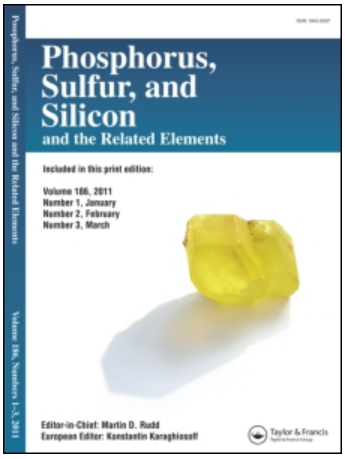

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Sulfur Migration in Organic Synthesis

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Sulfur Migration in Organic Synthesis

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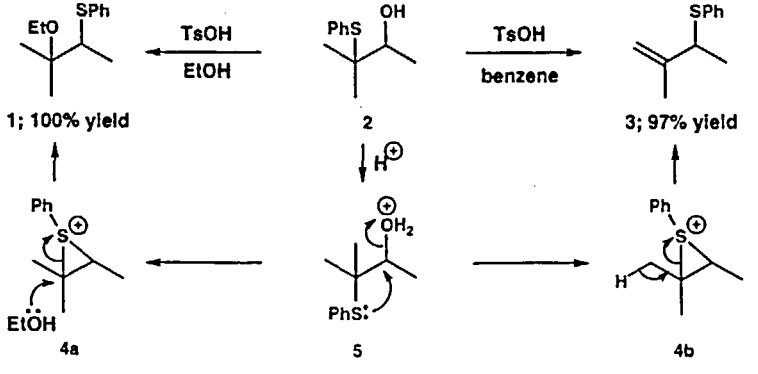
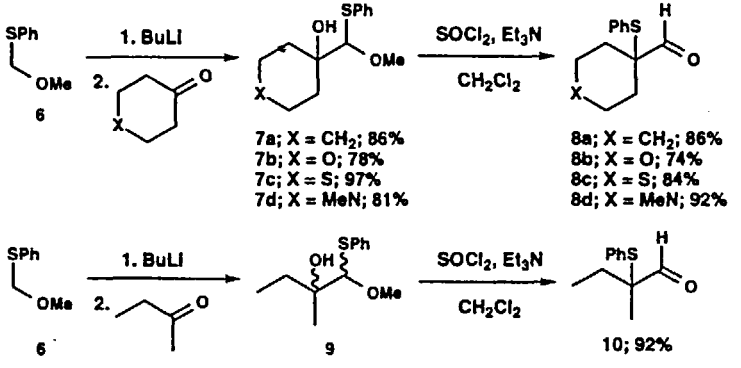
Stereospecific synthesis of alkenes and heterocycles is achieved in high yield by asymmetric aldol or Sharpless AD reactions and PhS migration.

Keywords: rearrangement; asymmetric; sulfur; aldol; AD

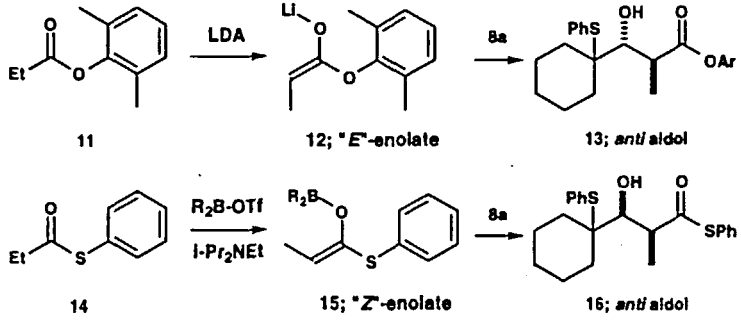
Our work on sulfur migration began with the observation[1] that a simple 2-PhS-alcohol **2** rearranged with PhS migration in very high yield in acid solution to give either a rearranged ether **1** or an allylic sulfide **3** from the same sulfonium salt by nucleophilic attack **4a** or loss of a proton **4b**.



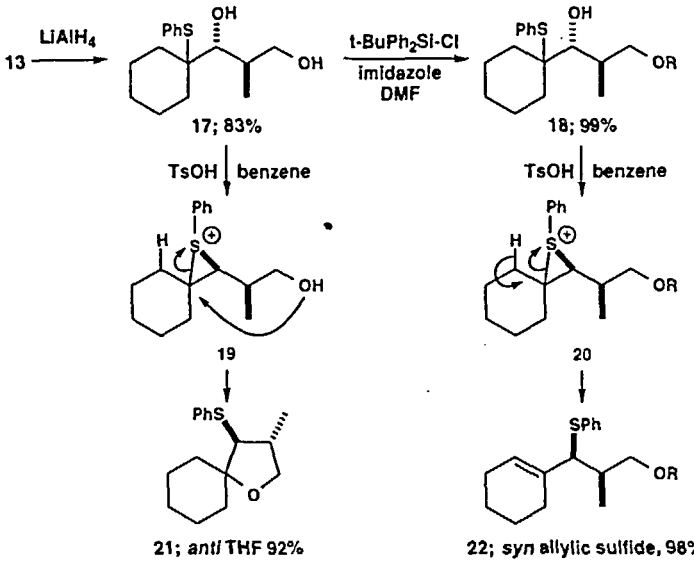
We have since used the work of de Groot and Jansen[2] to make a series of 2-PhS-aldehydes **8** and **10**.[3] The adducts **7** and **9** could rearrange by PhS or MeO migration but sulfur is better at participation across space and oxygen is better at forming a π-bond so PhS migrates and MeO stays behind.



