagnesium bromide in ether or THF converted **1** into the 3-*C*-phenyl-D-*allo* derivative **7** in 84% yield, accompanied by only minor proportions of side products; the latter were the 3-*C*-phenyl-D-*gluco* adduct **8** and the product (**9**) of 5,6-dioxolane ring-opening. The structures of **8** and **9** were confirmed by an acetylation–deacetylation sequence, and by n.m.r. spectroscopy. The 3-*C*-phenyl-D-*allo* derivative **7** could be converted in 95% yield into its 3-benzyl ether **10**. Cyclohexylmagnesium bromide reacted with **1** in ether or THF at various temperatures to give 3-*C*-cyclohexyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**11**) in low yields; the main product generally encountered was **3**, with variable proportions of **4**, 1,2-*O*-isopropylidene-α-D-allofuranose (**18**), the hydrate **5**, and a dimeric product **19** (further characterized as its oxime **20**). Compound **11** was, however, obtainable in >95% yield by reducing **7** with hydrogen in the presence of rhodium-on-alumina. Phenylmagnesium bromide reacted with the 4-ketone derivative **25** in THF at 0° to give 83% of 1,6-anhydro-2,3-*O*-isopropylidene-3-*C*-phenyl-β-D-talopyranose (**26**), and no side-products were detected.

*Supported, in part, by Grant No. GM-11976 (The Ohio State University Research Foundation Project 1820) from the National Institute of General Medical Sciences, National Institutes of Health, U.S. Public Health Service, Bethesda, Md. 20014.
†For a preliminary report, see ref. 1. For related studies, see ref. 2.

INTRODUCTION

As previously pointed out[1,2], there exist compounds that contain a chiral, tertiary-alcohol group having aryl, cyclohexyl, or ethyl groups at the chiral center, and that are biologically important as neurotransmission agents or analogs thereof. Their physiological properties are critically dependent on the absolute configuration of the chiral center[3,4]. Convenient and versatile, stereospecific syntheses of optically pure molecules containing such asymmetric centers are thus of considerable interest in this regard. This paper[1] is concerned with reactions of the protected *keto*-sugar derivatives **1** and **25** with Grignard reagents to afford precursors of physiologically active, tertiary alcohol derivatives. The high stereospecificity attainable in many such Grignard reactions[5,6] renders carbohydrate precursors of potential value for synthesis of optically pure compounds that might be utilized to devise efficient syntheses of (*R*)- and (*S*)-2-(benzyloxy)-2-cyclohexyl(or 2-ethyl-, or 2-phenyl)-propanal and related, chiral, tertiary aldehydes, and dioxolane derivatives thereof, of interest as anticholinergic agents[3]. Earlier work in evaluating such types of molecules has been beset by problems of chiral compounds that may have been incompletely resolved, because the routes used for synthesis most generally required optical resolution, a procedure in which it is frequently difficult to ensure complete optical purity of the products. For this reason, it was considered that further detailed work on the preparation of optically pure aldehydes, dioxolanes, and benzyl alcohol derivatives, obtained by way of Grignard reactions on suitable carbohydrate derivatives, followed by excision of asymmetric centers not required, would provide a useful basis for further study in this area. Thus far, this type of approach has been mainly investigated by Inch and his co-workers[7].

Moreover, it was considered desirable to investigate those factors that govern the addition reactions of Grignard reagents to carbohydrate substrates having well established and readily varied stereochemistry. This paper possibly constitutes the first systematic study of the reaction of Grignard reagents with a glycosulose derivative as a function of temperature, solvent, concentration, and nature of the halogen.



According to the experimental conditions, it is shown that wide variations may occur in the products formed; the results may be accommodated within the framework of general knowledge on the nature of Grignard additions, and they provide general guidelines for influencing the reaction toward the *C*-branched products desired.

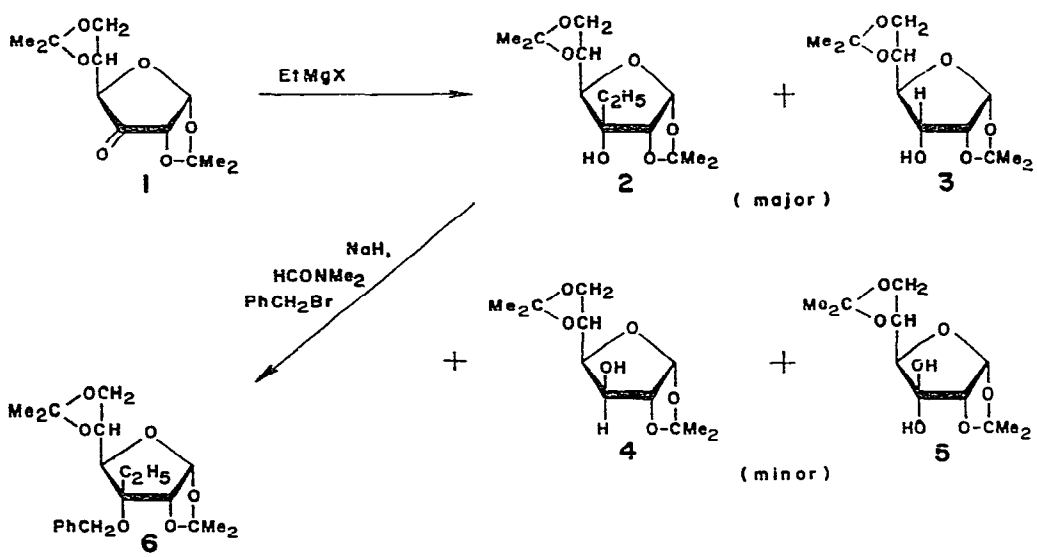
It is known in general that, when Grignard reagents (RMgX) react with carbonyl compounds, three different types of reaction may occur[8] (see formulas on previous page).

(*a*) Addition, the most usual reaction, occurs if the R group carrying a pair of electrons attacks the carbonyl carbon atom. (*b*) Reduction occurs when the R group of the Grignard reagent has a mobile hydrogen atom at its β position. (*c*) Enolization may compete successfully when addition is slowed by steric hindrance. In the enolization reaction, R^- removes a proton from an α carbon atom, giving the corresponding, saturated hydrocarbon (RH) and, at the same time, the resulting electron pair on the α carbon atom forms a carbon–carbon double-bond. Hydrolysis of this product gives an unstable enol that then regenerates the starting ketone.

The following results illustrate, with reference to the glycosulose **1**, all three types of process, and establish conditions most effective for favoring the addition mode.

DISCUSSION

The ketone[9] **1** reacted with ethylmagnesium bromide in ether at −14 to give 3-*C*-ethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**) in 63% yield. The D-*allo* configuration was attributed to **2** on the basis that the ketone **1** undergoes[10] stereospecific reduction by sodium borohydride to give 1,2:5,6-di-*O*-isopropylidene-α-D-



allofuranose, and also reacts stereospecifically with ethynylmagnesium bromide to give the corresponding 3-*C*-ethynyl-*allo* derivative[5]. Moreover, compound **2** has also been prepared by an independent route[11], and its physical data were in fair agreement with published values. Despite the tertiary nature of its hydroxyl group, compound **2** underwent conversion into its 3-benzyl ether in 90% yield by use of a large excess of sodium hydride and α-bromotoluene in *N*,*N*-dimethylformamide.

As may be seen in Table I, all modifications of the experimental conditions failed to improve the yield of **2**, and led to production of more side-products. Systematic, column chromatography of these side-products allowed the isolation of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[9,12] (**3**), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[13] (**4**), and the starting ketone **1** (recovered as its hydrate[9] **5**). Compounds **3**, **4**, and **5** were identical with known, reference samples. Use of ethylmagnesium iodide in ether at −12° consistently lowered the yield of **2** to 38%, but, at room temperature or above, a yield of 52% was obtained. The use of pure tetrahydrofuran (THF) or 1:1 THF–ether as the solvent considerably decreased the yields

TABLE I

SIDE PRODUCTS IN THE ADDITION OF ETHYLMAGNESIUM HALIDES TO KETONE **1**

Reagent	*Solvent*	*Temperature*	*Product yields*[a] (%) *after recrystallization*			
			2	**3**	**4**	**5**
EtMgI	Et_2O	reflux	52–49	25–23	10–7	6
EtMgI	Et_2O	−10 to −12°	38–34	45–42	5–3	5
EtMgI	1:1 Et_2O–THF	20°	38–34	46–42	5	3
EtMgBr	Et_2O	−12 to −14°	63–58	15–12	5–3	0
EtMgBr	THF	−12 to −14°	17–15	65–60	6	5
EtMgBr	1:1 Et_2O–THF	−12 to −14°	24–22	45–43	4	22–18
EtMgBr	Et_2O[b]	20°	36–32	30–26	10–8	18–14

[a]Concentration of EtMgX ~1.25M before addition of the ketone. [b]Final concentration of EtMgBr <0.1M before addition of the ketone.

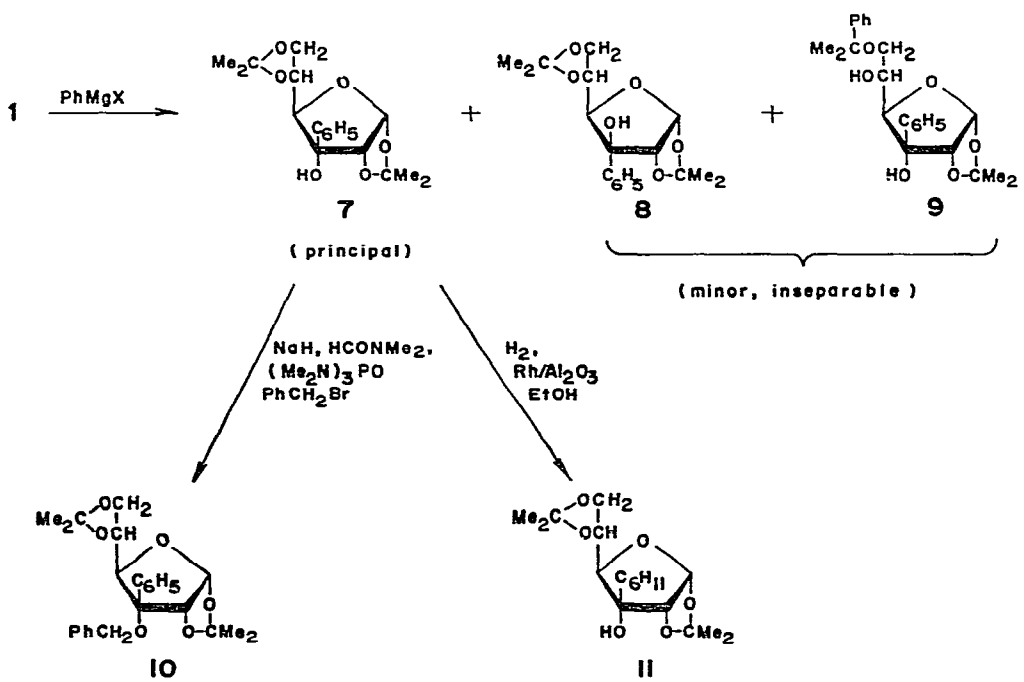
of **2** in all of the experiments tried. Only 17% of **2** was obtained when ethylmagnesium bromide was used in pure THF at −14°, but, under the same experimental conditions, 1:1 ether–THF raised the yield to 24%, thus indicating that THF tends to disfavor the addition reaction. When the ketone **1** was treated at room temperature with a very dilute, ethereal solution (<0.1M) of ethylmagnesium bromide, the yield of **2** was decreased considerably. This last result suggests that the addition mode of reaction is favored by high concentrations of the Grignard reagent. In no instance was 3-*C*-ethyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose isolated; the addition reaction is highly stereospecific under all conditions examined.

Among the side-products isolated, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**4**) was always produced, usually in ~5% yield. The hydrate **5** of the starting ketone (**1**) was usually isolated in 3–6% yield, but, surprisingly, when the ketone **1**

was treated with an ~1.2M ethereal solution of ethylmagnesium bromide at −14°, no appreciable proportion of **5** could be detected after conventional processing of the mixture. When the reaction was performed under the same conditions, but in 1:1 ether–THF, the yield of **5** was raised to 22%. A substantial proportion of **5** was also obtained when **1** was treated with a dilute, ethereal solution (<0.1M) of ethylmagnesium bromide at ~20°. As a large excess of Grignard reagent was used in these reactions, for an average time of 20 h at ~25°, a large proportion of the starting material was complexed as an unreactive enol salt. Neutralization of the salt during isolation generated the enol, which ketonized and was then hydrated to give **5**.

