Asymmetric Diels–Alder Reactions of Sulphinyl-activated Dienophiles obtained *via* a Self-induced Chiral Oxidation†

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The Diels–Alder cycloaddition of activated vinyl sulphoxides (**1**), that are readily obtained by a self-induced chiral oxidation, proceeds highly diastereoselectively to form the corresponding cycloadducts (**4**) that can be converted into 2-substituted norbornadienes (**5**) of high enantiomeric purity.

The large number of studies on the features responsible for the degree of asymmetric induction in the Diels–Alder reaction,[1] indicates the importance of a highly differentiated *si* and *re* face of the dienophile,[2] the proximity of the chiral centre to the reactive site,[3] and the conformational rigidity owing to hydrogen bonding or chelation with metals.[3,4] The use of chiral vinyl sulphoxides, which takes advantage of their electron withdrawing ability and of the position of the chiral centre directly bonded to one of the reactive carbon atoms, has only recently been recognized,[5] but initial results do not look promising from a synthetic viewpoint because of the difficulty in introducing the chiral sulphoxide function with standard procedures. Because the sulphoxide moiety imparts moderate dienophilicity to the double bond,[6] an extra activating function, preferably in a *cis* relationship to avoid the possible formation of stereoisomers, is necessary to give a rapid and *endo* stereoselective cycloaddition.[7]

This communication describes the results obtained with the use of the sulphinyl-activated chiral dienophiles (**1**) in which the aforementioned structural features have been assembled and are readily available in high overall yield by standard chemical reactions. Furthermore (**1**) contains an activating function in a *cis* relationship which not only imparts higher dienophilicity but is also amenable to a variety of synthetically useful transformations from the adducts.[8]

The preparation of dienophile (**1a**) entails morpholine-catalysed Michael addition of hydroxythiol (**2**) to benzenesulphonylacetylene (CH_2Cl_2, 0 °C, overnight) to afford in 85%

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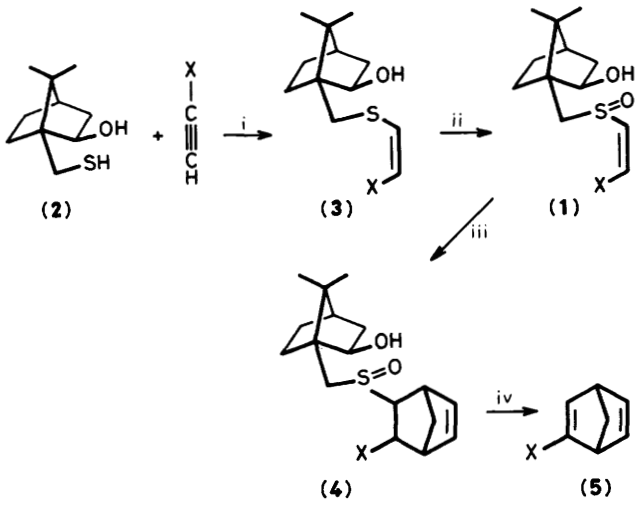

a; X = $PhSO_2$–
b; X = *p*-$ClC_6H_4SO_2$–
c; X = $MeCO_2$–

Scheme 1. *Reagents:* i, MeCN, morpholine (for **a** and **b**), MeOH : H_2O 9 : 1 (for **c**); ii, *m*CPBA, CH_2Cl_2; iii, cyclopentadiene, CH_2Cl_2; iv, DBU.

