

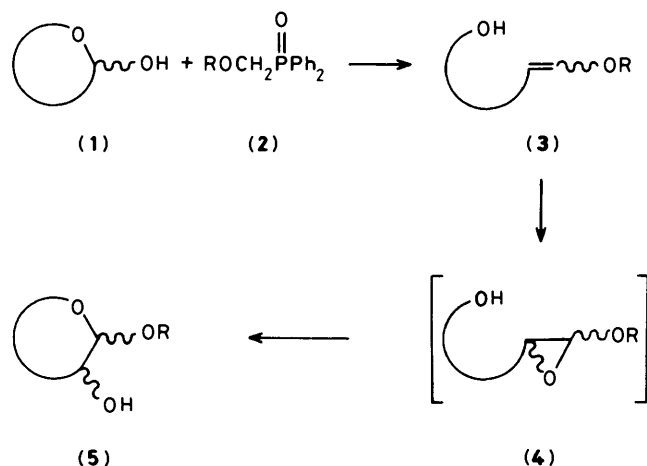
Formation of Glycosides by Epoxidation-Ring Closure of Open-chain Hydroxyenol Ethers obtained from Sugars

Francesco Nicotra, Luigi Panza, Fiamma Ronchetti, Giovanni Russo,* and Lucio Toma
 Dipartimento di Chimica Organica e Industriale and Centro di Studio per le Sostanze Organiche Naturali del
 CNR, Via Venezian 21, 20133 Milano, Italy

Z- and *E*-Hydroxyenol ethers, obtained from aldopentoses by a Horner–Wittig reaction, have been epoxidized using *m*-chloroperbenzoic acid or *t*-butyl hydroperoxide. A spontaneous intramolecular cyclization of the intermediate epoxides due to the free hydroxy group present in the starting enol ethers occurs, giving 1,2-*trans*-glycopyranosides from *E*-enol ethers. From *Z*-enol ethers, 1,2-*cis*-glycopyranosides are obtained, although in the case of complex aglycones the cyclization is not entirely stereospecific. The stereochemical course of both the epoxidation reaction and the pyranose ring formation from the intermediate epoxides is discussed.

The stereospecific synthesis of glycosides is a major problem in carbohydrate chemistry due to the growing interest in glycosides and oligosaccharides as components of biologically important compounds such as glycoproteins, glycolipids, and immunodeterminants.

Recently¹ we described a novel approach to the synthesis of the glycosidic linkage (Scheme 1), according to which the introduction of the aglycone moiety occurs before the ring closure of the glycosyl component. In our scheme the enol ether



Scheme 1.

(3) was obtained from a C_{n-1} aldose (1) by homologation with an alkoxyphosphine oxide (2) in which the alkoxy group corresponded to the aglycone; in this way an enol ether with the desired number of carbon atoms was obtained. The ring closure was effected by treatment with an epoxidizing agent through the formation of an intermediate epoxide (4), which was opened by the free hydroxy group to give the glycosyl unit (5) in which the hydroxy group at C-2 came from the epoxidic oxygen.

Our preliminary communication showed the application of this scheme to a simple case in which the glycosyl moiety came from *D*-arabinose and the aglycone was a methyl group.

In this paper we explore the scope of the process, testing it also in more complex cases. We chose *D*-arabinose and *D*-ribose to build the glycosyl structure. The former should lead to glucosides and mannosides, two of the most important glycosides; *D*-ribose was chosen in order for us to obtain information

about the stereochemistry of the process, since *D*-ribose differs from *D*-arabinose in having the opposite configuration at C-2.

As the aglycone component we used, besides a simple alcohol such as methanol, protected forms of galactose and glycerol, which are important constituents, respectively, of oligosaccharides and glycolipids.

The whole process is reported in Scheme 2.

Horner–Wittig reaction.—The hydroxyenol ethers (11a–d) and (12a–d) were prepared by reaction of 2,3,5-tri-*O*-benzyl-*D*-arabinose (6)² or 2,3,5-tri-*O*-benzyl-*D*-ribose (7)³ with the proper phosphine oxide according to the procedure of Suzuki and Mukaiyama.^{4,5}

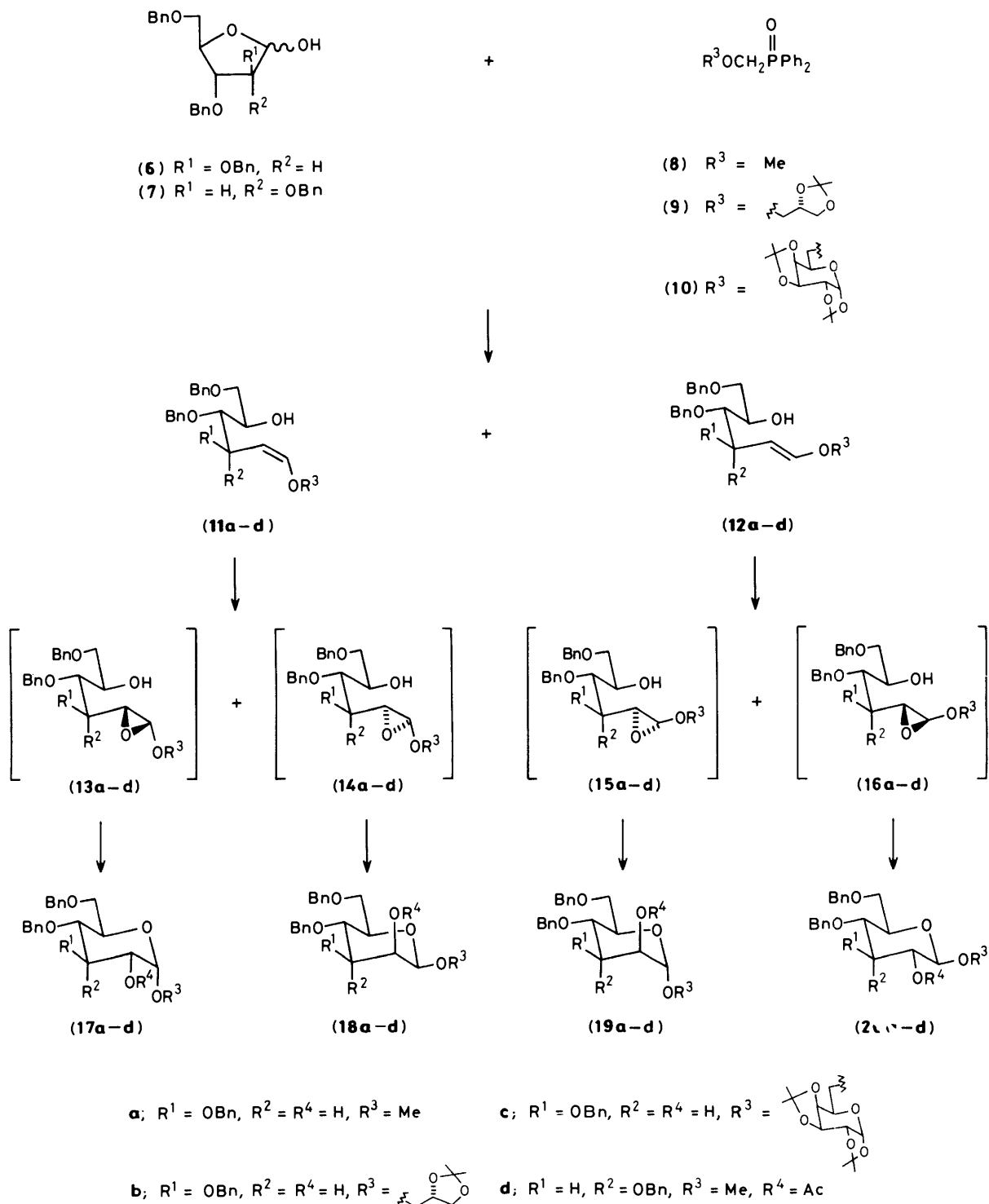
Methoxymethyldiphenylphosphine oxide (8) was obtained from chloromethyl methyl ether by reaction with triphenylphosphine followed by alkaline hydrolysis of the corresponding phosphonium salts according to Warren and co-workers.⁶ However this procedure, when applied to more complex chloro ethers,⁷ gave low yields. We found that better yields could be obtained by an Arbuzov⁸ reaction of the proper chloro ether with ethyl diphenylphosphinite.

