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UNSATURATED CARBOHYDRATES. PART 29[1] THEIR APPLICATION TO THE SYNTHESIS OF STEREOSPECIFICALLY DOUBLY AND TRIPLY BRANCHED DERIVATIVES

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Abstract: Treatment of 2,3-dideoxy-α-D-erythro-hex-2-enopyranosyl derivatives having 2-haloethyl substituents separately at O-1 and O-4 with tri-n-butyltin hydride together with a radical initiator gave products **16** and **5,6** with tetrahydrofuranyl rings cis-fused to C-1, C-2 and C-3, C-4, respectively. When these reactions, which afforded compounds with stereospecific branch-points at C-2 and C-3, were carried out in the presence of methyl acrylate or with allyltri-n-butyltin as radical carrier, the main products had the same bicyclic structures, but had additional branch-points at C-3 and C-2, and possessed the α-D-gluco- and α-D-altro-configurations, respectively.

The D-gluco-allyl adduct **19** was converted into the 4-en-6-als **25,26**, and these products gave mainly a mixture of epimeric cyclopentano-furanopyrans (which were characterised as the acetates **27,28**) on treatment with tri-n-butyltin hydride and radical initiator.

A notation is proposed for classifying intramolecular radical addition reactions of carbohydrates.

Introduction

The use of free radical reactions has, in recent years, added very markedly to the range of efficient carbon-carbon bonding reactions available in organic synthesis, and great advantage has been taken of these new developments.[2] In particular, the stereo- and regio-selectivities imposed upon intramolecular processes have been exploited in the production of many mono- and oligo-cyclic compounds.[3]

Carbohydrate chemistry has offered scope for application of radical procedures and intermolecular addition of carbon radicals to carbohydrate enones has illustrated the validity of this approach for the synthesis of compounds containing deoxy branched structures,[4] and the reverse procedure i.e. the addition of carbohydrate-derived carbon radicals to electron deficient alkenes likewise gives C-C linked products - either deoxy branched sugar derivatives (from non-terminal C-radicals) or extended chain compounds (from sugar chain terminal species).[5] The stereoselective factors operating in the course of these processes are of special significance and in these latter carbohydrate substitution reactions they permit the preferential introduction of axial groups at positions adjacent to the ring oxygen atoms of pyranoid compounds and equatorial substituents at other centres. Giese's contributions to the development of the basic appreciation of these factors and of carbohydrate radical chemistry is particularly notable.[2,6]

Our interests in the merits of selective free radical reactions of carbohydrates was attracted by bromine substitution processes which we encountered and have studied in some detail,[7] and our experience with unsaturated sugar derivatives[1] drew our attention to the opportunities offered by application of radical addition reactions to such compounds for the

preparation of simple and complex branched-chain substances of potential value in natural product synthesis; particular merit was attached to the intramolecular approach. Since the work described here on simple ring closures involving 2-haloethyl substituents bonded to O-1 or O-4 of 2,3-dideoxyhex-2-enopyranosyl compounds was commenced, two groups[8] have reported that these radical induced ring closures give good yields of products having tetrahydrofuranyl rings cis-fused at C-1, C-2 and C,3-C,4 i.e. pyranoid compounds with stereospecifically introduced branch-points at C-2 and C-3, respectively. Other recent related work has described reciprocal reactions whereby carbohydrate carbon radicals have been trapped within unsaturated substituent groups bonded either to a carbon atom of the molecule or attached by way of one of the oxygen atoms.[9] It is suggested that these two intramolecular processes be classified as $S^{\cdot}\text{-}C^{c=c}$ and $C^{\cdot}\text{-}S^{c=c}$ (substituent radical addition to carbohydrate alkene trap within the same molecule; carbohydrate radical addition to substituent alkene trap within the same molecule). Otherwise, carbohydrate carbon atom radicals may be added intramolecularly to alkene groups of the same sugar chain to give functionalised carbocyclic products[10] ($C^{\cdot}\text{-}C^{c=c}$); furthermore addition of a radical derived from a substituent group may be trapped by an alkene within another such group ($S^{\cdot}\text{-}S^{c=c}$) and bicyclic products would thus be formed from monocyclic carbohydrate derivatives.[11]

Commonly, these reactions have been carried out by use of halogenated compounds from which radicals have been generated by use of tri-n-butyltin hydride in the presence of a radical initiator, and the intramolecularly trapped radicals have been stabilised by bonding to hydrogen atoms of the reagent. Very importantly, however, they may react further by intramolecular or intermolecular processes prior to stabilisation by hydrogen abstraction, and the above notation can be extended, for example, to $S^{\cdot}\text{-}C^{c=c}\ E^{c=c}$ implying the intramolecular addition of a substituent radical to a carbohydrate alkene followed by intermolecular trapping by an added alkene. The various options (which disregard exo, endo possibilities) are represented schematically in Figure 1.

