Carbanions in Carbohydrate Chemistry: Synthesis of *C*-Glycosyl Malonates[1]

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The condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with sodio diethyl malonate led to crystalline diethyl 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) malonate. The corresponding dibenzyl ester proved to be a versatile intermediate for the preparation of crystalline β-D-glucopyranosyl malonic acid and β-D-glucopyranosyl acetic acid derivatives. The anomeric configuration in these *C*-glycosides was determined by a chemical correlation. With 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride and sodio diethyl malonate, the major product was a 1,2-*O*-ketal derivative resulting from an attack of the carbanion on the 1,2-acetoxonium ion. The condensation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide with sodio diethyl malonate was conducted with, and without added bromide ion and the mechanistic implications of the results are discussed. *C*-Glycosides were also prepared in the D-mannofuranose series and their transformation into the D-lyxofuranose series (anomeric mixture) is described. The utility of n.m.r. shift reagents, and an apparent differential complexation by $Eu(DPM)_3$ and $Eu(FOD)_3$-d_{27} is demonstrated.

La condensation du bromure de 2,3,4,6-tétra-*O*-acétyl-α-D-glucopyrannosyle avec le malonate de diéthyle sodé a conduit au diéthyl 2-(2,3,4,6-tétra-*O*-acétyl-β-D-glucopyrannosyle) malonate cristallin. L'ester dibenzylique correspondant s'est révélé un intermédiaire général pour la préparation des dérivés des acides β-D-glucopyrannosyle malonique et β-D-glucopyrannosyle acétique cristallins. La configuration anomérique de ces *C*-glycosides fut déterminée par corrélation chimique. Avec le chlorure de 2,3,4,6-tétra-*O*-acétyl-β-D-glucopyrannosyle et le malonate de diéthyle sodé le produit prépondérant fut le dérivé *O*-acétal-1,2 résultant de l'attaque du carbanion sur l'ion acétoxonium-1,2. La condensation du bromure de 2,3,4,6-tétra-*O*-benzyle-α-D-glucopyrannosyle avec le malonate de diéthyle sodé fut effectuée à la fois en présence et en l'absence d'ion bromure externe et les applications mécanistiques sont discutées. Les *C*-glycosides furent également préparés dans la série D-mannofurannose et leur transformation en D-lyxofurannose (mélange anomérique) est décrite. On démontre l'utilité des réactifs qui induisent des déplacements en r.m.n. ainsi que la complexation différentielle apparente par $Eu(DPM)_3$ et $Eu(FOD)_3$-d_{27}.

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As part of a program on the exploration of newer synthetic methods, we have been interested in functionalized *C*-glycosyl compounds (1) as intermediates in the synthesis of naturally-occurring *C*-nucleosides and their analogs (2). The few known members of this class of compounds possess diverse biological properties that are, in several instances, of medicinal significance.

The well-known *C*-alkyl and -aryl glycosyl compounds (3) are of limited synthetic utility, since these groups do not lend themselves to facile transformations into other more versatile functional groups such as ketonic, aldehydic, and carboxylic groups.[3] Such functionalized *C*-glycosyl compounds would be ideal precursors to *C*-nucleosides and related compounds (4). In a previous short communication (1), we had reported on a general method for the synthesis of functionalized *C*-glycosyl compounds by the condensation of sodio malonates with glycosyl halide derivatives. In this paper, we disclose details of this and subsequent work in the D-glucose and D-mannose series, and we discuss the relevant synthetic and mechanistic aspects of the reaction. The feasibility of such condensations with the relatively unstable acylglycosyl halides was initially explored with appropriately substituted D-glucopyranosyl halides. Inasmuch as the ultimately desired products were β-*C*-

[1]Part of a series on "Preparative and exploratory carbohydrate chemistry." Taken from the Ph.D. thesis of A.G.P., 1973.

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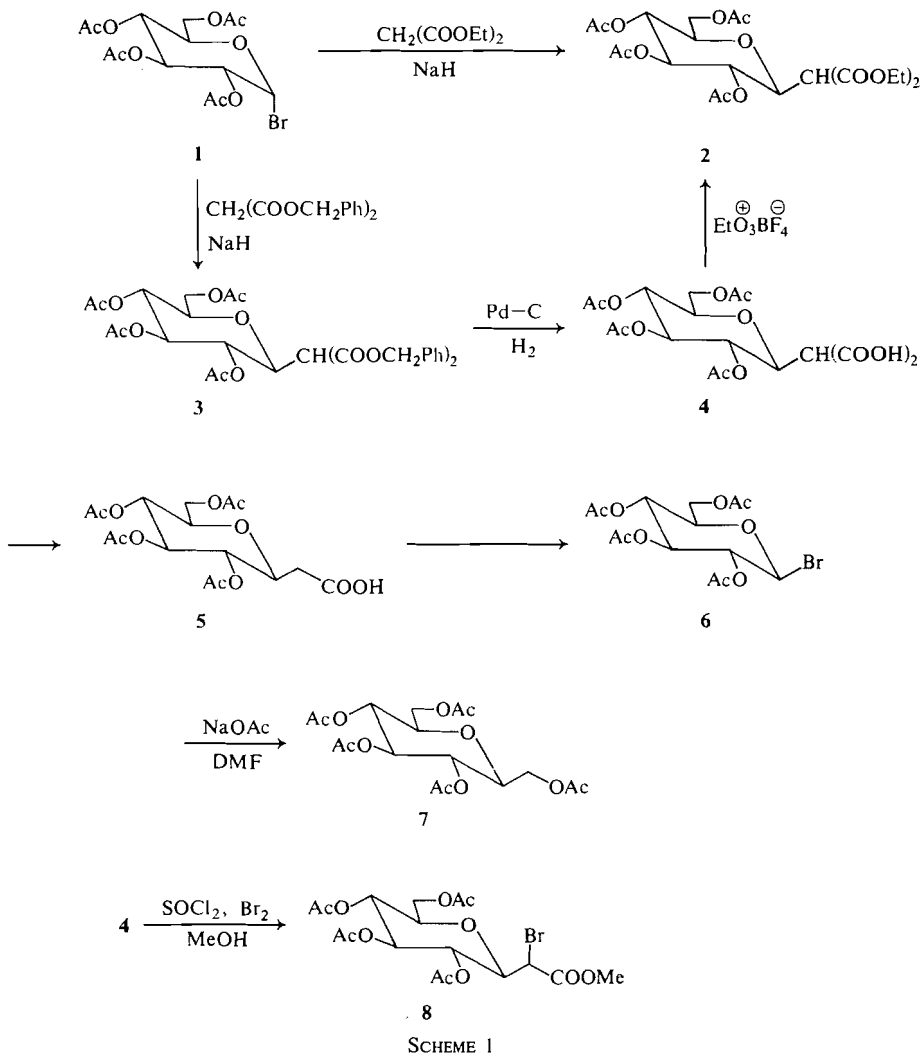
[3]See, however, ref. 4.

glycosyl compounds, the selection of D-glucopyranosyl halides with participating acyloxy groups at C-2 would permit the study of the stereochemistry of the reaction at the anomeric center (5). It was of interest to see whether the participating ability of the 2-acetoxy groups in α-acetobromoglucose **1** would lead to the same stereochemical result in *C*-glycosidation, as with related *O*- and *N*-glycosidations.

