Synthesis of Oligosaccharides by Cycloaddition. Part 5.[1] Cycloaddition on *cis*- and *trans*-Dienyl Ethers of Sugars and Regioselective Removal of Ethoxycarbonyl from Substituted Malonic Esters

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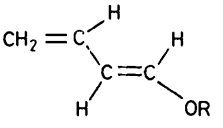
Both *cis*- and *trans*-3-*O*-(buta-1,3-dienyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose react with diethyl mesoxalate to give near quantitative yields of 2,2-bisethoxycarbonyl-2,3-dihydro-6*H*-pyran-(6*R*,*S*)-yl ethers (5) and (7), with the *S*-isomer predominating. Removal of ethoxycarbonyl then gives disaccharide analogues, mainly the derivatives *trans*-disubstituted at C-1′ and C-5′ of the newly-built unit, *i.e.* the α-glycosides (9) and (15). Cycloaddition onto the corresponding ethers of benzyl 2-*O*-allyl-4,6-di-*O*-benzylidene-α-D-galactopyranoside proceeds in the same way, giving a preponderance of the *R*-isomer. The faces of the *cis*- or *trans*-dienyl ethers which are the more reactive towards both diethyl mesoxalate and glyoxylic esters show similar disposition of atoms close to the sugar. This new sequence, which avoids the wasting of *cis*-dienyl ethers, is considered a significant improvement in the synthesis of disaccharides by cycloaddition.

In the previous papers of this series we have shown that the cycloaddition of glyoxylic esters to the *trans*-dienyl ethers of protected sugars leads to chiral dihydropyranyl ethers. These have proved to be suitable starting materials for synthesis of a variety of oligosaccharides, some with 1,2-*cis*-glycosidic linkages, such as the blood-group A trisaccharide antigenic determinant [2] or the pseudo-disaccharide component of kasugamycine.[3] A major drawback in such synthetic schemes was that *cis*-dienes were inert towards glyoxylic esters—a not unexpected finding. As our preparations of dienyl ethers gave mixtures of *cis*- and *trans*-derivatives in roughly equal proportions, this unreactivity has so far meant inefficient utilization of the starting protected sugar. While studying the addition of diethyl mesoxalate as a possible method of access to branched-chain sugars, we discovered that this more active dienophile could also add to the *cis*-ether. Addition of diethyl mesoxalate to 1,3-dienes [4] and alkoxybutadienes [5] has already been reported by Zamojski *et al.*, in the course of their researches on the total synthesis of sugars. Furthermore, we found that decarboxylation of the adducts according to a published procedure [6] gave analogues of the dihydropyrans already prepared from glyoxylic esters.

RESULTS

The addition of diethyl mesoxalate to the *trans*-diene (1) was complete in 3 h at 100 °C. Distillation then gave in 90% yield a mixture of two components with close mobility on t.l.c. Column chromatography allowed separation of a major, less polar, oily component from a more polar, crystalline one, in the head and tail fractions respectively, but was otherwise inefficient as a means of quantitative resolution. The 240 MHz ^{1}H n.m.r. spectra of these compounds are compatible with their formulation as the cycloaddition products (5) and (7). Correlations described below attribute *S*-configuration (5) to the major one and the *R*-configuration (7) to the other. Their proportions in the reaction mixture were estimated from integration of the n.m.r. signals of the 4′-H, 4″-H protons as $S : R = 68 : 32$.

Reaction of diethyl mesoxalate with the *cis*-diene (3) was slower, needing 36 h for completion at 100 °C.