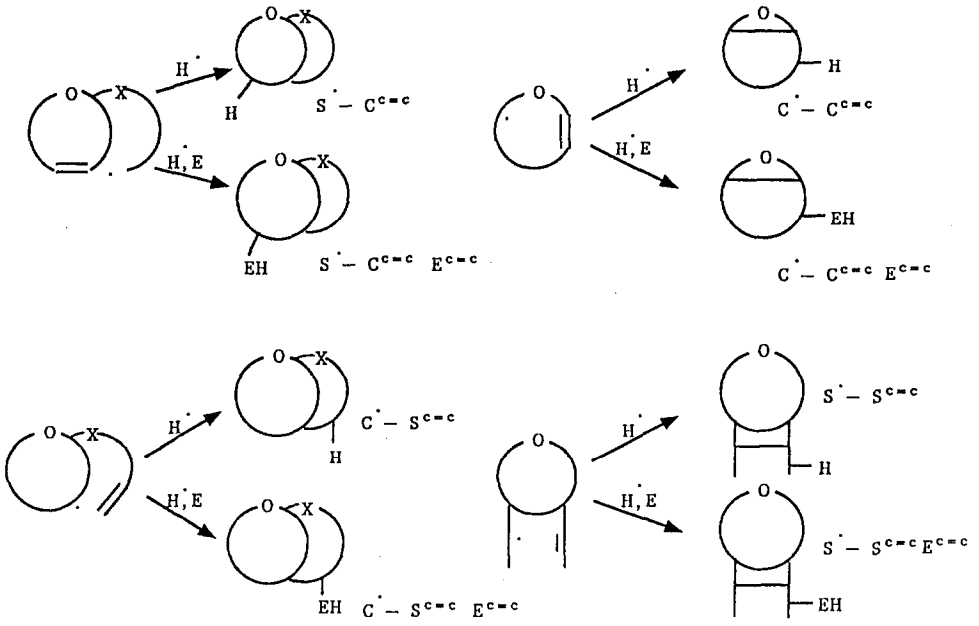


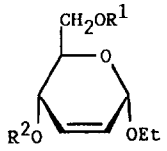
Figure 1. A notation for carbohydrate radical cyclisation reactions. (X Represents a point of joining of an O- or C-substituent to the carbohydrate chain).

Since the S·-C$^{c=c}$ E$^{c=c}$ strategy could lead by highly selective processes to doubly branched derivatives with potential for further synthesis, we undertook an investigation of this approach and have extended it by a S·-C$^{c=c}$ procedure to the synthesis of a triply branched carbohydrate. Such compounds have potential for the production of multi-C-substituted tetrahydropyran derivatives of the kind that occur in some terpenoid substances such as the trichothecenes.[12]

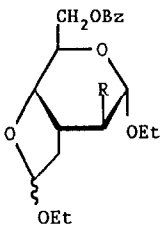
Results and Discussion

Reaction of the hydroxybenzoate **1**, made from the readily available diol **2** by selective benzoylation, with ethylvinyl ether in dichloromethane in the presence of N-iodosuccinimide,[13] gave the iodoacetals **3** and **4** as mixed epimers in equal proportions. Treatment of them with tri-n-butyltin hydride in benzene in the presence of azobis-isobutyronitrile (AIBN) gave the furanopyrans **5** and **6** which were isolated in 44 and 42% yield, respectively, the configurations at the new ethyl acetal centres being assigned by application of Hudson's Isorotation Rule[14] whereby isomers with the S-configuration at the acetal (anomeric) centre are the more dextrorotatary. Chapleur and Moufid[8b] reported that analogous ring closure in the case of the 6-O-trityl analogues of compounds **3**, **4** gave separable products in the ratio 1:1. Use of the p-nitrobenzoate rather than the benzoate **2** had the attraction of involving a crystalline starting material and affording a crystalline ethoxyiodide despite the formation of epimers, but the nitro-group of the latter proved unstable towards tri-n-butyltin hydride[15] and this approach could therefore not be utilised.

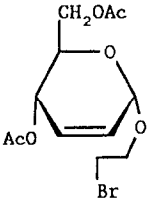
When the ring closure of compounds **3** and **4** was repeated with added methyl acrylate in a procedure developed by Stork and Sher,[13] and without optimisation of the conditions used, six products were formed: the epimeric pairs of the mono-(**7**,**8**), di-(**9**,**10**) and tri-(**11**,**12**)acrylate adducts (45:28:27%, gas chromatographic/mass spectrometric determination).



	R^1	R^2
1	Bz	H
2	H	H
3,4	Bz	CH(OEt)CH_2I



	R
5,6	H
7,8	$CH_2CH_2CO_2Me$
9,10	$CH_2CH(CO_2Me)CH_2CH_2CO_2Me$
11,12	$[CH_2CH(CO_2Me)]_2CH_2CH_2CO_2Me$
13,14	$CH_2CH{=}CH_2$



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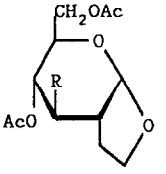


