Stereochemical observations on the bromate induced monobromopentahydroxylation of benzene by catalytic photoinduced charge transfer osmylation. A concise synthesis of (±)-pinitol

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The use of lower temperatures in the title reaction favours the formation of the *neo* diastereoisomer of the deoxybromoinositol whose diisopropylidene derivative can be converted in three steps to (±)-pinitol.

We have recently described the first examples of a direct stereocontrolled polyhydroxylation pathway from arenes to cyclitols based on catalytic photoinduced charge-transfer osmylation and featuring the use of barium chlorate as a stoichiometric reoxidant.[1] Here we also reported the single unoptimised experiment shown in Scheme 1, whereby the selection of sodium bromate as an alternative 'co-oxidant' led to apparent suppression of the normal third osmylation sequence leading to the *meso* derivative, *allo*-inositol hexaacetate **1**, and formation of the two deoxybromoinositols **2** and **3** in a highly diastereoselective manner and in a combined yield of 18.8%. We now present the results of a study which was designed to probe the stereochemical origins of this unusual monobromopentahydroxylation reaction, together with the elaboration of these readily available products in a concise synthesis of (±)-pinitol.

Casual inspection of the products formed in Scheme 1 clearly suggests that they may be formally derived by the *trans* addition of hypobromous acid at some intermediate stage following the initial formation of the osmate ester of benzene diol. In the first instance, we were therefore intrigued to discover whether bromohydrin formation could be encouraged at the diene stage through an increase in the concentration of bromate anion, particularly since the isolation of minor amounts of the bromoconduritols C **4** and F **5** implied that such a pathway was possible. A systematic study revealed, however, that even at very high concentrations of bromate (2.65 M *cf.* 0.22 M Scheme 1) there was no essential change, either in the relative ratio of *allo*-inositol hexaacetate **1** to brominated products **2** and **3**, or in the diastereoisomeric ratio **2**:**3**.

By way of contrast however, as shown in Table 1, the influence of temperature on the reaction was shown to exert a highly significant effect, with the *neo* diastereoisomer **2** predominating at lower temperature and the *chiro* derivative **3** favoured at higher temperatures.

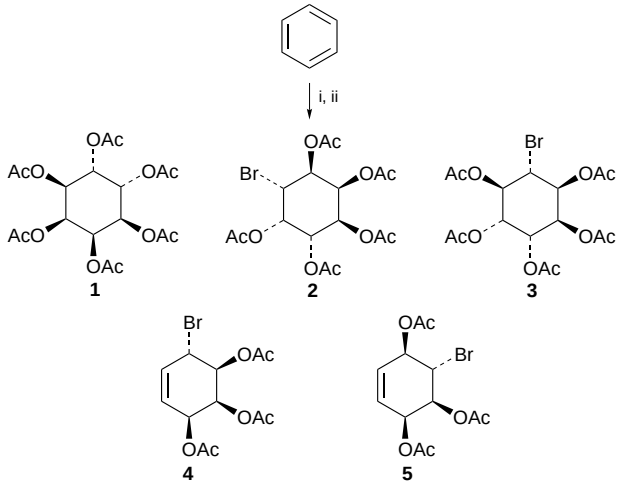
Table 1 Yields and relative ratios of products as a function of temperature[a]

	Product yield (%)		Relative ratio
T/°C	**1**	**2** + **3**	**2**:**3**
2	5.1	12.6	2:1
15	7.4	16.3	1:1
30	7.7	18.8	1:5
45	5.7	16.4	1:5

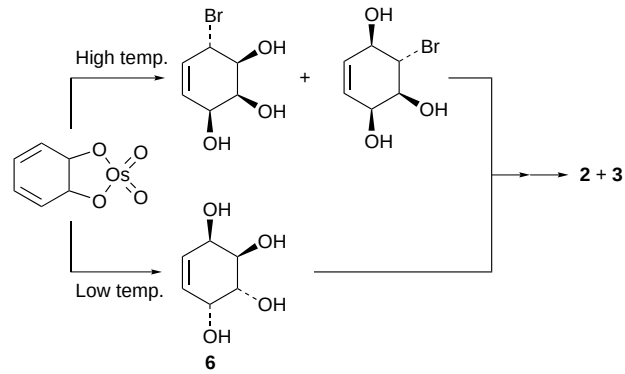
[a] All reactions were run at 0.36 M concentration of bromate using OsO_4 (1.3 mol%) as catalyst with irradiation for 43 h.

