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Stereoselective Synthesis of 3-(Phenylsulphonyl)-2,5 Disubstituted Tetrahydrofurans *via* 5-*Endo*-trig Ring-Closure Reactions

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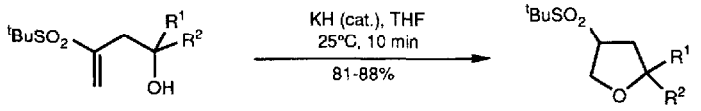
Key Words: cyclization; 5-*endo*-trig; stereoselective; tetrahydrofurans; vinylic sulphone

Abstract: *The synthesis and stereoselective 5-*endo*-trig cyclization reactions of a series of sulphonyl-substituted homoallylic alcohols are reported. Some competing reactions are described, and a model is proposed to account for the observed stereoselectivity.*

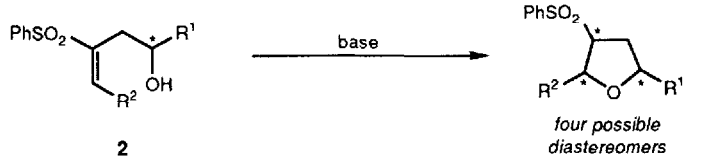
The Michael-acceptor property of vinylic sulphones is well-documented, and has contributed to the widespread use of this functional group in organic synthesis.[1] Carbon,[2] nitrogen,[3] oxygen[4] and other heteroatomic nucleophiles[5] react efficiently at the electrophilic β-position. Cyclic ethers have been synthesized by the intramolecular attack of alcohols on vinylic sulphones. An early report[6] described the synthesis of 4-(*tert*-butylsulphonyl)-2-substituted tetrahydrofurans *via* 5-*endo*-trig[7] cyclization of (*tert*-butylsulphonyl)-substituted homoallylic alcohols **1** using catalytic base (Scheme 1). The cyclization substrates were synthesized by nucleophilic addition to benzaldehyde or symmetrical ketones of the alkenylzinc species generated from 2-(*tert*-butylsulphonyl)-3-bromopropene.[8]



1

Scheme 1

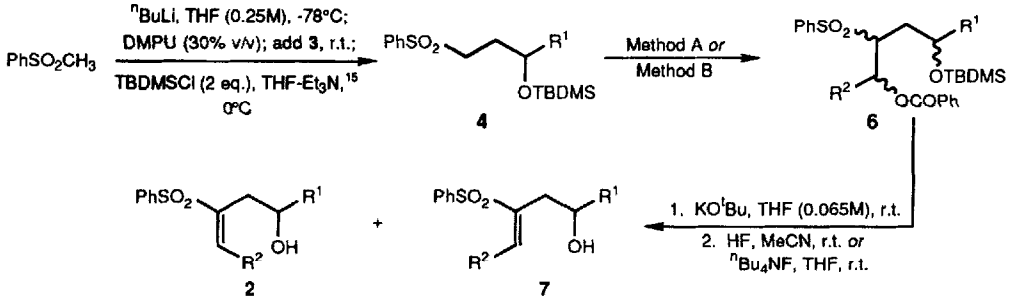
We became interested in the stereochemical aspects of this unusual cyclization process. In particular, we were keen to assess the extent of 1,4-asymmetric induction in the ring-closure reactions of more highly-substituted substrates **2** bearing a substituent on the β-position of the vinylic sulphone group (Scheme 2).



2

Scheme 2

Attempts to prepare **2a** ($R^1 = R^2 = Me$) *via* nucleophilic ring-opening of 2-methyloxirane with (*E*)-1-lithio-1-(phenylsulphonyl)propene[9] gave consistently low yields, even in the presence of added $MgBr_2$[9] or $BF_3{\cdot}OEt_2$.[10] We reasoned that **2** would be accessible *via* epoxide ring-opening by a sulphone-stabilized carbanion prior to formation of the α,β-unsaturated linkage.[11] Reaction of lithio(phenylsulphonyl)methane with epoxides **3** followed by protection *in situ* of the resulting secondary alkoxides gave silyl ethers **4** (Scheme 3). Reaction of lithiated **4** with aldehydes **5** followed by benzoylation[12] either *in situ* (**4b, i, j**) or in a separate step gave benzoates **6** as diastereomeric mixtures. Potassium *tert*-butoxide-mediated elimination[13] of the elements of benzoic acid from **6** followed by deprotection[14] and chromatography gave **2**, and in some cases the geometric isomers **7** in high overall yields for the five-step, three-component sequence (Table 1).