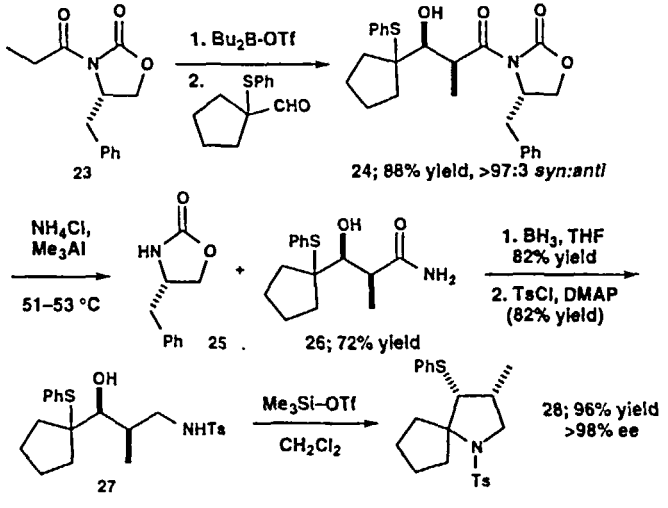
These aldehydes were combined[3] with suitable enolates in stereoselective aldol condensations to give *anti* aldols such as by Heathcock's method[4] and *syn* aldols such as by Masamune's method[5].



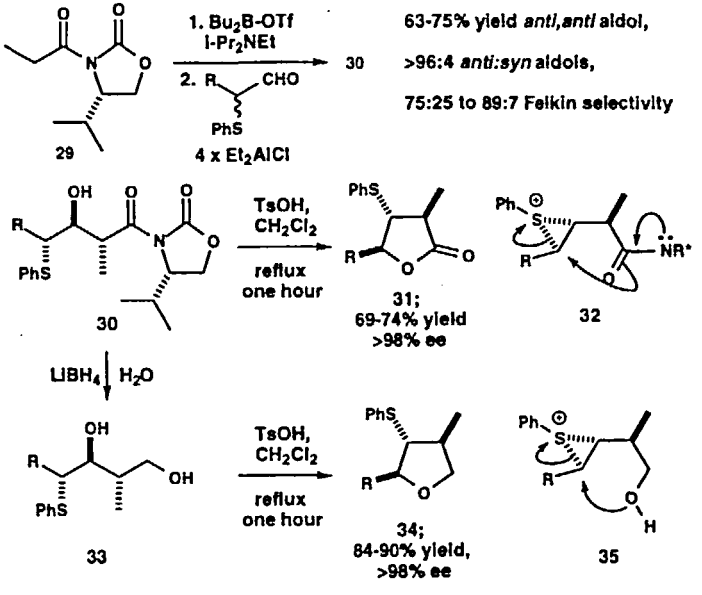
Reduction of these aldols gave an *anti* **17** and a *syn* diol which could be rearranged in acid to give tetrahydrofurans **21** or, if the primary alcohol is selectively protected by a silyl group, allylic sulfides **22** stereospecifically with PhS migration (see mechanisms **19** and **20**).[3]



Absolute control over stereochemistry is achieved using the Evans phenylalanine-based auxiliary[6] **25** to give a single enantiomer of the *syn* aldol **24** and hence the pyrrolidine[7] **28**.

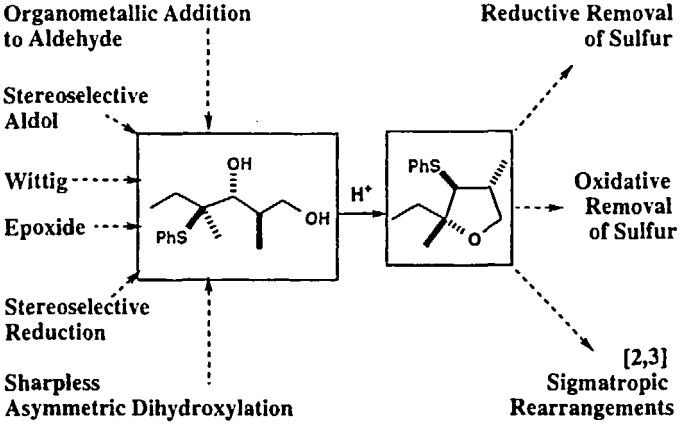


Rearrangement with nitrogen participation requires synthesis of the amide **26** using Weinreb's method,[8] conversion to the sulfonamide **27** and rearrangement with Me_3Si-OTf instead of acid.[9] A remarkable extension of this approach[10] allows the kinetic resolution of racemic and enolisable 2-PhS aldehydes during asymmetric aldol reactions with Evans valine-derived auxiliary under Heathcock's *anti*-selective conditions[11] using an excess of a Lewis acid (Et_2AlCl). Presumably the aldehyde is racemising faster than it is captured by the asymmetric boron enolate. Reasonable yields of *anti,anti* products **30** can be isolated (R = alkyl).



