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SYNTHESIS OF CONFIGURATIONALLY STABLE ALLYLIC SULPHOXIDES VIA DIASTEREOSELECTIVE OXIDATION.

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Abstract. Low temperature meta-chloroperbenzoic acid oxidation of allylic sulphide derived from (1S)-10-mercaptoisoborneol proceeds in a completely diastereoselective fashion to afford a configurationally stable allylic sulphoxide. The factors affecting the selectivity of the oxidation and the optical stability of the product are discussed.

The use of allylic sulphoxide in stereoselective synthesis has recently received a great deal of interest.[1-5] These products were shown to add very stereoselectively as Michael donors to cyclopentenones affording exclusively the corresponding γ-sulphinyl adducts.[1-3] We reported[4,5] a two step synthesis of unsaturated diols by stereocontrolled addition of α-allyl sulphinyl anion to chiral aldehydes, followed by [2,3]-sigmatropic rearrangement and quenching of the intermediate sulphenate esters.[6,7]

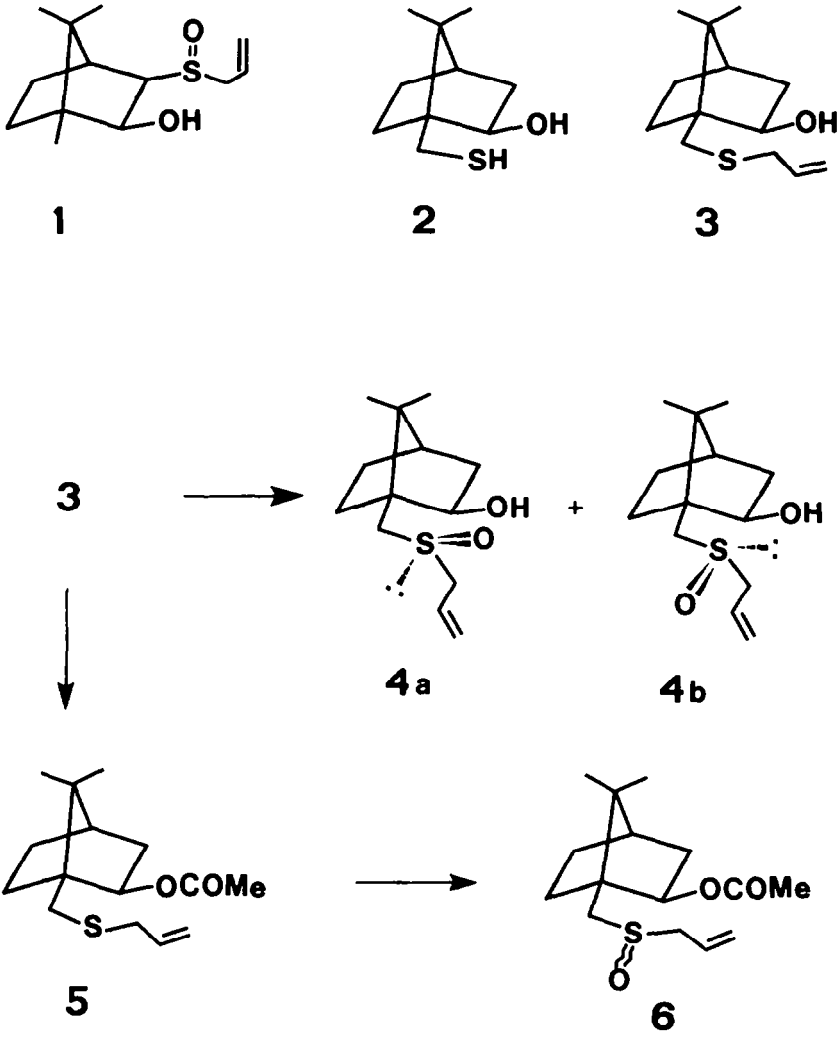
Unfortunately optically active allylic sulphoxides readily undergo thermal racemization at sulphur[6] and are therefore of unpractical use as enantiomerically pure reagents. For this reason an easy entry to configurationally stable allylic sulphoxides can be regarded as valuable.

