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Kinetic and Thermodynamic Control in the Stereospecific Synthesis of Cyclic Ethers via Phenylsulfanyl (PhS) Migration

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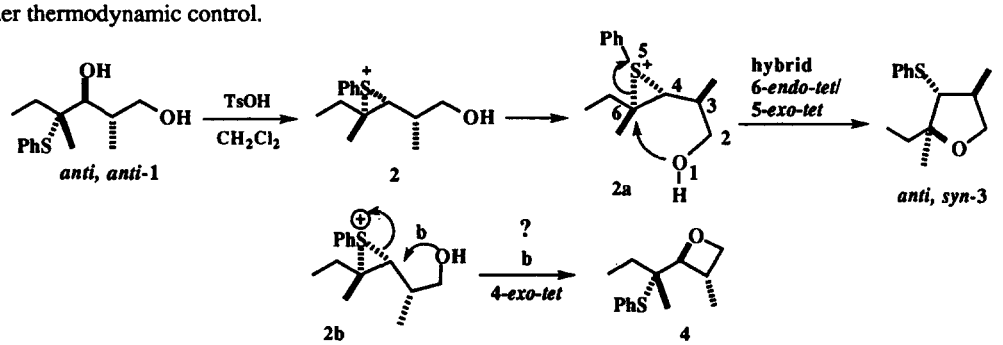
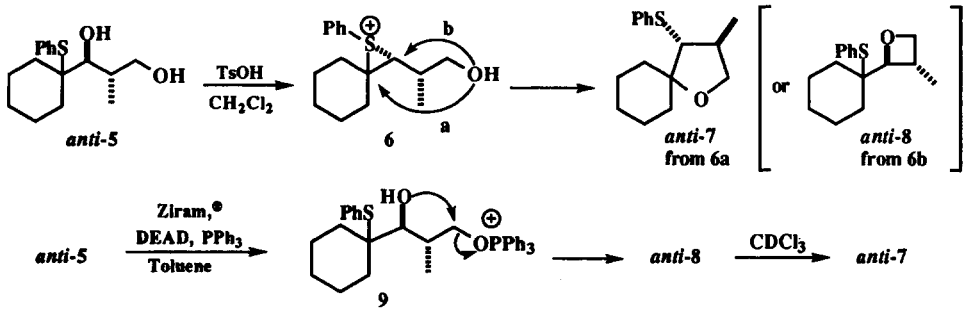
Abstract: The factors controlling the stereospecific cyclisation of 1,3-diols with PhS migration to give THFs rather than oxetanes are reassessed in the light of evidence that these reactions are under thermodynamic control. Rearrangement of cyclic sulfites gives the nearest approach to kinetic control.

Rearrangement[1] of optically active 1,3-diols such as **1** leads stereospecifically by phenylsulfanyl (PhS) migration in acid solution ($TsOH/CH_2Cl_2$) to tetrahydrofurans (THFs) **3**. In such reactions we have always observed[2] attack by the primary hydroxyl group at the more substituted end of the episulfonium ion in the intermediate **2** in spite of the partial *endo* nature (by Baldwin's rules) of this mode of attack. There is no doubt that the attack is concerted as inversion is observed[1] at the migration origin (C-6 in **2a**). The alternative unrearranged oxetanes such as **4** are never formed. We have suggested that a loose S_N2 transition state could be responsible and have outlined stereoelectronic factors (Baldwin's rules, Thorpe-Ingold effect, stereochemistry in the product) which help to predict which product will be formed in competitive cyclisations,[3] but which are all fundamentally kinetic. We now offer evidence that these reactions are in fact under thermodynamic control.