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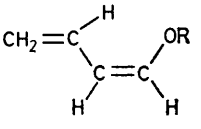

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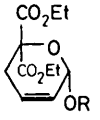

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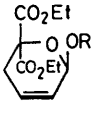

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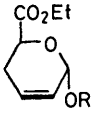

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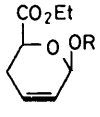

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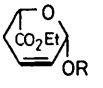

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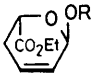

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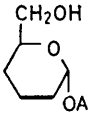
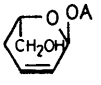
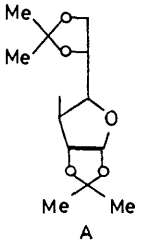


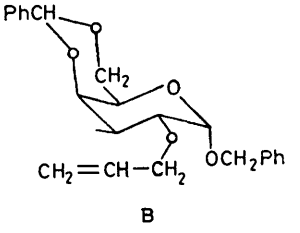
(17)



(18)



A



B

Distillation then gave, in 85% yield, a 92 : 8 mixture of the *S* and *R* adducts (5) and (7). Thus there is even greater stereoselectivity towards the *S*-configuration than in the case of the *trans*-diene.

Removal of ethoxycarbonyl from these substituted diethyl malonates (5) and (7) readily occurs when treated by the method of Krapcho and Lovey.[6] However, as solvent, we used hexamethylphosphoramide (HMPA) rather than dimethyl sulphoxide, as this led to a definite improvement in yields [82% from diester (5)]. Removal of ethoxycarbonyl from the major adduct gave a mixture of two compounds which may be considered as disaccharide derivatives modified in the non-reducing unit.* These could be separated by column chromatography. One of them (66%) was identified as the α-D-derivative (9) by lithium aluminium hydride reduction of the ester function, followed by catalytic hydrogenation of the double bond, to give the known crystalline alcohol (17). The other product (16%) disappeared on acidic isomerization with boron trifluoride–ether, proof of its *cis*-(β)-configuration.[7] The resulting *trans* isomer was identified as the α-L-derivative (15) by lithium aluminium hydride reduction to the known [7] crystalline alcohol (18). Thus the two products obtained by removal of ethoxycarbonyl from the major cycloaddition adduct were (9) (66%) and (13) (16%). Assuming retention of configuration at C-1′ during this reaction, this is proof that this major adduct has structure (5), with *S*-configuration at C-1′. It is interesting to note that our method was regioselective, giving four times more *trans*-product (9) than the *cis*-isomer (13).

Conversely, the same treatment of the minor, crystalline cycloaddition product gave, in 85% yield, a mixture of the β-D-glycoside (11) (16%) with its α-L-isomer (15) (84%). These configurations were proved by the same methods as above. They indicate that the minor, crystalline adduct has structure (7) with *R*-configuration at C-1′.

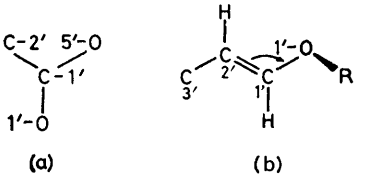
These experiments were extended to the *trans*-diene (2), the starting material in our synthesis of the blood-group A trisaccharide antigenic determinant,[2] and to its *cis*-isomer (4). The reaction of the *trans*-diene (2) is complete within 3 h at 80 °C and gives, in 82% yield, an 85 : 15 mixture of the *R*- and *S*-dihydropyrans (8) and (6), respectively. Similarly, the *cis*-diene (4), when kept at 80 °C for 11 h gives a 4 : 1 mixture of dihydropyrans (8) and (6) in 63% yield. Assignment of configuration at C-1′ in these derivatives rests on their further transformations.

Removal of ethoxycarbonyl from the adducts to the *cis*-diene (4) gave, as expected four products, (10), (12), (14), and (16), in varying yields. After isomerization with boron trifluoride, only the *trans*-(α)-derivatives (10) and (16) were present. The isomer melting at 111 °C (obtained in 48% *overall* yield) was proved to be the derivative with the α-L structure (16) by reduction with lithium aluminium hydride to a primary alcohol, followed by saturation of the double bond and acidic hydrolysis to give 2,3,4-trideoxy-L-*glycero*-hexose ($[\alpha]_D^{20}$ −41°). Conversely, similar treatment of the other isomer, m.p. 132 °C, gave 2,3,4-trideoxy-D-*glycero*-hexose ($[\alpha]_D^{20}$ +37°), proof of the α-D configuration (10) (*cf.* ref. 7).