yield the required *cis* adduct (**3a**) exclusively. The known 10-mercaptoisoborneol (**2**)[9] is obtained from $LiAlH_4$ reduction of the commercially available 1-(*S*)-(+)-camphor-10-sulphonyl chloride in 67% yield together with the epimeric 10-mercaptoborneol (yield 15%). The two diastereisomeric thiols can be obtained in pure form by medium pressure column chromatography. Adduct (**3**) is suited to asymmetric oxidation as it contains a chiral substituent as well as a proximate hydroxy group, which directs the oxidation more efficiently[10] and helps in giving conformational rigidity through hydrogen bonding with the sulphoxide during the cycloaddition reaction. On oxidation with *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane, a 90 : 10 mixture of epimeric sulphoxides, as determined by 200 MHz ^{1}H n.m.r. spectroscopy, is obtained in 95% yield. This diastereoisomeric mixture reacts readily with cyclopentadiene to afford a 90 : 10 mixture of cycloadducts in quantitative yield. The more abundant isomer crystallizes from methanol to afford one pure diastereoisomer (m.p. 70 °C; $[\alpha]_D^{22}$ −8.42°, *c* 1, $CHCl_3$). *X*-Ray structure analysis (Figure 1) confirms the proposed structure and allows assignment of the absolute configuration of the newly formed chiral carbon centres.‡ In fact, since the absolute configuration of the chiral auxiliary is known to be *S* it can be deduced that the chirality of the carbon atom linked to the sulphoxide is *R* and consequently the one attached to

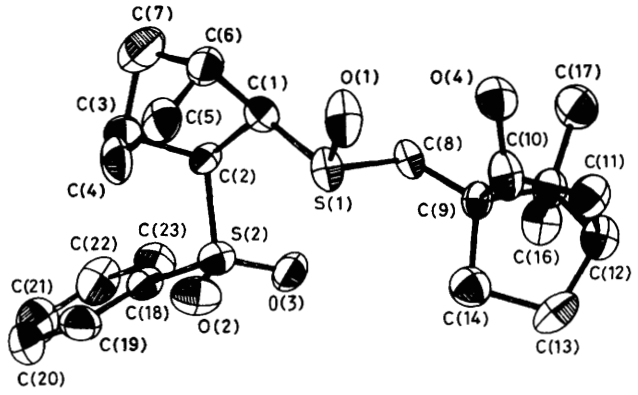

Figure 1. Molecular structure of (**4a**) showing all non-hydrogen atoms. Absolute configuration as deduced from C(9) known as *S*: S(1) = *R*; C(1) = *R*; C(2) = *S*. O(1)–O(4) 2.735 Å.

the sulphone has the *S* configuration. Hence the cycloaddition takes place at the *re* face with respect to the sulphoxide which is the *si* face with respect to the sulphone. The *X*-ray structure also shows the hydrogen bonding between the hydrogen and the sulphoxide functions [O(1)–O(4) 2.735 Å], to which conformational rigidity is ascribed.

In order to obtain crystalline substances the *p*-chloro derivative (**1b**) has been prepared in a similar manner starting from solid *p*-chlorobenzenesulphonylacetylene. In this case it is possible to isolate the pure sulphoxide (**1b**) (m.p. 140 °C; $[\alpha]_D^{22}$ +425.00°, *c* 1, $CHCl_3$) by direct crystallization with methanol from the reaction mixture after *m*CPBA oxidation. Reaction of diastereoisomerically pure sulphoxide (**1b**) with cyclopentadiene results in a 91 : 9 mixture of diastereoisomeric adducts from which it is possible to isolate by crystallization with methanol the predominant one (m.p. 240 °C; $[\alpha]_D^{22}$ −12.50°, *c* 0.2, $CHCl_3$).

The methoxycarbonyl derivative (**1c**) is obtained with slight modification of the previously described method.[11] With this substrate it is possible to use the crude mixture of borneol and isoborneol as obtained from the $LiAlH_4$ reduction of 1-(*S*)-(+)-camphor-10-sulphonyl chloride because only the *cis*-isobornyl derivative crystallizes from light petroleum. Oxidation with *m*CPBA in dichloromethane affords a 96 : 4 ratio of epimeric sulphoxides, and cycloaddition of a pure sample to cyclopentadiene gives exclusively the *endo* adduct in a diastereoisomeric ratio higher than 98 : 2, as determined from the 200 MHz ^{1}H n.m.r. spectrum§ (m.p. 130 °C; $[\alpha]_D^{22}$ +4.44°, *c* 1, $CHCl_3$). Elimination of the chiral adjuvant with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gives 2-methoxycarbonylnorbornadiene (**5c**) ($[\alpha]_D^{22}$ −39.22°, *c* 0.1, $CHCl_3$) in 80% yield in high enantiomeric purity with recovery of the chiral auxiliary possible. This norbornadiene has been used in its racemic form as starting material for the synthesis of biologically active analogues of the prostaglandin endoperoxides PGH_2 and PGG_2.[12]