To the best of our knowledge, there are very few precedents for the reaction of cyclic α-haloethers with carbanions.[4] Thus, the reaction of 2-chlorotetrahydropyran with sodio diethyl malonate gave the 2-diethyl malonate derivative that could be further transformed into the corresponding acetic acid derivative by decarboxylation (6). In another report (7), α-acetobromoglucose was heated with sodio α-formamido diethyl malonate in ethanol and a product was isolated to which the structure of 2-(β-D-glucopyranosyl) glycine was assigned. In our hands, this reaction led to a complex mixture of products and subsequent condensations with acylglycosyl halides were done, with few exceptions, in non-hydroxylic solvents. No reaction was observed between α-acetobromoglucose and sodio diethyl malonate in benzene at room temperature. In tetrahydrofuran or dimethoxyethane, starting halide was recovered in high yield (~80%) but small amounts of 2,3,4,6-tetra-*O*-acetyl-D-glucal, formed by a base-catalyzed dehydrobromination, and the expected *C*-glycosyl malonate were formed. Another by-product, presumably formed by a transesterification reaction with the reagent, was also formed in some cases. This syrupy product had a higher content of diethyl malonyl residues with respect to acetate groups and was not further investigated. The distribution and nature of products in the condensation reaction (Scheme 1) were quite sensitive to the nature of the solvent and to the ratio of carbanion to halide. Optimum conditions were attained in 1,2-dimethoxyethane as solvent, in which the carbanion is soluble and not highly aggregated as it is in benzene (8). The maximal yield of crystalline product, designated as diethyl 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) malonate (**2**), was 20%. Although this product could be crystallized directly from processed reaction mixtures after seeding, alternate methods of its isolation were also investigated. Since the product **2** was contaminated with the halide **1** (~20%) and the transesterification product and because of the similarities in chromatographic mobilities, the methods of separation were primarily concerned with selective transformations of **1** into products that had different polarities compared to **2**. Thus in one method, the remaining halide **1** in the mixture was converted into tetra-*O*-acetyl-D-glucopyranose and the resulting mixture was purified by chromatography. In another method, the halide **1** was transformed into 2,3,4,6-tetra-*O*-acetyl-D-glucal and the latter was removed from the mixture by ozonolysis. The desired *C*-glycoside **2** was obtained in approximately 20% yield by both methods.

Attempts to deacetylate the product **2** or to selectively hydrolyze the malonic ester groups, under mildly basic or acidic conditions, led to mixtures. These difficulties were attributed, in part, to the presence of the acidic malonic ester proton, which once removed in the basic medium, would afford a carbanionic species that would in turn undergo further reactions. This conclusion was supported by the observation that analogous compounds in another series (9), in which the malonate proton was absent, underwent smooth deacylation. Since our aim was to introduce functionalized substituents at the anomeric center capable of undergoing a variety of transformations that would eventually lead to *C*-nucleosides, we turned our attention to the dibenzyl ester analog of **2** as a more versatile source of *C*-glycosyl compounds. Condensation of **1** with sodio dibenzyl malonate in 1,2-dimethoxyethane gave a good yield of the *C*-glycosyl malonate **3** (Scheme 1). Some starting halide (~20%) was present in the crude product but no other-side-product was detected. Hydrogenation of the mixture over 20% palladium-on-charcoal gave crystalline 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) malonic acid **4** in 51% overall yield (based on the halide **1**). The structural and anomeric configurational relationships between **2** and **3** were ascertained by esterification of the diacid **4** with triethyloxonium fluoroborate (10) and isolation of crystalline **2**. The diacid derivative **4** could also be decarboxylated quantitatively in refluxing acetic acid and the

[4]While this manuscript was in preparation, the synthesis of a *C*-glycosyl malonate based on our initial approach (1) was reported, see ref. 32.



SCHEME 1

resulting monoacid **5** was isolated in crystalline form.

Although the preparative merit of the above reactions was demonstrated, there remained to assign the anomeric configuration to the *C*-glycosyl compounds **2** and **3**. Spectroscopic and polarimetric data, which can be reliably used for such assignments in *O*- and *N*-glucosyl derivatives, were not too informative in the case of **2** or **3**. Thus, even at 220 MHz the region of the anomeric and C-2 protons remained obscured by the H-6,6′ and the methylene protons of the malonic ester portion. In the presence of $Eu(DPM)_3$ and $Eu(FOD)_3$-d_{27}, however, characteristic paramagnetic shifts of some of the hydrogen atoms were observed, thus simplifying the otherwise complex spectrum of **2** (Fig. 1). At a finite concentration of shift reagent, attained by incremental additions, the patterns of H_m, H-1, and H-6,6′ were all resolved and allowed a first-order analysis. The H-6,6′ signals underwent a large downfield shift, relative to other signals. This behavior was in agreement with similar observations in the spectra of peracetylated carbohydrates in the presence of $Eu(DPM)_3$ (11). Although the H-1 and H_m signals could be adequately analyzed, a definitive anomeric assignment could not be made because the H-2 signal was still unresolved. The relatively large H-1,H-2 coupling constant could not be taken as an unambiguous indication of a 1,2-*trans* arrangement of protons, because of the lack of

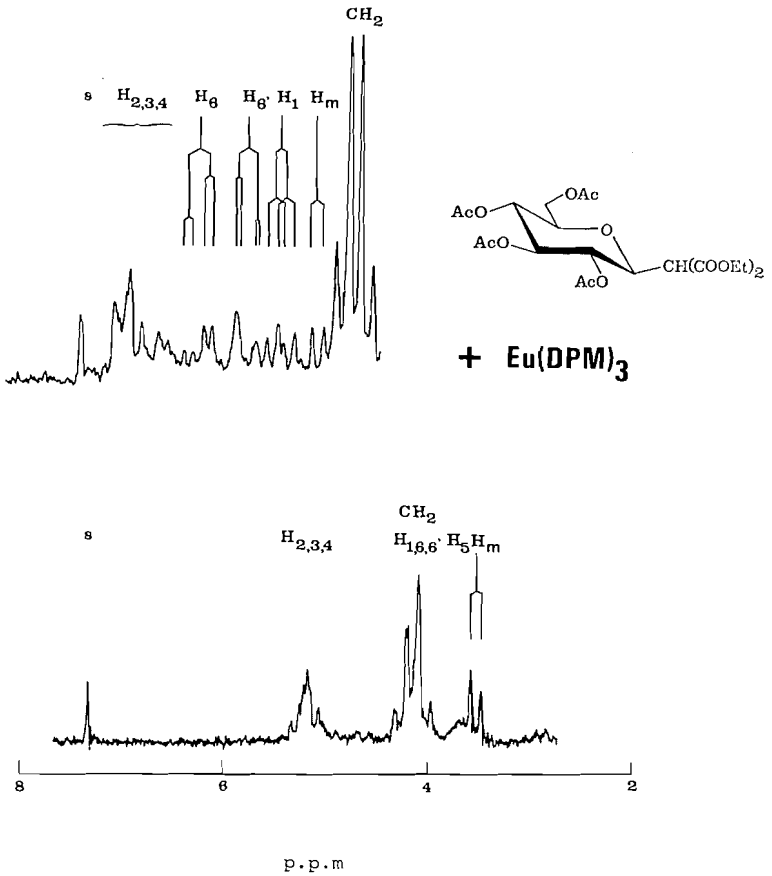


FIG. 1. Nuclear magnetic resonance spectrum of diethyl 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) malonate **2** (lower spectrum) and in the presence of $Eu(DPM)_3$, in $CDCl_3$ at 60 MHz (upper spectrum). H_m refers to the malonic ester proton.

adequate models in the series. In the presence of $Eu(FOD)_3$-d_{27}, a different pattern of paramagnetic shifts was observed (Fig. 2). Incremental addition of the reagent caused a rapid shift of the H-2 triplet, from which a coupling constant could be calculated and correlated with that found in the H-1 pattern.

The two shift reagents were apparently interacting at different sites of the polyfunctional substrate **2**. From the above data, a β-configuration could be assigned to **2** with reasonable assurance. Chemical proof for the anomeric assignment was nevertheless obtained by a correlation with the reference compound **7** (12). Application of the modified Hundsdiecker reaction (13) to the acid **5** gave the crystalline bromide **6** in 87% yield. The latter was solvolyzed in the presence of anhydrous sodium acetate in *N*,*N*-dimethylformamide to give the known crystalline 1,3,4,5,7-penta-*O*-acetyl-2,6-anhydro-D-glucitol **7**, thus conclusively establishing the structure, as well as the β-anomeric configuration of **2** (and **3**).

The mass spectrum of **2** was in accord with its structure, and revealed a fragmentation pattern that was characteristic of its structure. Whereas a common fragmentation pathway of hexopyranose peracetates (14) involves cleavage of the glycosyloxy bond and the formation of a cyclic glycosyl oxonium ion at *m/e* 331, the corresponding *C*-glycosyl malonates do not give such an ion but fragment to give an ion that retains a portion of the C-1 substituent. Some of these fragments are shown in Scheme 2.

