Synthesis and structure of 2-aryl-5,5-disubstituted-1,3-dioxanes and conversion into chiral (1,1,1-trishydroxymethyl) methane derivatives

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Received 6 November 2001; revised 4 January 2002; accepted 24 January 2002

Abstract—Pentaerythritol, (1,1,1-trishydroxymethyl)methyl methane and (1,1,1-trishydroxymethyl)nitromethane are converted into 2-aryl-5,5-bis(hydroxymethyl), 2-aryl-5-hydroxymethyl-5-methyl- or 2-aryl-5-hydroxymethyl-5-nitro-1,3-dioxanes and a range of derivatives. X-Ray and NMR analysis establishes that the latter is obtained as a single diastereomer whose structure is unambiguously determined. These materials can be elaborated to chiral derivatives of the starting (1,1,1-trishydroxymethyl) methanes. © 2002 Elsevier Science Ltd. All rights reserved.

Pentaerythritol (1), (1,1,1-trishydroxymethyl)methyl methane (2) and (1,1,1-trishydroxymethyl)nitromethane (3) are readily available and inexpensive materials. They have numerous potential uses for synthesis.1 We have been interested in elaborating these materials to fully differentiated multifunctional intermediates, specifically of type 6 (i.e. with at least two of R1–R3 being protected with orthogonal protecting groups), with at least three differentiated functionalities for further elaboration. We report here the conversion of 2 and 3 into such chiral derivatives and provide structural proof of the diastereomeric outcomes of intermediate dioxane formation with 3.

All approaches used the potential of benzylidene or p-methoxybenzylidene acetals to select two hydroxymethyl groups, with subsequent reductive acetal half-opening to differentiate the two acetal oxygens.

Pentaerythritol has four equivalent groups and so an initial further differentiation is required. Although it is possible to obtain monoacetals by direct reaction of pentaerythritol, and subsequently to differentiate the two remaining hydroxyls, product separations due to the over-protection potential at each step are generally required.2 The obvious strategy is initially to derivatize one group, and thus work proceeded by preparation of the known3 orthoformate 7 (using triethyl orthoformate). The one remaining free hydroxyl was derivatized as its acetate or as a t-butyldiphenyl silyl ether, and in each case the orthoformate was removed using water to give 4 or 5, respectively.4 In both cases, the main issue was the incomplete removal of the orthoformate protecting group. We ascertained that this could be largely controlled in the case of acetate 4. The monoacetyl pentaerythritol (4) could be obtained in about 80% yield on prolonged warming during hydrolysis. However, previously when we conducted the aqueous cleavage reaction without heating, the unknown formyl derivative 8 was obtained in 90% yield.

In the case of the silylated derivative 5, however, even on prolonged heating, a mixture of triol 5 and the novel formyl diol 9 was always obtained. Purified 4 and 5 were converted to the corresponding benzylidene acetals 10 and 12, respectively, but yields were variable, around 30–40% after purification. In the case of the reaction forming 10, this was in part due to concomi-
tant formation of the spirocyclic bis-acetal 11 (requiring in situ deacylation). This presumably exists as the symmetrical doubly equatorial spirocyclic structure shown (Schemes 1 and 2). 5

However, the modest yields and variable reproducibility of efficient benzylidene acetal formation terminated pursuit of the pentaerythritol route. (1,1,1-Trishydroxymethyl)methyl methane (2) and (1,1,1-trishydroxymethyl)nitromethane (3) were chosen for evaluation since one group is already differentiated thus circumventing the initial part of the pentaerythritol elaboration. The same basic strategy was applied, with direct conversion of these triols to the cyclic acetals, using, in this case, either benzaldehyde or 4-methoxybenzaldehyde.

The reaction of (1,1,1-trishydroxymethyl)methyl methane with benzaldehyde generated a diastereoisomeric mixture (typically 3:1 or greater). Assignment can be made by comparison with data and analysis reported by Stoddart 6a and also by others. 6b,c The major isomer is 14a, with phenyl and hydroxymethyl groups cis, and reported NMR data for each isomer corresponded with literature. We observed the same outcome for the synthesis of 13b/14b.

