Stereospecific Synthesis of *S*-Phenyl-*S*-(sulfinylmethyl)-sulfoximines and their Stereoselective Alkylation under the Influence of the Two Chiral Centers

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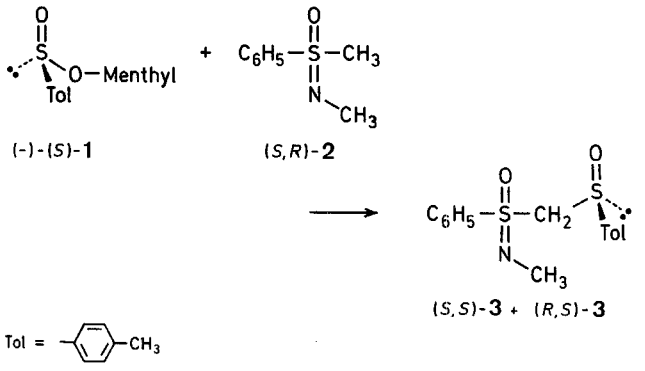
Chiral sulfur synthons[1,2] have been employed in the preparation of various classes of optically active derivatives, namely amines, alcohols, aldehydes, hydroxyacids, lactones, and esters[1-4]. Although high degrees of stereoselective bond formation have been achieved, the objective of further increasing the efficiency of asymmetric synthesis is still a challenge. Stereoselectivity induced by the synergic effect of two chiral groups in the molecule might represent an effective approach to this goal. We therefore prepared enantiomerically pure compounds having two chiral sulfur moieties β to each other, and examined their behaviour in asymmetric nucleophilic reactions.

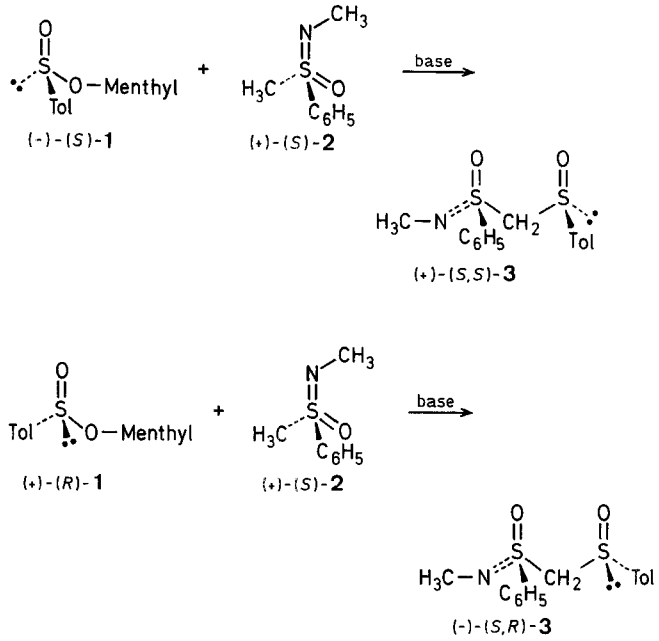
The preparation of *S*-(sulfinylmethyl)-sulfoximines, a new class of compounds, was accomplished by an Andersen-type reaction of sulfinic esters with metallated *N*,*S*-dimethyl-*S*-phenylsulfoximine. Thus, the condensation of the lithio derivative of racemic *N*,*S*-dimethyl-*S*-phenylsulfoximine [(*S*,*R*)-**2**] with (−)-menthyl (*S*)-*p*-toluenesulfinate[1] [(−)-(*S*)-**1**] affords a mixture of the diastereoisomeric *S*-(sulfinylmethyl)-sulfoximines (*S*,*S*)-**3** and (*R*,*S*)-**3** in a 1 : 1 ratio.



Separation of the two isomers of **3** was found to be difficult, however. We therefore performed the reaction with enantiomerically pure (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine[6] [(+)-(*S*)-**2**] and the diastereoisomerically pure menthyl *p*-toluenesulfinates (−)-(*S*)-**1** and (+)-(*R*)-**1**[5] and obtained the