The main side-product encountered in all of these Grignard reactions was 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[10,12] (**3**). As shown in Table I, the yields of **3** are approximately in inverse proportion to the yields of the 3-*C*-ethyl-*allo* adduct **2**. When the Grignard reaction was conducted with ethylmagnesium iodide in ether at room temperature or above, compound **3** was isolated in 25% yield. When ethylmagnesium iodide was used, in ether or 1:1 THF–ether at −12°, the yield of **3** increased to 45–46%. These results indicate that use of THF tends to favor the reduction process leading to **3**, especially at low temperatures; the yields of **4** remained essentially unchanged.

As the use of ethylmagnesium bromide in ether at −14° gave the 3-*C*-ethyl-*allo* adduct **2** in 63% yield, and only 15% of compound **3** was formed, this procedure was used as a preparative method for compound **2**. Under the same conditions, ethylmagnesium iodide in ether at −12° gave a 45% yield of **3** and 38% of **2**, thus de-



monstrating the influence of the halide in the Grignard reaction. When ethylmagnesium bromide was used in pure THF at −14°, the reduced product **3** was isolated in 65% yield, or in 45% yield if THF was replaced by 1:1 ether–THF. These last results clearly show that THF favors the reduction process, regardless of the temperature or nature of the halogen. When ethylmagnesium bromide was used at low concentration (<0.1M) in ether, compound **3** was again the main product of the reaction, as it was when the reaction was conducted in THF.

Phenylmagnesium halides have no mobile protons, and are thus not expected to give competing reduction or enolization reactions. Indeed, the ketone **1** was found to undergo only addition reactions when phenylmagnesium bromide or iodide was used in ether or THF under a wide range of experimental conditions: 1,2:5,6-di-*O*-isopropylidene-3-*C*-phenyl-α-D-allofuranose (**7**) was obtained in 80–84% yield (see Table II). This reaction course resembles the behavior of **1** with ethynylmagnesium bromide[5]. Only two, minor side-products were usually produced, and these were formulated as the 3-*C*-phenyl-D-*gluco* adduct **8**, and compound **9**, which arises through an attack of the reagent on the non-fused dioxolane ring.

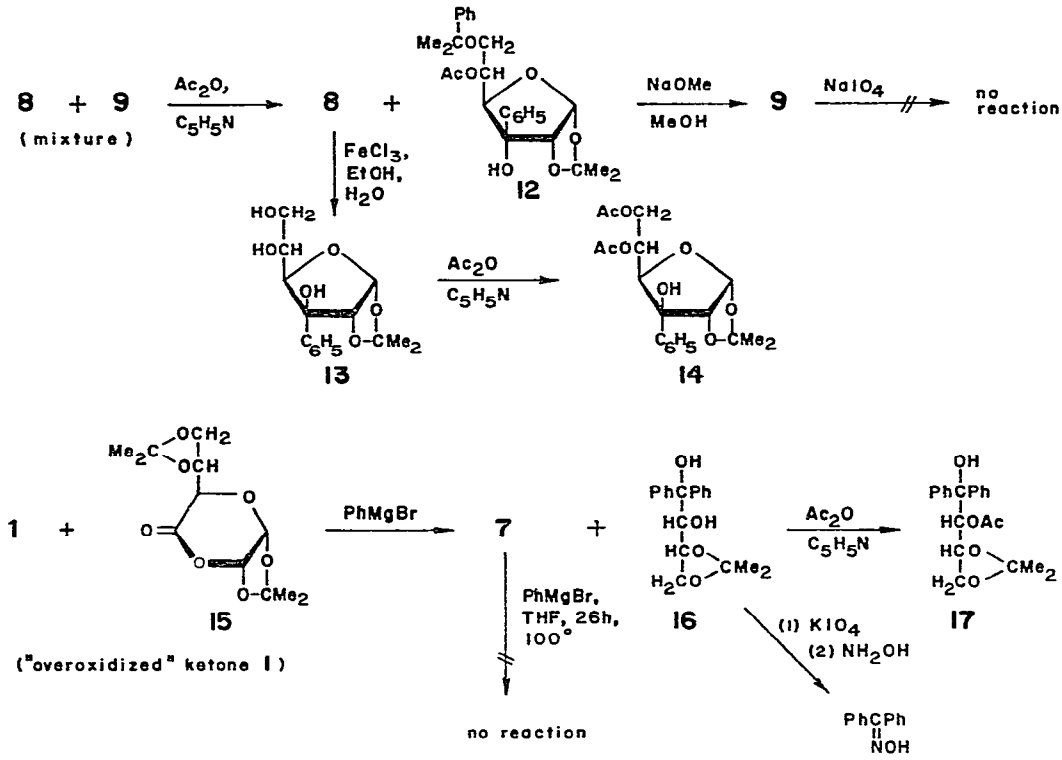
TABLE II

SIDE PRODUCTS IN ADDITION OF PHENYLMAGNESIUM HALIDE TO THE KETONE **1**

Reagent	*Solvent*	*Temperature*	*Product yields (%) of pure crystalline compound*		
			7	**8**	**9**
PhMgBr	ether	25° (or reflux)	84	3	3
PhMgBr	THF	25°	83	1.1	0.7
PhMgBr	THF (conc. soln.)	reflux	65–75	5–6	5–6
PhMgBr	THF	−6 to −8	83	~6	7–8
PhMgI	THF–ether	20°	80–74	3	0

The ring-opened product **9** and the D-*gluco* adduct **8** were obtained as an inseparable mixture that migrated as practically a single zone in t.l.c. Acetylation of the mixture with acetic anhydride in pyridine converted compound **9** into its 5-acetate **12**, which could be readily separated from compound **8**. The crystalline acetate **12** was then deacetylated, to afford pure compound **9**.

The absolute configuration at C-3 in the adducts **7** (principal) and **8** (minor or negligible) was evident upon comparison of their n.m.r. spectra in chloroform-*d* at 100 MHz. The H-4, H-5, H-6, and H-6′ signals of **8** resonated at δ 4.64, 4.42, 3.96, and 3.66, respectively, and H-2 resonated at δ 4.33. The relative deshielding of H-4, and also H-5, and the higher-field position of the H-2 signal, are consistent with the phenyl group's exerting a deshielding effect from the lower part of the molecule, indicating the *gluco* configuration for **8**. For compound **7**, H-2 resonates at lower field (δ 4.45) than for compound **8**, but H-4 and H-5 resonate at higher field (δ 4.15 and 3.75, respectively) than for compound **8**. The H-6 and H-6′ resonances of



compound 7 were also observed at higher field than for compound **8**. These data are consistent with the *allo* configuration for compound **7**, and this configuration is to be anticipated for the principal adduct by comparison with numerous, related addition-reactions[5,11] to **1**.

The analytical data and the n.m.r. spectrum of compound **9** indicated addition of the Grignard reagent to the carbonyl group, and also opening of the 5,6-acetal ring by a second molecule of the reagent to give a mono[(dimethylphenyl)methyl] ether. The *allo* configuration was attributed to compound **9** by examination of its n.m.r. spectrum in chloroform-*d* at 100-MHz. The H-2 signal was observed at δ 4.16 and that of H-4 at higher field (δ 3.82), indicating that no strong deshielding effect was exerted on H-4. A complex multiplet at δ 2.84–3.34 was observed for H-5, H-6, and H-6′, indicating that H-5 was not subject to deshielding by the 3-*C*-phenyl group. That the acetate (**12**) of **9** was the 5-acetate could also be deduced by comparison of its n.m.r. spectrum at 100 MHz in chloroform-*d* with that of the deacetylated analog **9**. In compound **12**, the H-5 signal was shifted downfield to δ ~4.3, out of the original multiplet for H-5, H-6, and H-6′. This observation indicates that **12** is the 5-acetate, and, hence, the *O*-(dimethylphenyl)methyl group is at O-6. Further evidence supporting the structure assigned to **9** is its failure to react with sodium metaperiodate.

Partial hydrolysis of 1,2:5,6-di-*O*-isopropylidene-3-*C*-phenyl-α-D-glucofuranose

(**8**) gave the crystalline 1,2-isopropylidene acetal **13**, whose n.m.r. spectrum and that of its derived 5,6-diacetate (**14**) (see Table IV) gave additional confirmation of the structure assigned to compound **8**.

1,2:5,6-Di-*O*-isopropylidene-3-*C*-phenyl-α-D-allofuranose (**7**) was converted in 95% yield into its 3-benzyl ether **10** by use of a large excess of sodium hydride and α-bromotoluene in 9:1 *N*,*N*-dimethylformamide–hexamethylphosphoric triamide. Compound **7** could also be readily and quantitatively hydrogenated in ethanol by hydrogen in the presence of 5% rhodium-on-alumina, to give 3-*C*-cyclohexyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**11**).

Only one side-product (**8**, 3%) was obtained when the ketone **1** was treated with phenylmagnesium iodide in THF–ether at room temperature, but the use of phenylmagnesium bromide under a wide range of different experimental conditions inevitably led to the formation of the 5,6-ring-opened product **9** as a side product (0.7–8%). This type of reaction is somewhat unusual, although related examples have been reported in other areas of organic chemistry[14]. However when a concentrated solution of the principal product (**7**) and phenylmagnesium bromide in THF was boiled for 26 h under reflux (bath temp. 100°), no reaction occurred, and compound **7** was recovered. This result demonstrates that the carbonyl group at C-3 is required in the 5,6-dioxolane ring-opening process; the Grignard reagent presumably coordinates with the carbonyl-oxygen atom. As product **9** is the 6-[(dimethylphenyl)methyl] ether, coordination of a magnesium atom with O-5 may be inferred. As the attack on the 5,6-dioxolane ring appears to occur only with concomitant addition to the carbonyl group, it may be presumed that a dimeric form of phenylmagnesium bromide is involved in this reaction, and effects coordination at O-3 and at O-5, thus leaving the absolute configuration at C-5 unchanged; compound **9** should, therefore, be the *allo* adduct. It has, in fact, been demonstrated[15,16] that phenylmagnesium iodide in ether solution exists only as PhMgI, whereas phenylmagnesium bromide exists in a dimeric form, especially in THF.

On some occasions, an unexpected side-product was encountered when the 3-ketone **1** was treated with phenylmagnesium bromide. The reason for this behavior was traced to a contaminant in some of the large-scale preparations of the starting ketone. In addition to the ketone, some batches contained a small proportion of the known lactone[17] **15** that presumably arises by a Bayer–Villiger type of oxidation of the ketone. This contaminant led to the formation, in addition to the anticipated adduct **7** (isolated in ~70% yield), of a small proportion (maximum, 10%) of a diphenyl derivative identified as compound **16** by various reactions, including acetylation to compound **17**, and degradation by periodate to yield benzophenone, identified as its oxime. The diphenyl derivative **16** predictably arises through addition to the lactone **15**.

In an initial attempt to prepare the cyclohexyl analog of the 3-*C*-phenyl derivative **7**, the ketone **1** was treated with cyclohexylmagnesium bromide in ether or THF. However, the yield of the desired cyclohexyl adduct **11** was unacceptably low, as shown in Table III, and there were several additional products. The highest yield

(35%) of **11** was obtained when the ketone **1** reacted with cyclohexylmagnesium bromide in ether at −14°. These experimental conditions had already given the best yield in the preparation of the corresponding 3-*C*-ethyl adduct (**2**) by treating the ketone **1** with ethylmagnesium bromide.

