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Hydrogenolysis of the 4,6-*O*-Ketals of Glucopyranosides. Configuration-Dependent High Regio- and Stereo-selectivity of the Diastereoisomeric Acetophenone Derivatives*

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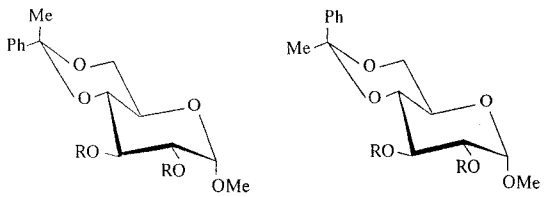
Hydrogenolysis (reductive cleavage) of the (*R*) isomers of the acetophenone 4,6-*O*-derivatives of glucopyranosides with $LiAlH_4/AlCl_3$ gives the 4-*O*-(1′-phenylethyl) ethers with (*R*) configuration; the corresponding (*S*) isomers produce the respective (*R*) 6-*O*-(1′-phenylethyl) ethers are produced. The hydrogenolysis of other 4,6-*O*-ketals affords O 4 ether derivatives; the two diastereoisomeric 4,6-*O*-s-butylidene derivatives (cyclic ketals) give O 4-ethers with the opposite absolute configuration. The stereoselectivity of these reactions is explained by the development of a four-centre transition state. The absolute configuration of the ethers has been determined by means of circular dichroism measurements.

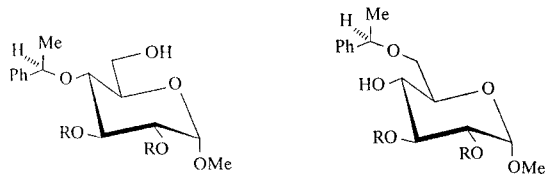
Introduction

Previous reports[1,2] on the reaction of glucopyranosides with acetophenone claimed the formation of a single product, and the configuration at the chiral centre of the dioxan skeleton was assigned as (*R*), so as to carry *equatorial* phenyl and *axial* methyl groups. Our detailed studies on this reaction demonstrated the presence of an unstable kinetic and a very stable thermodynamic product, and on the basis of spectroscopic investigations[3] the (*R*) and (*S*) absolute configuration, respectively, was assigned to the kinetic and the final, thermodynamic product—thus the earlier assignation of the configuration was disproved. These results have also been supported by X-ray measurements.[4]

The hydrogenolysis (reductive cleavage) of the diastereoisomeric acetals with the $LiAlH_4/AlCl_3$ reagent showed high regio- and stereo-selectivity: the thermodynamic and the kinetic products afforded 6-*O*-(1′-phenylethyl) and 4-*O*-(1′-phenylethyl) ethers, respectively. The formation was detected in each case of a single diastereoisomer, whose absolute configuration was supposed to be (*R*). In the present paper this supposition is substantiated with circular dichroism measurements and chemical transformation. However, despite numerous attempts, the reason for the high regioselectivity still cannot be explained.



(1) (3) (5) R = H, R = Me, R = $PhCH_2$ (2) (4) (6)



(7) (9) R = Me, R = $PhCH_2$ (8) (10)

* Dedicated to Professor Stephen J. Angyal on the occasion of his 80th birthday.

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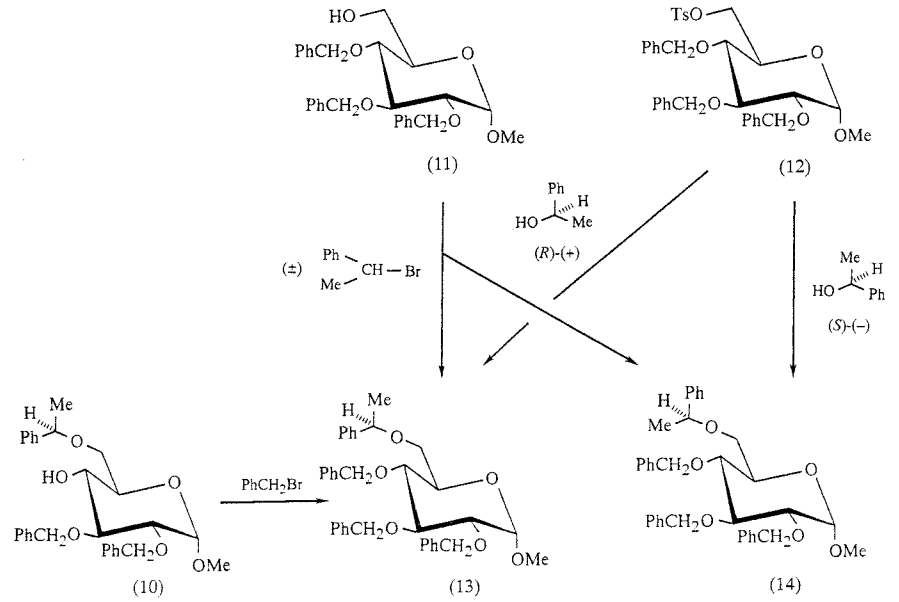
Discussion

The preparation of the acetophenone ketals (1)–(6) was carried out as described in a previous paper,[3] and the hydrogenolysis of (3)–(6) gave the ethers (7)–(10). The physical constants, the data of the fully assigned ^{13}C n.m.r. spectra and the ^{1}H n.m.r. chemical shift values of the protons of certain characteristic functional groups have been summarized.[3]