0039-7881/82/0932-0767 $ 03.00

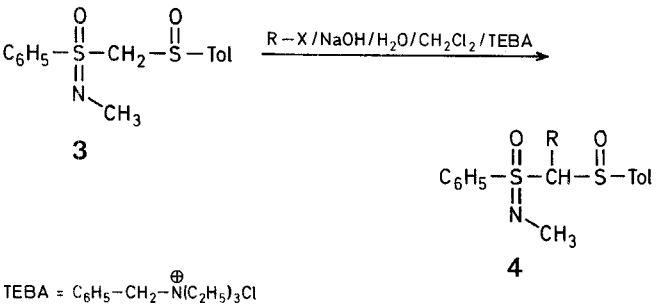
diastereoisomerically pure *N*-methyl-*S*-(4-methylphenylsulfinylmethyl)-*S*-phenylsulfoximines (+)-(*S,S*)-**3**, $[\alpha]_D^{25}$: +235° (acetone), and (−)-(*S,R*)-**3**, $[\alpha]_D^{25}$: −196° (acetone), respectively. The enantiomeric purity of compounds **3** may be checked by the careful inspection of the ^{1}H-N.M.R. spectra: the spectrum of (+)-(*S,S*)-**3** shows a singlet in the methylene proton region at $\delta = 4.3$ ppm, whereas the spectrum of (−)-(*S,R*)-**3** shows an AB system centered at $\delta = 4.33$ ppm. No trace of (−)-(*S,R*)-**3** could be found in (+)-(*S,S*)-**3** and vice versa.



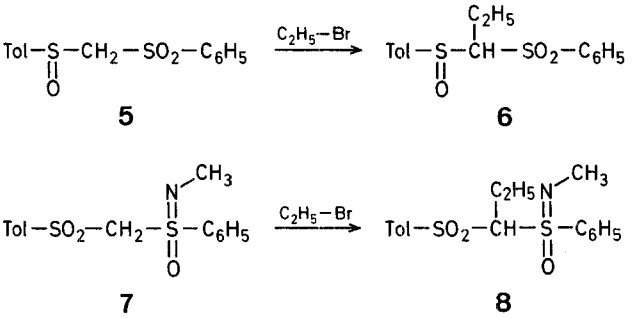
The absolute configurations were assigned to compounds **3** on the basis of the reasonable assumption[1,2,4] that the reactions proceed with inversion of chirality at the sulfinyl S-atom while the chirality at the sulfoximine S-atom is not affected in the process.

Having at hand a stereospecific synthesis of *S*-(sulfinylmethyl)-sulfoximines **(3)**, we examined the possibility of chirality transfer from sulfur to carbon in C—C bond forming reactions. Compounds **3** have two chiral functions, both capable of inducing asymmetry in reactions involving chiral or prochiral groups α to the S-atoms[1-4]. Since the diastereoisomeric (+)-(*S,S*)-**3** and (−)-(*S,R*)-**3** have the same absolute configuration at the sulfoximine S-atom and opposite configuration at the sulfinyl S-atom, reactions of **3** with an achiral partner should in one of the two cases proceed with higher stereoselectivity than in the other due to a synergic effect of the two chiral centers. This is indeed the case for the reactions examined by us, i.e., the reaction of the diastereoisomerically pure compounds **3** with alkyl halides, allyl bromide, and 2-propynyl bromide using phase-transfer catalysis (50% aqueous sodium hydroxide/dichloromethane as liquid phases and TEBA as catalyst). As can be seen from the Table, stereoselectivity of the substitution reaction leading to compounds **4** is higher when the *S*-(sulfinylmethyl)-sulfoximine (+)-(*S,S*)-**3** is used as substrate, only one of the possible stereoisomers being formed (as determined by ^{1}H-N.M.R. analysis). These results represent the first example of a double asymmetric induction by two chiral sulfur moieties.

Since both the chiral sulfinyl and the chiral sulfoximine groups are capable[1-4,7] of giving rise to high e.e. values (enantiomeric excess) in substitution reactions it is difficult to assign a dominant role in the aforementioned process to either



one of the two groupings. To gain further information, we performed an analogous alkylation reaction with ethyl bromide using 4-methylphenylsulfinylmethyl phenyl sulfone **(5)** and *N*-methyl-*S*-phenyl-*S*-(4-methylphenylsulfonylmethyl)-sulfoximine **(7)** as substrates under the conditions used in the alkylation of compounds **3**. The starting compound (+)-(*S*)-**5**, m.p. 71-72 °C, $[\alpha]_D^{25}$: +251° (chloroform), was obtained from (−)-(*S*)-**1** and metallated methyl phenyl sulfone as already described[8]; compound (−)-(*S*)-**7** was obtained by oxidation of the *S*-(sulfinylmethyl)-sulfoximine (+)-(*S,S*)-**3** with hydrogen peroxide/acetonitrile. Ethylation of (+)-(*S*)-**5** afforded a mixture of two diastereoisomers **6**, $[\alpha]_D^{25}$: +84.0° (acetone) in the ratio 95 : 5 while ethylation of (−)-(*S,S*)-**7** afforded a mixture of two diastereoisomers **8**, $[\alpha]_D^{25}$: −6.8° (acetone) in a ratio of ~1 : 1. [Alkylation of racemic sulfinylmethyl sulfones using sodium hydride or butyllithium as base has previously been reported[9] to give a 3 : 2 mixture of diastereoisomers after crystallization]. These results seem to indicate that in the case of the *S*-(sulfinylmethyl)-sulfoximines the sulfinyl group exerts the stronger effect in asymmetric induction.