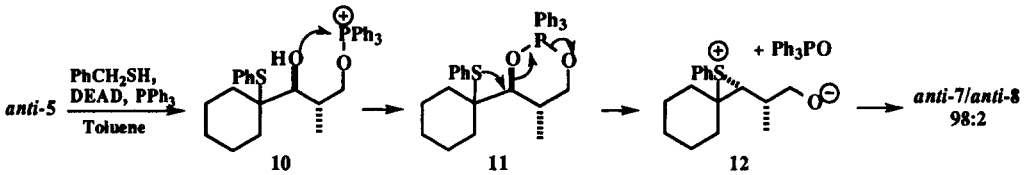


This evidence arises from two sources. We have been able to make the alternative products of cyclisation, the oxetanes such as **4**, which would result from a 4-*exo-tet* cyclisation **2b** and we have discovered a reaction - the thermal decomposition of cyclic sulfites - which allows the original rearrangement to occur *in the absence of acid*. No equilibration can occur between the oxetane and the THF in the absence of acid.

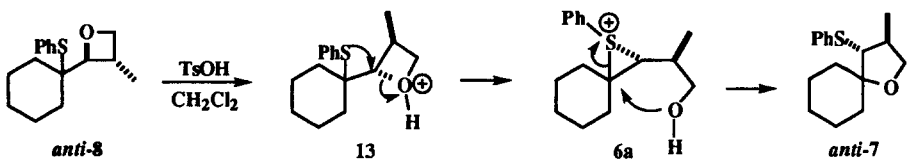
We have shown[2] that rearrangement of diol *anti*-**5** in $TsOH/CH_2Cl_2$ gives the THF *anti*-**7** in quantitative yield, by the hybrid 6-*endo-tet*/5-*exo-tet* cyclisation[2,4] **6a** of the episulfonium ion **6**. The alternative cyclisation (4-*exo-tet*) **6b** would give the oxetane *anti*-**8** which we had never observed. In an attempt to convert the primary alcohol to a thiol,[5] we reacted the diol *anti*-**5** with Ziram® (zinc dimethyldithiocarbamate; Fluka 96480) under Mitsunobu conditions[6] and obtained to our surprise, this very oxetane *anti*-**8**. The stereochemistry of the oxetane is the same whether it is formed via the episulfonium ion **6** (two inversions) or from the Mitsunobu intermediate **9** (no change in stereochemistry).



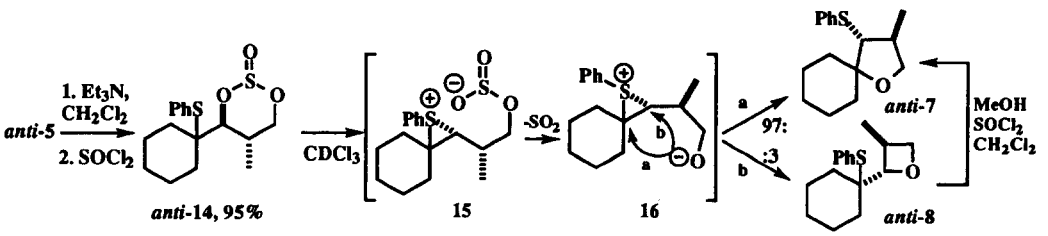
The role of Ziram® in the oxetane formation is not obvious. Repeating the reaction with $PhCH_2SH$, instead of Ziram® as the potential nucleophile, gave predominantly THF *anti*-**7** and only a trace of the oxetane *anti*-**8** (ratio 98:2), *via* the phosphorane **11** which was detected by ^{31}P NMR (δ_P –55 ppm; reference 85% H_3PO_4) and evidently decomposes by a [1,2] PhS Shift. Ziram® presumably inhibits the formation of this phosphorane **11** and thus promotes the 4-*exo*-*tet* cyclisation (e.g. **9**) to form the oxetane *anti*-**8**.