* Carbohydrate nomenclature is henceforth more convenient.

From the known constitution of the *trans*-products (16) and (10) we may deduce that of the initial adducts: compound (16) could be accurately estimated only after the treatment with boron trifluoride–ether. A part of the amount recovered might have originated from isomerization of the *cis*-derivative (14), but there were only traces of this in the mixture obtained after the removal of the ethoxycarbonyl group. So the high overall recovery (48%) of the *trans*-derivative (16) indicates that the major product of cycloaddition to the *trans*-diene (2) (80% yield) has the *R*-configuration. The stereoselectivity is the same with the *cis*-diene (4).

The major products obtained from the cycloaddition of diethyl mesoxalate or glyoxylic esters [7] to the dienyl ethers (1) and (3) derived from ' diacetone-glucose ' have the same configuration at C-1′. Viewing along



(a) The common configuration at C-1′ of adducts to dienes (1) and (3), as seen from 1′-H; (b) view of the more reactive face of dienes (1) and (3) and the less reactive face of dienes (2) and (4)

the C-1′–1′-H bond, it may be seen that C-2′, the ring oxygen, 5′-O, and the glycosidic oxygen, 1′-O, are arranged clockwise (Figure). This configuration results from an attack by the carbonyl oxygen of the dienophile from one side of the plane defined by atoms 1′-O, C-1′, and C-2′; using the definition described in our previous paper,[1] this would be called the ' negative ' side, since clockwise rotation through *ca.* 120° would bring the C-1′–C-2′ bond coincident with C-1′–1′-O.

We also find that the major adducts of the dienyl ethers derived from a protected galactose, (2) and (4), in all investigated cases of cycloaddition,[1,2] have the same configuration at C-1′. But in this case, the common configuration is opposite and corresponds to an addition from the ' positive ' sides of the dienyl ethers.

In any conformer of these dienyl ethers involved in the cycloaddition, the two faces are clearly differentiated because of the chirality of the sugar moiety, either in steric accessibility, or in orbital reactivity, by asymmetric overlap with orbitals of some of the sugar atoms. This difference, which involves atoms of the dienyl ethers close to the sugar appears to be a more important factor of stereoselectivity than the configuration of the diene or the nature of the dienophile.

The above reactions are interesting as instances of easy cycloadditions to *cis*-dienes and as extensions of the method of removal of ethoxycarbonyl of Krapcho and

Lovey to fairly complicated malonic esters. On the other hand, they may provide in some cases the best routes to dihydropyranyl ethers, useful for oligosaccharide synthesis. They can easily be scaled up: we have prepared up to 45 g of a mixture containing only compounds (5) and (7) by operations involving only distillations. Removal of ethoxycarbonyl followed by column chromatography afforded 31.2 g of pure α-D-glycoside (9).

EXPERIMENTAL

Chromatographic separations were made using either silica gel columns or plates coated with a thin layer of silica gel. ^{1}H N.m.r. spectra were recorded at 240 MHz, for solutions in deuteriochloroform (unless otherwise stated), and are reported as p.p.m. downfield from internal Me_4Si. Coupling constants were obtained by double irradiation techniques. In the description of spectra, 4''-H refers to the pseudo-equatorial proton on C-4'.

3-O-[2,2-*Bisethoxycarbonyl*-2,3-*dihydro*-6H-*pyran*-(6R *and* S)-*yl*]-1,2:5,6-*di*-O-*isopropylidene*-α-D-*glucofuranose* (7) *and* (5).—A mixture of the *trans*-dienyl ether (1) (4.60 g; 1.47 mmol), diethyl mesoxalate (4.9 g), and hydroquinone (10 mg) was maintained at 100 °C for 3 h under nitrogen. Distillation gave a mixture of adducts (5) and (7), b.p. 180 °C at 0.01 mmHg (6.45 g; 90%), which was fractionated by column chromatography (CH_2Cl_2–cyclohexane–acetone, 25 : 8 : 1). Elution gave first the S-*isomer* (5) as an oil (2.134 g), homogeneous on t.l.c., $[\alpha]_D^{20}$ −45° (*c* 0.9 in CH_2Cl_2), δ 2.43 (1 H, m, 4'-H), 2.83 (1 H, dd, J_{gem} −17.7 Hz, $J_{3',4'}$ 5.1 Hz, 4''-H), 4.80 (1 H, d, $J_{1,2}$ 3.4 Hz, 2-H), 5.53 (1 H, $J_{1',2'}$ 2.2 Hz, $J_{1',3'}$ 1.3 Hz, 1'-H), 5.73 (1 H, m, $J_{2',3'}$ 10.5 Hz, 2'-H), 5.84 (1 H, d, 1-H), and 6.04 (1 H, m, 3'-H) (Found: C, 56.7; H, 7.1; O, 36.0. $C_{23}H_{34}O_{11}$ requires C, 56.8; H, 7.0; O, 36.2%).