TABLE III

SIDE PRODUCTS IN THE ADDITION OF CYCLOHEXYLMAGNESIUM BROMIDE TO KETONE **1**

Temperature	*Solvent*	*Product yields (%) of pure crystalline compound*					
		3	**4**	**5**	**11**	**18**[a]	**19**
0°	THF	55–50	6–4	10	4–3	20–18	0
−16°	THF	66	5–4	12	5–4	—	0
Reflux	THF	12	11	—	6.3	26	0
Reflux	Et_2O	10	9.5	—	4.2	4	2
−14	Et_2O	35–32	6	10–8	35–30	7–5	0

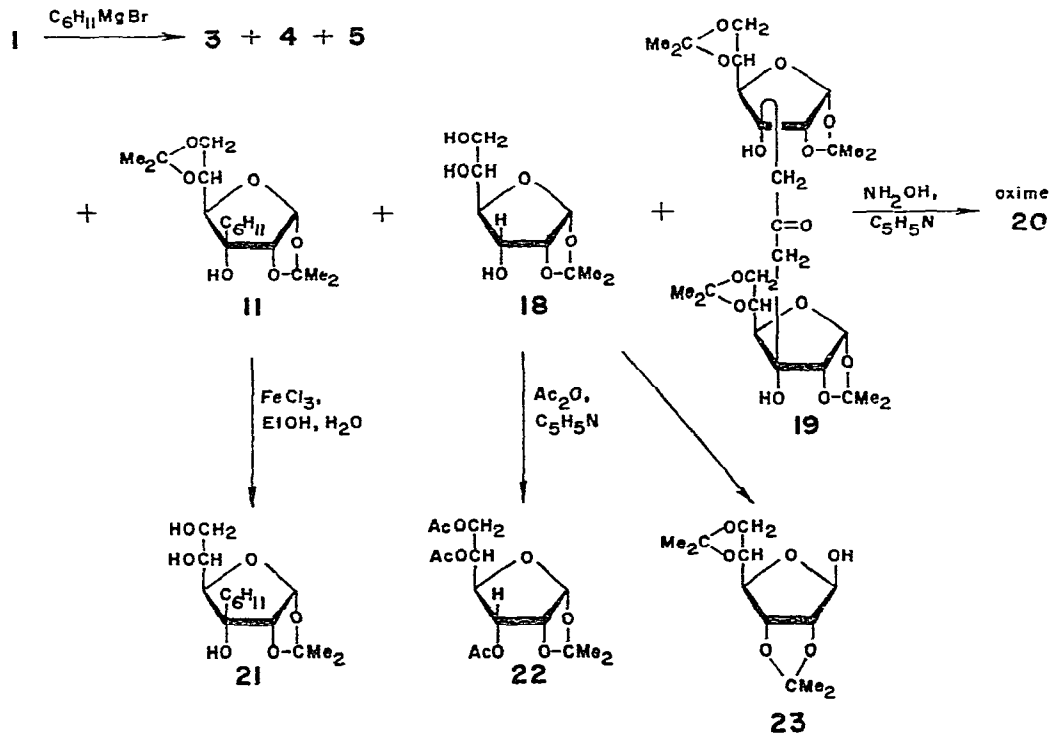
[a]After conventional isolation.

The 3-*C*-cyclohexyl-*allo* adduct **11** thus obtained had the same physical data (in all respects) as those of the sample prepared by catalytic reduction of the corresponding 3-*C*-phenyl-*allo* derivative **7**. Compound **11** was further characterized as its 5,6-deacetonated derivative **21**.

When the Grignard reaction was conducted in boiling ether, or THF, under reflux, a very complicated mixture was obtained, and the yields of other products increased at the expense of **11**, as indicated in Table III. At 0° or below, the reaction course resembled that observed with ethylmagnesium bromide; the solvent and the temperature influenced the course of the reaction in the same way, and the same side-products (**3**, **4**, and **5**) were formed in both reactions. However, in addition, the monoisopropylidene acetal (**18**) of D-allofuranose[18] was isolated; it arose in each instance when the Grignard reaction was conducted in ether or THF at 0° or above, but was absent from the products of the low-temperature reactions. It should be noted that compound **18** was also produced when the crude mixture was washed with water or cold aqueous solutions (to remove the magnesium salts), and the yields of **18** given in Table III do not necessarily indicate the exact amounts produced in the Grignard reaction.

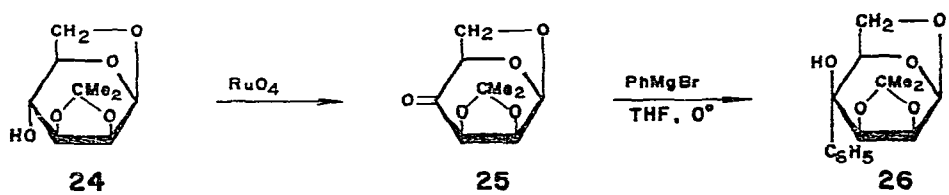
Compound **18** was further characterized as its known[19] triacetate **22**. Acetonation of **18** did not give the 1,2:5,6-diisopropylidene acetal **3**, but, instead, a 50% yield of 2,3:5,6-di-*O*-isopropylidene-β-D-allofuranose (**23**). This type of acetone-group migration for allose has already been observed by Ballard and B. E. Stacey[20] and others[21].

The reaction of **1** with cyclohexylmagnesium bromide in boiling ether gave a low yield of a dimeric product (**19**) that was not found when the reaction was conducted in ether at 0° or in THF. The n.m.r. spectrum of **19** in chloroform-*d* at 100 MHz showed that the molecule was fully symmetrical. The protons at C-1 and C-2 gave two



doublets (at δ 5.72 and 4.62), the tertiary hydroxyl group gave a singlet at δ 3.30, and the isopropylidene group gave 4 singlet resonances. The two methylene groups at the positions α to the carbonyl group gave two doublets, at δ 2.52 and 3.20, displaying a geminal coupling-constant of 16 Hz. This product is evidently a dimer, presumably arising from the condensation of one molecule of acetone, *produced in the reaction mixture*, with two molecules of the starting ketone **1**. Compound **19** was further characterized as its oxime (**20**).

The reaction of phenylmagnesium bromide with 1,6-anhydro-2,3-*O*-isopropylidene-β-D-*lyxo*-hexopyranos-4-ulose[22] (**25**) in THF at 0° gave an 83% yield of crystalline 1,6-anhydro-2,3-*O*-isopropylidene-4-*C*-phenyl-β-D-talopyranose (**26**), and no significant side-products could be detected. The *talo* configuration assigned to **26** was amply confirmed by comparison of its ^{1}H-n.m.r. spectrum with that of the starting ketone **25**. The phenyl group did not exhibit any major deshielding effect on



the ring protons, thus indicating that it had an axial and *exo* disposition. Furthermore, the ketone **25** is known[23] to undergo stereospecific reduction to 1,6-anhydro-2,3-*O*-isopropylidene-β-D-talopyranose, and ethynylation of **25** is equally stereospecific[6]; the configuration of the aldose acetal was supported by lanthanide shift-reagent studies[24].

The foregoing, comparative studies illustrate that the classic Grignard reaction between an organomagnesium halide and a ketone may be utilized with suitably protected glycosuloses for the stereospecific production of chiral, tertiary alcohol derivatives. Under appropriate conditions, phenylmagnesium bromide reacts, without complicating side-reactions, to give the adducts in excellent yield; these results parallel earlier work in this laboratory with ethynylmagnesium bromide[5]. When ethylmagnesium halides were used, the yield of classic adduct decreased, and side-products formed through reduction and enolization of the ketone became more significant. This trend became still more evident when cyclohexylmagnesium halides were used; the *C*-cyclohexyl branched-chain sugars were better prepared by reduction of the *C*-phenyl analogs. In all instances, competing side-reactions were minimized when reaction-temperatures were kept low. In addition to providing insight into factors influencing the yield in these reactions, this study has established practical, large-scale routes to *C*-branched-chain sugars, and also their benzyl ethers, having phenyl and cyclohexyl groups at an optically pure, tertiary alcoholic center. Such molecules may usefully serve as precursors to optically pure, tertiary alcohols having a single asymmetric center.

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure below 45°. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. A Perkin–Elmer Model 141 polarimeter and 1-dm tubes were used for measurement of specific rotations. I.r. spectra were recorded with a Perkin–Elmer Model 137 grating i.r. spectrophotometer, and n.m.r. spectra at 100 MHz with a Varian HA-100 spectrometer. Chemical shifts refer to an internal standard of tetramethylsilane ($\delta = 0.00$), and are recorded, together with spin-coupling values (Hz), in Table IV. T.l.c. was performed on 0.25-mm layers of silica gel 60 on precoated plates (5 × 10 cm; Merck, non-activated); zones were detected by u.v. light, and with sulfuric acid and subsequent heating. Developing solvents used were 49:1 (v/v) chloroform–methanol (solvent A), 7:3 (v/v) ether–light petroleum ether (solvent B), 1:1 (v/v) ether–light petroleum ether (solvent C), and 47:3 (v/v) benzene–acetone (solvent D). Column chromatography was conducted with silica gel 60 (70–230 mesh ASTM, Merck). Microanalyses were performed by W. N. Rond. Mass spectra were recorded by C. R. Weisenberger with an AEI MS-9 double-focusing, high-resolution spectrometer operating at an ionizing potential of 70 eV and an accelerating potential of 8 kV. X-Ray powder diffraction data give interplanar spacings, Å, for CuKα radiation. The camera diameter was 114.59 mm. Relative intensities were

TABLE IV

100-MHz, N.M.R.-SPECTRAL DATA

Solvent	*Compd.*	*Chemical shifts*[a] (*δ*) (*first-order couplings, Hz, in parentheses*)								*Others*
		H-1	*H-2*	*H-4*	*H-5*	*H-6*	*H-6'*	CMe_2	tert-*OH*	
$CDCl_3$	**2**	5.68d (4.0)	4.33d	←——3.74–4.18m—→ (4)		(1.8, 8.0)		1.32s, 1.40s 1.56s	2.52s	1.00t, CH_3 (7.0); 1.80q, CH_2 of ethyl
$CDCl_3$	**6**	5.64d (3.6)	4.46d	←——3.88–4.30m—→				1.32d, 1.56s		1.02t, CH_3 (7.8) 1.92q, CH_2 of ethyl; 4.66d, 4.85d, – CH_2 of benzyl (11); 7.18–7.46m, Ph
$CDCl_3$	**7**	6.08d (4)	4.45d	4.15d (5)	3.75m	3.54dd (7, 8.4)	3.10dd (6.4, 8.4)	1.16s, 1.35s, 1.38s, 1.68s	3.26s	7.32s, Ph
$CDCl_3$	**12**	5.86d (4)	4.20d	←—~4.30m—→		←——3.0t——→ (2)		1.09s, 1.38s	3.22s	1.13s, 1.15s, CH_3; 1.76s, Ac; 6.98–7.24m, Ph
$CDCl_3$	**8**	6.04d (3.5)	4.33d	4.64d (4,5)	4.42m	3.96dd (8.5, 6.5)	3.66dd (8.5, 7.0)	1.15s, 1.20s 1.26s, 1.58s	4.04s	7.26–7.68m, Ph
Me_2SO-d_6	**13**	5.88d (3)	4.16d	4.52d (4.2)	3.72m	←3.06–3.50m—→ (11, 5.0)	(11, 6.0)	1.14s, 1.42s	5.92s	4.62t, OH-6 (5); 4.80d, OH-5 (5); 7.16–7.64m, Ph
$CDCl_3$	**14**	5.98d (3.6)	4.28d	4.74d (9)	5.22m	←4.24–4.60m—→ (2.8, 12)	(6.2, 12)	1.22s, 1.24s	4.03s	1.58s, 2.02s, Ac 7.24–7.60m, Ph
$CDCl_3$	**9**	5.76d (4)	4.16d	3.82d (9)	←——~2.84–3.34m—→			1.02s, 1.16s	~3.24[b]	1.16s, 1.32s, CH_3; 2.16[b], OH-5 7.14m, Ph
C_6D_6	**10**	5.86d (4)	4.56d	4.80d (5)	3.90m	3.61dd (8.0, 6.0)	3.06dd (8.0, 6.2)	1.21s, 1.40s 1.48s	—	4.38d, 4.74d, CH_2 of benzyl (11); 7.06–7.54m, Ph
$CDCl_3$	**11**	5.64d (3.6)	4.38d	←——3.76–4.30m—→ (5.5)		(4.0, 8.0)	(4.0, 8.0)	1.32s, 1.35s 1.42s, 1.55s	2.58s	0.7–2.26m, cyclohexyl

TABLE IV (*continued*)