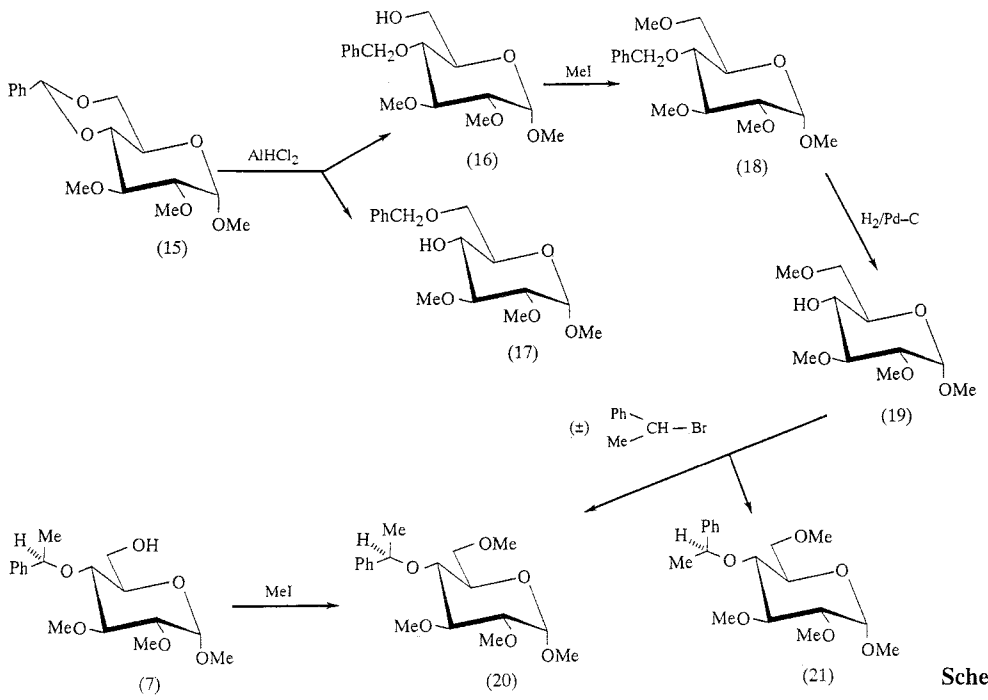
Although the n.m.r. data provided unequivocal information about the regioselectivity of the reductive cleavage reaction, no explanation was obtained for the stereoselectivity. From a knowledge of the optical rotation values[5] of the 1-phenylethanol enantiomers, an (*R*) configuration was assigned to both ether series on the basis of optical superposition theory.[6]

For the determination of the absolute configuration of the ether derivatives obtained the following experiments were carried out. Methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[7] (11) was tosylated and the resulting ester (12)[8] was treated, separately, with (*R*)-(+)- and (*S*)-(−)-1-phenylethanol. Of the products (13) and (14) from the S_N2-type reaction the former proved to be identical with the compound synthesized by the benzylation of (10). When (11) was alkylated with (±)-1-phenylethyl bromide[9] a mixture of (13) and (14) was isolated and the two diastereoisomers were separated by chromatography (see Scheme 1).

Since it appeared rather tedious to find similar convincing chemical evidence in the case of the 4-*O*-(1′-phenylethyl) ethers, our only goal was to distinguish between the two diastereoisomers occasionally



Scheme 1



Scheme 2

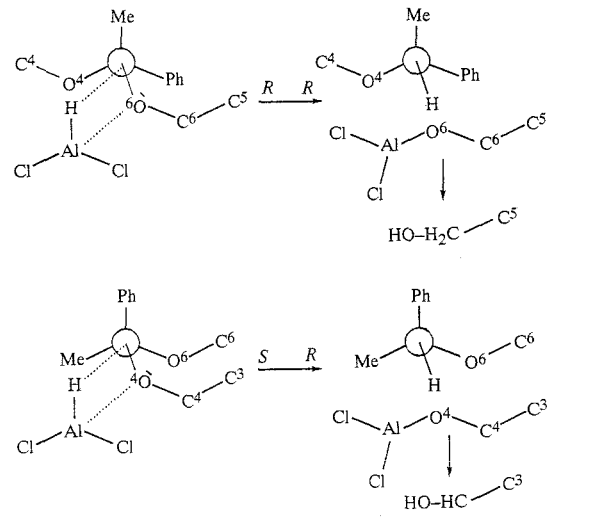
produced upon hydrogenolysis of the (*R*) isomers (3) and (5) by applying both chromatographic and spectroscopic methods. For these experiments methyl 2,3,6-tri-*O*-methyl-α-D-glucopyranoside[10] (19), lacking a chromophore, was selected and synthesized as follows. Hydrogenolysis of methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside[11] (15) gave a 77:23 mixture of the crystalline methyl 4-*O*-benzyl-2,3-di-*O*-methyl-α-D-glucopyranoside (16) and the corresponding syrupy 6-*O*-benzyl derivative (17). Methylation of (16) furnished (18), which was converted into (19) upon removal of the benzyl group with catalytic hydrogenation. Alkylation of (19) with (±)-1-phenylethyl bromide gave the respective two diastereoisomers (20) and (21), which could be identified according to the ^{1}H n.m.r. spectrum and separated by means of chromatography. Methylation of (7), obtained by hydrogenolysis of (3), gave (20) with higher chromatographic mobility (see Scheme 2).

For (7) the final determination of the configuration was carried out by circular dichroism measurements. The circular dichroism parameters of (*R*)-(+)- and (*S*)-(−)-1-phenylethanol were measured and compared with those of compounds (7) and (8) (see Table 1). The results unequivocally prove that the configuration of the newly developed chiral centre is *R* in both series of the ethers produced upon reductive ring cleavage of the ketal.

