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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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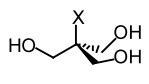
Abstract—Pentaerythritol, (1,1,1-trishydroxymethyl)methyl methane and (1,1,1-trishydroxymethyl)nitromethane are converted into 2-aryl-5,5-bis(hydroxymethyl), 2-aryl-5-hydroxymethyl-5-methyl- or 2-aryl-5-hydroxymethyl-5-nitro-1,3-dioxanes and a range of derivatives. X-Ray and NMR analysis establishes 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.

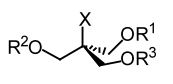
Pentaerythritol (**1**), (1,1,1-trishydroxymethyl)methyl methane (**2**) and (1,1,1-trishydroxymethyl)nitromethane (**3**) are readily available and inexpensive materials. They have numerous potential uses for synthesis.[1] We have been interested in elaborating these materials to fully differentiated multifunctional intermediates, specifically of type **6** (i.e. with at least two of R^1–R^3 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 diastereochemical 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.

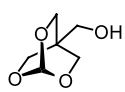
Pentaerythritol has four equivalent groups and so an initial further differentiation is required. Although it is possible to obtain monoacetals by direct reaction of pentaerythritol, and subsequently to differentiate the two remaining hydroxyls, product separations due to the over-protection potential at each step are generally required.[2] The obvious strategy is initially to derivatize one group, and thus work proceeded by preparation of the known[3] 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.



1 X=CH_2OH
2 X=CH_3
3 X=NO_2
4 X=CH_2OAc
5 X=$CH_2OTBDPS$



6 $R^1 \neq R^2 \neq R^3$



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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-

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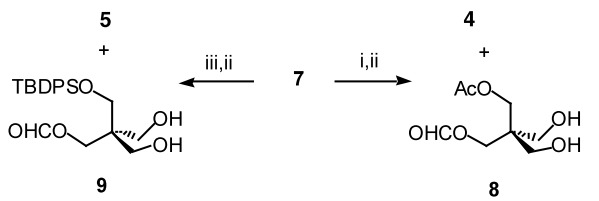
tant formation of the spirocyclic bis-acetal **11** (requiring in situ deacylation). This presumably exists as the symmetrical doubly equatorial spirocyclic structure shown (Schemes 1 and 2).[5]

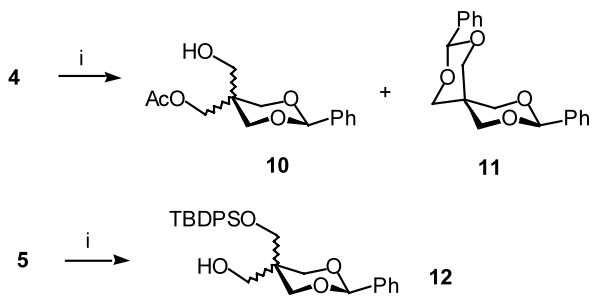
However, the modest yields and variable reproducability of efficient benzylidene acetal formation terminated pursual of the pentaerythritol route. (1,1,1-Trishydroxymethyl)methyl methane (**2**) and (1,1,1-trishydroxymethyl)nitromethane (**3**) were chosen for evaluation since one group is already differentiated 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**[7] 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 ^{1}H resonances for the three methylene groups in **15** and **16** are essentially identical, indicating they have the same diastereomeric structure. Interestingly, the *t*-butyl acetal analogue has also been previously reported, with data in that case showing a diastereomeric mixture of acetals (Scheme 3).[10]



Scheme 1. (i) AcCl, Pyr; (ii) H_2O, heat; (iii) TBDPSCl, ImH.



Scheme 2. (i) PhCHO, CSA, MeCN.

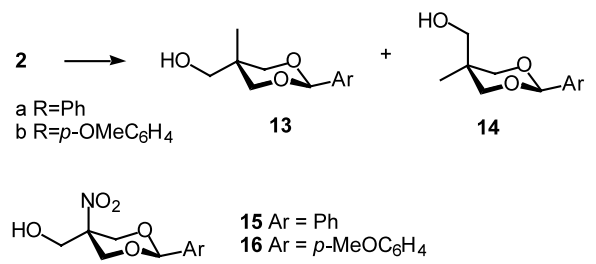
Lack of reported data for, or proof of, related stereostructures, encouraged us to establish unambiguously this stereostructure. Establishing this in one case would, by the NMR analogy between them, also support assignment of the other acetal. Proof of the isomeric structure was provided by X-ray structure 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,



Scheme 3.

