Tetrahedron Letters,Vol.23,No.50,pp 5367-5370,1982 0040-4039/82/505367-04$03.00/0
Printed in Great Britain

A STEREOSELECTIVE SYNTHESIS OF XYLITOL

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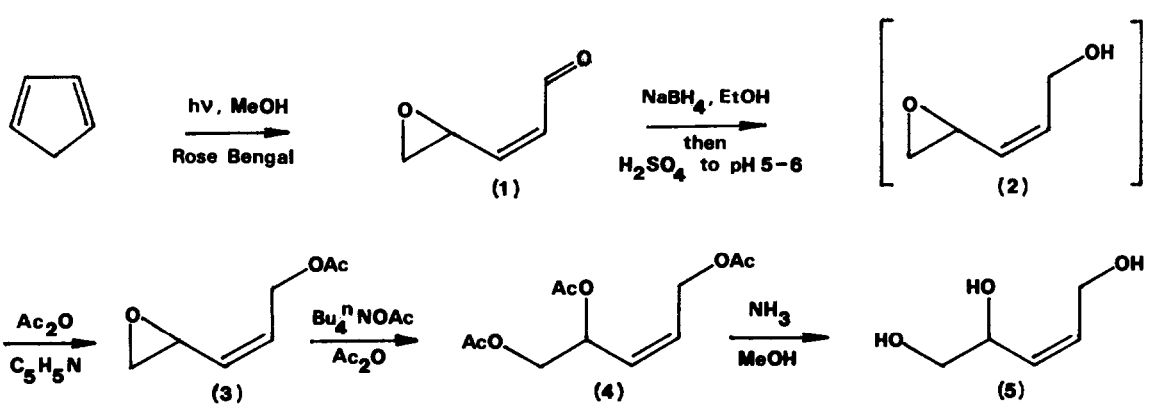
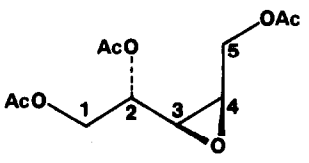
Rel-(2S,3R,4R)- (6) and rel-(2R,3R,4R)- (7) 1,2,5-triacetoxy-3,4-epoxypentanes have been obtained in seven steps starting from cyclopentadiene. Both diastereoisomers afford xylitol pentaacetate (8) selectively upon epoxide cleavage with acetate ion. In the case of (6), rel-(1s,3R,4r,5S)-3,5-bisacetoxymethyl-1-methyl-2,6,7-trioxabicyclo-[2.2.1]heptane (11) has been isolated and characterised as an intermediate in the reaction.

The potential commercial importance of xylitol as a sweetener[1] has led us to examine a number of different approaches[2] to the stereoselective synthesis of this pentitol. Since it is a meso compound we recognised that there is no need, in principle at least, to involve any chiral starting material or auxiliary in a synthesis designed to afford xylitol rather than the other two pentitols, arabinitol or ribitol. The problem is one of defining relative and *not* absolute stereochemistry. Epoxidation of 3-hydroxypenta-1,4-diene has been examined[2,3] as the first step in one possible synthetic approach to the pentitols and it has been concluded[2] that the diastereoselectivities characterising the epoxidation steps and the regioselectivities governing the subsequent epoxide cleavages are not sufficiently high to constitute an attractive selective synthesis of the pentitols. Other achiral precursors and chiral substrates, derived from 2,3-*O*-isopropylidene-D-glyceraldehyde by appropriate Wittig reactions, have also been employed[4] very recently and highly stereocontrolled syntheses of the pentitols and other alditols have been achieved by resorting to the use of the elegant method of chiral epoxidation-kinetic resolution developed by Sharpless *et al.*[5] and implicating cyclic carbonates in the epoxide cleavages. Here, we wish to report how xylitol may be prepared stereoselectively from an *achiral starting material* (cyclopentadiene) and *without using a chiral auxiliary* amongst the reagents employed.

