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Scope and limitations of the [1,2]-alkylsulfanyl (SMe, SEt and SCH_2Ph) and sulfanyl (SH) migration in the stereospecific synthesis of substituted tetrahydrofurans †

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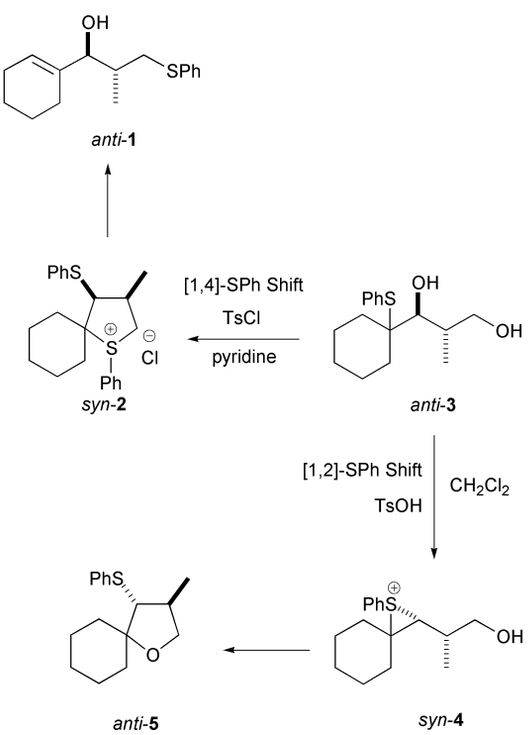
Acid catalysed rearrangement of a series of 4-RS-1,3-diols (R = Me, Et, Bn and H) with toluene-*p*-sulfonic acid in dichloromethane gives stereospecifically substituted tetrahydrofurans *via* a [1,2]-SR shift in near quantitative yield. We comment on the structural variation of the migrating (RS) substituent and that of the migration origin and terminus on the outcome of the title reaction. We also report on the surprising similarity between an alkylsulfanyl (RS) and sulfanyl (SH) migrating group.

In a series of papers, we have reported numerous rearrangements of substituted 1,3-diols (*e.g. anti*-**3**) involving [1,2]-SPh shift[1] (to give tetrahydrofuran *anti*-**5**), [1,3]-,[2] [1,4]-SPh shift[3,4] (to give allylic alcohols *anti*-**1**) and [2,3]-SPh shifts to give a variety of stereoisomerically pure heterocyclic[6,7] and allylic[3] derivatives involving stereospecific C–O, C–N, C–S and C–C bond formation (Scheme 1). Apart from minor use of aromatic derivatives, such as 4-Me-[2] and 4-MeO-PhS[5] groups we have always used the phenylsulfanyl (PhS) group. This was chosen due to its UV activity and ease of removal,[7] but also because many of these 2-PhS-aldehyde precursors were easily synthesised from commercially available starting materials (PhSCl or $PhSCH_2OMe$).[8,9] Furthermore, there was no danger in the loss of the Ph group by nucleophilic attack on the sulfonium ion intermediates such as the thiolanium ion *syn*-**2** and the episulfonium ion *syn*-**4** during the migration process. We now report on the cyclisation of a new class of 1,3-diol with structural variation at the migrating (RS) substituent (where R = Me, Et, Bn and H) and comment on their relative performance, and in particular the use of a sulfanyl (SH) migrating group.[10]



Scheme 1

We required the 2-RS-aldehydes **8a–c**, **11**, **14**, **17** and **20** for this study. These were synthesised by sulfenylation[11] of the silyl enol ethers **7**, **10**, **13**, **16** and **19** (derived from the parent aldehydes **6**, **9**, **12**, **15** and **18**) with RSCl—freshly prepared by the addition of sulfonyl dichloride (SO_2Cl_2) to a stirred solution of RSSR in CH_2Cl_2. The yields were excellent and this procedure appears to be as efficient for simple alkyl groups (*e.g.*, R = Me and Et) as that previously reported[1] for a phenyl group (R = Ph) (see entry d in Table 1). The yield was slightly reduced when using the more reactive benzylsulfanyl chloride (BnSCl) (Scheme 2).

We synthesised the diol precursors using either the reliable *anti*-stereoselective aldol reaction of the lithium (*E*)-enolate **22** of Heathcock's ester (2,6-dimethylphenyl propionate **21**)[12,13] or the *syn*-stereoselective aldol from the boron (*Z*)-enolate **24** of Masamune's ester (*S*-phenyl thiopropionate **23**)[14] with 2-RS-aldehydes giving predictably single diastereoisomeric adducts with greater than 98% stereocontrol (Schemes 3 and 5).

