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Scope and Limitation of the [1,4] SPh Shift in the Synthesis of Allylic Alcohols

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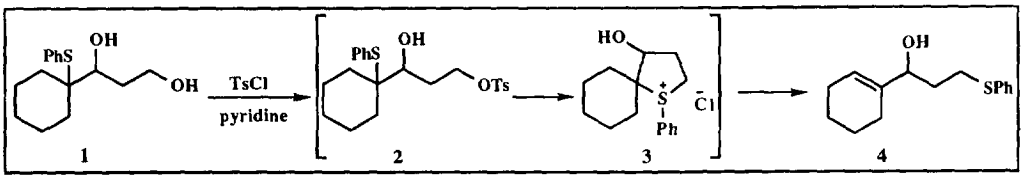
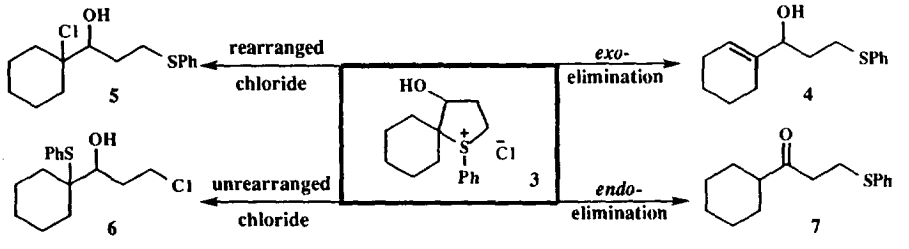
Abstract: Rearrangement of 4-PhS-1,3-diols with TsCl in pyridine gives allylic alcohols. We discuss the scope and limitaton of this reaction using structural variations, which help to elucidate the mechanism of the reaction. All reactions proceed in high yield and give synthetically useful products.

Rate enhancement by [1,4] participation by a sulfur atom *via* five-membered cyclic sulfonium salts is a well documented effect,[1] but to our surprise there has been no systematic study into the use of the reaction in organic synthesis. We have previously reported[2] that treatment of 4-phenylsulfanyl-1,3-diol **1** with TsCl in pyridine gave, instead of the expected tosylate **2**, the allylic alcohol **4** in 97% yield, presumably *via* the sulfonium ion **3** by a [1,4] SPh shift. We now report a general procedure for the synthesis of allylic alcohols by the [1,4] SPh shift. We comment on the effects of stereochemistry and structural variation at the migration origin and terminus (including the effect of ring size), all of which help to elucidate the mechanism. We also disclose methods which allow the isolation of primary tosylates analogous to **2**.



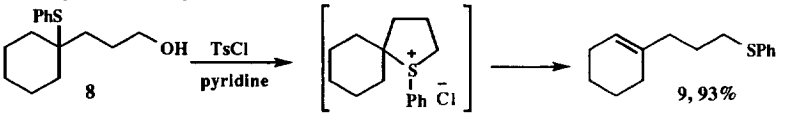
Four possible products from the spirocyclic sulfonium salt **3** are the allylic alcohol **4** (by elimination *exo* to the sulfonium ring[3] with [1,4] SPh shift), the ketone **7** (by *endo*[3] elimination with [1,4] SPh shift), the rearranged chloride **5** (substitution at the migratory origin with [1,4] SPh shift), and the unrearranged chloride **6** (substitution at what would be the migration terminus but with no SPh migration).

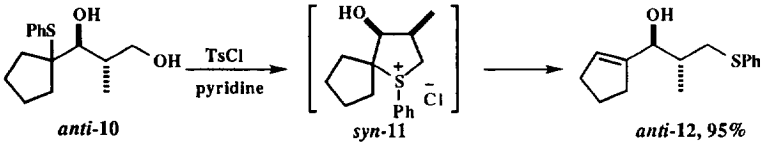


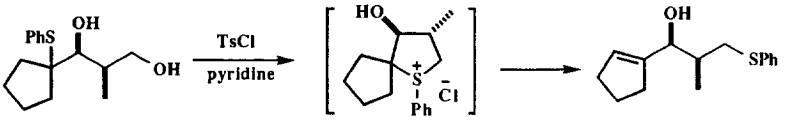
Scheme: Four possible products from the rearrangement of diol **1** *via* the sulfonium ion **3**.

