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STEREOSELECTIVE TOTAL SYNTHESIS OF METHYL α-D- AND α-L-GLUCOPYRANOSIDES*†

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ABSTRACT

Methyl α-L- and α-D-glucopyranosides have been synthesized from methyl (*R*)- and (*S*)-(2-furyl)glycolates (**3**), respectively. The key intermediates, methyl 6-*O*-benzyl-2,3-dideoxy-L(and D)-hex-2-enopyranosid-4-uloses (**13**), were obtained in seven steps from the ester **3**, without change of configuration of the asymmetric center, which became C-5 in the sugar molecule. Reduction of the ketone group at C-4 in the glycoside **13** with sodium borohydride afforded the corresponding methyl 6-*O*-benzyl-2,3-dideoxy-*erythro*-hex-2-enopyranosides (**14**). Epoxidation of the double bond in **14**, followed by oxirane ring-opening in the anhydro sugar **16**, and subsequent catalytic hydrogenolysis of the benzyl group led to the title compounds.

INTRODUCTION

The total synthesis of optically pure monosaccharides[1–6] from nonsugar precursors usually requires resolution at the final or at an intermediate stage of the synthesis. Therefore, the choice of a product having a desired absolute configuration is possible only by comparison with the naturally occuring sugar. When the absolute configuration of the natural sugar is not known, separate steps may be necessary to establish it[2]. On the other hand, starting from D-threaric acid[7], L-glutamic acid[8], or L-alanine[9], optically active pentoses and 6-deoxyhexoses have been obtained. These syntheses did not require a resolution step and, even more significantly, the absolute configurations of the final products could be selected at the outset of the synthetic sequence. It appeared desirable to extend this approach on other types of monosaccharides. The general method for stereoselective, total synthesis of monosaccharides from furan derivatives developed by us[10], and summarized in Scheme I, seemed well suited for this purpose.

Thus far, this route has afforded only racemic sugars[11]. However, starting with an enantiomerically pure 2-furylcarbinol (**1**) of known absolute configuration, it

*Dedicated to the memory of Professor J. K. N. Jones, F.R.S.
†Preliminary report of part of this work: O. Achmatowicz, Jr., R. Bielski, and P. Bukowski, *Abstr., 9th Intern. Symp. Chem. Natural Products*, Ottawa, Canada, June 24–28, 1974, p. 38A.

R = H, CH_3, CH_2OH, CH_2NO_2, or CH_2NHAc

Scheme I

should be possible to obtain optically pure monosaccharides of the desired absolute configuration. As the result of a six-step, stereoselective transformation, the carbinol carbon atom in a 2-furylcarbinol **1** (R = H, CH_3, CH_2OH, CH_2NO_2, or CH_2NHAc) becomes a C-5 in the final product **2**, and defines the configurational series (D or L) of the monosaccharide obtained*, which should therefore be related to the configuration of the asymmetric center in the starting furan derivative.

The present report describes how this approach may be put to practice, as exemplified by the total synthesis of methyl α-L- and α-D-glucopyranosides.

