Asymmetric synthesis of epoxides from aldehydes mediated by (+)-(2*R*,5*R*)-2,5-dimethylthiolane

Karine Julienne,[a] Patrick Metzner *[a] and Vivien Henryon[b]

[a] *Laboratoire de Chimie Moléculaire et Thio-organique (UMR CNRS 6507), ISMRA-Université, 6, boulevard du Maréchal Juin, 14050 Caen, France. E-mail: Patrick.Metzner@ismra.fr*

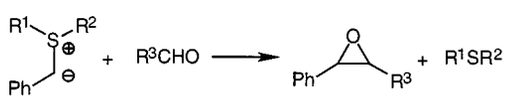
[b] *Rhône Poulenc Industrialisation, Centre de Recherches des Carrières, 85, avenue des Frères Perret, 69192 Lyon, France*

Received (in Cambridge) 30th September 1998, Accepted 28th January 1999

Nonracemic epoxides were prepared by reaction of (+)-(2*R*,5*R*)-2,5-dimethylthiolane, benzyl bromide and a mineral base with an aldehyde. Various parameters (solvent, base, aldehyde, sulfide) have been investigated. These studies led to the optimisation of a practical and simple procedure. Acetonitrile or *tert*-butyl alcohol were used in the presence of water and potassium or sodium hydroxide at room temperature. These conditions gave 87–93% yields with aromatic or branched aliphatic aldehydes and enantiomeric excesses ranged from 66 to 96%. Kinetic studies and stereochemical analyses have been carried out and a transition state was suggested to rationalize the observed stereochemistry.

Introduction

Efficient asymmetric epoxidation reactions from sulfur ylides and carbonyl compounds have begun to emerge [1,2] these last few years (Scheme 1). The use of various chiral sulfides has been

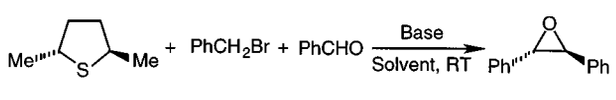


Scheme 1

investigated for either one- (one pot reaction) [3–13] or two-steps (pre-isolation of the sulfonium salt) [14–20] procedures. Catalytic cycles have also been reported.[3,6,8,9] Our contribution brings progress mostly in terms of simplicity. *trans*-2,5-Dimethylthiolane is among the most simple C_2 symmetric sulfides one can imagine. This molecule had never been used in any efficient asymmetric process. We achieved the preparation of the enantiopure (+)-(2*R*,5*R*)-dimethylthiolane **1** in excellent yield (95%) over two steps from commercial C_2 symmetric (2*S*,5*S*)-hexanediol. Similar results were reported [21] simultaneously by Haufe *et al.* Enzymatic [22–27] or chemical [28–32] synthesis of diols with C_2-symmetry has been extensively reported. Interesting is the fact that baker's yeast [22] and *Pichia farinosa* yeast [27] lead selectively to each of the opposite enantiomers. Both enantiomers of our chiral thiolane auxiliary are thereby potentially available to lead to the opposite asymmetric inductions in the epoxidation process. This last point is an important feature of a general method for asymmetric synthesis. A further attractive feature of our sulfide is the easy extension to various substituted derivatives (diethyl- and diisopropylthiolanes). Indeed the corresponding diol precursors can be made available.[28,30] The simplicity and flexibility of the designed sulfide make it highly attractive and our first results have been reported in a preliminary note.[33] In this full paper we report a detailed analysis of the asymmetric preparation of epoxides mediated by dimethylthiolane **1** with optimisation of the various parameters through their effects on yield and stereoselectivity, and kinetic approaches of the steps involved in a one pot reaction.

Results and discussion

Choosing the chiral auxiliary is obviously critical for the outcome of an asymmetric synthesis. In our case, we show that, in turn, the efficiency of the chiral auxiliary is highly sensitive to the epoxidation reaction conditions. In other words, the reaction conditions are critical, not only for the chemical outcome of the reaction, but also for the level of asymmetric induction provided by the chiral auxiliary. We now report how we have tackled this issue. Stilbene oxide synthesis (Scheme 2) was taken as a model for the study of the reaction conditions.

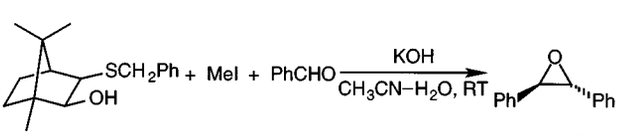


1 *trans*-(*S*,*S*)-**2**

Scheme 2

Standard basic conditions were first investigated with a biphasic system: CH_2Cl_2 (15 ml per mmol of **1**)–NaOH aq. 50% (4 ml per mmol of **1**). We intended to use a one pot procedure, with the *in situ* formation of the sulfonium salt and subsequently the ylide. Thus, thiolane (1 equiv.), benzyl bromide (1 equiv.) and benzaldehyde (1 equiv.) were mixed together at room temperature in the basic medium. The reaction was completed within 72 h and a good yield of stilbene oxide was obtained (86%). The *trans* isomer was not exclusively obtained and the diastereomeric excess (de) was 76%. A modest but encouraging enantiomeric excess (ee) of 42% was measured for the (*S*,*S*)-*trans* isomer.

