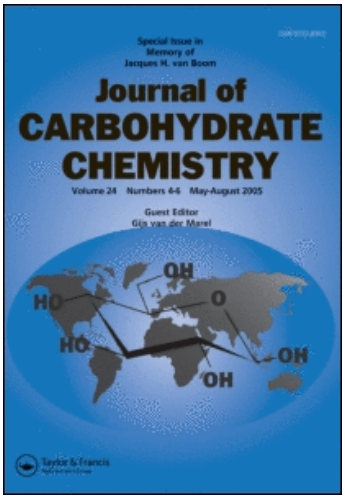

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Regiospecific Dehydration of Some Branched Cycloses and Cyclitols Derived From Activated 2,6-Heptodiulose Derivatives

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Communication

REGIOSPECIFIC DEHYDRATION OF SOME BRANCHED CYCLOSES AND CYCLITOLS DERIVED FROM ACTIVATED 2,6-HEPTODIULOSE DERIVATIVES

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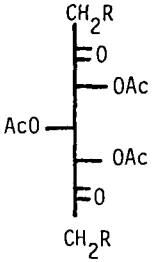
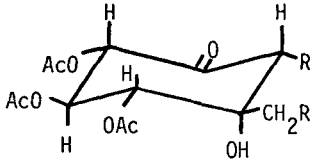
The stereoselective base catalyzed conversion of tri-O-acetyl-1,7-dichloro-1,7-dideoxy-xylo-2,6-heptodiulose to DL-(2,3,4,6/5)-4,5,6-tri-O-acetyl-2-chloro-3-C-(chloromethyl)-3,4,5,6-tetrahydroxy-cyclohexanone has been described,[1] and it has also been shown that branched cyclose formation from the corresponding 1,7-dibromo and 1,7-diazido-2,6-heptodiuloses also occurs in the same stereoselective manner.[1] Reduction of the cyclose ketone function followed by appropriate deprotective leads to branched epi-inositols.[1,2] The general structure of the starting 2,6-heptodiulose, and the product cyclose and cyclitol are given as I, II and III respectively.



I



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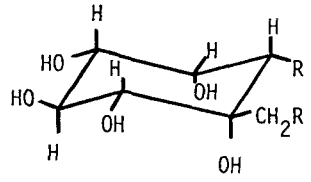

III

R = Br, Cl or N_3

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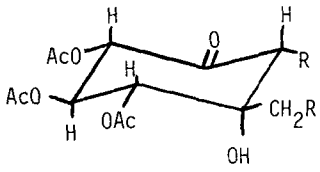
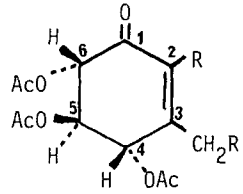
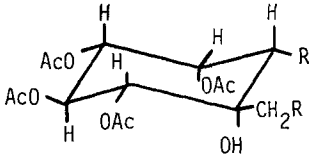
A common structural feature of the branched cycloses (II) and cyclitols (III) is the presence of the 3° hydroxyl group on the carbocyclic ring. While investigating the chemistry of these cycloses and cyclitols we became interested in finding a suitable method for eliminating this hydroxyl group from the ring by a mild regiospecific dehydration process in order to generate branched and unsaturated cycloses and cyclitols. Conceivably such unsaturated molecules might, after appropriate reductions, be converted to branched cyclitols lacking the 3° hydroxyl group. Valienamine and



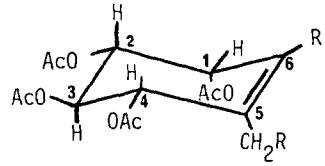
1 R = Cl
2 R = OAc



3 R = Cl
4 R = OAc



5 R = N_3
6 R = Cl



7 R = N_3
8 R = Cl

validamine are examples of naturally occuring unsaturated and saturated branched aminocyclitols respectively, and are found as structural components of the Streptomyces produced validamycins.[3]

We have now determined that the pyridine-thionyl chloride reagent for alcohol dehydration[4,5] is well suited for our cyclose and cyclitol systems. The chloromethyl cyclose 1 and the acetyloxymethylcyclose 2 each underwent regiospecific loss of water to give the α,β-unsaturated cyclohexanones 3 and 4. In order to prepare DL-(4,5,6)-tri-O-acetyl-2-chloro-3-(chloromethyl)-4,6/5-trihydroxy-2-cyclohexen-1-one (3), a solution of 1 (109 mg, 0.294 mmol) in chloroform (2 mL) containing thionyl chloride (0.06 mL) was cooled to 0 °C. The cooled reaction mixture was treated with pyridine (0.3 mL)

Table 1

^{1}H NMR Chemical Shifts (PPM) and Coupling Constants (Hz) for Compounds 3,4,7 and 8 at 90 MHz[a]