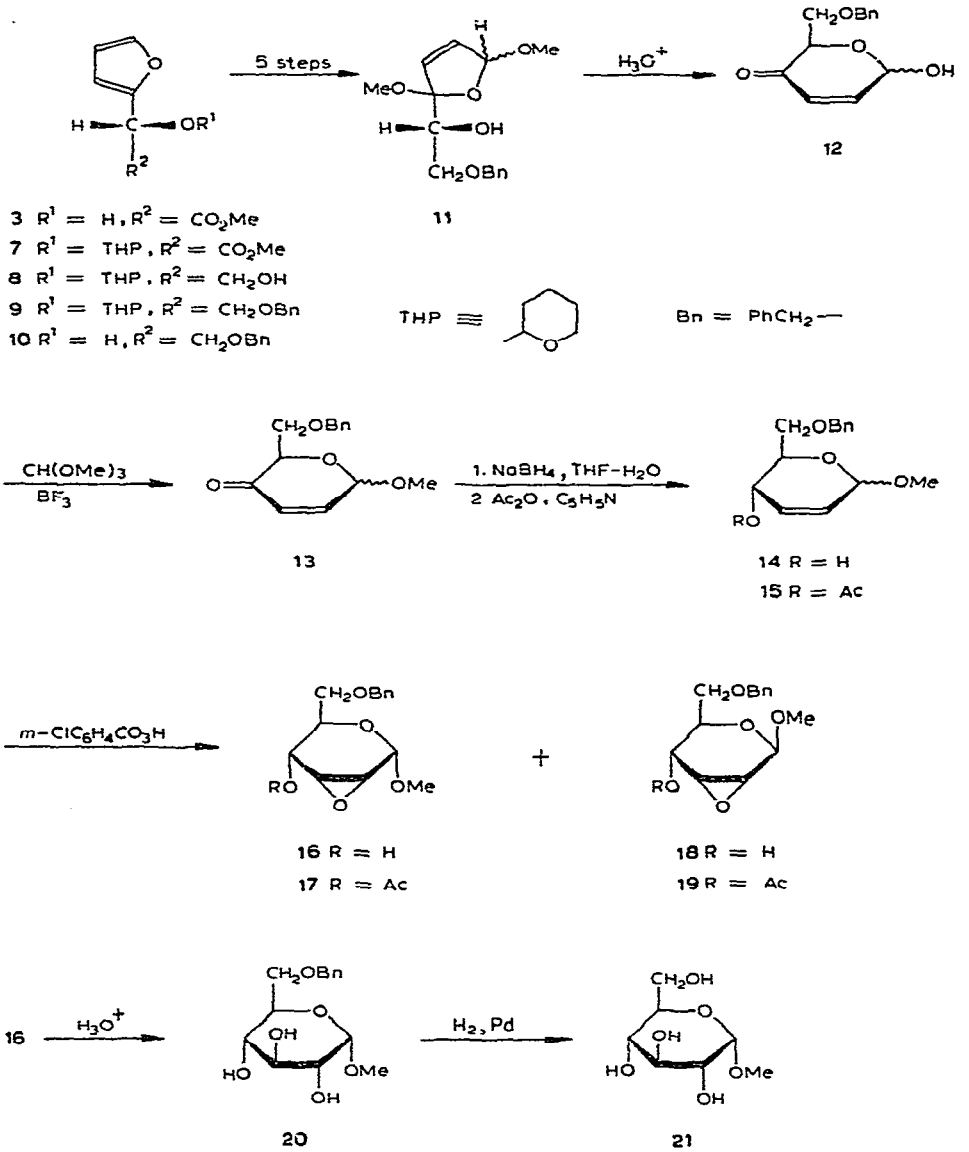
RESULTS AND DISCUSSION

The furan derivatives used as substrates were the readily available methyl esters of (*R*)- and (*S*)-2-furylglycolic acid (**3**). Their preparation and assignment of their absolute configuration have been described previously[12]. Reduction of the racemic methyl (2-furyl)glycolate and conversion of the resulting diol into methyl 2,3-dideoxy-α- and β-DL-hex-2-enopyranosid-4-uloses has also been published already[10,13]. In the preparation of the corresponding optically active compounds, difficulties might arise at the stage of hydrolysis of the respective 2,5-dimethoxy-2,5-dihydrofuran derivatives because of possible epimerization at the carbinol carbon atom[10]. This crucial question was settled by preparation of the optically active methyl 2,3-dideoxy-α- and β-hex-2-enopyranosid-4-uloses (**4** and **5**) from methyl (*R*)-(−)-(2-furyl)-glycolate **3** of 95% optical purity[12]. Comparison of the optical rotations (for the 6-benzoate **6** of the α anomer) with literature data for methyl 6-*O*-benzoyl-α-D-*glycero*-hex-2-enopyranosid-4-ulose[14], and methyl β-D-*glycero*-hex-2-enopyranosid-4-ulose[15] obtained from D-glucose, demonstrated the enantiomeric relation of the respective compounds and indicated about 90% optical purity in the synthetic samples. Therefore, it could be concluded that the configuration at the carbinol asymmetric center in the starting ester **3** was not altered during the foregoing transformations, and the extent of racemization was small†. This point was clearly demonstrated by completion

*Except in case of the pentoses, namely, when R = H.

†Further experiments, described later, showed that degree of racemization is, in fact, negligible.

of the synthesis of methyl α-L and α-D-glucopyranosides from methyl (*R*)-(−)- (95% optical purity) and (*S*)-(+)-(2-furyl)glycolates (93% optical purity), respectively. The following report pertains to the transformations conducted separately upon both enantiomers of the ester 3 (compare Experimental).

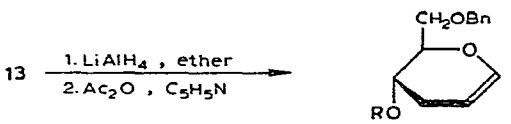


Scheme II (For the sake of simplicity, formulas in this Scheme denote only compounds of the D series)

To avoid undesirable reactions*, the primary hydroxyl group in (2-furyl)-1,2-dihydroxyethane[10] was protected as the benzyl (Bn) ether. To achieve this, methyl (2-furyl)glycolate (3) was converted into the tetrahydropyran-2-yl (THP) derivative 7, which was reduced with lithium aluminum hydride to give the diol 8. The latter, upon treatment with benzyl bromide in the presence of sodium hydroxide, and subsequent acid hydrolysis, gave the benzyl ether 10. Compound 10 reacted with bromine in methanol[17] to yield a mixture of *cis* and *trans* isomers (t.l.c., ^{1}H-n.m.r.) of 2,5-dimethoxy-2,5-dihydrofuran (11). Acid hydrolysis of 11 gave the glycosulose 12, migrating as a single spot in t.l.c. However, its ^{1}H-n.m.r. spectrum revealed the presence of the α and β anomers in approximately 7:3 ratio. Moreover, the anomeric relation of the components was consistent with the mutarotation observed for 12 in chloroform solution.

The next three steps of the synthesis were performed on the mixture of anomers, without separation of the resulting compounds.