We turned to the use of another heterogeneous medium: CH_3CN–KOH. Surprisingly, we had to confront a problem which had never been clearly mentioned in the literature. In anhydrous acetonitrile and in the presence of KOH, benzaldehyde was readily transformed into cinnamonitrile *via* deprotonation of acetonitrile. During preliminary investigations with camphor-derived sulfide **3** (Scheme 3), we solved this problem by adding a minimum amount of water to the reaction mixture (Table 1). We showed that at least 2% of water in acetonitrile



3 *trans*-(*R*,*R*)-**2**

Scheme 3

Table 1 Influence of the $CH_3CN–H_2O$ ratio[a]

Entry	$CH_3CN–H_2O$ (Vol)	Oxirane (%)	Aldehyde (%)	Cinnamonitrile (%)	de (%)	ee (%)
1	CH_3CN	0	58	42	—	—
2	99:1	0	91	9	—	—
3	98:2	75	25	0	91	68
4	95:5	73	27	0	90	74
5	90:10	76	24	0	86	73
6	75:25	91	9	0	88	76
7	50:50	93	7	0	84	76
8	H_2O	79	21	0	81	74

[a] Procedure: a solution of **3** (1 equiv.), methyl iodide (2 equiv.), benzaldehyde (1.2 equiv.) and powdered KOH (2 equiv.) in $CH_3CN–H_2O$ mixture (4 ml per mmol of **3**) was stirred at room temperature for 48 h.

Table 2 Influence of solvent[a]

Entry	9:1 Solvent mixture	Time/h	Oxirane yield (%)	de (%)	ee (%)
1	$CH_3CN–H_2O$	24	92	88	84
2	$DMF–H_2O$	1	—	—	—
3	$DMSO–H_2O$	2	15	88	64
4	$EtOH–H_2O$	72	15	84	94
5	$Pr^iOH–H_2O$	72	59	86	90
6	$Bu^tOH–H_2O$	48	92	86	88
7	H_2O	96	90	74	86
8	H_2O–EtOH	96	87	78	83
9	$H_2O–Pr^iOH$	96	90	76	84

[a] Procedure: a solution of **1** (1 equiv.), benzyl bromide (2 equiv.), benzaldehyde (1 equiv.) and powdered KOH (2 equiv.) in 9:1 solvent mixture (4 ml per mmol of **1**) was stirred at room temperature.

was necessary to avoid cinnamonitrile formation and for epoxide to be formed instead. In a reaction mixture containing 5% or more of water, we could measure the same enantiomeric excess values as those reported by Dai and coworkers.[9] The reaction could even be carried out in water; while the diastereoselectivity was decreased, the enantioselectivity was similar.

The synthesis of stilbene oxide was then carried out, *via* (2*R*,5*R*)-dimethylthiolane **1**, in a 9:1 mixture of CH_3CN and H_2O at room temperature (Table 2, entry 1). The reaction was completed in 24 hours. The crude product, according to ^1H NMR after work-up, was very clean and a high yield (92%) was obtained after purification on silica gel. Moreover, both the enantioselectivity and the diastereoselectivity, were much better (88% de, 84% ee) than those measured in dichloromethane (76% de, 42% ee).

This first high stereoselectivity led us to further investigate solvent effects. Various solvents were used in a 9:1 mixture with water (Table 2). In some cases, the yield of stilbene oxide was dramatically decreased due to predominant side reactions that consume either benzaldehyde or benzyl bromide. In DMF (entry 2), no epoxide was observed because benzyl bromide was hydrolysed into benzyl alcohol in 1 hour under these conditions. In DMSO (entry 3), benzyl bromide was transformed to dibenzyl ether (solvolysis and Williamson alkylation) and benzaldehyde disappeared at the same time (Cannizzaro reaction). In EtOH (entry 4), benzyl bromide was readily transformed into benzyl ethyl ether and again the yield for stilbene oxide was very low (15%). In Pr^iOH (entry 5), a slow transformation of benzyl bromide into benzyl alcohol and ethers was observed. A moderate yield for stilbene oxide was thus obtained (59%).

Using $CH_3CN–H_2O$, $Bu^tOH–H_2O$ or H_2O as solvent (entries 1,6,7) provided excellent yields of epoxide (>90%). However, with CH_3CN, a benzyl bromide consuming reaction was also observed: tribenzylamine was formed from acetonitrile and benzyl bromide in the presence of KOH. The use of more than one equivalent of benzyl bromide and KOH is therefore recommended to achieve a high yield.

