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TETRAHEDRON: *ASYMMETRY*

Practical methods for the preparation of spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-(2*S*)-oxide by resolution and asymmetric sulfoxidation

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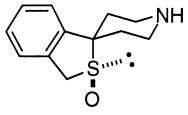
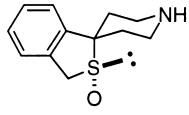
Abstract

We report simple and efficient methods for the preparation of enantiomerically pure spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-(2*S*)-oxide (*S*)-**1**, a key intermediate for the synthesis of tachykinin receptor antagonist, by resolution and asymmetric sulfoxidation. Racemic (*RS*)-**1** can be resolved with (*S*)-(+)-mandelic acid in acetonitrile to give (*S*)-**1** of >99% *ee*. We also describe the asymmetric sulfoxidation of sulfide **5** in excellent enantiomeric excess and high chemical yield by the use of the Davis reagent.

Chiral sulfoxides are important compounds both as subunits in a number of natural products and medicines, and as chiral auxiliaries in asymmetric syntheses.[1] For this reason, it is of great benefit to develop efficient methods for the preparation of chiral sulfoxides with high enantiomeric purity. Spiro[benzo[*c*]thiophene-1(3*H*),4′-piperidine]-(2*S*)-oxide (*S*)-**1** is one of the key constituents of biologically active compounds such as tachykinin receptor antagonists.[2] Since the (*S*)-configuration of sulfoxide has been shown to be an essential requirement for more potent binding affinities in one of our recent studies,[2a] we have relied on the use of large amounts of enantiomerically pure (*S*)-**1** in various phases of our program to design potent, orally active tachykinin receptor antagonists.



(*S*)-**1**



(*R*)-**1**

At first, we investigated the resolution of racemic sulfoxide (*RS*)-**1**. Racemic sufoxide (*RS*)-**1** was prepared in 50–60% yield from (2-bromophenyl)methanethiol **2** in five steps via a modified version of Parham's method (Scheme 1).[3] Compound **2** was converted to a dianion with *n*-BuLi in THF at −78°C, and then converted to compound **4** by treatment with *N*-Boc-piperidin-4-one **3**. Compound **4** was treated with aqueous H_2SO_4 at 100°C to cyclize, and then converted to sulfide **5** by treatment with Boc_2O and

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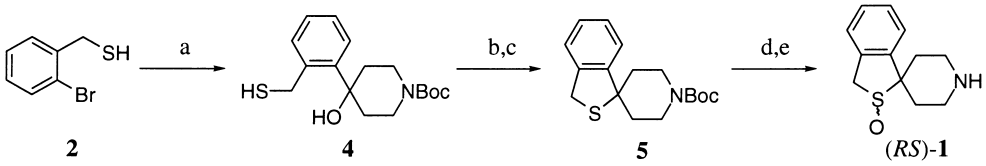
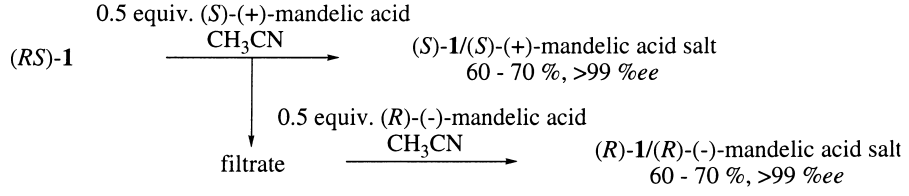
triethylamine. Racemic sulfoxide (*RS*)-**1** was cleanly provided by oxidation of **5** via treatment with *m*-chloroperbenzoic acid (*m*CPBA) or Oxone® followed by deprotection of the amine.



Reagents : a) i) *n*-BuLi, ii) *N*-Boc-piperidin-4-one **3**, THF, -78 °C; b) aq. H_2SO_4, 100 °C; c) Boc_2O, Et_3N, CH_2Cl_2; d) *m*CPBA or oxone, CH_2Cl_2; e) 4N HCl/dioxane followed by 5% NaOH.

Scheme 1.

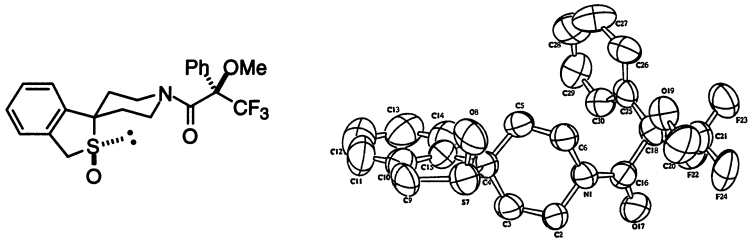
In conducting the resolution, we initially examined various combinations of resolving reagent (mandelic acid, tartaric acid, dibenzoyltartaric acid and camphorsulfonic acid) and solvent. The optically active sulfoxide (*S*)-**1** was most efficiently prepared by resolution of (*RS*)-**1** with (*S*)-(+)-mandelic acid in acetonitrile. Treatment of an acetonitrile solution of racemic (*RS*)-**1** with 0.5 equiv. of (*S*)-(+)-mandelic acid resulted in 60–70% yield (based on mandelic acid) of (*S*)-**1**/(*S*)-(+)-mandelic acid salt with >99% *ee* (Scheme 2). Recrystallization from acetonitrile or ethanol gave white crystals (mp 197.0–200.0°C, $[\alpha]^{24}_{D}$ +78.3 (*c* 1, MeOH)), and a subsequent base treatment gave (*S*)-**1** of 99.8% *ee* in 75–85% recovery.[4]



Scheme 2.

