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Secondary and Tertiary Alcohols as Nucleophiles in the Stereospecific Synthesis of Substituted Tetrahydrofurans by Cyclisation of 1,3-Diols with Phenylsulfanyl Migration

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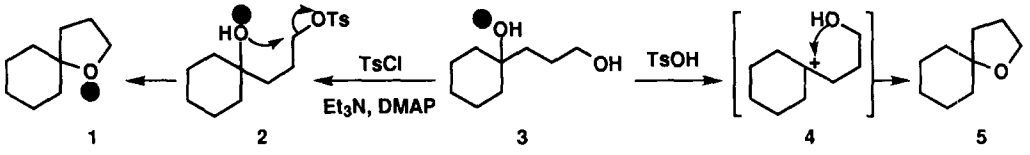
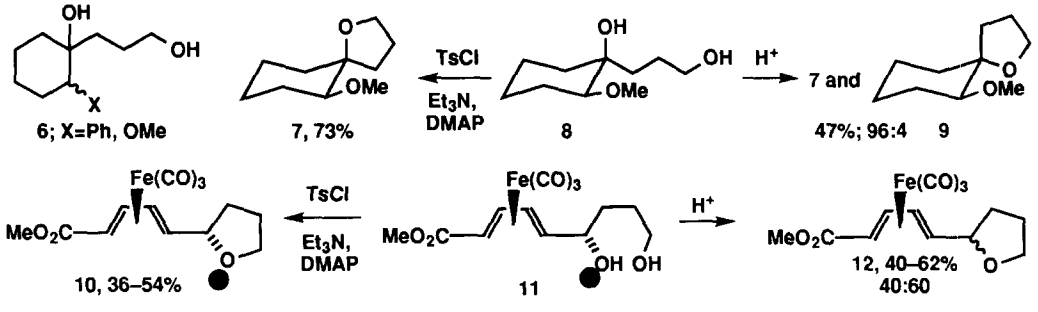
Abstract: Rearrangement of a series of 4-phenylsulfanyl-1,3-diols with TsOH gives tetrahydrofurans stereospecifically and in high yield even if the nucleophile is a secondary or tertiary alcohol. We discuss the stereochemistry and acceptable substution patterns of the diols which will carry out this reaction and define their limits.

The cyclisation of 1,4-diols to give tetrahydrofurans sounds like the simplest example of an intramolecular substitution reaction. Diol **3** with a primary and a secondary alcohol cyclises in TsCl and base by the S_N2 mechanism **2** with the loss of the primary OH group[1] and by the S_N1 mechanism **4** in acid with the loss of the tertiary OH group.[2, 3] Except for any oxygen label, the products **1** and **5** are the same.

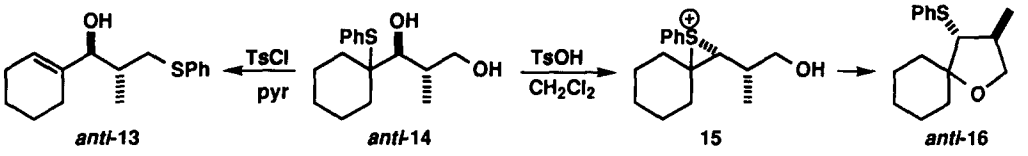


Further work, chiefly by Paquette, Grée and their groups has shown that the reaction is not so simple. Minor modifications such as the addition of a Ph or MeO **6** substituent,[1] and their stereochemistries, e.g. **8** can encourage the primary OH group to leave, even in acid solution, e.g. to give mainly **7**, while labelling and stereochemistry is also lost in acid solution with iron tricarbonyl cation complexes from **11**.[4] Some of these cyclisations occur in surprisingly poor yield.



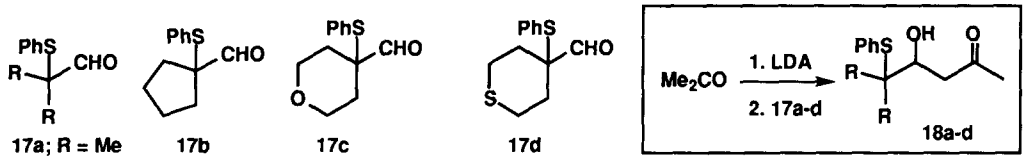
We have previously shown[5] that 4-phenylsulfanyl-1,3-diols, e.g. *anti*-**14** cyclise under very similar conditions to give tetrahydrofurans *anti*-**16** with PhS migration. This approach has some advantages. The yields are generally almost quantitative, the reaction is stereospecific with inversion occurring at both the migration origin and terminus, and the 1,3 relationship between the alcohols in the starting material allows us to use reliable stereoselective aldol reactions to produce single diastereoisomers or enantiomers[6] of the products. Mechanistic and stereochemical ambiguities disappear because the THF can be formed only if the primary alcohol captures the episulfonium ion **15** formed by PhS-assisted loss of the secondary alcohol. The

TsCl reaction gives rise to a completely different product - the allylic alcohol *anti*-**13** from a [1,4]-PhS shift.[7] The choice of the leaving group determines the distance, [1,2] or [1,4], of the PhS migration rather than the direction of the cyclisation.



