Tetrahedron Letters, Vol. 34, No. 40, pp. 6443-6446, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Cyclization of γ,δ-Epoxy-α-cyanosulphones. A Simple, Diastereoselective Route to Cyclopropane Carboxylic Acids.

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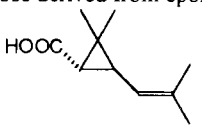
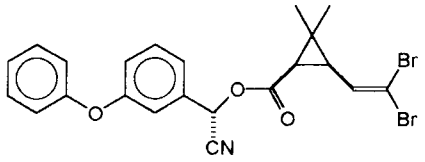
Abstract: cyclisation of α-cyano-α-sulphonyl-γ,δ-epoxy carbanions proceeds with high yields and complete diastereoselectivity, to yield cyclopropanolactones, useful intermediates in the synthesis of *cis*-substituted cyclopropane carboxylic acids.

Trans-substituted derivatives of cyclopropane carboxylic acid are abundant in nature, an example being chrysanthemic acid **1**, while compounds containing the *cis*-substituted cyclopropane ring are less common. The latter ring, however, is present in *cis*-pyrethroids, a class of synthetic insecticides, several orders of magnitude more active than natural *trans*-pyrethroids.[1] To this class belongs, for example, deltamethrine **2**, the most potent insecticide known at the time of its discovery, and still widely used for its exceptional activity, combined with low toxicity for mammals[2].

Straightforward retrosynthetic analysis of **2** leads to the *cis* hydroxyacid derivative **3** as common intermediate in the synthesis of *cis*-pyrethroids and, in turn, to epoxides **4a** and **4b** as possible precursors. However, base catalyzed cyclisation of **4** yields *trans*-**3**, or, in the best case, mixtures of *cis* and *trans* isomers[3] and, indeed, this route has been followed for a total synthesis of *trans*-chrysantemic acid **1**[4], starting from **4a** (R=Me),. The same *trans*-diastereoselectivity is also observed in the cyclisation of other monoactivated carbanions, such as those derived from epoxysulfones **4c**[5].



1



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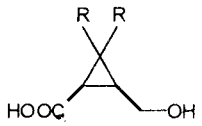

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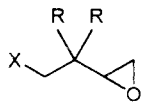
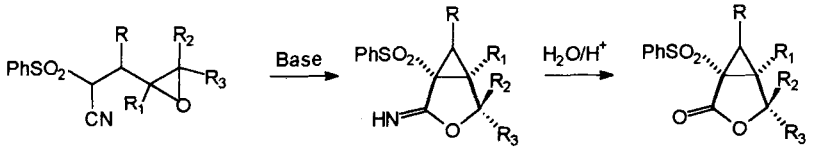


a: X= COOMe
b: X= CN
c: X= $PhSO_2$

4a-c

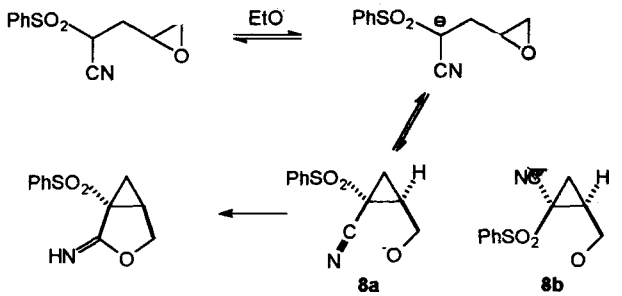
In this communication we report that cyclisation of cyanosulphonylepoxides **5**[6] leads, with complete diastereoselection, to the imines **6** and, after hydrolysis, to the lactones **7**, the *cis* fusion being, of course, imposed by the cyclopropane ring.[7] Data in Table 1 indicate that the reaction is quite general, giving access to a number of substituted cyclopropanolactones. High yields are obtained under a variety of experimental conditions (entries 1-3); however, giving the high acidity of the precursors **5**, very strong bases and anhydrous conditions are not strictly required and the reaction can be conveniently carried out with sodium ethoxide in ethanol. Comparable yields and complete diastereoselectivity are also obtained in the corresponding intermolecular reactions in which phenylsulphonylacetonitrile or ethyl phenylsulphonylacetate are alkylated with epibromohydrin (entries 9-10). In this case the very fast rate of the intramolecular ring opening of the epoxide, following the intermolecular alkylation, ensures that double alkylation of the carbanion does not compete with cyclisation.