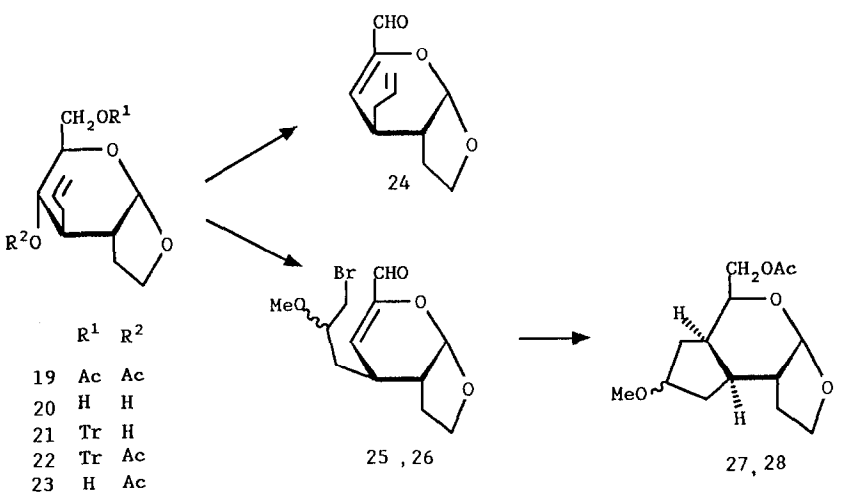
	R
16	H
17	$CH_2CH_2CO_2Me$
18	$CH_2CH(CO_2Me)CH_2CH_2CO_2Me$

Allyltri-n-butyltin[16] has previously been used as a radical allylating agent in carbohydrate chemistry and has afforded access to allyl C-glycosides[17] and to branched allyl derivatives[18] acting both as a radical initiator on phenyl 1-thioglycosides and C-iodinated compounds and as a radical trap. This reagent, together with AIBN, when used with the iodides **3** and **4** likewise initiated the reaction and caused radical trapping after ring closure to provide the doubly branched compounds

(**13**, **14**) in 84% isolated yield. The products, which were separated chromatographically, showed a $J_{4,5}$ value in the ^1H n.m.r. spectrum of 9.5 Hz indicating that their carbohydrate rings retained a conformation related to $^4C_1$, with H-4,5 axial, but the $J_{3,4}$ value of 7.8 Hz showed that there was ring flattening caused by the five-membered ring. The coupling between H-1 and H-2 (4.0 Hz) did not permit configurational assignment at C-2, but the altro-structure illustrated is strongly favoured in view of the known trans-nature of reactions of the kind used,[13] of the fact that the alternative allo-epimer would have required approach of the allylating reagent to C-2 from the side cis-both to the new C-3 substituent and to the aglycone, and of the finding that compound (**15**) undoubtedly afforded products with the branches in the trans-relationship. In coming to this conclusion that compounds **13**, **14** have an axial allyl group we recognise that there was a propensity for the intermediate C-2 radical to react to give an equatorially substituted product. In the comparable case of 1,2,4,6-tetra-O-acetyl-3-deoxy-3-iodo-ß-D-glucopyranose the same reagent afforded the equatorial 3-C-allyl-D-gluco-product and the axial allo-epimer in the ratio 6:1,[18] and in the case of the bicyclic **13**, **14** this ratio would have been reduced by the presence of the fused ring and the axial ethoxy aglycone both of which disfavour equatorial allylation at C-2. No epimers at this position were observed in the 300 MHz proton or ^{13}C n.m.r. spectra and it is therefore concluded that the steric factors precluded the formation of any significant proportions of equatorial products.

Reaction in the reverse sense using 2-bromoethyl 4,6-di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**15**), easily available by treatment of tri-O-acetyl-D-glucal with 2-bromoethanol in the presence of catalytic boron trifluoride,[19] afforded the crystalline compound **16** in 64% isolated yield (lit.[8b] 76, 88%) together with 8% of the product of reductive debromination.

Repetition of this cyclisation in the presence of methyl acrylate (4 mol equiv.) gave the adduct **17** with greater selectivity than was the case with the iodides **3** and **4**, 53% of the crystalline product being isolated together with the ethyl glycoside (28%) and the product of trapping of two molecules of methyl acrylate (**18**, 7%). Cyclisation with allyltri-n-butyltin afforded the doubly branched adduct **19** in 56% yield and the product of reductive cyclisation **16** (27%). Assignment of the D-gluco-configuration to compounds **17** and **19** followed from their $J_{3,4}$ and $J_{4,5}$ values which were both 8.3 Hz for the former and both 9.7 Hz for the latter compound.



	R^1	R^2
19	Ac	Ac
20	H	H
21	Tr	H
22	Tr	Ac
23	H	Ac

Since the allyl group of compound **19**, following, for example, addition of a halogen-containing reagent, represents a further potential radical source, we set out to determine whether its terminal carbon atom could be bonded to C-4 of the carbohydrate ring, and to this end the derived diol **20** was produced and from it, by selective substitution, the 6-trityl ether **21** and its acetate **22**. Removal of the trityl group and oxidation with dimethyl sulphoxide/oxalyl chloride/triethylamine[20] gave the corresponding aldehyde which underwent spontaneous ß-elimination of acetic acid[21] to yield the enal **24**. This product did not undergo selective electrophilic additions at the allyl double bond - presumably because the ring oxygen atom counteracted the electron withdrawing effect of the aldehyde group - and therefore the hydroxyacetate **23** was treated with a molar equivalent of N-bromosuccinimide in methanol and afforded a product the main fraction (55%) of which was shown by gas chromatography/mass spectrometry to be a mixture of two monobromo-monomethoxy adducts giving the expected molecular ions and evidence for the presence of one bromine atom and one methoxy group. The ^{1}H and ^{13}C n.m.r. spectra were also consistent with those expected, and a DEPT ^{13}C experiment indicated that the carbon atom bearing the methoxy group was methine in character and that bonded to bromine was methylene. That is, addition had occurred mainly in the Markownikov sense and the main products were compounds **25** and **26**.

