Scope and limitation of the [1,2]-phenylsulfanyl (PhS) migration in the asymmetric synthesis of tetrahydrofurans and tetrahydropyrans from common triol precursors

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Triols containing three secondary hydroxy groups were reacted with either (i) toluene *p*-sulfonic acid or (ii) trimethylorthoacetate–pyridinium toluene *p*-sulfonate followed by toluene *p*-sulfonic acid.

In the previous two articles[1,2] we demonstrated how enantiomerically enriched triols (*e.g.* **2**) could be converted in a single step to THFs (*e.g.* **1**) (thermodynamic control) or in two steps to THPs (*e.g.* **3**) (kinetic control–equilibration sequence) (Scheme 1). The subject of the final communication in this series is our attempts to assess the generality of these reactions, particularly by replacement of the primary hydroxy in **2** with a secondary alcohol.
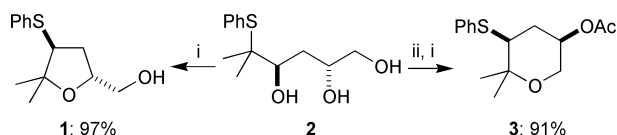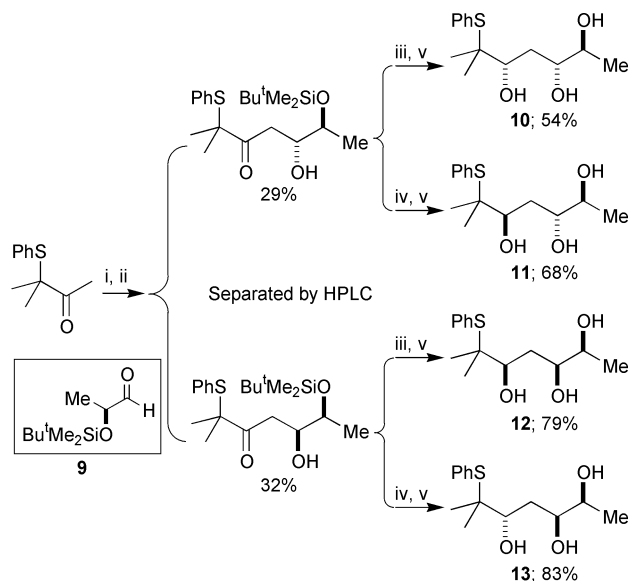

Scheme 1 *Reagents*: i, TsOH, CH$_2$Cl$_2$, 40 °C; ii, (MeO)$_3$CMe, C$_5$H$_6$N$^+$ TsO$^-$, CH$_2$Cl$_2$, rt.

Triols **7** and **8** were prepared by essentially the same method as used previously,[1] *i.e.* by Sharpless asymmetric dihydroxylation[3] of the styrene **6** and diastereoselective reduction of the β-hydroxyketones (Scheme 2).[4,5] Styrene **5** was derived from the homoallylic alcohol **4** by a Heck reaction with iodobenzene. The remaining triols **10–13** were prepared by an aldol reaction[6] of the lactic acid derived aldehyde **9**, followed by stereocontrolled reduction (Scheme 3). We were able to prepare all diastereoisomers of the triol target molecules since the aldol route gave poor diastereoselectivity and necessitated a difficult separation of the aldol products by preparative HPLC.
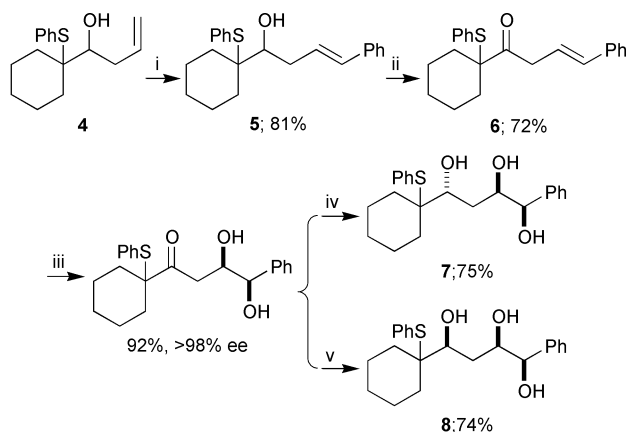

Scheme 2 *Reagents*: i, PhI, 5 mol% Pd(OAc)$_2$, 10 mol% Ph$_3$P, Et$_3$N, MeCN, 80 °C, 24 h; ii, PDC, CH$_2$Cl$_2$, rt; iii, AD-mix-β, MeSO$_2$NH$_2$, Bu^{t}OH–H$_2$O, rt; iv, Me$_4$N$^+$ BH(OAc)$_3$$^-$, AcOH–MeCN, −20 °C, 7 days; v, Et$_2$BOMe, THF–MeOH, −78 °C then NaBH$_4$.