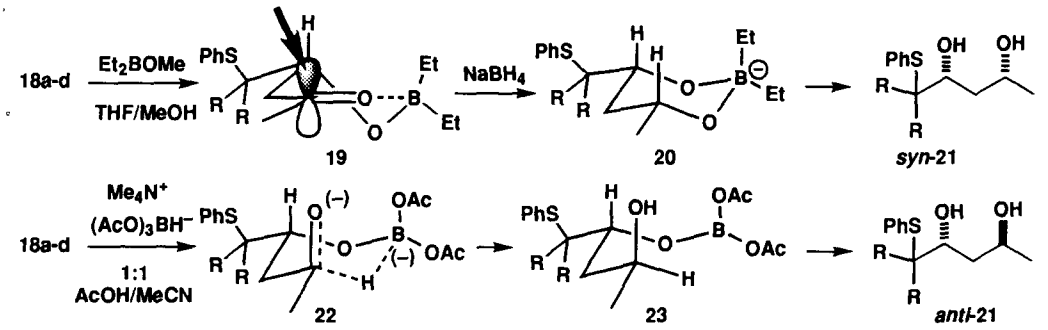
anti-**13** *anti*-**14** **15** *anti*-**16**

A salient feature of this methodology was the cyclisation of a primary alcohol onto an episulfonium ion created by the loss of a secondary alcohol. Indeed we had supposed that this was a limitation. We assumed that a secondary or tertiary alcohol would take part in the acid-catalysed reaction as a leaving group rather than a nucleophile because simple data[8] suggested that [1,4]-RS participation is about as efficient as [1,2]. We now report that this limitation does not exist: the capture of episulfonium ions by both secondary and tertiary alcohols is an efficient and high yielding route to THFs (up to certain limits). We comment on the effects of stereochemistry and of structural variations of the cyclising nucleophile.



17a; R = Me **17b** **17c** **17d** **18a-d**

The key compounds in our chemistry are the aldol products **18** from the lithium enolate of acetone and the 2-phenylsulfanyl aldehydes **17**. These aldehydes are excellent electrophiles for the aldol reaction as they cannot enolise and the extra reactivity from the α-PhS group compensates for steric hindrance. The required secondary alcohols could be made by reduction of the ketone in **19** and we needed complimentary stereoselective methods to give *syn* and *anti* diols in high yields.



19 **20** *syn*-**21**

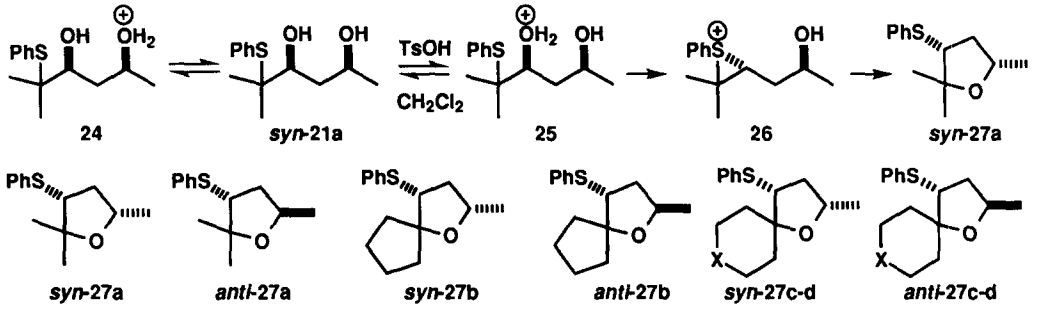
22 **23** *anti*-**21**

We found the methods of Prasad and Evans to be the best. Prasad's reduction with $NaBH_4$ in the presence of the chelating Lewis acid Et_2BOMe[9] (1 hr at –78 °C) delivers axial hydride to the intermediate **19** and gave essentially complete selectivity in favour of the *syn* diol **21**. Evans's triacetoxyborohydride[10] (1 week at –20 °C) delivers hydride intramolecularly **22** and gave high, though not complete, *anti* selectivity [table 1; the ratio with $LiAlH_4$ is given for comparison, the crystalline diastereoisomers are surprisingly easy to separate (R_f difference 0.1-0.2) by column chromatography]. In the intermediate **19** and the transition state **22** the large PhS-CR_2 group occupies an equatorial position and so enhances the stereoselectivity.