It was expected that radicals formed by cleavage of the carbon-bromine bonds of compounds **25**, **26** would add intramolecularly to C-4 since the latter was electron deficient and also by virtue of the 5-exo-nature of the addition.[22] Any bromide present with the halogen bonded to C-2 of the allyl group would be inhibited from reacting at C-4 for steric reasons and at C-5 for electronic and stereoelectronic reasons.[22] Treatment of the bromoenals under usual ring closing conditions followed by reduction of the aldehyde and acetylation gave after chromatography two products (gas chromatographic analysis) the main component of which was shown by ^{13}C n.m.r. to have undergone loss of the alkene group and of the bromine atom. The accurate mass of the molecular ion further established that ring closure had occurred and that the product was the desired tricyclic, triply branched epimeric products **27,28**. The presence of the acetoxymethyl and the methoxy ring substituents was confirmed by mass spectrometry and the ^{13}C DEPT n.m.r. spectrum revealed the presence of three high field methylene and three such methine carbon atoms.

The ^{1}H and ^{13}C n.m.r. spectral characteristics of the compounds prepared are recorded in Tables 1-3.

Experimental

^{1}H and ^{13}C n.m.r. spectra were measured in $CDCl_3$ using a Varian FT80A or Bruker AC300 instrument. The DEPT experiments were carried out by the procedures of Doddrell et al.[23]

Gas chromatography/mass spectrometry was carried out using a Hewlett-Packard HP5995 system fitted with a split injector (20:1 split), a 12 m Hewlett-Packard HP-1 fused silica column (0.2 mm i.d.; 0.33 μm film) and an open split interface to the mass spectrometer. Gas chromatographic operating conditions were: injector temperature 250°C; oven temperature held at 50°C for 2 min, then raised at 6°/min to 250°C, helium carrier gas, inlet pressure 10 lbs/in^2. Mas spectra were scanned repetitively for 25-650 amu at an ionising voltage of 70eV. Accurate masses were determined by use of ammonia chemical ionisation on a VG 70-250s instrument.

Specific rotations were measured in chloroform within the concentration range 1-2% using a Perkin Elmer 241 polarimeter.

Ethyl 6-O-Benzoyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**1**).- Benzoyl chloride (0.89g, 1.1 mol equiv.) in dichloromethane (10 ml) were added slowly to a solution of ethyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (1g) in pyridine (10 ml) at 0°C and the mixture was stirred at this temperature for 3h and for 12h at 20°C. After filtering, benzene was added and the solution was extracted with dilute hydrochloric acid, washed with water and dried ($MgSO_4$). Column chromatography gave the syrupy 6-benzoate, 1.23g, 77%, $[\alpha]_D$ -2° ($CHCl_3$). (Found : C, 63.8; H, 6.8 $C_{15}H_{18}O_5$ requires

C, 64.7; H, 6.5%).

Ethyl (2'R),(2'S)-2',4-Anhydro-6-O-benzoyl-2,3-dideoxy-3-C-(2'-ethoxy-2'-hydroxyethyl)-α-D-ribo-hexopyranoside (**5,6**).- The benzoate **2** (0.52g) in dichloromethane (5 ml) was stirred with N-iodosuccinimide (0.45g, 1.05 mol equiv.) at -20°C, ethylvinyl ether (0.18g, 1.3 mol equiv.) in dichloromethane (2 ml) was added dropwise and the mixture was stirred for 6h, filtered and the solvent was evaporated. The residue in chloroform was washed with water and dried ($MgSO_4$). Removal of the solvent and chromatography on silica gel gave the ethoxyiodides (**3,4** 0.71g, 88%) which showed a consistent ^1H n.m.r. spectrum (2 EtO, CH_2I, CH_2CHOEt). To these in refluxing benzene (15 ml) and under oxygen-free nitrogen a solution of tri-n-butyltin hydride (0.49g, 1.1 mol equiv.) and azobis-isobutyronitrile (10mg) in benzene (10ml) was added slowly over 16h. Removal of the solvent gave a syrup which was dissolved in acetonitrile (50 ml) and extracted (x5) with light petroleum. Evaporation of the acetonitrile and resolution of the two component residue on silica gel (light petroleum, ethyl acetate, 2:1) gave the cyclised products : (S)-isomer **5**, 0.22g, 44%, $[\alpha]_D$ +129° (Found : C, 65.2; H, 7.2. $C_{19}H_{26}O_6$ requires C, 65.1; H, 7.5%); (R)-isomer **6**, 0.21g, 42%, $[\alpha]_D$ +25° (Found : C, 65.1; H,7.5%).

Cyclisation of the Iodides **3,4** in the Presence of Methyl Acrylate.- To the iodides **3,4** (0.3g) and methyl acrylate (0.28g, 5 mol equiv.) in refluxing benzene (15 ml), tri-n-butyltin hydride (0.21g, 1.1 mol equiv.) and AIBN (0.005g) in benzene were added over 16h. The crude products were isolated as for compounds **5**, **6** and were separated on silica gel to give a sample (0.07g, 26%) of a fraction having ^{13}C n.m.r. characteristics of the monoacrylate adducts **7,8**:

The unfractionated products were shown by gas chromatography/mass spectrometry to consist of the mono-, di- and tri-acrylate adducts **7,8**; **9,10**; **11,12** in the ratios 45:28:27.