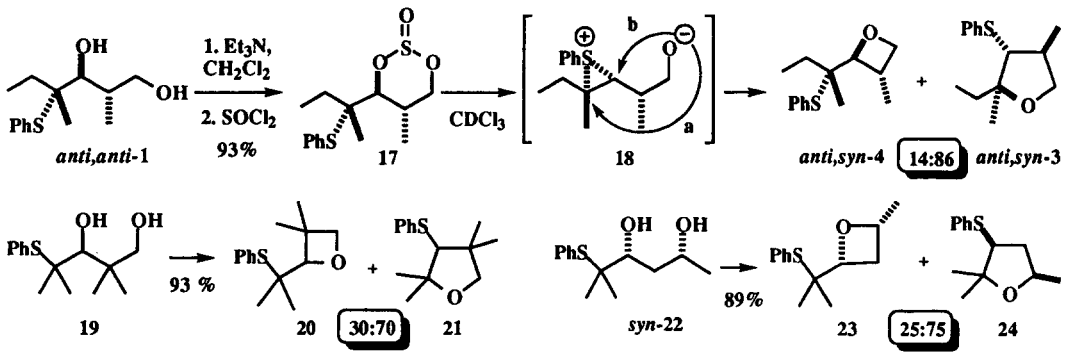
With the oxetane *anti*-**8** available from the Ziram® reaction we were immediately able to demonstrate why we had never detected oxetanes as products of the acid-catalysed rearrangement of **5**. Under the conditions of the rearrangement ($TsOH/CH_2Cl_2$) the oxetane *anti*-**8** rearranged rapidly and completely (100% yield) to the THF *anti*-**7** presumably by reversion to the same episulfonium ion **6**.



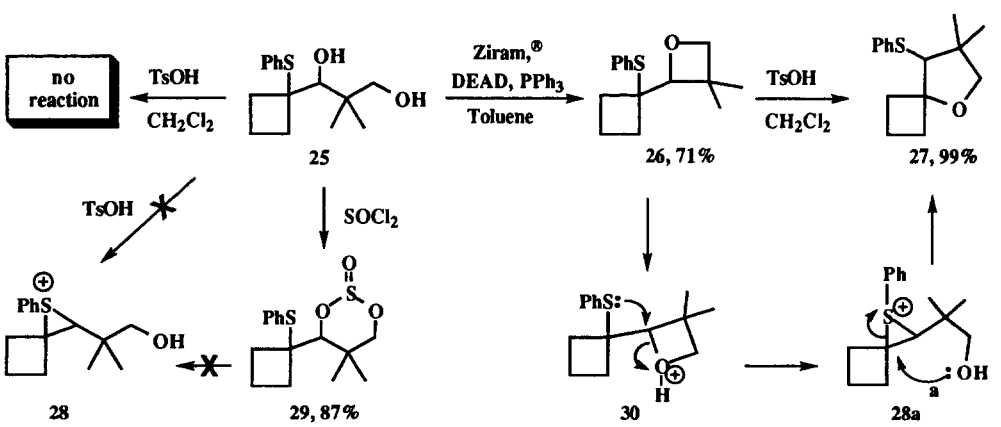
Even in $CDCl_3$ in an NMR tube the oxetane **8** was unstable and decomposed ($t_{1/2}$=2 days) without added acid to the same THF *anti*-**7**. It was clear that the THF must be the thermodynamic product of the acid-catalysed rearrangement, but the question remained whether the oxetane *anti*-**8** or the THF *anti*-**7** was the kinetic product. This question could be studied only by carrying out the rearrangement in the absence of acid to prevent conversion of oxetane to THF. This we were finally able to do[7] by treating the diol *anti*-**5** with base (two equivalents of Et_3N) followed by $SOCl_2$ which gave the cyclic sulfite[8] *anti*-**14** in 95% yield.



