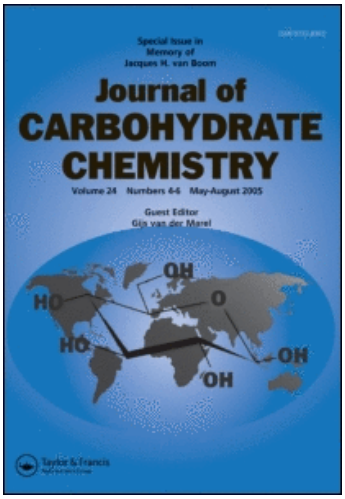

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Use of Unsaturated Sugars as Alkylating Agents. Addition of Enol Esters and Ethers to Glycals

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USE OF UNSATURATED SUGARS AS ALKYLATING AGENTS. ADDITION OF ENOL ESTERS AND ETHERS TO GLYCALS

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ABSTRACT

Addition of enol esters to acetylated 1,5-anhydro-D-hex-1-enitols (acetylated-D-glycals) in the presence of a Lewis acid catalyst yields acetylated 3-deoxy-α-D-hex-2-enopyranosyl compounds which can serve as starting materials for the synthesis of other C-(α-D-hexopyranosyl) compounds.

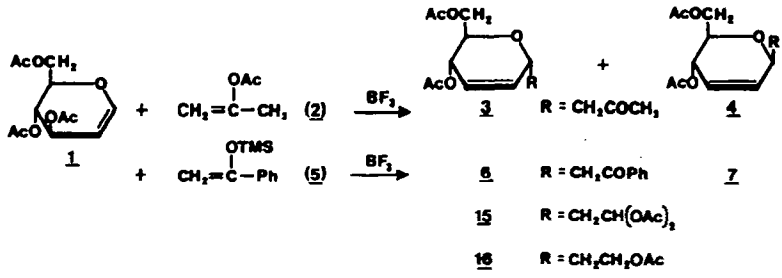
INTRODUCTION

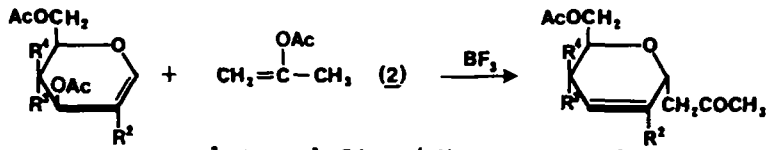
α-D-C-Glycopyranosides have been obtained heretofore only by photochemical addition to glycals[2-5] or by a sigmatropic (Claisen) rearrangement of glycals.[6-9] Other reactions give β-D-C-glycopyranosides or anomeric mixtures of C-glycosides. We recently reported[10] a simple, efficient, stereoselective synthesis of C-(α-D-hexopyranosyl) compounds via addition of enol esters to glycals, another example of a reaction wherein unsaturated sugars are used as alkylating agents[11] and another example of addition of nucleophiles to glycals.[12] Reported in this presentation was reaction of glycal 1 with enol ester 2 and enol ether 5 to give, respectively, C-glycoside pairs 3-4 and 6-7 and reaction of glycals

8 and 10 with enol ester 2 to give stereoselectively C-glycosides 9 and 11, respectively. Subsequently Dawe and Fraser-Reid[13] submitted their results with the reaction of 1 with 5 to yield 6 plus 7. We now report additional data relating to the synthesis and characterization of C-glycosyl analogs of pyranosides produced via the addition of enol esters and ethers to glycals.