We found some limitations to our application of the Horner–Wittig reaction; whereas in the case of the phosphine oxides of primary alcohols this reaction proceeded smoothly in moderate-to-good yields, in the case of phosphine oxides of sterically hindered secondary alcohols the ylide was unreactive with respect to the sugar aldehyde.† Moreover the reaction was found to be incompatible with the presence of benzyl protecting groups; when we tried to obtain the corresponding ylide from a phosphine oxide derived from 2,3,4-tri-*O*-benzyl- α -*D*-glucopyranose we observed the formation of a complex mixture of products accompanied by the elimination of benzyl alcohol.

The Horner–Wittig reaction described above gave *Z/E* mixtures of the various enol ethers in ratios ranging from 2:1 to 3:1, depending on the sugar moiety and the phosphine oxide employed. In each case the isomers were easily separated by flash chromatography and each isomer was used separately.

Epoxidation–Ring-closure Reaction.—All the experiments but two were effected with *m*-chloroperbenzoic acid (MCPBA). We tried several experimental conditions and found that the best results were obtained when the epoxidation reaction was carried out in the presence of Na_2HPO_4 (see Experimental section).

† Unpublished results.



Scheme 2.

As shown in Table 1, the epoxidation of the *E*-enol ethers (12) always gave the 1,2-*trans*-glycopyranosides (19) + (20).

The *Z*-methyl enol ethers (11a) and (11d) gave the 1,2-*cis*-glycopyranosides (17a)⁹ + (18a)¹⁰ and (17d) + (18d), but when the *Z*-enol ether (11b) or (11c), with a more complex substituent at C-1, was epoxidized, besides the 1,2-*cis*-glycopyranosides (17b) + (18b) and (17c)¹¹ + (18c),⁹ a third cyclization product, the 1,2-*trans*-isomer (19b) or (19c), was formed. The anomers (20b) or (20c) were not found.

We also employed vanadyl acetylacetonate $\text{VO}(\text{acac})_2$ -*t*-butyl hydroperoxide¹² as epoxidizing agent. This procedure gave promising results in the case of the methyl enol ethers (11a) and (12a) (Table 2); however, it could not be applied to more complex enol ethers such as (11c), as extensive decomposition was observed.

Epoxidation of the *Z*-enol ether (11a) gave complementary results and higher stereoselection with respect to the MCPBA epoxidation, whereas in the case of substrate (12a) similar

Table 1. MCPBA epoxidation

Enol ether	Products	Yield (%) ^a	Proportions ^b
(11a)	(17a) + (18a)	82	64:36
(11b)	(17b) + (18b) + (19b)	55	60:14:26
(11c)	(17c) + (18c) + (19c)	61	60:16:24
(11d)	(17d) + (18d) ^c	59	34:66
(12a)	(19a) + (20a)	86	90:10
(12b)	(19b) + (20b)	78	75:25
(12c)	(19c) + (20c)	81	85:15
(12d)	(19d) + (20d) ^c	68	48:52

^a Isolated products. ^b Determined by h.p.l.c. ^c The obtained 2-hydroxy derivatives were acetylated to facilitate separation and identification.

Table 2. VO(acac)₂-TBHP epoxidation

Enol ether	Products	Yield (%) ^a	Ratio ^b
(11a)	(17a) + (18a)	45	7:93
(12a)	(19a) + (20a)	48	86:14

^a Isolated products. ^b Determined by h.p.l.c.

stereoselectivity results were obtained with MCPBA and with VO(acac)₂ (see Tables 1 and 2).

Stereochemical Course of the Epoxidation Reaction.—The stereochemistry of the whole process results from three factors in Scheme 1, *i.e.* (i) the *Z/E* configuration of the enol ethers, (ii) the stereoselection during their epoxidation, and (iii) the stereospecificity of the attack on the epoxide ring. The intermediate epoxides (13)—(16) were neither isolated nor detected in the reaction mixture, nevertheless the stereochemistry of the epoxidation step can be inferred from the stereochemistry at C-2 of the ultimate glycoside, which is the same as in the (presumed) intermediate epoxides. *Z*-Enol ethers (11a—c), obtained from 2,3,5-tri-*O*-benzyl-*D*-arabinose (6), preferentially afforded the (1*R*,2*R*)-epoxides (13a—c). This result can be rationalized on the assumption that during the reaction the C-1—C-3 part* of these *Z*-enol ethers is in the conformation depicted in Figure 1.^{13,14} The epoxidizing agent

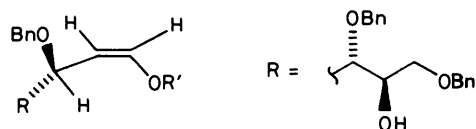


Figure 1.

preferentially approaches the double bond from the less hindered side. The same model analogously works well for the *Z*-enol ether (11d) obtained from *D*-ribose. In this case however, owing to the opposite configuration at C-3,* the attack of the epoxidizing agent occurs from the opposite side to that observed before and the (1*S*,2*S*)-epoxide (14d) was formed preferentially.

