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Scope and Limitation of [1,4]-SBenzyl Participation and Debenzylation in the Stereochemically Controlled Synthesis of Substituted Thiolanes

Jason Eames,[a,c] Nikolai Kuhnert,[a,c] Ray V. H. Jones[b] and Stuart Warren[a]*

[a]University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England
[b]Process Technology Department, ZENECA Grangemouth Works, Earls Road, Grangemouth FK3 8XG, Scotland
[c]Current Address: The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, England

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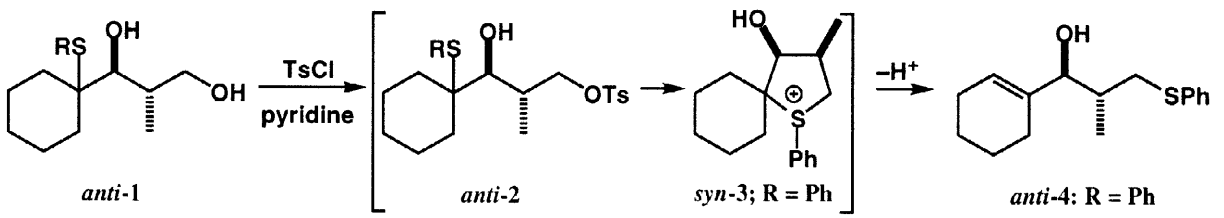
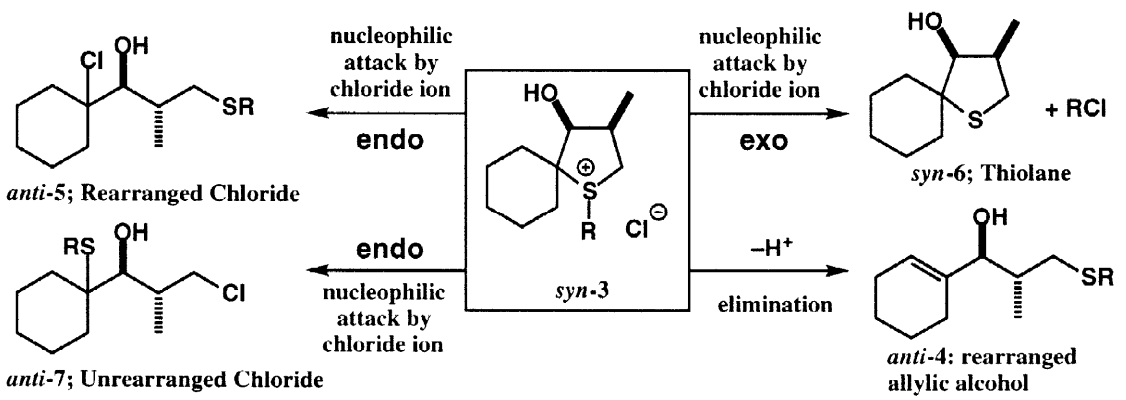
Abstract: Treatment of a series of 4-benzylsulfanyl-1,3-diols with TsCl in pyridine gives substituted 3-hydroxy-thiolanes in high yield by 1,4-SBn participation and debenzylation with chloride ion. The reaction is stereospecific at three stereogenic centres, and relatively insensitive to structure.

[1,4]-SR Participation by a sulfur atom *via* a five membered cyclic sulfonium salt is a well documented kinetic effect.[1] It has generally been used to enhance the rate of substitution,[1] but recently we have used this strategy to synthesise allylic alcohols, e.g. **4**; R=Ph in 97% yield, by *exo*-elimination[2] of sulfonium salt **3** with an overall [1,4]-SPh shift.[2,3]



Exploration of related migrating groups RS (R = Ar, Alk, H) revealed that, in contrast to the acid-catalysed rearrangement to give THFs,[4] different groups gave different products. We report here the formation of thiolanes by rearrangement of 4-benzylsulfanyl-1,3-diols such as **1** with TsCl/pyridine when R is benzyl (Bn) and in the following paper[5] on the formation of 1,2-oxathianes when R = H. The four possible nucleophilic substitution or elimination products from attack of chloride ion on the spirocyclic sulfonium salt **3** are the allylic alcohol **4** (by *exo*- elimination with [1,4]-SR shift), the rearranged chloride **5** (by *endo*-substitution at the migration origin[2] with [1,4]-SR shift), the unrearranged chloride **7** (by *endo*-substitution at the migration terminus without SR shift) and the thiolane **6** (by *exo*-substitution at the R group in **3**).