Table 1. Circular dichroism parameters (Δε) of (*R*)- and (*S*)-1-phenylethanol (A) and (B), and 1′-phenylethyl ethers (7) and (8)

λ (nm)	(A)	(B)	(7)	(8)
268	−0·10	+0·14	−0·14	−0·16
261	−0·12	+0·16	−0·15	−0·16
256	−0·09	+0·11	−0·09	−0·13

The observed high stereoselectivity provides new insights of the mechanism of the hydrogenolysis of dioxan-type acetals; these were inaccessible with the same ring opening of benzylidene acetals. The experimental facts that from an (*S*)-acetal an ether is produced with an (*R*)-configuration (with inversion), and that an (*R*)-acetal gives an (*R*)-ether (with retention), suggest that a mechanism involving the so-called oxocarbonium-type intermediate is to be rejected, since in such a case racemization of both centres should have occurred. A process starting with an oxocarbonium intermediate combined with a push–pull mechanism is not probable either, as this would be accompanied by inversion at both centres. The observed product ratio corresponds to a four-centre[12] intermediary state, where the hydride anion is provided by the coordinating chloroalane, and the C–H bond forms simultaneously with cleavage of the C–O bond from the direction of this original bonding (see Scheme 3).



Scheme 3. Four-centre mechanism in the case of acetophenone acetals.

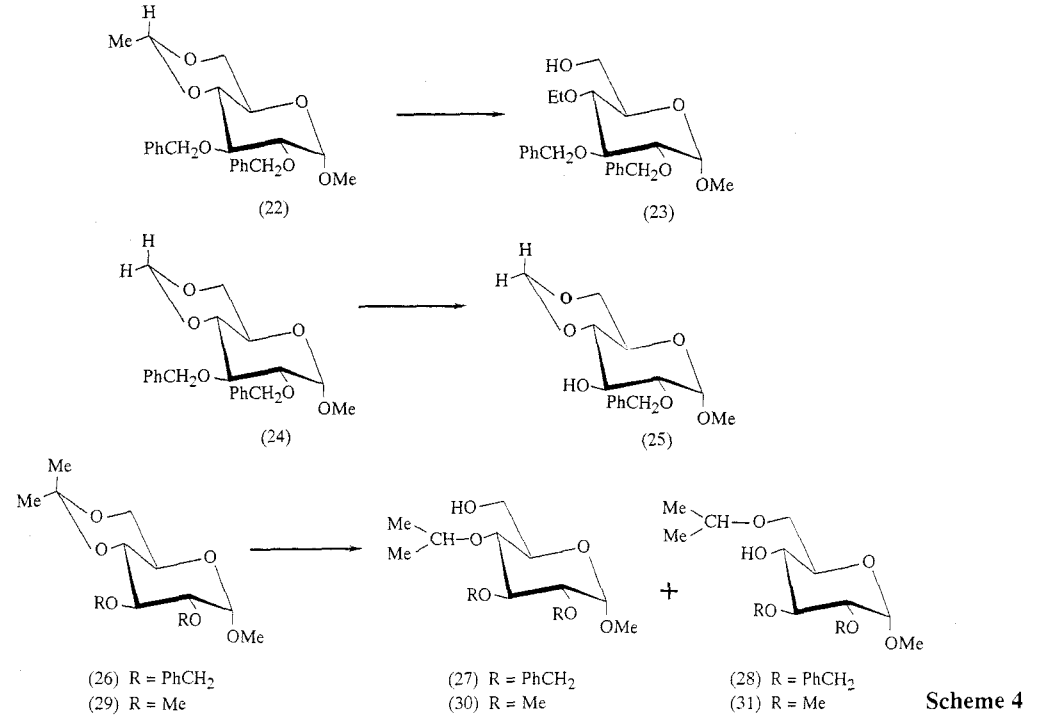
The other crucial question in the hydrogenolysis of the acetals is the regioselectivity. According to recent knowledge regioselectivity is influenced by the electronic effects[13] determining the stability of the oxocarbonium ion, π-interactions,[14] differences in the electron density of the acetal oxygen atoms,[15] or steric factors.[16] In the case of the 4,6-*O*-benzylidene derivatives of hexopyranosides steric effects, and particularly the steric bulk of the C3 substituent,[17] have been considered as the most important factor. Under the reaction conditions employed the only exceptions were the acetophenone derivatives. It is to be noted, however, that the hydrogenolysis of the diastereoisomeric pairs into the corresponding ethers is completed at different rates: the (*R*)-acetals afforded the 4-*O*-ethers in 5 min with quantitative yield, whereas the formation of the 6-*O*-ethers from the (*S*)-acetals required a reaction time of 40–45 min.[3]

For studying factors influencing the regioselectivity of the hydrogenolysis of acetals and ketals the following experiments were carried out (see Scheme 4). Cleavage of methyl 2,3-di-*O*-benzyl-4,6-*O*-ethylidene-α-D-glucopyranoside (22) gave a 9:1 product mixture, from which the major product, methyl 2,3-di-*O*-benzyl-4-*O*-ethyl-α-D-glucopyranoside (23), was isolated as crystals in 79% yield. The regioselectivity of this reaction was essentially similar to those of the corresponding benzylidene acetals.[17] The hydrogenolysis of certain ketal derivatives was also investigated. Thus, hydrogenolysis of methyl 2,3-di-*O*-benzyl-4,6-*O*-methylene-α-D-glucopyranoside[18] (24) for 56 h resulted only in a 30% conversion, and, instead of the formation of the expected methyl ether, cleavage of the C3 benzyl ether function was observed and crystalline methyl 2-*O*-benzyl-4,6-*O*-methylene-α-D-glucopyranoside (25) was isolated.