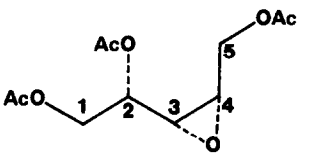
The epoxyaldehyde (1) can be obtained according to a literature procedure[6] in good



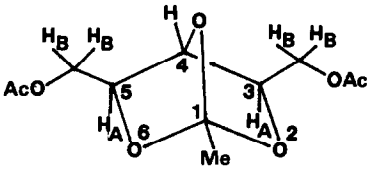
yield by photo-oxygenation of cyclopentadiene monomer in MeOH using Rose Bengal as dye-sensitiser. The conversion of (1) to the *cis*-trihydroxypentene (5) was achieved in four steps: (*i*) Chemoselective reduction of the CHO group in (1) with $NaBH_4$ in EtOH at -40°C gave the *cis*-hydroxyepoxypentene (2), provided[7] the reaction mixture was acidified prior to isolating the product. On account of its instability, (2) was not characterised but was (*ii*) acetylated immediately to afford (45%) the *cis*-acetoxyepoxypentene (3), which was then (*iii*) treated with Bu^n_4NOAc in Ac_2O at 105°C to yield (71%) the *cis*-triacetoxypentene (4). (*iv*) De-*O*-acetylation of (4) afforded (94%) the desired *cis*-trihydroxypentene (5). Epoxidation of (5), followed by acetylation of the products is expected to lead to two diastereoisomeric triacetoxy-3,4-epoxypentenes (6) and (7). In the event, g.l.c. analysis[8] indicated the presence of these



Isomer A ≡ (6)



Isomer B ≡ (7)



Compound Z ≡ (11)

two products in a 30:70 ratio following epoxidation (*p*-$O_2NC_6H_4CO_3H$ in THF) of (5) and acetylation (Ac_2O, C_5H_5N) of the products. The diastereoisomers were separated by h.p.l.c. on SiO_2 with EtOAc-hexane (1:8) as eluant. The first and minor component eluted from the column was designated as Isomer A. The second and major component eluted from the column was designated at Isomer B. It was not possible to assign relative configurations to Isomers A and B on the basis of their high resolution ^1H n.m.r. spectra.[9] The vicinal coupling constants for $J_{2,3}$ of 8.1 Hz in Isomer A and of 8.3 Hz in Isomer B are too similar in magnitude. Thus, it was decided to investigate the consequences of epoxide cleavage in Isomers A and B by heating them in Ac_2O containing Bu^n_4NOAc (5 mol %) at 121°C. The reactions were followed by g.l.c.[8] at 180°C. The results are summarised in the Figure. Initially, in the case of Isomer A, DL-arabinitol pentaacetate DL-(9) was the major product of the reaction. However, after 2 hours, xylitol pentaacetate (8) became the major product, and eventually after 23 hours, when the reaction was complete, the ratio of (8) to DL-(9) was 65:35. Also, the peak on the g.l.c. trace corresponding to the starting material showed an unexpected and dramatic increase in its relative intensity before undergoing the expected decrease in its relative intensity. This behaviour is consistent with the production of an intermediate (Compound Z), during the reaction of Isomer A to afford both (8) and DL-(9). After establishing optimum reaction conditions (5 hours at 112°C) for the formation of this intermediate, it was isolated (30% yield) as a white crystalline material, m.p. 112-114°, δ ($CDCl_3$, 400 MHz) 4.71 (1H, s, H-4), 4.06 (2H, A portion of an AB_2 system, J_{AB} 6.5 Hz, $J_{3,4} = J_{4,5} < 0.2$ Hz, H-3 and H-5), 4.03 (4H, B portion of an AB_2 system, J_{AB} 6.5 Hz, 2 x CH_2OAc), 2.10 (6H, s, 2 x OAc), and 1.78 (3H, s, Me), on addition of a solvent mixture of EtOAc-light petroleum (b.p. 60-80°) (3:7) to the crude reaction mixture remaining after evaporation of the Ac_2O. G.l.c. analysis[8] of the crystals revealed that they have the same retention time as Isomer A and so correspond to Compound Z. Elemental analysis showed that the empirical formula is $C_{11}H_{16}O_7$, supporting the view that Compound Z is