E-Enol ethers (12a—c) gave preferentially the (1*R*,2*S*)-epoxides (15a—c). This can be explained by an attack of the epoxidizing agent from the less hindered side of the *E*-enol ether in the preferred conformation depicted in Figure 2.^{13,14} The degree of stereoselection is higher for the *E*-enol ethers (12a—c) than for the corresponding *Z*-isomers (11a—c) and reflects the

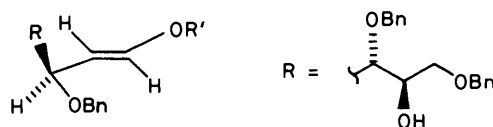


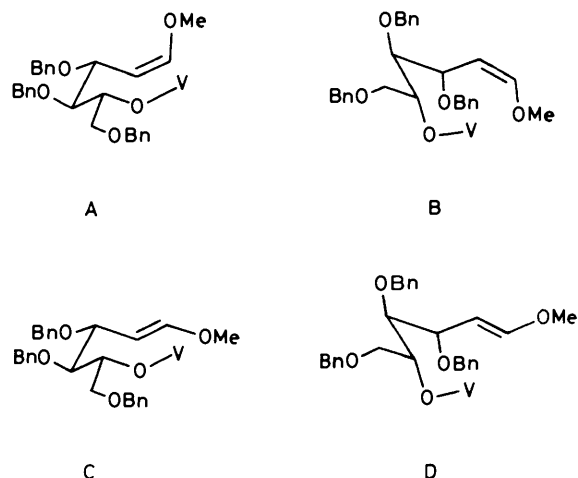
Figure 2.

higher difference in steric hindrance for the two groups out of plane: H *vs.* C-4—C-6 fragment* with respect to OBn *vs.* C-4—C-6 fragment.*

The *E*-enol ether (12d) gave the expected products (19d) and (20d) but without stereoselection (Table 1).

If the stereoselection in this epoxidation reaction depended only on the stereocentre C-3* adjacent to the double bond, the stereochemical course expected for compound (12d) would be complementary to that of the enol ether (12a). The fact, however, that the reaction proceeds for (12d) with a degree of stereoselection substantially different from that for (12a) indicates that in this case there is some contribution, opposite to that of C-3, due to the other stereocentres (C-4 and/or C-5).*

The high stereoselectivity obtained in vanadium-catalysed epoxidation of enol ethers (11a) and (12a) can be explained with a 1,4-asymmetric induction¹⁵ due to the bishomoallylic hydroxy group. Two different reactive conformations can be envisaged for each enol ether, where the vanadium co-ordinates with the C-5* hydroxy group. In both cases the main product derives from the reaction of the less strained conformation A or C of the vanadium complex.

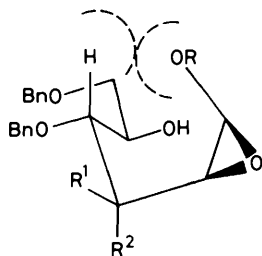


Stereochemical Course of the Ring Closure.—The configuration at C-1 and C-2 in the glycosyl part of the ultimate glycosides is consistent in all cases but two, with an inversion of configuration at C-1 deriving from an attack of the C-5 free hydroxy group on C-1 of the intermediate epoxides. Opening of the epoxides obtained from the *E*-enol ethers (12a—d) always afforded 1,2-*trans*-glycosides, and opening of the epoxides (13a), (14a), (13d), and (14d) obtained from the *Z*-methyl enol ethers (11a) and (11d) gave 1,2-*cis*-glycosides. The *Z*-enol ethers (11b) and (11c), on the other hand, gave, besides the expected glycosides (17b), (18b), (17c), and (18c), their isomers (19b) and (19c), indicating that in these two cases the opening of the intermediate epoxides occurs in a non-stereospecific manner. This lack of stereospecificity may be understood by examination of models of the reactive conformations of the (1*S*,2*S*)-epoxides (14a—d). In order to give the glycosides (18a—d) by attack from

* Numbering based on the olefin function being at C-1—C-2.

* Numbering based on the olefin function being at C-1—C-2.

the hydroxy group at C-5 with inversion of configuration at C-1, these epoxides must adopt a crowded boat-type conformation with a severe flagpole interaction between the —OR group at C-1 and the hydrogen at C-4 (Figure 3). This conformation is

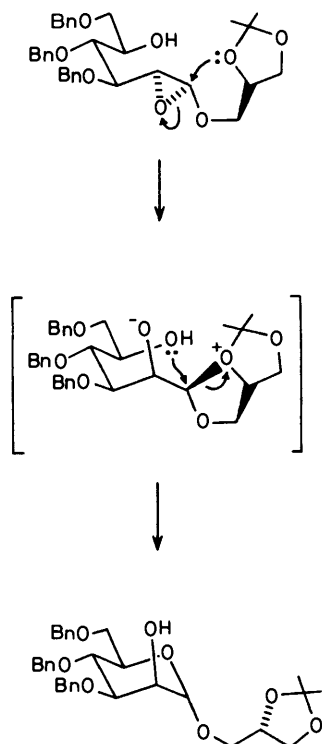


(14a–c) R¹ = OBn, R² = H

(14d) R¹ = H, R² = OBn

Figure 3.

adopted in the case of the epoxides (14a) and (14d), in which the aglycone moiety is methanol. Two alternative hypotheses can be made for the reaction of epoxides (14b) and (14c), in which the aglycone moiety is more complex than methanol: (a) an S_N1-type ring-closure operates with opening of the epoxide to give the stabilized cation at C-1. This is then attacked by the hydroxy group at C-5 in a non-stereospecific way with ring-closure to give a mixture of α- and β-glycosides; (b) the epoxides (14b) and (14c) partly give rise to the glycosides (18b) and (18c) through the conformation depicted in Figure 3; however, the difficulty of attaining the above conformation implies the presence of an important competitive process in which the (1S,2S)-epoxide is opened by one oxygen atom of the aglycone. The intermediate oxonium ion¹⁶ [which in Scheme 3 represents the one derived from the epoxide (14b)] is then attacked by the hydroxy group at C-5, giving rise to a double inversion which results in the formation of the glycosides (19b) and (19c).



