Kinetic and Thermodynamic Control in the Synthesis of Tetrahydro-Pyrans and -Furans from 1,4-Diols by Stereospecific Phenylsulfanyl (PhS) Migration: Competition Between *exo* and *endo* Transition States and between [1,2] and [1,4] Sulfanyl Participation

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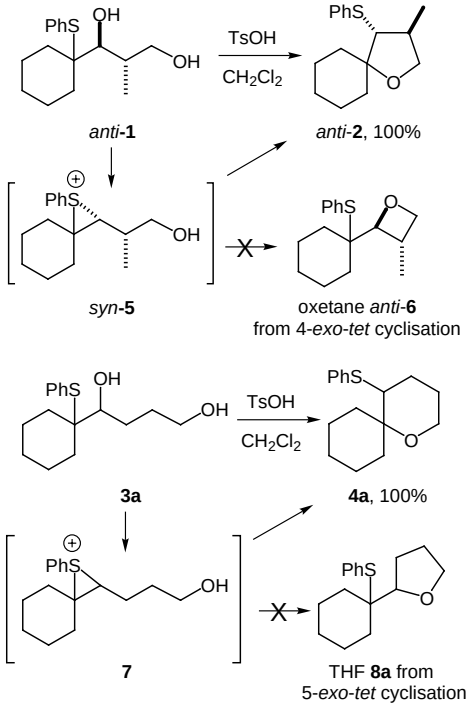
Abstract: The factors controlling the cyclisation of 1,4-diols with PhS migration to give THPs rather than THFs are reassessed. Furthermore we provide evidence for a competition between [1,2] and [1,4] sulfanyl participation and cyclisation onto a five membered cyclic sulfonium salt.

Key words: cyclisations, heterocycles, thermodynamic and kinetic control, sulfur chemistry, rearrangements

The acid-catalysed cyclisation of 1,3-diols[3] such as **1** and 1,4-diols[4] such as **3** occurs by attack of the primary hydroxy group at the more substituted end of the intermediate sulfonium ion **5** or **7** leading to THFs **2** or THPs **4** respectively in spite of the partial *endo* nature (by Baldwin's rules[5,6]) of this mode of attack. Nevertheless there is no doubt that the reaction takes place by a concerted substitution pathway since clean inversion at a chiral migration origin is always observed.[3,4]

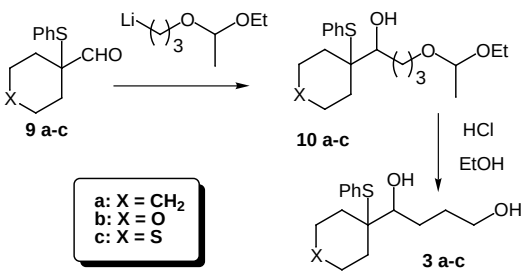


Scheme 1

We have shown that the cyclisation of the 1,3-diols under these conditions is under thermodynamic control and that in the *absence of acid* the sulfonium ion **5**, made from cyclic sulfites, gives 20-30% of oxetanes **6** as kinetic products by the 4-*exo-tet* cyclisation.[5]

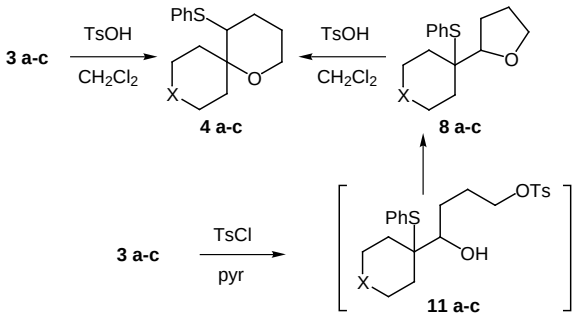
Competition between the 4-*exo-tet* cyclisation and the kinetically less favoured hybrid 6-*endo*/5-*exo-tet* cyclisation to give the THF **2** is probably biased because the oxetane *anti*-**6**, and the transition state leading to it, are destabilised by ring strain. A more equitable competition arises in the cyclisation of 1,4-diols **3** where neither product is strained and we might expect the pure 5-*exo-tet* cyclisation to be more kinetically favoured. This paper concerns thermodynamic *versus* kinetic control in the cyclisation of 1,4-diols such as **3**. Additionally we provide evidence for a competition between [1,2] and [1,4] sulfanyl participation when a second sulfide is present in the molecule undergoing cyclisation.