Reaction of (1,1,1-trishydroxymethyl)nitromethane (3) under the same conditions generated 15 or 16, but in both cases as a single diastereomer in high yields. 8 There are previous literature reports of these acetals, but no data appears to have been reported, 9 so assignment by comparison was unavailable. The 1H resonances for the three methylene groups in 15 and 16 are essentially identical, indicating they have the same diastereomeric structure. Interestingly, the t-butyldimethyl silyl ether analogue has also been previously reported, with data in that case showing a diastereomeric mixture of acetals (Scheme 3). 10

Lack of reported data for, or proof of, related stereostructures, encouraged us to establish unambiguously this stereostructure. Establishing this in one case would, by the NMR analogy between them, also support assignment of the other acetal. Proof of the isomeric structure was provided by X-ray structure analysis of the t-butyldimethyl silyl ether derivative 20 [R = TBDMS] (Fig. 1).

This proved that the single diastereomer formed in this case is as shown for 16, with nitro and aryl rings cis, and the nitro axial. By NMR comparison this also confirms the stereostructure as shown for 15. Although this molecule contains a plane of symmetry, the crystal structure shows this does not pack with this symmetry. The aryl ring is twisted relative to the O1–O3–C4–C6 plane. The preferences of 5-substituents on 1,3-dioxanes have been the subject of various conformational analytical studies over the years. 11 The nitro group favours an axial orientation in the analogue of 15 lacking the 5-hydroxymethyl. The rationale for this preference is the electrostatic interaction of the endocyclic oxygen lone pairs and the nitro nitrogen. 12

All the acetals were elaborated by protection of the remaining free hydroxyl with various protecting groups, to allow, ultimately, evaluation of choices of residual protecting groups in the target differentiated systems (and to enhance the options for orthogonality of protecting groups). These are shown in Table 1 for the synthesis of 17–20 with five different protecting groups introduced overall. Additionally, 2-carbon and 3-carbon ether extended analogues of 17 have been prepared (Table 1), which should facilitate synthesis of further analogues of 21–23 with extended and alternatively functionalized groups.

All three acetals 17, 19 and 20 [R = TBDMS] (reacted with DIBAL-H) give cleanly high yields of the corresponding chiral tetrafunctional methanes 21–23 (Scheme 4). This thus provides a convenient and scalable access to two families of chiral systems of this sort (bearing a methyl or a nitro).

We have prepared a range of diastereomeric derivatives (e.g. 24–26) to attempt either crystallization or chromatographic separation of the ultimate enantiomers, but to date none has proven cleanly separable. We also prepared a glucoside derivative of 22. We do, however,
In summary, several new derivatives of pentaerythritol are reported, and selective routes to provide novel fully differentiated, and thus chiral, derivatives of (1,1,1-trishydroxymethyl)methane (2) and (1,1,1-trishydroxymethyl)nitromethane (3) are described. The latter clearly offers scope for numerous elaborations and evaluation of enantioseparation methods is underway.

Acknowledgements

Arab Student Aid International and the British-Arab Charitable Foundation are thanked for support to R.M. The British Council are also thanked for supporting a prior exchange visit (R.M.). NMR, HPLC and IR characterization used instrumentation funded by EPSRC grants GR/L52246 (NMR), GR/M30135 (IR) and GR/L84391 (HPLC). Julie Simkins is thanked for some early preliminary work.
References

4. These results and all work on pentaerythritol differentiation reported here is taken from: Cooper, M. L. M.Sc. Thesis UMIST, 1996.
5. (a) 1H NMR shows two identical aryl rings and acetal protons; 13C shows two types of ring methylenes (axial or equatorial with respect to the other ring); (b) Jin, T.-S.; Li, T.-S.; Zhang, Z.-H.; Yuan, Y.-J. Synth. Commun. 1999, 29, 1601–1606.
8. If the reaction is left for extended times equilibration occurs to an approximately 1:1 diastereomeric mixture.
13. The 2-carbon (n=2) homologation involved (high-yielding) O-allylation, followed by dihydroxylation-periodate cleavage, reduction and then silylation.