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Asymmetric synthesis of tetrahydrofurans and tetrahydropyrans with competitive [1,2]-phenylsulfanyl (PhS) migration (II): synthesis of protected tetrahydropyrans

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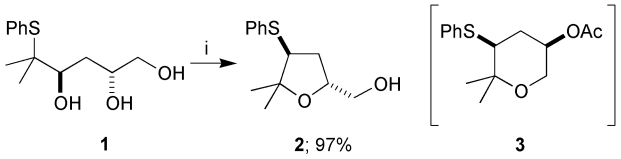
Enantiomerically enriched triols were treated with trimethylorthoacetate and pyridinium toluene *p*-sulfonate to give a mixture of unrearranged THF and rearranged THP; treatment of the product mixture with toluene *p*-sulfonic acid equilibrated the mixture to the THP.

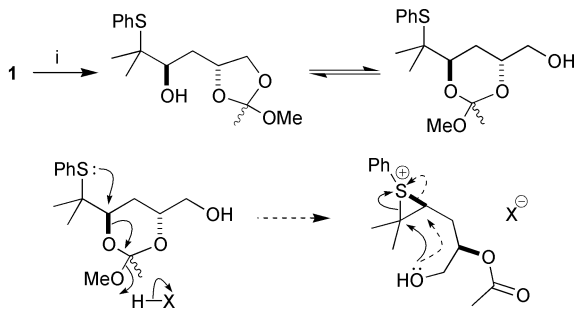
In the preceeding article[1] we reported the preparation of enantiomerically enriched triols (*e.g.* **1**) and their conversion to the thermodynamic tetrahydrofuran (THF) products (*e.g.* **2**) (Scheme 1). In this publication we disclose details of how the same cyclisation precursors can be converted to the complementary tetrahydropyran (THP) products (*e.g.* **3**).



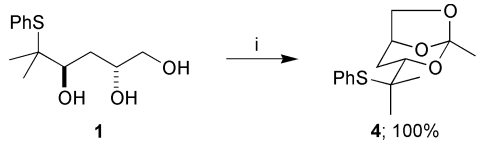
Scheme 1 *Reagents*: i, TsOH, CH_2Cl_2.

An obvious approach to the THPs would be an orthogonal protecting group strategy, which would leave the secondary hydroxy nucleophile protected and the primary hydroxy unprotected and available for cyclisation. Alternatively, we envisaged a situation where it would be possible to protect the secondary hydroxy nucleophile and simultaneously activate the other secondary hydroxy group to nucleophilic displacement. By using an orthoester in the appropriate conditions an exchange could be set up between a 5- and a 6-membered orthoester (Scheme 2). So long as the 5-membered orthoester was inert under these reaction conditions it would be possible to trigger the episulfonium ion formation and protect the secondary hydroxy group as its acetate.

Pyridinium *p*-toluenesulfonate (PPTS) (pK_a ~ 5.5) was chosen as the acid catalyst for this reaction because orthoesters exchange under general acid catalysis,[2] but we did not expect such a weak acid to promote direct formation of the episulfonium ion. Hence triol **1** was treated with 1 eq. of trimethylorthoacetate with PPTS as the acid catalyst. In the first instance the product was the orthoester **4** which is formed by exchange of all three molecules of MeOH (Scheme 3). However, with longer

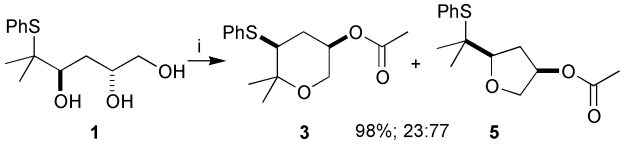


Scheme 2 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+$ TsO^-, CH_2Cl_2.



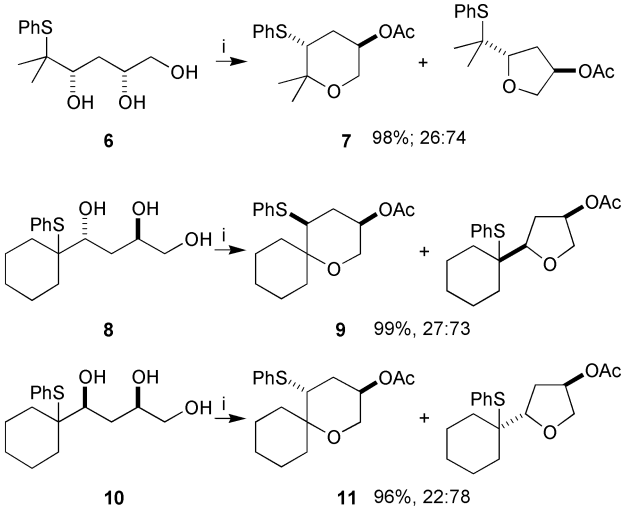
Scheme 3 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+$ TsO^-, CH_2Cl_2, rt, 2 min.

reaction times we obtained none of this orthoester but two heterocyclic products. The two heterocycles were the unrearranged[3] THF **5** and the rearranged[3] THP **3**: both products derive from cyclisation of the primary hydroxy nucleophile, but to different ends of the episulfonium ion intermediate (Schemes 2 and 4).