The last fractions of the chromatography contained the pure R-*isomer* (7) (0.57 g), m.p. 66.5—68 °C (cyclohexane), $[\alpha]_D^{20}$ +24° (*c* 1.4 in CH_2Cl_2), δ([$^2H_6$]acetone) 2.68 (2 H, m, 4'-H, 4''-H), 5.60 (1 H, broad, $J_{1',2'}$ 2.1 Hz, $J_{1',3'}$ 0.9 Hz, 1'-H), 5.73 (1 H, dm, $J_{2',3'}$ 10.5 Hz, 2'-H), and 6.14 (1 H, m, 3'-H) (Found: C, 56.85; H, 7.0; O, 36.45. $C_{23}H_{34}O_{11}$ requires C, 56.8; H, 7.0; O, 36.2%).

Integration of the n.m.r. signals of protons 4'-H and 4''-H in the distilled mixture indicated a ratio *S* : *R* of 68 : 32.

Reaction of the *cis*-dienyl ether (3) (1.685 g; 5.36 mmol) with diethyl mesoxalate (1.8 g) in the presence of hydroquinone (10 mg) was complete after 36 h at 100 °C under nitrogen. Distillation then gave a 92 : 8 mixture of *S* (5) and *R* (7) isomers, b.p. 160—180 °C (2.22 g; 85%).

O-(*Ethyl* 2,3,4-*Trideoxy*-α-D-glycero-*hex*-2-*enopyranosyl-uronate*)-(1 ⟶ 3)-1,2:5,6-*di*-O-*isopropylidene*-α-D-*glucofuranose* (9).—A solution of the *S*-isomer (5) (243 mg; 0.3 mmol), water (0.02 ml), and NaCl (88 mg) in HMPA (1.6 ml) was heated at 180—190 °C for 2.5 h, under nitrogen. Chromatography (ether–light petroleum, 1 : 1) then gave a mixture of compounds (9) and (13) (168 mg; 82%) (Found: C, 57.7; H, 7.2; O, 34.7. $C_{20}H_{30}O_9$ requires C, 58.0; H, 7.2; O, 34.8%). A second chromatography ($CHCl_3$–toluene–acetone, 14 : 6 : 1) yielded the β-L-glycoside (13) (18%), an oil, δ 2.40 (2 H, m, 4'-H, 4''-H), 4.95 (1 H, d, $J_{1,2}$ 3.6 Hz, 2-H), 5.32 (1 H, narrow d, 1'-H), 5.71 (1 H, dm, $J_{2',3'}$ 10 Hz. 2'-H), 5.90 (1 H, d, 1-H), and 6.04 (1 H, m, 3'-H).

The more polar component of the mixture was the α-D-*glycoside* (9) (64%), an oil, $[\alpha]_D^{20}$ −45° (*c* 1.2 in CH_2Cl_2), δ 2.34 (2 H, 4'-H, 4''-H), 4.48 (1 H, dd, $J_{4',5'}$ 10 Hz, $J_{4'',5'}$ 5 Hz, 5'-H), 4.69 (1 H, d, *J* 3.6 Hz, 2-H), 5.38 (1 H, m, $J_{1',2'}$ 2.6 Hz, 1'-H), 5.77 (1 H, dm, $J_{2',3'}$ 10 Hz, 2'-H), 5.89 (1 H, d, 1-H), and 6.05 (1 H, m, $J_{3',4''}$ 5 Hz, 3'-H) (Found: C, 58.0; H, 7.3; O, 34.6. $C_{20}H_{30}O_9$ requires C, 58.0; H, 7.2; O, 34.8%).