Having access to the anomerically substituted malonic and acetic acid derivatives (Scheme 1), experiments were attempted in order to introduce a versatile functional group such as a halogen

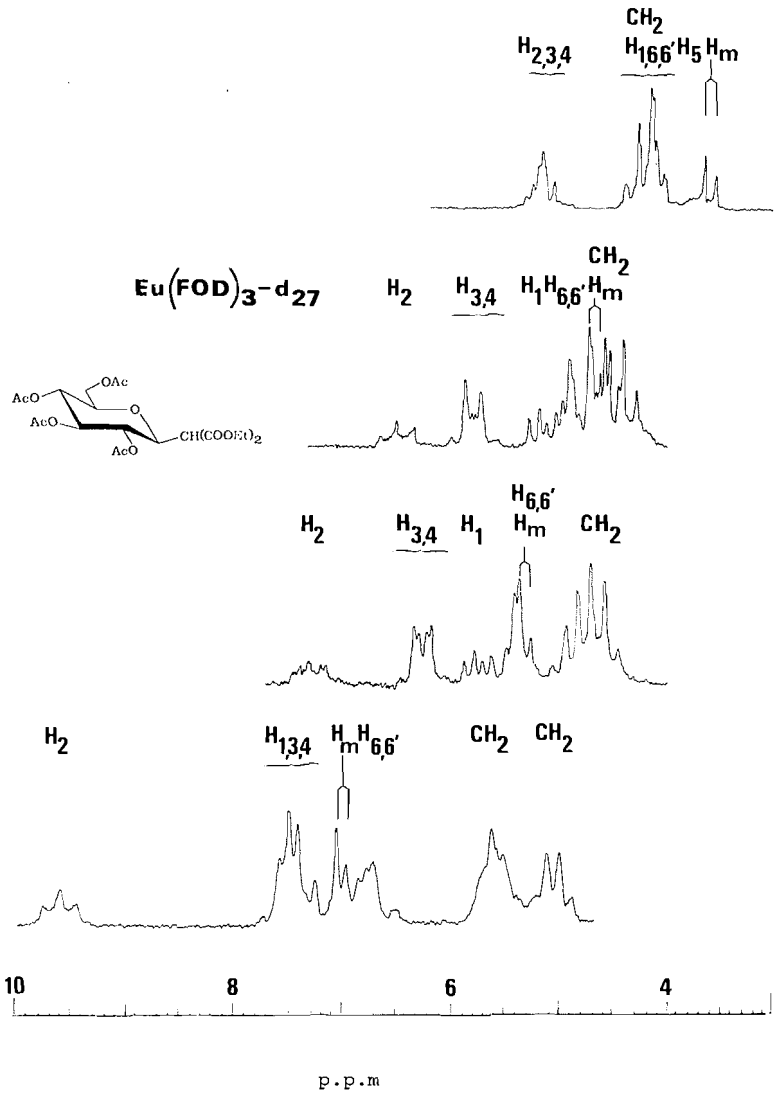
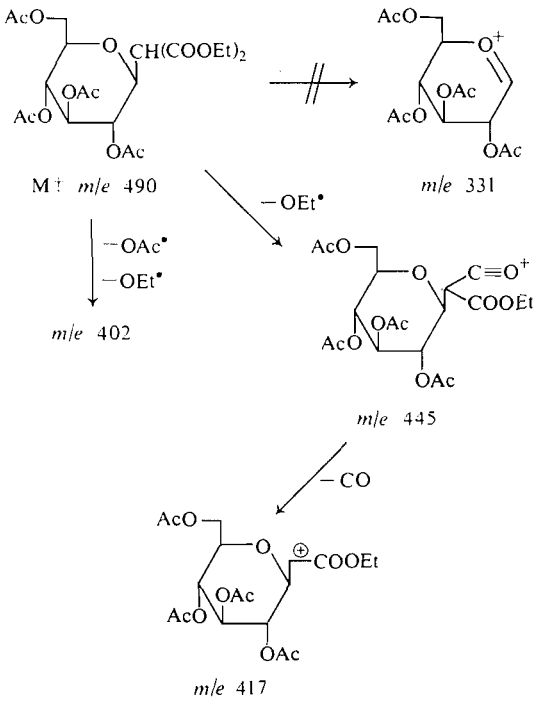


FIG. 2. Partial n.m.r. spectra of diethyl 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) malonate **2** (upper spectrum) and in the presence of incremental amounts of $Eu(FOD)_3$-d_{27} (lower spectra), in $CDCl_3$ at 60 MHz. H_m refers to the malonic ester proton.

atom in the 2-position of the anomeric substituent. Treatment of the acid **5** with bromine in carbon tetrachloride (15), or with sulfuryl chloride and thionyl chloride (16), or with *N*-bromosuccinimide (17) were unsuccessful. However, when the malonic acid derivative **4** was treated with bromine in thionyl chloride (18) and the product was then treated with methanol, a 57% yield of the crystalline α-bromoester **8** was obtained. The above discussed reactions demonstrate not only the feasibility of C—C condensation reactions at the anomeric center but also illustrate the possibility of effecting various selective transformations in the *C*-aglycon portion. The functionalized anomeric substituents in these and related *C*-glycosyl compounds could then be used in the elaboration of various β-oriented heterocyclic systems, including those found in the medicinally important *C*-nucleosides.

The formation of β-*C*-glucosyl compounds can be explained by considering the following possibilities (Scheme 3): (*a*) a direct S_N2-type reaction on the anomeric carbon atom of the halide **1** or



SCHEME 2

on an ion-pair in which the bromide ion has a specific α-orientation (**A**); (*b*) formation of an oxonium ion with possible stabilization by electronegative atoms in the solvent,[5] followed by β attack by the carbanion[6] (**B**); (*c*) formation of a 1,2-acetoxonium ion from the oxonium ion and subsequent attack of the carbanion on the anomeric carbon atom; (*d*) irreversible epimerization of an initially-formed α-*C*-glucosyl compound.[7] In order to gain further insight into some of these mechanistic possibilities, a model reaction was chosen, that would in all probability, proceed by way of 1,2-acetoxonium ions (5). When β-acetochloroglucose **9** was allowed to react with sodio diethyl malonate in 1,2-dimethoxethane or *N*,*N*-dimethylformamide, the sole product of the reaction was the ketal **10** (Scheme 4). The intervention of a 1,2-acetoxonium ion intermediate was therefore evident. In view of the absence of any ketal product in the reaction of **1** and the carbanion in 1,2-dimethoxyethane, it can be concluded that acetoxonium ions are not involved in the formation of the β-*C*-glucosyl compounds **2** and **3**. Most likely then, the mechanism involves attack on an ion-pair species in which the bromide has an α-orientation as in **A**. To test this hypothesis and to further study the role of the solvent, the condensation of **1** and sodio diethyl malonate was carried out in *N*,*N*-dimethylformamide, which would promote a better charge separation of paired ionic species and would allow a more effective participation of the C-2 acetoxy group. The product in this case consisted of a mixture of the *C*-glycoside **2** (~20%), the ketal **10** (~30%), and 2,3,4,6-tetra-*O*-acetyl-D-glucal (>50%). These results imply the initial formation, in part, of an acetoxonium ion and the products **2** and **10** could arise by way of a mixed pathway. A direct attack of the carbanion on the anomeric carbon atom of the acetoxonium ion **C** in this solvent cannot be excluded.

The structure of **10** was proved by spectroscopic and chemical means. Acetolysis gave α-D-glucose pentaacetate **14** (Scheme 4), as would be expected of a 1,2-ketal but not a *C*-glycoside.[8] Acetyl malonate was isolated and identified in this reaction. Conclusive proof of the 1,2-ketal structure was obtained by sequential methylation, hydrolysis (19), and oxidation to a lactone with bromine. The crystalline phenylhydrazide derivative **13**, obtained from the lactone, was identical with an authentic sample of 3,4,6-tri-*O*-methyl-D-gluconic acid phenylhydrazide (20).