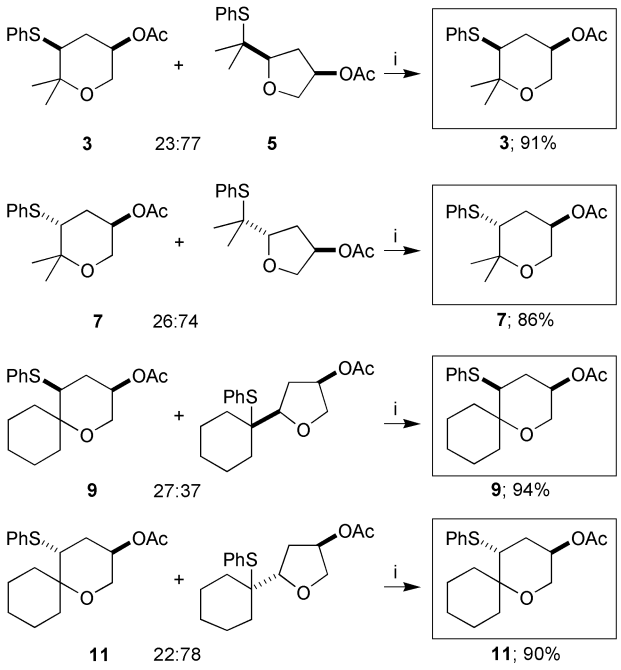


Scheme 4 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+$ TsO^-, CH_2Cl_2, rt, 24 h.

This result is important in the context of our research programme because it constitutes the first example of cyclisation on to the less substituted end of an episulfonium ion (where the alternative cyclisation would not give a 7-membered ring).[4] This raised the question of whether these reactions were therefore under kinetic control. (We have previously shown that cyclisations catalysed by toluene *p*-sulfonic acid are under thermodynamic control.[5,6]) To address this question we performed three control experiments. First we took a sample of the triol and treated it with PPTS, without adding trimethylorthoacetate, and showed that no reaction occurred. Secondly the 77:23 THF **5**: THP **3** mixture isolated from the cyclisation



Scheme 5 *Reagents*: i, $(MeO)_3CMe$, $C_5H_6N^+$ TsO^-, CH_2Cl_2, rt, 24 h.

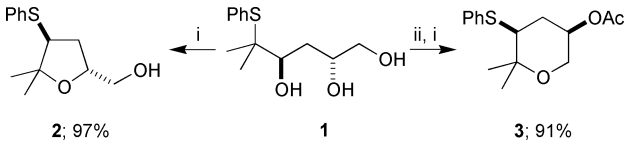


Scheme 6 *Reagents*: i, TsOH, CH_2Cl_2, 40 °C, 24 h.

reaction was resubmitted to the PPTS acid catalyst: no equilibration of the mixture occurred. Finally we confirmed the second experiment by showing that a pure sample of the unrearranged THF **5** was not converted to the THP **3** by PPTS. At this point we could conclude this orthoester-promoted cyclisation is in fact under kinetic control.

Following the reaction of triol **1**, we also cyclised triols **6** (the diastereoisomer of **1**), **8** and **10** under the same conditions and observed in each case that the unrearranged THF was the major product (Scheme 5). For the case of the 2,4-*syn* triols **6** and **10** none of the bicyclic orthoester intermediate could be isolated.

In order to exploit this interesting mechanistic observation synthetically we reasoned that treatment of the THF–THP mixtures with a strong acid, toluene *p*-sulfonic acid, should lead to equilibration of the mixture to the rearranged THPs. Indeed



Scheme 7 *Reagents*: i, TsOH, CH_2Cl_2; ii, $(MeO)_3CMe$, $C_5H_6N^+$ TsO^-.

this was observed in all four cases; complete equilibration occurred to give the THPs **3**, **7**, **9** and **11**, protected as their acetates (Scheme 6). Hence this two-step synthetic procedure can give the THP products (which are complementary to the THF products of the one-step toluene *p*-sulfonic acid cyclisation) without the need for any purification of the intervening mixture.

In summary, we have demonstrated a rapid approach to enantiomerically enriched THPs or THFs from a common triol precursor depending on the choice of reagent (Scheme 7). For THF synthesis the episulfonium ion is formed directly, under specific acid catalysis. Use of the orthoester route promotes episulfonium ion formation under general acid catalysis and results in THP–THF mixtures that can be equilibrated to THP.

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Notes and references

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3 We use the terms ‘rearranged’ and ‘unrearranged’ to designate cyclisation products that have been formed either with or without [1,2]-PhS rearrangement respectively.
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