Scheme: Four possible products from the rearrangement of 4-RS-1,3-diol **1** *via* the sulfonium salt **3**

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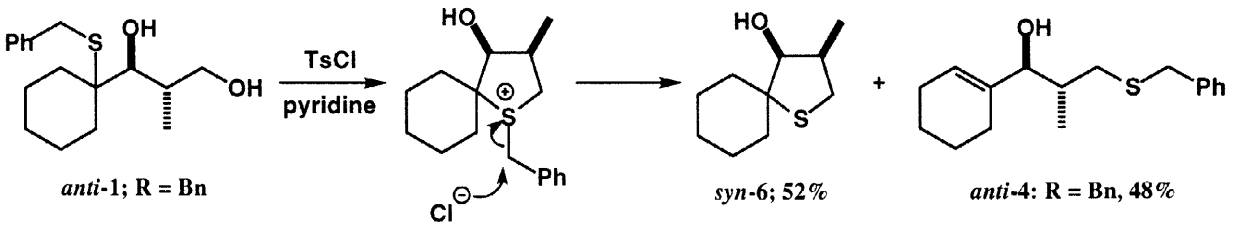
We describe the rearrangement of a series of 4-benzylsulfanyl-1,3-diols **1**; R=Bn, **8**, **10**, **12**, **14**, **17**, **19**, **21**, **23**, **26** and **28** with TsCl in pyridine. These diols were prepared using our aldol methodology[6] and some have previously been reported.[4] Treatment of *anti*-**1**; R=Bn with TsCl in pyridine gave both the spirocyclic thiolane *syn*-**6** (52%) and the allylic alcohol *anti*-**4**; R=Bn (48%). Evidently, competitive debenzylation of the sulfonium salt **3**; R=Bn (presumably by an S_N2 mechanism)[7,8] to give the thiolane *syn*-**6** and E2 reaction of **3** to give the allylic alcohol *anti*-**4**; R=Bn must occur at similar rates. The choice of the migrating substituent R in **3** to promote dealkylation is important since *exo*-cleavage occurs only when R = Bn. For simple alkyl migrating groups (e.g. **1**; R = Et and Me) only allylic alcohols are formed in near quantitative yield.[4] This is not surprising as S_N2 displacements are at least two orders of magnitude faster at a benzyl group than at a comparable ethyl group.[9] Attempts to enhance the rate of dealkylation (*exo*-cleavage of **3**; R=Bn) by addition of a better nucleophile (iodide as NaI) or performing the reaction with one equivalent of BuLi also proved unsuccessful. When R=H a different reaction occurred to give 1,2-oxathianes.[5]



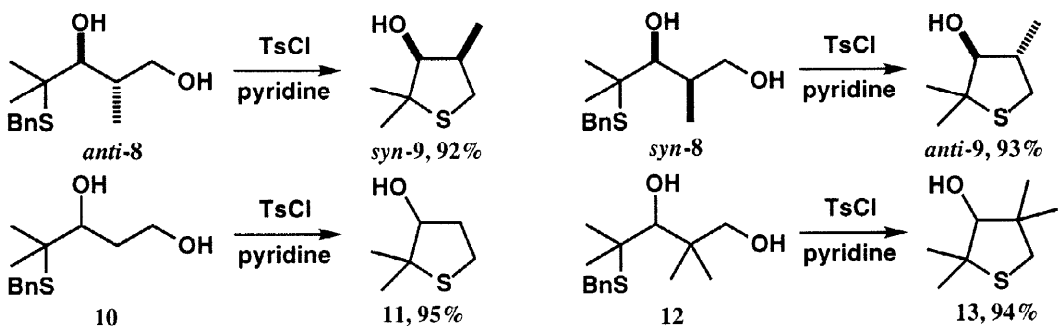
anti-**1**; R = Bn

syn-**3**; R = Bn

syn-**6**; 52%

anti-**4**: R = Bn, 48%

We turned to acyclic diols to increase thiolane yield as formation of allylic alcohols by *exo*-elimination of an axial proton is likely to be particularly favourable in a six-membered ring.[2] Treatment of the 4-benzylsulfanyl-1,3-diols *anti*- and *syn*-**8**, **10**, and **12** with TsCl in pyridine gave the substituted thiolanes *anti*- and *syn*-**9**, **11**, and **13** as single products in near quantitative yield. Unlike some cyclisations associated with [1,2]-RS shifts,[10] the reaction is sensitive neither to the Thorpe-Ingold effect (number of methyl groups at C-2) nor to the developing stereochemistry within the sulfonium salt. Thus *anti*-diol **8** gave the *syn*-thiolane **9**, whereas *syn*-diol **8** gave *anti*-thiolane **9** stereospecifically (500 MHz NOESY spectra on *anti*- and *syn*-**9**) and in excellent yield. This is retention at both C-2 and C-3.