The rearrangement of the simple cyclic 1,3-diols *anti*-**26a–c** (R = Me, Et and Bn) with a symmetrical migration origin was studied (Scheme 4), primarily to see whether there were any unusual effects on the rearrangement upon changing from a phenylsulfanyl (PhS) migrating substituent, since we have previously observed significant changes in the mechanistic pathway in related diols when investigating [1,4]-SR shifts.[10] These diols were synthesised from the 2-RS-aldehyde **8a–c** (R = Me, Et and Bn) and the lithium (*E*)-enolate **22** giving diastereoisomerically pure aldol *anti*-**25a–c** (R = Me, Et and Bn) in excellent yield (Table 1). Subsequent reduction ($LiAlH_4$ in ether) gave the diols *anti*-**26a–c** required for the rearrangement study. Treatment of these under our usual conditions[1] (catalytic TsOH in refluxing CH_2Cl_2 for 5 minutes) gave stereospecifically the spirocyclic tetrahydrofurans *anti*-**28a–c** in high

† Experimental details are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b007284m/

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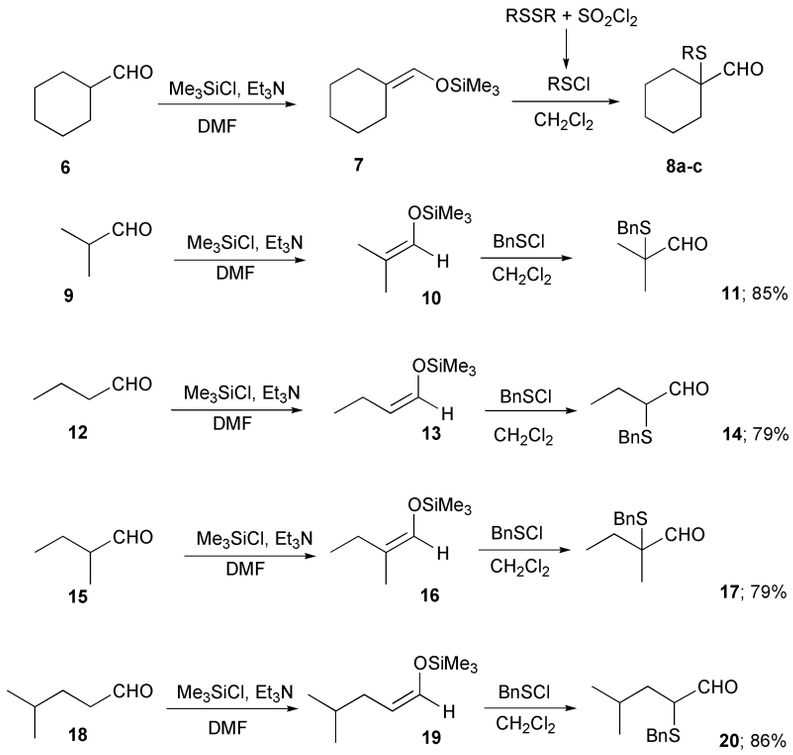
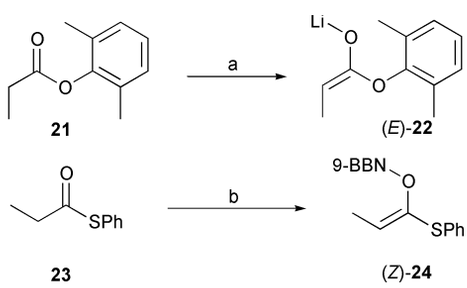
Table 1 The yield for the synthesis of 4-RS-1,3-diols *anti*-**26a**–**c** and THF *anti*-**28a**–**c**

Series R	RS-aldehyde	Yield (%)	Aldol	Yield (%)	Diol	Yield (%)	THF's	Yield (%)
a; Me	**8a**	97	*anti*-**25a**	89	*anti*-**26a**	89	*anti*-**28a**	99
b; Et	**8b**	98	*anti*-**25b**	93	*anti*-**26b**	94	*anti*-**28b**	99
c; CH_2Ph	**8c**	83	*anti*-**25c**	93	*anti*-**26c**	95	*anti*-**28c**	99
d; Ph[1]	**8d**	98	*anti*-**25d**	84	*anti*-**3**	89	*anti*-**5**	92