Compound	H-3	H-4	H-5	H-6	CH_aH_b	CH_aH_b	CH_3CO[b]	$^3J(3,4)$	$^3J(4,5)$	$^3J(5,6)$	$^2J(CH_aH_b)$
3		6.17 m	5.57 m	5.54 m	4.59 d	4.26 d	2.19 2.12 2.04		8.3	12.0	12.0
4		6.18 m	5.61 m	5.61 m	4.85 m	4.82 m	2.28 2.16 2.10 2.05 2.02		8.0	11.6	14.3
	H-1	H-2	H-3	H-4	CH_aH_b	CH_aH_b	CH_3CO[b]	$^3J(3,4)$	$^3J(2,3)$	$^3J(1,2)$	$^2J(CH_aH_b)$
7	5.99 d	5.22dd	5.51 m	5.76 d	4.03 d	3.78 d	2.20 2.10 2.05 2.00	7.7	11.4	4.4	13.5
8	5.82 d	5.20dd	5.47 m	5.83 d	4.34 d	3.76 d	2.14 2.07 2.00 1.94	8.0	10.6	2.85	12.0

a. All spectra recorded in $CDCL_3$ solution using Me_4Si as an internal standard.

b. Each CH_3CO signal was observed as a three proton signlet.

and then stirred at 0 °C for 2 h. The resultant solution was diluted with dichloromethane (10 mL), washed twice with water (10 mL), dried (Na_2SO_4) and evaporated to give 86 mg (82%) of 3), mp 98-100 °C. Recrystallization from ethanol-water gave an analytical sample; mp 102.5-103.5 °C; IR (KBr) 1760 (C=O), 1720 (C=O), 1635 (C=C) cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_7Cl_2$ (353.16): C, 44.21; H, 4.00; Cl, 20.08. Found: C, 44.30; H, 4.06, Cl, 20.04.

DL-(4,6/5)-3-(acetyloxymethyl)-2,4,5,6-tetra-O-acetyl-2,4,5,6-tetrahydroxy-2-cyclohexen-1-one (4) was prepared in 65% isolated yield by a procedure similar to that described for the preparation of 3. Crystallization from ethanol-water gave an analytical sample of (3): mp 110-111 °C, IR (KBr) 1760 (C=O); 1720 (C=O), 1635 (C=C) cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_{11}$ (400.35): C, 51.00; H, 5.04. Found: C, 51.07, H, 5.05.

The presence of the electron withdrawing ring azido group on the cyclitol 5 and the chlorine atom on the cyclitol 6 fostered the base catalyzed regiospecific elimination to occur as shown (7 from 5, 8 from 6). For the preparation of 7, DL-1,2,3,4-tetra-O-acetyl-6-azido-5-(azidomethyl)-5-cyclohexen-1,2,4/3-tetrol, a solution of 5 (990 mg, 2.07 mmol) in pyridine (20 mL) was cooled to 0 °C and thionyl chloride (0.23 mL) was added to the solution. After standing overnight at -5 °C the solution was evaporated to dryness. The crude residue was suspended in methylene chloride, washed with water, dried ($MgSO_4$) and evaporated to give 720.3 mg of an amorphous solid. Crystallization from ethanol-water gave 708 mg (88%) of (7), mp 99-100 °C. Recrystallization from ethanol gave an analytical sample: mp 99-100 °C; IR (KBr) 2200 sh and 2100 (N=N=N), 1760 (C=O), 1655 (C=C) cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_6O_8$ (410.35): C, 43.91; H, 4.42; N, 20.48. Found: C, 44.11; H, 4.45; N, 20.29.

The unsaturated chloromethylcyclitol DL-1,2,3,4-tetra-O-acetyl-6-chloro-5-(chloromethyl)-5-cyclohexen-1,2,4/3-tetrol (8) was prepared in 82% yield by a similar procedure. Crystallization from ethanol-water gave an analytical sample of (8); mp 120-122 °C, IR (KBr) 1760 and 1740 (C=O) and 1655 (C=C) cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_8Cl_2$ (397.21): C, 45.36; H, 4.57; Cl, 17.85. Found: C, 45.43; H, 4.61; Cl, 17.77.

The 90 MHz ^1H NMR spectra for compounds 3,4, 7 and 8 could not be interpreted on a first order basis. However, the chemical shift and

coupling constant values (Table 1) for these compounds were obtained from the simulated spectra using the Bruker Instruments PANIC Program for iterative analysis. The coupling constants obtained from the iterative spectra established the stereochemical assignments given to the structures 3, 4, 7 and 8.

In the four eliminations described, the yields reported are isolated yields. However, ^{1}H NMR and TLC (toluene-ether, 3:1) indicated that a single product was produced in each reaction.

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