2,3-Dideoxyhex-2-enopyranos-4-ulose (12), treated with methyl orthoformate in the presence of boron trifluoride, gave a 7:3 mixture of methyl α- and β-glycosides (13). Treatment of 13 with lithium aluminum hydride at room temperature effected reduction of the carbonyl group, together with reductive rearrangement of the double bond[18], leading to the 3-deoxyglycal 22, which was characterized spectroscopically (i.r. and ^{1}H-n.m.r.) as its 4-acetate[16] 23.



22 R = H
23 R = Ac

On the other hand, reduction of the carbonyl group in 13 with sodium borohydride in THF–water gave a product exhibiting properties consistent with structure 14. The configuration at C-4 in compounds 14 or 15 could not be deduced from ^{1}H-n.m.r. data. However, on the basis of previous studies[11,19], it could be predicted that, for the $^0H_5$(D) [$^5H_0$(L)] conformation, prevailing for both anomers of 13, stereoelectronic factors decidedly favor the approach of a metal hydride from the β side of the pyranoid ring. Consequently, the *erythro* configuration (α and β) was assigned to the carbinols 14.

Epoxidation of 14 with freshly purified *m*-chloroperoxybenzoic acid gave a product consisting essentially of two components (t.l.c.), which were separated by chromatography on a column of silica gel. These compounds and their 4-acetates gave

*Formation of the 1,6-anhydride during glycosidation has already been mentioned[10]; the 3,6-anhydride is formed as the main product during oxirane ring-opening in methyl 2,3-anhydro-α-allopyranoside[20] (an intermediate in the synthesis of methyl glucopyranosides).

TABLE I

^{1}H-N.M.R. CHEMICALS SHIFTS (δ) AND COUPLING CONSTANTS (Hz) FOR COMPOUNDS 12–19

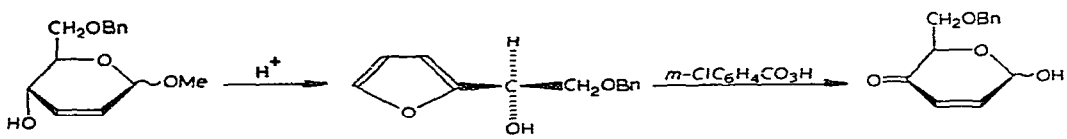
Compound	*Solvent*	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*OMe*	*Other protons*	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$
α-12	$CDCl_3$	5.57	6.95–6.60	6.0		4.70	3.98–3.60		4.52 (s, CH_2); 7.21 (s, Ph)	3.3	[b]	10.4			[b]	[b]
β-12[a]	$CDCl_3$	5.41	6.95–6.60	6.06		4.70	3.98–3.60		4.52 (s, CH_2); 7.21 (s, Ph)	[b]	1.2	10.4			[b]	[b]
α-13	CCl_4	5.02	6.71	5.96		4.42	3.79–3.76	3.48	4.52 (s, CH_2); 7.28 (s, Ph)	3.4	0.5	10.5			[b]	[b]
β-13[a]	CCl_4	5.10	6.74	5.99		4.22	3.79–3.76	3.50	4.52 (s, CH_2); 7.28 (s, Ph)	1.9	1.5	10.5			[b]	[b]
14[a]	$CDCl_3$	α-4.86 β-5.02	5.72	5.93	4.16	3.75	3.75	3.42	4.60 (s, CH_2); 7.35 (s, Ph); 2.91 (s, OH)	[b]	[b]	10.5	[b]	7.5	[b]	[b]
15[a]	CCl_4	α-5.01 β-5.17	5.64		4.62	3.80	3.38	3.27	1.84 (s, α-Ac); 1.82 (s, β-Ac); 4.39 (s, CH_2); 7.08 (s, Ph)	[b]	[b]	[b]	[b]	[b]	[b]	[b]
16	C_6D_6	4.84	3.12	3.17	3.73	3.85	3.62	3.25	4.39 (s, CH_2); 7.17 (s, Ph)	3.0		4.5	1.6	[b]	[b]	[b]
17	C_6D_6	4.49	3.03	3.25	5.06	4.14	3.44	3.26	1.65 (s, OAc); 4.31 (s, CH_2); 7.18 (s, Ph)	3.3		4.2	1.7	9.8	4.0	3.8
18	C_6D_6	4.69	[c]	[c]	4.03		3.47 3.72	3.39	4.51 (s, CH_2); 7.33 (s, Ph)	0			1.6	8.7	[b]	[b]
19	C_6D_6	4.64	3.20	3.38	5.38	3.80	3.51	3.32	1.66 (s, OAc); 4.40 (s, CH_2); 7.28 (s, Ph)	0		4.4	1.7	9.0	4.6	3.4

[a]Measured on the anomeric mixture. [b]Could not be obtained from the spectrum. [c]Obscured by the OMe signal.

analytical and spectral (i.r. and ^{1}H-n.m.r.) data expected for methyl 6-*O*-benzyl-2,3-anhydropyranosides. In the ^{1}H-n.m.r. spectra of the 4-acetates **17** and **19**, the $J_{4,5}$ values of 9.8 and 9.0 Hz, respectively, confirmed that both compounds have the *erythro* configuration and that the pyranoid ring adopts the $^0H_5$(D) [$^5H_0$(L)] conformation. The configuration in the oxirane ring and the stereochemistry of the methoxyl group at C-1 in both compounds **17** and **19** was established unequivocally from the $J_{1,2}$ and $J_{3,4}$ values[20].