The cyclic sulfite[8] *anti*-**14** decomposed to give SO_2 and a 97:3 ratio of THF *anti*-**7** and oxetane *anti*-**8.** In $CDCl_3$ in an NMR tube, without isolation of the sulfite, the reaction mixture gave a 80:20 ratio of THF *anti*-**7** and oxetane *anti*-**8.** No equilibration occurred under either conditions but addition of a trace of HCl (provided by adding methanol to a CH_2Cl_2 solution of $SOCl_2$) converted the product entirely to THF *anti*-**7.** These are the products from the cyclisation of the alkoxide ion (instead of the alcohol in the rearrangement of *anti*-**5** in acid) onto the episulfonium ion **16.** We suggest that the 80:20 ratio represents the kinetic products from the cyclisation of **18** and is a good model for the distribution of kinetic products from the cyclisation of the 1,3-diol *anti*-**5.** Of course, the ratio from **5** need not be the same as the ratio from **17**, but it is a good model because no equilibration occurs under these basic conditions.



Acid-catalysed rearrangement of the 1,3-diols *anti,anti*-**1**, **19**, and *syn*-**22** gave the THFs *anti,syn*-**3**, **21** and *syn*-**24** as expected. Each diol was converted into the cyclic sulfite, e.g. **17**, and allowed to rearrange in $CDCl_3$ solution. The cyclic sulfite from **19** could not be isolated and the cyclisation products were formed directly in 93% yield. Similar amounts of the oxetanes *anti,syn*-**4**, **20**, and **23** were formed in these series: the THF:oxetane ratios were 86:14, 70:30, and 75:25. The mixtures were again converted into pure THFs with $MeOH/SOCl_2/CH_2Cl_2$. Again we suggest that these ratios approximate to the kinetic ratios for cyclisation of the diols in acid solution.



Perhaps the most extraordinary result we report is the behaviour of the cyclobutane **25.** This diol did not rearrange in acid solution to give the THF **27**, or any other product, while the cyclic sulfite **29**, formed in excellent yield without the normally essential addition of base, was stable and did not rearrange to either the

oxetane **26** nor the THF **27**. Without the cyclobutane ring, with other ring sizes or in open chain compounds, the [1,2]-PhS shift is outstandingly rapid and efficient. Evidently the spiro[2.3]hexane transition states leading to the episulfonium ion **28** is too strained. However, the oxetane **26**, formed by the usual Ziram® route, did rearrange to the THF **27** in quantitative yield. The transition state for the closure of **30** to the episulfonium ion **28** is doubly spirocyclic and looks even more strained but the high energy of the oxetane **26** must compensate for this. We have shown that the cyclobutane ring in **25** also supresses the [1,4]-PhS shift.[9,10]

In conclusion, we have shown that:

1) The rearranged THFs from the hybrid 6-*endo*/5-*exo*-*tet* cyclisation, step **a** in **2**, **6**, **16** and **18**, disfavoured by Baldwin's rules, are the thermodynamic products of the acid-catalysed cyclisation.

2) The pure 4-*exo*-*tet* cyclisation to give oxetanes, favoured by Baldwin's rules, step **b** in **2**, **6**, **16** and **18**, is responsible for 20–30% of the kinetic product. The rest - by far the majority - is the THF.

3) The oxetanes from the pure *exo* cyclisation equilibrate rapidly to the rearranged THFs under the conditions ($TsOH/CH_2Cl_2$) of the acid catalysed cyclisation.

4) During the equilibration of the *oxetanes* to the THFs, the original episulfonium ion is re-formed and the mechanism of formation of the thermodynamic product must be the disfavoured hybrid *exo*/*endo* cyclisation.

The nearest analogy for these results is the formation of β- and γ-lactones during halolactonisation[11-13] and sulfenyl-lactonisation[14] of β,γ-unsaturated acids. The β-lactone is the kinetic product, formed by a 4-*exo*-*tet* cyclisation[4] onto a halonium or episulfonium ion, but is unstable even in basic solution, unlike our oxetanes, as carboxylate is so much better a leaving group than alkoxide, and the β-lactones rearrange to the the γ-lactones on standing.

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References and Notes

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