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The Thorpe-Ingold Effect in the Synthesis of Tetrahydro-Furans and Pyrans by Competitive Cyclisation with Phenylthio Migration

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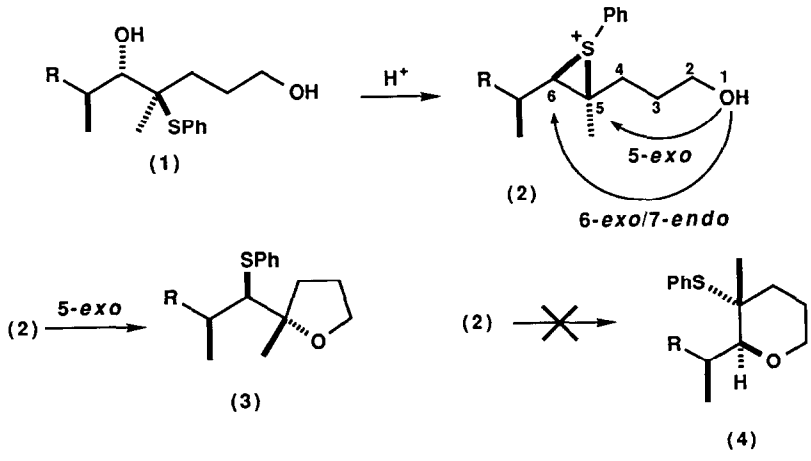
Abstract: In cyclisations of triols with two tethered hydroxyl nucleophiles (giving ethers by acid-catalysed phenylthio migration) a *gem*-dimethyl group in the carbon chain bearing one of the OH groups favours cyclisation of that chain whether the new ring is five- or six-membered and whether the cyclisation is *exo* or *endo* in the Baldwin sense.

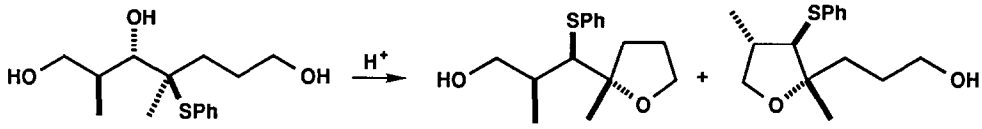
Tetrahydrofurans (THFs)[1,2] or tetrahydropyrans (THPs)[3] are formed regio- and sterospecifically during the acid-catalysed cyclisations of diols with suitably placed phenylthio (PhS-) groups. Participation[1] (and eventual migration[2,3]) by a neighbouring PhS group ensures stereospecific inversion at both the migration origin (C-5 in **2**) and terminus (C-6 in **2**), and regiospecific attack by the hydroxyl group on the intermediate episulphonium ion (**2**) at the more substituted carbon atom.[4] Related cyclisations giving similar products[5] by electrophilic attack on double bonds show poorer selectivities. Cyclisation of the *anti,anti*-diol (**1**) leads exclusively [the alternative cyclisation leading to the THP (**4**) does not occur] to the tetrahydrofuran *anti,syn* (**3**) by inversion at C-5 and C-6. The formation of (**3**) is a 5-*exo*-tet cyclisation[6] but the regioselectivity comes from preferential attack at the more substituted carbon atom (C-5 in **2**) rather than any consideration of Baldwin's rules. The alternative THP product (**4**) would come from attack at a secondary carbon atom (C-6 in **2**) and the loose transition state would be less able to share the positive charge.[4] The degree of control available both during the synthesis of the precursors and in the cyclisation itself[2-4] means that either *exo* or *endo* routes [(**5**) is an *endo* product] to either THFs or THPs are successful and therefore that these cyclic ethers may be made with substituents and chiral centres either inside (**5**) or outside (**3**) the newly formed ring in good yield by attack at the tertiary centre.[3,4]



We have evaluated[4] the contribution made by stereoelectronic factors in controlling the cyclisation of triols such as (**1**; R = CH_2OH) and concluded that four factors are important:

