

Preparation of Optically Active Epoxides Via Sulfur Ylides. Origin of the Chiral Induction.

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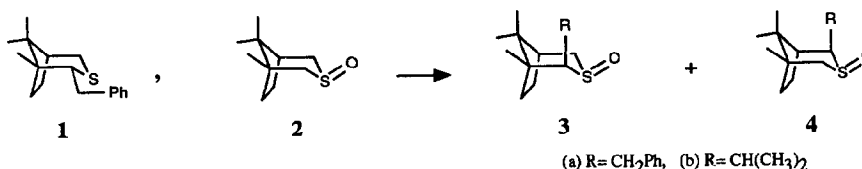
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Abstract: The sulfonium ylide derived from (1R, 2S, 3R, 5S)-2,3-dibenzyl-1,8,8-trimethyl-3-thianiumbicyclo-[3.2.1]octane perchlorate **6** (prepared from (1R,3S)-(+)-camphoric acid) transfers its benzylidene group to some carbonyl compounds with ee's approaching enantiomeric purity. It is suggested that in this system the chiral induction is due to the facial selectivity at the ylide rather than the carbonyl carbon.

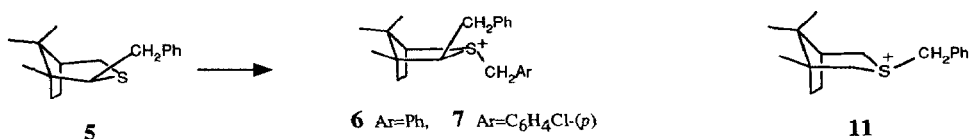
Recently we reported some encouraging results in the preparation of optically active epoxides by reaction of sulfur ylides, prepared from C_2 symmetric thiolanes with aromatic aldehydes.¹ In that approach we considered only C_2 symmetric thiolanes since such compounds could yield only one sulfonium salt and hence likely only one ylide, thus increasing the chance of success in the chirality transfer. Examination of molecular models indicated that the thiane **1** should also yield a single sulfonium salt, the result of exo alkylation and thus have the potential for the preparation of optically active epoxides.

Based on literature precedent² we had expected that **1** would be available from the sulfoxide **2**³ via α -carbanion formation, benzylation and subsequent reduction. In the event, the first two steps of this sequence afforded, to our surprise, the axially substituted products **3** and **4a**.⁴ The structure of **3** was determined by single crystal X-ray structure diffraction;⁵ it was also consistent with an extensive series of nOe experiments.⁶ Similar mnr experiments also clearly pointed to the structures **4a** and **4b**⁷ and not the equatorially substituted products⁸. These unusual results and other reactions of the carbanions derived from **2** will be considered in a separate publication.

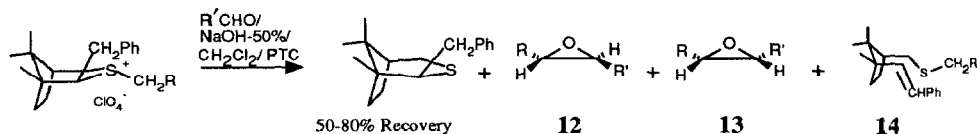


Reduction of the sulfoxides **3**, **4a** and **4b** with SnCl₂/CH₃COCl in CH₃CN-DMF at 0°C⁹ afforded the expected thianes. The coupling constants between the remaining hydrogens at C-4 and C-5 strongly support an thiane ring in a half chair conformation.¹⁰

S-Alkylation of **5** with PhCH₂Br or *p*-ClC₆H₄CH₂I in dry ether in the presence of AgClO₄ afforded **6** and **7**



respectively, as white foams. The nmr spectrum of **6** showed that the expected 2 benzylic AB quartets, one at $\delta=4.17$ and 4.53 ppm and the other at $\delta=2.83$ and 3.35 ppm due to the S⁺-benzyl and C-benzyl groups respectively. The remaining pattern was quite similar to that observed for **5** except for the increased deshielding of the hydrogens α to the sulfur. Irradiation of the S-benzyl hydrogens showed nOe enhancements of the two syn hydrogens at C-2 and C-4 and the endo hydrogens of the 2-carbon bridge. Thus S-alkylation had occurred preferentially trans to the C-2 benzyl group. Similar stereochemical results are assumed to have occurred for the other sulfonium salts **7-10**. In contrast, for **11** irradiation of the S-benzyl group gave nOe enhancements in the axial and equatorial hydrogens at C-2 and C-4. Thus equatorial S-alkylation had occurred preferentially.