Solvent	*Compd.*	*Chemical shifts*[a] (*δ*) (*first-order couplings, Hz, in parentheses*)								*Others*
		H-1	*H-2*	*H-4*	*H-5*	*H-6*	*H-6'*	*CMe_2*	tert-*OH*	
C_6D_6	**16**	3.80–4.04m		—	—	—	—	1.04s, 1.26s	3.68s	2.68d, OH-3 (3) 4.70t[c], H-3 (3) 6.90–7.68m, Ph
$CDCl_3$	**16**	3.70–4.10m		—	—	—	—	1.22s, 1.37s	3.54s	2.66d, OH-3 (3); 4.80t[c], H-3 (3); 7.16–7.64m, Ph
Me_2SO-d_6	**17**	3.76–4.04m			—	—	—	1.10s, 1.16s	6.16s	1.84s, Ac; 6.08d, H-3 (<2); 7.14–7.56m, Ph
$CDCl_3$	**21**	5.80d (3.0)	~4.86	4.26dd (6.0, 3.0)	5.28m	4.44dd (12.0, 3.8)	4.10dd (12.0, 7.0)	1.29s, 1.50s	—	2.01s, 2.03s, 2.09s, Ac, ~4.86, H-3
$CDCl_3$	**23**	5.32d[d] (8.0, 0.0)	4.82d (6.0, 0.0)	←3.98–4.38m→ (4.5, 0.0)		(9.0, 5.0)	3.86dd (9.0, 5.0)	1.28s, 1.32s 1.42s	—	4.54d, H-3 (6.0, 0.0); 4.28d, OH-1 (8)
$CDCl_3$	**22**	5.68d (4)	4.38d	←3.60–4.10m→				1.31s, 1.53s	2.94s[e]	0.80–2.20m, cyclohexyl; 2.64t[b], OH-6 (~6) 2.94s[e], OH-5
$CDCl_3$	**19**	5.72d (4.0)	4.62d	←3.72–4.28m→				1.30s, 1.32s 1.42s, 1.55s	3.30s	2.52d, 3.20d, $(CH_2)_2CO$ (16)
$CDCl_3$	**20**	1.74d (3.8)	4.32d					1.34,s 1.41s	3.0s	3.0–3.36, 2d, 2H, $(CH_2)_2CO$ (14.0, 16.0); 2.36–2.66[f], 2H, $(CH_2)_2CO$ (14.0 16.0)
		1.78d (3.8)	4.46d	←3.76–4.16m→				1.44s, 1.58d	4.78s	
$CDCl_3$	**26**	5.43d (3.5)		4.27–4.47m			3.76dd (8.0, 6.0)	1.34s, 1.63s	3.69s	4.27–4.47m, H-3; 7.35–7.83m, Ph

[a]Multiplicities of the signals given by d, doublet; m, multiplet; q, quartet; s, singlet; t, triplet. [b]Broadened signal. [c]Gives a doublet after addition of D_2O. [d]Gives a singlet at *δ* 5.32 after addition of D_2O. [e]Gives a singlet at *δ* 3.04 (OH-3) and a doublet (3) at *δ* 3.18 (OH-5) after addition of D_2O. [f]Pseudo-triplet.

estimated visually: m, moderate; s, strong; v, very; w, weak. The strongest lines are numbered (1, strongest).

Reactions of ethylmagnesium halides with 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (**1**). — Crystalline 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose hydrate (**5**) was prepared as already described[9]. The corresponding free ketone **1** was prepared by dissolving **5** in benzene and evaporating the resulting solution at atmospheric pressure until no water was present. The excess of solvent was removed under diminished pressure in a rotary evaporator, to give a white solid that was used without recrystallization. The yields of products obtained upon addition of ethylmagnesium halides to the free ketone **1** in ether, THF, or a 1:1 mixture of these two solvents, at various temperatures, are summarized in Table I. A typical example is given here, describing the isolation of all significant products formed in the reaction of **1** with ethylmagnesium bromide in 1:1 ether–THF at −12 to −14°. Unless otherwise specified in Table I, all of the other Grignard reactions were performed similarly by using 5 equivalents of magnesium turnings, 4 equivalents of ethyl halide per equivalent of the free ketone **1**, and relative volumes of solvents as close as possible to those used in the following example.

Ethylmagnesium bromide was prepared by dropwise addition of a solution of ethyl bromide (0.10 mol, 4 equiv.; 11.1 g, 7.6 ml) in dry THF (40 ml) to a magnetically stirred suspension of magnesium turnings (128 mmol, 5 equiv.; 3.11 g) in dry ether (40 ml). After the end of the exothermic reaction, the mixture was stirred for 2 h at ~25°, and then cooled to between −12 and −14°. A solution of the free ketone **1** (from 7.0 g of the hydrate; 25.7 mmol) in 1:1 THF–ether (80 ml) was slowly added during 90 min. The mixture was kept for a further 2 h at that temperature, and then allowed to warm overnight to room temperature. Water (~20 ml) was carefully added, and then Celite (15–20 g), and the resulting mixture was stirred for some time before being filtered through Celite. The Celite pad was washed with THF, and the combined filtrates were evaporated to dryness to give a yellow oil (7.0 g). T.l.c. (solvent B) showed the oil to be a mixture of 4 products, giving rise to 3 spots, having R_F 0.70 (compound **2**), 0.47 (double spot; mixture of the ketone hydrate **5** and **4**), and 0.34 (tailing spot; **3**), respectively. T.l.c. (solvent A) clearly showed this oil to be a mixture of 4 products, having R_F 0.73 (**2**), 0.64 (**5**), 0.56 (**3**), and 0.41 (**4**). The oil was chromatographed on a column (4 × 80 cm) of silica gel with 13:7 ether–light petroleum ether as eluant. The first fraction obtained was pure *3-C-ethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose* (**2**: 1.8 g, 6.3 mmol, 24%) which, on recrystallizing from 1:1 light petroleum ether–cyclohexane and cooling to 0°, gave white needles (1.6 g, 22%), m.p. 95–96°, $[\alpha]_D^{19}$ +21° (*c* 1.4, chloroform); {lit.[11] m.p. 87–88°; $[\alpha]_D^{20}$ +22° (*c* 1.00, chloroform)}; ν_{max}^{KBr} 3600 cm^{-1} (OH); *m/e* 288 (<1) (M^+), 273 (27) ($M^+ - \cdot CH_3$), 259 (<1) ($M^+ - \cdot C_2H_5$), 230 (<1) ($M^+ - C_3H_6O$), 187 (6) ($M^+ - C_5H_9O_2\cdot$), 157 (19), 155 (8), 131 (9) ($C_5H_9O_2CHOH^+$), 101 (63) ($C_5H_9O_2^+$), 100 (100) ($C_5H_8O_2^+$), 85 (22) (100 − $\cdot CH_3$), 59 (59) ($C_3H_7O^+$), 43 (95) ($C_2H_3O^+$); X-ray diffraction powder data: 9.45 s, 7.93 s, 7.28 vs (1,1,1), 5.75 vw, 5.42 m, 5.08 vs (1,1,1), 4.74 vw, 4.49 s, 4.32 vs (1,1,1), 4.19 m, 3.99 w, 3.61 s, 3.16 m, 2.99 m, 2.87 vs, 2.76 m, and 2.68 w.

Anal. Calc. for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.24; H, 8.56.

The second fraction (2.1 g) isolated was a mixture of the starting ketone hydrate **5** and *1,2:5,6-di*-O-*isopropylidene*-α-D-*glucofuranose* (**4**). The third fraction (2.9 g, 11.5 mmol; 45%) was pure *1,2:5,6-di*-O-*isopropylidene*-α-D-*allofuranose* (**3**), which was recrystallized from the minimal volume of cyclohexane; yield 2.8 g (43%), m.p. 77°, $[\alpha]_D^{20}$ +38° (*c* 1.4, water) {lit.[12] m.p. 76–77°, $[\alpha]_D^{22}$ +37.7° (in water)}.

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.43; H, 7.64.

Fraction 2 (2.1 g) was rechromatographed on a column (2.5 × 50 cm) of silica gel with solvent A as the eluant. Pure *1,2:5,6-di*-O-*isopropylidene*-α-D-ribo-*hexofuranos-3-ulose hydrate* (**5**; 1.64 g, 22%) was eluted first, and was recrystallized from 1:1 (v/v) ether–light petroleum ether as white needles (1.33 g, 18%), m.p. 111–112°, $[\alpha]_D^{26}$ +46° (*c* 2.2, ethanol) {lit.[9] m.p. 111–112°, $[\alpha]_D^{25}$ +44° (*c* 1, ethanol)}. The i.r., n.m.r., and mass spectra were identical to those of an authentic sample prepared by oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose.

Anal. Calc. for $C_{12}H_{20}O_7$: C, 52.16; H, 7.30. Found: C, 52.16; H, 7.01.

Pure *1,2:5,6-di*-O-*isopropylidene*-α-D-*glucofuranose* (**4**) was finally isolated as a white solid; yield 0.335 g [1.28 mmol (5%)], which was recrystallized from cyclohexane as white needles (0.268 g, 4%), m.p. 110°, $[\alpha]_D^{20}$ −12° (*c* 1.2, chloroform); lit.[13] m.p. 110–111°, $[\alpha]_D^{20}$ −13.5° (chloroform); the i.r., n.m.r., and mass spectra, and also the X-ray powder diffraction data were identical to those for an authentic sample.

Anal. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.46; H, 7.77.

When the ketone **1** was to be treated with ethylmagnesium bromide in dilute ethereal solution, the Grignard reagent was prepared as already indicated, and the solution was then diluted with ether to a concentration of <0.1M before the additton of the ketone.

Practical preparation of 3-C-*ethyl-1,2:5,6-di*-O-*isopropylidene*-α-D-*allofuranose* (**2**). — The ketone **1** (from 14.0 g of the corresponding hydrate; 51 mmol) was treated with ethylmagnesium bromide as just described, in pure ether at −12 to −14°. On isolation as before, a yellow oil (15.0 g) was obtained. A solution of this oil in benzene (500 ml) was extracted with water (5 × 300 ml), and the extracts were evaporated to yield a gum (6.4 g). The benzene phase was evaporated to dryness to give a white solid (8.4 g) which, by t.l.c. (solvent B), proved to be almost pure 3-*C*-ethyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**2**). This product was dissolved in hot cyclohexane (~30 ml), light petroleum ether (30 ml) was added, and the solution was slowly cooled to 0°, to afford pure **2** as white needles (7.0 g; 24 mmol, 47%), m.p. 95°. The gum (6.4 g) from the water extracts was mixed with the gum obtained by evaporating the mother liquors of recrystallization, and the mixture was chromatographed on a column (4 × 60 cm) of silica gel. Elution of the column with 3:2 ether–benzene gave pure **2** (2.480 g; total yield, 9.480 g; 33 mmol, 63%), which was recrystallized from 1:1 cyclohexane–light petroleum ether. The total yield of pure, crystalline **2** was 8.360 g (29 mmol, 58%).

3-O-Benzyl-3-C-ethyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**6**). — A solution of **2** (1.225 g, 4.25 mmol) in anhydrous *N,N*-dimethylformamide (20 ml) was stirred for 2 h at ~25° with sodium hydride (10 molar equivs., 0.920 g). α-Bromotoluene (12 ml) was then slowly added during 30 min, and the resulting solution was stirred for 24 h at ~25°. Methanol (5 ml) was carefully added, followed by water (100 ml), and the mixture was extracted with chloroform (2 × 100 ml). The extract was dried (magnesium sulfate), evaporated to dryness (70–80°/0.1 torr), and the residual, colored oil was chromatographed on a column (3 × 60 cm) of silica gel. Elution with solvent B gave pure compound **6**, yield 1.443 g (90%), which was recrystallized from cyclohexane to give fine, white needles (1.186 g, 73%): m.p. 106°, $[\alpha]_D^{20}$ +44.5° (*c* 1.2, methanol); R_F 0.67 (3:2 petroleum ether–ether); ν_{max}^{KBr} 1515, 855, and 705 cm^{-1} (monosubstituted phenyl), no hydroxyl band: *m/e* 378 (<1) ($M^{\ddagger}$), 363 (6) ($M^{\ddagger} - \cdot CH_3$), 320 (1) ($M^{\ddagger} - C_3H_6O$), 247 (4) ($M^{\ddagger} - C_5H_9CHOH\cdot$), 185 (8), 171 (6), 157 (16), 140 (8), 133 (7), 113 (6) ($C_6H_9O_2^+$), 101 (58) ($C_5H_9O_2^+$), 100 (24) ($C_5H_8O_2^+$), 99 (3) ($C_5H_7O_2^+$), 97 (4), 92 (8), 91 (100) ($C_7H_7^+$), 85 (7) ($C_4H_5O_2^+$), 77 (2) ($C_6H_5^+$), 59 (6) ($C_3H_7O^+$), 58 (2) ($C_3H_6O^{\ddagger}$), 57 (44), and 43 (20) ($C_2H_3O^+$): X-ray diffraction powder data: 9.87 vs (2,2), 8.93 vs (2,2), 7.05 s, 6.60 w, 6.02 s, 5.52 m, 5.12 s, 4.79 s, 4.55 m, 4.25 vs (1), 4.04 vw, 3.85 w, 3.65 w, 3.45 vw, and 3.28 m.