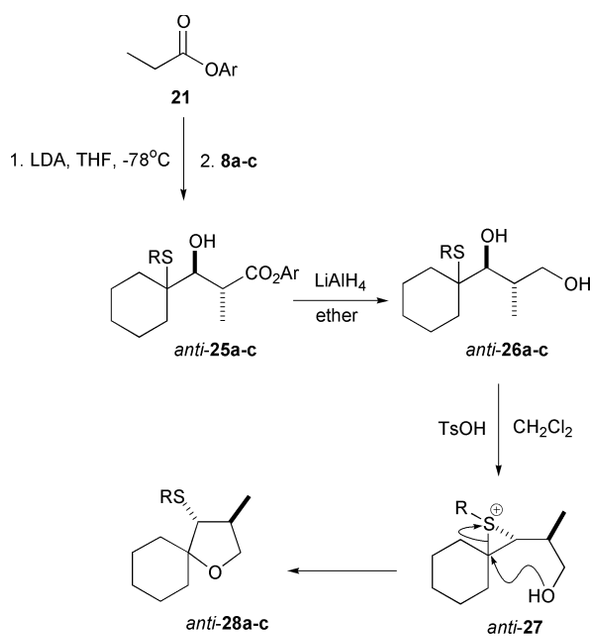
Scheme 2



Scheme 3 *Reagents and conditions*: a LDA, THF, −78 °C; b 9-BBN-OTf, toluene, −30 °C.

yield, presumably *via* a hybrid 6-*endo*/5-*exo*-*tet* cyclisation[1] of the episulfonium ion *anti*-**27** with an overall [1,2]-SR shift. These reactions were essentially as good as those with the SPh group,[1,15] and the yields were near quantitative, giving very little room for any dealkylation of the intermediate episulfonium ion **27**.

For the remainder of this study, we chose to use a benzylsulfanyl (BnS) migrating group since this would be a better substituent[16] for observing any possible S_N2 dealkylation of intermediate episulfonium ions and would also give access to the more interesting free sulfanyl (SH) group by reductive removal of the benzyl group.[17] We synthesised all the possible structural combinations of the acyclic 4-BnS-1,3-diols **31**, *anti*- and *syn*-**33** and **37** to probe the effect of stereochemistry on the [1,2]-RS shift. These diols were made by the addition of the lithium enolate of ethyl acetate, 2,6-dimethylphenyl propionate or isobutyrate as well as addition of the *syn*-stereoselective boron enolate of Masamune's thioester *S*-phenyl thiopropionate[14] to the aldehyde **11**, followed by simple