Scheme 3 *Reagents*: i, LDA, THF, −78 °C; ii, aldehyde **9**; iii, Et$_2$BOMe, THF–MeOH, −78 °C then NaBH$_4$; iv, Me$_4$N$^+$ BH(OAc)$_3$$^-$, AcOH–MeCN, −20 °C, 7 days; v, Bu$^n_4$N$^+$ F$^-$, THF, rt.

The toluene *p*-sulfonic acid catalysed cyclisations are under thermodynamic control and so we used long reaction times to ensure equilibrium was established. The triols in the lactic acid series (*i.e.* triols **10–13**) all rearranged to give the THFs (**14–17**, respectively) as the major product (Scheme 4). We were particularly interested to establish the outcome of rearranging the ²,⁴*anti*,⁴,⁵*anti* triol **11**, since the THP **18** derived from this triol would have the maximum number of equatorial substituents (Fig. 1). Despite this 'favourable' arrangement of substituents in the THP product, the THF was still the major
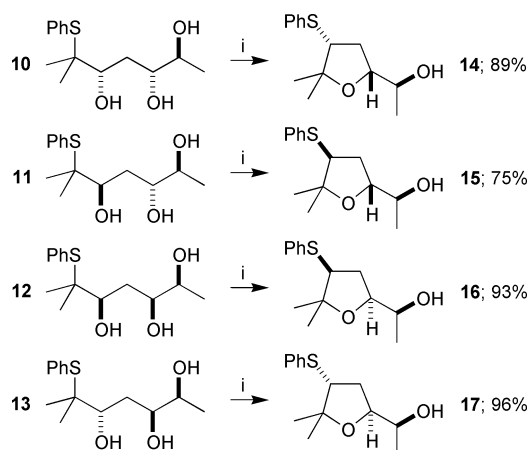
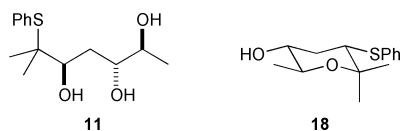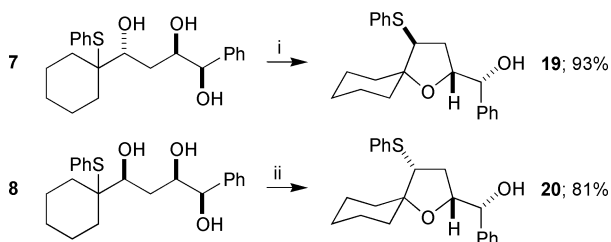**Scheme 4** *Reagents*: i, TsOH, CH$_2$Cl$_2$, 40 °C.

Fig. 1

product, though THP **18** did account for 17% of the equilibrium.

The rearrangement of the triols **7** and **8** required careful handling (presumably due to the benzylic hydroxy group). The $^{2,4}anti,^{4,5}syn$ triol **7** rearranged exclusively to THF **19** after being heated to reflux in dichloromethane for 24 h (Scheme 5). The $^{2,4}syn,^{4,5}syn$ triol **8**, however, had to be rearranged at rt (3 days) to avoid decomposition. Again, the THF **20** was the only isolated product.
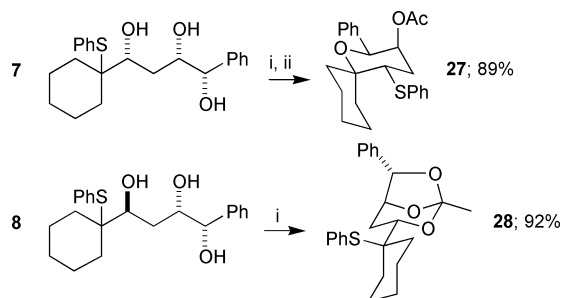

Scheme 5 *Reagents*: i, TsOH, CH$_2$Cl$_2$, 40 °C; ii, TsOH, CH$_2$Cl$_2$, rt.

The products of the kinetically controlled orthoester rearrangement reported in the preceding communication[2] were equilibrated with toluene *p*-sulfonic acid in dichloromethane with the aim of converting the unrearranged[7] THFs to THPs.