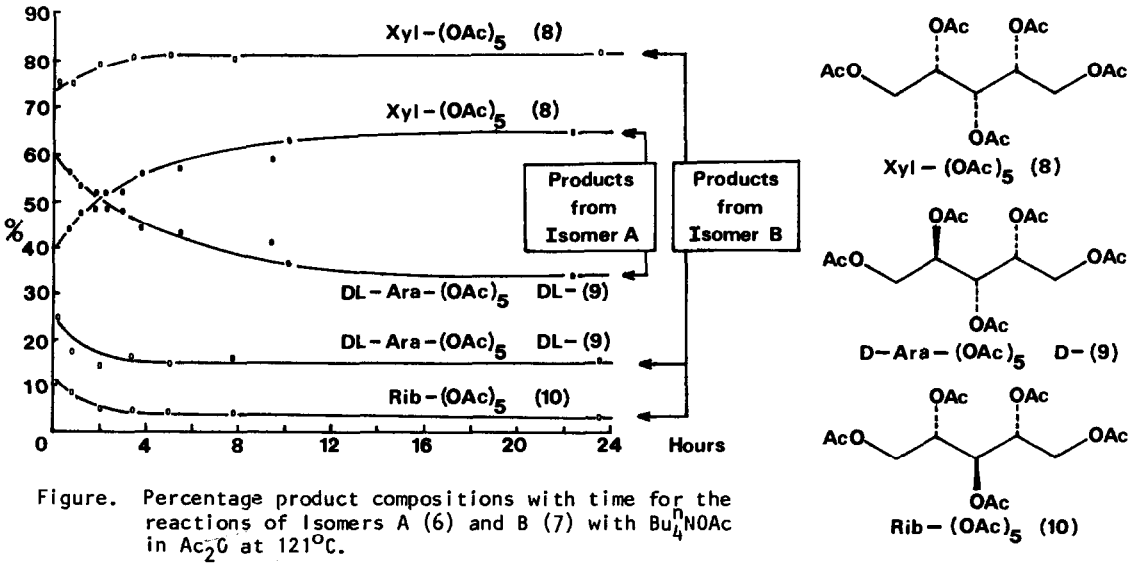
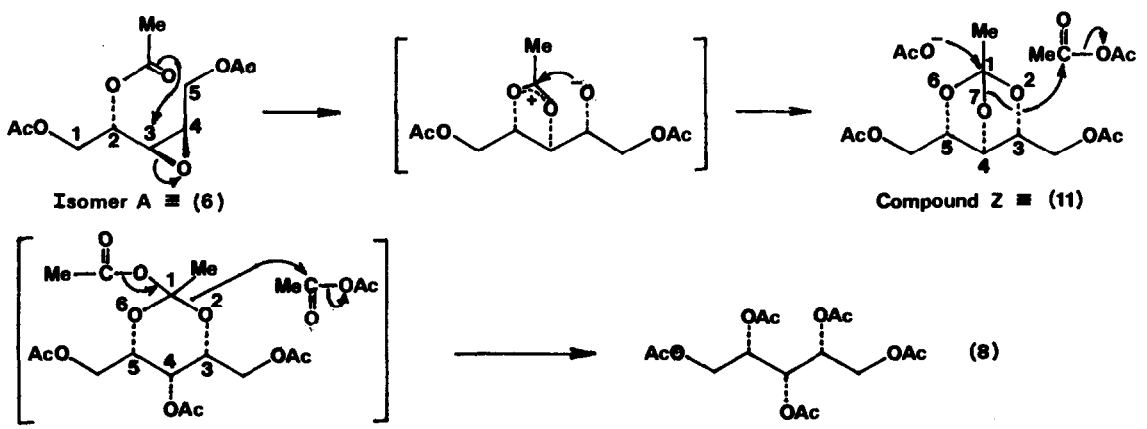


Figure. Percentage product compositions with time for the reactions of Isomers A (6) and B (7) with Bu^n_4NOAc in Ac_2O at 121°C.

isomeric with Isomer A. When Compound Z was heated in Ac_2O in the presence of Bu^n_4NOAc, the major product (>98% diastereoselectivity) was xylitol pentaacetate (8). On the basis of the spectral, chromatographic, analytical, and chemical evidence, the structure of Compound Z is proposed to be that of a bicyclic orthoester (11) which is closely related to a previously[10] reported glycerol analogue. The assignment of this structure to Compound Z allows a mechanism to be proposed (Scheme) by which Isomer A, assuming it has the *ribo* configuration (6), might be converted into (11) in the presence of ^-OAc ion in Ac_2O. The *ribo* configuration facilitates the participation of the acetoxy group at C-2 in the intramolecular displacement at C-3 leading to the opening of the oxirane ring in (6). This generates a dipolar intermediate which leads directly to (11) with the *xylo* configuration. Nucleophilic attack by ^-OAc ion at the electrophilic bridgehead carbon atom (C-1) leads to an intermediate in which the *xylo* configuration is retained. This cyclic intermediate will then react (Scheme) with Ac_2O such that only xylitol