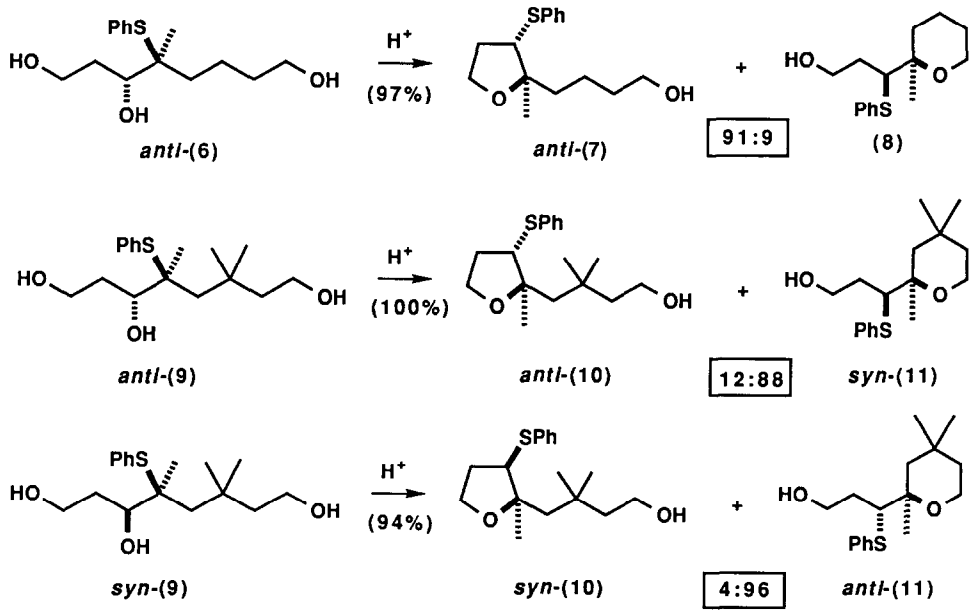
1. Cyclisation occurs to the more substituted end of the episulphonium ion intermediate.
2. Baldwin's rules predict that the 5-*exo-tet* is preferred to the hybrid 5-*exo*/6-*endo-tet* cyclisation.
3. There is a preference for developing *anti* over developing *syn* stereochemistry.
4. The Thorpe-Ingold effect favours the formation of the more substituted ring.

Factors 2-4 are not independent but interact strongly. Thus cyclisation of (**1**; R = CH_2OH) gives only the 5-*exo*/6-*endo* (disfavoured by Baldwin's rules) product (**5**) because this has two extra substituents in an *anti* relationship in the ring in comparison to the alternative 5-*exo* product (**3**; R = CH_2OH). It seemed that the Thorpe-Ingold effect could overcome Baldwin's rules if the stereochemistry was right.



(1; R = CH_2OH) (3; R = CH_2OH) 0% (5) 99%

The Thorpe-Ingold effect[7] means different things to different authors[8] but all are agreed that substitution in a carbon chain favours cyclisation both kinetically and thermodynamically. Its classical manifestation is the "*gem*-dimethyl effect" in which geminal dimethyl substituents both accelerate cyclisation and stabilise the cyclic product.[8] We now confirm that the Thorpe-Ingold effect is indeed important in cyclic ether formation by demonstrating that the presence of *gem*-dimethyl groups can switch the regioselectivity of a cyclisation either between THF and THP formation or between the *exo* and the *endo* modes. The question of developing *syn* or *anti* relationships disappears as the *gem*-dimethyl carbon atom is not a chiral centre.

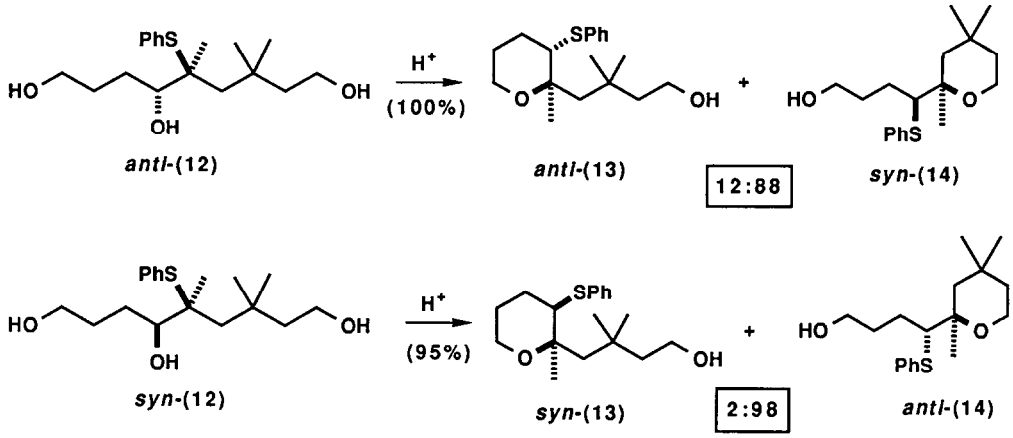


anti-(6) *anti*-(7) (8)

anti-(9) *anti*-(10) *syn*-(11)

syn-(9) *syn*-(10) *anti*-(11)

