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CYCLOFUNCTIONALISATION OF EPOXYALCOHOL DERIVATIVES. 1. DELIVERY OF FUNCTIONALISED CARBON FOR STEREOSPECIFIC SYNTHESIS OF DIHYDROFURANS AND DIHYDROXYACIDS

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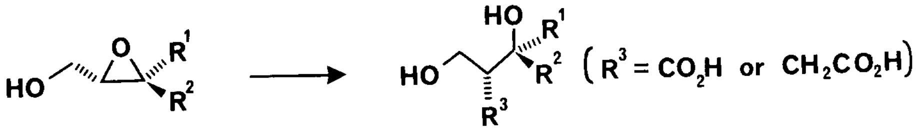
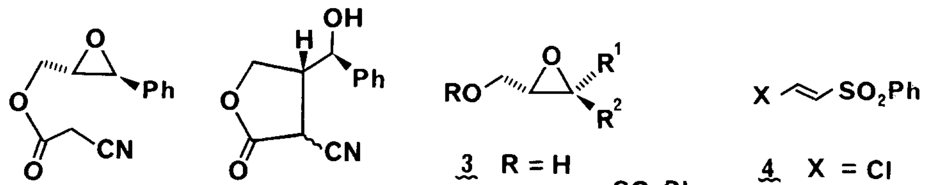
Abstract: E-2-(Phenylsulfonyl)vinyl ethers of 2,3-epoxyalcohols are stereospecifically rearranged to 3-(phenylsulfonyl)-4-(1-hydroxyalkyl)-4,5-dihydrofurans on treatment with LDA. Oxidation of these compounds or the derived des-sulfonyl compounds provides esters or lactones which correspond to regiospecific delivery of $-CO_2H$ or $-CH_2CO_2H$ to C-2, with inversion.

The addition of asymmetric epoxidation[1] to existing methods for stereocontrolled epoxyalcohol synthesis[2] has amplified the synthetic utility of these substances[3]. After initial OH derivatisation, intramolecular delivery of oxygen or nitrogen to C-2 has found recent application to the synthesis of polyols[4,5] and aminosugars[5]. Absent from these cyclofunctionalisations is a process for delivery of carbon. Herein, we present methodology for the transformations shown in Eq. 1.



Eq 1

Attempts to cyclise cyanoester (1) to lactone (2) failed presumably for stereoelectronic reasons[6], the enolate π-system being unable to achieve colinearity with the oxirane C2-O bond. Use of a vinyl anion seemed a possible solution to this problem: some precedent exists in the 5-exo-Tet cyclisation of O-lithiophenyl glycidyl ethers[7]. In the event, choice of phenylsulfonyl as the activating group allowed α-deprotonation[8], cyclisation and subsequent functional group manipulation[9].



1 2

3 R = H
6 R = $CH=CHSO_2Ph$

4 X = Cl
5 X = SO_2Ph

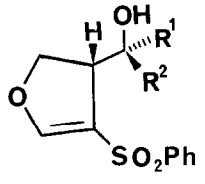
Reaction of a 2,3-epoxyalcohol (3) with E-chlorovinyl phenyl sulfone (4)[10] or E-1,2-bis-(phenylsulfonyl)ethene (5)[11] [NaH-THF] produced ether (6), reagent (5) being preferred for maximum yields. Upon generation of the vinylsulfonyl carbanion[12] [LDA, -70^{o}] followed by warming to 0^{o}, cyclisation with C-2 inversion occurred to give the dihydrofuran (7). Table 1 shows results for some representative 2,3-epoxyalcohols. The 3,4-epoxyalcohol (8) was similarly converted to (9).

Table 1

	Epoxyalcohol[a]		Phenylsulfonylvinyl ether[b,d]	Dihydrofuran[c,d]
	R^1	R^2	(Method A, % yield) (Method B, % yield)	(% yield)
3a	H	Ph	6a (62) (77) mp 54-5^{o}	7a (72) mp 99-101^{o}
3b	Ph	H	6b (55) (74)	7b (50) mp 120-2^{o}
3c	CH_2OBn	H	6c (58) (76)	7c (51) mp 140-2^{o}
3d	Me	Me	6d (59)	7d (59)

Notes

(a) Racemic substances from mCPBA oxidation of the allylic alcohols.
(b) From (3) with 1.2 eq (4) [Method A] or 1.2 eq (5) [Method B] and 1.2 eq NaH, THF, -20^{o} to 0^{o} for 0.5 h.
(c) 1.3 eq LDA in THF-hexanes, -70^{o} to 0^{o} for 0.25 h.
(d) Isolated, uncorrected yield of chromatographically pure oil or crystalline solid. All new compounds gave appropriate microanalyses and mass spectra. For selected spectroscopic data, see Footnote 13.