anti-**8**

syn-**9**, 92%

syn-**8**

anti-**9**, 93%

10

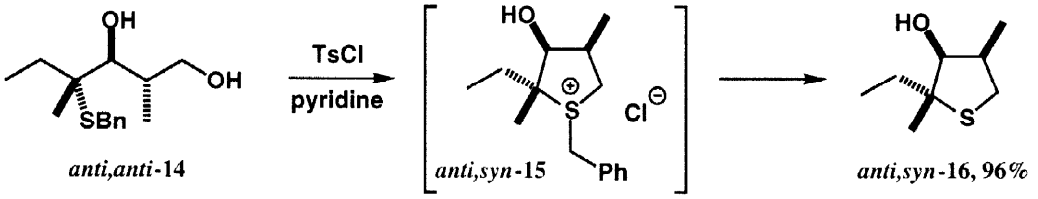
11, 95%

12

13, 94%

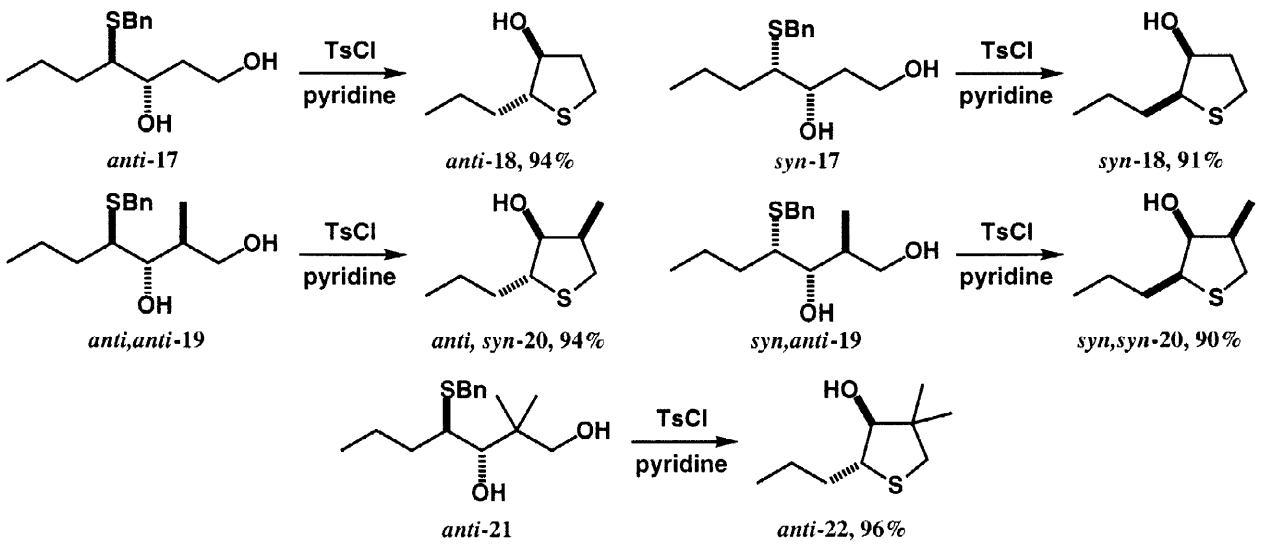
We next considered substitution and stereochemistry at the tertiary migration origin. The cyclohexyl group in **1** had given a mixture of thiolane **6** and allylic alcohol **4** while methyl groups in **8**, **10**, and **12** gave thiolane alone as elimination is unfavourable. An ethyl group is somewhere between the two and we used *anti,anti*-**14** to explore this question and stereochemistry in the same compound. In fact the diol *anti*, *anti*-**14** gave only the *anti*, *syn*-thiolane **16** with TsCl in pyridine in near quantitative yield. Retention of all the three

contiguous stereogenic centres was observed (500 MHz NOESY spectrum). No elimination occurred into the ethyl substituent at the migration origin though this is favoured in elimination with a [1,2]PhS shift.[2,11]



anti,anti-14 — *anti,syn*-15 — *anti,syn*-16, 96%

Another way to reduce the likelihood of elimination is to have a secondary migration origin and we rearranged a series of such compounds with two or three stereogenic centres to continue our investigation of stereochemistry at the same time. All these diols *anti*- and *syn*-**17**, *anti,syn*- and *syn,anti*-**19**, and *anti*-**21** gave the corresponding thiolanes stereospecifically (NOESY) and in excellent yield regardless of the number and the stereochemistry of the substituents. The successful formation of *syn,syn*-**20** is particularly remarkable as the all *syn* stereochemistry is already present in the sulfonium salt and developing *syn* stereochemistry is unfavourable in THF formation by rearrangement of compounds with a secondary migration origin.[10]

