Asymmetric synthesis of tetrahydrofurans and tetrahydropyrans with competitive [1,2]-phenylsulfanyl (PhS) migrations (I): thermodynamic control

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Triols were prepared in enantiomerically enriched form by a short route that included a Sharpless asymmetric dihydroxylation; treatment of these triols with toluene *p*-sulfonic acid gave THFs as thermodynamic products.

Previously, we have reported the outcome of competitive cyclisations between two primary hydroxy groups at the end of separate or branched side chains (**1** and **2**, Fig. 1).[1,2] We then wished to investigate cyclisations of 2,4,5-triols (bearing a phenylsulfanyl group at C-1) with primary and secondary hydroxy groups in the same side-chain (Scheme 1). In each case two modes of cyclisation are possible: route (**A**) would result in tetrahydropyran (THP) formation, route (**B**) in tetrahydrofuran (THF) formation.

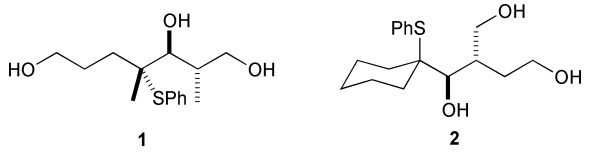
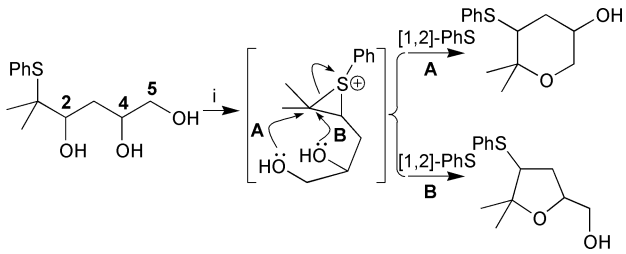
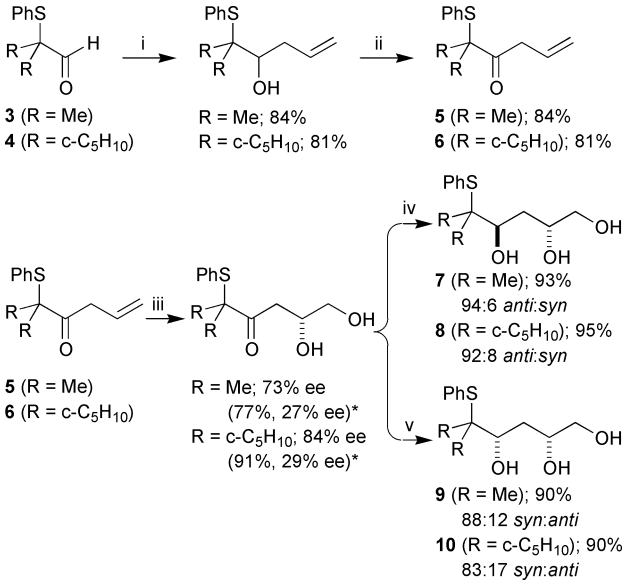


Fig. 1



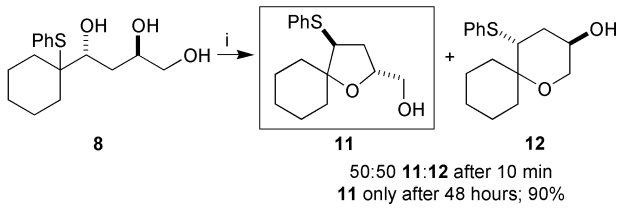
Scheme 1 *Reagents*: i, TsOH, CH_2Cl_2.



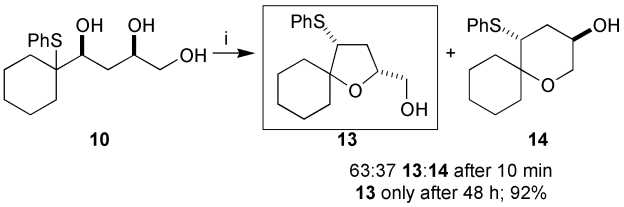
Scheme 2 *Reagents*: i, CH_2=$CHCH_2MgBr$, Et_2O, rt; ii, PCC, CH_2Cl_2, rt; iii, $K_2OsO_2(OH)_4$, $(DHQD)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, Bu^tOH–H_2O, 0 °C; iv, Me_4N^+ $BH(OAc)_3^-$, AcOH-MeCN, −20 °C, 7 days; v, Et_2BOMe, THF–MeOH, −78 °C then $NaBH_4$. * Yields and enantiomeric excesses in parentheses denote those obtained using AD-mix-β at 25 °C.