Cyclisation of the triol[9] (**6**) gave predominantly the THF (**7**) by a 5-*exo*/6-*endo* pathway and only a trace of the THP (**8**) by the 6-*exo* pathway. These compounds have the fewest substituents possible and illustrate that even then there is one more substituent (PhS) on the ring in the *endo* product than in the *exo* product. Both products have the quaternary centre in the ring simply because cyclisation always occurs to that end of the episulphonium ion. The THF (**7**) is also favoured by the developing *anti* relationship between PhS and the hydroxybutyl side chain. Addition[9] of a *gem*-dimethyl group to the side chain which would form the THP (**9**) reverses this selectivity, regardless of the stereochemistry of the products. These reactions are best carried out in CH_2Cl_2 at room temperature for maximum regioselectivity, giving the THPs *syn* and *anti*-(**11**) in high yield. All these cyclisations are of course stereospecific. Selectivity is slightly higher when there is a developing *syn* relationship in the endo product (**10**) between the PhS group and the longer side chain, but the Thorpe-Ingold effect clearly dominates the stereochemical factor. The presence of the *gem*-dimethyl group inside the ring is evidently more important than the ring size or the stereochemistry.



We had already established that there is an inherent preference for the *endo* product[4] when both products are THFs and had attributed this to the Thorpe-Ingold effect. It remained to be established that, when the ring sizes are the same, a *gem*-dimethyl group can reverse this selectivity in favour of the *exo* cyclisation. We chose to do this with THPs to provide further examples of stereospecific *exo* and *endo* closure of THPs. The *syn* and *anti* triols[9] (**12**) both cyclise stereospecifically to give the *exo* products *syn* and *anti*-(**14**), with the PhS group on the side chain and not on the ring. In the cyclisation of both (**9**) and (**12**), more of the *endo* products are formed when the side chains on the THF ring in (**10**) and on the THP ring in (**13**) are *anti* to the PhS group. The ratios are remarkably similar in spite of the difference in ring sizes, though we would expect *endo* products to be more favoured the larger the ring size.[6] Either product may be formed stereospecifically and essentially quantitatively by selective protection.[4,9]

In these examples at any rate, the size of the ring being formed (5 or 6 membered), Baldwin's rules, and the stereochemical relationships developing during the PhS migration are relatively unimportant compared with the Thorpe-Ingold effect. We have also investigated cases where stereochemistry dominates because the Thorpe-Ingold effect is very similar for the two possible products.[10] These cyclisations are excellent approaches to THFs and THPs having stereochemical control and functionality (OH) for further development. In deciding whether protection is necessary to ensure chemoselective cyclisation, all four factors (above) must be considered.

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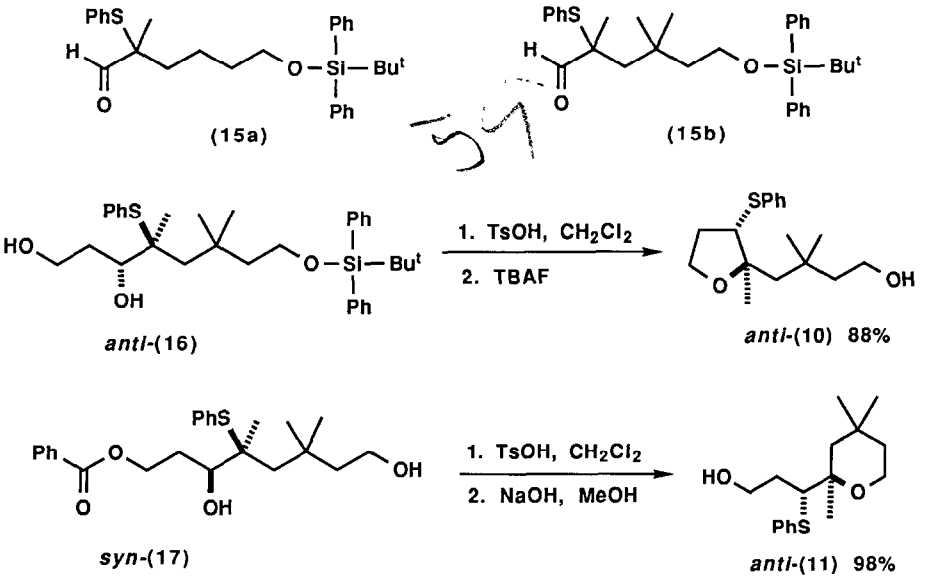
9. The compounds used in this work were made from the aldehydes (**15a** or **b**) by methods similar to those used in previous work, see references 3 and 4. Authentic samples of products were made *via* protected intermediates, e.g. (**16**) and (**17**). In general THFs are characterised by CH_2O geminal, *cis* vicinal, and *trans* vicinal coupling constants of 8-9 Hz, while THPs have geminal couplings of about 11 Hz and the usual axial/equatorial vicinal couplings somewhat larger or smaller than 8-9 Hz.



10. Sansbury, F. H.; Warren, S. *in preparation.*

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