In recent studies on the ^{1}H-n.m.r. spectra and conformations of methyl 6-deoxy-2,3-anhydrohexopyranosides[21], we have determined values of the coupling constants for *cis* and *trans* orientations of the H-1–H-2 and H-3–H-4 atoms, which have permitted differentiation of pseudoaxial (*pax*) and pseudoequatorial (*peq*) dispositions of H-1 and H-4. These are as follows: *cis*-$J_{1peq,2}$ 3.1, *cis*-$J_{1pax,2}$ 0.8–1.0, *cis*-$J_{3,4peq}$ 5.4, *cis*-$J_{3,4pax}$ 1.5–1.9, *trans*-$J_{1peq,2}$ 0.6, *trans*-$J_{1pax,2}$ ~0.1, *trans*-$J_{3,4peq}$ ~0.4, and *trans*-$J_{3,4pax}$ ~0 Hz. Comparison of these values with the ^{1}H-n.m.r. data (Table I) of the epoxides obtained established the *α-allo* and *β-allo* configurations for the major (**16**) and minor (**18**) products, respectively.

It should be pointed out that epoxidation of **14** with commercial *m*-chloroperoxybenzoic acid (which contained about 30% of *m*-chlorobenzoic acid as a stabilizer) unexpectedly gave 6-*O*-benzyl-2,3-dideoxy-α- and *β*-hex-2-enopyranos-4-ulose (**12**) as the only product isolated. The same result was obtained when pure *m*-chloroperoxybenzoic acid containing a trace of *p*-toluenesulfonic acid was used. The following rationale for this transformation is offered. The mixture of carbinols (**14**) undergoes acidic degradation to 2-(2-benzyloxy-1-hydroxyethyl)furan (**10**) (the formation of **10** from **14** in the presence of *p*-toluenesulfonic acid was observed in t.l.c.). After oxidation, the furan ring in the latter rearranges to give the glycosulose **12**, a reaction already reported[22] for a number of furylcarbinols.



14 10 12

It is noteworthy that these transformations proceed without loss of optical activity, in accord with earlier observations of the acidic degradation of 2,3-unsaturated sugars to furan compounds[23] and the mechanism suggested by Zamojski *et al.*[24] for this reaction.

Scission of the oxirane ring in 2,3-anhydro sugars having the *α-allo* configuration is not usually regioselective[25,26]. It was observed that base-catalyzed hydrolysis of the anhydride **16** gave two methyl pyranosides in 1:1 ratio (t.l.c.). On the other hand, acid-catalyzed hydrolysis was found to be more regioselective; treatment of **16** with 1% sulfuric acid yielded the same methyl pyranosides but in the ratio of about 9:1.

The main product **20**, after isolation by chromatography on silica gel, exhibited $[\alpha]_D$ −83.1° and $[\alpha]_D$ +82.0° for the L and D series, respectively. Its *α-gluco* configuration was proved by direct comparison (t.l.c., i.r., and ^{1}H-n.m.r. spectroscopy) with an authentic sample of methyl 6-*O*-benzyl-α-D-glucopyranoside ($[\alpha]_D$ +87.1°).

Catalytic hydrogenolysis of the protecting benzyl group in **20** yielded methyl α-L- and α-D-glucopyranosides (**21**), exhibiting optical rotations of $[\alpha]_D$ −150.2 and $[\alpha]_D$ +147.6°, respectively, and i.r. spectra superposable on that of an authentic sample of methyl α-D-glucopyranoside.

The foregoing values for the optical rotations show 95% optical purity of the synthetic methyl α-L-glucopyranoside and 93% for the methyl α-D-glucopyranoside. These values are approximately equal to the optical purity of the corresponding methyl (*R*)- and (*S*)-(2-furyl)glycolates used as starting materials.

CONCLUSION

A general method for stereoselective synthesis of monosaccharides from furan compounds has provided a convenient route to a number of classes of sugar compounds[11,27]. The present paper has described the total synthesis of methyl α-L- and α-D-glucopyranosides from methyl (*R*)- and (*S*)-(2-furyl)glycolates, proceeding without loss of optical purity and with retention of configuration of the asymmetric carbon atom in the starting material. The results demonstrate the applicability of this method to the synthesis of enantiomerically pure sugars of specified absolute configuration.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler block and are uncorrected. Bath temperatures are given for boiling points. I.r. spectra were obtained with a Unicam SP-200 spectrometer, with KBr discs for solids and films for liquids. U.v. spectra were measured for ethanolic solutions with a Unicam SP-500 spectrometer. ^{1}H-N.m.r. spectra were obtained with a Jeol JNM-4H-100 instrument operating at 100 MHz. Optical rotations were measured with a Hilger–Standard polarimeter. Gas–liquid chromatographic analyses were made with Willy Giede gas chromatograph model 18.3. For column chromatography, silica gel Schuchardt (100–200 mesh) was used. All reactions and chromatographic separations were monitored by t.l.c. on silica gel G (E. Merck). Solvents were removed under vacuum.