Direct rearrangement of the aldol **30** releases the auxiliary and gives reasonable yields of optically pure lactones **31**. Reduction to the diol **33** leads to THFs in good yield. These two cyclisations (arrows on diagrams **32** and **35**) occur by nucleophilic attack at a secondary carbon atom. Previously all examples have involved cleavage of the weaker bond from S^+ to a tertiary carbon atom. The theme of this lecture is the

way PhS migration can be controlled so that *which* hydroxyl group leaves, *which* acts as a nucleophile, and *where* it attacks can be predicted. We shall also look at compounds with three hydroxyl groups. In synthetic terms we have now demonstrated the usefulness of these reactions in many ways. The compounds can be made by many different routes and, after rearrangement, the PhS group can be removed oxidatively or reductively[9] or after [2,3] sigmatropic rearrangement of sulfoxides[9] or sulfonium salts.[12] The diagrams shown below are illustrative only.

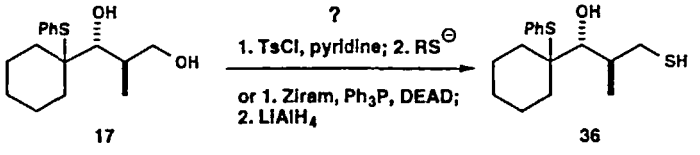


COMPETITION BETWEEN TWO HYDROXYL GROUPS

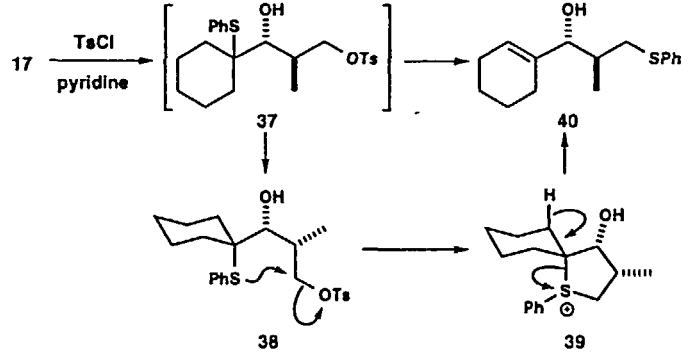
In the examples so far with two free hydroxyl groups, the secondary hydroxyl group has always acted as the leaving group while the primary hydroxyl has been the nucleophile. We discovered how to reverse the roles of these two OH groups accidentally during attempts to convert the alcohol into a thiol **36** and make tetrahydrothiophenes by PhS migration.

Though we achieved this goal by other chemistry[13], we initially supposed that the two most sensible approaches would be (a) to convert the primary alcohol selectively into a tosylate and displace with a suitable sulfur nucleophile and (b) the remarkably efficient Ziram reaction discovered by Rollin[14] which converts even secondary alcohols into

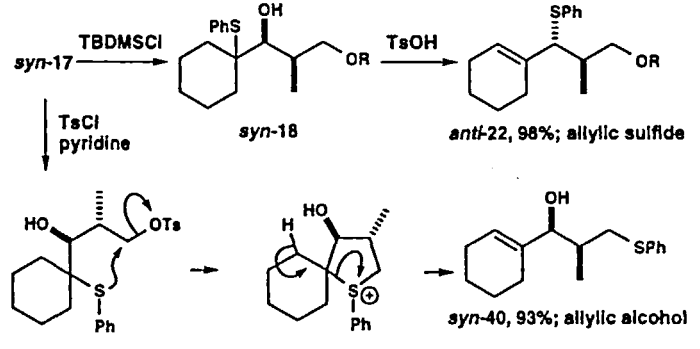
dithiocarbamates with clean inversion under Mitsunobu conditions. In the event both approaches led to the accidental discovery of new reactions.



Reaction with TsCl and pyridine gave,[15] presumably via the primary alkyl tosylate **37** and the 1,4-PhS shift shown in mechanisms **38** and **39**, an allylic alcohol **40**.

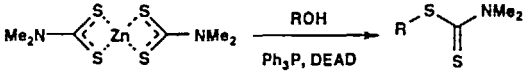


In this reaction the primary alcohol becomes the leaving group but the secondary OH group is not involved.



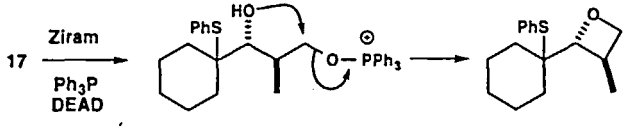
The reaction is general and stereospecific and we can illustrate this with the *syn* diastereoisomer of **17** to demonstrate that the product is a transposed version of the elimination reaction with [1,2]-PhS migration: the OH and SPh groups are in each others' places in the two products **22** and **40** which also belong to two different stereochemical series. The allylic sulfide **22** is formed when the secondary OH is the leaving group and rearrangement occurs by a [1,2]-PhS shift. The allylic alcohol **40** is formed when the primary alcohol acts as the leaving group and a [1,4]-PhS shift follows.

