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ELECTROPHILE-MEDIATED CYCLIZATIONS IN CARBOHYDRATE CHEMISTRY: SYNTHESIS OF HIGHLY FUNCTIONALIZED RIBOFURANOSE AND RIBOPYRANOSE COMPOUNDS

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Abstract: Iodine-mediated cyclization of (Z)- and (E)-D-ribohept-2-enonates 1 and 2 gave exclusively the β-ribofuranose and α-ribofuranose derivatives 3 and 4, respectively. Cyclization of the (Z)- and (E)-2-heptene-1-ol derivatives 5 and 6 gave ribofuranose products (7 and 8) and a ribopyranose (9), respectively.

Recent reports regarding the application of electrophile-mediated cyclizations to the synthesis of carbohydrates, pseudomonic acid precursors,[1,2] and C-nucleosides[3,4] prompted the reporting of some of our preliminary results in this area.

Reaction of 5-O-benzyl-2,3-O-isopropylidene-D-ribofuranose[5] with 1.5 eq of carbethoxymethylidene triphenylphosphorane in dichloromethane[1,2] gave (Z)-ethyl-7-O-benzyl-4,5-O-isopropylidene-2,3-dideoxy-D-ribohept-2-enonate (1, $J_{2,3}$ = 12.0 Hz; H-4 app t δ = 5.68 ppm, due to the anisotropic effect of a syn carbonyl group).[2,5-8,9] The stereochemistry of 1 was unequivocally proven by THP protection[10] (76%), isomerization to the (E)-hept-2-enonate derivate (98%, crude),[11] and hydrolysis[10] to the (E)-hept-2-enonate 2, (60%; $J_{2,3}$ = 16.0 Hz; H-4 app t δ = 4.85 ppm, unaffected by the anti oriented carbonyl group).[12]

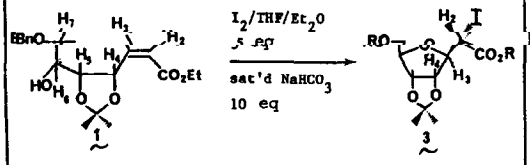
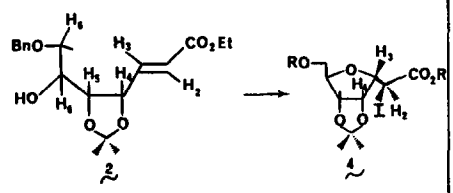
Cyclization of the (Z)-hept-2-enonate 1 gave exclusively the β-ribofuranose product 3 (3,6-anhydro-7-O-benzyl-2-deoxy-2-iodo-4,5-O-isopropylidene-D-allo-heptonate, 3, 61%)[13] while cyclization of the (E)-hept-2-enonate 2 gave exclusively the α-ribofuranose product (3,6-anhydro-7-O-benzyl-2-deoxy-2-iodo-4,5-O-isopropylidene-D-altro-heptonate, 4, 56%) in contrast to a previous report.[4] The stereochemical assignments were made on the basis of ^{13}C NMR,[4,5,14,15] chemical shifts of H-3,[16] and fully decoupled ^1H NMR spectra (Table I). A plausible rationalization for the stereospecificity observed in the iodine-mediated cyclization of 1 and 2 is shown in eq 1 and 2.

Dibal reduction[18,19] of 1 and 2 gave 5 and 6 in 54% and 62% yields, respectively. Cyclization of 5 (eq 3) gave a 60:40 mixture of β/α ribofuranose products 7 and 8 (61%, ^1H

and ^{13}C NMR assay). Cyclization of 6 (eq 4) gave a single diastereomer (9, 61%) whose spectral data are consistent with a ribopyranose structure.[20-23]

Although all of the controlling factors in the electrophile-mediated cyclization of carbohydrate derivatives 5 and 6 are not clear, the following conclusions concerning the cyclizations may be drawn: (1) the reaction is most likely under kinetic control since subjecting 7 and 8 to the reaction conditions resulted in no change in the β/α ratio. In this system, the α-anomer is the thermodynamically more stable;[24] (2) removing the electron-withdrawing functionality in 1 significantly decreases the stereospecificity of the cyclization of 5; (3) the double bond geometry plays a significant role in the regiochemical and stereochemical consequences of the cyclizations.[25]