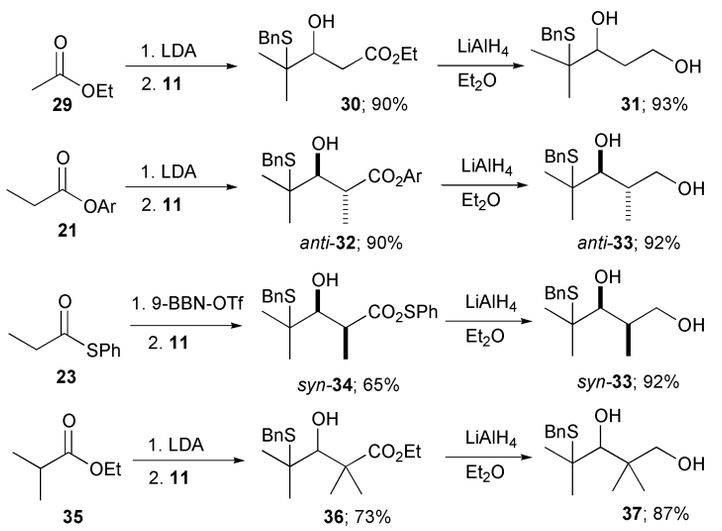


Scheme 4

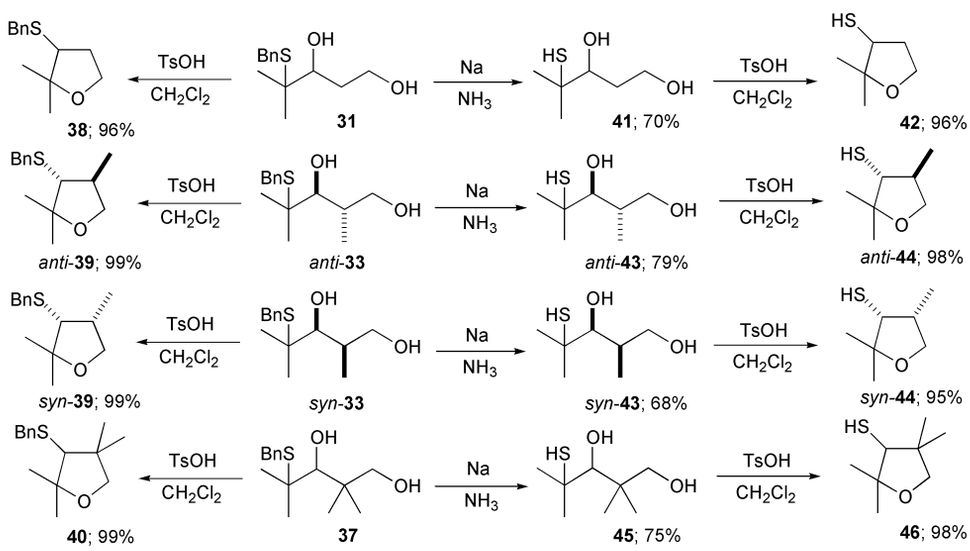
$LiAlH_4$ reduction in ether (Scheme 5). The relative stereochemistry obtained using the stereoselective aldol reaction with 2,6-dimethylphenyl propionate and *S*-phenyl thiopropionate is very reliable and the corresponding phenylsulfanyl derivatives have previously been reported.[23] Subsequent rearrangement of these diols **31**, *syn*- and *anti*-**33** and **37** with TsOH in CH_2Cl_2 gave stereospecifically the tetrahydrofurans **38**, *syn*- and *anti*-**39**

Table 2 The yield for the synthesis of 3-BnS THF's **38**, **39** and **40** and THF's **42**, **44** and **46**

RS-aldehyde	Aldol	Yield (%)	Diol	Yield (%)	3-BnS-THF's	Yield (%)	Thiols	Yield (%)	3-HS-THF's	Yield (%)
11	**30**	95	**31**	93	**38**	96	**41**	70	**42**	96
11	*anti*-**32**	90	*anti*-**33**	92	*anti*-**39**	99	*anti*-**43**	79	*anti*-**44**	98
11	*syn*-**34**	65	*syn*-**33**	92	*syn*-**39**	99	*syn*-**43**	68	*syn*-**44**	95
11	**36**	73	**37**	87	**40**	99	**45**	75	**46**	98



Scheme 5

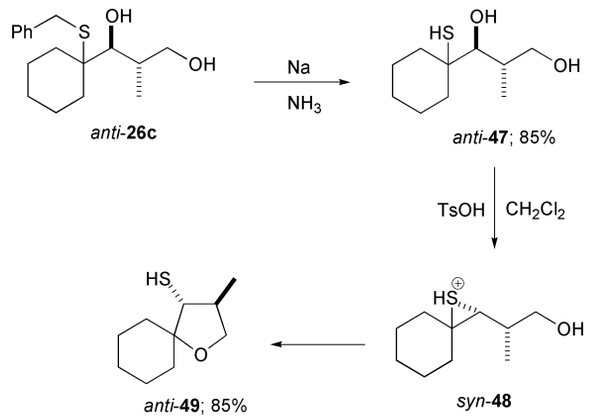


Scheme 6

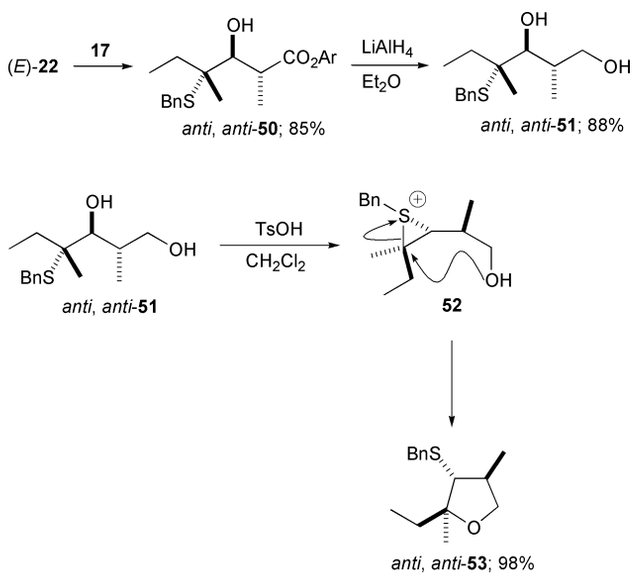
and **40** in near quantitative yield (the lowest yield being 96%). Their behaviour is identical to that of the PhS analogues (Table 2).[1] These reactions occur cleanly and cyclisation onto the episulfonium ion is stereospecific: the *anti*-diol **33** gives the *anti*-tetrahydrofuran **39**, whilst the *syn*-diol **33** gives the *syn*-tetrahydrofuran **39** (Scheme 6).