The second unexpected reaction occurred in the reaction with Ziram, the inexpensive zinc dithiocarbamate formed from zinc oxide, CS_2 and Me_2NH, which normally reacts with alcohols to give dithiocarbamates by a Mitsunobu S_N2 reaction.[14]



41 **42**

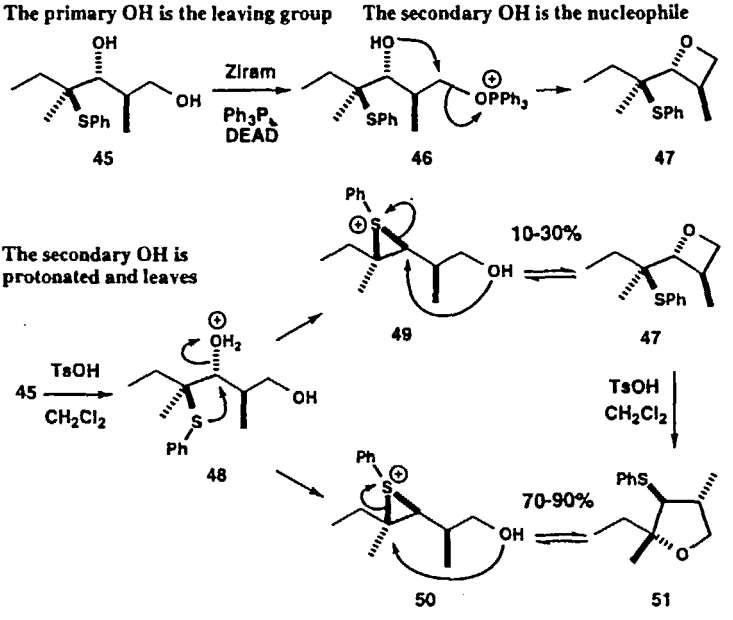
Application of this reaction to diols such as *anti*-**17** gave good yields of oxetanes such as **44** and no dithio-carbamates.[16] Presumably a Mitsunobu intermediate such as **43** undergoes internal S_N2 reaction with the secondary alcohol acting as the nucleophile.



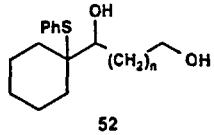
43 **44**

This was a result of great significance in our understanding the acid-catalysed [1,2]-PhS shifts.[16] The oxetanes are alternative products from these reactions but we had never observed them. Turning to general diol structures **45** with more stereochemistry we can show that the same oxetane **47** with the same stereochemistry is formed by the Ziram reaction **46** and by rearrangement. With the oxetane available, we could show that it rearranges to the THF **51** under the conditions (TsOH, CH_2Cl_2) of

the acid catalysed [1,2]-PhS shift. Experiments with cyclic sulfites derived from the diols[16] suggest that the oxetane forms about 10-30% of the initial product from the sulfonium ion.



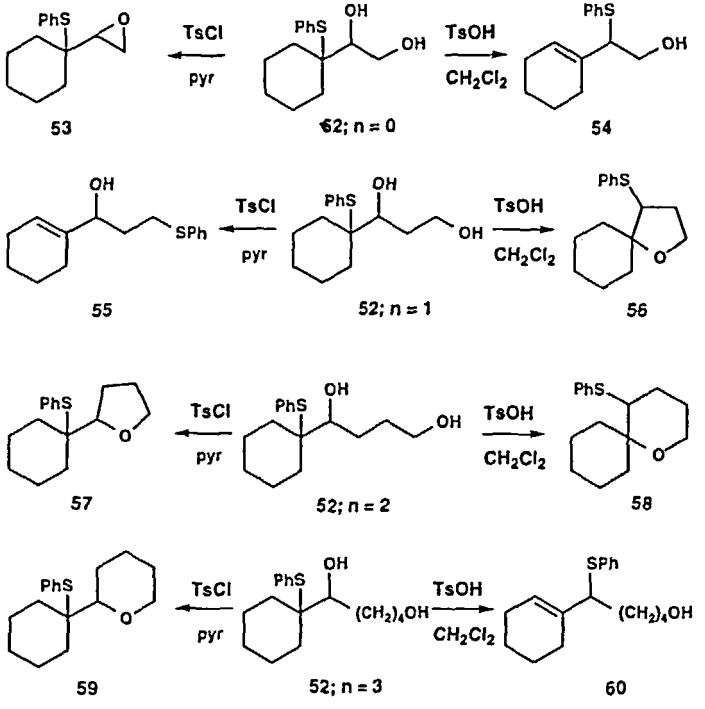
The TsCl/pyridine reaction also gave insight into the nature of the rearrangement process by allowing us to make previously inaccessible alternative products and exposing them to the acidic conditions of the [1,2]-PhS shift. To illustrate this series of experiments[15] we will use the simplest compounds with no stereochemistry **52**; n = 0-3.