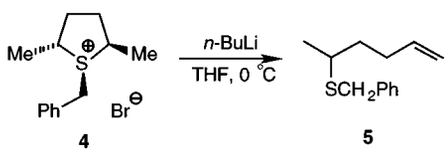
Table 3 Influence of base[a]

Entry	Base	Time/ days	Oxirane yield (%)	de (%)	ee (%)
1	KOH	4	87	86	88
2	NaOH	4	90	86	88
3	$NaHCO_3$	7	—	—	—
4	Na_2CO_3	7	49	88	90

[a] Procedure: a solution of **1** (1 equiv.), benzyl bromide (1.2 equiv.), benzaldehyde (1 equiv.) and powdered base (1.2 equiv.) in $Bu^tOH–H_2O$ 9:1 (4 ml per mmol of **1**) was stirred at room temperature.

The best and very high enantiomeric excess (94%) was measured in $EtOH–H_2O$ 9:1 (entry 4). But we have already noticed that the yield in this solvent was very low. Two experiments were thus carried out in mixtures of an alcohol and water with a reverse ratio of 1:9 (entries 8,9). First we expected a better yield (no side reaction), and this was achieved, and second to maintain the enantioselectivity, but the de and ee were similar to those obtained in water, *e.g.* decreased. Finally, considering the three parameters, yield, de and ee, a 9:1 mixture of Bu^tOH and water (entry 6) was the optimal solvent for the epoxidation reaction.

Base strength was then investigated (Table 3). Four experiments were carried out in $Bu^tOH–H_2O$ 9:1. Changing the counter-cation from K^+ to Na^+ (entries 1,2) did not make any difference. A weaker base than KOH or NaOH was not suitable. Sodium hydrogen carbonate (entry 3) did not provide any epoxidation. Sodium carbonate (entry 4) afforded a very slow conversion of benzaldehyde into stilbene oxide. Nevertheless the epoxidation reaction did occur. In contrast, a strong base such as *n*-BuLi, used in anhydrous THF, led to the ring cleavage of the ylide (Scheme 4). The thiolanium salt **4** was isolated from



4 **5**

Scheme 4

condensation of **1** and benzyl bromide in acetone at room temperature. Addition of *n*-butyllithium at 0 °C afforded instantaneously the sulfide **5**. We assume that the mechanism involves an α′,β-elimination.[34,35] The ylide formation is followed by an intramolecular elimination. This mechanism had never been observed during our epoxidation reactions in protic conditions, where the ylide was formed reversibly. We thus believe that the low equilibrium concentration of the ylide, compared to the high concentrations of benzaldehyde (epoxidation) and water (reprotonation), is the key to an efficient epoxidation reaction avoiding ring cleavage of the ylide. We therefore decided not to further investigate epoxidation reactions in aprotic conditions. Moreover it avoids isolation of the sulfonium salt that cannot

Table 4 Asymmetric synthesis of oxiranes[a]

		$CH_3CN–H_2O$ 9:1 (24 h)			$Bu^tOH–H_2O$ 9:1 (48 h)		
Entry	Aldehyde	Yield (%)	de (%)	ee (%)	Yield (%)	de (%)	ee (%)
1	PhCHO	92	88	84	92	86	88
2	*p*-ClPhCHO	93	86	76	89	84	86
3	*p*-MePhCHO	92	82	66	88	84	88
4	*c*-C_6H_{11}CHO	90	50	94	87	30	96
5	*n*-BuCHO	7	40	93	—	—	—

[a] Procedure: a solution of **1** (1 equiv.), benzyl bromide (2 equiv.), aldehyde (1 equiv.) and powdered KOH (2 equiv.) in $CH_3CN–H_2O$ 9:1 (4 ml per mmol of **1**), or NaOH (2 equiv.) in $Bu^tOH–H_2O$ 9:1 (4 ml per mmol of **1**), was stirred at room temperature for 24 or 48 h.

be obtained in high yields in anhydrous solvents such as THF, diethyl ether or dichloromethane, because of an unfavourable equilibrium constant. Thus we also avoided the use of silver or sodium salts[36] ($AgBF_4$, $NaBF_4$) to generate, isolate and store the corresponding sulfonium salts.

Reactions in $Bu^tOH–H_2O$ 9:1 showed that reducing the base and benzyl bromide stoichiometries from 2 to 1.2 equivalents (Table 2, entry 4 and Table 3, entry 1,2) doubled the reaction time to 4 instead of 2 days. On the other hand the use of a large excess of KOH or NaOH led to dibenzyl ether formation and no epoxidation. Our standard conditions thus involve 2 equivalents of a mineral base (KOH or NaOH) and benzyl bromide.

It was also observed that at a higher temperature (100 °C), the epoxidation reaction was still very clean and completed in only 3 hours (79% yield) but as anticipated the stereoselectivity was decreased (74% de, 70% ee). Further reactions were then carried out at room temperature (20–24 °C).