Scheme 3.

Experimental

M.p.s were determined on a Büchi apparatus and are uncorrected. N.m.r. spectra were recorded for solutions in deuteriochloroform with tetramethylsilane as internal standard on Bruker WP 80 (80 MHz) and Varian Associates XL 200 (200 MHz) spectrometers.

Optical rotations were determined on a Perkin-Elmer 241 polarimeter for chloroform solutions. T.l.c. was performed on Merck 60 F-254 (0.25 mm thickness) silica gel plates; compounds were detected by u.v. light or by a 50% aqueous H₂SO₄ spray, followed by heating at 110 °C for 5 min. Column chromatography was performed on Merck 60 silica gel (70–230 mesh). Flash chromatography was performed on Woelm 0–63 silica gel (<230 mesh). High-pressure liquid chromatography (h.p.l.c.) was performed on a Varian LC 5020 instrument equipped with a 254 nm u.v. detector. MCPBA refers to *m*-chloroperbenzoic acid (85%), TBHP refers to a 3.4M-solution of *t*-butyl hydroperoxide in toluene,¹⁷ VO(acac)₂ refers to vanadyl acetylacetonate, and AcOEt refers to ethyl acetate.

(*R*)-1-*O*-Diphenylphosphinoylmethyl-2,3-*O*-isopropylidene-glycerol (9).—(*R*)-1-*O*-Chloromethyl-2,3-*O*-isopropylidene-glycerol (0.72 g, 4 mmol), obtained from (2*S*)-1,2-*O*-isopropylidene-glycerol according to the method of David *et al.*,⁷ was dissolved in ethyl diphenylphosphinite (3 ml). The reaction mixture was warmed to 150 °C. After 2 h the excess of ethyl diphenylphosphinite was distilled off (140 °C; 0.4 mmHg) and the crude product was purified by chromatography (toluene–acetone 1:1) to obtain the pure phosphine oxide (9) (1.08 g, 78%).

6-*O*-Diphenylphosphinoylmethyl-1,2:3,4-*di-O*-isopropylidene-α-*D*-galactopyranose (10).—Compound (10), prepared as described for (9) but starting from 1,2:3,4-*di-O*-isopropylidene-α-*D*-galactopyranose¹⁸ and purified by chromatography (CH₂-Cl₂–97:3), was obtained in 89% yield.

Horner–Wittig Reaction.—The enol ethers were obtained according to Suzuki and Mukaiyama's method.^{4,5} The *Z*–*E* mixtures were separated in all cases but one by flash chromatography (hexane–ethyl acetate 8:2); compounds (11c)/(12c) were separated with benzene–AcOEt (8:2) as eluant. The *Z*-enol ethers were always eluted first. The following compounds were thus prepared.

(*Z*)-(2*R*,3*R*,4*R*)-1,3,4-Tribenzyloxy-6-methoxyhex-5-en-2-ol (11a). Oil, [α]_D²⁰ –12° (c 1.2 in CHCl₃); δ_H (80 MHz) 2.9 (1 H, br s, OH), 3.60 (3 H, s, Me), 3.4–4.7 (12 H, m, 1-H₂, 2-, 3-, 4-, and 5-H, and CH₂Ph), 6.13 (1 H, d, *J*_{5,6} 5.5 Hz, 6-H), and 7.1–7.4 (15 H, m, Ph) (Found: C, 74.8; H, 7.1. C₂₈H₃₂O₅ requires C, 75.0; H, 7.2%).

(*E*)-(2*R*,3*R*,4*R*)-1,3,4-Tribenzyloxy-6-methoxyhex-5-en-2-ol (12a). M.p. 54 °C (from hexane); [α]_D²⁰ –32° (c 1.0 in CHCl₃); δ_H (80 MHz) 2.9 (1 H, br s, OH), 3.53 (3 H, s, Me), 3.4–4.7 (11 H, m, 1-H₂, 2-, 3-, and 4-H, and CH₂Ph), 4.83 (1 H, dd, *J*_{4,5} 9.3, *J*_{5,6} 13.5 Hz, 5-H), 6.45 (1 H, d, *J*_{5,6} 13.5 Hz, 6-H), and 7.1–7.4 (15 H, m, Ph) (Found: C, 74.7; H, 7.1%).

(2*S*)-1-*O*-[(3'*R*,4'*R*,5'*R*)-5'-Hydroxy-3',4',6'-tribenzyloxyhex-1'(Z)-enyl]-2,3-*O*-isopropylidene-glycerol (11b). Oil, [α]_D²⁰ –13° (c 1.5 in CHCl₃); δ_H (80 MHz) 1.33 and 1.38 (6 H, 2 s, Me), 2.95 (1 H, br s, OH), 3.4–4.8 (17 H, m, 1-H₂, 2-H, 3-H₂, 2', 3', 4', and 5'-H, 6'-H₂, and CH₂Ph), 6.24 (1 H, d, *J*_{1',2'} 5.2 Hz, 1'-H), and 7.1–7.4 (15 H, m, Ph) (Found: C, 71.9; H, 7.3. C₃₃H₄₀O₇ requires C, 72.2; H, 7.4%).

(2*S*)-1-*O*-[(3'*R*,4'*R*,5'*R*)-5'-Hydroxy-3',4',6'-tribenzyloxyhex-1(*E*)-enyl]-2,3-*O*-isopropylidene-glycerol (12b). Oil, [α]_D²⁰ –18° (c 1.0 in CHCl₃); δ_H (80 MHz) 1.37 and 1.43 (6 H, 2 s, Me), 2.9 (1 H, br s, OH), 3.4–4.7 (16 H, m, 1-H₂, 2-H, 3-H₂, 3', 4', and 5'-H, 6'-H₂, and CH₂Ph), 4.86 (1 H, dd, *J*_{2',3'} 9.2, *J*_{1',2'} 12.9 Hz, 2'-H),

6.41 (1 H, d, $J_{1,2}$ 12.9 Hz, 1'-H), and 7.1—7.4 (15 H, m, Ph) (Found: C, 72.1; H, 7.4%).