The value of this method is in the synthetic utilisation of the highly diastereoselective oxidation of compounds of type (**3**) induced by the proximity of the chiral hydroxy group, that eliminates the need to prepare the enantiomerically pure sulphoxides. Similar effects of intramolecular hydroxy functions in directing oxidations have been documented[10] and have been attributed to hydrogen bonding with the percar-

‡ *Crystal data:* $C_{23}H_{31}O_4S_2$ crystallizes from methanol in the orthorhombic system, space group $P2_12_12_1$, a = 14.592(4), b = 12.023(4), c = 12.735(4) Å, U = 2234 Å^3, Z = 4, D_c = 1.293 g cm^{-3}. 2241 Reflections were collected on a four-circle Philips PW 1100 diffractometer up to θ = 25°, θ—2θ scan mode, Mo-K_α monochromatized radiation (λ = 0.7107 Å). The structure was solved by direct methods using the phasing program 'Multan,' and refined by block-diagonal least squares with anisotropic thermal parameters for non-hydrogen atoms. Hydrogen atoms were found on a Δ*F* map, but not refined. The final *R* factor for 1441 observed reflections [$I \geq 3\sigma(I)$] was 0.0564. The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Rd., Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

§ A single diastereoisomer from the 200 MHz ^{1}H n.m.r. spectrum. Control experiments show 98 : 2 as the maximum observable diastereoisomeric ratio.

boxylic acid during approach to the substrate. Significantly, if oxidation of (**3**) is carried out in acetone or methanol as solvent, poorer diastereoselection (*ca.* 60:40) in the formation of the sulphoxide is observed.

In our opinion this synthetic sequence greatly facilitates the preparation of chiral Diels–Alder adducts.

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References

1 L. A. Paquette in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, 1984, vol. III, p. 455.
2 W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 876; G. Helmchen and R. Schmierer, *ibid.*, 1981, **20**, 208; T. Poll, G. Helmchen, and B. Bauer, *Tetrahedron Lett.*, 1984, **25**, 2191.
3 W. Choy, L. A. Reed, III, and S. Masamune, *J. Org. Chem.*, 1983, **48**, 1137; S. Masamune, L. A. Reed, III, J. T. Davis, and W. Choy, *ibid.*, 1983, **48**, 4441.
4 For Lewis acid catalysed Diels–Alder reactions in which the catalyst does not have only an activating function see for example: D. A. Evans, K. T. Chapman, and J. Bisaha, *Tetrahedron Lett.*, 1984, **25**, 4071; D. A. Evans, K. T. Chapman, and J. Bosaha, *J. Am. Chem. Soc.*, 1984, **106**, 4261; M. M. Midland and R. S. Graham, *ibid.*, 1984, **106**, 4294.
5 C. Maignan and R. A. Raphael, *Tetrahedron*, 1983, **39**, 3245.
6 L. A. Paquette, R. E. Moerck, B. Harirchian, and P. D. Magnus, *J. Am. Chem. Soc.*, 1978, **100**, 1597.
7 T. Koizumi, I. Hakamada, and E. Yoshii, *Tetrahedron Lett.*, 1984, **25**, 87; C. Maignan, A. Guessous, and F. Rouessac, *ibid.*, 1984, **25**, 1727.
8 For the utilization of sulphones in organic synthesis see: P. D. Magnus, *Tetrahedron*, 1977, **33**, 2019.
9 E. L. Eliel and W. J. Frazee, *J. Org. Chem.*, 1979, **44**, 3598.
10 R. S. Glass, W. N. Setzer, U. D. G. Prabhu, and G. S. Wilson, *Tetrahedron Lett.*, 1982, **23**, 2335 and cited references.
11 F. Montanari, *Tetrahedron Lett.*, 1960, 18; W. E. Truce and G. J. W. Tichenor, *J. Org. Chem.*, 1972, **37**, 2391.
12 E. J. Corey, M. Shibasaki, K. C. Nicolaou, C. L. Malmsten, and B. Samuelsson, *Tetrahedron Lett.*, 1976, 737.