Benzylidenation of various aldehydes was achieved in $CH_3CN–H_2O$ 9:1 and $Bu^tOH–H_2O$ 9:1 using either KOH or NaOH (Table 4). Reactions were completed at room temperature within 24 hours in acetonitrile and 48 hours in *tert*-butyl alcohol. Aromatic and aliphatic aldehydes were used.

Benzylidene transfer is quantitative (entries 1–4) and excellent yields, ranging from 87 to 93%, were obtained after purification on silica gel. The observation that the enantiomeric excess is increased in *tert*-butyl alcohol is confirmed for aldehydes other than benzaldehyde. Furthermore, smaller ee variations were observed from one substrate to another: 86–96% instead of 66–94% in acetonitrile.

A limit to sulfur ylide epoxidation is usually encountered with aliphatic aldehydes as they are very prone to enolisation and subsequent aldol reaction. We nevertheless examined two substrates: cyclohexanecarbaldehyde and valeraldehyde (entries 4,5). The latter example led to a mediocre oxirane yield whereas an excellent yield was secured with the branched cyclohexanecarbaldehyde as well as an excellent enantioselectivity of 96% for the *trans*-oxirane.

Diastereoisomeric excesses were about 85% when starting from aromatic aldehydes, but values of 50 and 30% were measured from cyclohexanecarbaldehyde. So there is also an issue of diastereoselectivity for the epoxidation reaction. This question was recently examined by Aggarwal *et al.*[37] It was shown that kinetic and thermodynamic factors control the stereoselectivity. The one pot epoxidation procedure involves four steps: benzylthiolanium formation, deprotonation, condensation of the ylide with benzaldehyde and betaine ring closure. We have studied the kinetics of the first two steps.

Dimethylthiolane **1** and two equivalents of benzyl bromide were brought together in a 9:1 mixture of $CD_3CN–D_2O$. The conversion of thiolane into benzylthiolanium bromide **4** *versus* the reaction time was measured by ^1H NMR (Fig. 1). The reaction mixture composition was stable after about 20 hours. The equilibrium ratio of sulfide:sulfonium salt was 5:95. The sulfonium salt formation is reversible, slow, and is probably a rate determining step.

To monitor the deprotonation, two equivalents of KOD (compared to the initial amount of chiral auxiliary) were added

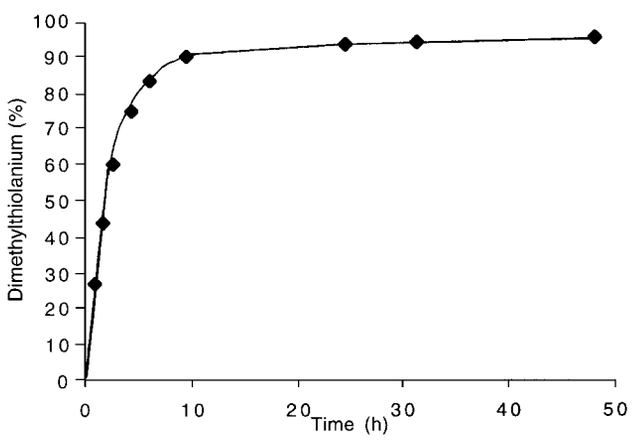


Fig. 1 Dimethylthiolanium salt **4**–dimethylthiolane **1** equilibrium.

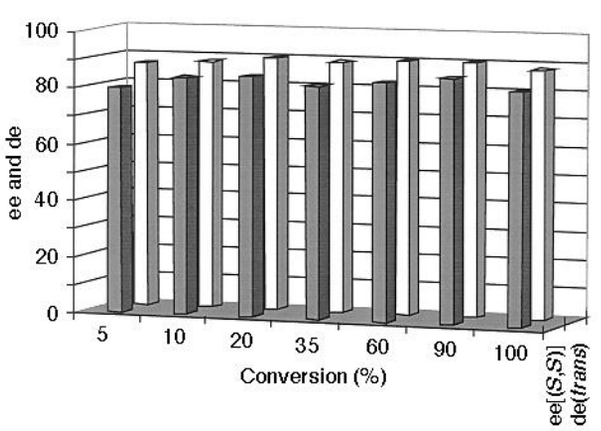


Fig. 2 Linearity of diastereo- and enantiomeric excess values for the formation of stilbene oxide.

to the 95:5 thiolanium–thiolane mixture. A ^1H NMR spectrum was run 10 minutes after addition: the benzyl hydrogens were completely exchanged within this time. So the ylide was formed rapidly and reversibly. The thiolanium salt deprotonation cannot be a rate determining step. At the same time, and as previously emphasised, the high reversibility due to protic conditions allows the ylide to be kept at a low concentration. Reversibility avoids ring cleavage and rapidity enables epoxidation.