***N*-Methyl-*S*-(4-methylphenylsulfinylmethyl)-*S*-phenylsulfoximines (+)-(*S,S*)-3 and (−)-(*S,R*)-3; General Procedure:**

To a stirred solution of diisopropylamine (3.4 ml, 23.6 mmol) in dry tetrahydrofuran (10 ml) cooled at −78 °C, a 1.6 normal solution (14.8 ml) of butyllithium in hexane is added and the temperature allowed to reach −10 °C. The mixture is then cooled to −78 °C and (+)-(*S*)-*N,S*-dimethyl-*S*-phenylsulfoximine [(+)-(*S*)-**2**; 2 g, 11.8 mmol] in dry tetrahydrofuran (5 ml) is added dropwise. The solution is stirred at −20 °C for 10 min, then cooled to −78 °C, a solution of (−)-(*S*)- or (+)-(*R*)-menthyl *p*-toluenesulfinate (**1**; 3.47 g, 11.8 mmol) in dry tetrahydrofuran is added and stirring is continued for 6 h at room temperature. The mixture is quenched with saturated ammonium chloride solution (20 ml) and extracted with dichloromethane (3 × 30 ml). The organic extract is dried with sodium sulfate and evaporated in vacuo. The residual product is purified by column chromatography on silica gel (petroleum ether/ether 70/30, then ether as eluents).

Isomer (−)-(S,S)-**3**, from (−)-(*S*)-**1**; yield: 2.43 g (67%); m.p. 45-47 °C; $[\alpha]_D^{25}$: +235° (c 1, acetone).

$C_{15}H_{17}NO_2S_2$	calc.	C 58.63	H 5.54	N 4.56
(307.2)	found	58.50	5.55	4.58

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): $\delta = 2.4$ (s, Ar—CH_3); 2.8 (s, N—CH_3); 4.3 (s, 2H); 7.2-8.0 ppm (m, 9 H_{arom}).

Table. Alkylation of (+)-(*S,S*)-**3**, (−)-(*S,R*)-**3**, **5**, and **7** with Alkyl Halides under Phase-Transfer Conditions

Educt	Alkyl halide	Alkylated product	Reaction time [h]	Yield [%]	$[\alpha]_D^{25}$ [a]	Diastereomeric ratio[b]	m.p. [°C] (n_D^{20})	Molecular formula[c]	
(+)-(*S,S*)-**3**	$H_2C{=}CH{-}CH_2{-}Br$[d]	**4a**	2.5	93	+ 97.7°	100:0	(1.606)	$C_{18}H_{21}NO_2S_2$	(347.5)
(−)-(*S,R*)-**3**	$H_2C{=}CH{-}CH_2{-}Br$[d]	**4a**	2.0	87	− 49.0°	83:17	(1.672)	$C_{18}H_{21}NO_2S_2$	(347.5)
(+)-(*S,S*)-**3**	$C_6H_5{-}CH_2{-}Br$[d]	**4b**	5.0	77	+ 86.3°	100:0	98–100°	$C_{22}H_{23}NO_2S_2$	(397.5)
(−)-(*S,R*)-**3**	$C_6H_5{-}CH_2{-}Br$[d]	**4b**	3.0	79	− 34.4°	80:20	(1.672)	$C_{22}H_{23}NO_2S_2$	(397.5)
(+)-(*S,S*)-**3**	$HC{\equiv}C{-}CH_2{-}Br$[d]	**4c**[e]	3.0	91	+ 80.0°	100:0	(1.600)	$C_{18}H_{19}NO_2S_2$	(345.5)
(−)-(*S,R*)-**3**	$HC{\equiv}C{-}CH_2{-}Br$[d]	**4c**[e]	1.5	73	− 28.5°	100:0	(1.673)	$C_{18}H_{19}NO_2S_2$	(345.5)
(+)-(*S,S*)-**3**	$C_2H_5{-}Br$[f]	**4d**	5.5	80	+ 103.0°	100:0	78–80°	$C_{17}H_{21}NO_2S_2$	(335.5)
(−)-(*S,R*)-**3**	$C_2H_5{-}Br$[f]	**4d**	26	82	− 18.2°	80:20	(1.593)	$C_{17}H_{21}NO_2S_2$	(335.5)
(+)-(*S,S*)-**3**	$C_2H_5{-}J$[f]	**4d**	48	70	+ 103.0°	100:0	78–80°	$C_{17}H_{21}NO_2S_2$	(335.5)
(+)-(*S,S*)-**3**	$n\text{-}C_4H_9{-}Br$[f]	**4e**	170	30	+ 84.6°	100:0	(1.568)	$C_{19}H_{25}NO_2S_2$	(363.5)
5	$C_2H_5{-}Br$[f]	**6**	18	61	+ 84.0°	95:5	(1.689)	$C_{16}H_{18}O_3S_2$	(322.3)
7	$C_2H_5{-}Br$[f]	**8**	48	66	− 6.8°	1:1	(1.560)	$C_{17}H_{21}NO_3S_2$	(351.4)