In order to assess the relative thermodynamic stabilities of the cyclisation products of 1,4-diols, THF and THP respectively, we had to synthesise both compounds independently and study their interconversion under the rearrangement conditions. The potentially kinetic product THF **8a** which would result from a 5-*exo-tet* cyclisation of **7** has never been observed under acidic conditions, but can be made in base (TsCl, pyridine) from the same diol.[4a] We chose to study three series of carbocyclic and heterocyclic six-membered rings based on **9a–c**; X = CH_2, O, and S. The synthesis of the required 1,4-diols was straightforward. Yields were generally excellent and given in Table 1.



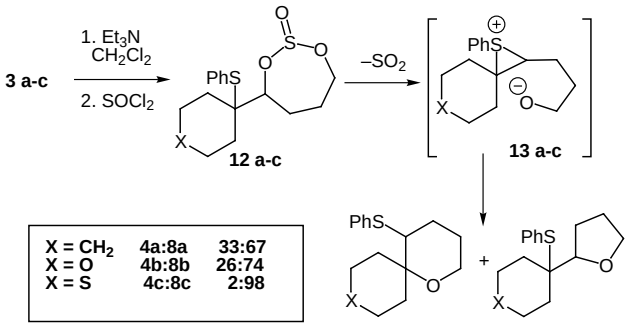
Scheme 2

Acid catalysed rearrangements of the diols **3a–c** gave exclusively the THPs **4a–c**. Compound **3c** needed considerably longer reaction times (11 hours compared with 5 min for **3a** and **3b).** The THFs **8a–c** (the alternative cyclisation products) were obtained by direct ether formation (treatment of diols **3a–c** with TsCl/pyr *via* the primary toluene-*p*-sulfonates **11a–c**). Subjection of these THFs **8a-c**, to acid catalysis gave the THPs **4a–c** again in almost quantitative yields.



Scheme 3

It is clear that the THPs **4a–c** are the thermodynamic products from the acid catalysed rearrangements. The question still remained whether the THP or the THF would be the kinetic product of the reaction. We therefore carried out the rearrangement in the absence of acid to prevent rearrangement of the THFs.[5] The required cyclic sulfites **12a–c** were synthesised from the diols **13a–c** with $SOCl_2$ in basic solution. They decomposed on heating with loss of SO_2 to give the THPs **4a–c** and THFs **8a–c** in ratios of (X = CH_2) 33:67, (X = O) 26:74 and (X = S) 2:98. Presumably both sulfites **12a, b** decompose *via* the episulfonium ion **13a–c** which is captured by a 5-*exo-tet* cyclisation



Scheme 4

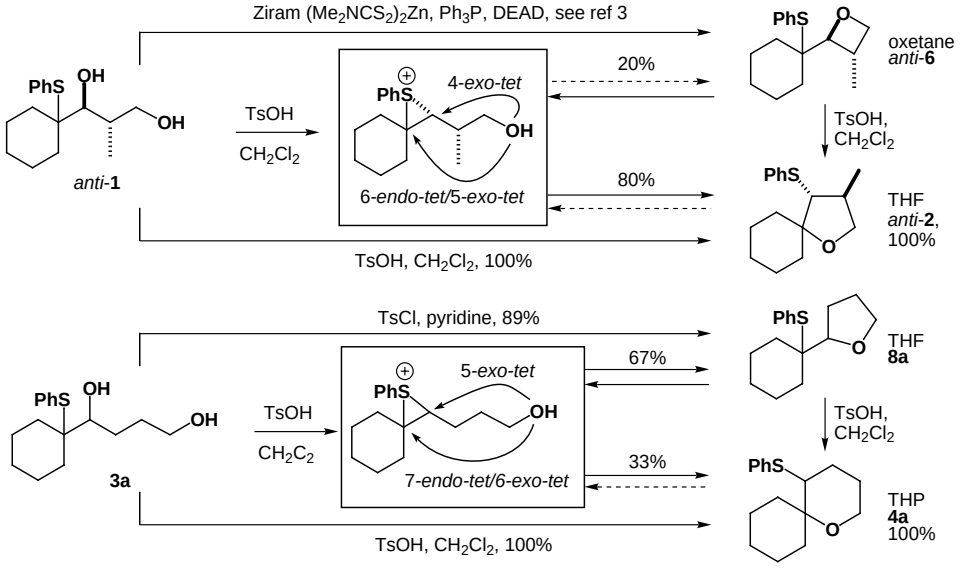
(favoured by Baldwin's rules) to give the THFs **8a, b** as the major kinetic products. We suggest that the ratios of 67:33 and 74:26 (THF:THP) give the approximate ratios of the kinetic products of cyclisation of diols **3a, b**.