A remaining question was whether an SH grouping itself could be used in this [1,2]-SR reaction. It offered particular interest as simple loss of a proton might occur easily in the [1,2]-SH shift. The next step was to remove the benzyl group to give the free sulfanyl (SH) group.[17] This was easily achieved by reduction with sodium in liquid ammonia in good yield (60–90%) to give the thiols **41**, *anti*- and *syn*-**43**, **45** and *anti*-**47** as pleasant smelling liquids. Rearrangement of this series of 4-HS-1,3-diols **41**, *anti*- and *syn*-**43**, **45** and *anti*-**47** gave the tetrahydrofurans **42**, *anti*- and *syn*-**44**, **46** and *anti*-**49** in good yield (Table 2). Though the yields of the sulfanyl tetrahydrofurans are as high as the phenyl- and alkylsulfanyl cases, the reaction is much slower. One hour's refluxing with catalytic TsOH in CH_2Cl_2 is necessary rather than just a few minutes. The reaction certainly does proceed with inversion at the migration terminus and therefore *via* a protonated episulfide such as *syn*-**48** (Scheme 7). We have never observed any episulfide formation under these conditions, presumably showing that proton loss from **48** must be slower than capture of the episulfonium ion with the OH group. The longer reaction time indicates, as might be expected, that the sulfanyl (SH) group is less nucleophilic than a comparable alkyl or arylsulfanyl group.

To establish whether this [1,2]-SBn shift occurs stereospecifically with clean inversion at both the migration origin and terminus, we synthesised a series of 4-BnS-1,3-diols with an unsymmetrical acyclic tertiary migration origin. These diols were synthesised from the chiral 2-BnS-aldehyde **17** by reaction with Heathcock's enolate (*E*)-**22** and with acetone (Schemes 8 and 9). The C(3,4)-Felkin–Anh selectivity[18] was good (Table 3), whereas the C(2,3)-stereocontrol (>98 : <2) in *anti*,*anti*-**50**



Scheme 7



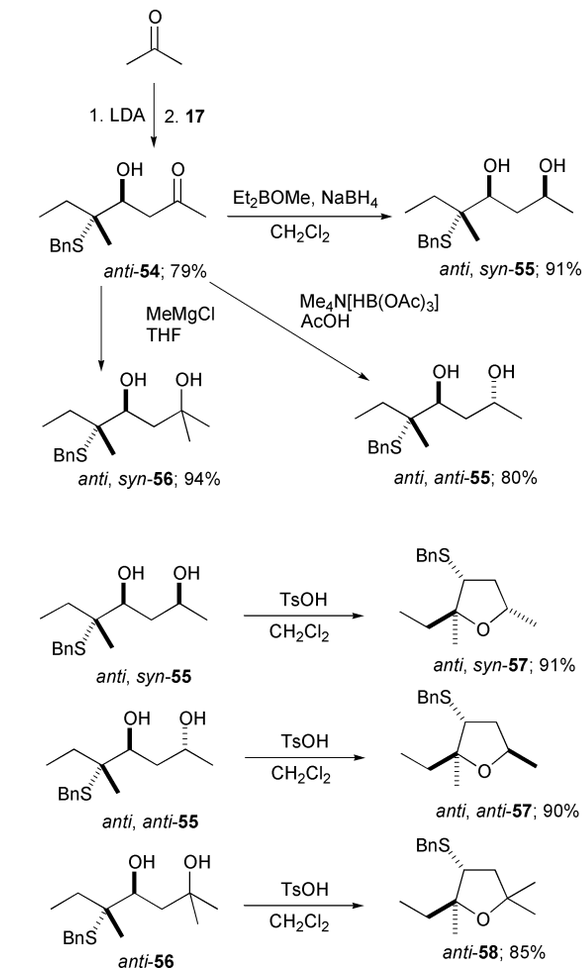
Scheme 8

was very well controlled by (*E*)-enolate geometry.[13] Simple reduction ($LiAlH_4$ in ether) of the ester *anti*,*anti*-**50** gave the 1,3-diol *anti*,*anti*-**51**, which has the all-important stereogenicity at the migration origin and what would become the migration terminus in the tetrahydrofurans. Acid catalysed rearrangement of this diol (TsOH in CH_2Cl_2) gave the corresponding tetrahydrofuran *anti*,*anti*-**53** as a single diastereoisomer. Evidently, the cyclisation *via* the episulfonium ion **52** was stereospecific with inversion at both the migration origin and terminus (determined by NOE differences). Clean inversion occurs at a tertiary stereocentre, and thus the cyclisation must be occurring *via* a rather loose S_N2–tight S_N1 transition state to account for the observed stereochemical outcome.