A solution of the α-D-glycoside (9) (637 mg) in ether (10 ml) was reduced in the usual way by a solution of $LiAlH_4$ (120 mg) in ether (10 ml). After the usual work-up, the residue was dissolved in ether (15 ml) and hydrogenated at room temperature and atmospheric pressure to give the alcohol (17) (419 mg; 72%), m.p. 114—115 °C (methanol–ether) (lit.,[7] 112—115 °C).

Integration of the n.m.r. signals of the 2-H protons in the reaction mixture showed a ratio of α-D to β-L [(9) : (11)] of 4 : 1.

O-(*Ethyl* 2,3,4-*Trideoxy*-α-L-glycero-*hex*-2-*enopyranosyl-uronate*)-(1 ⟶ 3)-1,2:5,6-*di*-O-*isopropylidene*-α-D-*glucofuranose* (15).—A solution of the *R*-isomer (7) (293 mg; 0.6 mmol), water (0.015 ml), and NaCl (100 mg) in HMPA (2 ml) was heated at 190 °C for 1.5 h under nitrogen. Chromatography (ether–light petroleum) then gave a mixture of compounds (11) and (15) (213 mg; 85%) (Found: C, 57.9; H, 7.25. $C_{20}H_{30}O_9$ requires C, 58.0; H, 7.2%). A second chromatography ($CHCl_3$–toluene–acetone, 7 : 3 : 1) allowed partial resolution to give, as the less polar component, the α-L-*glycoside* (15) (71%), m.p. 95—97 °C, $[\alpha]_D^{20}$ +15° (*c* 1 in CH_2Cl_2), δ 2.34 (2 H, 4'-H, 4''-H), 5.24 (1 H, m, $J_{1',2'}$, 2.8 Hz, 1'-H), 5.72 (1 H, dm, 2'-H), 5.91 (1 H, d, $J_{1,2}$ 3.6 Hz, 1-H), and 6.06 (1 H, m, 3'-H) (Found: C, 58.0; H, 7.0; O, 34.8. $C_{20}H_{30}O_9$ requires C, 58.0; H, 7.2; O, 34.8%).

Reduction of the α-L-glycoside (15) (138 mg) in ether (5 ml) by a solution of $LiAlH_4$ (30 mg) in ether (5 ml), followed by the usual work-up and chromatography (ether–light petroleum, 7 : 1) gave the alcohol (18) (49%), m.p. 148 °C (lit.,[7] 148—149 °C).

The more polar component of the reaction mixture was the β-D-glycoside (11) (16%), an oil, δ 2.4 (2 H, 4'-H, 4''-H), 4.77 (1 H, d, $J_{1,2}$ 3.6 Hz 2-H), 5.48 (1 H, broad s, 1'-H), 5.71 (1 H, dm, 2'-H), 5.93 (1 H, d, 1-H), and 6.12 (1 H, m, 3'-H).

Integration of the n.m.r. signals of the 1'-H protons, showed a ratio of (11) : (15) in the reaction mixture of 84 : 16.

Isomerizations.—To 5% solutions of the derivatives in ether were added 2 drops of boron trifluoride–ether per 10 ml of solution. After 2 h at room temperature, the solutions were evaporated and the residues analysed by thin-layer and column chromatography (ether–light petroleum, 1 : 2). From the 84 : 16 mixture of the α-L-(15) and β-D-(11) isomers were obtained the α-L-isomer (15) (64%) and the β-D-isomer (9) (10%). In the same way, a 4 : 1 mixture of the α-D-isomer (9) and the β-L-isomer (1) [3] gave a mixture of compounds (9) (67%) and (15) (16%).