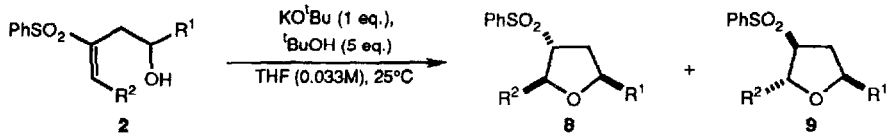
Method A: ^{n}BuLi, THF (0.2M), -78°C; add **5**; PhCOCl, -78°C to r.t.
Method B: 1. ^{n}BuLi, THF (0.2M), -78°C; add **5**; HOAc-THF, -78°C; 2. ^{n}BuLi, THF (0.25M), -78°C; PhCOCl, -78°C to r.t.

Scheme 3

Entry	R^1	R^2	Yield of **4**[16]	Yield of **6**[17] (Method)	Yield of **2** + **7**[18]	Ratio **2** : **7**
a	Me	Me	85	71 (B)	92	100:0
b	Me	^{i}Pr		57 (A)	80	38:62
c	Me	CH_2OBn		41 (B)	65[19]	75:25
d	Me	Ph		89 (B)	85	86:14
e	Me	2,4-$(MeO)_2C_6H_3$		83 (B)	94	83:17
f	$^nC_{10}H_{21}$	Me	77	66 (B)	68	100:0
g	CH_2OBn	Me	71	67 (B)	85	100:0
h	CH_2OBn	2,4-$(MeO)_2C_6H_3$		70 (B)	82	86:14
i	$(CH_2)_2C(Me)O(CH_2)_2O$	Me	77	96 (A)	69[20]	100:0
j	Ph	Me	96	89 (A)	55	100:0
k	Ph	2,4-$(MeO)_2C_6H_3$		80 (B)	55	80:20

Table 1

Initial cyclization reactions were carried out on THF solutions of **2** using potassium *tert*-butoxide as the base. Extensive experimentation established that cyclization proceeded more slowly and cleanly when 5 eq. *tert*-butanol was added to the reaction mixture prior to the addition of base. Reactions were carried out at 25°C[6] in a thermostatted bath: even slight decreases in temperature retarded the cyclization process (Scheme 4).



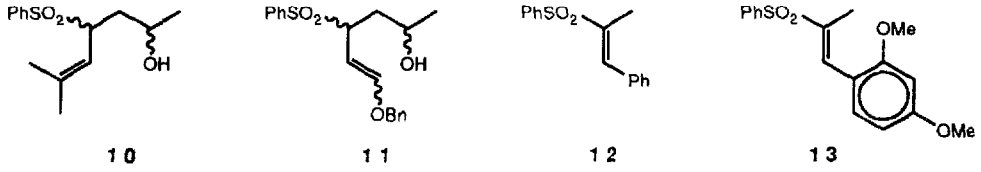
Scheme 4

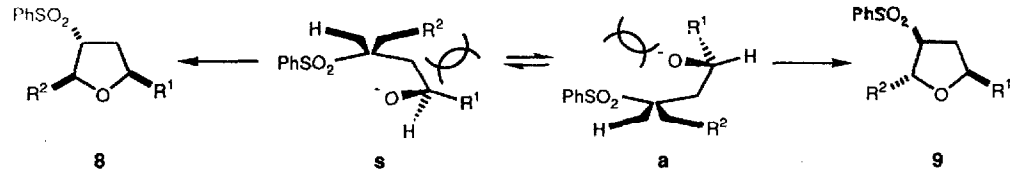
Of the four possible diastereomeric tetrahydrofuran products only **8** and **9**, in which the R^2 and phenylsulphonyl groups are *anti* were formed. In all cases **8** and **9** were separable by chromatography. The yields and diastereomer ratios are presented in Table 2. The structures of **8** and **9** were assigned in all cases by n.O.e. experiments,[21] and in the case of **9a**, **8d**, **8f**, **8j** and **9j** by X-ray crystallography.[22]