RESULTS AND DISCUSSION

3,4,6-Tri-O-acetyl-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (1, tri-O-acetyl-D-glucal)[14] reacted smoothly with 2-acetoxy-1-propene (2, isopropenyl acetate), in the presence of a Lewis acid catalyst, to afford a high yield of (4',6'-di-O-acetyl-2',3'-dideoxy-α-D-erythro-hex-2'-enopyranosyl)propanone (3) accompanied by small amounts of the less polar isomer, (4',6'-di-O-acetyl-2',3'-dideoxy-β-D-erythro-hex-2'-enopyranosyl)propanone (4). Structural assignments of the products are based on ^{1}H-NMR spectra (200 MHz), chemical shifts and coupling constants recorded for compounds 3 and 4 being determined by a series of ^{1}H decoupling experiments. For compound 4, $J_{4',5'}$ is 8.5 Hz (axial-axial arrangement); whereas for 3, the main product, $J_{4',5'}$ is 5.7 Hz, indicating an equilibrium between the $^5H_0$ and $^0H_5$ conformers, a likely consequence of introducing a pseudo-axial substituent at the "anomeric" center. The values of $J_{4'5'}$ are in agreement with those found for anomeric pent-2-enopyranosides.[15] Compound 3 gave a positive iodoform test and formed a crystalline p-toulenesulfonylhydrazone; mp 114°, $[\alpha]^{20}D$ + 39° (c 1.0, CH_2Cl_2).





8	R^2 = OAc, R^3 = OAc, R^4 = H	9
10	R^2 = OAc, R^3 = H, R^4 = OAc	11
12	R^2 = NAc_2, R^3 = OAc, R^4 = H	13

The BF_3-catalyzed reaction of 1 with 1-trimethylsilyloxy-1-phenylethene (5) followed the pattern observed for reaction with 2, affording two acetophenone derivatives (6 and 7, combined yield 94%) which exhibited spectral features analogous to those of 3 and 4. The alpha configuration is assigned to the major product (6) on the basis of comparison of the ^{1}H-NMR spectra and specific optical rotation values of both products.

Other glycals (8, 10, 12) reacted with 2 in the presence of BF_3, affording compounds 9, 11, and 13 (single isomer in each case, $J_{4',5'}$~7.0 Hz for compounds 9 and 13 and 2.5 Hz for compound 11).

Glycal 1 also reacted under these conditions with acetoxyethene (14, vinyl acetate) affording a 1,1-diacetoxy-2-glycosylethane derivative. Apparently, the intermediate carbocation was stabilized by addition of AcO^- rather than by expulsion of Ac^+ as in the reaction with 2. Use of $FeCl_3$-Ac_2O catalyst in the reaction of 1 with 14 resulted in an 83% yield of 2-(4',6'-di-O-acetyl-2',3'-dideoxy-α-D-erythro-hex-2'-enopyranosyl)ethane-1,1-diol 1,1-diacetate (15).

EXPERIMENTAL

(4',6'-Di-O-acetyl-2',3'-dideoxy-α- and -β-D-erythro-hex-2'-enopyranosyl)propanone (3 and 4). 1 (2.72 g, 10 mmole) was dissolved in dichloromethane (5 mL). 2 (5 mL) and boron trifluoride etherate (4 drops) were added in that order, and the reaction mixture was kept at room temperature in a stoppered flask. When tlc on silica gel (1:1 v/v pet. ether-ethyl acetate) revealed the

absence of 1 (0.5 h), the reaction mixture was diluted with dichloromethane (20 mL) and washed with an aqueous sodium bicarbonate solution and water. The organic layer was dried with anhydrous magnesium sulfate and filtered through a 2-cm layer of basic alumina. The sorbent was subsequently washed with more dichloromethane (50 mL), and the combined solutions were evaporated. The excess of isopropenyl acetate was removed by evaporation of the residue with toluene; yield of 3 + 4 after chromatography, 2.29 g (85%). Column chromatography of the reaction products on silica gel using 9:1 v/v pet. ether-ethyl acetate afforded first the minor component, 4: yield 5%; bp 170°/0.8 torr; $[\alpha]^{20}_{D}$ +65° (c 1.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 2.06 (s, 6H, Ac), 2.20 (s, 3H, $COCH_3$), 2.67 (2Xpd, 2H, CH_2CO), 3.73 (m, 1H, H-5'), 4.18 (m, 2H, CH_2OAc), 4.63 (bs, 1H, H-1'), 5.26 (bd, 1H, $J_{4',5'}$ 9.0 Hz, H-4'), 5.75 (m, 1H, $J_{2',3'}$ 10.5 Hz, H-3'), 5.85 (m, 1H, H-2'), followed by the major component, 3: yield 80%; bp 170°/0.8 torr; $[\alpha]^{20}_{D}$ +110° (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 6H, Ac), 2.20 (s, 3H, $COCH_3$), 2.74 (2Xpd, 2H, CH_2CO), 3.94 (m, 1H, H-5'), 4.18 (m, 2H, CH_2OAc), 4.72 (m, 1H, $J_{1'-CH}$ 5.7 + 8.2 Hz, $J_{1',2'}$ 1.5 Hz, $J_{1',3'}$ 2.0 Hz, H-1'), 5.12 (m, 1H, $J_{3',4'}$ 1.5 Hz, $J_{2',4'}$ 2.7 Hz, $J_{4',5'}$ 5.7 Hz, H-4'), 5.82 (2m, 1H, $J_{2',3'}$ 10.5 Hz, H-2'), 5.95 (2m, 1H, H-3').