[a] *c* 1, in acetone.
[b] As determined by ^{1}H-N.M.R. spectroscopy.
[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.33; H, ±0.12; N, ±0.05.
[d] At 0 °C.
[e] This compound decomposes at room temperature to give a mixture of several products. Nevertheless it could be fully characterized.
[f] At 25 °C.

*Isomer (−)-(S,R)-***3**, from (+)-(*R*)-**1**; yield: 2.43 g (67%); n_D^{20}: 1.5910; $[\alpha]_D^{25}$: −196° (*c* 1, acetone).

$C_{15}H_{17}NO_2S_2$	calc.	C 58.63	H 5.54	N 4.56
(307.2)	found	58.60	5.54	4.55

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.4 (s, Ar—CH_3); 2.8 (s, N—CH_3); 4.3 (AB system, 2H); 7.1–8.0 ppm (m, 9H_{arom}).

(−)-(*S*)-*N*-Methyl-*S*-(4-methylphenylsulfonyl)-*S*-phenylsulfoximine [(−)-(*S*)-7]:

To a stirred solution of (−)-(*S,S*)-*N*-methyl-*S*-(4-methylphenylsulfinyl)-*S*-phenylsulfoximine [(−)-(*S,S*)-**3**; 1 g, 3.25 mmol) in methanol (5 ml) are added hydrogen peroxide (30%; 42 mmol), acetonitrile (6.4 ml, 0.12 mol), and a few drops of 1 normal sodium hydroxide. The mixture is stirred at room temperature for 4 h, methanol and the acetonitrile are removed in vacuo, and the residue is dissolved in chloroform (20 ml). The solution is washed with water (2 × 10 ml) and dried with sodium sulfate. Removal of the solvent affords the product which is purified by column chromatography (silica, eluent ether); yield: 0.87 g (83%); m.p. 48 °C; $[\alpha]_D^{25}$: −30.2° (acetone).

$C_{15}H_{17}NO_3S_2$	calc.	C 55.72	H 5.26	N 4.33
(323.3)	found	55.70	5.28	4.34

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 2.4 (s, Ar—CH_3); 2.7 (s, N—CH_3); 4.7 (bs, 2H); 7.2–7.9 ppm (m, 9H_{arom}).

Alkylation of *S*-(Sulfinylmethyl)-sulfoximines (3), 4-Methylphenylsulfinylmethyl Phenyl Sulfone (5), and *N*-Methyl-*S*-(4-methylphenylsulfonylmethyl)-*S*-phenylsulfoximine (7) with Alkyl Halides under Phase-Transfer Conditions; General Procedure:

A 50% sodium hydroxide solution (0.1 ml) is added to a stirred solution of the substrate (**3**, **5**, **7**; 1.3 mmol), benzyltriethylammonium chloride (TEBA; 0.065 mmol), and the alkyl halide (1.3 mmol) in dichloromethane (3 ml). The mixture is stirred at 0 °C or at room temperature for the appropriate time (see Table). The two phases are separated and the aqueous phase is extracted with dichloromethane (3 × 10 ml). The combined organic layers are dried with sodium sulfate, evaporated in vacuo, and filtered through silica gel (eluent ether) to remove the catalyst. Removal of the solvent affords the product.

Received: January 14, 1982

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