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Efficient Alkylsulfanyl (SMe, SEt and SCH_2Ph) and Sulfanyl (SH) Migration in the Stereospecific Synthesis of Substituted Tetrahydrofurans

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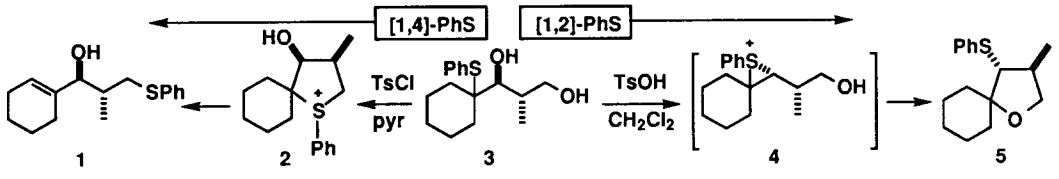
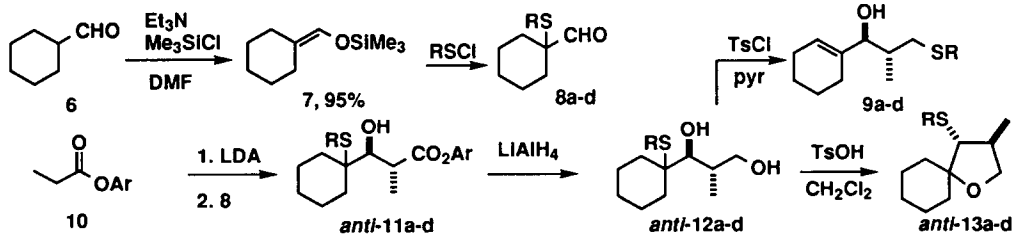
Abstract: Treatment of a series of 4-RS-1,3-diols (R=Me, Et, Bn and H) with TsOH in CH_2Cl_2 gives substituted tetrahydrofurans. We discuss the scope of this reaction using structural variation of the migrating (RS) substitutent. All reactions proceeed in high yield and give synthetically useful products.

In a series of papers we have reported rearrangements on diols such as **3** involving [1,2]-,[1] e.g. to give **5**, [1,3]-,[2] [1,4]-,[3,4] e.g. to give **1** and [2,3][5]-PhS migrations to give a variety of products in which new C–O, C–N, C–S, and C–C bonds were formed stereospecifically to give single diastereoisomers or enantiomers[6] of heterocycles[7] and allylic derivatives.[3] Aside from minor excursions into the 4-Me-[2] and 4-MeO-phenylS groups,[5] we have used only the PhS group. We chose this group because it is u.v. active and easy to remove, because the essential 2-PhS aldehyde starting materials can be made from commercially available PhSCl or $PhSCH_2OMe$,[8,9] and because there is no danger of the loss of the Ph group by nucleophilic attack on sulfonium ion intermediates such as **2** and **4**. We now report that a variety of AlkylS groups can in fact be used in some of these reactions without dealkylation, and on the performance of the SH group.



The required 2-RS-aldehydes **8** to prepare the diols corresponding to **3** but with methyl- ethyl- and benzylsulfanyl groups instead of PhS were made by sulfenylation of silyl enol ether **7** of the parent aldehyde **6** with RSCl, prepared[10] from RSSR and SO_2Cl_2. The aldehydes **8** were subjected to *anti*-stereoselective aldol reactions with the lithium enolate of Heathcock's 2,6-dimethylphenyl propionate[11,12] **10** to give, after reduction ($LiAlH_4$, ether, two hours), the diols *anti*-**12a-d**.



All these diols *anti*-**12a-d** rearranged stereospecifically with a [1,2]-RS shift to give the THFs *anti*-**13a-d** in good yield with catalytic TsOH in refluxing CH_2Cl_2 and with a [1,4]-RS shift to give the allylic alcohols **9a-d** in good yield with TsCl in pyridine. These reactions are essentially as good as those with the