Substrate	R^1	R^2	time (min)	Yield of **8** + **9**	Ratio **8** : **9**
2a	Me	Me	40	81	57:43
2b	Me	^{i}Pr	1	0	-
2c	Me	CH_2OBn	1	0	-
2d	Me	Ph	15	18	100:0
2e	Me	2,4-$(MeO)_2C_6H_3$	16	60	80:20
2f	$^nC_{10}H_{21}$	Me	16	81	57:43
2g	CH_2OBn	Me	23	86	64:36
2h	CH_2OBn	2,4-$(MeO)_2C_6H_3$	90	76	67:33
2i	$(CH_2)_2C(Me)O(CH_2)_2O$	Me	15	61	50:50
2j	Ph	Me	6	76	67:33
2k	Ph	2,4-$(MeO)_2C_6H_3$	11	19	80:20

Table 2

Exposure of of substrates **2b** and **2c** to the cyclization conditions resulted in rapid isomerization to the allylic sulphones **10** and **11**, respectively. The low yields of tetrahydrofurans obtained from reaction of **2d** and **2k** may be ascribed to the predominant formation of **12** (from **2d**) and **13** (from **2k**), presumably *via* an uncoupling reaction involving loss of R^1CHO. Alkene **13** was formed to a lesser extent in the reaction of **2e**. It would appear that the electron-rich 2,4-dimethoxyphenyl group suppresses the fragmentation pathway to some extent, presumably by destabilizing the conjugate base of **13**; the lower yield of tetrahydrofuran obtained from reaction of **2k** than from reaction of **2e** may reflect the additional enthalpic favourability of benzaldehyde formation concomitant with fragmentation of the former. That the 5-*endo*-trig cyclization reaction is kinetically controlled was established by the quantitative recovery of unchanged **8a** upon isolation and re-exposure to the cyclization conditions. Inspection of the available reactive conformations of **2** indicates that both conformers **s** and **a** leading respectively to 2,5- *syn* and *anti* tetrahydrofurans **8** and **9** suffer destabilizing interactions (Scheme 5).[23] This may account for the modest *syn*-selectivity observed in most cases.





Scheme 5

In summary, readily available sulphonyl-substituted homoallylic alcohols **2** undergo rapid, high-yielding 5-*endo*-trig cyclization to give substituted tetrahydrofurans **8** and **9** with low to moderate stereoselectivity. We are currently investigating the effect of double bond geometry on cyclization stereochemistry,[23] and are looking at methods for the elaboration of **8** and **9**.[24] The results of these studies will be reported in due course.

Acknowledgements

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References and notes

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15. 2 Eq. TBDMSCl in THF (1M) was treated with 2.5 eq. Et_3N and the resulting suspension centrifuged to remove triethylammonium chloride prior to use of the supernatant solution.
16. Yields cited herein (%) are for isolated, pure materials, characterized by ^1H nmr, ir, ms and elemental combustion analysis.
17. For Method B, yields cited are for the two steps from **4**.
18. Yields cited are for the two steps from **6**.
19. Elimination carried out at -78°C. Use of higher temperatures resulted in the formation of **11**.
20. Deprotection carried out using $^nBu_4NF$ in THF.
21. For example, **8f** showed a 5% n.O.e. between H-2 and H-5, whilst **9f** exhibited a 0% n.O.e. between H-2 and H-5. We thank Mr R. N. Sheppard of this department for these experiments.
22. We thank Dr D. J. Williams and Ms A. M. Z. Slawin of this department for these determinations.
23. A preliminary experiment has shown that **7b** cyclizes rapidly to give a 1:8 mixture of **8b** and **9b**, whilst **7a** undergoes rapid isomerization to **2a** followed by cyclization to give **8a** and **9a**.
24. For example, treatment at -93°C of a THF solution of **8a** with ^{n}BuLi followed by DMPU-THF and PhSSPh effected stereoselective phenylsulphenylation (90%; 20:1 retention:inversion of C-3 configuration).

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