Anal. Calc. for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.43; H, 8.13.

Reactions of phenylmagnesium halides with 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexo-furanos-3-ulose (**1**). — *1,2:5,6-Di-O-isopropylidene-3-C-phenyl-α-D-allofuranose* (**7**). The yields of all products obtained by treating the free ketone **1** with phenylmagnesium bromide or iodide in ether or THF at various temperatures are summarized in Table II. The following, typical example describes the preparation of compound **7** by the use of phenylmagnesium bromide in ether. This reaction was used for a large-scale preparation of **7**.

A solution of bromobenzene (2 molar equivs., 0.46 mol; 72 g, 48 ml) in dry ether (200 ml) was added dropwise during 30 min to a mechanically stirred suspension of magnesium turnings (16 g; 0.69 mol, 3 molar equivs.) in dry ether (150 ml) so as to maintain gentle boiling under reflux (the reaction was initiated by adding a crystal of iodine). The mixture was boiled for 1 h more, and then cooled to ~25°. A solution of the free ketone **1** (64 g, 0.23 mol) in ether (200 ml) was added dropwise during 1 h. At the end of the addition, the Grignard complex precipitated as a thick gum that proved impossible to dissolve, even when more ether was added. The mixture was boiled for 5 h under reflux, diluted with THF (200 ml), and cooled. The excess of phenylmagnesium bromide was decomposed by carefully adding water (20 ml). Celite (~25 g) was added with stirring, and the mixture was filtered through a Celite pad that was then washed with THF. The combined filtrates were evaporated to dryness, a solution of the residue in chloroform (500 ml) was washed with water (3 × 200 ml), and the washes were extracted with chloroform (100 ml). The combined organic phases were dried (sodium sulfate), and evaporated to dryness, to give a white solid (88 g) that, by t.l.c. (solvent C), was found to contain a major product (**7**)

having R_F 0.67, a minor, double spot having R_F 0.35 (products **8** and **9**), traces of products moving much more slowly, and two spots migrating between R_F 0.75 and 0.90 that did not react with sulfuric acid; the fastest-moving one was presumably biphenyl. Recrystallization of this solid from cyclohexane gave the pure 3-*C*-phenyl-α-D-*allo* derivative **7** as white crystals (52 g; 0.15 mol, 68%), m.p. 96–97°.

The mother liquors from the recrystallization of **7** were evaporated to dryness, and the residual gum (36 g) chromatographed on a column (5.5 × 90 cm) of silica gel that was eluted with solvent C. Pure **7** (17 g) was eluted first, and was cystallized from cyclohexane to give an additional 13.6 g of crystalline **7**: total yield, 65.6 g; 0.19 mol, 84%. The analytical sample was recrystallized once more from cyclohexane, and had m.p. 98°, $[\alpha]_D^{28}$ +47.2° (*c* 1.3, chloroform); ν_{max}^{KBr} 3450 (OH), 1490, 782, and 700 cm^{-1} (monosubstituted phenyl); *m/e* 336 (<1) (M^+), 231 (13) ($M^+ - \cdot CH_3$), 221 (2) ($321 - C_5H_8O_2\cdot$), 206 (3), 205 (24), 203 (3), 162 (10), 149 (13), 148 (78), 147 (47), 146 (3), 145 (17), 144 (2), 131 (16) ($C_5H_9O_2CHOH^+$), 129 (2) ($C_5H_7O_2\dot{C}HOH$), 105 (80) ($C_6H_5CO^+$), 101 (22) ($C_5H_9O_2^+$), 100 (100) ($C_5H_8O_2^+$), 99 (2) ($C_5H_7O_2^+$), 91 (9), 85 (10) ($100 - \cdot CH_3$), 79 (5), 78 (7) ($C_6H_6^+$), 77 (18) ($C_6H_5^+$), 59 (22) ($C_3H_7O^+$), 58 (10) ($C_3H_6O^+$), and 43 (62) ($C_3H_3O^+$); X-ray diffraction powder data: 10.15 m, 8.06 m, 7.10 m, 6.60 s (1,1,1), 6.25 w, 5.02 s (1,1,1), 4.54 s (1,1,1), 4.39 w, 4.17 m, and 3.59 vw.

Anal. Calc. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.21.

The second fraction to be eluted from the column used to purify the mother liquors was a mixture of 1,2:5,6-di-*O*-isopropylidene-3-*C*-phenyl-α-D-glucofuranose (**8**) and 1,2-*O*-isopropylidene-3-*C*-phenyl-6-*O*-(2-phenyl-2-propyl)-α-D-allofuranose (**9**) as a gum (7.0 g) that showed a double spot in t.l.c. in all chromatographic solvents used; R_F 0.35 (solvent C).

Isolation of products **8** *and* **9**. A solution of the gummy mixture (7.0 g) in dry pyridine (50 ml) was treated overnight at ~25° with acetic anhydride (5 ml). Methanol (20 ml) was added, and the solution was kept for 2 h at ~25°, and then evaporated to dryness. Traces of pyridine and acetic acid were removed by evaporating toluene several times from the residue. The resulting, colored solid (7.5 g), shown by t.l.c. to be a mixture of two, main products, R_F 0.42 and 0.31 (solvent D), was dissolved in hot, abs. ethanol. On careful cooling to 0°, the solution deposited white, crystalline needles (3.225 g; 7.0 mmol, 3%) of *5-O-acetyl-1,2-O-isopropylidene-3-C-phenyl-6-O-(2-phenyl-2-propyl)-α-D-allofuranose* (**12**), m.p. 180°. The analytical sample was recrystallized once more from abs. ethanol: m.p. 181–182°, $[\alpha]_D^{28}$ +33.5° (*c* 1.3, chloroform); R_F 0.42 (solvent D); ν_{max}^{KBr} 3500 (OH), 1720 (CO), 1500, 775, 765, and 700 cm^{-1} (monosubstituted phenyl); *m/e* 457 (<1) (M^+), 442 (<1) ($M^+ - \cdot CH_3$), 338 (<1) ($M^+ - C_6H_5\dot{C}Me_2$), 280 (<1) ($338 - C_3H_6O$), 279 (3), 205 (17), 149 (9) ($C_6H_5CMe_2OCH_2^+$), 148 (21), 147 (18), 120 (11), 119 (100) ($149 - CH_2O$), 118 (4), 117 (2), 115 (8), 105 (32), 103 (4), 101 (2), 100 (20) ($C_5H_8O_2^+$), 91 (15), 85 (3) ($C_5H_8O_2^+ - \cdot CH_3$), 79 (3), 78 (2) ($C_6H_6^+$), 77 (5) ($C_6H_5^+$), 59 (4) ($C_3H_7O^+$), and 43 (21) ($C_2H_3O^+$); X-ray diffraction powder data: 12.27 s, 10.10 vs (1), 8.70 vw,

7.07 vs (3), 5.90 s, 5.59 s, 5.24 s, 4.92 s, 4.70 s, 4.49 s, 4.25 s, 3.88 vs (2), 3.73 w, 3.57 m, 3.51 w, 3.25 m, 3.04 vw, and 2.94 m.

Anal. Calc. for $C_{26}H_{32}O_7$: C, 68.40; H, 7.07. Found: C, 68.68; H, 7.02.

The mother liquors from the recrystallization of **12** were evaporated to dryness, and the residual gum (3.7 g) was chromatographed on a column (3 × 60 cm) of silica gel that was eluted with 19:1 benzene–acetone. Pure *1,2:5,6-di-*O*-isopropylidene-3-*C*-phenyl-*α*-*D*-glucofuranose* (**8**) was isolated as a gum, yield 2.330 g (3%), that did not crystallize; it was further characterized as its monodeacetonated derivative (**13**), and the corresponding diacetate **14**. Compound **8** had $[\alpha]_D^{23}$ +101.4° (*c* 2, chloroform); R_F 0.31 (solvent D); ν_{max}^{film} 3450 (OH), 1510, 768, and 700 cm^{-1} (monosubstituted phenyl).

*1,2-*O*-Isopropylidene-3-*C*-phenyl-*α*-*D*-glucofuranose* (**13**). — A solution of **8** (6.0 g, 18 mmol) and ferric chloride (3.0 g) in 9:1 (v/v) ethanol–water (100 ml) was kept for 3 h at ~25° and 1 h at 70°. At that stage, t.l.c. (19:1 chloroform–methanol) indicated that reaction was complete, and so the solution was evaporated to dryness. Water (200 ml) was added, and the resulting solution was extracted with chloroform (4 × 80 ml). The dried (sodium sulfate) extract was evaporated to dryness, to give a white solid (4.0 g) that, on dissolution in hot ethyl acetate and slow cooling to 0°, gave white crystals of compound **13**, yield 3.2 g (63%), m.p. 146–147°. The analytical sample was recrystallized once more from ethyl acetate, and had m.p. 148–149°, $[\alpha]_D^{28}$ +98.7° (*c* 1.8, chloroform); ν_{max}^{KBr} ~3450 (broad, OH), 1480, 790, 770, and 690 cm^{-1} (monosubstituted phenyl); *m/e* (296 (<1) ($M^{\ddagger}$), 281 (2) ($M^{\ddagger} - \cdot CH_3$), 263 (<1) ($281 - H_2O$), 161 (5), 150 (4), 149 (40), 148 (10), 147 (14), 105 (17) ($C_6H_5CO^+$), 103 (9), 101 (7), 100 (100) ($C_5H_8O_2^{\ddagger}$), 91 (4), 85 (23) ($100 - \cdot CH_3$), 79 (3), 78 (4) ($C_6H_6^{\ddagger}$), 77 (12) ($C_6H_5^+$), 71 (8) ($C_3H_3O^+$), 59 (9) ($C_3H_7O^+$), and 43 (23) ($C_2H_3O^+$): X-ray diffraction powder data: 11.11 vs (2), 8.71 vs (3), 6.68 w, 5.45 vs (1), 5.09 w, 4.59 m, 4.38 m, 4.17 m, 4.00 m, 3.81 vw, 3.58 w, and 3.43 w.

Anal. Calc. for $C_{15}H_{20}O_6$: C, 60.07; H, 6.80. Found: C, 60.19; H, 6.79.

*5,6-Di-*O*-acetyl-1,2-*O*-isopropylidene-3-*C*-phenyl-*α*-*D*-glucofuranose* (**14**). — A solution of **13** (1.0 g, 3.5 mmol) in pyridine (10 ml) and acetic anhydride (1 ml) was kept for 20 h at ~25° and then poured into ice–water (150 ml). The precipitated gum was dissolved in abs. ethanol, and the solution was evaporated to dryness, to afford **14** as a colorless glass that was dried under vacuum; $[\alpha]_D^{28}$ +87.6° (*c* 1.0, chloroform); R_F 0.55 (9:1 benzene–acetone); ν_{max}^{film} 3450 (OH), 1750 (broad, CO), 1500, 765, and 698 cm^{-1} (monosubstituted phenyl); *m/e* 380 (7) ($M^{\ddagger}$), 365 (2) ($M^{\ddagger} - \cdot CH_3$), 205 (2), 175 (2), 162 (10), 161 (2), 149 (9), 148 (12), 147 (10), 145 (6), 115 (5), 106 (1), 105 (15) ($C_6H_5CO^+$), 103 (3) [$(MeCO)_2OH^{\ddagger}$], 101 (5), 100 (100) ($C_5H_8O_2^{\ddagger}$), 91 (2), 85 (3) ($100 - \cdot CH_3$), 79 (1), 78 (1) ($C_6H_6^{\ddagger}$), 77 (4) ($C_6H_5^+$), 59 (3) ($C_2H_7O^+$), and 43 (31) (CH_3CO^+).