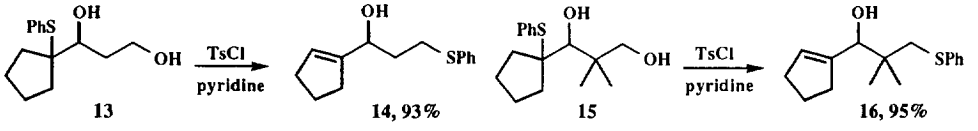
We describe the rearrangement of a series of 4-phenylsulfanyl-1,3-diols **10**, **13**, **15**, **17** and **19** with TsCl in pyridine. These 1,3 diols were prepared by our aldol methodology[4] and some of them have already been reported. We first established that the secondary alcohol grouping was unnecessary. The simplest case, alcohol **8**, rearranged successfully to the cyclohexene **9** in 93% yield. We then considered the effect of ring

size and ring strain upon the products formed from spirocyclic sulfonium salts like **3** but with carbocyclic rings of different sizes. The five-membered ring compounds **10**, **13** and **15**, like the six-membered rings,[2] gave high yields of allylic alcohols **12**, **14** and **16**, whether there were no substituents **13**, gem-dimethyl groups **15**, or two substituents (OH and Me) on neighbouring carbon atoms **10** arranged *syn* or *anti* around the cyclic sulfonium ion **11**. This reaction[5] is independent of the developing stereochemistry within the sulfonium salt: *anti*-diol **10** gives the *anti*-allylic alcohol **12** stereospecifically *via* the *syn*-sulfonium salt **11** while *syn*-diol **10** gives *syn*-allylic alcohol **12** *via* the *anti*-sulfonium salt **11**.

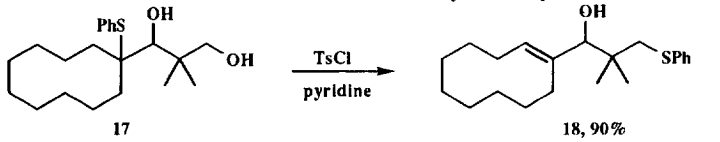


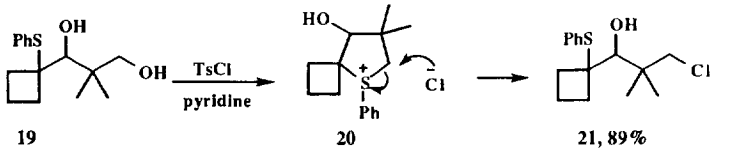




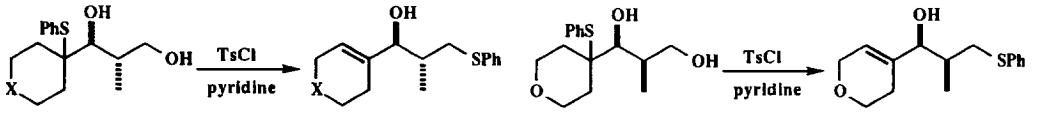


A medium ring behaves in the same way, the cyclodecane **17** giving the (*E*)-allylic alcohol **18** in good yield. Moving to a smaller ring size with the cyclobutane **19** was an attempt to prevent the *exo*-elimination since the cyclobutene corresponding to **4** would be strained. Reaction of diol **19** gave only the unrearranged chloride **21** in 89% yield, with no SPh migration. We believe this reaction occurs *via* the sulfonium salt **20** as [1,4] PhS participation is very efficient, essentially as efficient as [1,2] PhS participation *via* episulfonium ions.[1] The substitution reaction **20** appears to be governed by a tight S_N2 transition state with attack occurring at the less hindered site of the sulfonium ion. Eliel has previously observed such behaviour.[6]

