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Strategy for contra-thermodynamic radical-chain epimerisation of 1,2-diols using polarity-reversal catalysis

Hai-Shan Dang and Brian P. Roberts*

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK

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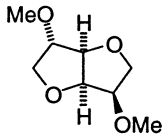
Abstract

Polarity-reversal catalysis by thiols has been applied to provide an efficient method for the conversion of appropriate 1,2-diols into less or similarly stable diastereoisomers by epimerisation of their acetonides under radical-chain conditions.

Keywords: radicals and radical reactions; catalysis; thiols; diols; isomerisation; carbohydrates.

We have reported previously that thiols catalyse selective radical-chain epimerisation of organic molecules at chiral tertiary CH centres that are activated by an attached oxygen atom.[1] For example, the readily available di-*O*-methyl-1,4:3,6-dianhydro-D-glucitol **1** is isomerised to the thermodynamically more stable, but rarer, di-*O*-methyl-1,4:3,6-dianhydro-L-iditol **2** when heated in refluxing octane in the presence of tri-*tert*-butoxysilanethiol[2] [$(Bu^tO)_3SiSH$, TBST] as catalyst, 2,2-di-*tert*-butylperoxybutane (DBPB) **3** as initiator and collidine.[3] The mechanism of the epimerisation process is shown in Scheme 1 and the function of the thiol is to act as a protic polarity reversal catalyst[4] to promote the thermoneutral transfer of hydrogen from the parent diastereoisomer **4** to the nucleophilic chain-carrying radical **5**. In the absence of thiol, the direct abstraction of hydrogen from **4** by **5** is slow because of the lack of favourable polar effects in the transition state.[4]



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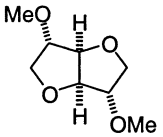

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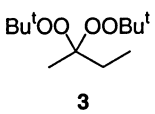

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A potential drawback of this methodology as a procedure for the conversion of one diastereoisomer to a more desirable one is that the direction of change is necessarily always

* Corresponding author.

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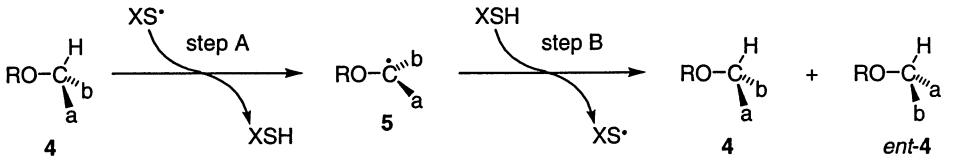
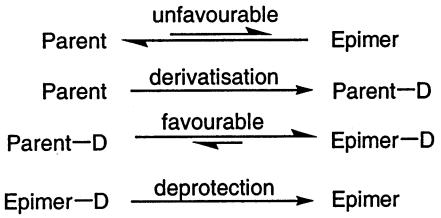


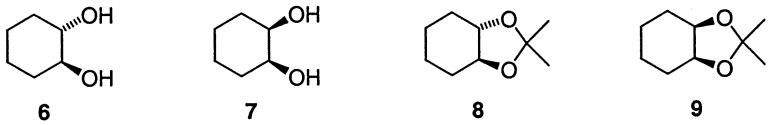
Scheme 1.

towards thermodynamic equilibrium. In this communication we present methods for the efficient conversion of a parent diastereoisomer into a less or similarly stable epimer; the general strategy is outlined in Scheme 2. The parent is first converted to a derivative, chosen such that the corresponding derivative of the desired epimer is significantly more stable. The parent derivative is then isomerised under radical-chain conditions to give an equilibrium mixture that favours the derivative of the epimer, followed by deprotection of the latter to give the required compound.

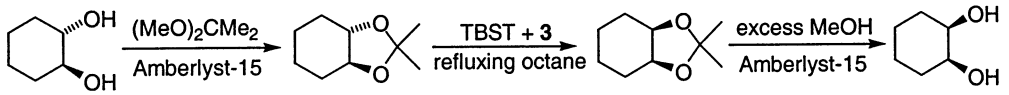


Scheme 2.

Experiments with 1,2-diols and their derivatives serve both to validate and illustrate this approach. According to molecular mechanics calculations using the MMX forcefield,[5] the most stable conformation of *trans*-cyclohexane-1,2-diol **6** is more stable than that of the *cis*-isomer **7** by 2.9 kJ mol^{-1}. Both isomers of the diol are readily converted to the corresponding acetonides **8** and **9** by treatment with excess 2,2-dimethoxypropane in the presence of an acidic ion-exchange resin (Amberlyst-15). The *trans*-diastereoisomer is now destabilised with respect to the *cis* form by the extra strain present when a five-membered dioxolane ring is *trans* fused to the cyclohexane ring and molecular mechanics calculations indicate that the *trans*-acetonide is *less stable* than the *cis* form by 2.6 kJ mol^{-1}. Heating either the *trans*- or the *cis*-acetonide in refluxing octane (bath temperature 140–145°C) for 2.5 h in the presence of TBST (3×3 mol%), the peroxyketal DBPB[6] (3×3 mol%) and collidine (1×10 mol%), as described previously, led to the same equilibrium mixture of isomers in which the *cis*-acetonide predominated to the extent of 95%.[7] No detectable epimerisation takes place in the absence of the thiol. The acetonide **9** could be readily deprotected by treatment with excess methanol in the presence of Amberlyst-15 at room temperature to give the *cis*-diol in a pure state after one recrystallisation from ethyl acetate. The sequence of derivatisation, epimerisation and deprotection summarised in Scheme 3 thus provides an efficient procedure for the conversion of *trans*-cyclohexane-1,2-diol into the *cis*-isomer, based on the principle generalised in Scheme 1.