The structural nature of the cyclising alcohol (OH group) was also found to be unimportant on the outcome of the reaction. A secondary or tertiary OH group behaved identically to a cyclising primary OH group to give similar tetrahydrofurans in high yield. The diols *anti*,*syn*- and *anti*,*anti*-**55** containing the required secondary OH group were synthesised using the reliable *syn*[19] and *anti*-1,3-stereoselective[20] reduction developed by Prasad and Evans and their co-workers as shown in Scheme 9. Treatment of these diols *anti*,*syn*- and *anti*,*anti*-**55** with TsOH in CH_2Cl_2 gave stereospecifically the tetrahydrofurans *anti*,*syn*- and *anti*,*anti*-**57** in excellent yield. Inversion at the migration origin and retention of configuration at the cyclising secondary alcohol were observed. The rearrangement of the diol **56** (synthesised by the addition of MeMgCl to the ketone *anti*-**54**) with a cyclising tertiary OH group also proceeded cleanly to give the tetrahydrofuran *anti*-**58** in near quantitative yield (Scheme 9). The reaction appears to be

Table 3 The yield for the synthesis of 4-BnS 3-hydroxyl esters-**50**, **54**, **59** and **62**

RS-aldehyde	Aldol	Aldol C(2,3) selectivity	Aldol C(3,4) selectivity (Felkin–Anh)	Yield (%)
17	*anti*,*anti*-**50**	>98 : <2	89 : 11	85
17	*anti*-**54**	—	86 : 14	79
14	*anti*-**59**	—	67 : 33	91
20	*anti*,*anti*-**62**	>98 : <2	75 : 25	92



Scheme 9

insensitive to the substitution pattern and the relative stereochemistry of the cyclising nucleophile.

Another variant was the rearrangement of 1,3-diols such as *syn*- and *anti*-**60**, *anti*,*anti*- and *syn*,*anti*-**63** with a secondary migration origin. These diols were synthesised by our usual aldol and reduction methodology as shown in Schemes 10 and 11. However, this case was slightly different since the addition of the pre-cooled aldehyde **14** and **20** was required to prevent enolisation of the aldehyde (by the enolate) in the aldol step. The Felkin selectivity[18] C(3,4) observed was moderate, and was significantly lower than in previous cases involving the sterically demanding tertiary 2-BnS-aldehyde **17** (Table 3). The relative C(2,3) stereochemistry was well controlled (always >98 : <2). Acid catalysed rearrangement of these 4-BnS-1,3-diols gave stereospecifically the tetrahydrofurans *anti*- and *syn*-**61**, *anti*, *anti*- and *syn*,*anti*-**64** in quantitative yield (Schemes 10 and 11). The reaction was stereospecific since a different diastereoisomeric diol *anti*- and *syn*-**63** leads to a different diastereoisomeric tetrahydrofuran **64** in both cases (Table 4). The yields were slightly lower than those of the corresponding diols with a tertiary migration origin, and the reaction times were at least one order of magnitude longer. Clearly, the rate determining form-

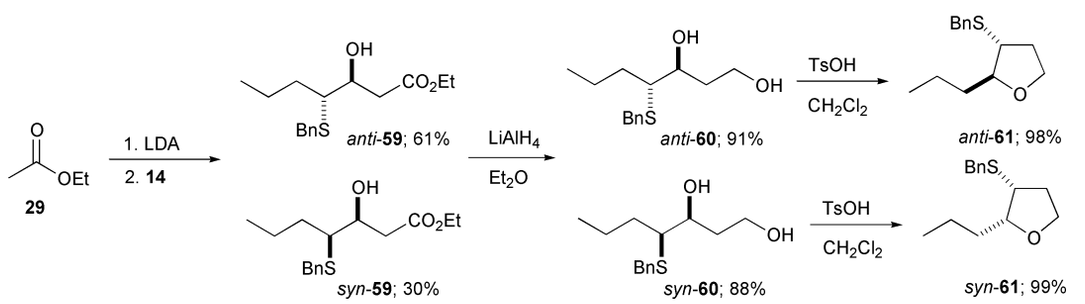
Table 4 The yield for the synthesis of 4-BnS diols and THF's **53**, **57**, **58**, **61** and **62**

Ester/ketone	Diols	Yield (%)	3-BnS-THF's	Yield (%)
anti,*anti*-**50**	*anti*,*anti*-**51**	88	*anti*,*syn*-**53**	98
anti-**54**	*anti*,*syn*-**55**	91	*anti*,*syn*-**57**[a]	91
anti-**54**	*anti*,*anti*-**55**	80	*anti*,*anti*-**57**[b]	90
anti-**54**	*anti*-**56**	94	*anti*-**58**	85
anti-**59**	*anti*-**60**	91	*anti*-**61**	98
syn-**59**	*syn*-**60**	88	*syn*-**61**	99
anti,*anti*-**62**	*anti*,*anti*-**63**	93	*anti*,*anti*-**64**	99
syn,*anti*-**62**	*syn*,*anti*-**63**	91	*syn*,*anti*-**64**	98