Anal. Calc. for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 60.04; H, 6.58.

*1,2-*O*-Isopropylidene-3-*C*-phenyl-6-*O*-(2-phenyl-2-propyl)-*α*-*D*-allofuranose* (**9**).— A solution of **12** (3.8 g, 8.3 mmol) and sodium methoxide (3 mmol) in abs. methanol

(100 ml) was boiled for 5 h under reflux. At this stage, t.l.c. (solvent D) indicated that the starting material (R_F 0.42) had been converted into a single product having R_F 0.31. A few drops of water were added, followed by Dowex-50 (H^+) resin until the mixture became neutral. The resin was filtered off, and the filtrate evaporated to dryness. The resulting gum (3.350 g) was purified on a small column (2 × 40 cm) of silica gel by using 19:1 benzene–acetone as the eluant, to afford **9** as a gum (3.0 g, 7.2 mmol; 86%) that became a glass on keeping under vacuum. Compound **9**, which failed to react with sodium periodate, had $[\alpha]_D^{28}$ +44.5° (*c* 1.3, chloroform); ν_{max}^{film} 3500 (OH), 1610, 1490, 870, 763, and 698 cm^{-1} (monosubstituted phenyl); *m/e* 414 (>1) ($M^{\mp}$), 341 (1), 238 (2), 237 (12), 219 (5), 206 (2), 205 (11), 183 (6), 180 (2), 161 (2), 149 (20) ($C_6H_5CMe_2OCH_2^+$), 148 (31), 147 (19), 121 (5), 120 (12), 119 (100) ($C_6H_5CMe_2^+$), 118 (6), 117 (3), 106 (3), 105 (37) ($C_6H_5CO^+$), 103 (6), 101 (7), 100 (77) ($C_5H_8O^+$), 91 (14), 85 (5) ($100 - \cdot CH_3$), 79 (4), 78 (3) ($C_6H_6^{\pm}$), 77 (9) ($C_6H_5^+$), 71 (6), 59 (8) ($C_2H_7O^+$), and 43 (12) (CH_3CO^+).

Anal. Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.36; H, 7.32.

3-O-Benzyl-1,2:5,6-di-O-isopropylidene-3-C-phenyl-α-D-allofuranose (**10**). — To a solution of compound 7 (230 g, 0.65 mol) in anhydrous *N,N*-dimethylformamide (2 liters) and anhydrous hexamethylphosphoric triamide (200 ml) was slowly added, during 1 h, sodium hydride (180 g as a 50% suspension in oil: 5 molar equivs., 3.9 mol), and the resulting suspension was stirred for 4 h at ~25° and then cooled to 0°. α-Bromotoluene (200 ml) was now added dropwise during 1 h, and the mixture was stirred for 12 h at ~25°. This procedure was repeated twice, until 600 ml of α-bromotoluene had been added. Methanol (100 ml) was then carefully added, and the mixture was poured into water (15 liters) with vigorous stirring. The resulting emulsion was stirred for several hours at ~25°, and filtered through Celite; the filtrate was discarded. The brown, gummy solid was successively washed with light petroleum ether (600 ml) and 1:1 chloroform–ethanol (600 ml). The resulting, yellow solid (70 g) was then crystallized from cyclohexane, to afford **10** as colorless crystals (47 g), m.p. 137–138°. The mother liquors were mixed with the previous washing liquors, and evaporated to an oil (~600 ml) that was dissolved in cyclohexane (600 ml): the solution was kept for 12 h at 0°, and the suspension filtered. The yellow crystals (122 g) were recrystallized from abs. ethanol, to afford pure **10** (98 g), m.p. 137–138°. The mother liquors of crystallization were combined and evaporated to a heavy oil (~600 ml) that was poured onto two dry columns (6 × 100 cm) of alumina. The columns were washed with light petroleum ether until no more oil was eluted from the columns. Further elution with solvent C gave pure **10** as a white solid (122 g; total collected, 267 g, 0.62 mol; 95%). The analytical sample was recrystallized from abs. ethanol, m.p. 131.5–132.5° and 137–138°, $[\alpha]_D^{25}$ +110° (*c* 1.5, benzene); ν_{max}^{KBr} no hydroxyl band, 1500, 782, 758, 715, and 702 cm^{-1} (monosubstituted phenyl); *m/e* 426 (<1) ($M^{\pm}$), 411 (2) ($M^{\mp} - \cdot CH_3$), 368 (<1) ($M^{\pm} - C_3H_6O$), 262 (2), 238 (4), 210 (2), 209 (2), 205 (3), 161 (3), 158 (2), 145 (3), 133 (2), 116 (4), 106 (3), 105 (52) ($C_6H_5CO^+$), 103 (2), 102 (1), 101 (26) ($C_5H_9O_2^+$), 100 (5) ($C_5H_8O_2^+$), 92 (6), 91 (100) ($C_6H_5CH_2^+$), 85 (3) ($C_4H_5O_2^+$), 77 (4) ($C_6H_5^+$), 59 (2) ($C_3H_7O^+$), and 43 (11) (CH_3CO^+); X-ray

powder diffraction data: 10.33 vs (2), 9.16 m, 7.46 vs (3), 5.77 m, 5.08 m, 4.79 vs (1), 4.49 s, 4.24 s, and 3.94 m.

Anal. Calc. for $C_{25}H_{30}O_6$: C, 70.40; H, 7.09. Found: C, 70.60; H, 7.36.

3-C-Cyclohexyl-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**11**). — A solution of **7** (10.0 g, 29 mmol) in abs. ethanol (100 ml) was hydrogenated for 36 h at ~25° over 5% rhodium-on-alumina at a pressure of 75 lb.in.$^{-2}$. The suspension was then filtered through Celite, and the colorless filtrate evaporated to dryness to afford a white solid (10.2 g, 100%) [showing a single spot in t.l.c., R_F 0.58 (solvent C; starting material **7**, R_F 0.48)] that crystallized from petroleum ether (b.p. 70–110°) as colorless prisms; yield 8.00 g (80%), m.p. 91–92°, $[\alpha]_D^{28}$ +11.8° (*c* 1.5, chloroform); ν_{max}^{KBr} 3500 (OH) and 1360 cm^{-1} (CMe_2); *m/e* 328 (2), 327 (10) ($M^+ - \cdot CH_3$), 241 (5) ($M^+ - C_5H_9O_2^+$), 212 (4), 211 (37) ($C_5H_8O_2COC_6H_{11}^+$), 168 (3), 156 (2), 155 (6), 154 (5), 137 (2), 131 (7), 113 (4), 112 (3), 111 (53) ($C_6H_{11}CO^+$), 102 (2), 101 (30) ($C_5H_9O_2^+$), 100 (100) ($C_5H_9O_2^+$), 99 (5), 98 (4), 85 (13) ($100 - CH_3^-$), 84 (3), 83 (47) ($C_6H_{11}^+$), 81 (4), 72 (5), 71 (15), 67 (3), 59 (17) ($C_3H_7O^+$), 58 (2) ($C_3H_6O^+$), 57 (2), 55 (14), and 43 (29) ($C_2H_3O^+$); X-ray diffraction powder data: 14.97 m, 11.32 s, 9.93 vs (2), 9.11 vw, 8.18 vs (3), 6.75 m, 6.32 s, 5.82 m, 4.94 vs (1), 4.73 m, 4.55 m, 4.38 m, 4.08 w, and 3.91 w.

Anal. Calc. for $C_{18}H_{30}O_6$: C, 63.13; H, 8.83. Found: C, 63.33; H, 8.84.

Reaction of phenylmagnesium bromide with the "overoxidized ketone" 1: isolation of 1,2-O-isopropylidene-4,4-di-C-phenyl-L-erythritol (**16**). — For certain large-scale preparations of the ketone hydrate **5**, t.l.c. in 19:1 benzene–methanol showed that the expected ketone **5** (R_F 0.47) was contaminated by a slightly faster-moving component, namely, (2*R*,3*R*,6*R*)-6-[(5*R*)-2,2-dimethyl-1,3-dioxolan-5-yl)-2,3-*O*-isopropylidene-5-oxo-1,4-dioxane-2,3-diol (**15**, R_F 0.50) which, upon reaction with phenylmagnesium bromide in THF or ether, gave a side product (**16**) not encountered when the Grignard reaction was conducted with the pure, recrystallized ketone hydrate **5**. A solution of the crude ketone **1** (50 g, ~0.19 mol) in dry THF (250 ml) was added dropwise during 30 min to a magnetically stirred solution of phenylmagnesium bromide (0.38 mol, 2 molar equiv.) in dry THF (150 ml). The resulting solution was boiled under reflux for 4 h, and processed as previously described, to give an oil (72 g) that could not be crystallized. T.l.c. in 4:1 benzene–ethyl acetate showed the oil to be a mixture of 4 products that were visible in u.v. light and that reacted with sulfuric acid: these had R_F 0.56 (**7**), 0.45 (**16**), and 0.38 (minor, **8** and **9**). The oil was chromatographed on two columns (6 × 100 cm) of silica gel that were eluted with 4:1 benzene–ethyl acetate. Two fractions were collected: A, impure **7** (52 g); and B, impure product **16** (9.0 g) contaminated by **7**, **8**, and **9**. Fraction A was crystallized from cyclohexane to give pure compound **7** (34.2 g) as white needles, m.p. 97–98°. The mother liquors of crystallization of fraction A (17 g) were chromatographed on a column (4.5 × 85 cm) of silica gel (solvent D). Pure **7** (7.0 g), pure **16** (5.0 g), and pure **8** plus **9** (0.3 g) were isolated. Fraction B (9.0 g) was chromatographed on a column (4.5 × 85 cm) of silica gel (solvent D) to afford pure **7** (2.5 g; total collected, 43.7 g; 0.13 mol, 69%), pure **16** (3.0 g; total collected, 8.0 g), and a mixture of **8** and **9** (0.9 g, total collected, 1.2 g).

The diphenyl derivative **16** (8.0 g) crystallized from petroleum ether as cotton-like needles (6.0 g; 18.5 mmol, 10%) m.p. 114–115°, $[\alpha]_D^{28}$ +155° (*c* 1.5, chloroform); ν_{max}^{KBr} 3500 (OH), 1375 (CMe_2), 1610, 1490, 758, and 700 cm^{-1} (monosubstituted phenyl); *m/e* 299 (1) ($M^+ - \cdot CH_3$), 256 (<1) ($M^+ - C_3H_6O$), 241 (2), 221 (3), 196 (2), 193 (2), 184 (9), 183 (100) ($C_{13}H_{11}O^+$), 182 (4), 181 (2), 167 (3), 165 (3) ($183 - H_2O$), 152 (2), 131 (3) ($M^+ - C_{13}H_{11}O\cdot$), 114 (2), 106 (3) ($183 - C_6H_5\cdot$), 105 (39) ($183 - H\cdot - C_6H_5\cdot$), 101 (8) ($131 - CH_2O$), 91 (1), 78 (2) ($C_6H_6^+$), 77 (17) ($C_6H_5^+$), 74 (4), 73 (2), 61 (2), 59 (14) ($C_3H_7O^+$), 56 (3), and 43 (13) ($C_2H_3O^+$); X-ray diffraction powder data: 13.69 w, 11.70 w, 10.27 w, 8.38 vw, 6.55 m, 5.33 s (1), 4.82 s (2,2), 4.48 s (2,2), 4.40 s, and 3.84 m.

Anal. Calc. for $C_{19}H_{22}O_4$: C, 72.61; H, 7.05. Found: C, 72.65; H, 7.12.