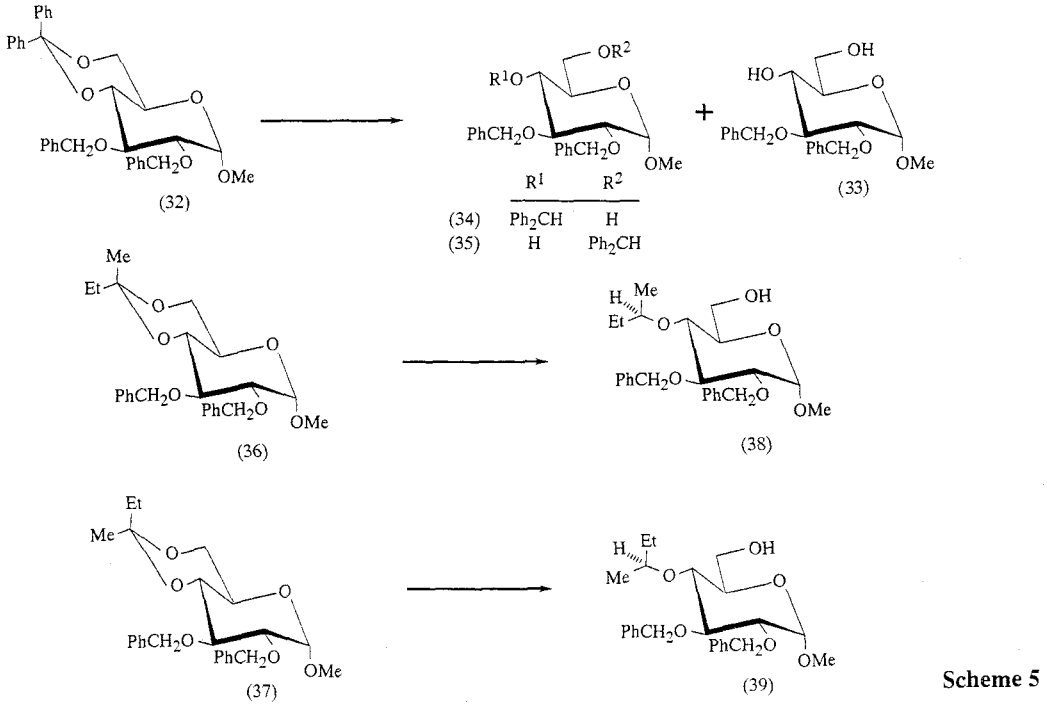
Hydrogenolysis of methyl 2,3-di-*O*-benzyl-4,6-*O*-isopropylidene-α-D-glucopyranoside[19] (26) furnished a 93:7 (g.l.c.) mixture where the crystalline 4-*O*-isopropyl

ether (27) was the major product and the minor product, the 6-*O*-isopropyl derivative (28), could also be isolated by chromatography. For investigating the effect of the steric bulk of the C3 substituent the cleavage of methyl 4,6-*O*-isopropylidene-2,3-di-*O*-methyl-α-D-glucopyranoside[20] (29) was also carried out, and the ratio of the 4-*O*-isopropyl (30) and 6-*O*-isopropyl (31) ethers produced was found to be 58 : 42 (g.l.c.), thus essentially similar to that observed for the corresponding 4,6-*O*-benzylidene acetals.[17]

Then we were looking forward to the hydrogenolysis of methyl 2,3-di-*O*-benzyl-4,6-*O*-diphenylmethylene-α-D-glucopyranoside (32), which was prepared from methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[21] (33) and dichlorodiphenylmethane. It had been shown previously that the diphenylmethyl ethers, produced upon hydrogenolysis of diphenylmethylene acetals, can be cleaved[22] with dichloroalane; therefore the hydrogenolysis of (32) was performed with chloroalane. The conversion was still very low (40%) since a significant



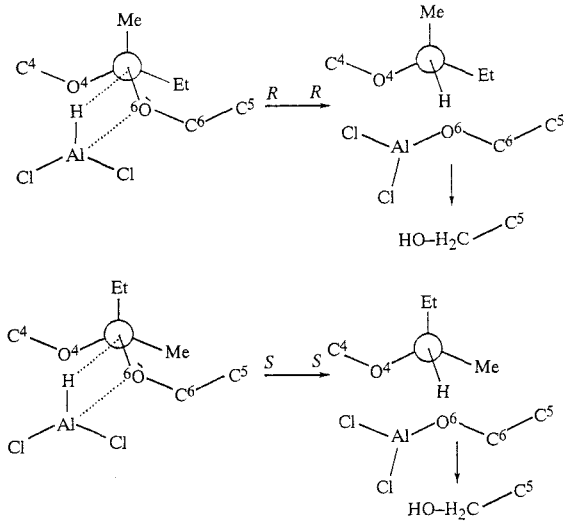
Scheme 4



Scheme 5

quantity of (33) was regenerated. The exclusive product of the hydrogenolysis was methyl 2,3-di-*O*-benzyl-4-*O*-diphenylmethyl-α-D-glucopyranoside (34). The hydrogenolysis of (32) was also accomplished by Garegg's method[23] with $NaCNBH_3$–HCl reagent, and its exclusive product was the 6-*O*-diphenylmethyl ether (35). These reactions did not provide further data concerning the regioselectivity of the process (see Scheme 5).