Table 1: Yields of starting materials, rearranged THPs and unrearranged THFs

Acetal	Diol	THP[a]	THF	Sulfite
99 % **10a**	99 % **3a**	5 min 100 % **4a**	89 % **8a**	96 % **12a**
89 % **10b**	96 % **3b**	5 min 99 % **4b**	99 % **8b**	96 % **12b**
91 % **10c**	95 % **3c**	11 h 99 % **4c**	96 % **8c**	98 % **12c**

[a]yields and reaction conditions are identical for either synthesis from 1,4-diols **3a–c** or THFs **8a–c**.

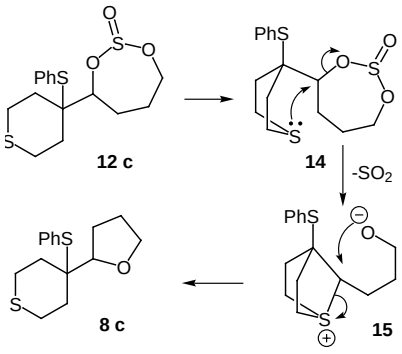
We can summarise the regioselectivities in cyclisation onto the two classes of episulfonium ions in the diagrams below for X = CH_2. All four classes of heterocycles (**2**, **4**, **6** and **8**) can be made in good yield either by acid-catalysed cyclisation for the spirocyclic compounds or by special methods for the others. The *exo:endo* selectivity is



Scheme 5

greater with the larger ring both because of the relaxation of Baldwin's rules and because the THF **8** is less strained than the oxetane **6**. Series **b** with X = O shows the same tendency.[7]

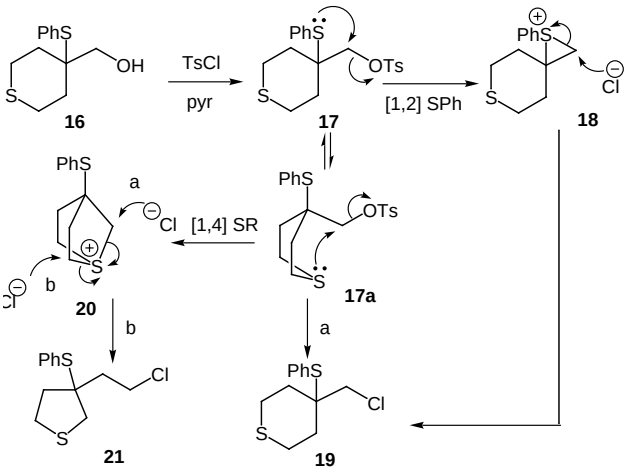
The very high *exo* selectivity in the cyclisation of the sulfide **11c** X=S may be explained by [1,4] SPh participation. Eliel[8] has shown that [1,2] and [1,4] SR participation are about equally efficient, but since a rather stable bicyclic sulfonium ion **15** is formed,[9] [1,4] participation **14** may be favoured in this case. Capture by the tethered alkoxide in **15** can lead only to THF **8c**. The THP can come only from competing [1,2]-SPh participation *via* episulfonium ion **13c**. Apparently the direct interconversion between the bicyclic sulfonium ion **15** and the episulfonium ion **13** would involve a very strained transition state and does not occur. By increasing the time of reflux for the acid catalysed rearrangement of THF **8c** (TsOH in CH_2Cl_2 gives THF:THP ratios of 90:10 after 10 min; 64:36 after 15 min; 38:62 after 30 min; 10:90 after 5h and 0:100 after 11h) we realise thermodynamic control. It is worth noting that THF **8c** is the kinetic product of both the [1,2]-SPh participation and the [1,4]-SR participation.