*3-O-Acetyl-1,2-O-isopropylidene-4,4-di-C-phenyl-*L*-erythritol* (**17**). — A solution of **16** (2.0 g, 6.3 mmol) in dry pyridine (20 ml) and acetic anhydride (5 ml) was kept for 24 h at ~25°, and then evaporated to dryness. Toluene was evaporated several times from the resulting gum, and then ethanol was evaporated from it to give a white solid (2.2 g) which, upon crystallization from 1:3 chloroform–ethyl acetate, gave pure **17** as white crystals (1.9 g, 84%), m.p. 214–215°, $[\alpha]_D^{28}$ +141.5° (*c* 1.0, chloroform); R_F 0.72 (7:3 benzene–ethyl acetate); ν_{max}^{KBr} 3450 (OH), 1720 (CO), 1370 (CMe_2), 1580, 750, and 695 cm^{-1} (monosubstituted phenyl); *m/e* 341 (1) ($M^+ - \cdot CH_3$), 282 (1) ($341 - C_2H_3O_2\cdot$), 241 (2), 225 (3), 223 (1), 221 (4), 197 (1), 196 (6), 194 (4), 193 (1), 184 (17), 183 (100) ($C_{13}H_{11}O^+$), 182 (2) ($C_{13}H_{10}O^+$), 167 (5), 166 (5) ($C_{13}H_{10}^+$), 165 (6), 156 (2), 152 (2), 131 (1), 117 (2), 116 (9), 115 (5), 114 (2), 106 (3) ($C_7H_6O^+$), 105 (36) ($C_6H_5CO^+$), 103 (1), 101 (14) ($C_5H_9O_2^+$), 91 (2), 78 (2) ($C_6H_6^+$), 77 (19) ($C_6H_5^+$), 74 (1), 73 (5), 72 (3), 61 (3), 60 (2), 59 (10) ($C_3H_7O^+$), 57 (1), 56 (3), 51 (3), and 43 (35) ($C_2H_3O^+$); X-ray powder diffraction data: 12.27 s, 10.10 vs (1), 8.70 vw, 7.07 vs (3), 5.90 s, 5.59 s, 5.24 vs, 4.92 s, 4.70 vs, 4.49 s, 4.25 s, 3.88 vs (2), 3.73 w, 3.57 m, 3.51 w, 3.25 m, 3.04 vw, and 2.94 m.

Anal. Calc. for $C_{21}H_{24}O_5$: C, 70.78; H, 6.74. Found: C, 70.63; H, 6.79.

*Oxidation of 1,2-O-isopropylidene-4,4-di-C-phenyl-*L*-erythritol* (**16**) *with periodic acid.* — Quantitative, periodate oxidation of **16** according to the method of Fleury and Lange[25] showed that one molar equivalent of potassium periodate was consumed. Preparative, periodate oxidation was conducted as follows. An aqueous solution (500 ml) of potassium metaperiodate (1.48 g, 6 mmol) was slowly added during 1 h to a solution of **16** (1.70 g, 5.4 mmol) in methanol (300 ml). The resulting solution was kept in the dark for 20 h, concentrated under vacuum to 400 ml, and extracted with ether (3 × 100 ml). The ethereal extracts were dried (sodium sulfate), and evaporated to dryness, to give a yellow oil (1.034 g) which, by t.l.c. (solvent C), appeared to comprise mainly one component (made visible only in u.v. light and migrating like a reference sample of benzophenone, R_F 0.83), together with traces of **16** (R_F 0.60) and material having R_F 0.0. This oil was dissolved in pyridine (10 ml) containing hydroxylamine hydrochloride (1.0 g), the solution was kept for 18 h at ~25°, and evaporated to dryness, to give a gum that was dissolved in water (60 ml) and extracted with chloroform. The extract was dried (sodium sulfate), and evaporated

to dryness, and the resulting solid (1.1 g) rapidly chromatographed on a column (3 × 50 cm) of silica gel (solvent D). The first compound eluted was unreacted benzophenone (0.230 g; R_F 0.83 in solvent B), i.r. spectrum identical with that of an authentic sample. The second fraction was pure benzophenone oxime (0.600 g; 57%) which, in t.l.c. (solvent D), had R_F 0.55, the same as that of an authentic sample prepared from pure, commercial benzophenone. Crystallization from ether–petroleum ether gave colorless prisms, m.p. and mixed m.p. 143–143.5° (lit.[26] m.p. 144°); i.r. spectrum identical with that of an authentic specimen; n.m.r. data ($CDCl_3$): δ 7.14–7.46 (m, 10 H, phenyl protons), 9.46 (s, 1 H, OH); *m/e* 198 (6) (MH^+), 197 (37) ($M^{\ddagger}$), 196 (6) ($M^{\ddagger} - H\cdot$), 180 (100) ($M^{\ddagger} - OH\cdot$).

Action of phenylmagnesium bromide on compound **7**. — A solution of **7** (4.992 g, 14.8 mmol) and phenylmagnesium bromide (6 molar equivs., 88.8 mmol) in dry THF (100 ml) was boiled for 28 h under reflux (oil-bath temperature, 100°) and then cooled to 0°. Water (20 ml) was carefully added, and the mixture was processed as previously described, to give a crystalline solid that, by t.l.c., appeared to be almost entirely the starting material **7**, R_F 0.67 (solvent C). Only traces of a decomposition product having R_F 0.1 could be detected, and there was no product at R_F 0.35 corresponding to **8** or **9**.

*Reaction of cyclohexylmagnesium bromide with 1,2:5,6-di-*O*-isopropylidene-α-*D*-ribo-hexofuranos-3-ulose* (**1**). — The yields of all principal and side products encountered in the reaction of cyclohexylmagnesium bromide with the ketone **1** in ether or THF at various temperatures are summarized in Table III. Several side-products, such as **3**, **4**, and **5**, were common to the parallel reaction conducted with ethylmagnesium bromide; in t.l.c., the 3-*C*-cyclohexyl-*allo* adduct (**11**) migrated slightly faster than the corresponding 3-*C*-ethyl-*allo* derivative. The isolation procedure used was very similar to that used for the reaction of ethylmagnesium bromide with the ketone **1**. The following, typica example describes the reaction of cyclohexylmagnesium bromide with ketone **1** in ether at −14°; this reaction constitutes an alternative route to 3-*C*-cyclohexyl-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**11**), previously obtained by reduction of the corresponding 3-*C*-phenyl-*allo* derivative **7**, by ending the column chromatography after the elution of **11**. Cyclohexylmagnesium bromide was prepared by adding a solution of cyclohexyl bromide (4 molar equiv., 0.4 mol; 50 ml) in dry ether (100 ml) to a suspension of magnesium turnings (5 molar equiv., 12 g) in dry ether (100 ml). After the end of the exothermic reaction, the solution was stirred for an additional 2 h at ~25° and then cooled to −14°. A solution of the ketone **1** (94 mmol; from 25.6 g of hydrate **5**) in ether (200 ml) was then slowly added during 2 h with continuous stirring, and the resulting solution was kept for 2 h at −14° before being allowed to warm slowly overnight to room temperature. Water (~20 ml) and then Celite (~30 g) were added, and the mixture was stirred, and filtered through Celite, which was then washed with dichloromethane. The combined filtrates were evaporated to dryness, to afford an oil that, by t.l.c. (solvent B), appeared to be a mixture of 4 products: R_F 0.80 (**11**), 0.47 (double spot, **4**+**5**), and 0.34 (**3**); at this stage, none of the mono-*O*-isopropylidene-ailose

(**18**, R_F ~0) could be detected. A solution of this oil in chloroform was washed several times with water, and the water washes were extracted with chloroform (in some instances, a very stable emulsion was formed, which was broken by adding some acetic acid). The chloroform solution and extracts were combined, dried (sodium sulfate), and evaporated to dryness, to give a colored oil that was chromatographed on a column (5 × 80 cm) of silica gel (solvent B). Compound **11** was eluted first, as a white solid (11.6 g; 33 mmol, 35%), and it was dissolved in petroleum ether (50 ml). Slow cooling to 0° gave pure **11** as white crystals (9.6 g), m.p. 91–92°, undepressed on admixture with an authentic sample prepared by reduction of the 3-*C*-phenyl derivative **7**. Another crop (0.600 g) of **11** was obtained by concentrating the mother liquors of recrystallization to ~20 ml, and slowly cooling to 0°; total yield of pure **11**, 10.2 g (30%); $[\alpha]_D^{28}$ +11.7° (*c* 1.2, chloroform). The i.r., n.m.r., and mass spectra, and also the X-ray powder diffraction data, were identical with those of a sample prepared by reduction of **7**.

Further elution of the column gave an impure mixture of **4** and **5** (5.1 g) as a gum, followed by pure 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (**3**, 8.6 g, 35%) which crystallized from cyclohexane as white prisms (8.0 g; 30 mmol, 32%), m.p. 77°, $[\alpha]_D^{20}$ +38° (*c* 1.5, water) {lit.[12] m.p. 76–77°, $[\alpha]_D^{22}$ +37.7° (water)}. The ketone hydrate **5** was readily separated from **4** by rapid chromatography, as previously described, on a column (3.5 × 60 cm) with solvent A. Compound **4** (1.9 g) crystallized from cyclohexane (1.580 g; 6.1 mmol, 6%), m.p. and mixed m.p. 110–111°, $[\alpha]_D^{22}$ −12.5° {lit.[13] m.p. 110–111°, $[\alpha]_D^{20}$ −13.5° ($CHCl_3$)}. The ketone hydrate **5** (2.5 g; 9 mmol, 10%) crystallized from ether–petroleum ether as thin, white needles (2.0 g; 7.2 mmol, 8%), m.p. 110–111°, $[\alpha]_D^{26}$ +46° (*c* 2, ethanol) (lit.[9,10] m.p. 110–111°, $[\alpha]_D^{20}$ +44° in ethanol).

The aqueous extracts contained some 1,2-*O*-isopropylidene-α-D-allofuranose (**18**), and were evaporated to dryness. The resulting gum was chromatographed on a column (3.5 × 60 cm) of silica gel. Elution with 17:3 chloroform–methanol gave pure **18** (1.5 g, 7%) as a white solid that was recrystallized from chloroform or ethyl acetate; yield 1.2 g (5.4 mmol; 5%), m.p. 133°, $[\alpha]_D^{28}$ +43° (*c* 1.5, water); R_F 0.36 (9:1 chloroform–methanol) (lit.[18] m.p. 133–134°, $[\alpha]_D^{20}$ +44° in water).

Anal. Calc. for $C_9H_{16}O_6$: C, 49.08; H, 7.32. Found: C, 49.09; H, 7.36.

Compound **18** was further characterized as its triacetate **22**.

*3,5,6-Tri-*O*-acetyl-1,2-*O*-isopropylidene-α-D-allofuranose* (**22**). — A solution of **18** (1.5 g, 6.8 mmol) in dry pyridine (20 ml) and acetic anhydride (2.5 ml) was kept overnight at room temperature. Conventional processing gave an oil (2.3 g) that crystallized. Recrystallization of the resulting solid from pure ether afforded **22** as colorless crystals (1.670 g, 70%), m.p. 80–81°, $[\alpha]_D^{28}$ +122.8° (*c* 1.5, chloroform) (lit.[19] m.p. 79–81°, $[\alpha]_D$ +111.1° in chloroform); R_F 0.25 (solvent C); ν_{max}^{KBr} no hydroxyl band, ~1740 (broad, CO), and 1380 cm^{-1} (CMe_2); *m/e* 346 (<1) (M^+), 332 (2.6), 331 (18) ($M^+ - .CH_3$), 201 (9) ($M^+ - C_6H_9O_4\cdot$), 170 (2), 169 (15) ($M^+ - 3C_2H_3O_2\cdot$), 157 (2), 143 (24) ($331 - C_6H_9O_4\cdot - C_2H_3O\cdot$), 128 (3), 127 (8), 115 (6),

109 (6), 103 (2) [$(CH_3CO)_2OH^+$], 101 (2), 100 (1) ($C_5H_8O_2^+$), 97 (2), 86 (2), 85 (6), 81 (7) 73 (4), 70 (30), and 43 (100) ($C_2H_3O^+$).

Anal. Calc. for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40. Found: C, 52.04; H, 6.68.

