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CYCLOFUNCTIONALISATION OF EPOXYALCOHOL DERIVATIVES. 4. CYCLISATION OF SULFONYLACETATE DIANIONS: A SYNTHESIS OF "MeBMT".

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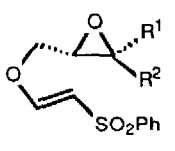
Abstract: *α,α-Dianions, derived from arenesulfonylacetate esters of 2,3-epoxyalcohols, cyclised to give 3-arenesulfonyl-4-(1-hydroxyalkyl)-γ-butyrolactones. Dianion fragmentation to regenerate the epoxyalcohol was a competing, substrate-dependent process. Sulfonyllactone (9) was elaborated efficiently to an advanced intermediate for the unusual aminoacid "MeBMT" (5), and also to stereodefined cyclopropane derivatives.*

In an earlier paper[1] we described the cyclisation of anions derived from the sulfonylvinyl ethers (**1**) to the dihydrofurans (**2**), which were converted to the lactones (**3**) in moderate overall yields. An efficient route from (**2**) to the versatile sulfonyllactones (**4**) could not be found. In this paper, continuing our exploration[2] of processes which deliver functional groups to C-2 of epoxyalcohols , we describe a two-step route from epoxyalcohols to (**4**), and reactions of these polyfunctionalised substances which result in : (a) a formal synthesis of the unusual aminoacid "MeBMT" (**5**), and (b) a convenient route to 1,2-disubstituted and 1,2,3-trisubstituted cyclopropanes whose relative and absolute stereochemistry is fully defined by that of the starting epoxyalcohol.



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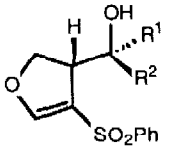

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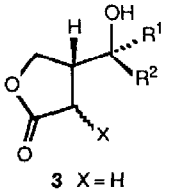
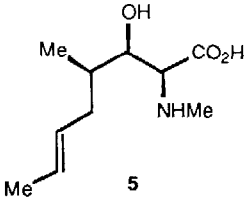
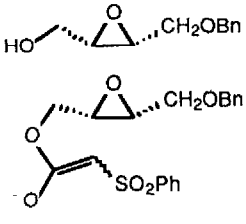


3 X = H
4 X = SO_2Ph



5

Racemic *cis*-epoxyalcohol (**6**) was converted [1.2 eq. $PhSO_2CH_2CO_2H$, 0.6 eq. DCCI, 0.05 eq. DMAP, CH_2Cl_2, RT, 20h][3] to ester (**7**). The derived monoanion (**8**) is not stereoelectronically predisposed to cyclise by C-C bonding, and solutions of (**8**)-Li or (**8**)-Na were relatively stable.[4]



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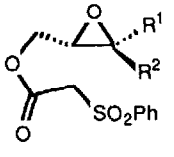
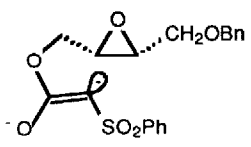


7 $R^1 = CH_2OBn$, $R^2 = H$, Ar = Ph
11 $R^1 = CH_2OBn$, $R^2 = H$, Ar = 4-MePh
12 $R^1 = R^2 = H$, Ar = 4-MePh
13 $R^1 = R^2 = Me$, Ar = 4-MePh
17 $R^1 = H$, $R^2 = CH_2OBn$, Ar = Ph
19 $R^1 = H$, R^2 = Ar = Ph

In contrast, treatment of (**7**) with LDA [2.2 eq., THF, approx. 0.1M in (**7**), -70° to -10°, then HOAc quench] gave the desired sulfonyllactone (**9**) (65-70% overall from (**6**). That (**9**) did *not* form when LDA was replaced by $LiN(TMS)_2$ is good evidence for the intermediacy of dianion (**10**), and indicates the base strength needed to further deprotonate (**8**): $HN(TMS)_2$, pK = 27; $HN(i\text{-}Pr)_2$, pK = 37. Dianion (**10**) may be regarded as a sulfonyl-stabilised version of known α-keto dianions[5] or as an oxyanion-substituted 2-alkoxy-1-sulfonylvinyl anion; the requisite geometry for cyclisation should be accessible through rapid equilibration.[6] Simple sulfone α,α-dianions are well known, and a recent example of their use in intramolecular epoxide opening has been reported.[7]

The cyclisation was extended to the toluenesulfonylacetate esters (**11**) - (**13**), which gave the corresponding sulfonyllactones (**14**) - (**16**)[8] in 68, 48 and 58% yields, respectively.