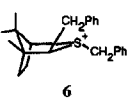
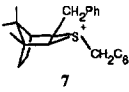
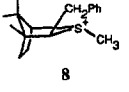
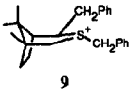
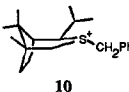
Reaction of **6** with benzaldehyde under PTC (CH₂Cl₂/50% NaOH/BTEAC), initially at 0°C then at room temp. for 3 h, afforded a mixture of *trans*- and *cis*-stilbene oxides **12** and **13** in 4.8:1 ratio (46%), together with recovered enantiomerically pure **5** (57%) and about 22% of the β -elimination product **14**. The stilbene oxides were carefully separated and the optical purity of the *trans* epoxide was determined as > 96% using chiral shift reagent [Eu(hfc)₃]. The rotation (-285°) clearly indicated the 2S,3S configuration.¹¹ Reaction of **6** with *p*-methylbenzaldehyde gave only *trans*-epoxide **12b**; again it was not possible to detect any enantiomeric impurity using the shift reagent. Benzylidene transfer from **6** to cyclohexanecarboxaldehyde under the usual conditions afforded a mixture of *trans*- and *cis*- epoxides, **12c** and **13c** in only fair yield. Both epoxides were shown by nmr shift experiments to have been formed with about 85% ee. When cyclohexanone was used as the carbonyl component the epoxide **12f** having the (S)-configuration¹² was obtained with >96 ee (see Table).

The transfer of the *p*-chlorobenzylidene group from **7** to formaldehyde gave the (S)-enantiomer of *p*-chlorostyrene oxide, **12d**, with 24% ee.¹³ In contrast, the transfer of the methylene group from the ylide derived from **8** to *p*-chlorobenzaldehyde afforded **12d** without significant chiral induction. The latter result is consistent with the lack of ee reported by Trost¹⁴ and Whitesell¹⁵ during the transfer of methylene groups to benzaldehyde from other chiral sulfonium salts.

Our results can be rationalized in the following manner. The ylide derived from the sulfonium salt **6** should adopt preferentially the conformation A rather than B since the aryl ring on the ylide have severe steric interactions with the endo hydrogens on the two-carbon bridge. Electrophilic attack by the carbonyl group on the ylide A will occur preferentially from the back (i.e. the Si-face) of the ylide). This fixes the chirality of that center as (R) in the intermediate betaine and as (S) in the final product.¹⁶ The chirality of the second center is dependent on the approach of the carbonyl compound to the ylide. The concept that facial selectivity with respect to the ylide rather than the carbonyl carbon controls the stereochemical outcome predicts that all transfers from A will result in products having preferentially the (S) chirality at the benzylic carbon derived from the ylide. The results shown in the Table verify this prediction.

The excess of the (R,R)-isomer of the *trans*-stilbene obtained from the ylides derived from the sulfonium salts

Table. Preparation of stilbene oxides via optically active sulfur ylides.^a

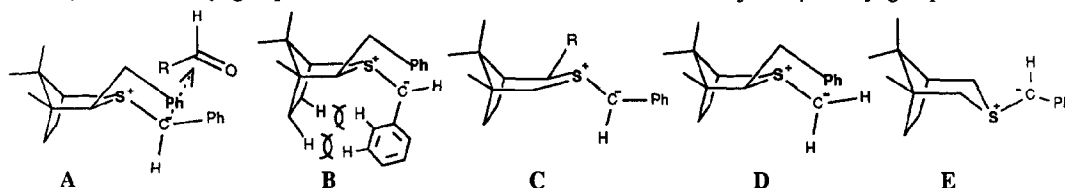
Sulphonium Perchlorate	Aldehyde or Ketone	Epoxides				Recovered Thiane	β -elimination (e.g. 14)
		12 (<i>trans</i>)		13 (<i>cis</i>)			
		Yield (%)	% ee ^b (config) ^c	Yield (%)	% ee ^b (config) ^c		
 6	PhCHO	12a	38 >96 (S,S)	13a	8 meso	57	22
	4-MeC ₆ H ₄ CHO	12b	32 >96 (S,S)			70	15
	C ₆ H ₁₁ CHO	12c	9 84 (-)	13c	14 86 (+)	56	32
	Cyclohexanone		12f <5	>96 (S) ¹²		46	35
 7	CH ₂ O		12d 49	24 (S) ¹³		84	10
	4-ClC ₆ H ₄ CHO		12d 46	<4 (S) ¹³		70	5
 8	C ₆ H ₅ CHO	12a	45 34 (R,R)	13a	12 <i>meso</i>	66	-
	C ₆ H ₅ CHO	12a	42 73 (R,R)	13a	20 <i>meso</i>	58	-
 9	4-ClC ₆ H ₄ CHO	12e	52 63 (R,R)	13e	25 66 (-)	68	-
	PhCHO	12a	39 15 (R,R)	13a	16 <i>meso</i>	82	-
 10	PhCHO	12a	39 15 (R,R)	13a	16 <i>meso</i>	82	-
	PhCHO	12a	39 15 (R,R)	13a	16 <i>meso</i>	82	-

a Typically the reactions were carried out in CH₂Cl₂/NaOH 50%/ cat. BnEt₃NHCl / CH₂Cl₂ - O°C on 1-mmol scale.

b From integration of Eu(hfc)₃-shifted, proton NMR spectra at 300 MHz of chiral epoxides.

c Based on $[\alpha]_D$ measurements.¹¹

9 and 10 is due to the blocking of the si-face of the ylide carbon by either the benzyl or isopropyl group (structure C). The lower chiral induction observed for the benzyl group transfer is probably due to the greater conformational mobility of the α -benzyl group in C vs A since the former lacks the additional adjacent β -methyl group.