TABLE I. PROTON-NMR AND ^{13}C NMR CHEMICAL SHIFTS (δ) FOR THE α-RIBOFURANOSE PRODUCT 3 AND THE β-RIBOFURANOSE PRODUCT 4[a]

	^{13}C	^{1}H (C_6D_6)	additional data
	114.1 ppm 25.7, 27.6 ppm	H-2 d, δ = 4.66 ppm, $J_{2,3}$ = 8.0 Hz H-3 dd, δ = 4.58 ppm $J_{2,3}$ = 8.0 Hz, $J_{3,4}$ = 3.0 Hz H-4 dd, δ = 4.88 ppm $J_{3,4}$ = 3.0 Hz	Decoupling of H_2 collapses H_3 to a singlet[b]
	112.7 ppm 25.2, 26.5 ppm	H-2 d, δ = 4.78 ppm $J_{2,3}$ = 10.6 Hz H-3 dd, δ = 4.96 ppm $J_{2,3}$ = 10.6 Hz, $J_{3,4}$ = 4.0 Hz H-4 dd, δ = 4.70 ppm $J_{3,4}$ = 4.0 Hz	Decoupling of H_2 collapses H_3 to a doublet with $J_{3,4}$ = 4.0 Hz

[a] Central solvent resonance at δ 77.27 at 22.63 MHz.
[b] This is seen when $CDCl_3$ is used as solvent. In C_6D_6 H_2 and H_3 are too close to permit decoupling of one without irradiating the other.

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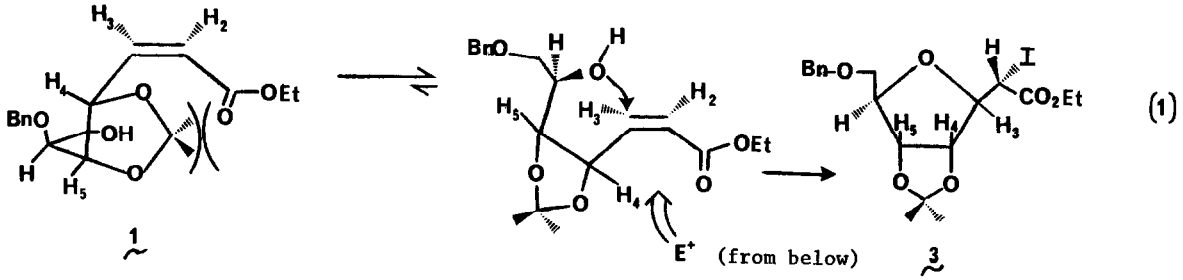
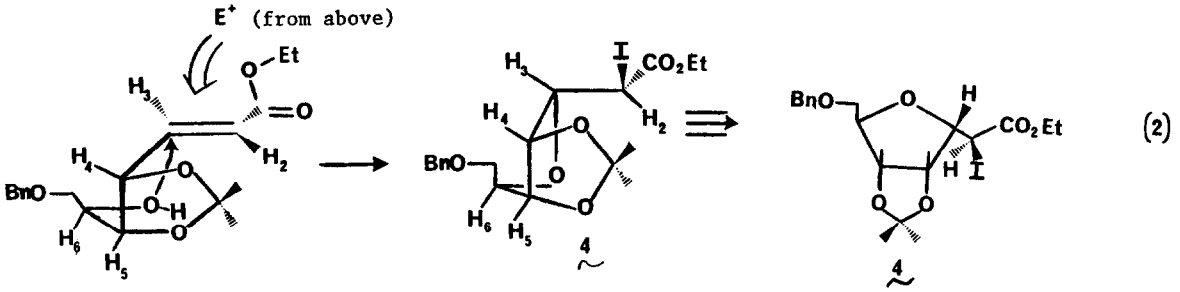
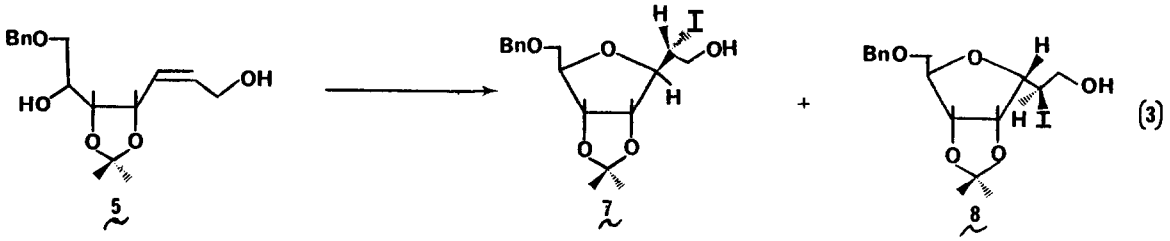