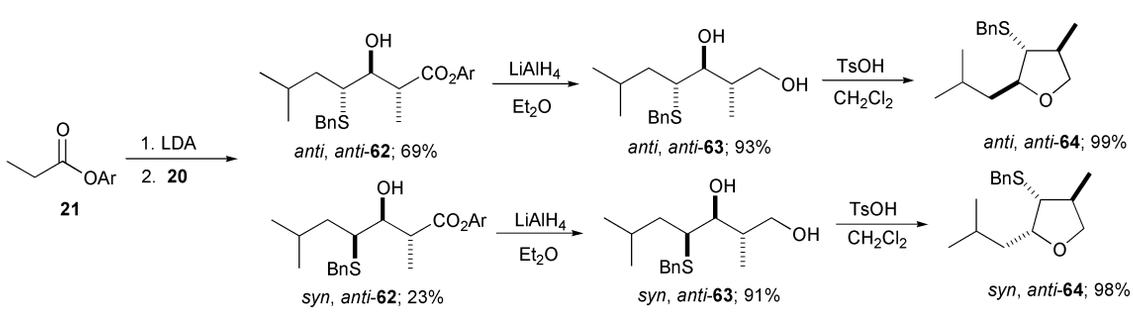
[a] Selectivity of diastereoselective reduction: *anti*,*syn*-**57**–*anti*,*anti*-**57**; >98 : <2. [b] Selectivity of diastereoselective reduction: *anti*,*anti*-**57**–*anti*,*syn*-**57**; 92 : 8.

ation of the intermediate episulfonium ion is slower and this is presumably due to the presence of the less substituted migration origin, a manifestation of the *exo*-component of the Thorpe–Ingold effect.[21,22]

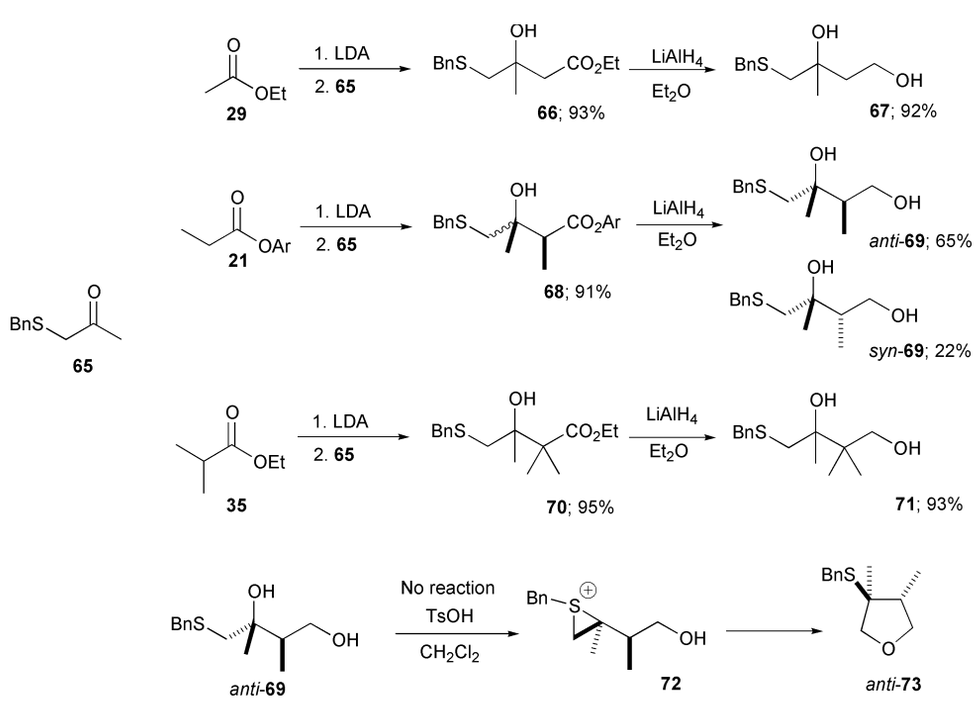
We rearranged a series of 1,3-diols with a primary migration origin in an attempt to probe this Thorpe–Ingold effect.[22] These were synthesised by the addition of the appropriate lithium enolate (derived from **21**, **29** and **35**) to the commercially available BnS-ketone **65** (Scheme 12). $LiAlH_4$ reduction gave the 4-BnS-1,3-diols **67**, *anti*- and *syn*-**69** and **71** in excellent yield (Table 5). Treatment of these diols (*e.g.* **69**) with TsOH in refluxing CH_2Cl_2 gave no tetrahydrofuran formation, even on prolonged reflux (24 hours) and simply gave recovered starting material. If the reaction was forced by prolonged reflux in a higher boiling solvent, such as toluene, these diols simply decomposed to give unidentified products. Presumably, the rate determining cyclisation step to form such an episulfonium