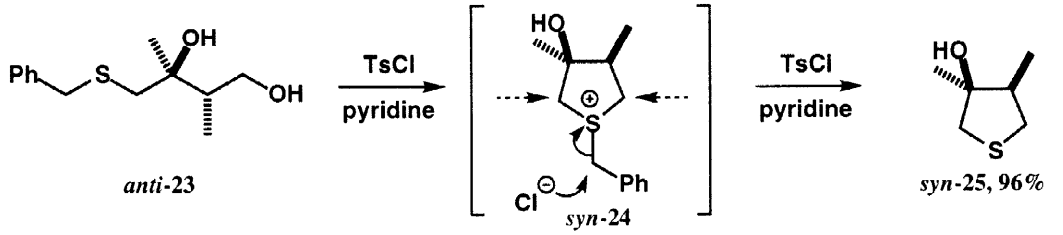


anti-17 — *anti*-18, 94% — *syn*-17 — *syn*-18, 91%

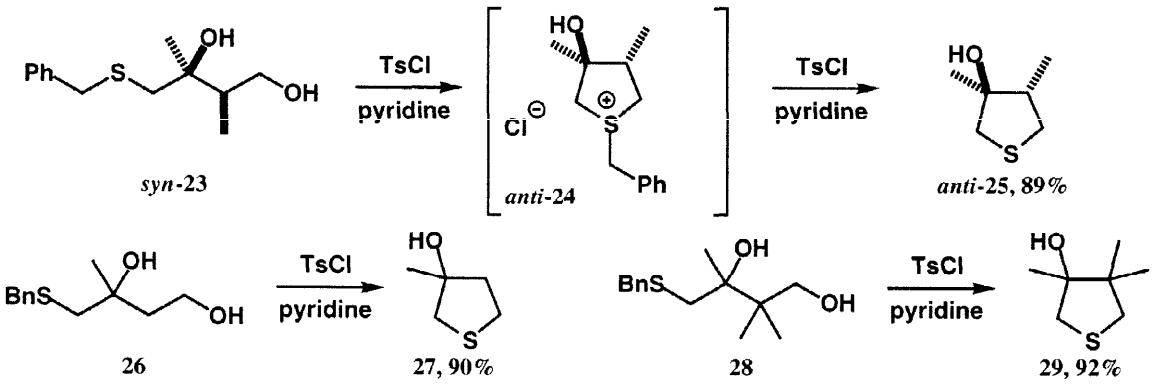
anti,anti-19 — *anti, syn*-20, 94% — *syn,anti*-19 — *syn,syn*-20, 90%

anti-21 — *anti*-22, 96%

We finally considered diols with a primary migration origin *anti* and *syn*-**23**, **26** and **28**. The sulfonium salts, e.g. **24**, from these diols have three attractive sites for S_N2 attack by chloride ion (see *syn*-**24**) and yet all gave the corresponding thiolanes **25**, **27** and **29** in excellent yield by *exo*-debenzylation[8] with complete regioselectivity. Attempts to isolate the sulfonium ion intermediate by precipitation of the chloride anion using $AgBF_4$ or $NaClO_4$ proved unsuccessful. A notable feature of all these thiolanes (e.g. *syn*-**25**) in the ^1H NMR is the characteristic geminal coupling constant of the CH_2S group (J 10.5 Hz); this geminal coupling is substantially larger than that of a tetrahydrofuran, which is typically 8.5 Hz.[6] Presumably, this is because sulfur is less electronegative, and the larger ring (longer C–S bonds) increases geminal coupling.



anti-23 — *syn*-24 — *syn*-25, 96%



This method for the synthesis of thiolanes is easy to perform (generally complete in 5 hours) and just requires an aqueous HCl work-up (to remove pyridine).[3] Furthermore, the reaction is insensitive to both the substitution at the migration origin and more importantly the developing stereochemistry within the thiolane. The only exception was the cyclohexane *anti*-**1**; R=Bn where competitive elimination occurred to give some allylic alcohol *anti*-**4.**

In summary, we have shown that rearrangements of 4-RS-1,3-diols with TsCl fall into three categories:

1) Debenzylation of S-benzylsulfonium salts is preferred to either elimination or *endo*-substitution.

2) Elimination is favoured when PhS is the migrating group and when there is a tertiary migration origin.[2,3]

3) *Endo*-substitution is favoured only when PhS is the migrating group and when there is a secondary migration origin.[2]

The nearest analogy to this work is the cyclisation and debenzylation of SBn sugar derivatives in low yield either with Ph_3P and iodine[7] or of preformed tosylates with NaI and $BaCO_3$ in acetone under reflux.[12]

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References and Notes

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