Experiments performed separately for each enantiomer are described jointly and only the optical rotations observed are reported separately. Elemental analyses are given for compounds of the L series. ^{1}H-N.m.r. data of compounds **12–19** are collected in Table I.

Substrates. — Methyl (*R*)-(−)- and (*S*)-(+)-2-furylglycolate (**3**) were obtained according to the procedure reported[12]: (*R*)-**3**, m.p. 44–45°, $[\alpha]_D$ −132.0° (*c* 0.91, chloroform), 95% optical purity, (*S*)-**3**, m.p. 44–45°, $[\alpha]_D$ +129.0° (*c* 0.93, chloroform), 93% optical purity.

Compounds **4**, **5**, **24**, **25**, and **26** were prepared exactly according to procedures described for the corresponding racemic compounds[10]. They exhibited physical (b.p. and t.l.c. mobility) and spectroscopic (i.r., u.v., and ^{1}H-n.m.r.) properties identical with the latter and gave the following optical rotations: (*S*)-2-(1,2-dihydroxyethyl)furan (**24**), $[\alpha]_D$ −34.3° (*c* 1.1, chloroform), 93.5% optical purity [lit.[23] for (*R*)-2-(1,2-dihydroxyethyl)furan, $[\alpha]_D$ +36.7° (chloroform)]; (*S*)-2-(1,2-*O*-isopropylidene-1,2-dihydroxyethyl)furan (**25**), $[\alpha]_D$ −25.2° (*c* 1.0, chloroform); 2,3-dideoxy-α- and β-L-*glycero*-hex-2-enopyranos-4-ulose (**26**), $[\alpha]_D$ +26.4° (*c* 1.35, water), $[\alpha]_D$ −18.2° (*c* 1.25, chloroform); methyl 2,3-dideoxy-α-L-*glycero*-hex-2-enopyranosid-4-ulose (**4**), m.p. 74–76°, $[\alpha]_D$ −15.6° (*c* 2.11, chloroform); and methyl 2,3-dideoxy-β-L-*glycero*-hex-2-enopyranosid-4-ulose (**5**), $[\alpha]_D$ −34.0° (*c* 1.16, chloroform), $[\alpha]_D$ +12.8° (*c* 1.10, ethanol), 90% optical purity [lit.[28] for methyl 2,3-dideoxy-β-D-*glycero*-hex-2-enopyranosid-4-ulose, $[\alpha]_D$ −14.3° (ethanol)].

Methyl 6-*O*-benzyl-α-D-glucopyranoside*, $[\alpha]_D$ +87.1° (*c* 0.91, chloroform), was obtained by treating methyl α-D-glucopyranoside with one molar equivalent of benzyl chloride and sodium hydroxide in dimethyl sulfoxide, with subsequent chromatographic separation of the main product, which showed the expected spectroscopic (i.r. and ^{1}H-n.m.r.) properties.

*Methyl 6-O-benzoyl-2,3-dideoxy-α-*L-glycero-*hex-2-enopyranosid-4-ulose* (**6**). — A solution of the glycopyranosid-4-ulose **4** (30 mg), benzoyl chloride (33 mg), and pyridine (0.025 ml) in chloroform (3 ml) was kept for two days at room temperature, washed successively with 5% aqueous hydrochloric acid and water, and then evaporated. Preparative t.l.c. (9:1 benzene–ethyl acetate) gave **6** (45 mg, 90%), m.p. 69–70°, $[\alpha]_D$ +6.9° (*c* 0.83, chloroform) of 90% optical purity (Found: C, 64.0; H, 5.6. $C_{14}H_{14}O_5$ calc.: C, 64.1; H, 5.4%). The m.p., and i.r. and u.v. data of **6** were identical with lit.[14] values for methyl 6-*O*-benzoyl-2,3-dideoxy-α-D-*glycero*-hex-2-enopyranosid-4-ulose ($[\alpha]_D$ −7.7° in chloroform).

Methyl (R)- *and* (S)-(*2-furyl*)-O-*tetrahydropyranylglycolate* (**7**). — A solution of the methyl ester **3** (12.95 g, 83 mmol) and *p*-toluenesulfonic acid (0.25 g) was chilled to 0° and 3,4-dihydro-2*H*-pyran (8.4 g, 0.10 mol) was added with stirring while the temperature was maintained below 15°. Stirring was continued for 0.5 h and the solution was diluted with ether (200 ml). It was washed with aqueous sodium hydrogencarbonate and water, and then evaporated. Distillation of the residue gave **7** (18.92 g, 95%), b.p. 110°/0.3 torr, [(*R*)-**7**, $[\alpha]_D$ −68.2° (*c* 2.22, chloroform); (*S*)-**7**, $[\alpha]_D$ +65.4° (*c* 0.91, chloroform)]; ν_{max} 1760 (C=O), 1220, 1200, 1120, and 1040 cm^{-1} (C–O–C); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.40 (m, H-5, furan), 6.40 (m, H-3 and H-4 of furan), 5.34 (s, H-α), 4.76 (m, 1 proton, THP), 3.81 (s, OCH_3) 3.55 (m, 2 protons, THP), and 1.95–1.45 (m, 6 protons, THP) (Found: C, 60.2; H, 6.5. $C_{12}H_{16}O_5$ calc.: C, 60.0; H, 6.7%).