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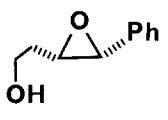

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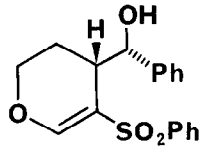

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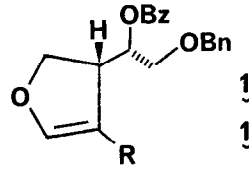
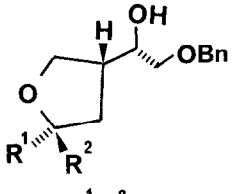
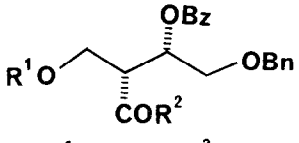


10 R = SO_2Ph
11 R = H

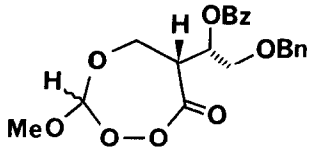
(Bn = $PhCH_2$; Bz = PhCO)



12 R^1R^2 = H, OMe
13 R^1R^2 = O



14 R^1 = H , R^2 = OMe
15 R^1 = CHO, R^2 = SO_2Ph
16 R^1 = CO_2Me, R^2 = OH
17 R^1 = CO_2Me, R^2 = OMe



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Modes for oxidative elaboration of these dihydrofurans are illustrated by the chemistry of (7c). After benzoylation to (10), desulfonylation [Na-Hg, NaH_2PO_4, MeOH, -20 to 0^o] gave (11) with a small amount of (12) formed via Michael addition-desulfonylation. Jones' oxidation of this mixture then afforded lactone (13)[13] in 67% overall yield from (7c). This corresponds to delivery of $-CH_2CO_2H$ to C-2.

Direct ozonolysis [5:1 CH_2Cl_2:MeOH at -70^o then Me_2S to 20^o] of benzoate (10) gave methylester (14)[13] in 70% yield. The oxosulfone (15) is the presumed precursor of (14), formate cleavage being catalysed by acid produced by facile solvolysis of the α-oxosulfone moiety[14]. An unusual but potentially useful "inversion" of blocking pattern was observed when the ozonolysis of (10) was run in 5:1:1 CH_2Cl_2:MeOH:pyridine. The major product (72%) was the carboxylic acid-methyl carbonate (16). Esterification [CH_2N_2] gave (17), identical in all respects with a sample prepared from (14) with MeOCOCl-pyridine. A possible explanation for the formation of acid (16) would involve pyridine-induced cyclisation of an intermediate methoxyhydroperoxide to (18) followed by β-elimination with peroxide bond cleavage.

Other aspects of the formation and chemistry of sulfonyldihydrofurans and applications to natural products synthesis will appear in forthcoming papers.

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References and Notes:

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   We thank Prof. Barry Sharpless for many helpful discussions on aspects of epoxy-alcohol formation and chemistry.
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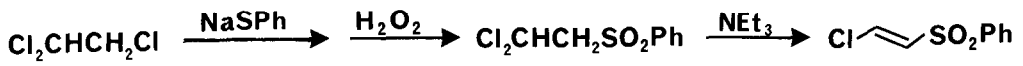
10. This substance, mp 50-51° was most conveniently prepared by the following sequence:



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12. Workup at -70° (H_2O) returned mostly (6), and quenching with TMSCl gave the expected vinylsilane. The Z isomer of (6c) could be prepared from Z-$PhSO_2CH{=}CHSO_2Ph$ and the alkoxide, but failed to produce any dihydrofuran on LDA treatment, indicating that the sulfonylvinyl carbanion has configurational stability at 0°C. These cyclisations were strongly retarded by the presence of an additional C-2 substituent on the epoxy-alcohol; we are currently exploring other aspects of inter and intramolecular reactions involving sulfonylvinyl anions.

13. Selected spectroscopic parameters: (6a), PMR (CDCl3): δ 3.24 (m, 1), 3.77 (d, 1, J=2.5), 4.12 (ABX, 2, J=3, 5.5 and 12), 5.82 (d, 1, J=13) and 7.2-8.0 (m, 11). (6b), PMR (CDCl3): δ 3.4-3.8 (m, 3), 4.20 (d, 1, J=4), 5.58 (d, 1, J=12) and 7.2-7.9 (m, 11). (7a), PMR (CDCl3): δ 2.74 (d, 1, J=4.5, exch. by D2O), 3.37 (m, 1), 4.10 (t, 1, J=10), 4.54 (dd, J=7.5 and 10), 5.18 (d, 1, J=2.5 after D2O exch.) and 7.2-8.1 (m, 11). (7b), PMR (CDCl3): δ 3.28 (m, 1), 4.1-4.3 (m, 3, 1H exch. by D2O), 5.83 (d, 1, J=8 after D2O exch.) and 7.1-8.0 (m, 11). (13), IR:ν_{max} = 1780, 1725 cm^{-1} (film). PMR (CDCl3): δ 2.65 (m, 2), 3.14 (m, 1), 3.66 (ABX, Z, J=5, 6 and 11), 4.15 (dd, 1, J=8 and 10), 4.44 (t, 1, J=8), 4.57 (s, 2), 5.37 (q, 1, J=5) and 7.3-8.2 (m, 10). (14), IR:ν_{max} = 3200 (br), 1740 and 1715 cm^{-1} (film). PMR (CDCl3): δ 2.62 (br. s, 1, exch. by D2O), 3.18 (q, 1, J=5), 3.66 (s, 3), 3.7-4.0 (m, 4), 4.57 (AB, 2, J=13), 5.65 (q, 1, J=5) and 7.25-8.1 (m, 10).

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