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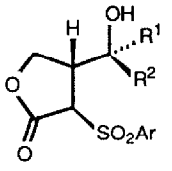
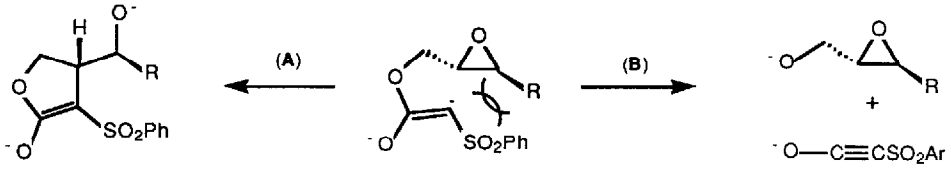


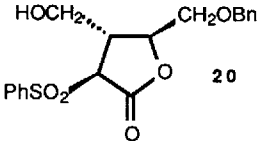
9 $R^1 = CH_2OBn$, $R^2 = H$, Ar = Ph
14 $R^1 = CH_2OBn$, $R^2 = H$, Ar = 4-MePh
15 $R^1 = R^2 = H$, Ar = 4-MePh
16 $R^1 = R^2 = Me$, Ar = 4-MePh
17 $R^1 = H$, $R^2 = CH_2OBn$, Ar = Ph
18 $R^1 = H$, $R^2 = CH_2OBn$, Ar = Ph

The process was less satisfactory when applied to some *trans*-epoxyalcohols: ester (**17**) , under the standard conditions, gave 35% of lactone (**18**) with 33% of recovered alcohol. This result is ascribed to steric repulsion in the configuration needed to allow cyclisation, affecting the apparently delicate balance between that process (**A**) and the fragmentation (**B**), **Scheme 1**. The extreme case was the *trans*-phenylcompound (**19**), which afforded the epoxyalcohol and the reagent/fragment derived $PhSO_2CH_2CON(i\text{-}Pr)_2$ as the major products.



Scheme 1

Reactions of (**9**) illustrate the synthetic potential of accessible educts. Isomerisation [trace NaOMe in MeOH] gave (**20**)[8] as the major component at equilibrium, and separate treatment of (**9**) and (**20**) with $MeSO_2Cl$ (1.1 eq.) and NEt_3 (4 eq.) the stereodefined cyclopropane lactones (**21**)[9,10] and (**22**)[10] (95% and 89%, respectively).



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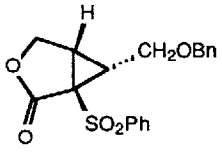

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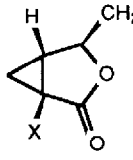
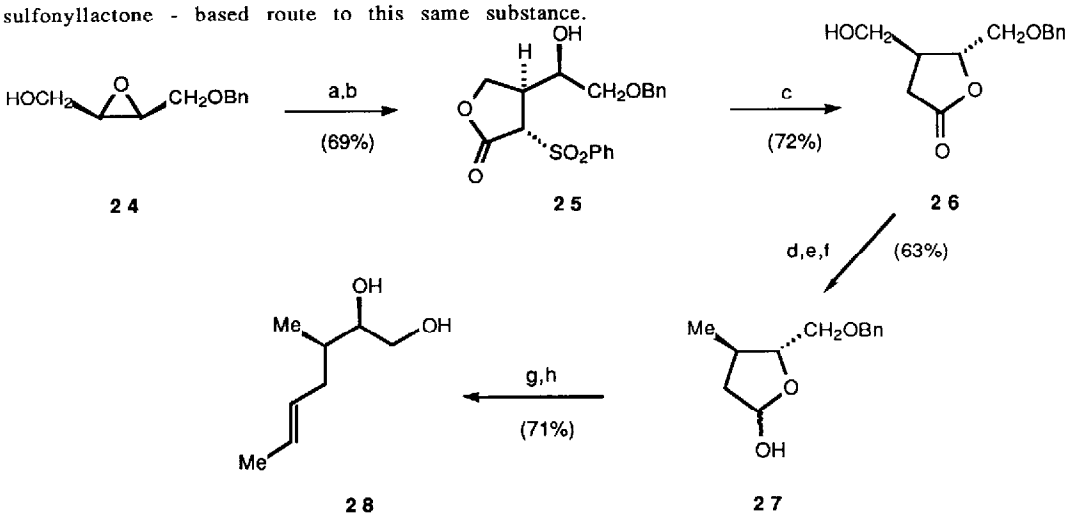