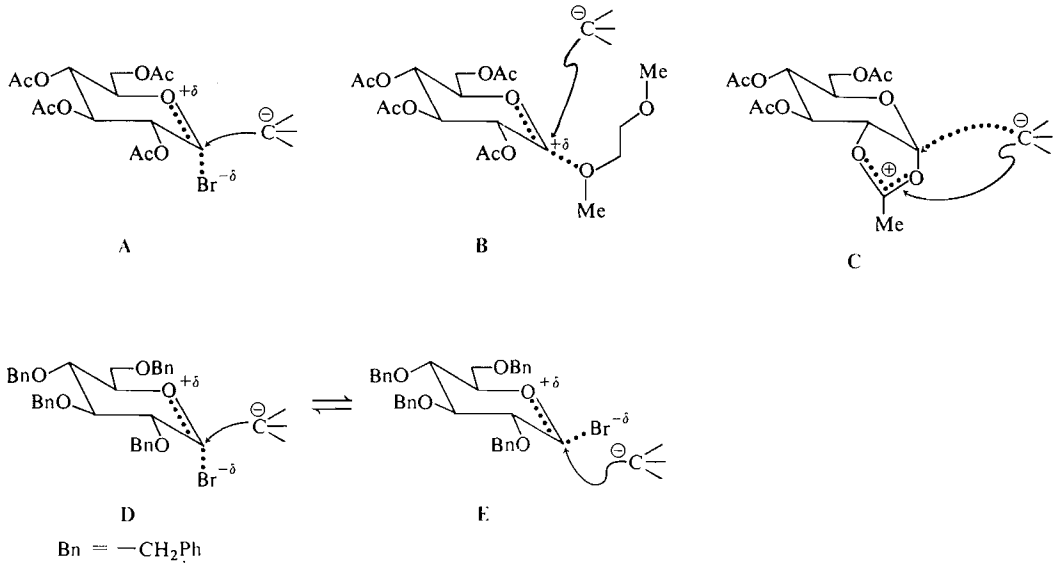
A study of the reaction of sodio diethyl malonate with glycosyl halides containing nonparticipating substituents was next undertaken, primarily for mechanistic reasons. Condensation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl bromide **15** (21) with sodio diethyl malonate in diethyl malonate afforded the anomeric *C*-glucosyl malonates **16** in high yield (Scheme 5). After hydrogenation and acetylation, a mixture was obtained that was richer in the β-anomer (approximately 3:1 β to α ratio). Two pathways could be envisaged to account for this result. A partial anomerization of the bromide **15** via ion-

[5]For a discussion of the formation of discrete oxonium intermediates with ether-type solvents in displacement reactions, see refs. 33 and 34; see also ref. 35.

[6]Anomerization, by return of bromide ion is considered somewhat unlikely because of the formation of the relatively insoluble sodium bromide during the reaction. The effective concentration of bromide ions in solution would be negligible.

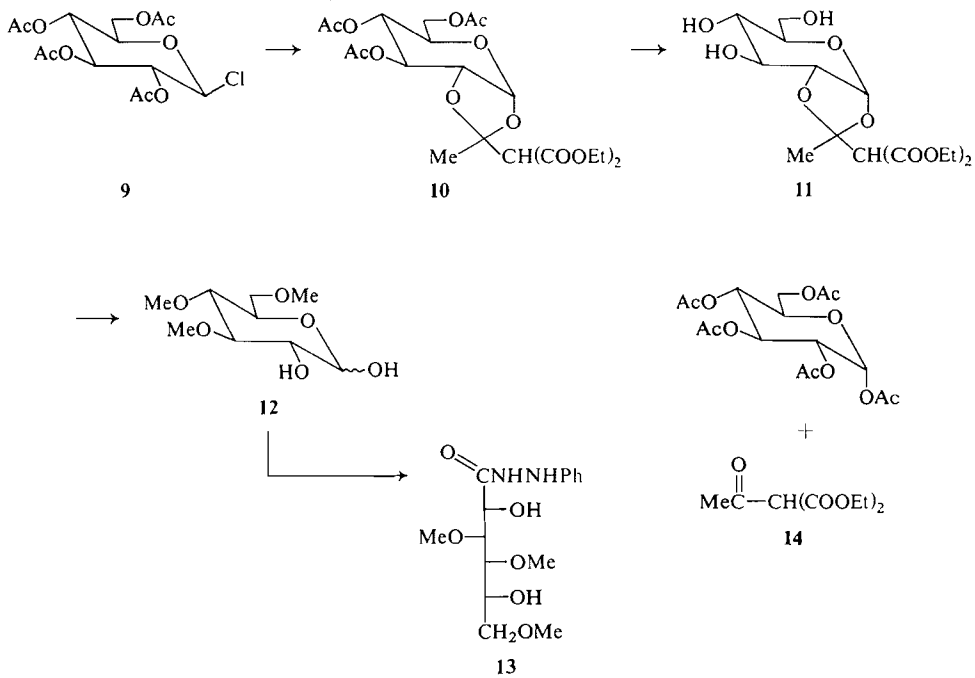
[7]Epimerization of this type has been experimentally observed in the D-ribofuranose series, see ref. 9 and references cited therein.

[8]Acetolysis of **2** under the same conditions gave unchanged product.



A B C D E

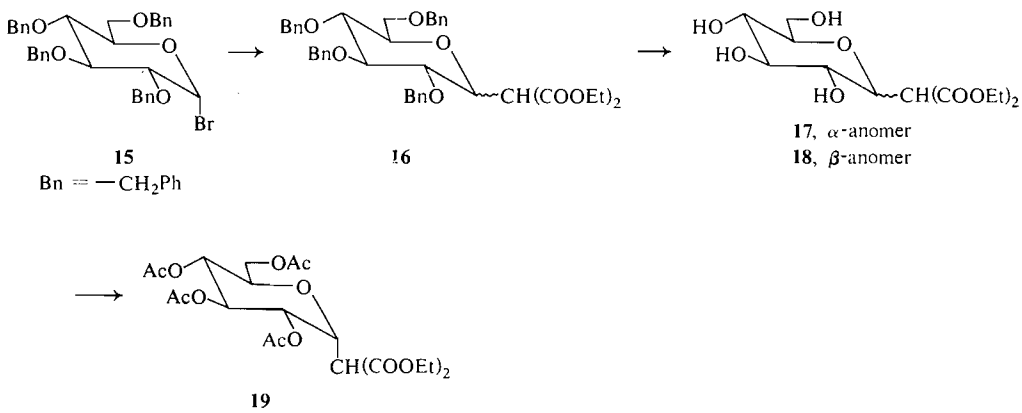
SCHEME 3



9 10 11 12 13 14

SCHEME 4

pair intermediates or oxonium-ion species, followed by attack of the carbanion on the anomeric carbon atom of two ion-paired species, in which the bromide ions were specifically α- and β-oriented (Scheme 3, **D** and **E**). Alternatively, the products could arise from attack of the carbanion on oxonium-ion species, possibly stabilized by solvent molecules (malonate). In view of the relative insolubility of the formed sodium bromide in the reaction mixture, appreciable anomerization by bromide ion return is somewhat unlikely and the alternative mech-



SCHEME 5

TABLE 1. Condensation of **15** with sodio diethyl malonate in the presence of added bromide ion[a]

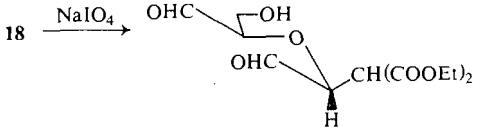
Malonate (equiv.)	Salt added (equiv.)	$[\alpha]_D$ of mixture[b]	α to β ratio	Yield (%)
10	—	0.6°	23:77	81
10	NaBr (10)	+4.3°	27:73	92
10	*n*-Bu_4NBr (1)	+28.5°	56:44	92
10	*n*-Bu_4NBr (5)	+39.9°	69:31	72
10	*n*-Bu_4NBr (10)	+42.0°	72:28	85

[a]For reaction conditions see Experimental.
[b]Optical rotation of the mixture after hydrogenation and acetylation.

anism may be operative. In order to test the mechanistic consequence of an induced anomerization, the condensation was done in the presence of a soluble source of bromide ion, the premise being that the return of the bromide ion from the β-side would create a finite concentration of the more reactive β-bromide in the equilibrium **D** ⇄ **E** (Scheme 3). This assumption was based on published data that β-D-glucopyranosyl halides, containing non-participating substituents at C-2, underwent alcoholysis more rapidly than did the α-anomers (21*a*, 22). If this type of reactivity were to be operative in the present case, where the nucleophile is a carbanion, then a higher proportion of the α-*C*-glucopyranosyl malonate should form in the presence of added bromide ion. The addition of 10 equiv. of tetra-*n*-butylammonium bromide to the solution containing **15**, *prior to the addition of the carbanion*, led to a mixture in which the α-anomer was indeed predominant (Table 1).[9] Crystalline diethyl 2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl) malonate **19** was isolated in 31% yield from such a condensation, after hydrogenolysis and acetylation. This result supports the contention that in the presence of added bromide ion, some β-bromide is formed either by direct anomerization or by attack of bromide ion on a solvated oxonium-ion intermediate. Since the equilibrium is in favor of the α-anomer because of the anomeric effect (23), the preponderance of the α-*C*-glucosyl compound must be the result of a faster reaction with the β-halide (Scheme 3, **E**). A crystalline by-product in the reactions where excess bromide ion was present was found to be tetraethyl 1,1,2,2,-ethanetetracarboxylate. The same compound was isolated from the reaction of 1,2-dibromocyclohexane with sodio diethyl malonate (24). Authentic product was obtained by treatment of a solution of sodio diethyl malonate with iodine.