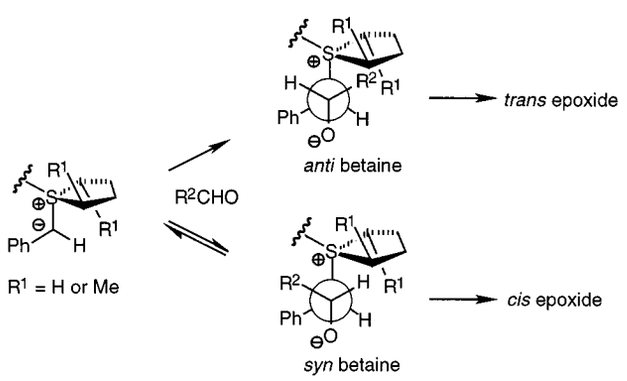
The reaction between the ylide and the aldehyde is believed to be partially reversible depending on which diastereomer of the betaine is formed.[37] Formation of the *anti*-betaine is irreversible but formation of the *syn*-betaine is partially reversible. There is no evidence that ring closure of the betaine to give the epoxide is reversible. We therefore monitored the one pot epoxidation reaction (conversion of benzaldehyde into epoxide, de and ee) at various time intervals up to 15 h (time required to go to completion) but did not observe any change in de or ee with time (Fig. 2, de and ee *versus* conversion). This suggests (although does not prove) that ring closure of the betaine is irreversible. Thus, the stereochemical determining step must be

Table 5 Diastereoselectivity issue[a]

		Thiolane (tetrahydrothiophene)		Dimethylthiolane **1**	
Entry	Aldehyde	Yield (%)	de (%)	Yield (%)	de (%)
1	PhCHO	92	70	92	88
2	*p*-ClPhCHO	93	76	93	86
3	*c*-C_6H_{11}CHO	92	0	90	50

[a] Procedure: a solution of thiolane (tetrahydrothiophene) or dimethylthiolane **1** (1 equiv.), benzyl bromide (2 equiv.), aldehyde (1 equiv.) and powdered KOH (2 equiv.) in CH_3CN–H_2O 9:1 (4 ml per mmol of sulfide) was stirred at room temperature for 24 h.

formation of the *anti*-betaine which implies that non-bonded interactions in the transition state leading to betaine formation determine the enantiomeric excess of the final epoxide. It supports the model (Scheme 5) that we have proposed [33] to account



Scheme 5

for the enantioselectivity observed in favour of the (*S,S*)-*trans*-oxiranes from (2*R*,5*R*)-dimethylthiolane **1**.

An increased *trans* selectivity was observed (Table 5) from thiolane (tetrahydrothiophene) to dimethylthiolane **1**. It was improved in all cases and a dramatic change was observed for the aliphatic aldehyde: de went up from 0% when R = H to 50% when R = Me. So the diastereoselectivity is not only dependent on the solvent (Table 2) and on the aldehyde (Table 4) but is also dependent on the sulfide (Table 5). Non-bonded interactions in the transition state do not give a satisfying rationalisation of this effect. Aggarwal's results [37] give in return an explanation: while the formation of the *trans*-betaine is irreversible, the formation of the *syn*-betaine is reversible. The higher *trans* selectivity observed for aromatic aldehydes, in solvents of increasing polarity (CH_2Cl_2 < DMSO, CH_3CN or alcohols) and with sulfur ylides of increasing steric hindrance, is due to a higher degree of reversibility. The whole mechanism is shown in Scheme 5. It must also be noted that the *cis*-oxirane, isolated when starting from cyclohexanecarbaldehyde, is produced with a high enantioselectivity (88%) and we hope to establish its absolute configuration in due time.

Conclusion

The epoxidation reaction conditions, *via* the simple C_2-symmetric chiral auxiliary (2*R*,5*R*)-dimethylthiolane **1**, have been studied. Our sulfide had been previously mentioned in the literature as a nonefficient chiral auxiliary. We have shown that it does not even lead to any epoxidation reaction due to ring cleavage of the corresponding ylide when using a strong base. However, we have proved through this study that conditions exist where a good asymmetric induction can be observed. They involve a practical procedure under mild conditions; a one pot process avoiding preformation and isolation of the sulfonium salt; and a protic reaction mixture avoiding ring cleavage of the thiolanium salt. Our search for simplicity has been attained both for the structure, synthesis of the chiral auxiliary, and for the benzylidenation procedure. Excellent yields and enantioselectivities were reached and a general mechanism has been proposed. Future prospects include the development of a practical catalytic version, the extension to a variety of halides and the synthesis of monosubstituted epoxides as well as other 3-membered rings such as aziridines and cyclopropanes.

Experimental

^1H and ^{13}C NMR spectra were recorded using a Bruker A. C. 250 spectrometer. Chemical shifts are given in ppm; *J* values are given in Hz. Mass spectra were obtained using a Nermag Riber R10 RH instrument operating in EI mode at 70 eV. IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrometer. Specific optical rotations (given in 10^{-1} deg cm^2 g^{-1}) were measured at 589 nm using a Perkin-Elmer 241 LC polarimeter. Mps stand uncorrected. Chromatographic purification of compounds was achieved with Merck 60 silica gel (63–200 μm). Thin layer chromatography (TLC) was used routinely to monitor the progress of epoxidation reactions. TLC plates were visualised by UV light and by treatment with a solution of molybdophosphoric acid (1 g in 100 ml *tert*-butyl alcohol) followed by thermal development. High pressure liquid chromatography (HPLC) was performed on a Waters instrument equipped with a M996 diode array detector (200–300 nm) and supported by a Millenium software, using a chiral OD column. Diastereomeric excesses were determined from ^1H NMR measurements from the crude products while enantiomeric excesses were determined by chiral HPLC after purification of the oxiranes on silica gel.