Reactions of the triols in the lactic acid series turned out to be very substrate dependent. Rearrangement of the $^{2,4}syn,^{4,5}anti$ triol **10** under kinetic conditions gave the unrearranged THF **22** as the major product (Scheme 6). Equilibration with toluene *p*-sulfonic acid gave only a 74:26 mixture of the rearranged THP **21** and unrearranged THF **22**. The inference here could be that it is unfavourable for the sulfur to occupy an axial position, indeed sufficiently unfavourable that it can partly overcome the driving force for 'downhill' migration.[8] The $^{2,4}anti,^{4,5}anti$-triol **11** behaved quite differently; after equilibration of an initial THF–THP mixture the only product identified was the THP **23**, with methyl, acetoxy and phenylsulfanyl groups all occupying equatorial positions (Scheme 6). The $^{2,4}syn,^{4,5}syn$-triol **12** gave,
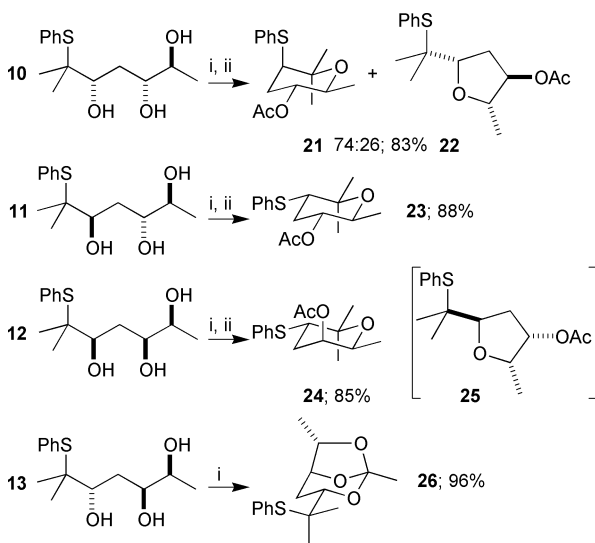
Scheme 6 *Reagents*: i, (MeO)$_3$CMe, C$_5$H$_6$N$^+$ TsO$^-$, CH$_2$Cl$_2$, rt; ii, TsOH, CH$_2$Cl$_2$, 40 °C.

Scheme 7 *Reagents*: i, (MeO)$_3$CMe, C$_5$H$_6$N$^+$ TsO$^-$, CH$_2$Cl$_2$, rt; ii, TsOH, CH$_2$Cl$_2$, rt.

after the two-step reaction sequence, the THP **24** with an axial acetate (the alternative THF **25** contains an unfavourable 2,3-*syn* relationship) (Scheme 6). Finally, in this series of compounds, the $^{2,4}anti,^{4,5}syn$-triol **13** gave a single product after treatment with trimethylorthoacetate and PPTS: the bicyclic orthoester **26**. Attempts to repeat the reaction at higher temperatures, or with longer reaction times, led only to decomposition products that were not characterised. It is interesting to note the stabilising effect of an *exo*-methyl group on these compounds. When triol **11** (with 2,4-*anti* stereochemistry) was reacted with the same reagent system no bicyclic orthoester intermediate was observed; presumably an *endo*-methyl group here destabilises the orthoester intermediate (if the corresponding orthoester forms at all).

The triols **7** and **8,** each containing a benzylic hydroxy group, behaved similarly to their analogues in the lactic acid series. Triol **7** was converted into the THP **27**, bearing an axial acetate, and triol **8** gave only the bicyclic orthoester **28**, which was not successfully transformed into the target heterocycles (Scheme 7).

In summary, we have demonstrated that for the general class of triols under investigation THFs are formed as thermodynamic products when toluene *p*-sulfonic acid is used as the catalyst. This is attributed to the 1,3-diaxial interactions which exist in the THPs when one of the C–C bonds of the tertiary migration origin is forced to enter an axial environment. The orthoester reaction was shown to be general apart from triols with $^{2,4}anti,^{4,5}syn$ stereochemistry in which case the intermediate bicyclic orthoester is overstabilised by a 6-*exo* substituent. The subsequent equilibration of the product mixture gives THPs as exclusive products in all cases except for triol precursors with $^{2,4}syn,^{4,5}anti$ stereochemistry.

Notes and references

1 D. House, F. Kerr and S. Warren, *Chem. Commun.*, 2000, 1779 (DOI: 10.1039/b005342m).
2 D. J. Fox, D. House, F. Kerr and S. Warren, *Chem. Commun.*, 2000, 1781 (DOI: 10.1039/b005341o).
3 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
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5 D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc.*, 1988, **110**, 3560.
6 E. P. Lodge and C. H. Heathcock, *J. Am. Chem. Soc.*, 1987, **109**, 3353.
7 By 'unrearranged' we mean a product in which the phenylsulfanyl group remains bound to the same carbon as it was before the cyclisation, *i.e.* a product that has not undergone a [1,2]-PhS rearrangement.
8 By 'downhill' we refer to the phenylsulfanyl group undergoing a [1,2] shift from a more substituted to a less substituted carbon atom. Sulfanyl groups generally only move 'downhill'; in exceptional cases they may undergo 'flat' migration, *i.e.* from one secondary centre to another. For more details see: D. J. Fox, D. House and S. Warren, *Angew. Chem., Int. Ed. Engl.*, manuscript in preparation.