Scheme 10



Scheme 11



Scheme 12

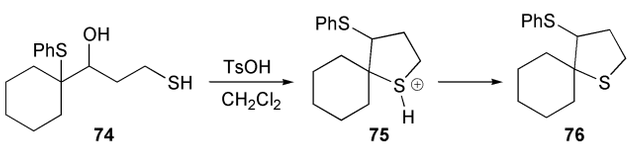
Table 5 The yield for the synthesis of 4-BnS-1,3-diols **67**, **69** and **71**

RS-ketone	Aldol	Aldol C(2,3) selectivity	Yield (%)	Diol	Yield (%)
65	**66**	—	93	**67**	92
65	*anti*-**68**–*syn*-**68**	75:25	91	*anti*-**69** *syn*-**69**	65 22
65	**70**	—	95	**71**	93

ion **72** is no longer favourable and an alternative unknown decomposition pathway is now favoured. This is not entirely surprising since it has been reported that the rate of a cyclisation can be improved by up to a million fold by the use of a *neo*-pentyl nucleophile.[22] Previous studies within our laboratory involving the PhS group have shown the cyclisation is also dependent on both the substituent pattern at the migration origin (tertiary cyclise more efficiently than secondary) and the *anti*- developing stereochemistry is preferred over *syn*- within the tetrahydrofuran framework.[23]

Rate enhancement of substitution by participation with a PhS group is well documented.[24] Participation by an arylsulfanyl group has also been reported, though much less frequently.[2,5] The use of alkylsulfanyl groups is even rarer. Within this area, MeS is the most common whereas the use of the more reactive BnS is very rare. However, there are cases where a benzylsulfanyl group is known to participate through a four-membered ring.[24] The sulfanyl (SH) group is a commonly used nucleophile in cyclisations resulting in cyclic sulfides, even in acidic conditions,[25,26] but is rarely seen as a participating group which accelerates a reaction, and also remains intact as SH at the end of the reaction. We believe our results report the first preparatively useful [1,2]-SH shift. In a destructive sense, participation by SH is believed to be the cause of the failure of $HS(CH_2)_2OH$ as a protecting group in a lysozyme synthesis.[27]

By comparison, we have already reported that [1,4]-SH participation[28] during PhS migration, as in the acid catalysed rearrangement of **74**, leads to thiolane formation **76** rather than [1,4]-SH migration (Scheme 13). Whereas the episulfonium



Scheme 13

ion *syn*-**48** does not lose a proton from sulfur, but rather continues SH migration to give the tetrahydrofuran *anti*-**49**, the thiolanium ion **75** does lose a proton under the same acidic conditions to give the thiolane **76**, presumably because both reactions are under thermodynamic control.

The effect of alkyl-S participation has been estimated as 30 times that of *O*-alkyl and 10^3 times that of alkyl participation.[29] A comparision of the solvolysis of *anti*-2-chlorocyclohexanol and *anti*-2-chlorocyclohexanethiol revealed that an SH group was about 10^4 times more efficient than OH as a participating group.[30] We cannot compare RS or SH participation with RO or OH participation, but it is clear that SH is at least an order of magnitude less effective than alkyl-S or aryl-S.

In conclusion, we have shown that migrating substituents RS (R = Me, Et, Bn and H) in diols like *anti*-**26** are as efficient as the previously reported PhS cases.[23] These [1,2]-RS shifts are indeed stereospecific with inversion observed at both the migration origin and terminus. The relative reaction rates of cyclisation are all similar, except for those with the sulfanyl (SH) migrating group, which are at least a magnitude slower. Furthermore, the cyclisation occurs more efficiently for a tertiary migration origin than a secondary, whereas migration from a primary migration origin does not occur and decomposition of the diol is observed. The yields for all these cyclisations are near quantitative (the lowest being 85%). The cyclisation occurs cleanly with complete stereochemical control giving virtually all the possible combinations of stereochemistry and substitution pattern within the tetrahydrofuran framework.

Experimental

Experimental details are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b007284m/.

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