A variety of reasons lead us to believe that this crossover in the diastereoisomeric ratio may be explained by the bifurcated reaction pathway shown in Scheme 2, whereby the low temperature reactions tend to pass *via* the intermediacy of conduritol E **6**, or an osmate ester derived therefrom, while formation of bromoconduritols **4** and **5** intervenes effectively at higher temperature.

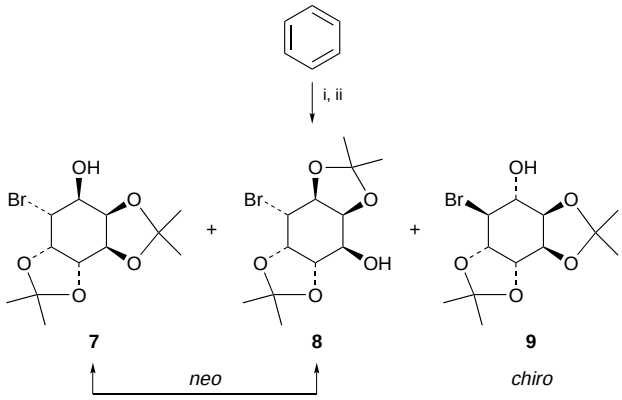
Thus, a significant clue was provided in a parallel low temperature experiment (2 °C) using chlorate anion (0.22 M) as the oxygen atom transfer reagent. Under these conditions, chlorohydrin formation is not observed, and osmylation of the third double bond in the *anti*-tetrol is sufficiently slow to permit isolation of significant amounts of both the inositol and conduritol acetates [**1** 6.1%, **6** (tetraacetate) 4.1%]. We therefore speculated that bromate disproportionation was



Scheme 1 *Reagents and conditions*: i, OsO_4 (cat.), *h*ν, $NaBrO_3$ (0.22 M), 45 °C; ii, AcOH, Ac_2O, (**1**) 7.7%, **2**:**3** 5.1:1, 18.8%, **4**:**5**, 1:5, 2.3%



Scheme 2



Scheme 3 *Reagents and conditions*: i, OsO_4 (cat.), *h*ν, $NaBrO_3$ (0.22 M), 15 °C; ii, acetone, TsOH, H_2O, (**7**) 8%, (**8**) 6.7%, (**9**) 2.5%

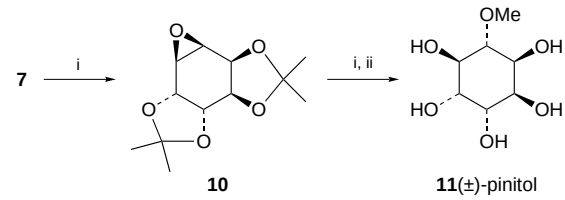
slower at lower temperatures and that the deoxybromoinositols **2** and **3** were formed by addition of hypobromous acid to conduritol E **6** during the work up stage, which involved a reductive quench of bromate residues with sodium metabisulfite. Indeed, this very combination has recently been shown to be an excellent method for bromohydrin formation.[2] Some support for this hypothesis came from an experiment in which a vast excess of cyclohexene was added as a sacrificial alkene following a photoosmylation at 2 °C, and prior to the addition of metabisulfite. In this instance, the relative proportion of the isolated bromohydrin acetates was significantly lower than before [**2** + **3**; 6.2%, compare 12.6% (Table 1)], and counterbalanced by the corresponding isolation of conduritol E (tetraacetate, 8.6%).

While the results presented in Table 1 clearly demonstrate that diastereoisomeric crossover has occurred, it should be noted that the strongly ionising conditions employed in the acetylation step almost certainly promote neighbouring group participation.[3] This aspect was highlighted when the products from a bromate driven photoosmylation reaction at 15 °C were isolated as their isopropylidene derivatives by treatment of the crude reaction mixture with acetone and toluene-*p*-sulfonic acid. (Scheme 3).