The optical rotations of the crystalline *C*-glucosyl compounds **2** and **19** show that Hudson's rules (25) are obeyed in this class of compounds. Chemical evidence for the anomeric purity was obtained from periodate oxidation of the *C*-glycosyl malonates **17** and **18**, respectively,

[9]It is also evident from the data in Table 1, that the addition of sodium bromide is of negligible effect. This further supports the need for the presence of a soluble source of bromide ions.



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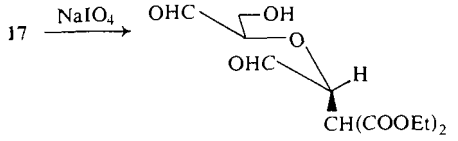


21

SCHEME 6

and the isolation of the epimeric dialdehydes **20** and **21** (Scheme 6).

The availability of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosyl halides (26, 27) prompted a study of their reactions with sodio diethyl malonate. Treatment of the bromide **22** (Scheme 7) with the carbanion in diethyl malonate as solvent gave the expected *C*-glycosyl malonates as an anomeric mixture in high yield. The preponderant anomer was the β-anomer. Both α- and β-anomers were isolated from the mixture by chromatography and their anomeric assignments were based on polarimetric and n.m.r. spectroscopic data. The β-anomer showed a higher negative rotation compared to the α-anomer. A larger H_1–H_2 coupling constant and a more deshielded malonic ester proton were found in the spectrum of the β-anomer. In the spectrum of the α-anomer however, H-4 was distinctly deshielded compared to the β-anomer.

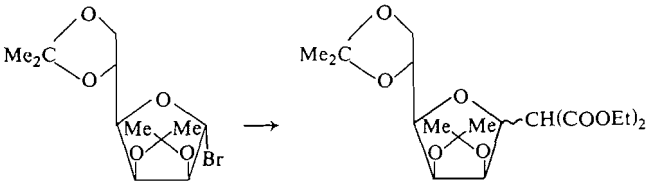
The preponderant formation of the β-anomer **24** can again be explained by invoking a direct attack of the carbanion on the anomeric carbon atom in **22** or in a tightly-paired ionic species, in which the bromide ion has an α-orientation. Epimerization, if taking place at all, must be in favor of the minor α-anomer, because of the bulky isopropylidene groups. In a more polar solvent such as ethanol, the reaction gave **23** and **24** in addition to the corresponding anomeric *O*-ethyl glycosides in approximately equal amounts. Although the reaction is not particularly useful from the preparative standpoint, it demonstrates the role of the solvent and the relative nucleophilicities of the alkoxide and the carbanion. The higher proportion of α-*O*- and -*C*-glycosides can be explained by a more effective separation of charges in the transition state leading to a more favored (less hindered) α attack.

The D-mannofuranose structure can be used as a precursor to the D-lyxo series. The mixture of *C*-glycosyl compounds **23** and **24**, rich in the β-anomer, was treated with dilute acetic acid to give the diol **25**. The latter was oxidized with sodium periodate and the 5-aldehyde derivative was reduced with sodium borohydride to give a mixture of the anomeric diethyl 2-(2,3-*O*-isopropylidene-D-lyxofuranosyl) malonates **26**.

Experimental

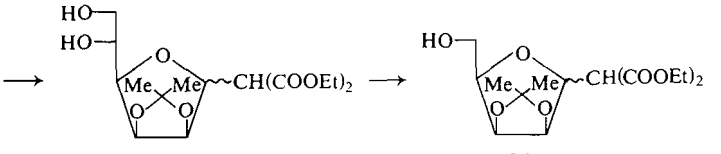
General

Melting points are uncorrected. Infrared spectra were recorded on a Beckman IR-8 spectrometer. Nuclear magnetic resonance spectra were obtained in chloroform-*d*



22

23, α-anomer
24, β-anomer



25 26

SCHEME 7

unless otherwise stated, at 60 and 220 MHz, with tetramethylsilane as internal reference (s, singlet; d, doublet; t, triplet; q, quartet; o, octet; m, multiplet; b, broad). Optical rotations were measured with a Perkin-Elmer model 141 automatic polarimeter. Mass spectra were done at low resolution on a Hitachi-Perkin-Elmer RMU-6D spectrometer with direct introduction of the sample in the ionizing chamber. Conventional processing, or processing in the usual manner, signifies drying of organic solution over anhydrous sodium sulfate, filtration, and evaporation under diminished pressure.

Chromatography

Thin-layer chromatography (t.l.c.) was done with plates coated with silica gel GF_{254} and with silica gel containing 2% boric acid (by weight). The following solvent systems were used: solvent A, chloroform–2,2,4-trimethylpentane–methanol (10:5:0.2); solvent B, chloroform–methanol (10:1); solvent C, toluene – ethyl acetate (10:1). The detection of *C*-glycosyl malonates was done with sulfuric acid in ethanol (20% by volume), followed by heating the plate at 100–110°.

The *C*-glycosyl malonates of the type described in this work appeared at first as orange-colored spots that eventually changed to dark brown on further heating. Glycosyl halides were detected by spraying the plates with a solution containing 20 g of silver nitrate and 20 ml of nitric acid in 100 ml of water. Black spots were produced within a few minutes at room temperature.

Column chromatography was performed with silica gel GF_{254} (with or without added 2% boric acid) by application of moderate suction. The conventional column was replaced by one fitted with a fritted disc (medium porosity) and a ground glass point that was connected to an appropriate suction flask. For the separation of components differing by 0.05 R_f units, a ratio of 1:20 of silica gel to substrate was found satisfactory.

Solvents and Handling of Carbanions

Due to the sensitivity of the glycosyl halides and the carbanions to moisture, all solvents used in the condensation reactions were dried rigorously prior to use. The preparation of the carbanions was done in a dry box and subsequent handling and transfers were performed with minimum exposure to air. These conditions are not mandatory for all condensations but they are advisable in the case of unstable glycosyl halides.

Diethyl 2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl) Malonate (2)

To a suspension of sodium hydride (10 g, 0.42 mol; previously washed with pentane) in 300 ml of 1,2-dimethoxyethane (DME) was added 65 ml of diethyl malonate, in portions and with stirring, until the evolution of hydrogen ceased, and the solution became clear. A solution of α-acetobromoglucose (56 g, 0.14 mol) in 50 ml of DME was slowly added, and after stirring overnight at room temperature, the solution was diluted with 2 l of ether and washed with water several times until the washings were neutral. The organic layer was then dried and processed as usual to give a mobile liquid, from which excess diethyl malonate was removed by distillation (30° at 10^{-3} Torr). A viscous yellowish syrup (32 g) was obtained that showed essentially three spots on t.l.c. (5 × 20 cm plate, solvent A), consisting of starting material **1** (~20%), and equal amounts of the title compound and a transesterified unknown product. Upon spraying the plate with sulfuric acid and heating, the spot corresponding to the title compound gave an orange color that turned to brown upon further heating.