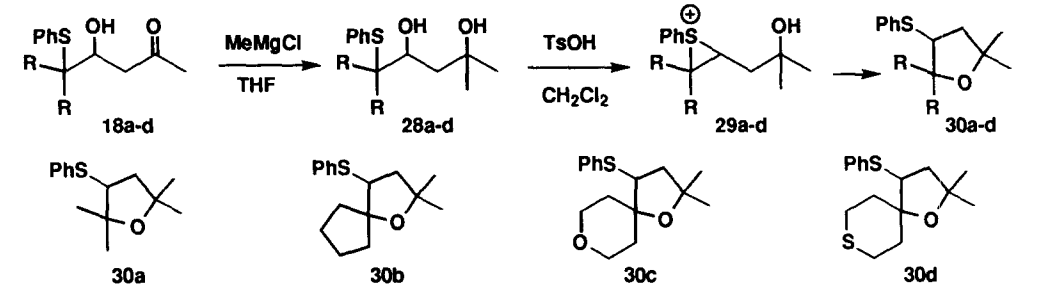
Table 1: Synthesis and Rearrangement of Diols **21** Yields of diols are all near quantitative.

	Aldol	Reduction Ratio *syn*:*anti*-**21**			Rearrangements ($TsOH/CH_2Cl_2$)			
Aldehyde	Yield (%)	$LiAlH_4$	Prasad	Evans	Product	Yield (%)	Product	Yield (%)
17a	92	60:40	>98:2	7:93	*syn*-**27a**	99	*anti*-**27a**	98
17b	90	70:30	>98:2	10:90	*syn*-**27b**	99	*anti*-**27b**	99
17c	90	67:33	>98:2	17:83	*syn*-**27c**	94	*anti*-**27c**	96
17d	89	61:39	>97:3	94:6	*syn*-**27d**	99	*anti*-**27d**	99

Rearrangement of all eight diols *syn*- and *anti*-**21a-e** gave excellent yields of the corresponding THFs **27** by stereospecific [1,2]-PhS migration (table 1). Stereochemistry is inverted at the migration terminus and retained at the nucleophilic centre. In no case was any product from [1,4]-PhS migration detected. It is difficult to believe that either secondary alcohol is more basic so low concentrations of cation **25** must rearrange at least two orders of magnitude faster than similar low concentrations of cation **24**. The heteroatoms in the other ring of **21c** and **21d** did not interfere with the reaction.[11]



A more severe test comes from the rearrangement of the tertiary alcohols resulting from the addition of MeMgCl to the same hydroxyketones **18**. Remarkably all these diols **28** rearranged to THFs **30** cleanly and in reasonable yield without any products of dehydration of the tertiary alcohols with or without PhS migration (table 2). The rate of [1,2]-PhS migration to give the episulfonium ions **29** must be very high if it is faster than loss of water from a tertiary alcohol and TsOH in refluxing CH_2Cl_2. These products **30** are all cyclic di-tertiary-alkyl ethers.



We introduced a stereogenic tertiary centre by addition of PhMgBr to the hydroxyketone **18b**. The reaction was not very stereoselective, giving a 36:64 mixture of *anti*- and *syn*-diols[12] **31** in 87% yield. Cyclisation of *anti*-diol **31** with $TsOH/CH_2Cl_2$ gave for the first time a mixture of products: *anti*- and *syn*-THFs **32** (ratio 33:66) in 95% yield. *Syn*-THF **32** is the product from retention at the tertiary centre and *anti*-

THF **32** presumably comes from epimerisation *via* a tertiary benzylic cation. Treatment of *syn*-**31** under the same conditions gave also a mixture of *anti*- and *syn*-THFs **32** (ratio 60:40) in 93% yield – again retention of configuration of the nucleophile leads to the major product. Reintroducing the 33:67 and 60:40 mixtures of *anti*- and *syn*-THF **32** to the conditions of the reaction gave both mixtures enriched in the more thermodynamically stable *anti*-THF **32**.

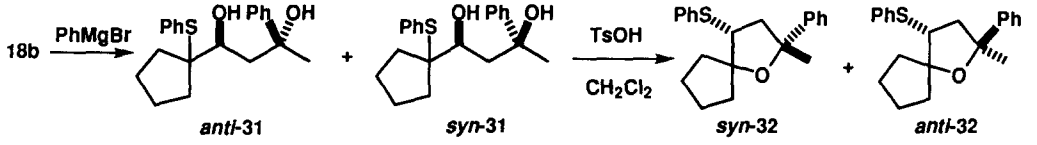


Table 2; Preparation of THFs from secondary/tertiary diols **28**

compound	series a, yield (%)		series b, yield (%)		series c, yield (%)		series d, yield (%)	
diol **28**	**28a**	84	**28b**	87	**28c**	89	**28d**	90
THF **30**	**30a**	99	**30b**	99	**30c**	76	**30d**	98

In conclusion, we have shown that secondary and tertiary alcohols act as nucleophiles in cyclisation of 1,3-diols to THFs with PhS migration. Secondary alcohols react stereospecifically. A secondary alcohol activated by [1,2]-PhS participation is more reactive in acid solution than a tertiary alcohol. All the reactions go in near quantitative yield and give synthetically useful products.

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12. The labelling of compounds as *syn* or *anti* usually follows Masamune's suggestion[13] of drawing the chain or ring in its best conformation and noting the relationship between the two most important groups, such as the two OH groups in **21**. This arbitrary method becomes particularly so with compounds **31** and **32**. It seems most helpful to use the two OH groups in **31** but the PhS and Ph groups in **32**.
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