*The preparation of methyl 6-*O*-benzyl-D-glucopyranosides as a mixture of α and β anomers has been reported[29] already.

(S)- *and* (R)*-*2-[1-(1-O-Tetrahydropyranyl-1,2-dihydroxyethyl)]furan* (**8**). — A solution of the ester **7** (16.2 g, 68 mmol) was slowly added to a stirred suspension of lithium aluminum hydride (2.5 g, 0.062 mol) in ether (100 ml). The mixture was cooled in an ice–water bath, and water (2.5 ml), 15% sodium hydroxide (2.5 ml), and water (7.5 ml) were added in succession. The precipitate was filtered off and washed with ethyl acetate (100 ml). Evaporation of the combined solvents gave **8** (14.4 g, 100%), b.p. 100°/0.3 torr, [(*S*)-**8**, $[\alpha]_D$ −37.8° (*c* 1.38, chloroform); (*R*)-**8**, $[\alpha]_D$ +35.4° (*c* 0.69, chloroform)]; ν_{max} 3450 (OH), 1120, 1025, 985 (C–O–C), 1505, and 880 cm^{-1} (furan); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.34 (dd, H-5 of furan), 6.30 (m, H-3, H-4 of furan), 4.82 (t, $J_{1,2}$ 2.2 Hz, H-1), 4.59 (m, 1 proton, THP), 3.84 (d, 2 protons, $J_{1,2}$ 2.2 Hz, H-2, H-2'), 4.05–3.50 (m, 2 protons, THP), 2.82 (s, OH), and 1.8–1.4 (m, 6 protons, THP) (Found: C, 62.3; H, 8.0. $C_{11}H_{16}O_4$ calc.: C, 62.2; H, 7.6%).

2-[1-(2-O-Benzyl-1-O-tetrahydropyranyl-1,2-dihydroxyethyl)]furan (**9**). — A solution of the diol **8** (14.2 g, 59 mmol) in dimethyl sulfoxide (100 ml) was stirred under nitrogen for 0.5 h with a solution of sodium hydroxide (4.5 g, 0.113 mol) in dimethyl sulfoxide (80 ml). Benzyl chloride (8.3 g, 0.065 mol) was added dropwise, stirring was continued for 24 h, and the mixture was poured on ice–water and extracted with ether. Evaporation of the solvents and distillation afforded the ether **9** (15.5 g, 87%) b.p. 155°/0.3 torr, [(*S*)-**9**, $[\alpha]_D$ −41.6° (*c* 1.54, chloroform); (*R*)-**9**, $[\alpha]_D$ +39.9° (*c* 0.71, chloroform)]; ν_{max} 1505, 880 (furan), 1460, 740, 695 (Ph), 1200, 1120, and 1025 cm^{-1} (C–O–C); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.35 (m, 6 protons, Ph and H-5 of furan), 6.34 (m, H-2 and H-3 of furan), 4.95 (m, H-1), 4.59 (s, 2 protons, CH_2 of benzyl), 4.57 (m, 1 proton, THP), 4.2–3.3 (m, 2 protons, THP), and 2.0–1.0 (m, 6 protons, THP) (Found: C, 71.7; H, 7.2. $C_{18}H_{22}O_4$ calc.: C, 71.5; H, 7.3%).

2-[1-(2-O-Benzyl-1,2-dihydroxyethyl)]furan (**10**). — The THP derivative **9** (12.8 g, 42 mmol) was treated at room temperature with *p*-toluenesulfonic acid (0.4 g) in abs. methanol. After 3 h the mixture was made neutral with triethylamine and then evaporated. The residue was diluted with ether, and the solution was washed with water, dried, and evaporated. Distillation yielded the benzyl ether **10** (9.0 g, 98%), b.p. 120°/0.2 torr, [(*S*)-**10**, $[\alpha]_D$ −16.5° (*c* 0.58, chloroform); (*R*)-**10**, $[\alpha]_D$ +15.3° (*c* 0.59, chloroform)]; ν_{max} 3450 (OH), 1505, 890 (furan), 1460, 745, 700 (Ph), 1150, 1120, and 1020 cm^{-1} (C–O–C); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.24 (m, 6 protons, Ph and H-5 of furan), 6.22 (d, 2 protons, *J* 1.4 Hz, H-3 and H-4 of furan), 4.86 (t, $J_{1,2}$ 5.7 Hz, H-1), 4.53 (s, 2 protons, CH_2 of benzyl), 3.34 (d, 2 protons, H-2 and H-2'), and 2.90 (s, OH) (Found: C, 71.6; H, 6.5. $C_{13}H_{14}O_3$ calc.: C, 71.5; H, 6.5%).

2-[1-(2-O-Benzyl-1,2-dihydroxyethyl)]-2,5-dimethoxy-2,5-dihydrofuran (**11**). — The ether **10** (9.0 g, 41 mmol) afforded[10] **11** (10.0 g, 87.5%), b.p. 160°/0.2 torr, [(*S*)-**11**, $[\alpha]_D$ −4.9° (*c* 1.21, chloroform); (*R*)-**11**, $[\alpha]_D$ +4.6° (*c* 0.73, chloroform)];

*Note the change of the notation (*R*, *S*) for the absolute configuration for the corresponding enantiomers of **7** and **8**.

