

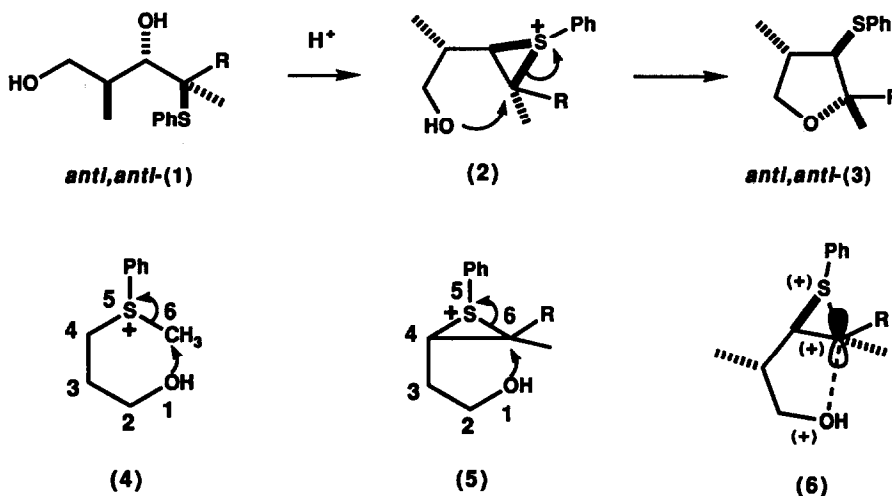
STEREOELECTRONIC FACTORS IN THE SYNTHESIS OF TETRAHYDROFURANS BY HYDROXYL PARTICIPATION IN PHENYLTHIO MIGRATION

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The factors controlling the title reaction were investigated with two tethered hydroxyl nucleophiles and include preferential attack at the more highly substituted carbon atom, preferential formation of the more highly substituted five-membered ring, and preferential closure in the *5-exo-tet* sense according to Baldwin's rules.

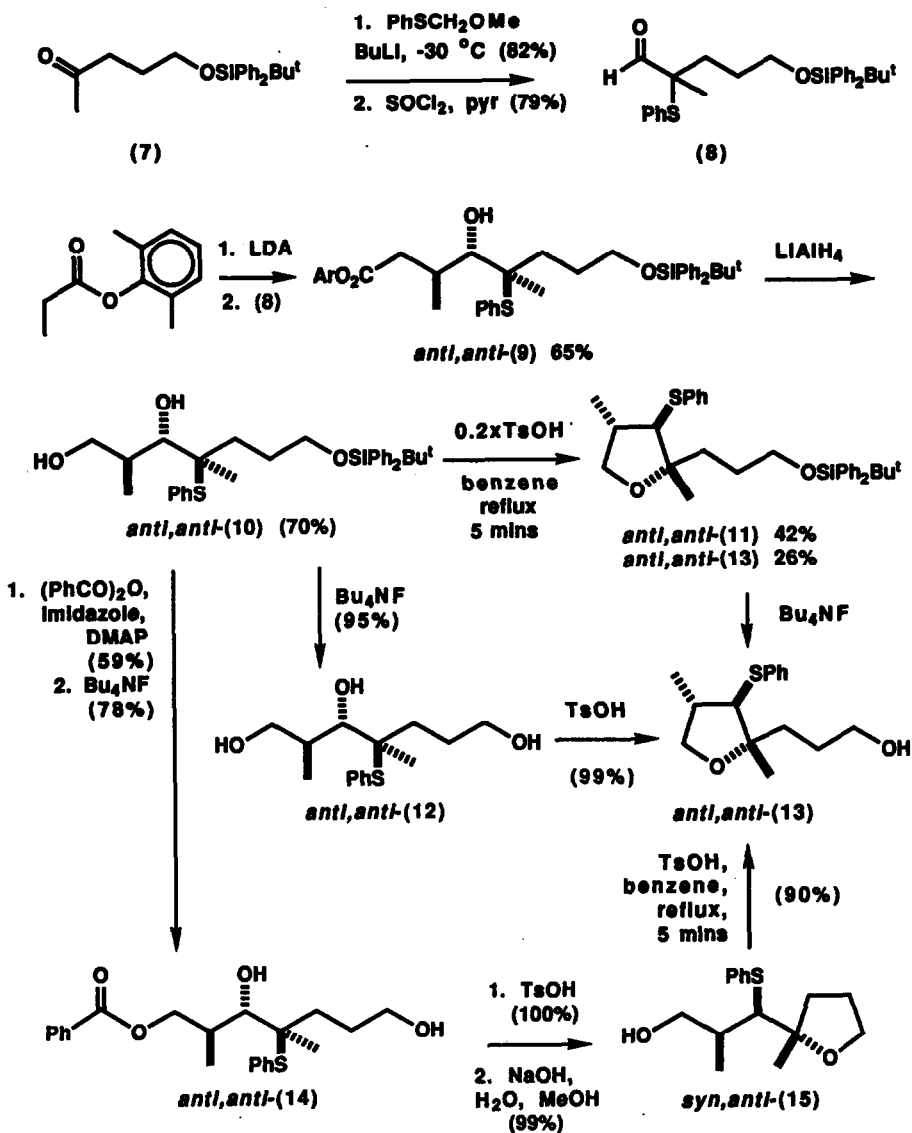
The stereospecific synthesis of cyclic ethers, e.g. (3), by hydroxyl capture of an episulphonium ion, e.g. (2), during acid-catalysed cyclisation of phenylthio (PhS-) alcohols, e.g. (1), with¹⁻³ or without⁴ PhS migration is a successful route to a variety of substituted tetrahydrofurans. These reactions, and the closely related cyclisations of unsaturated alcohols on treatment with RSCl and weak bases,⁵ suggest that the hydroxyl group prefers to attack the more substituted end of the episulphonium ion (2) via a loose S_N2 transition state, and that the ring size preference is 5>6>4. We have also detected one stereoelectronic factor² when both the PhS migration origin and terminus are secondary and now report on the evaluation of other stereoelectronic factors such as Baldwin's rules and the Thorpe-Ingold effect in competitive cyclisations of two tethered hydroxyl groups.