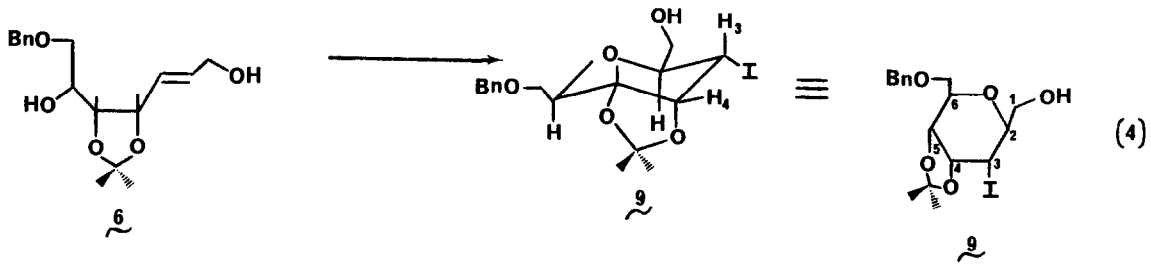
1 3 H-3 and H-4 are ANTI (1)



2 4 4 H-3 and H-4 are SYN (2)



5 7 8 (3)



6 9 9 (4)

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9. δ = 6.27 ppm dd, $J_{3,4}$ = 8.4 Hz, $J_{2,3}$ = 12.0 Hz, H-3,
δ = 5.97 ppm dd, $J_{3,4}$ = 12.0 Hz, $J_{2,3}$ = 1.2 Hz, H-2
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δ = 6.15 ppm dd, $J_{3,4}$ = 1.8 Hz, $J_{2,3}$ = 16.0 Hz, H-2
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21. The numbering of the C-atoms in compound 9 follows the heptulose nomenclature.
22. H-3 appears a a dd with $J_{2,3}$ = 10.3 Hz and $J_{3,4}$ = 3.6 Hz (from ^{1}H fully decoupled spectra) which establishes that H-2 and H-3 are axially oriented (i.e. trans) and that the $-CH_2OH$ group is oriented β;[20,21] (2) the 3.6 Hz coupling constant between H-3 and H-4 is indicative of an axial-equatorial coupling, and (3) other ^{1}H NMR and ^{13}C NMR data are consistent with structure 9.
23. All yields are reported for purified samples unless otherwise specified. Cyclization product yields are based on recovered starting material. All compounds described herein were fully characterized by ^{1}H NMR, ^{13}C NMR, ^{13}C ORD, CIMS, EIMS, IR, $[\alpha]_D^{25}$, and gave satisfactory elemental analyses (Robertson Laboratories Inc., Florham Park, NJ). All ^{1}H NMR spectra were recorded at 250 MHz (Bruker WM-250) and ^{13}C NMR data were obtained on a Bruker WM-250 spectrometer or a Bruker WM-90 spectrometer.
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25. Although the stereochemistry at C-2 in products 3, 4, 7, 8, and at C-3 in product 9 was not determined absolutely, the assignments are reasonable based on the proposed mechanism for the reaction.

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