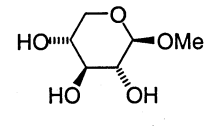


Methyl β-D-xylopyranoside **10** was converted into the acetonide **11** using the published method[8] and subsequent methylation afforded **12**,[9] which is predicted by molecular mechanics



Scheme 3.

calculations to be less stable than both its C-3 epimer **13** and its C-2 epimer **14**, by 8.1 and 8.0 kJ mol^{-1}, respectively. However, attempted isomerisation of **12**, under the conditions used to epimerise **8** to **9**, failed and **12** remained unchanged. Under more forcing conditions, in refluxing nonane with di-*tert*-butyl peroxide (20 mol%) as the initiator and three additions of TBST (3×5 mol%) during 3 h, partial isomerisation of **12** took place to give one major product (30%), believed to be **14**,[10] but the majority of **12** was unchanged. In marked contrast, the 4-deoxy analogue **15**[11] underwent epimerisation readily in refluxing octane under the conditions used to isomerise **8** and was converted essentially quantitatively into the C-3 epimer **16**.[12] The acetonide **15** is calculated to be less stable than **16** by 10.9 kJ mol^{-1} and less stable than its C-2 epimer by 6.5 kJ mol^{-1}. Deprotection of **16** (Amberlyst-15, excess MeOH, room temperature) gave the free *cis*-diol, methyl 4-deoxy-β-D-*erythro*-pentopyranoside **17**.[14]



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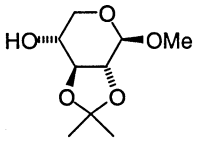

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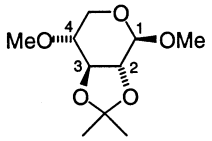

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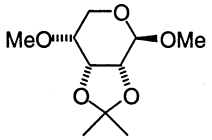

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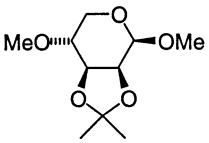

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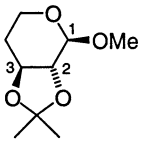

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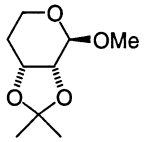

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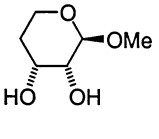
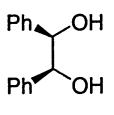


17

The large difference in the reactivity of **12** and **15** towards thiol-catalysed epimerisation at C-3 is probably the result of steric shielding of H-3 by the 4-methoxy group in the former, coupled with the deactivating polar effect of this methoxy group on abstraction of H-3 by the electrophilic thiyl radical.[15]

According to calculations using the MMX force-field, the most stable conformation of *meso*-1,2-diphenylethane-1,2-diol (*meso*-hydrobenzoin) **18** is marginally (by ca. 1 kJ mol^{-1}) more stable than that of the *dl*-form **19**. Although this result is of dubious quantitative significance,[16] it does serve to confirm that the two diastereoisomers are of similar stability and that direct epimerisation of the *meso*-form is unlikely to provide a useful route to the *dl*-form,[19] which is less easily prepared than *meso*-hydrobenzoin and is much more costly to obtain commercially. However, the *trans*-acetonide **21** derived from the *dl*-diol is calculated to be more stable by 12.1 kJ mol^{-1} than the *cis*-acetonide **20** obtained from the *meso*-diol, implying that radical-chain epimerisation of **20** should provide an efficient means to convert the *meso*-diol to the *dl*-diol under mild neutral conditions.



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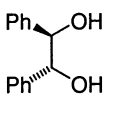

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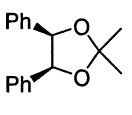

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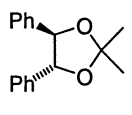

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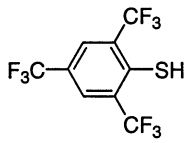

22

In accord with this, treatment of **20** with 2,4,6-tris(trifluoromethyl)thiophenol **22** as catalyst[21] and **3** as initiator in refluxing octane resulted in complete ($\geq 98\%$) conversion to the *trans*-acetonide **21**, which could be deprotected (Amberlyst-15, excess MeOH, reflux) to give the free *dl*-diol **19**. The choice of thiol catalyst for epimerisation of **20** proved to be critical and no significant conversion to **21** was observed when, under otherwise identical conditions, the thiol **22** was replaced by TBST or *tert*-dodecanethiol. With thiophenol itself, conversion of **20** to **21** took place only to the extent of 75%. For epimerisation to take place efficiently *both* steps A and B of Scheme 1 must be sufficiently rapid to maintain the propagation cycle. These results indicate that the S–H bonds in TBST and *tert*-dodecanethiol are too strong for this requirement to be met for the intermediate benzylic radical (step B is too slow), while the S–H bond in thiophenol is a little too weak for step A to occur efficiently, even though the abstraction is from a benzylic CH group.

Acknowledgements

We are grateful to Dr. Abil Aliev for assistance with the NMR experiments to determine the structure of **14** and we acknowledge financial support from the EPSRC.

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7. This equilibrium composition corresponds to a free energy difference of 9.8 kJ mol^{-1} at 126°C (the bp of octane), significantly larger than the calculated MMX energy difference between the *cis* and *trans* isomers. Using the MMFF94 force field, available in PCMODEL, the calculated energy difference increases to 9.7 kJ mol^{-1}.
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coupling constant. MS [EI, 70 eV (%)]: 188 (M^+, 3), 173 (32), 113 (33), 100 (55) and 59 (100). Found: C, 57.2; H, 8.7. $C_9H_{16}O_4$ requires C, 57.4; H, 8.6%.

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