6-O-[(3'R,4'R,5'R)-5'-Hydroxy-3',4',6'-tribenzoyloxyhex-1'(Z)-enyl]-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (**11c**). Syrup, $[\alpha]_D^{20} -43^\circ$ (c 1.0 in CHCl_3); δ_{H} (80 MHz) 1.30, 1.32, 1.46, and 1.46 (12 H, 4 s, Me), 2.9 (1 H, br s, OH), 3.5—4.9 (18 H, m, 2-, 3-, 4-, and 5-H, 6-H₂, 2'-, 3'-, 4'-, and 5'-H, 6'-H₂, and CH_2Ph), 5.48 (1 H, d, $J_{1,2}$ 5.5 Hz, 1-H), 6.27 (1 H, d, $J_{1,2}$ 5.5 Hz, 1'-H), and 7.1—7.4 (15 H, m, Ph) (Found: C, 69.1; H, 7.1. $\text{C}_{39}\text{H}_{48}\text{O}_{10}$ requires C, 69.2; H, 7.2%).

6-O-[(3'R,4'R,5'R)-5'-Hydroxy-3',4',6'-tribenzoyloxyhex-1'(E)-enyl]-1,2:3,4-di-O-isopropylidene- α -D-galactopyranose (**12c**). Syrup, $[\alpha]_D^{20} -57^\circ$ (c 1.0 in CHCl_3); δ_{H} (80 MHz) 1.28, 1.30, 1.45, and 1.53 (12 H, 4 s, Me), 2.9 (1 H, br s, OH), 3.5—4.8 (17 H, m, 2-, 3-, 4-, and 5-H, 6-H₂, 3'-, 4'-, and 5'-H, 6'-H₂, and CH_2Ph), 4.93 (1 H, dd, $J_{2,3}$ 9.3, $J_{1,2}$ 13 Hz, 2'-H), 5.55 (1 H, d, $J_{1,2}$ 5.5 Hz, 1-H), 6.36 (1 H, d, $J_{1,2}$ 13 Hz, 1'-H), and 7.1—7.4 (15 H, m, Ph) (Found: C, 69.0; H, 7.1%).

(Z)-(2R,3R,4S)-1,3,4-Tribenzoyloxy-6-methoxyhex-5-en-2-ol (**11d**). Oil, $[\alpha]_D^{20} +46^\circ$ (c 1.0 in CHCl_3); δ_{H} (80 MHz) 2.85 (1 H, br s, OH), 3.60 (3 H, s, Me), 3.4—5.0 (12 H, m, 1-H₂, 2-, 3-, 4-, and 5-H, and CH_2Ph), 6.19 (1 H, d, $J_{5,6}$ 5.3 Hz, 6-H), and 7.2—7.5 (15 H, m, Ph) (Found: C, 74.6; H, 7.0. $\text{C}_{28}\text{H}_{32}\text{O}_5$ requires C, 75.0; H, 7.2%).

(E)-(2R,3R,4S)-1,3,4-Tribenzoyloxy-6-methoxyhex-5-en-2-ol (**12d**). Oil, $[\alpha]_D^{20} +54^\circ$ (c 1.0 in CHCl_3); δ_{H} (80 MHz) 3.55 (3 H, s, Me), 3.3—5.1 (12 H, m, 1-H₂, 2-, 3-, 4-, and 5-H, and CH_2Ph), 6.45 (1 H, d, $J_{5,6}$ 13.3 Hz, 6-H), 7.1—7.6 (15 H, m, Ph) (Found: C, 74.7; H, 7.1%).

General Procedure for MCPBA Epoxidation.—In a typical procedure a solution of an *E* or *Z*-enol ether (0.2 mmol) in dichloromethane (5 ml) was cooled to 0 °C. Na_2HPO_4 (0.02 mmol) and MCPBA (45 mg, 10% molar excess) were added and the solution was left at 0 °C until the starting material had disappeared (t.l.c.). After 12—24 h, 5% aqueous FeSO_4 (2 ml) was added and the mixture was stirred at room temperature for 30 min, and then extracted with dichloromethane. The extract was washed successively with saturated aqueous NaHCO_3 and water, dried (Na_2SO_4), and evaporated under reduced pressure. The crude reaction mixtures from compounds (**11a—c**) and (**12a—c**) were carefully purified on SiO_2 (hexane—AcOEt 6:4 or 1:1) to separate the obtained glycosides (**17a—c**) from (**18a—c**), and (**19a—c**) from (**20a—c**). The glycosides obtained from compounds (**11d**) and (**12d**) were separated and identified after acetylation of the crude mixture with acetic anhydride-pyridine.

The relative ratios of the diastereoisomeric glycosides were determined by h.p.l.c. on Merck Hibar LiChrosorb Si-60, 25 cm \times 4 mm column, flow rate 1.5 ml min^{-1} , hexane—AcOEt 7:3 or 1:1 as solvent, depending on the analysed glycosidic mixture (yields are given in Table 1).

Epoxidation with VO(acac)₂-TBHP.¹³—To a solution of product (**11a**) or (**12a**) (100 mg, 0.22 mmol) in dry 1,2-dichloroethane (3 ml) (from P_2O_5), VO(acac)₂ (1%), Na_2HPO_4 (1%), and TBHP (0.072 ml of a 3.4M-solution,¹⁷ 10% excess) were added. The solution was heated at reflux for 4 h, and was then cooled, when aqueous 5% Na_2SO_3 (2 ml) were added. After 30 min the reaction mixture was extracted with dichloromethane, the extract was washed twice with water, dried (Na_2SO_4), and evaporated under pressure to give the crude products. The following compounds were thus prepared by one or both methods (see Tables 1 and 2).

Methyl 3,4,6-tri-*O*-benzyl- α -D-glucopyranoside (**17a**). M.p. 87—88 °C (from hexane) (lit.,⁹ 87—89 °C); R_{F} (hexane—AcOEt 6:4) 0.28; $[\alpha]_D^{20} +98^\circ$ (c 1.0 in CHCl_3) (lit.,⁹ +100°); δ_{H} (200 MHz) 2.14 (1 H, br s, OH), 3.41 (3 H, s, Me), 3.4—3.8 (6 H, m, 2-

3-, 4-, and 5-H, and 6-H₂), 4.80 (1 H, d, $J_{1,2}$ 3 Hz, 1-H), 4.4—4.9 (6 H, 3 ABq, CH_2Ph), and 7.1—7.4 (15 H, m, Ph).