3-(4',6'-Di-O-acetyl-2',3'-dideoxy-α- and -β-D-erythro-hex-2'-enopyranosyl)-1-phenylpropan-2-one (6 and 7). The title compounds were obtained in the same way as a 4:1 mixture (94% yield) and were resolved chromatographically. The less polar compound, 6, was obtained as a colorless oil; $[\alpha]^{20}_{D}$ + 42° (c 1.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 2.08 and 2.10 (2s, 6H, Ac), 3.25 (2Xpd, 2H, CH_2CO), 3.79 (m, 1H, H-5'), 4.18 (m, 2H, CH_2OAc), 4.86 (m, 1H, H-1'), 5.30 (m, 1H, $J_{4',5'}$ 9.2 Hz, H-4'), 5.77 (pt, 1H, $J_{2',3'}$ 10.2 Hz, $J_{1',3'}$ 2.0 Hz, $J_{3',4'}$ 2.0 Hz, H-3'), 5.95 (pt, 1H, $J_{1',2'}$ 1.7 Hz, $J_{2',4'}$ 1.7 Hz, H-2'), 7.50 (m, 3H, aromatic), 7.96 (m, 2H, aromatic). The more polar compound, 7, was also an oil; $[\alpha]^{20}_{D}$ +160° (c 1.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 2.02 and 2.06

(2s, 6H, Ac), 3.32 (2Xpd, 2H, $\underline{CH_2}CO$), 3.99 (m, 1H, H-5'), 4.18 (2Xpd, 2H, $\underline{CH_2}OAc$), 4.94 (m, 1H, H-1'), 5.15 (m, 1H, H-4'), 5.85 (m, 1H, $J_{2'3'}$ 10.5 Hz, J 3.0 Hz, J 1.7 Hz, H-3'), 6.85 (m, 1H, H-2'), 7.52 (m, 3H, aromatic), 7.97 (m, 2H, aromatic).

(2',4',6'-Tri-O-acetyl-3'-deoxy-α-D-erythro-hex-2'-enopyranosyl)propanone (9). 9 was prepared as before from 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-arabino-hex-1-enitol (8)[16] in 71% yield; $[\alpha]^{20}D$ +46° (c 1.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 2.0-2.2 (m, 14H, 3XAc, $CO\underline{CH_3}$ and $\underline{CH_2}CO$), 4.1-4.4 (m, 3H, $\underline{CH_2}OAc$ and H-5'), 4.70 (m, 1H, H-1'), 5.25 (m, 1H, $J_{4'5'}$ 7 Hz, H-4'), 5.85 (m, 1H, H-3').