A portion of the syrup (2 g) was dissolved in enough 95% ethanol to render it mobile, the solution was then seeded[10] and left at −20° for a few days, whereupon the title product **2** crystallized; yield 0.9 g, 20%; two recrystallizations from the minimum volume of 95% ethanol gave material having m.p. 88.5–89°; $[\alpha]_D^{25}$ − 18.5° (*c*, 3.0 $CHCl_3$); n.m.r. (at 220 MHz): 1.27, 1.29 (t, J = 7 Hz, CH_3CH_2); 3.61 (d, $J_{m,1}$ = 6.2 Hz; H_m); 3.71 p.p.m. (o, $J_{5,4}$ = 9 Hz; $J_{5,6}$ = 5 Hz, $J_{5,6'}$ = 2.5 Hz; H-5). For spectra in the presence of n.m.r. shift reagents, see Figs. 1, 2. Eu(DPM)$_3$: H_m (d, $J_{m,1}$ = 6.2 Hz); H_1 (dd, $J_{1,m}$ = 6.2 Hz; $J_{1,2}$ = 9.75 Hz); Eu(FOD)$_3$-d_{27}: H_m (d, $J_{m,1}$ = 6.2 Hz); H_1 (dd, $J_{1,m}$ = 6.2 Hz; $J_{1,2}$ = 9.75 Hz); H_2 ($t_1 H_{2,1} = H_{2,3}$ = 9.75 Hz). Mass spectral data: *m/e* 445 (M^+ − EtO•); 417 (M^+ − EtO•—CO).

Anal. Calcd. for $C_{21}H_{30}O_{13}$: C, 51.43; H, 6.17. Found: C, 51.21; H, 6.18.

Alternate methods for obtaining **2** involve preliminary transformation of the residual acetobromoglucose into tetra-*O*-acetyl-D-glucose (method A) and tetra-*O*-acetyl-D-glucose (method B).

Method A

The syrup (32 g) resulting from a similar condensation to that described above was treated with NaI–Et_3N according to Ferrier and Sankey (28) and the conversion of residual **1** into tetra-*O*-acetyl-D-glucal was followed by t.l.c. The resulting dark brown syrup was dissolved in methanol (100 ml) and the solution was treated with ozone for 3 h. After diluting with 500 ml of dichloromethane, the colorless solution was washed with alkaline hydrogen peroxide (30 vol. in *N* NaOH), then with water. The organic phase was processed as usual to give a syrup (32 g) that contained the *C*-glycoside **2** and presumably a transesterification product in approximately equal amounts. A portion (1.02 g) of the syrup was separated by chromatography on silica gel (Grace Davidson G 950; substrate–adsorbent ratio ~1:300) with chloroform as the developing solvent. The title compound **2** was obtained from the appropriate fractions after evaporation to a syrup and keeping at 0° for a few days; yield 0.4 g (20%).

Method B

A portion (2 g) of the above syrup resulting from the condensation reaction was dissolved in a mixture of 1:3 water–acetone and the solution was treated with 0.3 g of silver nitrate and 0.106 g of silver carbonate. After stirring at room temperature for 2 h, the suspension was filtered and the combined filtrates and washings were evaporated to a small volume. The solution was extracted with chloroform and the extracts were processed in the usual manner to give a syrup that showed **2** (R_f ~0.8), the transesterified product (R_f ~0.85), and tetra-*O*-acetyl-D-glucose (R_f ~0.5) in solvent A (20 cm plate). The *C*-glycoside **2** was separated by column chromatography as described under B and was obtained in 20% yield.

[10]Seed crystals were obtained by preparative t.l.c. on 0.1 g of sample; the syrup so obtained crystallized at 0°.

The R_f 0.85 component was separated and isolated as a colorless syrup. Its n.m.r. spectrum showed a much larger ratio of ethyl hydrogens to acetyl methyl hydrogens. This product, assumed to arise by transesterification, was not investigated further.

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl) Malonic Acid (4)

To a suspension of sodium hydride (3.5 g, 0.2 mol; previously washed with pentane) in 130 ml of 1,2-dimethoxyethane (DME) was added dibenzyl malonate (45 ml) until the evolution of hydrogen ceased. Acetobromoglucose (20 g, 49 mmol) dissolved in the minimum volume of DME was added to the clear solution and the whole was stirred at room temperature for 48 h. After the solution was concentrated (below 30°) to a small volume, ether (500 ml) was added and the solution was washed successively with *N* HCl (100 ml) and water. The organic phase was dried and evaporated to a syrup that was triturated with pentane several times to remove residual dibenzyl malonate. The remaining syrup (~80%) consisted essentially of *dibenzyl 2-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl) malonate* (**3**) as evidenced by t.l.c. (solvent A). The syrup was dissolved in ethanol and hydrogenated in the presence of 20% palladium-on-charcoal (29) (4.0 g). After 20 h, the catalyst was filtered and the filtrate was evaporated to a syrup that was dissolved in acetone, filtered, and the filtrate was evaporated. The title compound crystallized spontaneously and was recrystallized from ether to give **4** in several crops (10.5 g, 51%), m.p. 139–141°. After two recrystallizations, an analytical sample was obtained having m.p. 147° (with gas evolution); $[\alpha]_D^{25}$ −18° (*c*, 1.17 EtOH); n.m.r. (DMSO-d_6): 3.38 (d, $J_{m,1}$ = 7.5 Hz, H_m); 1.93, 2.02 p.p.m. (*s*, CH_3COO), etc.

Anal. Calcd. for $C_{17}H_{22}O_{13}$: C, 47.01; H, 5.11. Found: C, 46.89; H, 5.33.

2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl) Acetic Acid (5)

The above described product **4** (1.0 g, 2.3 mmol) was dissolved in 20 ml of glacial acetic acid and the solution was heated under reflux for 3 h. Evaporation of the solution to dryness gave the title compound in quantitative yield. Recrystallization from ether–pentane gave material having m.p. 104.5–105.5°. Three recrystallizations from the same solvent mixture gave pure material, m.p. 120–120.5°; $[\alpha]_D^{25}$ −4.3° (*c*, 1.95 $CHCl_3$); n.m.r.: 2.05, 2.10, 2.12 (s, CH_3COO); 2.62 (d, J = 6 Hz, CH_2COOH); 10.55 p.p.m. (*s*, $COOH$).

Anal. Calcd. for $C_{16}H_{22}O_{11}$: C, 49.23; H, 5.68. Found: C, 49.29; H, 5.96.

Esterification of 4 with Triethyloxonium Fluoroborate

An amount of **4** (30 mg) was dissolved in 2 ml of dichloromethane, the solution was cooled to 0° and treated with 0.2 g of triethyloxonium fluoroborate (10). After standing at 0° for 1 h, the solution was poured into aqueous sodium bicarbonate and chloroform was added. Processing the organic phase gave a syrup (20 mg, 59%) that had identical chromatographic and n.m.r. spectral properties to the diester **2**. Crystallization from the minimum volume of 95% ethanol gave **2**, m.p. and mixture m.p. 89–90°.

3,4,5,7-Tetra-O-acetyl-2,6-anhydro-1-bromo-1-deoxy-D-glycero-D-gulo-heptitol (6)

A solution of **5** (54 mg, 0.14 mmol) in 1 ml of carbon tetrachloride was treated with 30 mg of yellow mercuric oxide and 1 ml of carbon tetrachloride containing 40 mg of bromine and the mixture was heated under reflux in the dark for 3 h. The suspension was filtered through a bed (2 × 2 cm) of silica gel and the adsorbent was developed with chloroform. Evaporation of the chloroform solution gave the title compound which crystallized. The crystalline mass was triturated with cold ethanol and the crystals were filtered; yield 51 mg (87%). Two recrystallizations from 95% ethanol gave material having m.p. 119.5–120°; $[\alpha]_D^{25}$ −12.4° (*c*, 1.1 $CHCl_3$); n.m.r.: 2.05, 2.09, 2.11, 2.13 (*s*, CH_3COO), 3.45 p.p.m. (bs, CH_2Br), etc.

Anal. Calcd. for $C_{15}H_{21}O_9Br$: C, 42.37; H, 4.98. Found: C, 42.39; H, 5.05.