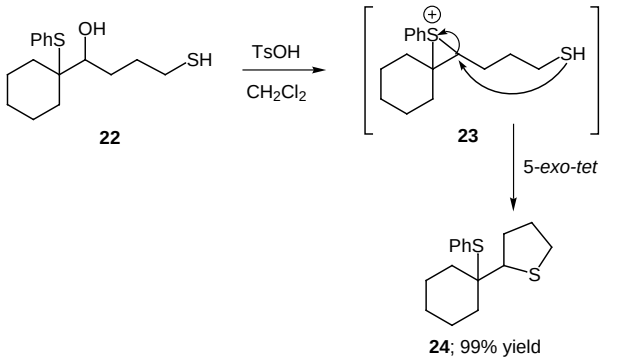
Scheme 6

Further evidence for competitive [1,2] and [1,4]-SR participation came from rearrangement of alcohol **16** (obtained from aldehyde **9c** by $LiAlH_4$ reduction) with TsCl in pyridine to give an inseparable mixture of isomeric chlorides **19** (by path a) and **21** (by path b) in a ratio of 52:48. The bicyclic sulfonium ion **20** from [1,4]-SR participation can be captured by chloride anion to give either **19** or **21**, whereas the spirocyclic sulfonium ion **18** from [1,2] participation can give only the unrearranged chloride **19**.

Related thiols **22** and sulfonamides with a 1,4-relationship between OH and SH or NHTs rearrange under acid catalysis to give only products, e.g. **24**, from 5-*exo-tet* opening, e.g. **23**, of the sulfonium ion.[10] All new compounds gave satisfactory ^1H and ^{13}C NMR spectra and HRMS data.[11]



Scheme 7



Scheme 8

In conclusion we have shown that:

1) The rearranged THPs from the hybrid 7-*endo*/6-*exo-tet* cyclisations of 1,4-diols **3a–c** leading to **4a–c**, are the thermodynamic products of the acid catalysed rearrangement.

2) The pure 5-*exo-tet* cyclisation to give THFs, favoured by Baldwin's rules, is responsible for 60-100% of the kinetic product depending on the substitution.

3) The THFs **8** rearrange rapidly under the reaction conditions to give the thermodynamic products **4**.

4) [1,4]-SR participation can compete with the usual [1,2]-SR participation.