7,8: 390(M-EtOH)$^+$; 364(M-EtOCH=CH_2)$^+$; 359(M-EtOH-MeO)$^+$; 345(M-EtOH-EtO)$^+$; 318(M-EtOCH=CH_2-EtOH)$^+$; 315(M-BzO)$^+$; 301(M-CH_2OBt)$^+$; 222(M-214); 196(M-EtOH-BzOH-EtOCH=CH_2)$^+$.

9,10: 476(M-EtOH)$^+$; 450(M-EtOHCH=CH_2)$^+$; 445(M-EtOH-MeO)$^+$; 431(M-EtOH-EtO)$^+$; 404(M-EtOCH=CH_2-EtOH)$^+$; 308(M-214); 282(M-EtOH-BzOH-EtOCH=CH_2)$^+$.

11,12: 531(M-EtOH-MeO)$^+$; 517(M-EtOH-EtO)$^+$; 490(M-EtOCH=CH_2-EtOH)$^+$; 394(M-214); 368(M-EtOH-BzOH-EtOCH=CH_2)$^+$.

Ethyl (2'S)-2-C-Allyl-2',4-anhydro-6-O-benzoyl-2,3-dideoxy-3-C-(2'-ethoxy-2'-hydroxyethyl)-α-D-altropyranoside (**13,14**).- To the iodo-compounds (**3,4**, 1g) and allyltri-n-butyltin (1.38g, 2.2 mol equiv.) in refluxing benzene (20 ml) and under oxygen-free nitrogen, AIBN (0.03g) in benzene (10 ml) was added over 16h. The solvent was removed and the residues were treated as for compounds **5,6** and separated on silica gel. The 2'S-isomer of the cyclised product (0.385g, 46%) had $[\alpha]_D$ +111° (Found : C, 67.4; H, 7.9. $C_{22}H_{30}O_6$ requires C, 67.6; H, 7.7%). The 2'R-isomer (0.32g, 38%), $[\alpha]_D$ +38° was shown to be a stereoisomer of the main product (^{13}C n.m.r. spectroscopy, mass spectrometry).

2-Bromoethyl 4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (**15**).- Tri-O-acetyl-D-glucal (5g) was dissolved in benzene containing 2-bromoethanol (3g, 1.3 mol equiv.), boron trifluoride etherate (0.5 ml) was added slowly and the solution was kept under nitrogen for 0.5h.[19] Washing with saturated aqueous sodium hydrogen carbonate (x2) and water, drying ($MgSO_4$) and removal of the solvent gave a product which crystallised on trituration with ethyl acetate/light petroleum. The unsaturated glycoside (4.73g, 76%) had m.p. 37.5-40°C, $[\alpha]_D$ +88° (Found : C, 43.4; H, 4.8. $C_{12}H_{17}BrO_6$ requires C, 42.8; H, 5.1%).

4,6-Di-O-acetyl-1,2'-anhydro-2,3-dideoxy-2-C-(2'-hydroxyethyl)-α-D-ribo-hexopyranose (**16**).- To the bromoethyl glycoside (1.0g) in refluxing benzene (20 ml) and under nitrogen, tri-n-butyltin hydride (0.95g, 1.1 mol equiv.) and azobis-isobutyronitrile (0.01g) in benzene (10 ml) were added over 16h. The crude products were prepared as for compounds **5,6** and on chromatographic separation as before gave ethyl 4,6-di-O-acetyl 2,3-dideoxy-α-D-erythro-hex-2-enopyranoside (0.06g, 8%) (n.m.r. characterisation) and the bicyclic adduct **16**, 0.49g, 64%, m.p. 69-71.5°C (from ether, light petroleum),

$[\alpha]_D$ +102° (Found : C, 55.8; H, 7.1. $C_{12}H_{16}O_8$ requires C, 55.8; H, 7.0%).

4,6-Di-O-acetyl-1,2'-anhydro-2,3-dideoxy-2-C-(2'-hydroxyethyl)-3-C-(methyl propanoat-3-yl)-α-D-glucopyranose (**17**).- To the bromoethyl glycoside **15** (3.0g) and methyl acrylate (3.1g, 4 mol equiv.) in refluxing benzene (60 ml) and under nitrogen, tri-n-butyltin hydride (2.85g, 1.1 mol equiv.) and AIBN (0.02g) in benzene (10 ml) were added over 16h. Processing as for compounds **5,6** gave the product of reductive cyclisation **16**, 0.64g, 28%, and the acrylate adduct **17**, 1.62g, 53% m.p. 56-58.5°C (from ethyl acetate/light petroleum), $[\alpha]_D$ +55° (Found : C, 55.6; H, 7.1. $C_{16}H_{24}O_8$ requires C, 55.8; H, 7.1%. A further fraction (0.27g, 7%) was established by gas chromatography/mass spectrometry to be the product (**18**) of addition of two molecules of methyl acrylate m/z 357$(M\text{-}CH_2OAc)^+$; 339$(M\text{-}AcOH\text{-}MeO)^+$; 328$(M\text{-}AcOH\text{-}CH_2CO)^+$.