As the ketals investigated above were of a symmetric structure, we were interested in whether the high stereoselectivity remains in the case of ketals carrying a chiral centre but missing the aromatic substituent. Thus, compound (33) was treated with 2,2-dimethoxybutane and the resulting two diastereoisomers (36) and (37) were separated by chromatography. The assignment of the configuration was carried out according to the ^1H and ^{13}C n.m.r. chemical shift values. Hydrogenolysis of (36) and (37) gave the diastereoisomeric 4-*O*-s-butyl ethers, and the homogenity of the diastereoisomers was assigned on the basis of the methyl proton of the new ether group.



Scheme 6. Four-centre mechanism in the case of s-butylidene acetals.

According to the reaction mechanism proposed for the acetophenone derivatives the absolute configuration of the s-butyl ethers produced can also be determined. It is established that the hydrogenolysis of both ketals proceeded with retention of configuration. Thus, from (*R*)-(36) and (*S*)-(37) methyl 2,3-di-*O*-benzyl-4-*O*-[(*R*)-s-butyl]-α-D-glucopyranoside (38) and the (*S*)-ether 39, respectively, are formed (see Schemes 5 and 6).

Experimental

General Methods

Solutions were concentrated at 40°C (bath) under diminished pressure. Chromatography was performed on Kieselgel 60. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter at room temperature for solutions in $CHCl_3$. The ^1H (200 MHz) and ^{13}C n.m.r. (50·3 MHz) spectra were recorded with a Bruker WP-200 SY spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Melting points were determined on a Kofler apparatus and are uncorrected. T.l.c. was performed on Kieselgel 60 F_{254} (Merck) with *A*, 7:3 hexane/EtOAc; *B*, 85:15 hexane/EtOAc; *C*, 95:5 CH_2Cl_2/EtOAc; *D*, 8:2 CH_2Cl_2/EtOAc; *E*, 9:1 CH_2Cl_2/acetone; *F*, 7:3 EtOAc/hexane, with detection by ultraviolet light and/or charring with sulfuric acid.

Methyl 2,3,4-Tri-O-benzyl-6-O-[(R)-1′-phenylethyl]-α-D-glucopyranoside (13) and Methyl 2,3,4-Tri-O-benzyl-6-O-[(S)-1′-phenylethyl]-α-D-glucopyranoside (14)

(A) To a stirred solution of (12) (619 mg, 1 mmol) in dry *N,N*-dimethylformamide (5 ml) were added, separately, (*R*)-(+)- and (*S*)-(−)-1-phenylethanol (0·14 ml, 1·2 mmol) at 90°C. After 20 h, the reaction mixtures were diluted with CH_2Cl_2, washed twice with water, dried (Na_2SO_4) and concentrated. The resulting syrups were purified by column chromatography (solvent *A*) to give (13) (R_F 0·66) and (14) (R_F 0·70).

Compound (13) had $[\alpha]_D$ +28° (*c*, 1·0) (Found: C, 76·0; H, 7·1. $C_{36}H_{40}O_6$ requires C, 76·0; H, 7·1%). ^1H n.m.r.: δ 4·66, q, 1H, CH_3CHPh; 1·45, d, 3H, CH_3CHPh. ^{13}C n.m.r.: δ 78·54, CH_3CHPh; 23·67, CH_3CHPh.

Compound (14) had $[\alpha]_D$ −11° (*c*, 1·0) (Found: C, 76·0; H, 7·2. $C_{36}H_{40}O_6$ requires C, 76·0; H, 7·1%). ^1H n.m.r.: δ 4·32, q, 1H, CH_3CHPh; 1·42, d, 3H, CH_3CHPh. ^{13}C n.m.r.: δ 78·94, CH_3CHPh; 24·01, CH_3CHPh.

(B) To a stirred solution of (11) (417 mg, 0·90 mmol) and KOH (210 mg, 4 equiv.) in dry *N,N*-dimethylformamide (3 ml) was added (±)-1-phenylethyl bromide (0·25 ml, 2 equiv.). The mixture was stirred for 60 min at room temperature, then diluted with EtOAc, washed with water until neutral, and concentrated to give a mixture of (13) and (14). The resulting crude syrup was purified by column chromatography (solvent *A*).

Methyl 4-O-Benzyl-2,3-di-O-methyl-α-D-glucopyranoside (16) and Methyl 6-O-Benzyl-2,3-di-O-methyl-α-D-glucopyranoside (17)

The method used for the conversion of (22) into (23) was applied to (15) to give a 77:23 mixture of (16) and (17) (g.l.c.). Recrystallization of the crude product from 1:4 EtOAc/cyclohexane gave (16) (65%), R_F 0·32 (solvent *E*), m.p. 96–97°C (Found: C, 61·5; H, 7·8. $C_{16}H_{24}O_6$ requires C, 61·5; H, 7·7%). $[\alpha]_D$ +136° (*c*, 0·63).

The mother liquor was concentrated and the residue was purified by column chromatography to give (17) (12%), R_F 0·40 (solvent *E*); $[\alpha]_D$ −103° (*c*, 0·69).

Methyl 4-O-Benzyl-2,3,6-tri-O-methyl-α-D-glucopyranoside (18)

To a stirred solution of (16) (1·07 g, 3·42 mmol) and KOH (390 mg, 2 equiv.) in dry dimethyl sulfoxide was added MeI (0·85 ml, 4 equiv.). The mixture was stirred for 2 h at room temperature, then diluted with CH_2Cl_2, and washed with water (5×30 ml) until neutral. The organic layer was dried (Na_2SO_4) and concentrated. The resulting crude syrup was purified by column chromatography to give (18) (1·0 g, 90%), R_F 0·36 (solvent *D*); $[\alpha]_D$ +115° (*c*, 1·19) (Found: C, 62·5; H, 8·1. $C_{17}H_{26}O_6$ requires C, 62·6; H, 8·0%).