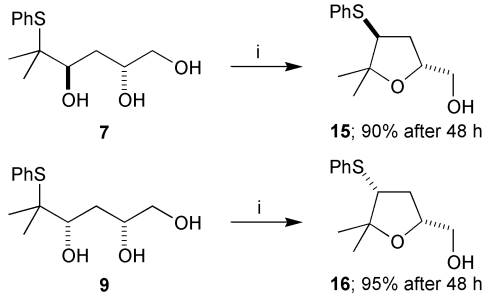
Two sets of diastereomeric triols were prepared for this study with different migration origins; for one pair (**7** and **9**) *gem*-dimethyl substitution was used and for the other (**8** and **10**) a cyclohexane ring was used (Scheme 2). The triols were readily synthesised starting from the aldehydes **3** and **4**. Grignard addition followed by oxidation gave the homoallylic ketones **5** and **6**. The asymmetric dihydroxylation reaction[3] gave optimum enantiomeric excess (73–84%) when Sharpless' PYR ligand was used.[4] Finally a 1,3-diastereocontrolled reduction gave either the 2,4-*anti*[5] (**7** and **8**) or 2,4-*syn*[6] diastereoisomers (**9** and **10**) of each triol.

Initially these compounds were subjected to our standard conditions for rearrangement: a 5 min reflux with 5 mol% toluene *p*-sulfonic acid in dichloromethane. To our initial disappointment, triol **8** gave a 50:50 mixture of THF **11** and THP **12** (Scheme 3).[7] Previously we have shown that these reaction are under thermodynamic control,[8,9] so resubmitting this mixture to the reaction conditions, or taking a fresh sample of the triol **8**, and heating to reflux in dichloromethane for 48 h led to the complete conversion into the spirocyclic THF **11** Scheme 3). Similarly the *syn*-triol **10** gave an initial product



Scheme 3 *Reagents*: i, TsOH, CH_2Cl_2, 40 °C.





Scheme 4 *Reagents*: i, TsOH, CH_2Cl_2, 40 °C.

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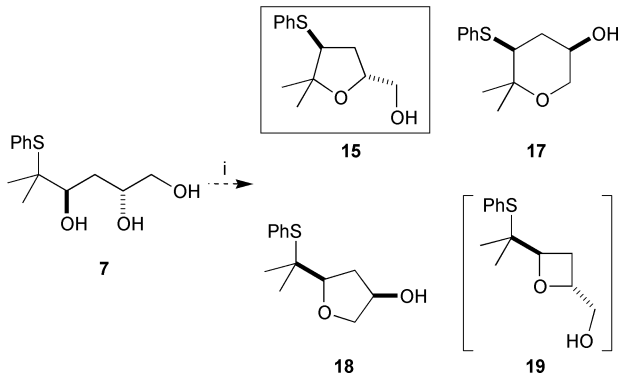

Scheme 5 *Reagents*: i, TsOH, $CDCl_3$.

distribution of 63:37 THF **13**:THP **14**, but after a prolonged reflux (48 h) gave only THF **13** (Scheme 4). These results were followed by rearrangement of the structurally related triols **7** and **9**. Again, short reaction times led to THF–THP mixtures, but a longer reaction time (48 h) led to THFs **15** and **16** (Scheme 4).

In contrast to other systems we have studied,[1,2] ring-size has become more important than the relative stereochemistry. A 2,4-*syn* THF is preferred to the alternative 2,4-*anti* THP, where one of the two substituents would enter an axial environment. More interestingly though, the 2,4-*anti* THF is preferred to the 2,4-*syn* THP, where both groups could now be equatorial. We presume in this case that the factor governing the cyclisation outcome (the degree of substitution being equal for both rings) is the *gem*-disubstituted migration origin. In the THP one of the C–C bonds is forced to be axial; presumably the 1,3-diaxial interactions are too severe and the flatter THF ring is preferred.

The rearrangement of triol **7** was followed by 400 MHz ^{1}H NMR spectroscopy. By recording spectra at regular intervals it was possible to watch the initial formation of the heterocycles **15**, **17** and **18** and the subsequent equilibration of the mixture to the THF **15** (Scheme 5). Interestingly, the unrearranged[10] THF **18** was observed as a metastable product but none of the oxetane **19**, which would also be formed by attack on the less substituted end of the episulfonium ion, was detected.

In summary we have demonstrated further evidence that [1,2]-PhS rearrangements are under thermodynamic control and that for a simple class of triols **7**–**10** the most stable products are the THFs **11, 13, 15** and **16**. We believe that in this case the difference in product stability can be attributed to the *gem*-disubstituted migration origin. In other cases we have investigated[1,2] the relative stability of products may be dependent on ring-size, stereochemistry or a thermodynamic Thorpe–Ingold effect.

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Notes and references

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7 The two types of heterocycle are readily distinguished by ^{1}H NMR spectroscopy: the hydrogen atom adjacent to the PhS group has a characteristic chemical shift in the range $3.0 < \delta_H < 3.5$ ppm. For the THPs this signal appears as a double doublet: for the THFs it is normally a triplet, or at least a double doublet with very similar coupling constants. Integration of these proton resonances provided an accurate means of assessing product ratios.
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10 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.