Our hypothesis also allows us to explain the Trost¹⁴ and Whitesell¹⁵ results. The carbon of the methylene ylide D is not prochiral. If the approach of an aldehyde such as cyclohexanecarboxaldehyde to A is almost random with respect to the facial selectivity of the aldehyde, as evidenced by an almost 1:1 *trans/cis* product mixture then

approach of benzaldehyde to **D** should also show little or no selectivity and thus no chiral induction in the styrene oxide product is expected. In contrast, the *S-p*-chlorobenzyl analog of **A** reacts with formaldehyde to produce *p*-chlorostyrene oxide with 24% ee. Again the sense of chirality of the product is due to the facial selectivity in the attack on the ylide and not the carbonyl carbon. The formation of (R,R)-stilbene oxide from **11** suggests that in this case the ylide preferentially adopts structure **E**. A small preference for attack from the rear, in this case the re-face, would generate preferentially the (R,R)-product.

Our results should help in the design of more efficient optically active sulfide auxiliaries. A number of practical problems such as better overall yields and avoidance of the loss of chiral auxiliary via a β -elimination and the potential of conducting the reaction catalytically with respect to the chiral auxiliary remain to be solved.

Acknowledgement. The support of this research by NSERC (Canada) is gratefully acknowledged.

References and Footnotes

- (a) Breau, L.; Ogilvie, W.W. and Durst, T., *Tetrahedron Letters*, **1990**, *31*, 35; (b) see Furukawa, N.; Sugihara, Y; and Fujihara H., *J. Org. Chem.* **1989**, *54*, 4222, for non C_2 -symmetric sulfur ylide.
- (a) Bory S., Lett R., Moreau B. and Marquet A., *Tetrahedron Lett.*, (1972), 4921; (b) Bory S. and Marquet, A., *Tetrahedron Lett.*, (1973), 4125.
- Prepared from (+)-(1R, 3S)-camphoric acid by reduction, ditosylation, $Na_2S \cdot 9H_2O$ treatment and oxidation.
- All new compounds were carefully characterized by ir., 1H , ^{13}C nmr, HRMS and elemental analysis.
- Gabe, E., Bensimon, C., unpublished results.
- Irradiation of the axial methyl protons at C-8 (δ 1.19) showed 11% of nOe enhancement for the two signals at δ 2.78 and δ 2.76, which were attributed to -CHPh and the axial proton at C-4 respectively.
- The irradiation of the C-8 axial methyl protons of **4a** (δ 1.29) showed 8% of nOe enhancement for the two signals at δ 3.47 and δ 2.74, which were attributed to -CHPh and the axial proton at C-2. Similarly for **4b**, the irradiation of the C-8_{AX} methyl protons (δ 1.21) showed a 15% nOe enhancement for the isopropyl methine proton (δ 2.42) and a 10% nOe with the axial proton at C-2 (δ 2.76).
- An isomer of **3b**, having the isopropyl group equatorial at C-4, has also been isolated in 7% yield.
- Kaiser G.V., Cooper R.D.G., Koehler R.E., Murphy C.F., Webber J.A., Wright I.G. and Van Heyningen E.M., *J. Org. Chem.*, (1970), *35*, 2430-2433.
- Such a conformation which results in considerable reduction of the steric interactions between the newly introduced substituents and the syn C-8 methyl group, compared to the chair conformation, is also supported by calculations using P.C. Model 4.0 (Still and Allinger) Babu C., private communication.
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- Durst, T.; Viau, V.; Elzen, V.D.; and Nguyen, C.H.; *J. Chem. Soc. Chem. Commun.* **1971**, 1334.
- Groves, J.T.; Meyers, R.S.; *J. Am. Chem. Soc.* **1983**, *105*, 5791-5796, have reported a greater Eu(hfc)₃ induced shift for the benzylic hydrogen of (R)-4-chlorostyrene oxide than for the corresponding hydrogen in the (S)-isomer. See also Johnson, C.R.; Schroeck, C.W.; *J. Am. Chem. Soc.* **1973**, *95*, 7418-7423 and Groves, J.T.; Viski, P.; *J. Org. Chem.* **1990**, *55*, 3628-3634.
- Trost, B.M.; Hammen, R.F.; *J. Am. Chem. Soc.* **1973**, *95*, 962.
- Whitesell, J.; Presented at the 8th IUPAC Synthesis Conference, July 1988, Nancy, France; and private communication.
- It has been shown [(a) Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R.; *J. Am. Chem. Soc.* **1973**, *95*, 7424. (b) Townsend, J. M.; Sharpless, K.B.; *Tetrahedron Letters*, **1972**, 3313.] that attack of the ylide on the carbonyl compound represents the rate-determining step in the epoxide formation.