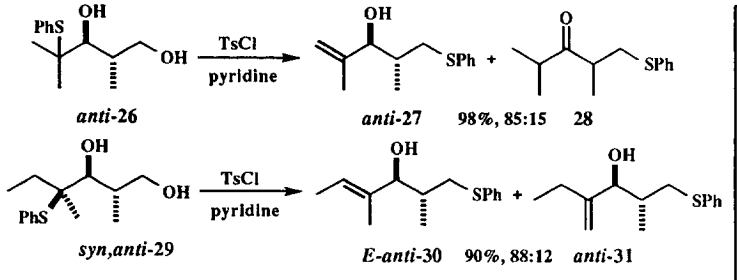


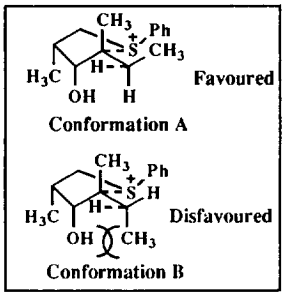


Additional hetereoatom substituents in the ring (X=O and S) did not interfere with the reaction. The diols *syn* and *anti*-**22** and *anti*-**24** gave only the expected allylic alcohols *syn* and *anti*-**23** and *anti*-**25** though with reduced yields (Table 1). It appears that participation by X does not occur.

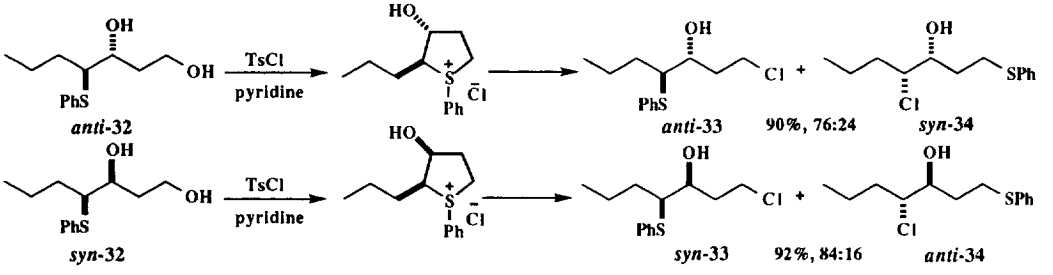


Investigating the acyclic diols **26** and **29** was an attempt to probe competition between *exo*- and *endo*-elimination. Reactions with carbocycles (e.g. **1**) and heterocycles (e.g. **22**) generally gave only *exo*-elimination. The four-membered ring compound **19** was an exception because of ring strain and we argued that *exo* elimination would also be disfavoured, though for a different reason, if the alkene were 1,1-disubstituted (e.g. **27**) instead of being in a ring. Treatment of diol *anti*-**26** with TsCl gave for the first time two products: the allylic alcohol *anti*-**27** (major) and the ketone **28** (minor) in a 85:15 ratio. The ketone **28** was formed *via* the enolate, a tetra-substituted alkene, by *endo*-elimination. Nevertheless, *exo*-elimination is still favoured kinetically. Reaction of diol *syn,anti*-**29** gave as the major product (88:12) the (*E*)-allylic alcohol *anti*-**30** (stereochemistry determined by a 500 MHz NOESY spectrum), the more thermodynamically stable of the three (*E*-**30**, *Z*-**30** and *exo* methylene) possible *exo* elimination products. Elimination occurs *via* transition state conformation **A**, as conformation **B** has unfavourable 1,3 diaxial interactions.[7]