4,6-Di-O-acetyl-1,2'-anhydro-3-C-allyl-2,3-dideoxy-2-C-(2'-hydroxyethyl)-α-D-glucopyranose (**19**).- AIBN (0.02g) in benzene (5 ml) was added over 16h to the bromoethyl glycoside (**15**, 1.0g) and allyltri-n-butyltin (1.97g, 2 mol equiv.) in refluxing benzene (20 ml). The crude products were isolated as for compounds **5,6** and separated by chromatography on silica gel to give the reductive ring-closed material **16** (0.21g, 27%) and the product of allylation (**19**) 0.495g, 56%, $[\alpha]_D$ +26° (Found : C, 60.4; H, 7.2. $C_{15}H_{22}O_8$ requires C, 60.4; H, 7.3%).

1,2'-Anhydro-3-C-allyl-2,3-dideoxy-2-C-(2'-hydroxyethyl)-α-D-glucopyranose (**20**).- The diacetate (**19**, 1.0g) was treated in triethylamine, methanol, water (50 ml, 1:5:4) for 2 h at 20°C and the solvents were removed to give a syrup which crystallised from ethyl acetate/ether to afford the diol (**20**), 0.65g, 91%, m.p. 111-112.5°C, $[\alpha]_D$ +62° (Found : C, 61.7; H, 8.7. $C_{11}H_{18}O_4$ requires C, 61.7; H, 8.5%).

4-O-Acetyl-1,2'-anhydro-3-C-allyl-2,3-dideoxy-2-C-(2'-hydroxyethyl)-6-O-triphenylmethyl-α-D-glucopyranose (**22**).- The diol (**20**, 2.0g) was stirred in pyridine (50 ml) containing triphenylmethyl chloride (3.9g, 1.5 mol equiv.) at 100°C for 1.5 h. After the solution had cooled to 20°C, acetic anhydride (10 ml) was added and stirring was continued for 2h after which the mixture was poured onto ice. Extraction with dichloromethane (x4) and washing of the extract with dilute hydrochloric acid and water followed by drying ($MgSO_4$) and removal of the solvent gave a syrup which was purified by chromatography on silica gel. Crystallisation from water/ethanol afforded the tritylated acetate (**22**), 4.1g, 87%. Recrystallised from this solvent it had m.p. 112-115°C, $[\alpha]_D$ +32° (Found : C, 77.1; H, 6.9. $C_{32}H_{34}O_5$ requires C, 77.1; H, 6.9%).

4-O-Acetyl-1,2'-anhydro-3-C-allyl-2,3-dideoxy-2-C-(2'-hydroxyethyl)-α-D-glucopyranose (**23**).- The trityl ether (**22**, 4.56g) was stirred in aqueous acetic acid (50 ml, 80%) at 50°C for 15 min, the solvent was evaporated to low volume and re-evaporated following the addition of toluene (x2) to give a syrupy which was resolved on silica gel to give the hydroxyacetate (**23**), 1.85g, 77%, $[\alpha]_D$ +47° (Found : C, 59.6; H, 7.6. $C_{13}H_{20}O_5.0.25\ H_2O$ requires, C, 59.9; H, 7.9%).

Oxidation of the Hydroxyacetate **23**.- Compound **23** (0.85g) in dichloromethane (5 ml) was added over 5 min with stirring at -50°C and under nitrogen to a solution of oxalyl chloride (0.35 ml) and dimethylsulphoxide (0.6 ml) in dichloromethane (2 ml) and stirring was continued for a further 15 min. Triethylamine (2.5 ml) was then added and the mixture was stirred for 5 min and allowed to warm to 20°C. Water (10 ml) was added and the aqueous layer was extracted with dichloromethane. Washing of the organic phase with dilute hydrochloric acid, drying ($MgSO_4$) and removal of the solvent gave a syrup which was purified on silica gel the give a product (0.52g, 79%) having n.m.r. characteristics consistent with it being the 4-en-6-al **24**.

6-Aldehydo-1,2'-anhydro-3-C-(3-bromo-2-(R,S)methoxypropyl)-2,3,4-trideoxy-2-C-(2'-hydroxyethyl)-ß-L-threo-hex-4-endialdo-1,5-pyranose (**25,26**).- The hydroxyacetate (**23**, 0.20g) and N-bromosuccinimide (0.15g, 1.1 mol equiv.) were dissolved in methanol (5 ml) at 20°C. After 5 min the solvent was removed, the residue was dissolved in dichloromethane (20 ml) and the solution was washed with aqueous sodium thiosulphate and then water. After drying and removal of the solvent a syrup was obtained which gave a ^{13}C n.m.r. spectrum indicating the presence of a methoxy group and the absence of the allyl alkene group.

Table 1. ^{1}H N.m.r. Chemical Shifts (δ values) for Compounds (80 or 300 MHz in $CDCl_3$)[a]

Carbon atoms are numbered according to the carbohydrate convention, branch chain atoms according to the pyranoid ring positions to which the branches are bonded and then by use of primes (′) from these atoms.