52

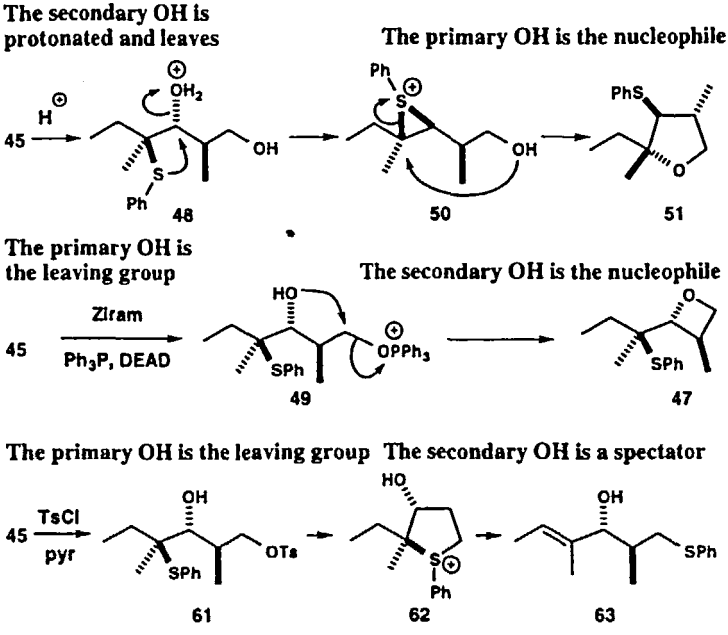
Rearrangements of these compounds with (a) TsOH in CH_2Cl_2 and (b) TsCl in pyridine gave in each case a different product. The products from the acid-catalysed reactions were all those of [1,2]-PhS

shifts. If the chain length n = 1 or 2 a 5- or 6-membered heterocycle is formed but if the chain length is shorter or longer, elimination is preferred to the formation of 3,4, or 7-membered rings.



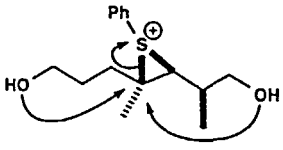
All the products formed with TsCl and pyridine result from the primary OH group acting as leaving group, the allylic alcohol **55** is formed by a [1,4]-PhS shift, but all the cyclisations to the three- (**53**), five- (**57**) and six-membered (**59**) rings occur without rearrangement. Most of the compounds formed with TsCl and pyridine (**53**, **57**, and **59**) rearrange to the other products (**54**, **58**, and **60**) in TsOH and CH_2Cl_2.

We can now summarise the situation with two hydroxyl groups to show, again on the general structure 45, the degree of control possible in these reactions:



COMPETITION BETWEEN TWO HYDROXYL GROUPS

The rest of the lecture concerns the situations which may arise when a third hydroxyl group is present. We have explored three such possibilities where there is competition in cyclisation reactions between two different nucleophiles. The first two involve competition between primary hydroxyl groups. Sara McIntyre investigated a third hydroxyl group attached at the other end on the molecule: in the example shown **64**, two different cyclisations are possible each leading to a THF. Francis Sansbury investigated two primary alcohols on branches of the same chain **65**. Cyclisation here may lead to compounds with different stereochemistries.



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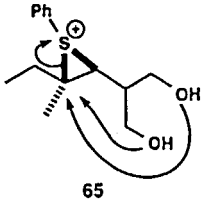
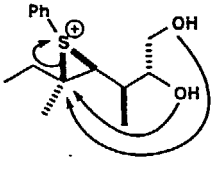


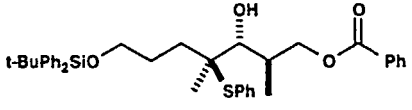
65

The third possibility **66** involves a primary and a secondary alcohol in the same chain. These cyclisations must involve competition between different ring sizes. Stereochemistry is also involved and you will see that we made the starting materials using the Sharpless AD reaction. These diagrams (**64**, **65**, and **66**) show idealised structures - we have not necessarily made these particular examples.

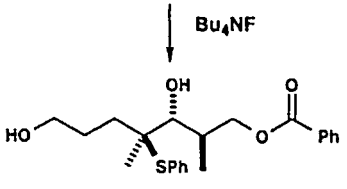


66

In the first examples[17] we made orthogonally protected triols such as **67** by stereoselective aldol reactions. Selective deprotection, acid-catalysed rearrangement, and a second deprotection gave authentic samples of the two possible THFs **72** and **73**.



67



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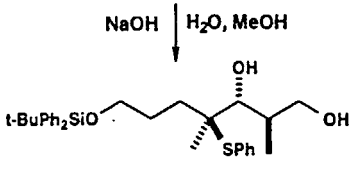

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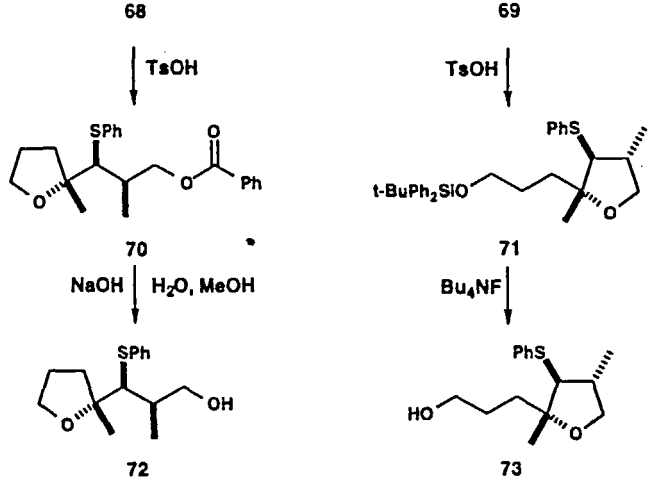
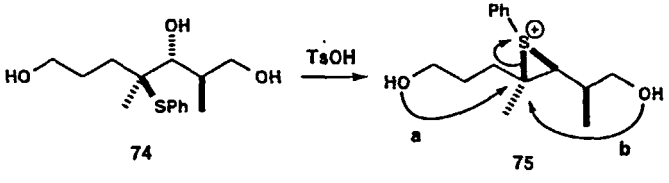