In a first approach to solve this problem Haynes and Ridley prepared both sulphur epimers of camphor-derived sulphoxide (1) and showed that they are optically stable below 100°C.[2] The role played by the proximal hydroxyl group in promoting the complete stereoselectivity of the oxidation of the parent sulphide to (1), and in contributing to the configurational stability of the sulphoxide moiety was suggested but not demonstrated.[2]

The elegant work by De Lucchi[8] on vinyl sulphoxides led us to devise a new and more straightforward route to camphor-derived allylic sulphoxides starting from (1S)-10-mercaptoisoborneol (2).[9]

As reported in the Scheme, standard procedure converted (2) into allylic sulphide (3) in 98% yield. Various reaction conditions were tested for the oxidation of (3) to the corresponding sulphoxide (4).

Oxidation of (3) with meta-chloroperbenzoic acid (mCPBA) in CH_2Cl_2 or in CH_3OH



(-78°C, 15 min.) afforded a single stereoisomeric sulphoxide (4a), m.p. 44.5-45°C, $[\alpha]_D^{25}$ + 28.9 (c 1, $CHCl_3$), within the limit of ^1H 300 MHz NMR spectroscopy. When the oxidation was performed with $NaIO_4$ in CH_3OH/H_2O (RT, overnight) a 66:34 mixture of separable diastereoisomeric sulphoxides (4a,b) was produced, the prevailing one being identical by ^1H NMR to that obtained in the mCPBA oxidations.

These results are markedly different from those obtained[8] in the oxidation of the corresponding vinyl sulphides, for which a high (90:10) degree of stereoselection was observed only by the use of mCPBA in aprotic solvents (CH_2Cl_2, -20°C). This was rationalized on the basis of an intramolecular hydrogen bonding effect which determines the preferential attack of the oxidizing agent on one of the two diastereotopic lone pairs of the sulphur atom.[8]

Our results could be explained either by a very stereoselective oxidation at low temperature or by an equilibrium of epimeric sulphoxides (4a,b) via a [2,3] -sigmatropic rearrangement to give the thermodinamically more stable product (4a).

However, when mCPBA oxidation of (3) in $CDCl_3$ (at -60°C) or in CD_3OD (at -78°C) was monitored by low temperature ^1H NMR spectroscopy the only detectable product was the one isolated after reaction work-up. Since equilibration at low temperature seems unlikely,[6] we can conclude that the isobornyl system promotes the complete stereoselectivity of the mCPBA oxidations.

In order to check the importance of the directing effect of the hydroxyl group,[10] sulphide (3) was converted into the acetoxy derivative (5). Oxidation of the latter with mCPBA (-78°C, CH_2Cl_2, 30 min.) or $NaIO_4$ (RT, CH_3OH/H_2O, overnight) gave a 65:35 mixture of epimeric sulphoxides (6). Thus, the essential role of the hydroxyl group in promoting a completely diastereoselective oxidation is demonstrated: very likely the intramolecular hydrogen bond is strong enough to survive at low temperature even in a protic solvent as CH_3OH, but it is more loose in CH_3OH/H_2O at room temperature. The restricted conformational mobility of (3) in the presence of the hydrogen bonding at low temperature is reflected in the stereoselectivity of the oxidation.

On the basis of De Lucchi's work[8] and inspection of molecular model of sulphide (3) the (S) absolute configuration can tentatively be assigned to the sulphur atom of sulphoxide (4a).

The matter of the configurational stability of sulphoxides such as (4) or (6) was then addressed. Compound (4a) is stable at room temperature or when heated through its melting point at 60°C: therefore it can be handled without any special pracaution. However, when heated at 90°C in toluene solution (an apolar solvent known to accelerate the rate of racemization of allylic sulphoxides[6]), (4a) epimerizes ($k = 2.22 \times 10^{-4} sec^{-1}$) to give a 92/8 mixture of (4a)/(4b), $[\alpha]_D^{22}$ + 5.7 (c 0.5, toluene), as determined by ^1H NMR analysis. Compound (4b), heated at 90°C in toluene, isomerizes at a comparable rate ($k = 2.25 \times 10^{-4} sec^{-1}$) to give the same 92/8 (4a)/(4b) mixture, $[\alpha]_D^{22}$ + 5.7 (c 0.5, toluene). In analogous conditions the 65/35 mixture of sulphoxide (6) equilibrates to a 54/46 mixture of epimers, at a slightly faster rate ($k = 8.51 \times 10^{-4} sec^{-1}$). From these data it can be inferred that the relatively rigid isobornyl system makes allylic sulphoxides such as (4) and (6) much more optically stable than their alkyl or aryl analogues (e.g. for p-tolyl allyl sulphoxides $k = 11.2 \times 10^{-4} sec^{-1}$ at 69°C in benzene). The presence of a free hydroxyl group in appropriate position to form an intramolecular hydrogen bond, slightly enhances this intrinsic stability.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian XL 300 instrument. Infrared spectra were recorded on a Perkin-Elmer 457 spectrometer. Elemental analyses were performed with a Perkin Elmer 240 instrument. Silica gel was used for analytical and flash chromatography; organic extracts were dried over sodium sulphate and filtered before removal of the solvent under reduced pressure. Toluene was distilled from sodium, MeOH from Mg turnings, CH_2Cl_2 from CaH_2. All reactions employing anhydrous solvents were run under Argon.