ν_{max} 3480 (OH), 1630 (C=C), 1460, 740, 695 (Ph), 1120, 1095, 1020, and 980 cm^{-1} (C–O–C); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.25 (s, 5 protons, Ph), 6.2–5.8 (m, 2 protons, $J_{3,4}$ 5.9 Hz, H-3 and H-4 of dihydrofuran), 5.61 (t, H-5 of *trans*-dihydrofuran), 5.42 (t, H-5 of *cis*-dihydrofuran), 4.38 (s, 2 protons, CH_2 of benzyl), 3.90–3.50 (m, 3 protons, H-1, H-2, H-2'), 3.49, 3.18 (2×s, OCH_3 *cis*), 3.40, 3.09 (2×s, OCH_3 *trans*), and 2.62 (s, OH) (Found: C, 64.0; H, 7.1. $C_{15}H_{20}O_5$ calc.: C, 64.2; H, 7.2%).

*6-O-Benzyl-2,3-dideoxy-α- and β-*glycero*-hex-2-enopyranos-4-ulose* (**12**). — The carbinol **11** (6.6 g, 23.5 mmol), dissolved in acetic acid (13 ml), was treated with 1% sulfuric acid (6.5 ml) for 3 h at room temperature, and then brought to pH 4.5–5.0 with aqueous sodium hydrogencarbonate. The product was extracted with ethyl acetate. Evaporation of the extract gave the homogeneous (t.l.c.) glycosulose **12** (5.5 g, 100%), b.p. 175°/0.3 torr, [L-**12**, $[\alpha]_D$ −23.0° (*c* 0.94, chloroform), after 6 h −61.7°; D-**12**, $[\alpha]_D$ +61.6° (after 5 h, *c* 1.32, chloroform)]; ν_{max} 3450 (OH), 1690, 1630 (O=C–C=C), 1460, 740, and 695 cm^{-1} (Ph) (Found: C, 65.9; H, 6.1. $C_{13}H_{14}O_4$ calc.: C, 66.6; H, 6.0%).

*Methyl 6-O-benzyl-2,3-dideoxy-α- and β-*glycero*-hex-2-enopyranosid-4-uloses* (**13**). — A solution of the glycopyranos-4-ulose **12** (5.35 g, 21.8 mmol) and trimethyl orthoformate (5.50 g, 50.9 mmol) in ether (200 ml) was treated with boron trifluoride etherate (0.5 ml) at room temperature. After 2 h, the mixture was neutralized with triethylamine, washed with water, dried, and evaporated. Distillation yielded the glycopyranosid-4-uloses **13** (5.1 g, 94%) b.p. 160°/0.1 torr, [L-**13**, $[\alpha]_D$ −8.1° (*c* 0.75, chloroform); D-**13**, $[\alpha]_D$ +7.7° (*c* 0.52, chloroform)]; ν_{max} 1695, 1635 (O=C–C=C), 1460, 745, 700 (Ph), 1105, and 1050 cm^{-1} (C–O–C); λ_{max}^{EtOH} 217 (ε 4600), 282 nm (1080) (Found: C, 67.7; H, 6.5. $C_{14}H_{16}O_4$ calc.: C, 67.7; H, 6.5%).

*Methyl 6-O-benzyl-2,3-dideoxy-α- and β-*erythro*-hex-2-enopyranosides* (**14**). — The methyl glycosides **13** (5.0 g, 20 mmol) in THF (100 ml) were added dropwise to a chilled (ice–water bath) solution of sodium borohydride (0.40 g, 10 mmol) in water (60 ml). After stirring for 0.5 h, the mixture was made neutral with acetic acid and extracted with ethyl acetate. Evaporation of the solvent and chromatography of the residue (4.7 g) on a column of silica gel (100 g) with 9:1 benzene–ether gave the alcohols **14** (3.15 g, 63%), b.p. 170°/0.2 torr, [L-**14**, $[\alpha]_D$ −21.0° (*c* 0.46, chloroform); D-**14**, $[\alpha]_D$ +17.6° (*c* 0.94, chloroform)]; ν_{max} 3450 (OH), 1460, 735, 695 (Ph), 1100, 1050, and 965 cm^{-1} (C–O–C) (Found: C, 67.3; H, 7.3. $C_{14}H_{18}O_4$ calc.: C, 67.2; H, 7.3%). Examination of the trimethylsilyl ethers[30] of **14** by g.l.c. showed a ratio of 2:1 for the α and β anomers and the presence of a third compound (~10%), presumably the *β-threo* isomer.

*Methyl 4-O-acetyl-6-O-benzyl-2,3-dideoxy-α- and β-*erythro*-hex-2-enopyranosides* (**15**). — The alcohols **14**, treated with 1:1 acetic anhydride–pyridine at room temperature afforded the acetates **20**, b.p. 165°/0.4 torr, ν_{max} 1740, 1235 (OAc), 1460, 735, 695 (Ph), 1100, 1045, and 965 cm^{-1} (C–O–C) (Found: C, 65.2; H, 7.1. $C_{16}H_{20}O_5$ calc.: C, 65.7; H, 6.9%).