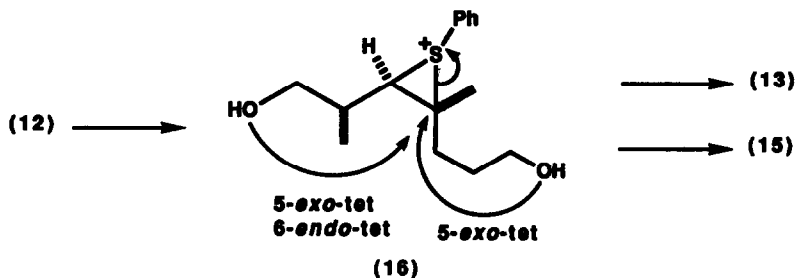
By the Thorpe-Ingold effect, we simply mean the preferential formation of the most highly substituted ring, whatever the reason,⁶ but the application of Baldwin's rules⁷ to these reactions deserves elucidation. The tight S_N2 reaction (4) is a simple 6-*endo-tet* reaction, and would presumably not occur in an intramolecular fashion as it is impossible to align OH, CH₃, and SPh at the required 180° and the penalties for straying even 20° off line are severe.⁸ The cyclisation (5) is better in two ways: inserting a short (C-C is shorter than C-S⁺) bond between C-4 and C-6 improves the alignment by incorporating some of the strain of the transition state (4) into

the intermediate (5). The cyclisation (5) is now both a 6-*endo-tet* and a 5-*exo-tet*. In addition, the two extra substituents at C-6 make a looser S_N2 transition state (6) possible. A partial positive charge can be supported at C-6, both partial bonds can be longer, and presumably the requirement for OH, C-6, SPh alignment at 180° becomes less stringent.