Methyl 2,3,6-Tri-O-methyl-α-D-glucopyranoside (19)

To a solution of (18) (653 mg, 2 mmol) in 1:1 EtOH/EtOAc (30 ml) were added acetic acid (3 ml) and 10% Pd–C (100 mg). Hydrogenolysis was performed at atmospheric pressure of H_2 for 5 h; the mixture was filtered and concentrated. From the residue toluene (3×10 ml) was evaporated to yield (19).[10]

Methyl 2,3,6-Tri-O-methyl-4-O-[(R)-1′-phenylethyl]-α-D-glucopyranoside (20) and Methyl 2,3,6-Tri-O-methyl-4-O-[(S)-1′-phenylethyl]-α-D-glucopyranoside (21)

(A) The method used for the conversion of (11) was applied to (19) to give (20) and (21). Column chromatography (solvent *F*) of the crude product gave (20) (38%) and (21) (29%).

Compound (20) had $[\alpha]_D$ +154° (*c*, 1·0) (Found: C, 63·4; H, 8·3. $C_{18}H_{28}O_6$ requires C, 63·5; H, 8·3%). ^{1}H n.m.r.: δ 1·51, d, 3H, C**H**$_3$CHPh. ^{13}C n.m.r.: δ 97·41, C 1; 83·96, C 2; 82·26, C 3; 79·32, CH_3**C**HPh; 75·59, C 4; 70·78, C 5; 69·90, C 6; 23·49, **C**H_3CHPh.

Compound (21) had $[\alpha]_D$ +126° (*c*, 1·0) (Found: C, 63·6; H, 8·3. $C_{18}H_{28}O_6$ requires C, 63·5; H, 8·3%). ^{1}H n.m.r.: δ 1·45, d, 3H, C**H**$_3$CHPh.

(B) The method used for the conversion of (16) into (18) was applied to (7) to give (20). Column chromatography (solvent *F*) of the crude product gave (20) (85%).

Methyl 2,3-Di-O-benzyl-4,6-O-ethylidene-α-D-glucopyranoside (22)

To a stirred solution of (33) (2·0 g, 5·34 mmol) in acetaldehyde dimethyl acetal (3 ml) was added *p*-toluenesulfonic acid (20 mg). After 2 h the mixture was diluted with CH_2Cl_2 (50 ml), then washed successively with aqueous 5% $NaHCO_3$ (3×10 ml) and water (3×10 ml) until neutral, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography to give (22) (0·85 g, 69%), R_F 0·67 (solvent *A*); $[\alpha]_D$ +19° (*c*, 1·16) (Found: C, 69·0; H, 7·1. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·1%). ^{1}H n.m.r.: δ 7·40–7·20, m, 10H, aromatic; 4·80, s, 2H, CH_2Ph; 4·71, q, 2H, CH_2Ph; 4·66, q, 1H, C**H**CH_3; 4·50, d, 1H, H 1; 4·02, dd, 1H, H 2; 3·90, t, 1H, H 3; 3·70–3·30, m, 4H, H 4,5,6,6′; 3·31, s, 3H, OCH_3; 1·32, d, 3H, CHC**H**$_3$.

Methyl 2,3-Di-O-benzyl-4-O-ethyl-α-D-glucopyranoside (23)

To a stirred solution of (22) (630 mg, 1·57 mmol) in dry 1:1 CH_2Cl_2/Et_2O (20 ml), $LiAlH_4$ (238 mg, 4 equiv.) and a solution of $AlCl_3$ (733 mg, 3·5 equiv.) in ether (5 ml) were added dropwise over 5 min at room temperature. The mixture was heated at reflux temperature for 1·5 h. After cooling, the excess of the reagent was decomposed by the addition of EtOAc and water. The organic layer was washed with water (3×10 ml), dried (Na_2SO_4), and concentrated. The residue was crystallized from cyclohexane to give (23) (380 mg, 79%), R_F 0·56 (solvent *E*), m.p. 77–81°C (Found: C, 68·7; H, 7·5. $C_{23}H_{30}O_6$ requires C, 68·6; H, 7·5%). $[\alpha]_D$ +43° (*c*, 1·59). ^{1}H n.m.r.: δ 7·40–7·20, m, 10H, aromatic; 4·82, q, 2H, CH_2Ph; 4·66, q, 2H, CH_2Ph; 4·53, d, 1H, H 1; 4·00–3·40, m, 8H, H 2,3,4,5,6,6′ and C**H**$_2$CH$_3$; 2·08, br s, 1H, 6-OH; 1·16, t, 3H, CH_2C**H**$_3$.

Methyl 2-O-Benzyl-4,6-O-methylene-α-D-glucopyranoside (25)

To a stirred solution of (24) (600 mg, 1·55 mmol) in dry 1:1 CH_2Cl_2/Et_2O (30 ml), $LiAlH_4$ (200 mg, 3·4 equiv.) and a solution of $AlCl_3$ (620 mg, 3 equiv.) in ether (5 ml) were added dropwise over 5 min at room temperature. The mixture was heated to reflux temperature and the hydrogenolysis for 56 h resulted only in a 30% conversion. After cooling, the excess of the reagent was decomposed by the addition of EtOAc and water. The organic layer was washed with water (3×10 ml), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (R_F 0·48, solvent *E*) to give (25) (44 mg, 10%), m.p. 122–124°C (from cyclohexane) (Found: C, 60·7; H, 6·8. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). $[\alpha]_D$ +144° (*c*, 0·67). ^{1}H n.m.r.: δ 7·42–7·20, m, 5H, aromatic; 5·04, d, J_{gem} 6·2 Hz, 1H, CH_{ax}; 4·80, q, 2H, CH_2Ph; 4·70, d, $J_{1,2}$ 2·2 Hz, 1H, H 1; 4·57, d, 1H, CH_{eq}; 4·11, q, $J_{2,3}$ 9·6 Hz, 1H, H 2; 3·80–3·56, m, 5H, H 3,4,5,6,6′; 3·36, s, 3H, OCH_3; 2·36, d, 1H, 3-OH.