(+)-(2*R*,5*R*)-2,5-Dimethylthiolane 1

Compound **1** was prepared according to ref. 33 and isolated as a colourless oil, bp_{12mmHg} 37 °C; $[a]_D^{25}$ +119 (*c* 4.0, pentane); ν_{max}/cm^{-1} (NaCl) 2956 (CH_3), 2922 (CH_2), 2862, 2360, 1446, 1374 and 1250; δ_H[250 MHz; $CDCl_3$–TMS] 1.30 (6H, d, *J* 6.5, 2 C*H*$_3$), 1.49–1.57 (2H, m), 2.13–2.24 (2H, m) and 3.52–3.65 (2H, m); δ_C[63 MHz; $CDCl_3$–TMS] 22.8, 39.6 and 44.5; *m*/*z* 116 (M$^+$, 11%), 115 (18), 101 (18), 82 (52), 79 (47), 73 (37), 67 (67), 59 (41) and 55 (100) [Found: M, 116.0659. $C_6H_{12}S$ requires 116.06597].

(+)-(1*R*,2*S*,3*R*,4*S*)-1,7,7-Trimethyl-3-(benzylthio)bicyclo-[2.2.1]heptan-2-ol 3

Compound **3** was prepared according to ref. 38–40 and isolated as a colourless oil, $bp_{0.15mmHg}$ 154–156 °C; $[a]_D^{30}$ +5.5 (*c* 2.0, acetone); ν_{max}/cm^{-1} (NaCl) 3430 (OH), 2952 (CH_3) and 2880; δ_H[250 MHz; $CDCl_3$–TMS] 0.75 (3H, s, C*H*$_3$), 0.93 (3H, s, C*H*$_3$), 0.99 (3H, s, C*H*$_3$), 1.01–1.08 (2H, m), 1.36–1.52 (1H, m), 1.68–1.74 (1H, m), 1.90 (1H, d, $J_{4,5exo}$ 4.3, H_4), 2.67 (1H, d, $J_{OH,2}$ 4.4, O*H*), 2.94 (1H, d, $J_{3,2}$ 7.5, H_3), 3.47 (1H, dd, $J_{2,OH}$ 4.4 and $J_{2,3}$ 7.5, H_2), 3.70 (2H, s, SC*H*$_2$Ph) and 7.26–7.33 (5H, m, H_{arom}); δ_C[63 MHz; $CDCl_3$–TMS] 11.9, 21.1, 21.5, 29.2, 33.3, 39.3, 46.9, 49.8, 53.1, 57.0, 79.1, 127.4, 128.8, 128.9 and 138.3; *m*/*z* 276 (M$^+$, 5%), 185 (M$^+$ − CH_2Ph, 10), 123 (M$^+$ − SCH_2Ph, 10), 91 (PhCH$_2^+$, 100) and 65 ($C_5H_5^+$, 15).

General procedure for the preparation of epoxides using camphor-derived sulfide 3, dimethylthiolane 1 or tetrahydrothiophene (Tables 1–5)

Experiments were run using the sulfide on a 0.2 mmol scale. Following indicated stoichiometries (Tables 1–5), a solution of sulfide, alkyl halide, aldehyde and powdered base in solvent was stirred at room temperature (20–24 °C). After the indicated reaction time, water was added and the aqueous phase was extracted with dichloromethane. The organic layer was dried over magnesium sulfate, filtered and then concentrated. The crude product was submitted to column chromatography

(70 : 30 petroleum ether–dichloromethane) to afford the desired oxirane. Oxirane structures were assigned by comparison with the literature data.[41] Conditions for chromatographic enantiomer analysis (solvents, retention times) were carried out as reported in ref. 33.