1,3,4,5,7-Penta-O-acetyl-2,6-anhydro-D-glycero-D-gulo-heptitol (7)

The above mentioned bromide 6 (30 mg, 0.07 mmol) was solvolyzed in 2 ml of DMF containing 30 mg (0.4 mmol) of anhydrous sodium acetate at 110° (36 h). The solvent was removed by azeotropic evaporation with 1-butanol, the resulting residue was dissolved in chloroform, and the solution was washed with water. Processing the organic phase in the usual way gave a syrup that crystallized; yield 20 mg (70%). Two recrystallizations from 2-propanol gave **7**, m.p. 94° (sublimes); $[\alpha]_D^{25}$ 0 ± 1° (*c*, 1.0 $CHCl_3$), (lit. (12), m.p. 89° $[\alpha]_D$ 0° ($CHCl_3$)).

Methyl 2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl) 2-Bromoacetate (8)

To a solution of the diacid **4** (0.25 g, 0.57 mmol) in 5 ml of dry thionyl chloride, were added 0.5 ml of bromine and 3 drops of a 1:1 acetic acid – hydrochloric mixture. The solution was heated at reflux for 3 h and then it was evaporated. After this process was repeated three times, the residue crystallized and the product was recrystallized from hot methanol to give the title compound (0.155 g, 57%); m.p. 145.5–146°; mass spectral data (AEI MS 902, at high resolution): M^+ 482.0419 and 484.0407 (Br isotope); calcd. for $C_{17}H_{22}O_{11}Br$: M^+ 482.0424 and 484.0404.

1,2-O-(2,2-Dicarbethoxy-1-methylethylidine)-3,4,6-tri-O-acetyl-α-D-glucopyranose (10) and its Acetolysis Product

To a solution containing sodium diethyl malonate (from 0.75 g of sodium and 6.0 ml of diethyl malonate) in 30 ml of *N*,*N*-dimethylformamide, were added 4 g (11 mmol) of β-acetochloroglucose **9** (30). After stirring at room temperature overnight, the solution was concentrated under vacuum, the residue was taken up in chloroform, and the solution was washed with water. Processing the organic layer in the usual manner gave the title compound as a chromatographically homogeneous syrup. The yield varied between 5 and 7 g (80–100%). Nuclear magnetic resonance: 1.30 (t, J = 7.5 Hz, CH_3CH_2); 1.89 (s, CH_3—C); 2.11, 2.13 (s, CH_3COO); 3.73 (s, H_m); 4.90 (q, $J_{4,5}$ = 8.25 Hz; $J_{4,3}$ = 3 Hz, H-4);

5.20 (t, $J_{3,4} = J_{3,2} = 3$ Hz, H-3); 5.75 p.p.m. (d, $J = 5.2$, H-1).

Acetolysis of **10** (50 mg in 1 ml of acetic anhydride, 1 ml of glacial acetic acid containing a micro drop of concentrated sulfuric acid, room temperature for 24 h, followed by conventional processing (aqueous sodium bicarbonate, extraction, etc.)) gave α-D-glucose pentaacetate (16 mg, 40%), m.p. 112–113° (from ethanol).

The mother liquors from the above described crystallization were concentrated to a syrup and the latter was extracted with pentane to give a mobile liquid that had an n.m.r. spectrum identical to acetyl diethylmalonate **14**; 2,4-dinitrophenylhydrazone derivative, m.p. and mixture m.p. 147° (lit. (31) m.p. 146–148°); n.m.r. for **14**: 1.28, 1.30 (t, CH_3CH_2); 2.04, 2.13, 2.21 (s, $CH_3C(=O)-C$ and $CH_3C(-O-)=C$); 3.40 (s, H_m, integration corresponds to ~0.8 H due to presence of enolic forms); 4.25 p.p.m. (m, CH_3CH_2).

Acid hydrolysis (*N* HCl; reflux; 2 h) of **10** gave a single sugar that was identified as glucose by chromatography in common solvent systems.

1,2-O-(2,2-Dicarbethoxy-1-methylethylidene)-α-D-glucopyranose (11)

A solution containing 4.2 g of **10** in 30 ml of ethanol was treated dropwise with a 1 *N* solution of sodium ethylate until a p*H* of 7.5–9 was attained. The p*H* was checked periodically, and after 2 h the solution was neutralized with Dowex-50(H^+) and the filtrate was processed in the usual manner to give a colorless chromatographically homogeneous syrup in quantitative yield; n.m.r.: 1.80 (*s*, CH_3—C); 5.75 p.p.m. (d, $J_{1,2} = 5$ Hz, H-1 etc.

3,4,6-Tri-O-methyl-D-gluconic Acid Phenylhydrazide (13) from 11

The above obtained product **11** (0.74 g, 2 mmol) was methylated with 2 ml of methyl iodide and 1.5 g of silver oxide in 10 ml of *N*,*N*-dimethylformamide. After stirring at room temperature for 24 h, the suspension was filtered, the precipitate was washed with chloroform, and the filtrate and washings were evaporated to dryness to give the tri-*O*-methyl derivative of **11** as a chromatographically homogeneous syrup (0.7 g, 86%); n.m.r.: 5.92, 5.96, 6.0 (*s*, OCH_3); 5.70 p.p.m. (d, $J_{1,2} = 6$ Hz, H-1). A portion (0.5 g) of the above mentioned product was hydrolyzed according to a literature procedure (19) to give 3,4,6-tri-*O*-methyl-D-glucose (**12**) (0.2 g). The latter was oxidized in carbon tetrachloride (1 ml) containing 2 drops of bromine. After 24 h at room temperature, the solution was evaporated to dryness; the residue was treated with 0.3 ml of phenylhydrazine and the resulting solution was heated on a steam bath for 2–3 min. The phenylhydrazide derivative **13** crystallized on cooling and it was recrystallized from ether–chloroform to give the pure product, m.p. and mixture m.p. 126° (lit. (20), m.p. 126–127°).

2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl Bromide (15)

Anhydrous hydrogen bromide was bubbled into a solution of 2,3,4,6-tetra-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-α-D-glucopyranose (0.1 g) (21*a*) in 2 ml of anhydrous dichloromethane. After 4–5 min, the precipitated *p*-nitrobenzoic acid was removed by filtration on a sintered-glass funnel and the filtrate was evaporated to dryness. The title compound (21) was obtained as a colorless syrup in quantitative yield; n.m.r.: 3.50 p.p.m. (d, $J_{1,2} = 4.5$ Hz, H-1).

Condensation of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl Bromide with Sodio Diethyl Malonate. Synthesis of Diethyl 2-(2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl) Malonate (19)

A. Without Added Bromide Ion

Finely cut sodium (0.23 g, 10 mmol; previously washed with pentane) was added to diethyl malonate (30 ml) and the solution was heated at 50° for 1 h and then cooled. The mixture was added to a solution of the bromide **15** (prepared from 0.7 g, 1 mmol, of the corresponding 1-*p*-nitrobenzoate) in the minimum volume of diethyl malonate and the whole was stirred at room temperature for 40 h. The solution was diluted with 200 ml of ether, washed with water, and the organic phase was processed as usual to give a mobile liquid from which excess diethyl malonate was removed by distillation (30° at 50×10^{-3} Torr). The residual viscous colorless syrup consisted entirely of a mixture of anomeric *C*-glycosides, namely diethyl 2-(2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranosyl) malonates, as evidenced by t.l.c. and n.m.r. data.

The syrup was dissolved in ethanol and hydrogenated in the presence of 20% palladium-on-charcoal during 24 h. After filtration of the catalyst and evaporation of the filtrate, a syrup (0.31 g, quantitative) was obtained that consisted of a 3:1 β to α ratio of *C*-glycosides (estimated from polarimetric data on an acetylated sample, see Table 1). The anomers could be readily distinguished by t.l.c. on silica gel containing 2% boric acid (solvent B); R_f 0.4 for the β-anomer and R_f 0.5 for the α-anomer. A portion (0.15 g) of the syrup was separated by preparative t.l.c. on the same support (20 × 20 cm plates) to give *diethyl 2-(α-D-glucopyranosyl) malonate* **17** and *diethyl 2-(β-D-glucopyranosyl) malonate* **18** as colorless syrups. These compounds were each converted into the crystalline acetates **19** and **2**, respectively, in essentially quantitative yield.