Compound (2) was prepared according to a literature method;[8] it had m.p. 72°C, $[\alpha]_D^{23}$ -57.0 (c 5, $CHCl_3$) (lit.[8] m.p. 70°C, $[\alpha]_D^{22}$ - 57.4, c 10, $CHCl_3$).

Synthesis of allyl sulphide (3). To an ice-cold solution of sodium methoxide (10 mmol) in CH_3OH (20 ml), 10-mercaptoisoborneol (10 mmol, 1.86 g) was added portionwise. After 30 min stirring at room temperature freshly distilled allyl bromide (10 mmol, 0.864 ml) in MeOH (5 ml) was added dropwise and the reaction mixture was stirred at room temperature overnight. Usual work-up afforded sulphide (3) (2.215 g, 98%), n_D^{22} 1.5242, $[\alpha]_D^{22}$ -41.0 (c 1, $CHCl_3$) that could be used without further purification. An analytically pure sample was obtained after flash chromatography (SiO_2, hexanes/diethylether 85/15 mixture as eluant). Found C% 69.06; H% 9.71. $C_{13}H_{22}OS$ requires: C% 68.97; H% 9.79. ^{1}H NMR: δ 5.74-5.88 (m, 1H, CH=C); 5.09-5.16 (m, 2H, CH_2=C); 3.86 (dd, 1H, J 7.5, 3.8, CH-O); 3.09-3.21 (m, 2H, CH_2-C=C); 2.70 (d, 1H, J 11.8, CH_A-S); 2.52 (d, 1H, J 11.8, CH_B-S); 2.33 (bs, 1H, OH); 1.00-1.83 (m, 7H), 1.04 and 0.82 (2s, 6H, CH_3).

Synthesis of allyl sulphide (5). To an ice-cold solution of freshly distilled acetyl chloride (2.0 mmol, 0.150 ml), pyridine (2.0 mmol, 0.160 ml), and 4-dimethylaminopirydine (0.2 mmol, 25 mg) in CH_2Cl_2 (10 ml), sulphide (3) (2.0 mmol, 450 mg) in CH_2Cl_2 (3 ml) was added dropwise and the reaction mixture stirred at room temperature overnight. Usual work-up gave a crude oil which was purified by flash chromatography (SiO_2, hexanes/diethylether 95/5 mixture as eluant) to give (5) in 65% yield; n_D^{22} 1.5065, $[\alpha]_D^{22}$ -42.3 (c 1, $CHCl_3$). Found: C% 67.04. H% 8.94. $C_{15}H_{24}O_2S$ requires: C% 67.12; H% 9.01. ^{1}H NMR: δ 5.48-5.90 (m, 1H, CH=C), 4.92-5.08 (m, 2H, CH_2=C); 4.70 (dd, 1H, J 7.4, 3.6, CH-O); 3.05 (d, 2H, J 7.5, CH_2-C=C); 2.65 (d, 1H, J 12.0, CH_A-S); 2.33 (d, 1H, J 12.0, CH_B-S); 2.00 (s, 3H, CH_3CO); 1.00-1.90 (m, 7H); 1.00 and 0.85 (2s, 6H, CH_3-C).

General procedure for the mCPBA oxidation. To a stirred solution of allyl sulphide (1 mmol) in the appropriate solvent (10 ml) cooled at -78°C (CH_2Cl_2, MeOH, or CD_3OD) or at -60°C ($CDCl_3$), a titrated solution of mCPBA (1 mmol) in the same solvent was added dropwise. The reactions were monitored by TLC (diethylether) or by ^{1}H NMR. The work-up involved addition of saturated aqueous solution of $NaHCO_3$ and extraction of the aqueous phase with dichloromethane. Evaporation of the organic solvent was performed below 30°C. The sulphoxides were obtained after flash chromatography.