Conversion of **18** *into 2,3:5,6-di-*O*-isopropylidene-β-*D*-allofuranose* (**23**). — A suspension of anhydrous cupric sulfate (6.0 g) in a solution of 1,2-*O*-isopropylidene-α-D-allofuranose (**18**; 3.0 g, 13.6 mol) in anhydrous acetone (60 ml) containing conc. sulfuric acid (0.5 ml) was stirred for 24 h at room temperature, and then made neutral with potassium carbonate. The mixture was diluted with water (180 ml), filtered from insoluble material, concentrated under vacuum (~200 ml), and the concentrate extracted with chloroform (4 × 60 ml). The extracts were dried (sodium sulfate), and evaporated to dryness, to afford a gum (3.2 g) that slowly crystallized. Recrystallization from ether–petroleum ether gave pure **23** as white crystals (1.820 g, 51%), m.p. 66–68°. A second recrystallization from cyclohexane raised the m.p. to 67.5–68°, $[\alpha]_D^{27}$ −25.6° (*c* 1.3, chloroform) {lit.[20] m.p. 65–67°, $[\alpha]_D^{23}$ −1° (water); lit.[21] m.p. 66–67°, $[\alpha]_D^{20}$ −27.4° (chloroform)}; R_F 0.62 (solvent B); ν_{max}^{KBr} 3460 (OH) and 1360 cm^{-1} (CMe_2). The mass spectrum was in agreement with literature data[20,21].

*3-C-Cyclohexyl-1,2-*O*-isopropylidene-α-*D*-allofuranose* (**21**). — In certain instances, compound **11** was isolated chromatographically as a gum that was resistant to crystallization. The conversion of **11** into its monoacetal **21** afforded a highly crystalline derivative that could readily be recrystallized. In a typical example, a solution of a sample (3.54 g) of this gum, containing mainly compound **11** (R_F 0.70 with 3:2 ether–petroleum ether), and ferric chloride (3.0 g) in 95% ethanol (100 ml) was kept for 20 h at ~25°, and then evaporated to dryness. A solution of the resulting solid in water (100 ml) was extracted with chloroform (3 × 60 ml). The aqueous solution was again extracted with chloroform (2 × 50 ml), and the extracts were combined, dried (sodium sulfate), and evaporated to dryness, to afford compound **21** as a white solid (2.8 g) that was recrystallized from 1:10 ethyl acetate–ether as cotton-like crystals; yield 2.4 g, m.p. 168–169°, $[\alpha]_D^{28}$ +7.8° (*c* 1.5, chloroform); R_F 0.50 (9:1 chloroform–methanol); ν_{max}^{KBr} ~3400 (intense OH) and 1370 cm^{-1} (CMe_2); *m/e* 287 (6) ($M^+ - \cdot CH_3$), 241 (4) ($287 - \cdot CH_2OH$), 212 (7), 211 (40) ($241 - CH_2O$), 167 (3), 156 (2), 155 (14), 154 (9), 129 (5), 112 (4), 111 (56) ($C_6H_{11}CO^+$), 101 (14), 100 (100) ($C_5H_8O_2^+$), 99 (6), 98 (7), 95 (2), 86 (7), 85 (17) ($100 - \cdot CH_3$), 84 (4), 83 (56) ($C_6H_{11}^+$), 81 (4), 79 (2), 73 (4), 71 (32), 67 (4), 61 (3), 59 (16) ($C_3H_7O^+$), and 43 (18) ($C_2H_3O^+$); X-ray diffraction powder data: 12.53 vs (1), 7.19 w, 6.55 vs (2,2), 6.19 vs (2,2), 5.59 w, 5.06 s, 4.74 s, 4.48 s, 4.23 w, 3.99 w, 3.63 w, 3.49 m, 3.15 m, 2.96 w, 2.76 w, 2.56 w, 2.47 w, and 2.37 w.

Anal. Calc. for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 59.58; H, 8.67.

*1,3-Bis(1,2:5,6-di-*O*-isopropylidene-α-*D*-allofuranos-3-yl)propanone* (**19**) *and its oxime* (**20**). — When cyclohexylmagnesium bromide was brought into reaction with the ketone **1** in ether, and the mixture was boiled for 5 h under reflux, a new product, having R_f 0.20 in t.l.c. (solvent B), could be observed; to it was attributed structure **19**. This dimer was isolated after chromatography of the mixture on a column of silica gel (solvent B) as previously described, and was eluted immediately after compound **3**; it

was isolated as a white solid that was recrystallized from abs. ethanol; m.p. 203.5°, $[\alpha]_D^{28}$ +62° (*c* 1.1, chloroform); ν_{max}^{KBr} 3400 (strong, OH), 1725 (CO), and 1375 cm^{-1} (CMe_2); *m/e* 575 (<1), 574 (<1) (M^+), 559 (<1) ($M^+ - \cdot CH_3$), 541 (<1) ($559 - H_2O$) 523 (<1) ($541 - H_2O$), 516 (<1) ($M^+ - C_3H_6O$), 501 (1.6) ($M^+ - \cdot CH_3 - C_3H_6O$), 498 (<1) ($M^+ - H_2O - C_3H_6O$), 483 (<1) ($498 - \cdot CH_3$), 481 (<1), 473 (>1) ($M^+ - C_5H_9O_2\cdot$), 458 (<1) ($473 - \cdot CH_3$), 443 (1.4), 385 (1.6), 301 (1.5), 243 (4), 215 (1), 198 (2), 185 (2), 165 (1), 157 (2), 143 (2), 137 (2), 131 (2), 125 (3), 101 (89), 100 (28), 85 (21), 59 (18), and 43 (100); X-ray powder diffraction data: 10.10 vs (3), 6.73 vs (2), 5.37 s, 5.14 s, 4.79 vs (1), 4.37 vs, 4.26 w, and 3.99 w.

An acceptable analysis was not obtainable for compound **19**, and it was therefore further characterized as its oxime. Compound **19** (1.34 g, 2.3 mmol) and hydroxylamine hydrochloride (1.0 g) were dissolved in pyridine (30 ml), and the solution was kept overnight at ~25°, evaporated to dryness, and the residual solid partitioned between water (100 ml) and chloroform (100 ml). The chloroform layer was dried (sodium sulfate), and evaporated to dryness, to afford **20** as a white foam (1.350 g) that crystallized from ether–petroleum ether as fine, white needles; yield 1.200 g (2.0 mmol, 87%), m.p. 173°, $[\alpha]_D^{28}$ +99.8° (*c* 2.7, ethyl acetate); R_F ~0.69 (tailing spot in 4:1 ether–petroleum ether); ν_{max}^{KBr} 3500 (OH) and 1380 cm^{-1} (CMe_2); *m/e* 589 (<1) (M^+), 575 (1), 574 (3) ($M^+ - \cdot CH_3$), 553 ($M^+ - 2H_2O$), 517 (1), 516 (3) ($M^+ - C_3H_6O - \cdot CH_3$), 498 (<1) ($516 - H_2O$), 474 (<1), 473 (2.2) ($M^+ - \cdot CH_3 - C_5H_9O_2\cdot$), 458 (1) ($473 - \cdot CH_3$), 440 (1) ($458 - H_2O$), 430 (1.4), 415 (<1), 401 (<1), 400 (4.5), 101 (83) ($C_5H_9O_2^+$), 100 (83) ($C_5H_8O_2^+$), 86 (3), 85 (33) ($100 - \cdot CH_3$), 84 (7), 83 (5), 82 (2.6), 59 (30) ($C_3H_7O^+$), 58 (8) ($C_3H_6O^+$), and 43 (100) ($C_2H_3O^+$); X-ray powder diffraction data: 14.48 w, 12.02 m, 10.04 vs (3), 8.25 vw, 6.88 s, 5.98 vs (2), 5.52 w, 5.27 w, and 5.11 vs (1).

Anal. Calc. for $C_{27}H_{43}NO_{13}$: C, 54.67; H, 7.30; N, 2.37. Found: C, 54.92; H, 7.26; N, 2.40.

1,6-Anhydro-2,3-O-isopropylidene-4-C-phenyl-β-D-talopyranose (**26**). — The ketone **25** was prepared according to the procedure already described[22], but it was adapted for larger-scale preparation. To a magnetically stirred suspension of ruthenium dioxide hydrate (12.8 g) in water (1.2 liters) was slowly added powdered, solid sodium metaperiodate until a dark-brown, translucent solution was obtained and no more solid ruthenium dioxide could be detected. This solution was poured into a 2-liter separating funnel, and extracted with carbon tetrachloride (~400-ml portions) until the extracts were almost colorless (~2 liters). The combined extracts were then slowly added to a magnetically stirred solution of **24** (10.9 g, 54 mmol) in alcohol-free chloroform (200 ml), and the resulting solution was stirred for 2 h at ~25°. Isopropyl alcohol (100 ml) was added, and the mixture was stirred for 30 min and then filtered through Celite, The colorless filtrate was evaporated to dryness, to afford **26** as a white, crystalline solid (9.4 g; 52 mmol, 94%) (R_F 0.46, one spot in 9:1 ether–petroleum ether), which was used without further purification. Ruthenium dioxide was recovered in 90–95% yield by filtration of the carbon tetrachloride suspension, obtained after the addition of isopropyl alcohol, through a hard, prepressed pad of

Celite that was then air-dried. The ruthenium dioxide layer, which split off spontaneously, was contaminated by only a few mg of Celite.

A solution of the ketone **25** (16.0 g, 89 mmol) in dry THF (170 ml) was added dropwise during 1 h to a solution of phenylmagnesium bromide (4 molar equivs, 350 mmol) in THF (170 ml) that had been cooled to 0°. The resulting solution was stirred for 2 h more at 0°, and then allowed to attain room temperature slowly (overnight). Water (20 ml) was carefully added, and then Celite (~20 g), and the mixture was stirred, and filtered through Celite. The clear filtrate was evaporated to dryness, and the residue dissolved in chloroform. The solution was washed with a cold, dilute, aqueous solution of ammonium chloride, dried (sodium sulfate), and evaporated to dryness, to afford compound **26** as a white solid (28 g) that was recrystallized from pure cyclohexane as thin, white crystals (19.5 g; 70 mmol, 78%). By concentrating the mother liquors of crystallization and adding ether (~10%), another crop (1.3 g) of **26** was obtained after cooling to 0°; total yield, 20.8 g (83%), m.p. 125.5–126°, $[\alpha]_D^{20}$ −90.7° (*c* 3.2, chloroform); R_F 0.51 (solvent D); ν_{max}^{KBr} 3550 (OH), 1380 (CMe_2), 1510, 865, 765, and 700 cm^{-1} (monosubstituted phenyl); *m/e* 279 (2), 278 (8.3) ($M^{\pm}$), 264 (<1), 263 (9) ($M^{\pm} - \cdot CH_3$), 235 (4) ($M^{\pm} - C_2H_3O\cdot$), 232 (3.6), 221 (5.5), 220 (41) ($M^{\pm} - C_3H_6O$), 217 (<1), 205 (<1), 203 (<1) (220−OH·), 178 (3.3), 177 (7.7) ($C_6H_5COC_3H_4O_2^{\pm}$), 176 (6), 175 (5), 174 (17), 173 (23.5) 157 (5), 150 (4), 149 (7.7), 148 (3.6), 147 (8.3), 146 (10), 145 (15.6), 144 (3), 143 (19), 136 (5), 134 (2), 133 (15.6), 132 (8), 131 (10), 129 (11), 128 (8), 127 (4), 120 (3), 118 (2), 117 (9), 116 (5), 115 (51), 106 (9) ($C_6H_5CHO^{\pm}$), 105 (100) ($C_6H_5CO^{+}$), 104 (23), 103 (11), 102 (4), 101) (7), 100 (48) ($C_5H_8O_2^{+}$), 85 (35) (100 − $\cdot CH_3$), 79 (6.6), 78 (8.8) ($C_6H_6^{\pm}$), 77 (28) ($C_6H_5^{+}$), 76 (5), 75 (2), 73 (7), 72 (3.3) ($C_3H_4O_2^{+}$), 71 (18), 70 (2.5), 69 (7), 68 (8), 60 (7), 59 (13) ($C_3H_7O^{+}$), 58 (5), 57 (10), 55 (16), 51 (10), 50 (5.5), and 43 (32) ($C_2H_3O^{+}$); X-ray diffraction powder data: 9.98 vs (1), 7.22 w, 6.00 vs (2), 5.27 w, 4.95 w, 4.68 vs (3), 3.92 w, 3.64 vw, 3.51 w, and 3.33 w.

Anal. Calc. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.80; H, 6.44.

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