Methyl 3,4,6-tri-*O*-benzyl- β -D-mannopyranoside (**18a**). Oil, R_{F} (hexane—AcOEt 6:4) 0.18; $[\alpha]_D^{20} -13^\circ$ (c 1.0 in CHCl_3) (lit.,¹⁰ -10.2°); δ_{H} (200 MHz) 3.43 (1 H, ddd, $J_{4,5}$ 9, $J_{5,6A}$ 2.5, $J_{5,6B}$ 4.5 Hz, 5-H), 3.55 (3 H, s, Me), 3.56 (1 H, dd, $J_{2,3}$ 3.5, $J_{3,4}$ 9 Hz, 3-H), 3.72 (1 H, dd, $J_{5,6B}$ 4.5, $J_{6A,6B}$ 10.5 Hz, 6-H_B), 3.79 (1 H, dd, $J_{5,6A}$ 2.5, $J_{6A,6B}$ 10.5 Hz, 6-H_A), 3.86 (1 H, t, J 9 Hz, 4-H), 4.09 (1 H, dd, $J_{1,2}$ 1, $J_{2,3}$ 3.5 Hz, 2-H), 4.33 (1 H, d, $J_{1,2}$ 1 Hz, 1-H), 4.5—4.9 (6 H, 3 ABq, CH_2Ph), and 7.1—7.4 (15 H, m, Ph).

Methyl 3,4,6-tri-*O*-benzyl- α -D-mannopyranoside (**19a**). Syrup, R_{F} (hexane—AcOEt 6:4) 0.29; $[\alpha]_D^{20} +51^\circ$ (c 1.0 in CHCl_3) (lit.,¹⁹ +59.7°); δ_{H} (200 MHz) 3.36 (3 H, s, Me), 3.5—3.9 (5 H, m, 3-, 4-, and 5-H, and 6-H₂), 4.03 (1 H, dd, $J_{1,2}$ 1.5, $J_{2,3}$ 3 Hz, 2-H), 4.80 (1 H, d, $J_{1,2}$ 1.5 Hz, 1-H), 4.4—4.9 (6 H, 3 ABq, CH_2Ph), and 7.1—7.4 (15 H, m, Ph).

Methyl 3,4,6-tri-*O*-benzyl- β -D-glucopyranoside (**20a**). M.p. 71—72 °C (from hexane) (lit.,⁹ 72—75 °C); R_{F} (hexane—AcOEt 6:4) 0.33; $[\alpha]_D^{20} -3^\circ$ (c 0.8 in CHCl_3) (lit.,⁹ -5°); δ_{H} (200 MHz) 2.29 (1 H, d, J 2 Hz, OH), 3.56 (3 H, s, Me), 3.4—3.8 (6 H, m, 2-, 3-, 4-, and 5-H, and 6-H₂), 4.17 (1 H, d, $J_{1,2}$ 7.5 Hz, 1-H), 4.48—4.96 (6 H, 3 ABq, CH_2Ph), and 7.1—7.4 (15 H, m, Ph).

(2S)-1,2-*O*-Isopropylidene-3-*O*-(3',4',6'-tri-*O*-benzyl- α -D-glucopyranosyl)glycerol (**17b**). Syrup, R_{F} (hexane—AcOEt 5:5) 0.42; $[\alpha]_D^{20} +84.8^\circ$ (c 0.5 in CHCl_3); δ_{H} (200 MHz) 1.36 and 1.43 (6 H, 2 s, Me), 3.5—4.1 (10 H, m, 1- and 3-H₂, 2'-, 3'-, 4'-, and 5'-H, and 6'-H₂), 4.31 (1 H, m, 2-H), 4.95 (1 H, d, $J_{1,2}$ 3 Hz, 1'-H), 4.4—5.0 (6 H, 3 ABq, CH_2Ph), and 7.1—7.4 (15 H, m, Ph) (Found: C, 69.8; H, 7.0. $\text{C}_{33}\text{H}_{40}\text{O}_8$ requires C, 70.2; H, 7.1%).

(2S)-1,2-*O*-Isopropylidene-3-*O*-(3',4',6'-tri-*O*-benzyl- β -D-mannopyranosyl)glycerol (**18b**). Syrup, R_{F} (hexane—AcOEt 5:5) 0.34; $[\alpha]_D^{20} +3.5^\circ$ (c 0.5 in CHCl_3); δ_{H} (200 MHz) 1.35 and 1.40 (6 H, 2 s, Me), 3.42 (1 H, ddd, $J_{4,5}$ 9, $J_{5,6A}$ 2.5, $J_{5,6B}$ 4.5 Hz, 5'-H), 3.54 (1 H, dd, $J_{2,3}$ 3, $J_{3,4}$ 9 Hz, 3'-H), 3.86 (1 H, t, J 9 Hz, 4'-H), 3.6—4.1 (6 H, m, 1-, 3-, and 6'-H₂), 4.11 (1 H, br d, $J_{2,3}$ 3 Hz, 2'-H), 4.29 (1 H, m, 2-H), 4.47 (1 H, br s, 1'-H), 4.5—5.0 (6 H, 3 ABq, CH_2Ph), and 7.1—7.4 (15 H, m, Ph) (Found: C, 69.9; H, 7.0%).

(2S)-1,2-*O*-Isopropylidene-3-*O*-(3',4',6'-tri-*O*-benzyl- α -D-mannopyranosyl)glycerol (**19b**). Syrup, R_{F} (hexane—AcOEt 5:5) 0.44; $[\alpha]_D^{20} +28.3^\circ$ (c 0.7 in CHCl_3); δ_{H} (200 MHz) 1.35 and 1.40 (6 H, 2 s, Me), 4.10 (1 H, br t, J 1.5 Hz, 2'-H), 3.4—4.2 (9 H, m, 1- and 3-H₂, 3'-, 4'-, and 5'-H, and 6'-H₂), 4.27 (1 H, m, 2-H), 4.4—4.9 (6 H, 3 ABq, CH_2Ph), 4.94 (1 H, d, $J_{1,2}$ 1.5 Hz, 1'-H), and 7.1—7.4 (15 H, m, Ph) (Found: C, 70.0; H, 6.9%).