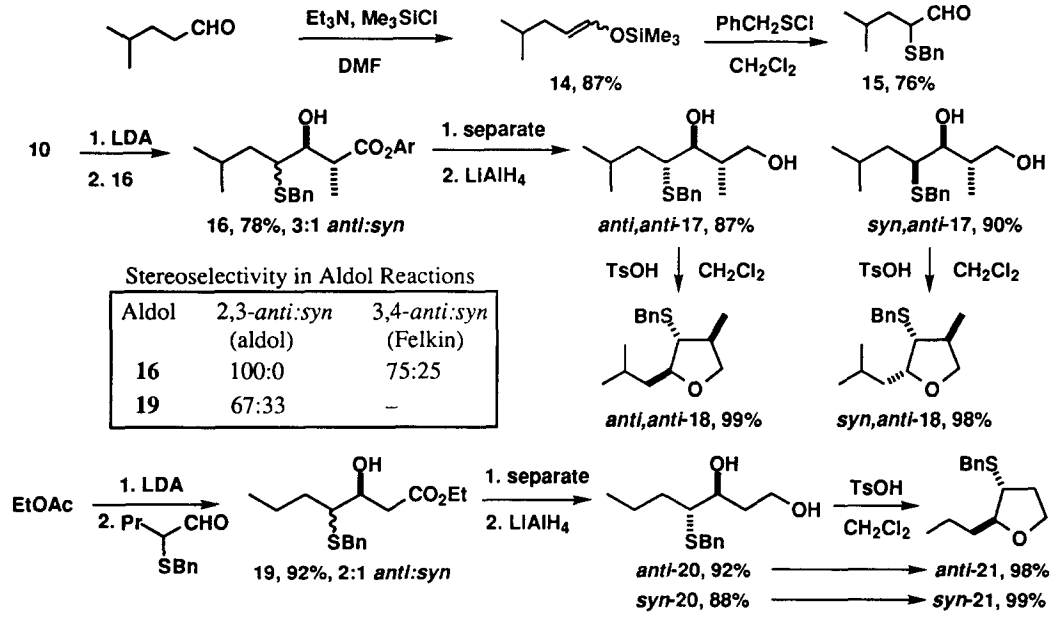
PhS group[13,1] (entry d, table 1) and the very high yields (94% is the lowest for a rearrangement step) leave little room for any dealkylation.

Table 1; Synthesis and rearrangement of the 4-Alkylsulfanyl-1,3-diols *anti*-**12**

Series, R	2-RS-aldehyde	Aldol	Diol	THF	allylic alcohol
a; Me	**8a**, 97%	*anti*-**11a**, 89%	*anti*-**12a**, 89%	*anti*-**13a**, 99%	*anti*-**9a**, 96%
b; Et	**8b**, 98%	*anti*-**11b**, 93%	*anti*-**12b**, 94%	*anti*-**13b**, 99%	*anti*-**9b**, 94%
c; $PhCH_2$	**8c**, 83%	*anti*-**11c**, 93%	*anti*-**12c**, 95%	*anti*-**13c**, 99%	–
d; Ph[a]	**8d**, 98%	*anti*-**11d**, 84%	*anti*-**12d**, 89%	*anti*-**13d**, 92%	*anti*-**9d**, 99%

[a]From earlier work.[1,13]

We wished to study two more variations. The SH group itself seemed to offer particular interest as loss of a proton might occur easily in the [1,2]-SH shift. The question of stereochemistry was also important in the same reaction as we wanted to establish that inversion did indeed occur at both the migration origin and terminus during [1,2]-RS migration (the [1,4]-RS migration is less interesting stereochemically as no change occurs at the stereogenic centres). We therefore prepared (by the above route: scheme 1 gives an example) and rearranged a series of benzylsulfanyl compounds having virtually all the possible variations in stereochemistry at the various centres along the chain. We hoped to be able to remove the benzyl group by reduction to give the SH group.

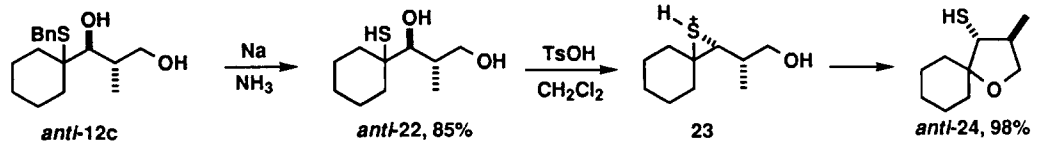


Stereoselectivity in Aldol Reactions

Aldol	2,3-*anti*:*syn* (aldol)	3,4-*anti*:*syn* (Felkin)
16	100:0	75:25
19	67:33	–

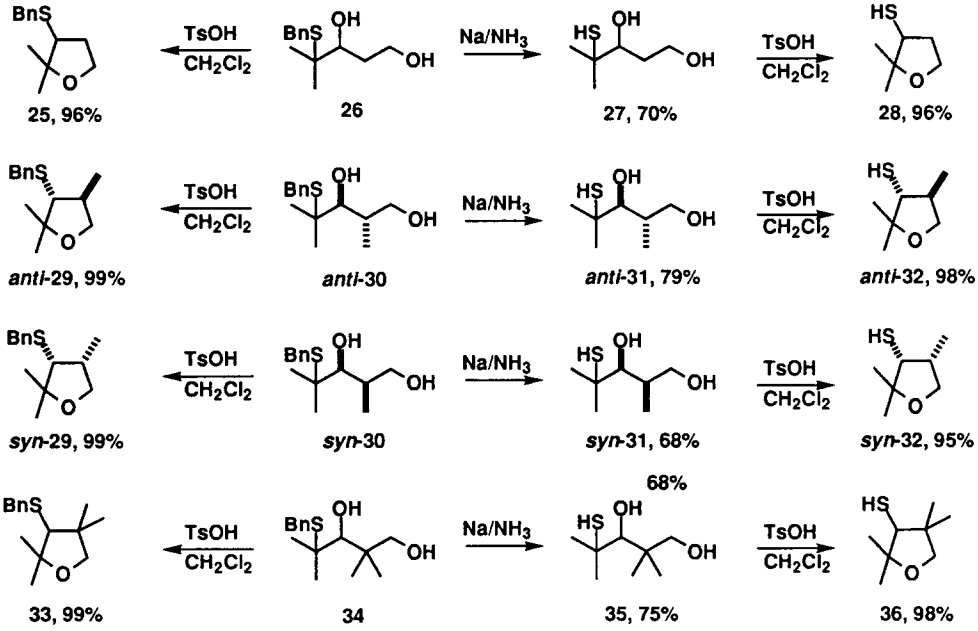
Scheme 1: Preparation and Rearrangement of 4-Benzylsulfanyl-1,3-alkanediols