5 **6** **7**

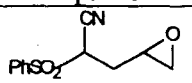
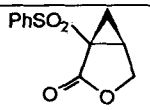
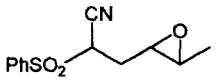
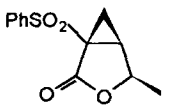
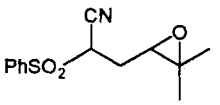
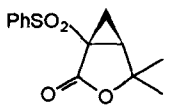
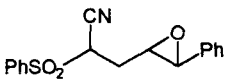
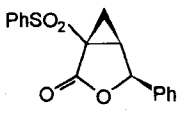
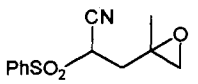
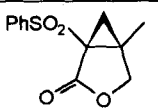
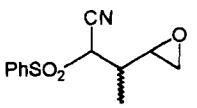
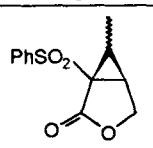
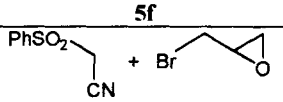
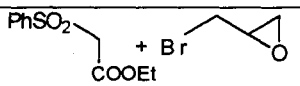
As to the origin of diastereoselectivity, we suggest that this does not follow from a preferential mode of approach of the carbanion to the epoxide, since we have shown that the same reaction, when leading to rings larger than cyclopropane, gives approximately 1:1 mixtures of diastereoisomers[8]. On the other hand, we have also shown that formation of cyclopropanes by cyclisation of bis-activated epoxycarbanions can be reversible[9]. In this hypothesis (Scheme 1) an equilibrium is established between the carbanion and the diastereomeric cyclopropanes **8a-b**. Only **8a** can further cyclize to an imine in which the configuration, locked by the fusion between the rings, must necessarily be *cis*.

Scheme 1

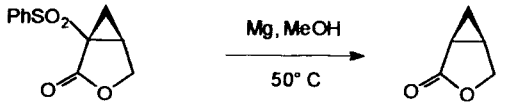


8a **8b**

Table 1. Cyclopropanolactones from cyano sulphonyl epoxides.

Entry	Epoxide	Lactone[10]	Method	% Yield
1	 **5a**	 **7a**	A[11] (NaOEt/EtOH, 25°C)	95
2	**5a**	**7a**	B (NaH,THF, 50°C)	95
3	**5a**	**7a**	C (nBuLi,THF, -78°C)	90
4	 **5b**	 **7b**	A	95
5	 **5c**	 **7c**	A	90
6	 **5d**	 **7d**	A	90
7	 **5e**	 **7e**	A	87
8	 **5f**	 **7f**	A	95
9		**7a**	A	90
10		**7a**	A	90

Finally, in order to demonstrate the synthetic potential of the reaction thus described, we have carried out the reductive desulphonylation of lactone **6a**. Out of several reducing agents tested, magnesium in methanol[12] gave the best results, yielding the lactone **9** in 75% yield (68% from phenylsulphonylacetonitrile and epibromohydrin). **9** is the condensation product of the *cis*-hydroxyacid **3** (R=H) and its ready formation by this route demonstrates the potential utility of this synthetic approach to the synthesis of *cis*-substituted cyclopropane carboxylic acids. Further applications to the synthesis of *cis*-pyrethrins are in progress and will be reported.



6a **9**

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5. Gaoni, Y., *J. Org. Chem.*, **1982**, *47*, 2564. Gaoni, Y.; Tomazic, A.; Potgieter, E., *J. Org. Chem.*, **1985**, *50*, 2943.
6. By alkylation of phenylsulphonylacetonitrile with the appropriate bromo-alkene (nBuLi/THF/-78 to -50 °C) followed by *m*-CPBA epoxidation (see ref. 8).
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8. Benedetti; F., Berti; F., Fabrissin, S.; Gianferrara, T., *J. Org. Chem.*, in press.
9. Benedetti, F.; Berti, F.; Fabrissin, S.; Gianferrara, T.; Risaliti, A., *J. Org. Chem.* **1991**, *56*, 3530.
10. Satisfactory elemental analyses were obtained for all lactones. **^{1}H-NMR**: **7a**: [1.48 (t), 2.18(dd), 3.18 (m), 3H, cyclopropane (J_{gem} = 5.4Hz, J_{trans} = 5.4Hz, J_{cis} = 8.6Hz)], [4.17 (dd), 4.36 (dd), 2H, CH_2, (J_{gem} = 9.8Hz, J_{trans} = 0.75Hz, J_{cis} = 4.8Hz)], 7.5-8.3 (m, 5H, Ph); **7b**: 1.52 (d, 3H, CH_3), [1.46 (t), 2.30 (dd), 3.20 (m), 3H, cyclopropane], 4.20 (m, 1H, CH), 7.5-8.3 (m, 5H, Ph); **7c**: 1.50 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), [1.55 (m), 2.40(m), 3.25 (m), 3H, cyclopropane], 7.5-8.3 (m, 5H, Ph); **7d**: [1.50 (t), 2.20 (dd), 3.50 (m), 3H, cyclopropane], 5.80 (d, 1H, CHPh), 7.20 (m, 5H, Ph), 7.5-8.3 (m, 5H, $PhSO_2$); **7e**: [1.55 (d), 2.25 (d), 2H, cyclopropane], 1.8 (s, 3H, CH_3), 4.11 (dd, 2H, CH_2), 7.6-8.1 (m, 5H, Ph); **7f**: [1.50 (m), 2.30(m), 3.20 (m), 2H, cyclopropane], 1.7 (d, 3H, CH_3), 4.2 (m, 2H, CH_2), 7.6-8.3 (m, 5H, Ph).
11. The epoxides (2.5 mmol) were dissolved in 100 ml of a 0.5M solution of sodium ethoxide in ethanol, and kept at 25°C for 12 hours. The reaction mixtures were then poured into 350 ml water, acetic acid was added to pH 4-5 and the aqueous solutions were left overnight at room temperature, to hydrolyze the imines. Extraction with dichloromethane gave the crude lactones which were then crystallized from ethanol.
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(Received in UK 16 July 1993; accepted 30 July 1993)