Obtention of benzyl (1-methylpent-4-enyl) sulfide 5

To a solution of **1** (58 mg, 0.5 mmol) in acetone (0.4 ml) was added benzyl bromide (59 µl, 0.5 mmol). The solution was stirred at room temperature (20–24 °C) for 20 h. After concentration, diethyl ether was added and the thiolanium salt **4** was filtered, and then dried under reduced pressure (30 mg, 0.1 mmol). Anhydrous THF (2 ml) was added and then *n*-butyllithium (1.6 M in hexane, 63 µl, 0.1 mmol) was slowly added at 0 °C. After 5 min, water was added. The product was extracted twice with diethyl ether. The organic phase was washed with water, dried over magnesium sulfate, filtered and then concentrated. Sulfide **5** (20 mg, 0.1 mmol) was isolated as a colourless oil, δ_H[250 MHz; $CDCl_3$–TMS] 1.26 (3H, d, *J* 6.7, CH_3), 1.46–1.73 (2H, m, CH_2), 2.08–2.17 (2H, m, CH_2), 2.66 (1H, sextet, *J* 6.7, C*H*), 3.73 (2H, s, SCH_2Ph), 4.91–5.07 (2H, m, CH_2=), 5.66–5.82 (1H, m, C*H*=) and 7.22–7.35 (5H, m, H_{arom}); δ_C[63 MHz; $CDCl_3$–TMS] 22.2, 29.9, 36.1, 38.2, 38.9, 114.4, 126.9, 128.4, 128.9, 138.3 and 140.6.

Formation of (2*R*,5*R*)-*S*-benzyl-2,5-dimethylthiolanium bromide 4 in CD_3CN–D_2O 9 : 1 and further deprotonation

Dimethylthiolane **1** (24 mg, 0.2 mmol) and benzyl bromide (48 µl, 0.4 mmol) were introduced into an NMR tube in a 9 : 1 CD_3CN–D_2O mixture (0.8 ml). TMS was used as internal standard. Thiolanium salt formation was then monitored by ^{1}H NMR. The **1** : **4** ratio *versus* time was measured on the basis of signals of the methyl groups of thiolane **1** and thiolanium salt **4**. Time (h)/**1** : **4**: 0.75/73 : 27, 1.5/56 : 44, 2.5/40 : 60, 4.25/25 : 75, 6/17 : 83, 9.5/10 : 90, 24.45/7 : 93, 31.3/6 : 94, 48/5 : 95 and 6 days/6 : 94. **1**: δ_H[250 MHz; CD_3CN–D_2O 9 : 1–TMS] 1.24 (6H, d, *J* 6.6, 2 CH_3), 1.46–1.54 (2H, m), 2.12–2.24 (2H, m) and 3.51–3.61 (2H, m); δ_C[63 MHz; CD_3CN–D_2O 9 : 1–TMS] 22.4, 39.6 and 44.5. **4**: δ_H[250 MHz; CD_3CN–D_2O 9 : 1–TMS] 1.09 (3H, d, *J* 6.9, CH_3), 1.63 (3H, d, *J* 6.8, CH_3), 1.75–1.93 (1H, m), 2.12–2.32 (1H, m), 2.47–2.58 (2H, m), 3.91–4.07 (1H, m), 4.17–4.32 (1H, m), 4.43 and 4.64 (2H, AB system, *J* 12.3, SCH_2Ph) and 7.29–7.62 (5H, m, H_{arom}); δ_C[63 MHz; CD_3CN–D_2O 9 : 1–TMS] 14.2, 18.3, 36.9, 37.1, 40.8, 57.8, 60.6, 128.6, 130.3, 130.4 and 130.9.

After 6 days, KOD (40 wt% in D_2O, 57 mg, 0.4 mmol) was added to the solution. ^{1}H NMR was run ten minutes after addition: the SCH_2Ph signal had disappeared (SCD_2Ph).

Formation of stilbene oxide 2 using dimethylthiolane 1 in CH_3CN–H_2O 9 : 1

To a solution of **1** (93 mg, 0.8 ml) in a 9 : 1 CH_3CN–H_2O mixture (3.2 ml) were added benzyl bromide (190 µl, 1.6 mmol), benzaldehyde (82 µl, 0.8 mmol) and powdered KOH (90 mg, 1.6 mmol). The mixture was stirred at room temperature (20–24 °C) and samples (0.4 ml) were taken at different times. Products were extracted with dichloromethane and crude mixtures were analysed by ^{1}H NMR and HPLC in order to measure benzaldehyde conversion into stilbene oxide, diastereo- and enantiomeric excesses *versus* time. Time (h) / conversion (%)/de (%)/ee (%): 0.25/5/87/80, 0.5/10/88/84, 1/20/90/85, 2/35/89/82, 4/60/90/84, 8/90/90/86 and 24/100/88/82.

Acknowledgements

We thank CNRS and Rhône Poulenc for their generous support for this study.