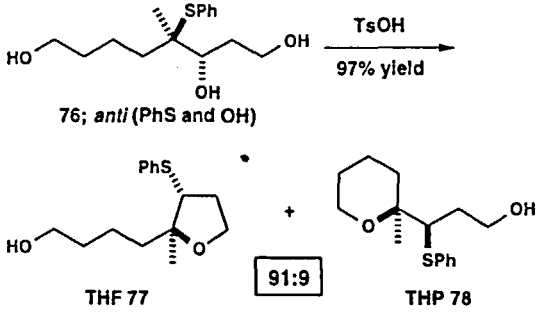
Complete deprotection of **67** gave the triol **74** which could rearrange in acid by the all exo-cyclisation **75a** (by Baldwin's rules) or the hybrid endo/exo cyclisation **75b** (the leaving group SPh is exo to the new THF ring but endo to the S_N2 mechanism).



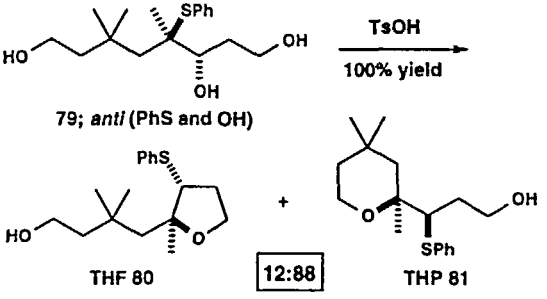
In fact the only product (99% yield) was **73** formed by cyclisation **75b**. Since we had both possible structures available, it was easy to show that this reaction too was under thermodynamic control - THF **72** rearranged completely into THF **73** under the conditions of the acid-catalysed rearrangement.[17]

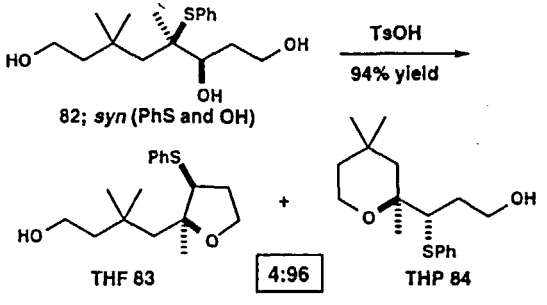
The only factor which seemed to favour compound **73** as the thermodynamic product was the Thorpe-Ingold effect. The THF rings of both **72** and **73** contain one quaternary centre but the ring in **73** has two

extra substituents (Me and PhS) lacking in **72**. The same factor applies in competition between five- (THF) and six-membered (THP) rings.[18]

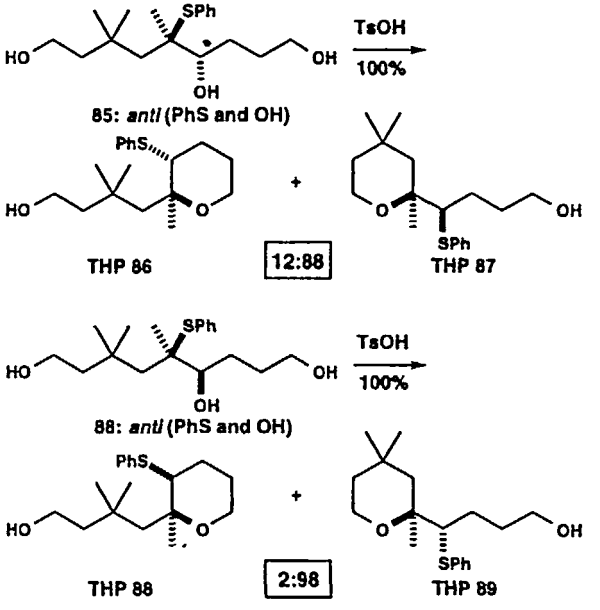


We therefore made compounds with geminal dimethyl groups in the otherwise unsubstituted chains and showed that the products of cyclisation were indeed controlled by the Thorpe-Ingold effect.





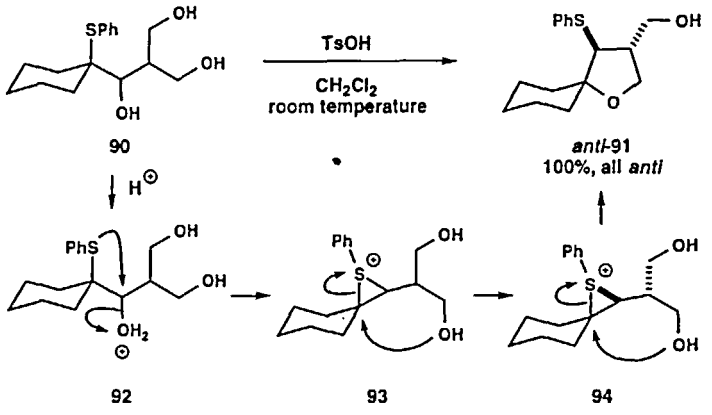
In this first example[18] there is some variation in stereochemistry as well as competition between ring sizes (THF or THP), but neither seems very important. To avoid any ring size effects we also studied compounds where both cyclisation products are THPs and obtained similar results. The Thorpe-Ingold effect does indeed matter.



