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6- vs 7- RING SELECTIVITY DURING ACETAL FORMATION

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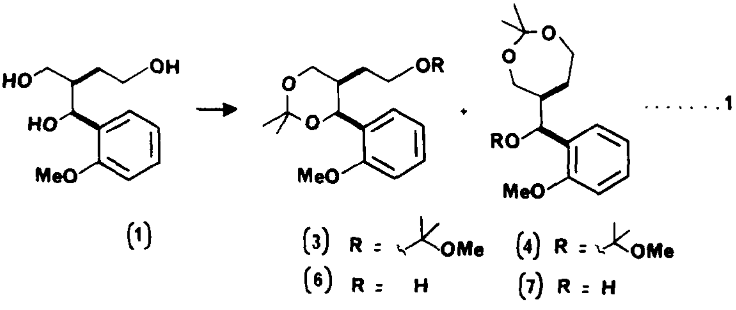
Summary: Acid-catalysed reaction of triol (1) with 2,2-dimethoxypropane gave both six- and seven-membered cyclic acetals. With 1,1-diethoxyethane the 1,3-dioxane was the sole product.

As part of a synthetic programme aimed at the production of receptor antagonists of thromboxane A2[1] we needed to differentiate the two primary hydroxyl functions of triol[2] (1), in a manner suitable for large scale operation.

We were surprised to find that treatment of (1) with excess 2,2-dimethoxypropane, (DMP), and a catalytic amount of p-TSA gave not only the expected 1,3-dioxane, (3), but also an equal amount of the isomeric 1,3-dioxepane,[3 4] (4), (Equation 1).



.... 1

(1)

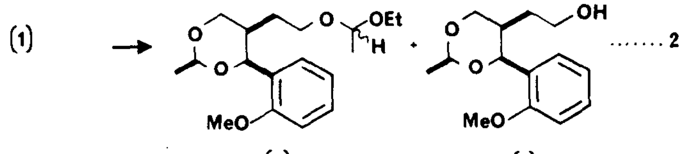
(3) R = OMe (4) R = OMe

(6) R = H (7) R = H

Use of only one equivalent of DMP gave the corresponding products, (6) and (7), initially in the ratio of 1:1, but when the reaction mixture was allowed to stand for 36 hours the ratio of (6) to (7) improved to 3:1, presumably reflecting the relative thermodynamic stabilities[5] of the two products.

Since we required a route that was free from chromatography, we were driven to consider ways by which greater selectivity of formation of six- vs seven-membered ring acetals might be achieved. We reasoned as follows: Formation of the C(2)-disubstituted dioxane, (3), introduces two destabilising 1,3-diaxial (CH_3/H) interactions; although similar considerations apply to the formation of dioxepane (4), the destabilisation should be relatively smaller, on account of the greater conformational flexibility of seven-membered rings.[5,6] If, however, we were to make the C(2)-monosubstituted acetals then we would expect only equatorial substitution at C(2). The dioxane would then no longer be destabilised relative to the dioxepane since no major 1,3-diaxial interactions would be introduced.[7]

Whether or not such a difference would significantly affect the experimentally observed ratio of products was difficult to predict,[8] but we were gratified to find that, when (1) was treated with excess 1,1-diethoxyethane and a catalytic amount of p-TSA, the dioxanes (8) and (9) were produced in high yield and with no trace of the isomeric dioxepanes,[9] (Equation 2).



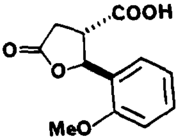
(8) (9)

.......2

On treatment of the crude mixture of (8) and (9) with pTSA in aqueous THF the desired hydroxyethyldioxane (9) was obtained in 72% overall yield from (1).

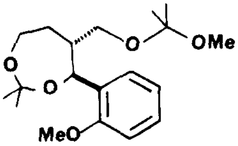
REFERENCES AND NOTES

1. A.G. Brewster and P.W.R. Caulkett, Eur. Pat. Appl, Publication No. 94239 A2.
2. Available via the REDAL reduction of paraconic acid (2), (G.D. Harris, personal communication).



(2)

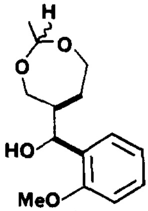
3. The other possible dioxepane product, (5), was never observed.



(5)

4. The competitive formation of a 1,3-dioxepane from 2-hydroxymethyl-1,4-butanediol has recently been described: M. R. Harnden and R.L. Jarvest Tetrahedron Lett., 1985, 26, 4265.

5. S. Kaarsemaker and J. Coops, Rec. Trav. Chim., 1952, 71, 261.
6. J.B. Hendrickson, J. Amer. Chem. Soc., 1961, 83, 4537.
7. Analogous arguments have been shown to apply to the reactions of glycerol and many sugars, where use of acetone favours formation of five-membered ring acetals, (dioxolanes), whereas aldehydes give predominantly the six-membered dioxanes.[10]
8. Formation of the dioxane (3) is further disfavoured relative to dioxepane (4) due to the introduction of 1,3-diaxial interactions between the C(5)-substituent and the ring oxygen lone-pairs. These interactions would still be present in the C(2)-monosubstituted acetals.
9. A small amount of (10) could, however, be transiently observed in the reaction mixture prior to complete consumption of triol (1). An authentic sample of (10) was obtained from the reaction of (1) with one equivalent of 1,1-diethoxyethane.



(10)

10. E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw Hill, New York, 1962, p200.

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