Compound	H-1	H-2α[b]	H-2β	H-3α[b]	H-3β	H-4	H-5	H-6	H-6′	H-2′	H-2″	H-2‴	H-3′	H-3″	H-3‴	Other protons[c]
1[a]	5.01	5.75	-	5.99	-	<3.8-4.2>		4.51	4.75	-	-	-	-	-	-	-
3,4	5.02	5.82	-	6.11	-	<	4.1-4.8		>	-	-	-	-	-	-	$C\underline{H}_2I$, 3.25; $C\underline{H}CH_2I$, 4.1-4.8
5	5.16	d	d	-	2.55	4.08	3.94	4.58	4.43	-	-	-	d	4.85	-	H-2′,3′, 1.25-2.1, 4H
6	5.15	d	d	-	2.42	4.08	4.10	4.63	4.43	-	-	-	d	4.84	-	H-2′,3′, 1.25-2.1, 4H
13	5.14	d	-	-	d	4.10	3.96	4.58	4.42	d	5.78	5.0	d	4.6	-	H-2,3,2′,3′, 1.7-2.4, 6H
15[a]	5.09	5.83	-	5.93	-	5.27	<	3.9-4.2	>	-	-	-	-	-	-	$C\underline{H}_2Br$, 3.53; $C\underline{H}_2CH_2Br$, 3.9
16[a]	5.32	-	d	d	d	4.80	<	3.7-4.4	>	d	d	-	-	-	-	H-2β,3α,3β,2′,1.5-2.5,5H; H-2″,3.7-4.4,1H
17[a]	5.35	-	d	d	-	4.83	d	4.29	d	d	d	-	d	d	-	H-2β,3α,2′,3′,3″,1.2-2.5,8H; H-5,6′,2″,3.7-4.1,4H
19	5.34	-	d	d	-	4.86	d	4.28	d	d	d	-	d	5.8	5.1	H-2β,3α2′,3′,1.7-2.2,6H; H-5,6′,2″,3.8-4.1,4H
20	5.30	-	d	d	-	3.52	<3.8-3.9>		3.64	d	3.92 4.05	-	d	5.92	5.1	H-2β,3α,2′,3′,1.6-2.5,6H
22	5.41	-	d	d	-	4.95	3.9	3.20	3.07	d	3.9	-	d	5.8	5.0	H-2β,3α,2′,3′,1.7-2.2,6H
23	5.36	-	d	d	-	4.79	3.7	3.55	3.7	d	3.91 4.08	-	d	5.8	5.1	H-2β,3α,2′,3′,1.8-2.4,6H
24	5.39	-	d	d	-	5.83	-	9.18	-	d	3.95 4.16	-	d	5.8	5.2	H-2β,3α,2′,3′,1.6-2.6,6H
25,26	5.41 5.46	-	d	d	-	5.8	-	9.19 9.20	-	d	4.0 4.2	-	d	d	d	H-2β,3α,2′,3′,1.6-2.4,6H; H-3″,3‴,OMe,3.35-3.5,6H

[a] 300 MHz unless labelled "a". [b] If protons cannot be identified as α- or β- etc they are recorded under 2α,3α. [c] Resonances for such groups as benzoyl, ethyl, acetyl, trityl were present as required by the assigned structures in all cases. [d] See under "Other Protons".

Dimethylsulphoxide (0.13 ml, 2 mol equiv.) in dichloromethane (5 ml) was added at -50°C with stirring and under oxygen-free nitrogen to a solution of oxalyl chloride (0.06 ml, 1.1 mol equiv.). After 2 min the unpurified methoxybromides in dichloromethane (5 ml) were added at -50°C over 5 min and stirring was continued for 15 min. Triethylamine (1 ml, 5 mol equiv.) was then added and after 5 min the mixture was allowed to warm to room temperature and partitioned between water (10 ml) and dichloromethane (50 ml). The organic phase was washed with dilute hydrochloric acid, then water and was dried ($MgSO_4$). Removal of the solvent gave a syrup (0.17g, 70%) shown by thin layer chromatography to consist mainly of one product which was isolated (0.13g, 55% from **23**) by chromatography on silica gel. This was mainly the enals **25, 26** (see Discussion): Found : m/z MH^+ 307.0354. $C_{12}H_{18}BrO_4$ requires 307.0368; 287, 289 $(M\text{-}OH)^+$; 275, 277 $(M\text{-}CHO)^+$; 273, 275 $(M\text{-}OMe)^+$; 225 $(M\text{-}Br)^+$; 153 $(M\text{-}CH_2CH(OMe)CH_2Br)^+$.

(1S,3S,4R,6R/S,8S,9R)-3-Acetoxymethyl-6-methoxy-2,12-dioxatricyclo[7.3.0.0^{4,8}]dodecane (**27, 28**).- Tri-n-butyltin hydride (104 mg, 1.1 mol equiv.) and AIBN (5 mg) in benzene (1 ml) were added over 16 h to the methoxybromides (**25, 26**, 0.10g) in refluxing benzene (5 ml) under oxygen-free nitrogen. The crude reaction products were isolated as for compounds **5, 6** were then dissolved in methanol (5 ml) and stirred after the addition of sodium borohydride (0.1g) for 15 min. The solvent was removed and the residue was treated with acetic anhydride (2 ml) and pyridine (4 ml) for 2 h after which time the mixture was poured onto ice. Extraction with dichloromethane (x4) and washing of the extract with dilute hydrochloric acid and water followed by drying ($MgSO_4$) and removal of the solvent gave a syrup from which the major product was isolated by chromatography on silica gel (32mg, 35%) and was shown to contain two components by gas chromatography. ^{13}C n.m.r. spectroscopy and mass spectrometry showed them to be the stereoisomeric tricyclic compounds **27, 28** (see Discussion). Found : m/z MH^+ 271.1542, $C_{14}H_{23}O_5$ requires 271.1545; 269 $(M\text{-}H)^+$; 210 $(M\text{-}AcOH)^+$; 197 $(M\text{-}CH_2OAc)$; 178 $(M\text{-}AcOH\text{-}MeOH)^+$; 165 $(M\text{-}CH_2OAc\text{-}MeOH)^+$.