Scheme. Proposed mechanism by which Isomer A (6) may be converted into xylitol pentaacetate (8) in the presence of Bu^n_4NOAc in Ac_2O.

pentaacetate (8) is formed. In addition, non-participative opening of the oxirane ring of isomer A (6) with $^{-}$OAc ion affords (8) if C-3 is attacked and DL-(9) if C-4 is attacked. The assignment of the *ribo* configuration to isomer A (6) means that isomer B has the *arabino* configuration (7). Non-participative ring opening of the oxirane ring in isomer B (7) with $^{-}$OAc ion affords DL-(9) if C-3 is attacked and (8) if C-4 is attacked.[11] The results summarised in the Figure indicate that isomer B (7) provides a more highly stereoselective route to (8) than does isomer A (6). However, if isomer A (6) could be converted more efficiently into the bicyclic orthoester intermediate (11), then a highly stereoselective route to (8) would result. The opportunity, therefore, exists to employ either (6) or (7) as intermediates in a stereoselective synthesis of xylitol from cyclopentadiene. So far, this has been achieved starting from the *isomeric mixture* of (6) and (7). When such a mixture was treated with $Bu^{n}_{4}NOAc$ in Ac_2O at 112°C, a mixture of pentitol pentaacetates was obtained (63%)[12] and xylitol pentaacetate (8) constituted 76% of these products. Chromatography on SiO_2 using EtOAc-light petroleum (b.p. 60-80°) (3:7) as eluant afforded (8) in 21% isolated[12] yield. De-*O*-acetylation (HCl, MeOH) led to the isolation[12] of 27% of a crystalline sample (*ex.* MeOH) of xylitol.

We thank Dr. W. Hewertson (ICI) for his interest and Prof. M.P. Schneider (Wuppertal) for helpful discussions.

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7. If acid was not added before the attempted isolation of (2), it underwent rearrangement to give 2-hydroxymethyl-2,5-dihydrofuran which was characterised as its acetate.

8. G.l.c. was carried out on a column (9 ft.) of Silicone OV-17 (3%) on Chromosorb WHP.

9. ^{1}H N.m.r. data for isomer A (6) : δ ($CDCl_3$, 400 MHz) 4.85 (1H, dxdxd, *J* 3.2, 5.7, 8.1 Hz, H-2), 4.48 (1H, dxd, *J* 3.9, 12.6 Hz, H-5), 4.45 (1H, dxd, *J* 3.2, 12.1 Hz), 4.26 (1H, dxd, *J* 5.7, 12.1 Hz, H-1), 4.11 (1H, dxd, *J* 7.1, 12.6 Hz, H-5), 3.28 (1H, dxdxd, *J* 3.9, 4.2, 7.1 Hz, H-4), 3.15 (1H, dxd, *J* 4.2, 8.1, H-3), and 2.10 (9H, s, 3xOAc). ^{1}H N.m.r. data for isomer B (7) : δ ($CDCl_3$, 400 MHz) 5.00 (1H, dxdxd, *J* 4.6, 5.6, 8.3 Hz, H-2), 4.40 (1H, dxd, *J* 4.2, 12.2 Hz, H-5), 4.33 (1H, dxd, *J* 4.6, 12.0 Hz, H-1), 4.18 (1H, dxd, *J* 6.8, 12.2 Hz, H-5), 4.16 (1H, dxd, *J* 5.6, 12.0 Hz, H-1), 3.33 (1H, dxdxd, *J* 4.2, 4.4, 6.8 Hz, H-4), 3.24 (1H, dxd, *J* 4.4, 8.3 Hz, H-3), and 2.13, 2.12, and 2.10 (9H, 3xs, 3xOAc).

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11. Although the trace amounts of ribitol pentaacetate (10) obtained (Figure) from isomer B (7) probably result from participation by one or more of the acetoxy groups during opening of the oxirane ring, we cannot be precise mechanistically about the nature of this side reaction.

12. No attempt has been made to optimise these yields.

(Received in UK 4 October 1982)