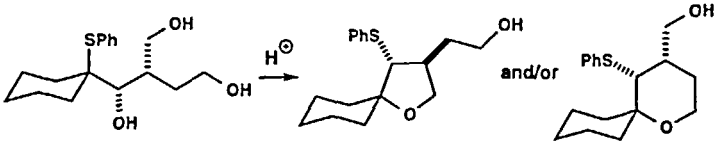
Competition between Primary OH Groups: Stereochemistry Decides

When two apparently identical primary hydroxyl groups are on branches from the main chain, as in the triol **90**, the presence of the stereogenic secondary alcohol means that the primary alcohols are in fact *diastereotopic* as if one of them cyclises in preference to the other a diastereoisomer of the product **91** will be formed. This is what happens.[19] The product is quantitatively the *anti* THF *anti*-**91** with no trace of the *syn* isomer. The episulfonium ion **93** could use either primary OH as nucleophile: in fact it selects the one which leads to *anti*-

91 as shown by the mechanism **94**. This is of course a kinetic argument - the reaction may well be reversible and under thermodynamic control.

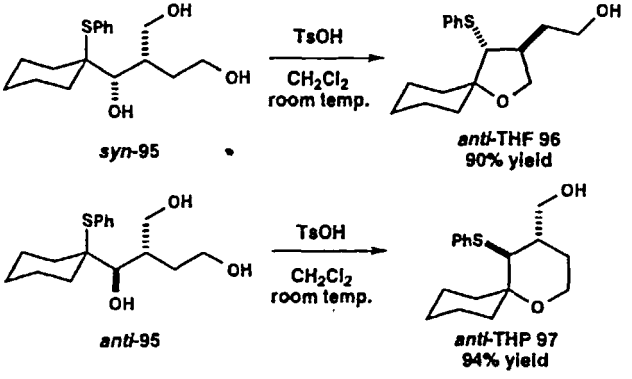


If the branches are of different lengths two things change: the branch point is already a stereogenic centre and the two possible heterocycles have different ring sizes. We chose to rearrange compounds such as **95** so that the two possible heterocycles would be a THF **96** and a THP **97**. It turns out that they have different stereochemistry: the *syn* triol **95** would give the *anti* THP **97** but the *syn* THF **96**. We have a test case to compare the relative importance of ring size and stereochemistry.



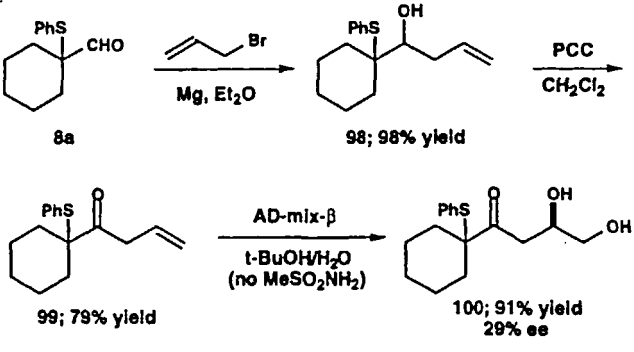
We were able to prepare both diastereoisomers of the triol **95** by an aldol reaction followed by reduction and rearranged each one separately. The result was surprising: only stereochemistry mattered! Each triol gave a good yield of a single compound - the one with *anti* stereochemistry regardless of ring size.[19] This again may be the result of thermodynamic control. Both these results could be regarded as

extensions of Thorpe-Ingold control as stabilisation by the Thorpe-Ingold effect[20] is greater when adjacent substituents are *anti*.



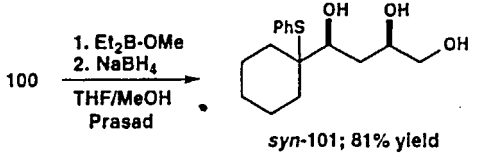
Sharpless Asymmetric Dihydroxylation and Sulfur Migration

To put three hydroxyl groups in the same chain we chose to use the Sharpless asymmetric dihydroxylation[21] on prochiral unsaturated ketones such as **99**. Subsequent reduction of the ketone inevitably leads to molecules with one primary and two secondary alcohols. In the event it also led to new and so far unexplained selectivities.

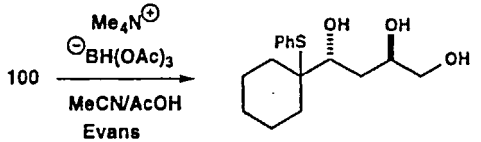


The preparation of the ketone **99** was straightforward but the AD reaction gave poor ees with this monosubstituted alkene. Reduction of the diol ketone **100** could be controlled to give either the *syn* or the *anti*

triol **101** using the methods of Prasad[22] and Evans.[23] In both of these the 1,3-relationship between the ketone and the secondary alcohol controls the stereochemistry of the reduction.