22 X = SO_2Ph
23 X = H

The latter substance was desulfonylated [Na-Hg, NH_4OCHO, THF-MeOH][11] to afford (**23**) (72%).

This route to chiral, racemic sulfonyllactones was also applied to a formal chiral, nonracemic synthesis of "MeBMT" (**5**), a constituent of the immunosuppressive cyclopeptide, Cyclosporine-A.[12] This unusual aminoacid also occurs as the N-acetyl derivative[13], and has been the subject of several synthetic studies.[14] In the original synthesis by Wenger,[14a] the diol (**28**) was a key intermediate, obtained from tartaric acid in about 13 steps. **Scheme 2** shows our sulfonyllactone - based route to this same substance.



24 **25** **26** **27** **28**

Scheme 2

Reagents: **a.** $PhSO_2CH_2CO_2H$, DCCI, DMAP; **b.** LDA; **c.** Na-Hg, K_2HPO_4, MeOH; **d.** $CO(Imidazole)_2$, then MeI, MeCN, reflux; **e.** Bu_3SnH, C_6H_6, reflux; **f.** i-Bu_2AlH, toluene, -70°; **g.** $MeCHI_2$, $CrCl_2$, DMF, RT; **h.** Li-NH_3(liq.).

Epoxyalcohol (**24**)[15] was converted to 3S,4S-sulfonyllactone (**25**), m.p. 91-93°, which was both isomerised [compare (**9**) to (**20**)] and desulfonylated to (**26**) in basic methanol. Conversion to the iodide followed by two selective reductions then gave the lactol (**27**). Olefinations of (**27**) with $MeCH{=}PPh_3$ and $MeCH{=}PEt_3$ were not very stereoselective, but application of the recently described $CrCl_2$ - diiodoalkane process[16] afforded a >95:5 *E*:*Z* ratio. Debenzylation gave the diol (**28**), identical (optical rotation, PMR, IR) with the previously reported material.[14a]

Other applications of this methodology to natural products synthesis will be reported elsewhere in detail.

Acknowledgements: We thank the Physical-Analytical department for spectra and analyses, and Professor R. Breslow for helpful discussions. These studies form part of the Ph.D. thesis of B.B.S., and we thank Professor A. K. Bose for his support in this regard.

References and Notes:

1. S. W. McCombie, B. B. Shankar and A. K. Ganguly, *Tetrahedron Letts.*, 1985, **26**, 6301.

2. S. W. McCombie and W. A. Metz, *Tetrahedron Letts.*, 1987, **28**, 383; S. W. McCombie and T. L. Nagabhushan, *ibid*, 5395.

3. B. Neises and W. Steglich, *Angew. Chem. Int. Ed.*, 1978, **17**, 522.

4. Slow decomposition resulted in regeneration of the epoxyalcohol; addition of BF3.Et2O resulted in attack by the enolate *oxygen* to give an unstable 2-(phenylsulfonylmethylene)-1,3-dioxolane. Compare: J. E. Baldwin and L. I. Kruse, *J.C.S. Chem. Commun.*, **1977**, 233.