All these diols in schemes 1 and 2 rearranged to give THFs with inversion at both the migration origin and terminus (determined by a 500 MHz NOESY spectrum) in excellent yield (table 2). The next step was to remove the benzyl group from some of these compounds to give a free sulfanyl group.[14] This could be accomplished in good yield (70-90%) with sodium in liquid ammonia and the free thiols, e.g. *anti*-**22**, were isolated as pleasant liquids. Rearrangement again gave THFs, e.g. *anti*-**24**, in good yield.



anti-12c *anti*-22, 85% 23 *anti*-24, 98%

Though the yields of sulfanyl-THFs such as **24** are very high, the reaction is much slower than with alkyl- or arylsulfanyl groups. One hour's refluxing with catalytic TsOH in CH_2Cl_2 was necessary instead of a few minutes. The reaction certainly proceeds with inversion at the migratory terminus (determined by a 500 MHz NOESY spectrum) and therefore via the protonated episulfide (such as **23**). We never observed any episulfides from these reactions under any conditions so proton loss from **23** must be slower than nucleophilic attack by the OH group. The longer reaction time indicates that, as might be expected, the sulfanyl (-SH) is less nucleophilic than an alkyl or aryl sulfanyl group.



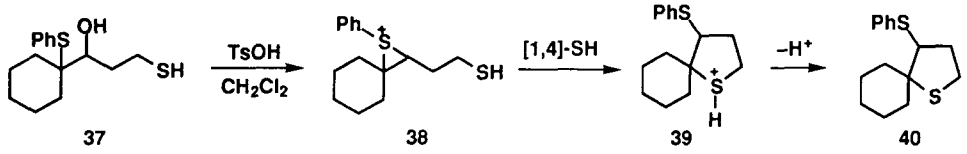
Scheme 2; Preparation and Rearrangement of 4-Benzyl sulfanyl- and 4-Sulfanyl-1,3-alkanediols

Table 2; Synthesis and Rearrangement of 4-$PhCH_2S$ (BnS-) and 4-HS-alkane-1,3-diols

Series	Stereo	Aldol	BnS-diol	HS-diol	BnS-THF	HS-THF
a	-	95%	**26**, 93%	**27**, 70%	**25**, 96%	**28**, 96%
b	*anti*	90%	*anti*-**30**, 92%	*anti*-**31**, 79%	*anti*-**29**, 99%	*anti*-**32**, 98%
b	*syn*	65%	*syn*-**30**, 92%	*syn*-**31**, 68%	*syn*-**29**, 99%	*syn*-**32**, 95%
c	-	92%	**34**, 90%	**35**, 75%	**33**, 99%	**36**, 98%

Participation by PhS is very well known[15] and participation by alkylsulfanyl groups has also been recorded, though less frequently. Benzylsulfanyl groups will participate through four-membered rings.[15] Sulfanyl is often used in cyclisations resulting in cyclic sulfides, even in acid solution,[16] but is rare as a participating group which accelerates a reaction but remains intact as SH at the end of the reaction. We

believe our results reported in this paper include the first preparatively useful [1,2]-SH shifts. In a destructive sense, participation by SH is believed to be the cause of a failure of $HS(CH_2)_2OH$ as a protecting group in a lysozyme synthesis.[17] We have already reported[18] that [1,4]-SH participation during PhS migration, as in the acid-catalysed rearrangement of **37**, leads to thiolane formation rather than [1,4]-SH migration. Whereas the episulfonium ion **23** does not lose a proton from sulfur, but rather continues SH migration to give the THF **24**, the thiolanium ion **39** does lose a proton under the same acidic conditions to give the thiolane **40**.



37 **38** **39** **40**

The effect of alkyl-S has been estimated as 30 times that of alkyl-O and 1000 times that of alkyl.[19] A comparison of the solvolysis of 2-chlorocyclohexanol and 2-chlorocyclohexanethiol revealed that SH was about 10^4 times more efficient than OH as a participating group.[20] We cannot compare RS or SH with RO or OH but it is clear that SH is at least an order of magnitude less effective than Alkyl-S or Aryl-S as a participating group.

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