Scheme 1

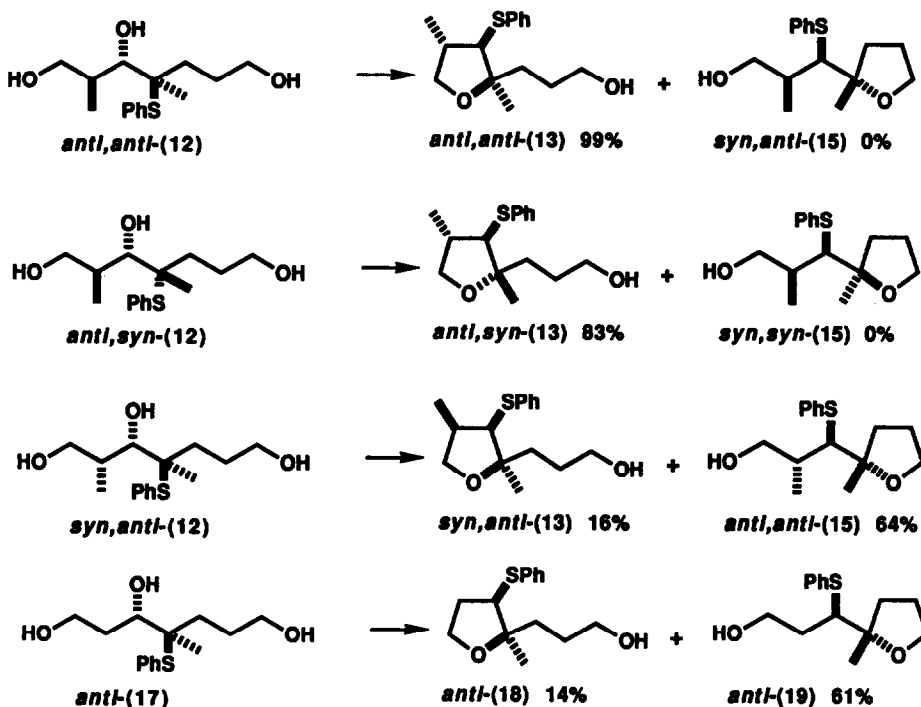


We evaluated the two possible modes of cyclisation (16) by studying a series of triols (12) and (17) and describe one stereoisomer of (12) in detail. The triol *anti,anti*-(12) was synthesised from the protected hydroxy-ketone (7) via a 2-PhS aldehyde⁹ (8), stereoselective aldol reaction,¹⁰ reduction,¹⁻³ and deprotection (Scheme 1).



The two possible cyclisations (4-*exo-tet* is never observed) were realised separately by selective protection of the two hydroxyl groups and authentic samples of *anti,anti*-(13) and *syn,anti*-(15) prepared by deprotection. Cyclisation of the triol *anti,anti*-(12) gave only the 6-*endo-tet* product *anti,anti*-(13) in high yield. This reaction is under thermodynamic control as the alternative product *syn,anti*-(15) rearranges to *anti,anti*-(13) under the reaction conditions. MM2 Calculations¹¹ suggest that *anti,anti*-(13) is about 5 kcal/mol more stable than *syn,anti*-(15), equivalent to an equilibrium constant of about 10^{3.5}.

Scheme 2



The extent of the Thorpe-Ingold effect in this stabilisation is revealed by changing the stereochemistry of the starting material to *anti,syn*-(12) and then to *syn,anti*-(12).¹² The *anti,syn* isomer again gave exclusively the 6-*endo-tet* product (13), but the *syn,anti* isomer, in which a less favourable *syn* relationship between Me and SPh is developing in the 6-*endo-tet* product (13), gives mostly the 5-*exo-tet* product (15). We found related behaviour in the cyclisation with PhS migration from a secondary migration origin to a secondary migration

terminus.² Removing the extra methyl group altogether, as in *anti*-(17)¹³ produces a similar ratio (Scheme 2). This ratio of about 4:1 must represent a minimum for the Baldwin's rule effect as the 6-*endo-tet* products (13) or (18) always have one extra substituent (the PhS group). In all these cases, high yields of either product may be obtained by selective protection (Table). We conclude that cyclisation is governed by these effects (both kinetically and thermodynamically), in decreasing order of importance:

- (i) Cyclisation to the more highly substituted end of the episulphonium ion is always preferred.
- (ii) A developing *anti* relationship is preferred to a developing *syn* relationship.
- (iii) Pure 5-*exo-tet* cyclisation is preferred to the hybrid 6-*endo*/5-*exo-tet* cyclisation.
- (iv) The more highly substituted ring is preferred.

Effects (ii) to (iv) are strongly inter-related: effect (iv), for example, may apply if an *anti* relationship is developing in the new ring, but not if a *syn* relationship is developing.

Table: Yields (%) of Pure Compounds (13), (15), (18), and (19) by Protection (Schemes 1 and 2)

Starting Material	6- <i>endo-tet</i> Products:		5- <i>exo-tet</i> products:			
	Cyclisation (10) – (11)	Desilylation (11) – (13)	Benzoylation of (10)	Desilylation to (14)	Cyclisation of (14)	Debenzoylation to (15)
<i>anti,anti</i> -(10)	99 ^a	78 ^a	59	78	100	99
<i>anti,syn</i> -(10)	87 ^a	82 ^a	-	-	-	-
<i>syn-anti</i> -(10)	61	89	90	78	74	93
<i>anti</i> -(17) ^b	66	c	84	74	99	89

^aBy cyclisation of the triol (12): desilylation is first. ^bStarting material is the precursor of (17), products are (18) and (19). ^c29% *Syn*-(18) formed by desilylation during the rearrangement.

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References and Notes

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11. MM2 Calculations were kindly carried out by Mr John Hollerton of Glaxo Group Research, Ware.
12. *Anti,syn*-(12) was made from the minor aldol product from the sequence shown in scheme 1. *Syn,anti*-(12) was made from the major product of Masamune's boron enolate of a PhS propionate, see refs 1-3 and 10.
13. *Anti*-(17) was made from the major product of an aldol reaction between the lithium enolate of ethyl acetate and the 2-PhS aldehyde (8).