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References and Notes

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(7) The slightly higher THF:THP ratio in the rearrangement of **3b** (X=O) in comparison with **3a** (X=CH_2) might suggest that there is some [1,4]-OR participation but this slight difference is not conclusive. For [1,4]-OR participation see: (a) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc*. **1967**, 89, 4008; (b) Martin, O. R.; Yang, F.; Xie, F. *Tetrahedron Lett*. **1995**, 36, 47.
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(11) Selected experimental and spectroscopic details.
5-(Phenylsulfanyl)-1-oxaspiro[5.5]undecane 4a;
TsOH (3 mg, 17 μmol) was added to a solution of diol **3a** (25 mg, 89 μmol) in CH_2Cl_2 (2 ml). The solution was refluxed for 5 min, cooled to r.t. and filtered through a silica plug using CH_2Cl_2 (5 ml). The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with light petroleum (40-60 °C)-ether (9:1) to give the *tetrahydropyran* **4a** (23.1 mg, 99 %) as an oil; R_f [light petroleum (40-60 °C)-ether (9:1)] 0.4; ν_{max} (film, $CDCl_3$)/cm^{-1} 1600 (SPh); δ_H(400MHz, $CDCl_3$) 7.49-7.17 (5 H, m, SPh), 3.66-3.56 (2 H, m, CH_2O), 3.03 (1 H, dd, *J* 11.17 and 4.26, C*H*SPh) and 2.22-1.05 (14 H, m, 7 x CH_2); δ_C(62.5MHz, $CDCl_3$) 136.1 (*i*-SPh), 13.5 (*m*-SPh), 128.9 (*p*-SPh), 126.6 (*o*-SPh), 75.4 (CO), 59.9 (CH_2O), 55.4 (*C*HSPh), 36.2, 27.1, 26.4, 25.9, 21.2 and 20.5 (6 x CH_2) (Found M^+, 262.1395. $C_{16}H_{22}OS$ requires M, 262.1391); *m/z* 262.1 (25%, M), 165.1 (100, C_4H_8SPh), 136.0 (80, C_2H_3SPh) and 109.0 (5, PhS).
2-[(1'-Phenylsulfanyl)cyclohexyl]tetrahydrofuran 8a;
TsCl (52 mg, 0.25 mmol) was added to a solution of diol **3a** (70 mg, 0.25 mmol) in pyridine (1 mL). The solution was stirred overnight. Ether (20 mL) was added, the solution was washed with HCl (10 ml, 3 M) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with light petroleum(40-60 °C)-ether (9:1) to give the *tetrahydrofuran* **8a** (65 mg, 98 %) as an oil; R_f [light petroleum (40-60 °C)-ether (9:1)] 0.2; ν_{max} (film, $CDCl_3$)/cm^{-1} 1600 (SPh); δ_H(400MHz $CDCl_3$) 7.56-7.24 (5 H, m, SPh), 3.89-3.82 (1 H, dt, *J* 6.67 and 6.68, OCH_AH_B), 3.72-3.70 (2 H, m, OCH_BH_A and CHO) and 2.08-1.18 (14 H, m, 7 x CH_2); δ_C(100MHz $CDCl_3$) 137.3 (*m*-SPh), 131.8 (*i*-SPh), 128.4 (*o*- and *p*-SPh), 84.4 (CHO), 68.7 (CH_2O), 56.6 (*C*SPh), 32.1, 30.2, 26.6, 26.3, 26.0, 21.8 and 21.7 (7 x CH_2) (Found M^+, 262.1389. $C_{16}H_{22}OS$ requires M, 262.1391); *m/z* 262.1 (30%, M), 191.1 (100, $C_6H_{10}SPh$), 153.1 (90, M — SPh), 123.0 (20, CH_2SPh), 81.1 (65, C_6H_9) and 71.1 (65, M — $C_6H_{10}SPh$).
1-[(1'-Phenylsulfanyl)cyclohexyl]-butane-1,4-sulfite 12a.
Thionyl chloride (21 mg, 13.2 μl, 0.17 mmol) was added to a solution of diol **3a** (50 mg, 0.17 mmol) and Et_3N (36 mg, 48 μl, 0.35 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred for 5 min. Saturated NH_4Cl (1 mL) was added and the solution was extracted with ether (3 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with light petroleum (40-60 °C)-ether (9:1) to give the *sulfite* **12a**; (41.2 mg, 96 %) as an oil; R_f [light petroleum(40-60 °C)-ether (9:1)] 0.2; ν_{max} (film, $CDCl_3$)/cm^{-1} 1550 (SPh); δ_H(400MHz, $CDCl_3$) 7.56-7.28 (5 H, m, SPh), 4.78 (1 H, d, *J* 10.56, CHO), 4.18-4.02 (2 H, m, CH_2O), 2.51 (1 H, dt, *J* 15.14 and 3.63, $CH_AH_BCH_2$) and 1.98-1.21 (13 H, m, $CH_AH_BCH_2$ and 5 x CH_2); δ_C(100MHz, $CDCl_3$) 137.7 (*m*-SPh), 130.6 (*i*-SPh), 129.2 (*p*-SPh), 128.9 (*o*-SPh), 79.5 (CHO), 65.5 (CH_2O), 50.8 (*C*SPh), 30.8, 30.7, 29.6, 27.5, 26.3, 21.8 and 21.7 (7 x CH_2) (Found M^+, 326.1010. $C_{16}H_{22}O_3S_2$ requires M, 326.1010); *m/z* 326.1 (80%, M), 262.1 (70, M — SO_2), 191.1 (100, $C_6H_{10}SPh$) and 109.0 (50, PhS).
By ^1H NMR the sulfite **12a**; X=CH_2 decomposed over 7 days to give the tetrahydropyran **4a** and tetrahydrofuran **8a** (67:33) as an inseparable mixture, identical spectroscopically to that obtained previously.

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