Methyl 2,3-anhydro-6-O-benzyl-α- and β-allopyranoside (**16**) *and* (**18**). — A

solution of the alcohols **14** (1.70 g, 6.8 mmol) in dichloromethane (30 ml) was stirred for 4 days with freshly purified *m*-chloroperoxybenzoic acid (1.3 g, 8.0 mmol) at room temperature. The solvent was evaporated off and the residue redissolved in benzene. The solution was washed with aqueous sodium hydrogencarbonate, evaporated, and the resulting syrup adsorbed on a column of silica gel (35 g). Elution with 9:1 benzene–ether and combination of appropriate (t.l.c.) fractions gave the *β-allo* epoxide **18**, (0.214 g, 12%) b.p. 180°/0.05 torr, [L-**18**, $[\alpha]_D$ +19.5° (*c* 1.61, chloroform)]; ν_{max} 3450 (OH), 1460, 745, 700 (Ph), 1120, 1080, 1005 (C–O–C), 1210, 860, and 820 cm^{-1} (epoxide) (Found: C, 62.9; H, 7.0. $C_{14}H_{18}O_5$ calc.: C, 63.1; H, 6.8%).

Further elution of the column with the same solvent afforded the *α-allo* epoxide **16** (0.85 g, 47%) b.p. 190°/0.2 torr, [L-**16**, $[\alpha]_D$ −93.9° (*c* 0.61, chloroform); D-**16**, $[\alpha]_D$ +91.0° (*c* 1.04, chloroform)]; ν_{max} 3450 (OH), 1460, 740, 695 (Ph), 1150, 1100, 1065, 990 (C–O–C), 1250, and 910 cm^{-1} (epoxide) (Found: C, 63.0; H, 6.8. $C_{14}H_{18}O_5$ calc.: C, 63.1; H, 6.8%).

Methyl 4-O-acetyl-2,3-anhydro-6-O-benzyl-β-allopyranoside (**19**). — This product had b.p. 190°/0.5 torr, [L-**19**, $[\alpha]_D$ −40.4° (*c* 0.99, chloroform)]; ν_{max} 1740, 1240 (OAc), 1460, 755, 700 (Ph), 1125, 1090, 1005 (C–O–C), 860, and 820 cm^{-1} (epoxide) (Found: C, 62.2; H, 6.6. $C_{16}H_{20}O_6$ calc.: C, 62.3; H, 6.5%).

Methyl 4-O-acetyl-2,3-anhydro-6-O-benzyl-α-allopyranoside (**17**). — This compound had b.p. 190°/0.4 torr, ν_{max} 1740, 1240 (OAc), 1460, 745, 700 (Ph), 1150, 1120, 1080, 1040 (C–O–C), 1250, and 920 cm^{-1} (epoxide) (Found: C, 62.0; H, 6.5. $C_{16}H_{20}O_6$ calc.: C, 62.3; H, 6.5%).

Methyl 6-O-benzyl-α-glucopyranoside (**20**). — Epoxide **16** (688 mg, 2.6 mmol) was heated to boiling with 1% sulfuric acid (7 ml) under reflux for 3 h. The solution was chilled, neutralized with aqueous barium hydroxide, filtered, and evaporated. the residue (780 mg) was resolved on a column of silica gel (16 g). Elution with 19:1 benzene–methanol afforded methyl 6-*O*-benzyl-α-altropyranoside (44 mg, 6.1%) and then the glucoside **20** (396 mg, 55%). The latter, after distillation, had b.p. 200°/0.3 torr, and it solidified; m.p. 58–60°, [L-**20**, $[\alpha]_D$ −83.1° (*c* 0.81, chloroform) (95.4% optical purity); D-**20**, $[\alpha]_D$ +82.0° (*c* 0.63, chloroform) (94.1% optical purity)]; ν_{max} 3450 (OH), 1460, 755, 720, 700 (Ph), 1160, 1060, and 1010 cm^{-1} (C–O–C) (Found: C, 59.1; H, 7.4. $C_{14}H_{20}O_6$ calc.: C, 59.1; H, 7.1%).

Methyl α-glucopyranoside (**21**). — A suspension of palladium oxide (60 mg) in acetic acid (5 ml) was agitated in an atmosphere of hydrogen for 6 h, the glucoside **20** (155 mg) in acetic acid (10 ml) was added, and hydrogenation was continued for 12 h. The catalyst was filtered off and the solvent evaporated to yield **21** (95 mg, 89%), which solidified. Recrystallization from methanol afforded: methyl α-L-glucopyranoside, m.p. 166–167°, $[\alpha]_D$ −150.2° (*c* 0.50, water), 95% optical purity; or methyl α-D-glucopyranoside, m.p. 165–167°, $[\alpha]_D$ +147.6° (*c* 0.91, water), 93% optical purity. Both synthetic methyl α-glucopyranosides gave i.r. (KBr) spectra superposable on that of methyl α-D-glucopyranoside ($[\alpha]_D$ +158.2°) obtained from natural D-glucose.

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