Methyl 2,3-Di-O-benzyl-4-O-isopropyl-α-D-glucopyranoside (27) and Methyl 2,3-Di-O-benzyl-6-O-isopropyl-α-D-glucopyranoside (28)

The method used for the conversion of (22) into (23) was applied to (26) to give a 93:7 mixture of (27) and (28) (g.l.c.). Recrystallization of the crude product from EtOH gave (27) (79%), R_F 0·42 (solvent *E*), m.p. 111–112°C (Found: C, 69·3; H, 7·8. $C_{24}H_{32}O_6$ requires C, 69·2; H, 7·7%). $[\alpha]_D$ +46° (*c*, 1·10). ^{1}H n.m.r.: δ 7·40–7·20, m, 10H, aromatic; 4·82, q, 2H, CH_2Ph; 4·66, q, 2H, CH_2Ph; 4·50, d, 1H, H 1; 4·08–3·40, m, 7H, H 2,3,4,5,6,6′ and C**H**$(CH_3)_2$; 3·30, s, 3H, OCH_3; 1·99, t, 1H, 6-OH; 1·14, d, 3H, CH_3; 1·10, d, 3H, CH_3.

The mother liquor was concentrated and the residue was purified by column chromatography to give (28) (5%), R_F 0·64 (solvent *E*); $[\alpha]_D$ +15° (*c*, 0·89). ^{1}H n.m.r.: δ 7·40–7·20, m, 10H, aromatic; 4·85, q, 2H, CH_2Ph; 4·66, q, 2H, CH_2Ph; 4·58, d, 1H, H 1; 3·90–3·40, m, 7H, H 2,3,4,5,6,6′ and C**H**$(CH_3)_2$; 3·32, s, 3H, OCH_3; 2·68, br s, 1H, 4-OH; 1·10, d, 6H, 2×CH_3.

Methyl 4-O-Isopropyl-2,3-di-O-methyl-α-D-glucopyranoside (30) and Methyl 6-O-Isopropyl-2,3-di-O-methyl-α-D-glucopyranoside (31)

The method used for the conversion of (22) into (23) was applied to (29) to give a 58:42 mixture of (30) and (31) (g.l.c.).

Methyl 2,3-Di-O-benzyl-4,6-O-diphenylmethylene-α-D-glucopyranoside (32)

To a solution of (33) (200 mg, 0·53 mmol) in dry pyridine (2 ml) were added 2 equiv. of dichlorodiphenylmethane (0·2 ml). The mixture was stirred for 3 days at 110°C. The dark-red solution was then poured onto crushed ice, and, after 1 h, the residue was diluted with dichloromethane, washed with 0·5 M sulfuric acid, then with water until neutral, dried (Na_2SO_4) and concentrated. The dark-red residue was passed through a short column of silica gel (solvent *B*). Crystallization (from ethanol, m.p. 142–143°C) of the crude product gave (32) (100 mg, 35%), R_F 0·22 (solvent *B*); $[\alpha]_D$ +37° (*c*, 0·58) (Found: C, 75·9; H, 6·4. $C_{34}H_{34}O_6$ requires C, 75·8; H, 6·4%). ^{1}H n.m.r.: δ 7·60–7·15, m, 20H, aromatic; 5·13 and 4·87, 2d, 2H, CH_2Ph; 4·83 and 4·63, 2d, 2H, CH_2Ph; 4·47, d, 1H, H 1; 4·09, dd, 1H, H 6; 4·08, t, 1H, H 3; 3·93, ddd, 1H, H 5; 3·75, t, 1H, H 6′; 3·70, t, 1H, H 4; 3·43, dd, 1H, H 2; 3·36, s, 3H, OCH_3. ^{13}C n.m.r.: δ 101·97, C_{acetal}; 99·21, C 1; 79·41, C 2; 78·88, C 3; 75·81, C 4; 75·48 and 73·85, 2×CH_2Ph; 64·11, C 6; 63·06, C 5; 55·23, OCH_3.

Methyl 2,3-Di-O-benzyl-4-O-diphenylmethyl-α-D-glucopyranoside (34)

A solution of (32) (100 mg, 0·186 mmol) in dry 1:1 dichloromethane/ether (10 ml) was treated with 1·5–1·5 equiv. of $LiAlH_4$ (7 mg) and $AlCl_3$ (25 mg). The mixture was refluxed until complete conversion of starting material (1·5 h). The solution was diluted with ether, the excess of $LiAlH_4$ was decomposed by successive addition of EtOAc and water, the organic layer was washed twice with water, dried (Na_2SO_4), and concentrated. Column chromatography of the crude product gave amorphous (34) (40 mg, 40%), R_F 0·19 (solvent *A*); $[\alpha]_D$ +129° (*c*, 0·25) (Found: C, 75·6; H, 6·8. $C_{34}H_{36}O_6$ requires C, 75·5; H, 6·7%). ^{1}H n.m.r.: δ 7·40–7·00, m, 20H, aromatic; 5·95, s, 1H, $CHPh_2$; 4·90 and 4·55, 2d, 2H, CH_2Ph; 4·78 and 4·63, 2d, 2H, CH_2Ph; 4·52, d, 1H, H 1; 4·07, t, 1H, H 3; 3·65, m, 1H, H 5; 3·53, dd, 1H, H 4; 3·49, dd, 1H, H 2; 3·45–3·40, m, 1H, H 6; 3·36, s, 3H, OCH_3; 3·33–3·20, m, 1H, H 6′; 0·90, br s, 1H, 6-OH. ^{13}C n.m.r.; δ 98·04, C 1; 83·71, $CHPh_2$; 82·62, C 3; 80·07, C 2; 75·85 and 73·37, 2×CH_2Ph; 74·01, C 4; 70·51, C 5; 61·71, C 6; 55·21, OCH_3.