5. C. J. Kowalski, M. L. O'Dowd, M. C. Burke and K. W. Fields, *J. Am. Chem. Soc.*, 1980, **102**, 5412. For a related, vinyl-substituted, sulfonyl stabilised dianion, see: P. T. Lansbury, G. E. Bebernitz, S. C. Maynard and C. J. Spagnuolo, *Tetrahedron Letts*, 1985, **26**, 169.

6. The geometry of (**10**) is not known; the depicted form would be favoured by maximal separation of charge, whereas metal coordination would favour the isomer. For equilibration and reactions of ROC(R')=C(Li)SO2Ph, see: S. W. McCombie, B. B. Shankar, A. K. Ganguly, A. Padwa, W. H. Bullock and A. D. Dyszlewski, *Tetrahedron Letts.*, 1987, **28**, 4127.

7. D. Tanner, H. H. Ming and M. Bergdahl, *Tetrahedron Letts.*, 1988, **29**, 6493.

8. All products gave satisfactory elemental analyses and mass spectra. The *trans* disposition of the arenesulfonyl residue in the sulfonyllactones was assumed on thermodynamic grounds, and was strongly indicated for (**9**) by NOE studies on the *O*-benzoyl derivative.
Selected PMR data, in CDCl3 : (**14**): δ = 3.38(m, 1), 3.91(m, 1) and 4.27(d, 1, J = 3.5); (**15**): δ = 3.43(m, 1), 3.75-3.95(ABX, 2, J = 8.7 and 4.8) and 4.53(t, 1, J = 8.7); (**16**): δ = 1.22(s, 3), 1.30(s, 3), 3.17(m, 1), 4.05(d, 1, J = 2.6) and 4.3-4.6(m, 2); (**20**): δ = 3.23(m. 1), 3.68(m, 2), 3.88(ABX, 2, J = 8.1 and 3.3) and 4.30(d, 1, J = 8.9).

9. An identical sample of (**21**) was obtained (35% overall from the allylic alcohol) by Cu-catalysed cyclisation of *Z*-BnOCH2CH=CHCH2OCOC(N2)SO2Ph.

10. For a related cyclisation, see: S. Takano, M. Tanaka, K. Seo, M. Hirama and K. Ogasawara, *J. Org. Chem.*, 1985, **50**, 931. For examples of the synthesis of cyclopropanes by addition of diazoalkanes to chiral, nonracemic unsaturated systems, see: J. Mann and A. Thomas, *Tetrahedron Letts.*, 1986, **27**, 3533; A. I. Meyers and D. Romo, *ibid*, 1989, **30**, 1745; B. de Lange and B. L. Feringa, *ibid.*, 1988, **29**, 5317.

11. Use of this *soluble buffer system* avoided the extensive attack on the lactone observed when K2HPO4 or KH2PO4 were employed.

12. R. M. Wenger, *Angew. Chem. Int. Ed.*, 1985, **24**, 77, and references therein.

13. H. Nakajima, T. Hamasaki, K. Nishimura, T. Kondo, S. Udawaga and S. Sato, *Agric. Biol. Chem.*, 1988, **52**, 1621.

14. (a) R. M. Wenger, *Helv. Chim. Acta*, 1983, **66**, 2308. (b) D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1986, 108, 6757. (c) D. H. Rich and D. Tung, *Tetrahedron Lett.*, 1987, **28**, 1139. (d) U. Schmidt and W. Sigel, *ibid.*, 1987, **28**, 2849. (e) A. V. R. Rao, T. G. M. Dhar, T. K. Chakraborty and M. K. Gurjar, *ibid.*, 1988, **29**, 2069.

15. Prepared by standard asymmetric epoxidation: T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, 1980. **102**, 5974. The resulting material (87-91% e.e.) was enriched to >97% e.e. by a single, low-temperature recrystallisation from ether-hexanes. The higher-melting 4-bromobenzyl ether (J. M. Chong and S. Wong, *J. Org. Chem*, 1987, **52**, 2596) was not so useful in this sequence, since partial debromination accompanied the desulfonylation.

16. T. Okazoe, K. Takai and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 951.

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