Table 2. ^1H-^1H Coupling Constants (J, Hz) for Compounds (80 or 300 MHz in $CDCl_3$)[a,b]

(For carbon atom numbering see Table 1)

Compound	$J_{1,2\alpha}$	$J_{1,2\beta}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
1[a]	1.9	-	10.3	<1	-	2.1	4.4	12.1
3,4	<2	-	10.3	-	-	-	-	-
5	1.9	4.4	7	7.4	9.4	2.7	7.2	11.7
6	2.2	5.4	-	-	9.8	2.0	6.4	11.7
13	4.0	-	-	7.8	9.5	2.5	7.2	11.6
15[a]	1.8	-	7.5	-	9	-	-	-
16[a]	-	3.9	-	9.5, 4.6	9.5	5	-	12.0
17[a]	-	3.5	-	8.3	8.3	4.9	-	12.1
19	-	4.2	-	9.7	9.7	4.9	-	12.2
20	-	4.3	-	9.7	9.7	3.7	-	12.2
22	-	4.5	-	9.4	9.4	2.7	4.6	10.2
23	-	4.0	-	9.7	9.7	4.0	-	8.5
24	-	3.7	-	5.0	-	-	-	-
25,26	-	4.0, 3.8	-	-	-	-	-	-

[a] 300 MHz unless labelled "a". [b] Many other couplings were observed in the 300 MHz spectra but were not analysed.

Table 3. ^{13}C N.m.r. Chemical Shifts (δ scale) for Compounds in $CDCl_3$

(For carbon atom numbering see Table 1)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-2′	C-2″	C-2‴	C-3′	C-3″	C-3‴	Other Carbons[a]
3,4	100.4 103.0	127.1[c] 127.2[c]	133.0[c] 133.1[c]	67.7[b] 67.9	67.9[b] 70.7	61.4 62.1	-	-	-	-	-	-	$\underline{C}H_2I$, 4.5,5.3; $\underline{C}HCH_2I$, 94.1, 94.2
5	103.8	31.2[c]	31.8	67.7[b]	74.5[b]	65.4	-	-	-	37.8[c]	96.9	-	
6	105.1	31.4[c]	32.9	68.4[b]	76.6[b]	65.3	-	-	-	37.6[c]	97.3	-	
7,8	103.7	37.8[d]	41.4[d]	68.4[b]	74.3[b]	65.5	31.6	27.3	173.8	37.5[c]	101.8	-	
13	103.6	36.8[d]	41.2[d]	68.1[b]	73.9[b]	65.5	36.2[c]	135.6	117.0	37.3	100.5	-	
14	104.9	36.4[d]	40.1[d]	68.9[b]	76.2[b]	65.6	36.4[c]	136.0	116.7	38.1[c]	101.1	-	
16	101.2	34.6	29.8[b]	66.5	69.5	65.4	30.1[b]	62.3	-	-	-	-	
17	101.2	39.7	40.3	69.9	69.9	65.6	31.1	63.2	-	26.5[b]	29.4[b]	173.5	$\underline{C}H_3O$, 51.6
19	101.3	39.8	40.4	69.5[b]	69.9[b]	65.5	29.5	63.2	-	35.7	135.4	117.2	
20	101.7	39.2[c]	41.8[c]	68.4[b]	72.8[b]	65.3	29.4	62.7	-	35.1	135.8	117.6	
22	101.2	39.5[c]	40.3[c]	69.9[b]	71.0[b]	65.6	29.3	63.0	-	35.8	135.7	117.0	
23	101.3	39.1[c]	39.4[c]	69.3[b]	71.4[b]	65.3	29.2	61.6	-	35.4	134.9	117.4	
24	98.4	40.7[b]	42.1[b]	122.0	149.2	186.6	28.0	67.7	-	33.8	134.7	118.2	
25,26	98.2, 98.4	40.1[a] 41.1	42.4[a] 43.4	121.8	149.2	186.5, 186.6	27.8, 28.1	67.8 67.9	-	33.4, 33.6	77.2 77.5	30.1 30.8	$\underline{C}H_3O$, 57.4, 59.1
27,28	99.5	37.5[b] 38.4	40.7[b] 41.0	33.3[b] 33.8	73.6	65.5 65.7	28.1[c] 28.4	68.0	-	33.6[c] 34.4	80.6 80.8	36.6[c] 37.4	$\underline{C}H_3O$, 56.2, 56.9

[a] Resonances for such groups as acetyl, benzoyl, ethyl, trityl were present as required by the assigned structures in all cases.
[b, c, d] Assigned resonances may be interchanged.

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