Methyl 2,3-Di-O-benzyl-6-O-diphenylmethyl-α-D-glucopyranoside (35)

A solution of (32) (150 mg, 0·28 mmol) and sodium cyanoborohydride (158 mg, 9 equiv.) in dry tetrahydrofuran (2 ml) containing powdered 3 Å molecular sieves was cooled to 0°C. Hydrogen chloride in Et_2O was added until the evolution of gas ceased. After 10 min the mixture was diluted with CH_2Cl_2 (15 ml), and washed with saturated aqueous $NaHCO_3$ and water until neutral. The organic layer was dried (Na_2SO_4) and concentrated. The resulting syrup was purified by column chromatography to give (35) (68 mg, 45%), R_F 0·42 (solvent *A*); $[\alpha]_D$ +22° (*c*, 0·50) (Found: C, 75·4; H, 6·7. $C_{34}H_{36}O_6$ requires C, 75·5; H, 6·7%). ^{1}H n.m.r.: δ 7·50–7·10, m, 20H, aromatic; 5·40, s, 1H, $CHPh_2$; 5·00–4·60, m, 5H, 2×CH_2Ph and H1; 3·90–3·50, m, 6H, H2,3,4,5,6,6′; 3·37, s, 3H, OCH_3; 2·40, s, 1H, 4-OH. ^{13}C n.m.r.: δ 98·04, C1; 84·33, C_{acetal}; 81·49 and 79·67, C2,3; 75·47 and 73·11, 2×CH_2Ph; 71·05 and 70·00, C4,5; 68·75, C6; 55·13, OCH_3.

Methyl 2,3-Di-O-benzyl-4,6-O-[(R,S)-s-butylidene]-α-D-glucopyranoside (36) and (37)

To a stirred solution of (33) (2·0 g, 5·34 mmol) in 2,2-dimethoxybutane (3·2 ml) was added *p*-toluenesulfonic acid (20 mg). After 2 h the mixture was diluted with CH_2Cl_2 (50 ml), then washed successively with aqueous 5% $NaHCO_3$ (3×10 ml) and water (3×10 ml) until neutral, dried (Na_2SO_4), and concentrated; the residue was purified by column chromatography.

Compound (36) (*R*) (37%): R_F 0·62 (solvent *B*), m.p. 78–79°C (from EtOH) (Found: C, 70·0; H, 7·6. $C_{25}H_{32}O_6$ requires C, 70·1; H, 7·5%). $[\alpha]_D$ +6° (*c*, 1·0). ^{1}H n.m.r.: δ 1·43, C_{acetal}–CH_3. ^{13}C n.m.r.: δ 100·69, C_{acetal}; 99·29, C1; 78·95, 2C, C2,3; 75·01 and 73·68, 2×CH_2Ph; 74·80, C4; 63·31, C5; 62·43, C6; 55·21, OCH_3; 34·94, **C**H_2CH$_3$; 17·11, C_{acetal}–**C**H_3; 7·59, CH_2**C**H_3.

Compound (37) (*S*) (32%): R_F 0·56 (solvent *B*), m.p. 66–67°C (from hexane) (Found: C, 71·2; H, 7·6. $C_{25}H_{32}O_6$ requires C, 70·1; H, 7·5%). $[\alpha]_D$ +24° (*c*, 1·0). ^{1}H n.m.r.: δ 1·34, C_{acetal}–CH_3. ^{13}C n.m.r.; δ 101·52, C_{acetal}; 99·25, C1; 79·15, C2; 78·96, C3; 75·13 and 73·74, 2×CH_2Ph; 74·36, C4; 62·94, C5; 62·21, C6; 55·20, OCH_3; 25·67, C_{acetal}–**C**H_3; 23·56, **C**H_2CH$_3$; 8·32, CH_2**C**H_3.

Methyl 2,3-Di-O-benzyl-4-O-[(R)-s-butyl]-α-D-glucopyranoside (38) and Methyl 2,3-Di-O-benzyl-4-O-[(S)-s-butyl]-α-D-glucopyranoside (39)

The method used for the conversion of (22) into (23) was applied to (36) and (37) to give (38) and (39), respectively. The crude products were purified by column chromatography (solvent *F*).

Compound (38) had m.p. 77–78°C (Found: C, 69·7; H, 7·9. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%). $[\alpha]_D$ +41° (*c*, 1·0). ^{13}C n.m.r.: δ 78·36, CH_3**C**HCH_2CH_3; 75·36, C4; 62·27, C6; 29·62, CH_3CH**C**H_2CH_3; 20·38, **C**$H_3CHCH_2CH_3$.

Compound (39) had m.p. 60–61°C (Found: C, 69·8; H, 8·0. $C_{25}H_{34}O_6$ requires C, 69·7; H, 8·0%). $[\alpha]_D$ +43° (*c*, 1·0). ^{13}C n.m.r.: δ 78·31, CH_3**C**HCH_2CH_3; 74·86, C4; 62·33, C6; 30·62, CH_3CH**C**H_2CH_3; 19·39, **C**$H_3CHCH_2CH_3$.

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