References

1 A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341.
2 V. K. Aggarwal, *Synlett*, 1998, 329.
3 N. Furukawa, Y. Sugihara and H. Fujihara, *J. Org. Chem.*, 1989, **54**, 4222.
4 V. K. Aggarwal, H. Abdel-Rahman, R. V. H. Jones, H. Y. Lee and B. D. Reid, *J. Am. Chem. Soc.*, 1994, **116**, 5973.
5 V. K. Aggarwal, A. Thompson, R. V. H. Jones and M. C. H. Standen, *Tetrahedron: Asymmetry*, 1995, **6**, 2557.
6 V. K. Aggarwal, J. G. Ford, A. Thompson, R. V. H. Jones and M. C. H. Standen, *J. Am. Chem. Soc.*, 1996, **118**, 7004.
7 V. K. Aggarwal, L. Bell, M. P. Coogan and P. Jubault, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2037.
8 V. K. Aggarwal, J. G. Ford, S. Fonquerna, H. Adams, R. V. H. Jones and R. Fieldhouse, *J. Am. Chem. Soc.*, 1998, **120**, 8328.
9 A.-H. Li, L.-X. Dai, X.-L. Hou, Y.-Z. Huang and F.-W. Li, *J. Org. Chem.*, 1996, **61**, 489.
10 S. S. Taj and R. Soman, *Tetrahedron: Asymmetry*, 1994, **5**, 1513.
11 S. S. Taj, A. C. Shah, D. Lee, G. Newton and R. Soman, *Tetrahedron*: *Asymmetry*, 1995, **6**, 1731.
12 C. P. Baird and P. C. Taylor, *J. Chem. Soc., Chem. Commun.*, 1995, 893.
13 C. P. Baird and P. C. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3399.
14 T. Durst, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1993, **74**, 215.
15 L. Breau, W. W. Ogilvie and T. Durst, *Tetrahedron Lett.*, 1990, **31**, 35.
16 L. Breau and T. Durst, *Tetrahedron: Asymmetry*, 1991, **2**, 367.
17 A. Solladié-Cavallo and A. Adib, *Tetrahedron*, 1992, **48**, 2453.
18 A. Solladié-Cavallo and A. Diep-Vohuule, *J. Org. Chem.*, 1995, **60**, 3494.
19 A. Solladié-Cavallo and A. Diep-Vohuule, *Tetrahedron: Asymmetry*, 1996, **7**, 1783.
20 V. K. Aggarwal, M. Kalomiri and A. P. Thomas, *Tetrahedron: Asymmetry*, 1994, **5**, 723.
21 S. Otten, R. Fröhlich and G. Haufe, *Tetrahedron: Asymmetry*, 1998, **9**, 189.
22 J. K. Lieser, *Synth. Commun.*, 1983, **13**, 765.
23 M.-J. Kim, I. S. Lee, N. Jeong and Y. K. Choi, *J. Org. Chem.*, 1993, **58**, 6483.
24 M.-J. Kim and I. S. Lee, *Synlett*, 1993, 767.
25 G. Caron and R. J. Kazlauskas, *Tetrahedron: Asymmetry*, 1994, **5**, 657.
26 H. Nagai, T. Morimoto and K. Achiwa, *Synlett*, 1994, 289.
27 H. Ikeda, E. Sato, T. Sugai and H. Ohta, *Tetrahedron*, 1996, **52**, 8113.
28 M. J. Burk, J. E. Feaster and R. L. Harlow, *Tetrahedron: Asymmetry*, 1991, **2**, 569.
29 M. J. Burk, J. E. Feaster, W. A. Nugent and R. L. Harlow, *J. Am. Chem. Soc.*, 1993, **115**, 10125.
30 M. J. Burk, T. G. P. Harper and C. S. Kalberg, *J. Am. Chem. Soc.*, 1995, **117**, 4423.
31 G. Solladié and N. Huser, *Tetrahedron Lett.*, 1994, **35**, 5297.
32 J. Bach, R. Berenguer, J. Garcia, T. Loscertales, J. Manzanal and J. Vilarrasa, *Tetrahedron Lett.*, 1997, **38**, 1091.
33 K. Julienne, P. Metzner, V. Henryon and A. Greiner, *J. Org. Chem.*, 1998, **63**, 4532.
34 W. H. Saunders, S. D. Bonadies, M. Braunstein, J. K. Borchardt and R. T. Hargreaves, *Tetrahedron*, 1977, **33**, 1577.
35 A. C. Knipe, in *The Chemistry of the Sulphonium Group – The Chemistry of Functional Groups*, ed. C. J. M. Stirling and S. Patai, Chichester, 1981, Part 1, p. 313.
36 V. K. Aggarwal, A. Thompson and R. V. H. Jones, *Tetrahedron Lett.*, 1994, **35**, 8659.
37 V. K. Aggarwal, S. Calamai and J. Gair Ford, *J. Chem. Soc., Perkin Trans. 1*, 1997, 593.
38 R. J. Goodridge, T. W. Hambley, R. K. Haynes and D. D. Ridley, *J. Org. Chem.*, 1988, **53**, 2881.
39 D.-S. Lee, S.-M. Hung, M.-C. Lai, H.-Y. Chu and T.-Y. Yang, *Org. Prep. Proced. Int.*, 1993, **25**, 673.
40 S.-M. Hung, D.-S. Lee and T.-K. Yang, *Tetrahedron Lett.*, 1990, **1**, 873.
41 V. K. Aggarwal, H. Abdel-Rahman, L. Fan, R. V. H. Jones and M. C. H. Standen, *Chem. Eur. J.*, 1996, **2**, 1024.

Paper 8/07623E