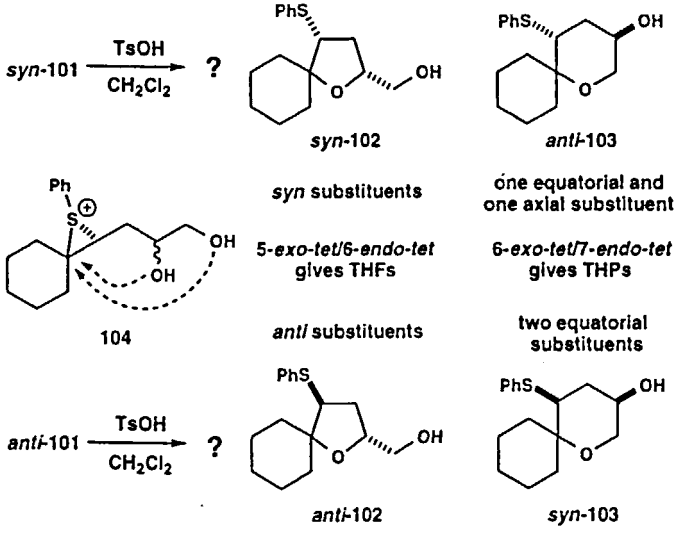


syn-101; 81% yield



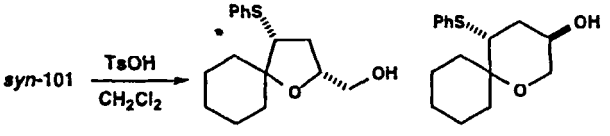
anti-101; 84% yield

The possibilities in the rearrangement of these triols are set out below: THFs or THPs can be formed by cyclisation of **104** and the chart summarises the effects of stereochemistry and Baldwin's rules.

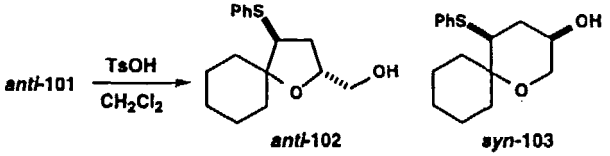


At first sight this might seem just another example of stereochemical control, but the stereogenic centres in the products are now

1,3-related so it is not obvious which product is more stable. For example, *syn*-**103** might be more stable than *anti*-**103** as it has both substituents equatorial. In the event we found that both *syn* and *anti*-**101** gave 50:50 mixtures of THFs **102** and THPs **103** after brief treatment with TsOH.



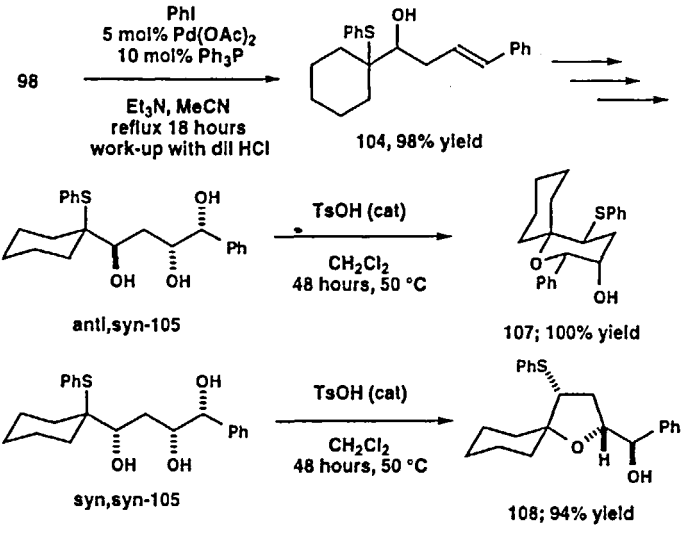
	syn-102	*anti*-103
TsOH, CH_2Cl_2, very short time	50%	50%
TsOH, CH_2Cl_2, days	97%	0%
TsCl, pyridine, days	0%	only product



	anti-102	*syn*-103
TsOH, CH_2Cl_2, days	90%	0%
TsCl, pyridine, days	0%	only product

The thermodynamic products, formed on prolonged reflux with TsOH in CH_2Cl_2, were the THFs **102** regardless of stereochemistry. But more surprising was the discovery that treatment with TsCl in pyridine, which we expected to turn the primary alcohol into a leaving group, instead gave the THPs **103** as the only products again regardless of stereo-chemistry. We have no convincing explanation of this result so far.

Finally, a Heck reaction on the alcohol **98** gave the styrene **104** which was converted by a similar sequence into the *anti,syn* and *syn,syn*-triols **105**.



So far we have determined only the structures of the thermodynamic products from the acid-catalysed rearrangements of these triols **105** but here too we had a surprise: *syn,syn* -**105** gave the THF **106** as the thermodynamic product, but *anti,syn* -**105** gave the THP **107**. We hope these compounds have higher ees (not yet determined) and we hope to be able to control these rearrangements to produce either THF or THP products by choice of conditions. It is clear that we have a long way to go in understanding these remarkable reactions as well as in applying them to the asymmetric synthesis of heterocycles.

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