(2',4',6'-Tri-O-acetyl-3'-deoxy-α-D-threo-hex-2'-enopyranosyl)-propanone (11). 11 was prepared as before from 2,3,4,6-tetra-O-acetyl-1,5-anhydro-D-lyxo-hex-1-enitol (10)[17] in 51% yield; mp 119°; $[\alpha]^{20}D$ -160° (c 1.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 2.02, 2.04 and 2.08 (3s, 9H, 3XAc), 2.18 (s, 3H, $CO\underline{CH_3}$), 2.71 (2 pd, 2H, $\underline{CH_2}CO$), 4.09 (m, 1H, H-5'), 4.18 (m, 2H, $\underline{CH_2}OAc$), 4.81 (m, 1H, H-1'), 5.25 (pd, 1H, $J_{4'5'}$ 2.5 Hz, $J_{3'4'}$ 6.0 Hz, H-4'), 5.81 (pd, 1H, $J_{1'3'}$ 1.5 Hz, H-3').

(4',5'-Di-O-acetyl-2'-N-acetylacetamido-2',3'-dideoxy-α-D-erythro-hex-2'-enopyranosyl)propanone (13). 13 was prepared from 3,4,6-tri-O-acetyl-2-N-acetylacetamido-1,5-anhydro-2-deoxy-D-arabino-hex-1-enitol (12)[18] as before in 61% yield; $[\alpha]^{20}D$ +42° (c 1.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 2.06 (s, 6H, 2XAc), 2.15 (s, 3H, $CO\underline{CH_3}$), 2.37 (s, 6H, 2XAcN), 2.78 (2pd, 2H, $\underline{CH_2}CO$), 4.02 (m, 1H, H-5'), 4.20 (m, 2H, $\underline{CH_2}OAc$), 4.85 (m, 1H, H-1'), 5.26 (m, 1H, $J_{4'5'}$ 7.5 Hz, $J_{3'4'}$ 3.0 Hz, H-4'), 5.82 (pd, 1H, $J_{1'3'}$ 1.5 Hz, H-3').

2-(4',6'-Di-O-acetyl-2',3'-dideoxy-α-D-erythro-hex-2'-enopyranosyl)ethane-1,1-diol 1,1-diacetate (15). To a stirred mixture of anhydrous ferric chloride (0.1 g) and acetic anhydride (0.1 mL) in dichloromethane (2.0 mL), 1 (0.272 g, 1 mmol) dissolved in dichloromethane (2.0 mL) and vinyl acetate (14) (2.0 mL) were added dropwise at room temperature. After addition was complete, the reaction mixture was stirred an additional 15 min, then diluted

with dichloromethane (50 mL) and washed successively with an aqueous sodium bicarbonate solution and water. The organic layer was dried with anhydrous magnesium sulfate and evaporated. From the residue, chromatographed on silica gel (10 mL) using 4:1 v/v pet. ether-ethyl acetate as eluant, 15 was obtained; yield 85%; bp 160°/0.1 torr; $[\alpha]^{20}\underline{D}$ +44° (c 1.0, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): 2.0-2.1 (4s, 12H, 4XAc), 1.9-2.2 (m, 2H, $\underline{CH_2}$), 3.96 (m, 1H, H-5'), 4.20 (2Xpd, 2H, $\underline{CH_2}OAc$), 4.40 (m, 1H, H-1'), 5.14 (d, 1H, $J_{4'5'}$, 7.0 Hz, H-4'), 5.85 (m, 2H, $J_{2'3'}$, 11.0 Hz, H-2' and H-3'), 6.97 [m, 1H, $\underline{CH}(OAc)_2$].

Additional proof of the structure of 15 was afforded via its reduction with $LiALH_4$ and subsequent acetylation of the product to give 1-acetoxy-2-(4'6'-di-O-acetyl-2',3'-dideoxy-α-D-erythro-hex-2'-enopyranosyl)ethane (16), the structure of which was assigned following analysis of its NMR spectrum; $[\alpha]^{20}$ D +38° (c 0.5, CH_2Cl_2); ^{1}H-NMR ($CDCl_3$): δ 1.80-2.10 (m, 2H, CH_2), 2.05, 2.09, 2.12 (3s, 9H, 3XAc), 3.94 (m, 1H, H-5'), 4.08-4.33 (m, 4H, $2X\underline{CH_2}OAc$), 4.37 (m, 1H, H-1'), 5.14 (m, 1H, H-4'), 5.86 (m, 2H, $J_{2'3'}$, 10.1 Hz, H-2', H-3').

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