Compound (4a), white solid, had m.p. 44.5-45°C, $[\alpha]_D^{22}$ +28.9 (c 1, $CHCl_3$). It

was obtained in 90% and in 85% yield in CH_2Cl_2 and in MeOH, respectively, with diethylether as eluant. Found: C% 64.56; H% 9.16. $C_{13}H_{22}O_2S$ requires: C% 64.42; H% 9.14. ^1H NMR: δ 5.82-5.97 (m, 1H, CH=C); 5.38-5.48 (m, 2H, CH_2=C); 4.01-3.73 (m, 1H, CH-O); 3.92 (d, 1H, J 3.3, OH); 3.45-3.57 (m, 2H, CH_2-C=C); 3.21 (d, 1H, J 13.3, CH_A-SO); 2.38 (d, 1H, J 13.3, CH_B-SO); 1.10-1.86 (m, 7H); 1.10 and 0.82 (2s, 6H, CH_3). IR (ν max): 3550, 2950, 1640, 1405, 1290, 1078, 1030, 1000.
Compound (6), 65/35 mixture of epimers, was a thick oil with n_D^{22} 1.5089, $[\alpha]_D^{22}$ -90.0 (c 1, $CHCl_3$). It was obtained in 82% yield in CH_2Cl_2 as solvent with diethylether as eluant. Found C% 63.24. H% 8.42. $C_{15}H_{24}O_3S$ requires: C% 63.34; H% 8.51. ^1H NMR: δ 5.80-6.00 (m, 1H, CH=C); 5.36-5.49 (m, 2H, CH_2=C), 4.81-4.88 (m, 1H, CH-O); 3.36-3.56 (m, 2H, CH_2-C=C); 3.03 and 3.02 (2d in 35:65 ratio, 1H, J 13.3 and 13.2, CH_A-SO); 2.63 and 2.48 (2d in 35:65 ratio, 1H, J 13.3 and 13.2, CH_B-SO); 2.04 and 1.98 (2s in 35:65 ratio, 3H, CH_3-CO); 1.10-2.00 (m, 7H); 1.06, 1.01, and 0.91 (3s, 6H overall, CH_3-C). IR (ν max): 2955, 1730, 1635, 1360, 1245, 1065, 1040, 1005).

General procedure for the $NaIO_4$ oxidation. To a stirred solution of allyl sulphide (1 mmol) in MeOH (10 ml) cooled at 0°C, a solution of $NaIO_4$ (1 mmol, 214 mg) in water (5 ml) was added dropwise, and the mixture stirred overnight at room temperature. Filtration of the white precipitate and usual work-up gave the crude products which were purified by flash chromatography. From compound (3) a 66:34 mixture of compounds (4a) and (4b) was obtained in 82% yield; compound (4a) (diethylether as eluant) was identical to the product of the mCPBA oxidations of (3). Compound (4b), a thick oil, had n_D^{22} 1.5285, $[\alpha]_D^{22}$ =-114.9 (c 1, $CHCl_3$); it was obtained with a 95/5 diethylether/methanol mixture as eluant. ^1H NMR: δ 5.53-6.00 (m, 1H, CH=C); 4.06 (dd, 1H, J 7.0, 5.2, CH-O); 3.47-3.60 (m, 2H, CH_2-C=C); 3.14 (d, 1H, J 13.7, CH_A-SO); 2.58 (bs, 1H, OH); 2.53 (d, 1H, J 13.7, CH_B-SO); 1.10-1.86 (m, 7H); 1.10 and 0.86 (2s, 6H, CH_3). IR (ν max): 3340, 2950, 1635, 1385, 1075, 1030, 1000.
From compound (5) a 64:36 mixture of (6) was obtained (83%) as a thick oil, n_D^{22} 1.5086 $[\alpha]_D^{22}$ -88.8 (c 1, $CHCl_3$). The ^1H NMR spectrum was essentially identical to that of the product of the mCPBA oxidation in CH_2Cl_2.

Isomerization of allylic sulphoxides (4a), (4b), (6). The solutions (c 0.5, toluene) were contained in a temperature controlled 1 dm polarimeter cell and rotations were recorded as a function of time using a Perkin Elmer 241 spectropolarimeter operating at 436 nm. Residual rotations (α_∞) were determined by letting the epimerizations proceed to constant rotations. Equilibrium diastereoisomeric compositions were evaluated by ^1H NMR analysis.

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