The supposition that the isolated ratio of deoxybromocyclitols from this experiment [**7** + **8** (*neo*, 14.7%) : **9** (*chiro*, 2.5%); 5.9 : 1] is probably a more appropriate reflection of the initial product distribution prior to derivatisation was also supported by a further blank experiment in which reaction of conduritol E **6** with sodium bromage–sodium metabisulfite was followed by neutralisation with sodium hydroxide and subsequent acetylation under less ionising acidic conditions with acetic anhydride in acetic acid to give **2** and **3** (72%, ratio **2** : **3**, 6.3 : 1).

From a preparative standpoint, irrespective of the fact that two competing pathways are operating, it is apparent that experimental conditions can be selected to favour either the *neo* or the *chiro* series as the major diastereoisomer. Moreover, in practical terms, a single recrystallisation of a mixture of **2** and **3** from EtOH at room temperature gives pure **3**, while advantage can be taken of the known relative insolubility of *neo*-inositol[4] to precipitate the parent bromocyclitol from **2** by simple acid catalysed hydrolysis using HCl in MeOH.

The ready availability of these protected building blocks in a single one-pot operation offers a variety of possibilities for further synthetic manipulation in the important cyclitol area. By way of illustration, we elected to prepare (±)-pinitol **11**, the



Scheme 4 *Reagents and conditions*: i, K_2CO_3, MeOH, heat 2 h, 83%; ii, Al_2O_3, MeOH, heat 24 h; iii, H_2O, THF, HCl (cat), 60% from **10**

3-*O*-methyl ether of *chiro*-inositol, with both enantiomers occurring in various plant sources. (+)-Pinitol has been shown to possess significant hypoglycemic and antidiabetic activity in diabetic albino mice.[5] Previous syntheses of pinitol, either in racemic form[6] or of either antipode,[7,8] have relied on the use of *cis*-dienediols available by microbial oxidation of arenes using *Pseudomonas putida*.

Thus, as shown in Scheme 4, ring closure of the bromohydrin **7** to epoxide **10** was smoothly accomplished using K_2CO_3 in MeOH (83%). The regiospecificity of the subsequent ring-opening of the epoxide with alumina in MeOH is governed by the necessity for a *trans* opening *anti* to the neighbouring isopropylidene groups and finds precedent in Hudlicky's elegant enantiodivergent synthesis of both antipodes.[8] An acidic work up to this reaction led to *in situ* deprotection to afford (±)-pinitol **11** in 60% isolated yield from **10**. The overall sequence therefore requires three operations and five discrete steps from benzene.

In summary, the present study has shown that the influence of temperature in the catalytic photoinduced charge transfer osmylation of benzene may be usefully controlled, either in the reaction using chlorate anion as oxidant to suppress tertiary osmylation at lower temperature and hence favourer conduritol E production, or to influence the stereochemical outcome in the bromate reaction leading to *neo* and *chiro* deoxybromoinositols.

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Footnote

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References

1 W. B. Motherwell and A. S. Williams, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 280.
2 H. Masuda, K. Takase, M. Nishio, A. Hasegawa, Y. Nishiyama and Y. Ishii, *J. Org. Chem.*, 1994, **59**, 5550.
3 For examples in the cyclitol area, see G. E. McCasland and E. C. Horswill, *J. Am. Chem. Soc.*, 1953, **75**, 4020 and references cited therein.
4 S. J. Angyal and D. C. Craig, *Carbohydr. Res.*, 1994, **263**, 149.
5 C. R. Narayanan, D. D. Joshi, A. M. Mujumdar and V. V. Dhekne, *Curr. Sci.*, 1987, **56**, 139.
6 S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron Lett.*, 1987, **28**, 225; H. A. J. Carless, J. R. Billinge and O. Z. Oak, *Tetrahedron Lett.*, 1989, **30**, 3113.
7 S. V. Ley, F. Sternfeld and S. Taylor, *Tetrahedron*, 1989, **45**, 3463.
8 T. Hudlicky, J. D. Price, F. Rulin and T. Tsunoda, *J. Am. Chem. Soc.*, 1990, **112**, 9439.

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