B. In the Presence of Added Bromide Ion

The previous experiment was repeated as described in A except that 10 equiv. of tetra-*n*-butylammonium bromide were added to a solution of the bromide **15** (from 0.33 g, 0.5 mmol, of the corresponding 1-*p*-nitrobenzoate) in diethyl malonate, approximately 10 min prior to the addition of the carbanion (from 0.115 g of sodium in 20 ml of diethyl malonate, 5 mmol). The same isolation procedure was followed as in A, except that the hydrogenated product was partitioned between ether and water. The ether phase afforded crystalline tetraethyl 1,1,2,2-ethanetetracarboxylate (approximately in a 1:5 ratio with respect to the sodio diethyl malonate used), m.p. and mixture m.p. 75–76° (lit. (24) m.p. 76°); n.m.r.: 1.27 (t, $J = 7.5$ Hz, CH_3CH_2); 4.25 (q, $J = 7.5$ Hz, CH_3CH_2); 4.12 p.p.m. (s, H_m).

The aqueous solution was evaporated to dryness and the residue was acetylated with acetic anhydride (1 ml) in pyridine (room temperature, 24 h). Conventional pro-

cessing gave a syrup[11] (0.25 g, 85%) that crystallized from a mixture of ether and pentane at 0° to give *diethyl 2-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl) malonate* **19** (0.16 g, 31%), m.p. 59–60° (resolidifies and melts at 72–73°); $[\alpha]_D^{25}$ 66.2° (*c*, 3.9 $CHCl_3$); n.m.r.: 1.27, 1.28 (t, CH_3CH_2); 2.0, 2.07 (s, CH_3COO); 3.87 p.p.m. (d, $J_{m,1}$ = 10.5 Hz, H_m) etc.

Anal. Calcd. for $C_{21}H_{30}O_{13}$: C, 51.43; H, 6.17. Found: C, 51.17; H, 6.17.

Tetraethyl 1,1,2,2-Ethanetetracarboxylate

Sodium (2.3 g, 0.1 mol) was dissolved in 10 equivalents of diethyl malonate and the solution was treated dropwise with iodine until the color persisted (~1 h). After standing at room temperature overnight, the solution was diluted with ether, washed with water, and the organic layer was processed as usual to give a mobile liquid from which excess diethyl malonate was removed by distillation. The crystalline residue consisted of the title compound; yield 32 g (quantitative, based on the amount of sodium used). Recrystallization from ether–pentane gave material with m.p. 75–76° (lit. (24), m.p. 76°).

*Periodate Oxidation and Anomeric Configurational Assignment of C-Glucosyl Malonates **17** and **18**. Isolation of Epimeric Dialdehydes*

*Dialdehyde **20***

An amount of **18** (80 mg) was dissolved in 2 ml of ethanol and the solution was treated with 3 equiv. of sodium metaperiodate in 2 ml of water. After 4 days in the dark, the solution was filtered, the precipitate was washed with ethanol, and the filtrate and washings were evaporated to dryness. The residue was extracted with chloroform, residual salts were removed by filtration, and the filtrate was evaporated to a syrup that was separated from traces of impurities by preparative t.l.c. (solvent B) to give the dialdehyde **20** (32 mg) as a syrup; R_f ~0.7 (silica gel – boric acid, solvent C); $[\alpha]_D^{25}$ −24° (*c*, 2.1 $CHCl_3$).

*Dialdehyde **21***

The same procedure was applied to **17**, to give the dialdehyde **21** as a syrup (R_f ~0.7); $[\alpha]_D^{25}$ 26° (*c*, 0.8 $CHCl_3$).

*Diethyl 2-(2,3:5,6-Di-O-isopropylidene-α- and β-D-mannofuranosyl Malonates (**23**, **24**)*

Finely cut sodium (1.67 g) was dissolved in 100 ml of diethyl malonate at 50–60°. The cooled solution was added to a solution of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl bromide **22** (6.7 g) (26, 27) in the minimum volume of diethyl malonate. The solution was stirred at room temperature overnight, diluted with a large excess of ether, and processed in the usual manner. Residual diethyl malonate was removed by distillation. The remaining colorless syrup (8.5 g, quantitative) consisted of an anomeric mixture of the title compounds in a ratio of 9:1 in favor of the β-anomer (n.m.r.). A portion of the syrup (0.2 g) was separated by preparative t.l.c. (solvent C) and the respective anomers were obtained as colorless syrups.

*Diethyl 2-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl) Malonate (**23**)*; R_f ~0.7 (solvent C); $[\alpha]_D^{25}$ 17 ± 0.2° (*c*, 3.6 $CHCl_3$); n.m.r.: 1.50 (m, CH_3C, CH_3CH_2); 3.66 (d, $J_{m,1}$ = 9 Hz, H_m); 4.05 (dd, $J_{4,5}$ = 5 Hz; $J_{4,3}$ = 2.5 Hz, H-4); 4.73 (d, $J_{1,m}$ = 9 Hz, H-1); 4.93 (d, $J_{3,4}$ = 2.5 Hz, H-3); *m/e* 387 ($M^+ - CH_3$). *Diethyl 2-(2,3:5,6-Di-O-isopropylidene-β-D-mannofuranosyl) malonate (**24**)*; R_f ~0.75 (solvent C); $[\alpha]_D^{25}$ −45.5° (*c*, 7.2 $CHCl_3$); n.m.r.: 1.40 (m, CH_3C, CH_3CH_2); 3.62 (d, d, $J_{4,3}$ = 3 Hz; $J_{4,5}$ = 7, H-4); 3.87 (d, $J_{m,1}$ = 10.5, H-m); 4.3 (m, CH_3CH_2, H-1, H-5, H-6,6′); 4.85 (d, d, $J_{2,1}$ = 3 Hz, $J_{2,3}$ = 6 Hz, H-2); 5.05 p.p.m. (d.d, $J_{3,2}$ = 6 Hz; $J_{3,4}$ = 3 Hz, H-3); *m/e* 387 ($M^+ - CH_3$); *m/e* 329 ($M^+ - CH_3 - CH_3COCH_3$).

When the above described condensation was carried out in ethanol (6.6 mmol of sodium and 2.2 mmol of the bromide **22**), a syrup (0.8 g) was obtained that consisted of approximately equal amounts of four compounds as estimated from the relative intensities of the charred spots (t.l.c. solvent C). A portion of the product was separated by preparative t.l.c. to give **23** (90 mg); **24** (78 mg) and the syrupy anomeric ethyl 2,3:5,6-di-*O*-isopropylidene-D-mannofuranosides; α-anomer (35 mg; R_f ~0.8); β-anomer (60 mg, R_f ~0.65). The n.m.r. spectra of the *O*-glycosides were compatible with their structures.

*Diethyl 2-(2,3-O-Isopropylidene-α,β-D-lyxofuranosyl) Malonates (**26**)*

The syrupy mixture of **23** and **24** (1:9 ratio) (2.7 g, 6.2 mmol) was dissolved in 30 ml of 70% aqueous acetic acid and the solution was heated at 50–60° for 70 min. The solution was concentrated to dryness by azeotropic distillation with toluene to give the diol **25** as a colorless chromatographically homogeneous syrup (quantitative). The n.m.r. spectrum of this product was in agreement with its structure.

An amount of this syrup (2.03 g, 6.2 mmol) was dissolved in 40 ml of 50% aqueous methanol containing 1.8 (8.4 mmol) of sodium metaperiodate. After standing in the dark for 2 h the solution was filtered and the filtrate was evaporated to dryness. The residue was taken up in ether, the salts were filtered, and the filtrate was evaporated to a syrup (quantitative) that was homogeneous by t.l.c. (R_f ~0.5, solvent C). An n.m.r. spectrum of the product showed a singlet at 9.50 p.p.m., indicative of the aldehyde group at C-5.

A portion of the product (0.862 g, 2.6 mmol) was dissolved in 30 ml of methanol, 0.5 g (10 mmol) of sodium borohydride was added and the solution was stirred at room temperature for 40 min. The solution was neutralized with a few drops of glacial acetic acid and evaporated to dryness. The residue was taken up in ether and the solution was processed to give diethyl 2-(2,3-*O*-isopropylidene-α,β-D-lyxofuranosyl) malonate (**26**) as a colorless syrup (0.447 g, 57%), R_f 0.5 (solvent C). The corresponding 5-methanesulfonate, obtained as a colorless syrup in the usual way showed the expected n.m.r. spectral characteristics and correct integration.

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[11]Polarimetric studies indicated an α to β ratio of approximately 3:1, see Table 1.

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