Benzyl 2-O-*Allyl*-4,6-O-*benzylidene*-3-O-[2,2-*bisethoxycarbonyl*-2,3-*dihydro*-6H-*pyran*-(6R *and* S)-*yl*]-α-D-*galactopyranoside* (8) *and* (6).—A mixture of the *trans*-dienyl ether (2) (0.9; 2 mmol), diethyl mesoxalate (0.46 g), and hydroquinone (10 mg) was kept at 80 °C for 3 h under nitrogen. Chromatography (CH_2Cl_2–cyclohexane–acetone, 20 : 10 : 1) then allowed separation of a mixture of adducts (6) and (8) (1.035 g; 82%) (Found: C, 65.0; H, 6.5. $C_{34}H_{40}O_{11}$

requires C, 65.4; H, 6.4%), δ 2.90 (dd, $J_{4',4''}$ −17.5 Hz, 4''-H, *S*-adduct) and 2.76 (dd, $J_{4'4''}$ −17.5 Hz, 4''-H, *R* adduct. Integration of the 4''-H n.m.r. signals showed the ratio of adducts *R*-(8) : *S*-(6) to be 85 : 15.

The reaction of the *cis*-dienyl ether (4) (2.64 g; 5.9 mmol) with diethyl mesoxalate (1.35 g) in xylene (5 ml) in the presence of hydroquinone (10 mg) was complete after 11 h at 80 °C under nitrogen. Chromatography then gave a 4 : 1 mixture of the *R*-(8) and *S*-(6) adducts (2.31 g; 63%) (Found: C, 64.7; H, 6.5. $C_{34}H_{40}O_{11}$ requires C, 65.4; H, 6.4%).

Benzyl 2-O-*Allyl*-4,6-O-*benzylidene*-3-O-[*ethyl* 2,3,4-*Trideoxy*-α-D- *and* -α-L-glycero-*hex*-2-*enopyranosyluronate*]-α-D-*galactopyranoside* (10) *and* (16).—Cycloaddition as above of diethyl mesoxalate with an unresolved mixture of the *cis*- and *trans*-dienyl ethers (2) and (4) gave a mixture of adducts (6) and (8). A solution of this mixture (2.35 g), water (0.1 ml), and NaCl (0.55 g) in HMPA (11 ml) was heated at 190 °C for 2 h under nitrogen. Chromatography (toluene–ether–light petroleum, 4 : 2 : 1) allowed isolation of a mixture of products (1.80 g; 87%) which was dissolved in ether (40 ml). Boron trifluoride–ether (0.2 ml) was added, and the solution was kept for 8 min at room temperature. Chromatography (same mixture as above) allowed the isolation of the *protected* α-L-*disaccharide* (16), as the less polar component [(1.07 g, 60% (calculated on the starting mixture)], m.p. 109—111 °C (from ether–light petroleum), $[\alpha]_D^{20}$ +208° (*c* 0.9 in CH_2Cl_2) (Found: C, 67.0; H, 6.5; O, 25.9. $C_{31}H_{36}O_9$ requires C, 67.4; H, 6.5; O, 26.0%).

The previously described sequence of reaction,[7] *i.e.* $LiAlH_4$ reduction of the ester function, hydrogenation of the double bond, and acidic hydrolysis, allowed isolation from compound (16) of the syrupy, reduced monosaccharide 2,3,4-trideoxy-L-*glycero*-hexopyranose, $[\alpha]_D^{20}$ −41° (water).

The more polar component of the above mixture was the protected α-D-*disaccharide* (10) (0.36 g), m.p. 130—132 °C (from ether–light petroleum), $[\alpha]_D^{20}$ +92° (*c* 0.7 in CH_2Cl_2) (Found: C, 67.4; H, 6.5; O, 26.1. $C_{31}H_{36}O_9$ requires C, 67.25; H, 6.7; O, 26.3%).

From compound (10), the previously described reaction sequence [1] allowed isolation of 2,3,4-trideoxy-D-*glycero*-hexopyranose, $[\alpha]_D^{20}$ +37° (water).

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