(2S)-1,2-*O*-Isopropylidene-3-*O*-(3',4',6'-tri-*O*-benzyl- β -D-glucopyranosyl)glycerol (**20b**). Syrup, R_{F} (hexane—AcOEt 5:5) 0.58; $[\alpha]_D^{20} +10^\circ$ (c 0.5 in CHCl_3); δ_{H} (200 MHz) 1.36 and 1.43 (6 H, 2 s, Me), 3.4—4.2 (10 H, m, 1- and 3-H₂, 2'-, 3'-, 4'-, and 5'-H, and 6'-H₂), 4.31 (1 H, d, $J_{1,2}$ 7.5 Hz, 1'-H), 4.32 (1 H, m, 2-H), 4.4—5.0 (6 H, 3 ABq, CH_2Ph), and 7.1—7.4 (15 H, m, Ph) (Found: C, 69.7; H, 6.9%).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3',4',6'-tri-*O*-benzyl- α -D-glucopyranosyl)- α -D-galactopyranose (**17c**). Syrup, R_{F} (hexane—AcOEt 5:5) 0.43; $[\alpha]_D^{20} +26^\circ$ (c 0.5 in CHCl_3) (lit.,¹¹ +31°); δ_{H} (200 MHz) 1.30, 1.32, 1.64, and 1.72 (12 H, 4 s, Me), 3.5—4.1 (9 H, m, 5-H, 6-H₂, 2'-, 3'-, 4'-, and 5'-H, and 6'-H₂), 4.23 (1 H, dd, $J_{3,4}$ 8, $J_{4,5}$ 2 Hz, 4-H), 4.32 (1 H, dd, $J_{1,2}$ 5, $J_{2,3}$ 2.5 Hz, 2-H), 4.62 (1 H, dd, $J_{2,3}$ 2.5, $J_{3,4}$ 8 Hz, 3-H), 4.91 (1 H, d, $J_{1,2}$ 3 Hz, 1'-H), 4.4—5.0 (6 H, 3 ABq, CH_2Ph), 5.51 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 7.1—7.4 (15 H, m, Ph).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3',4',6'-tri-*O*-benzyl- β -D-mannopyranosyl)- α -D-galactopyranose (**18c**). Syrup, R_{F} (hexane—AcOEt 5:5) 0.34; $[\alpha]_D^{20} -32^\circ$ (c 0.7 in CHCl_3); δ_{H} (200 MHz) 1.30, 1.33, 1.42, and 1.52 (12 H, 4 s, Me), 3.40 (1 H, ddd, J 2.5, J 4.5, $J_{4,5}$ 9.5 Hz, 5'-H), 3.54 (1 H, dd, $J_{2,3}$ 3, $J_{3,4}$ 9.5 Hz, 3'-H), 3.6—3.8 (3 H, m, 6'-H₂ and 6-H_A), 3.89 (1 H, t, J 9.5 Hz, 4'-H), 4.02 (1 H, m, 5-H), 4.11 (1 H, dd, $J_{5,6B}$ 3, $J_{6A,6B}$ 11 Hz,

6-H_B), 4.19 (1 H, dd, $J_{1,2}$ 1, $J_{2,3}$ 3 Hz, 2'-H), 4.20 (1 H, dd, $J_{3,4}$ 8, $J_{4,5}$ 2 Hz, 4-H), 4.30 (1 H, dd, $J_{1,2}$ 5, $J_{2,3}$ 2.5 Hz, 2-H), 4.50 (1 H, d, $J_{1,2}$ 1 Hz, 1'-H), 4.57 (1 H, dd, $J_{2,3}$ 2.5, $J_{3,4}$ 8 Hz, 3-H), 4.48—4.92 (6 H, 3 ABq, CH₂Ph), 5.52 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 7.1—7.4 (15 H, m, Ph).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3',4',6'-tri-*O*-benzyl- α -D-mannopyranosyl)- α -D-galactopyranose (**19c**). Amorphous solid, R_F (hexane-AcOEt 5:5) 0.40; $[\alpha]_D^{20} + 7^\circ$ (c 1.0 in CHCl₃) (lit.,¹¹ 9°); δ_H (200 MHz) 1.32, 1.32, 1.40, and 1.51 (12 H, 4 s, Me), 3.6—4.0 (8 H, m, 5-H, 6-H₂, 3'-, 4'-, and 5'-H, and 6'-H₂), 4.06 (1 H, br t, J 1.5 Hz, 2'-H), 4.18 (1 H, dd, $J_{3,4}$ 8, $J_{4,5}$ 2 Hz, 4-H), 4.20 (1 H, dd, $J_{1,2}$ 5, $J_{2,3}$ 2.5 Hz, 2-H), 4.59 (1 H, dd, $J_{2,3}$ 2.5, $J_{3,4}$ 8 Hz, 3-H), 4.4—4.9 (6 H, 3 ABq, CH₂Ph), 4.95 (1 H, d, $J_{1,2}$ 1.5 Hz, 1'-H), 5.49 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), and 7.1—7.4 (15 H, m, Ph).

1,2:3,4-Di-*O*-isopropylidene-6-*O*-(3',4',6'-tri-*O*-benzyl- β -D-glucopyranosyl)- α -D-galactopyranose (**20c**). Syrup, R_F (hexane-AcOEt 5:5) 0.53; $[\alpha]_D^{20} - 38^\circ$ (c 0.7 in CHCl₃) (lit.,¹¹ -42°); δ_H (200 MHz) 1.32, 1.34, 1.44, and 1.53 (12 H, 4 s, Me), 3.4—4.2 (9 H, m, 2'-, 3'-, 4'-, and 5'-H, 6'-H₂, 5-H, and 6-H₂), 4.22 (1 H, dd, $J_{3,4}$ 8, $J_{4,5}$ 2 Hz, 4-H), 4.31 (1 H, dd, $J_{1,2}$ 5, $J_{2,3}$ 2.5 Hz, 2-H), 4.35 (1 H, d, $J_{1,2}$ 5 Hz, 1'-H), 4.61 (1 H, dd, $J_{2,3}$ 2.5, $J_{3,4}$ 8 Hz, 3-H), 5.55 (1 H, d, $J_{1,2}$ 5 Hz, 1-H), 4.4—5.1 (6 H, 3 ABq, CH₂Ph), and 7.1—7.4 (15 H, m, Ph).

Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- α -D-allopyranoside (**17d**). Syrup, R_F (hexane-AcOEt 7:3) 0.40; $[\alpha]_D^{20} + 14^\circ$ (c 0.8 in CHCl₃); δ_H (200 MHz) 2.06 (3 H, s, Ac), 3.41 (3 H, s, Me), 3.68 (1 H, dd, $J_{3,4}$ 3, $J_{4,5}$ 10 Hz, 4-H), 3.74 (1 H, dd, $J_{5,6A}$ 2.5, $J_{6A,6B}$ 10.5 Hz, 6-H_B), 3.80 (1 H, dd, $J_{5,6A}$ 3.5, $J_{6A,6B}$ 10.5 Hz, 6-H_A), 4.18 (1 H, br t, J 3 Hz, 3-H), 4.28 (1 H, ddd, $J_{4,5}$ 10, $J_{5,6A}$ 3.5, $J_{5,6B}$ 2.5 Hz, 5-H), 4.4—4.8 (6 H, m, CH₂Ph), 4.78 (1 H, dd, $J_{1,2}$ 4.5, $J_{2,3}$ 3 Hz, 2-H), 4.83 (1 H, d, $J_{1,2}$ 4.5 Hz, 1-H), and 7.1—7.4 (15 H, m, Ph) (Found: C, 70.7; H, 6.6. C₃₀H₃₄O₇ requires C, 71.1; H, 6.8%).

Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- β -D-altropyranoside (**18d**). Syrup, R_F (hexane-AcOEt 7:3) 0.28; $[\alpha]_D^{20} + 25^\circ$ (c 0.8 in CHCl₃); δ_H (200 MHz) 2.06 (3 H, s, Ac), 3.48 (3 H, s, Me), 3.71 (1 H, dd, $J_{3,4}$ 3, $J_{4,5}$ 9.5 Hz, 4-H), 3.72 (1 H, dd, $J_{5,6B}$ 5, $J_{6A,6B}$ 10.5 Hz, 6-H_B), 3.78 (1 H, dd, $J_{5,6A}$ 3, $J_{6A,6B}$ 10.5 Hz, 6-H_A), 3.84 (1 H, dd, $J_{3,4}$ 3, $J_{2,3}$ 4.5 Hz, 3-H), 4.09 (1 H, ddd, $J_{4,5}$ 9.5, $J_{5,6A}$ 3, $J_{5,6B}$ 5 Hz, 5-H), 4.3—4.8 (6 H, m, CH₂Ph), 4.83 (1 H, d, $J_{1,2}$ 1.5 Hz, 1-H), 5.12 (1 H, dd, $J_{1,2}$ 1.5, $J_{2,3}$ 4.5 Hz, 2-H), and 7.1—7.4 (15 H, m, Ph) (Found: C, 70.9; H, 6.9%).

Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- α -D-altropyranoside (**19d**). Syrup, R_F (hexane-AcOEt 7:3) 0.42; $[\alpha]_D^{20} + 52^\circ$ (c 1.0 in CHCl₃); δ_H (200 MHz) 2.04 (3 H, s, Ac), 3.40 (3 H, s, Me), 3.6—

3.9 (3 H, m, 4-H and 6-H₂), 3.91 (1 H, t, J 1 Hz, 3-H), 4.2—4.9 (8 H, m, 1- and 5-H, and CH₂Ph), 5.12 (1 H, dd, $J_{1,2}$ 3, $J_{2,3}$ 1 Hz, 2-H), and 7.1—7.4 (15 H, m, Ph) (Found: C, 70.7; H, 6.6%).

Methyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl- β -D-allopyranoside (**20d**). Syrup, R_F (hexane-AcOEt 7:3) 0.47; $[\alpha]_D^{20} - 18^\circ$ (c 1.0 in CHCl₃); δ_H (200 MHz) 2.03 (3 H, s, Ac), 3.50 (3 H, s, Me), 3.65 (1 H, dd, $J_{3,4}$ 2.5, $J_{4,5}$ 9.5 Hz, 4-H), 3.71 (1 H, dd, $J_{5,6B}$ 4.5, $J_{6A,6B}$ 11 Hz, 6-H_B), 3.79 (1 H, dd, $J_{5,6A}$ 2, $J_{6A,6B}$ 11 Hz, 6-H_A), 4.09 (1 H, ddd, $J_{4,5}$ 9.5, $J_{5,6A}$ 2, $J_{5,6B}$ 4.5 Hz, 5-H), 4.27 (1 H, t, J 2.5 Hz, 3-H), 4.61 (1 H, dd, $J_{1,2}$ 8, $J_{2,3}$ 2.5 Hz, 2-H), 4.81 (1 H, d, $J_{1,2}$ 8 Hz, 1-H), 4.4—4.8 (6 H, 3 ABq, CH₂Ph), and 7.1—7.4 (15 H, m, Ph) (Found: C, 70.7; H, 6.5%).

Acknowledgements

We thank Prof. G. Ricca for the 200 MHz n.m.r. spectra.

References

- 1 F. Nicotra, L. Panza, F. Ronchetti, G. Russo, and L. Toma, *Tetrahedron Lett.*, 1985, **26**, 807.
- 2 S. Tejima and H. G. Fletcher, Jr., *J. Org. Chem.*, 1963, **28**, 2999.
- 3 R. Barker and H. C. Fletcher, Jr., *J. Org. Chem.*, 1961, **26**, 4605.
- 4 K. Suzuki and T. Mukaiyama, *Chem. Lett.*, 1982, 683.
- 5 K. Suzuki and T. Mukaiyama, *Chem. Lett.*, 1982, 1525.
- 6 C. Earnshaw, C. J. Wallis, and S. Warren, *J. Chem. Soc., Perkin Trans. I*, 1979, 3099.
- 7 S. David, J. Eustache, and A. Lubineau, *J. Chem. Soc., Perkin Trans. I*, 1974, 2274.
- 8 R. Rabinowitz and J. Pellon, *J. Org. Chem.*, 1961, **26**, 4623.
- 9 G. Ekborg, B. Lindberg, and J. Lonngren, *Acta Chem. Scand.*, 1972, **26**, 3287.
- 10 V. R. Srivastava and C. Schuerch, *Tetrahedron Lett.*, 1979, 3269.
- 11 H. B. Boren, G. Ekborg, K. Eklind, Per. J. Garegg, A. Pilotti, and C.-G. Shwahn, *Acta Chem. Scand.*, 1973, **27**, 2639.
- 12 K. B. Sharpless and T. R. Verhoeven, *Aldrichimica Acta*, 1979, **12**, 63.
- 13 G. J. Karabatsos and D. J. Fenoglio, *Top. Stereochem.*, 1974, **5**, 167.
- 14 J. K. Cha, W. J. Christ, and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247.
- 15 T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi, *Tetrahedron Lett.*, 1978, 2741.
- 16 B. Capon, *Quart. Rev.*, 1964, **18**, 45.
- 17 J. G. Hill, B. E. Rossiter, and K. B. Sharpless, *J. Org. Chem.*, 1983, **48**, 3607.
- 18 A. L. Raymond and E. F. Schroeder, *J. Am. Chem. Soc.*, 1948, **70**, 2788.
- 19 N. E. Franks and R. Montgomery, *Carbohydr. Res.*, 1968, **6**, 286.

Received 28th May 1986; Paper 6/1049