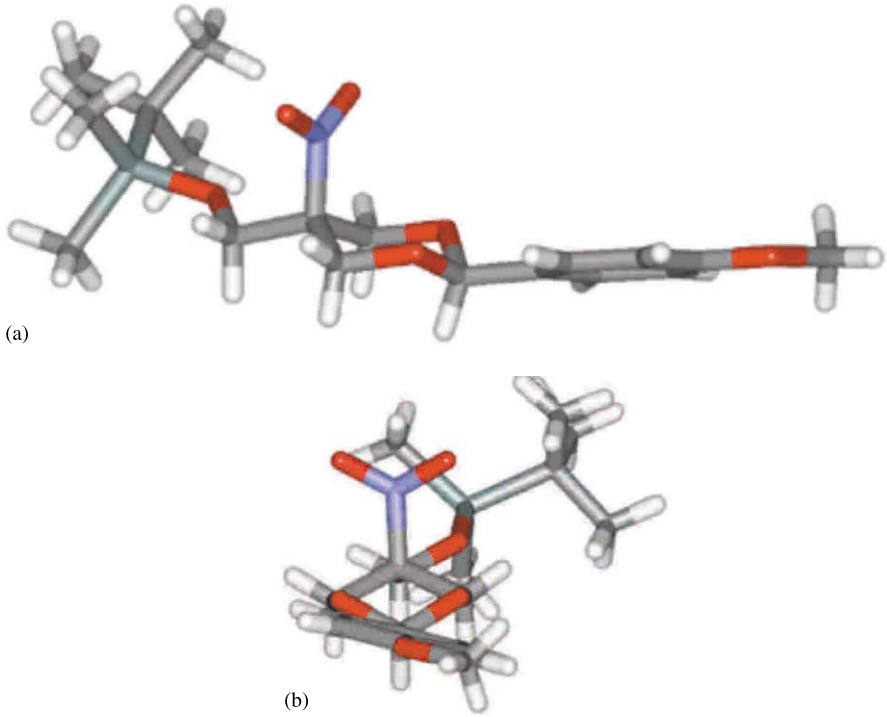
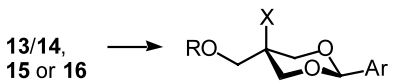


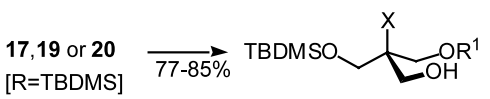
Figure 1. X-Ray structure of **20** [R = TBDMS]. Lower representation shows view from C2 end in the O1,O3,C4,C6 plane.

Table 1. 17 and **19** refer to diastereomeric mixtures, whilst **18** and **20** are single diastereomers as illustration



	X	Ar	R	Yield (%)
17	Me	Ph	SEM, MEM, TBDMS, allyl	65–75
			$TBDMSO(CH_2)_n$ [$n=2$, 3]	30–65[a]
18	NO_2	Ph	TBDMS	70
19	Me	PMP	MEM, TBDMS, TBDPS	60–70
20	NO_2	PMP	MEM, TBDMS	60–70

[a] For $n=3$, 60–65%; for $n=2$ yield is over four steps.[13]

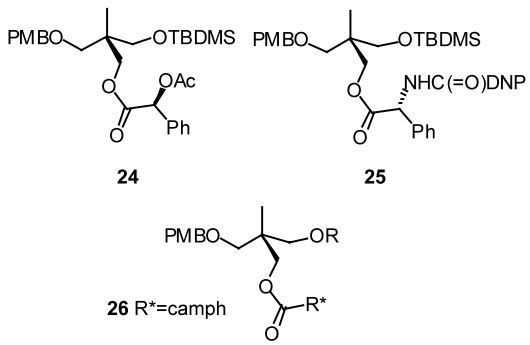


21 X = Me, R^1 = Bn
22 X = Me, R^1 = PMB
23 X = NO_2, R^1=PMB

Scheme 4.

now have alternative access to a key homochiral nitro system analogous to **23** by a different methodology, which will be reported in due course.[14]

However, in summary, this current route provides a three-step access to (±)-**21**–**23** for future investigation of enantioseparation methods.



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)methyl 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

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