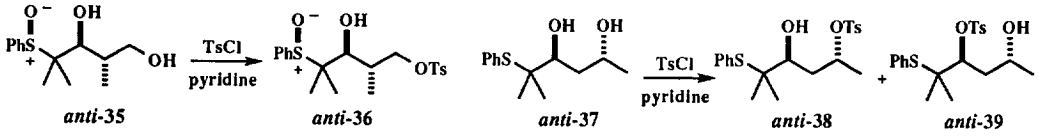


We next introduced stereochemistry at a secondary migration origin. Reaction of diols *syn* and *anti*-**32** under our usual conditions gave inseparable mixtures of rearranged **34** and unrearranged **33** chlorides but no allylic alcohols. A tight S_N2 reaction at the primary carbon of the sulfonium salt intermediate, giving **33** as the major product, is evidently preferred to elimination. Previous cases are different because cleavage of the weaker bond to the tertiary carbon atom in the sulfonium ions derived from, say **26** and **29** is preferred to substitution at either carbon atom. Substitution at the secondary centre is stereospecific (each isomer of **32** gives a single and different isomer of the minor product **34** : we assume it proceeds with inversion).



Attempts to isolate the original tosylate **2** under other conditions were unsuccessful. Addition of n-BuLi (1 eq) to a solution of diol **1** in THF at -78 °C and reaction with TsCl in THF gave only the allylic alcohol **4** in 96% yield. Isolation of analogous tosylates was achieved by inhibiting the participation of sulfur

sterically and electronically. Reaction of sulfoxide *anti*-**35** with TsCl in pyridine gave the tosylate *anti*-**36** in 95% yield. Participation by sulfoxide (PhSO) is slower than participation by PhS.[8] Reaction of *anti*-diol **37**, containing two secondary alcohols, with TsCl in pyridine gave a 96% yield of a mixture of secondary tosylates **38** and **39** in the ratio 88:12. No participation of SPh occurred in these secondary tosylates.



anti-**35** *anti*-**36** *anti*-**37** *anti*-**38** *anti*-**39**

In conclusion we have shown that the substituted 4-phenylsulfanyl-1,3-diols fall into three categories:
1) those with a tertiary migration origin and a primary migration terminus (Table 1)—these *all* rearrange to give allylic alcohols in excellent yield, except when *exo*-elimination is inhibited, as in the case of diol **19**.
2) those with a tertiary migration origin and a secondary migration terminus (e.g. diol **37**)—no rearrangement is observed, a mixture of the secondary tosylates is isolated.
3) those with a secondary migration origin and a primary migration terminus: (Table 2)—these give a mixture of rearranged and unrearranged chlorides by substitution on the intermediate sulfonium ion.

Table 1: Allylic Alcohols from the Rearrangement of 4-Phenylsulfanyl-1,3-diols with TsCl in Pyridine.[6]

Diol	**8**	*anti*-**10**	*syn*-**10**	**13**	**15**	**17**	*syn*-**22**	*anti*-**22**	*anti*-**24**	**29**
Product	**9**	*anti*-**12**	*syn*-**12**	**14**	**16**	**18**	*syn*-**23**	*anti*-**23**	*anti*-**25**	*anti*-**30**
Yield (%)	93	95	93	93	95	90	79	60	84	90[a]

[a]As an 8:1 mixture of *E*-*anti*-**30** and *anti*-**31**.

Table 2: Alkyl Chlorides from the Rearrangement of 4-Phenylsulfanyl-1,3-diols with TsCl in Pyridine.

Diol	Unrearranged chloride	Yield (%)	Rearranged Chloride	Ratio
19	**21**	89	–	100:0
anti-**32**	*anti*-**33**	90[a]	*syn*-**34**	76:24
syn-**32**	*syn*-**33**	92[a]	*anti*-**34**	84:16

[a]As inseparable mixture of unrearranged and rearranged chlorides, see text.

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References and Notes

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2. Djakovitch, L.; Eames, J.; Jones, R. V. H.; McIntyre, S.; Warren, S. *Tetrahedron Lett.*, **1995**, *36*, 1723-1726.
3. Of course, what is *exo* to the sulphonium ring in the spirocyclic intermediate **3** is *endo* to the cyclohexane ring and vice versa.
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5. A typical procedure is given in reference 2.
6. Eliel, E. L.; Hutchins, R. O.; Mebane, R.; Willer, R. L. *J. Org. Chem.*, **1976**, *41*, 1052-1057.
7. See Hannaby, M.; Judson, P.; Warren, S. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 2609-2614.
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