The *ee*-value of **1** could be determined by HPLC analysis. The sulfoxide **1** was converted to the *N*-Boc derivative with Boc_2O and triethylamine in CH_2Cl_2, and the resulting *N*-Boc-**1** was analyzed by chiral HPLC (column, Chiralcel OD (4.6ϕ×250 mm); eluent, *n*-hexane:2-propanol (80:20) mixture; flow rate, 0.8 ml/min; t_R of (*S*)-isomer, 21.9 min; t_R of (*R*)-isomer, 17.8 min). The stereochemistry of (*S*)-**1** was confirmed by X-ray analysis of the α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) amide of (*S*)-**1**. A single-crystal X-ray structure determination of the (*R*)-MTPA amide of (*S*)-**1** unambiguously established the relative configuration, and hence, the absolute stereochemistry of sulfoxide is *S*, as shown in Fig. 1.[5] This synthesis also led, of course, to the synthesis of (*R*)-**1** with the opposite configuration by using (*R*)-(−)-mandelic acid. Thus, (*RS*)-**1** could be efficiently resolved with mandelic acid with high enantiomeric purity and a good yield.

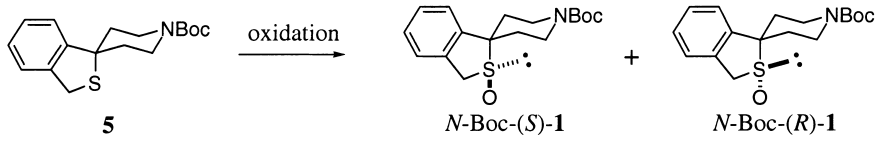
On the other hand, asymmetric oxidation of prochiral sulfide **5** is a straightforward route to chiral sulfoxide (*S*)-**1**. To date, there are relatively few general methods for the preparation of chiral sulfoxide



X-ray ORTEP of (*R*)-MTPA amide of (*S*)-1

Fig. 1.

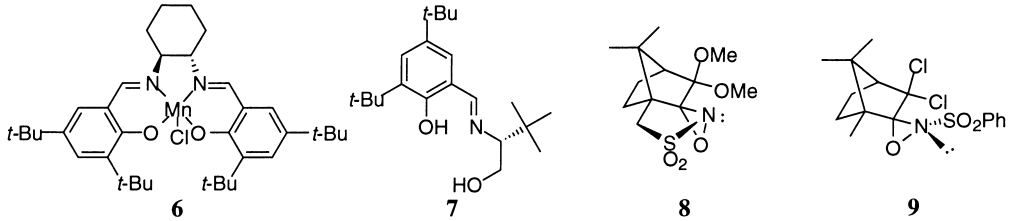
Table 1
Asymmetric sulfoxidation of **5**



5 *N*-Boc-(*S*)-**1** *N*-Boc-(*R*)-**1**

Run	Reagent[a] (eq)	Solvent	Temp (°C)	Yield (%)	%*ee* of (*S*)-**1**
1	(*S*,*S*)-DET (1.0), Ti(O-*i*-Pr)$_4$ (0.5) *t*-BuOOH (1.0)	CH_2Cl_2	- 30	20	54
2	(*S*)-Binaphthol (0.2), Ti(O-*i*-Pr)$_4$ (0.1) *t*-BuOOH (2.0)	CCl_4 - H_2O	0	46	17
3	(*S*,*S*)-Mn(III)salen **6** (0.01) PhIO (1.0)	CH_3CN	25	70	10
4	(*R*)-Schiff base **7** (0.15) $VO(acac)_2$ (0.1), H_2O_2	CH_2Cl_2	25	80	54
5	(+)-(2*R*,8a*R**)-[(8,8-dimethoxycamphoryl) sulfonyl]oxaziridine **8** (1.0)	toluene	25	90	74
6	"	THF	25	93	77
7	(-)-(3'*S*,2*R*)-*N*-(phenylsulfonyl)(3,3-dichloro-camphoryl)oxaziridine **9** (1.0)	CH_2Cl_2	25	93	94
8	"	toluene	25	95	96

a) structures of reagent



6 **7** **8** **9**

with high enantiomeric purity. The most successful methods for asymmetric sulfoxidation include the modified Sharpless procedure,[6] and much progress has been made through the use of enzymes,[7] or the use of chiral complexes with titanium,[8] manganese,[9] and vanadium[10] as catalysts, or the use of the chiral oxaziridines of Davis.[11] However, among these approaches to enantiomerically pure sulfoxide, the applicable sulfides are still limited mainly to aryl alkyl sulfides, and a significant decrease in enantioselectivity is seen for oxidation of dialkyl sulfides. In the present study, we examined several of the approaches for asymmetric sulfoxidation of **5**. The data in Table 1 summarize the results obtained in different oxidation conditions.

Attempts at titanium-mediated oxidation using diethyl tartarate (DET)[8f] or binaphthol[8d] as chiral ligands were unsatisfactory with diminished yield and enantioselectivity (run 1 and 2). Attempts at manganese-catalyzed[9c] and vanadium-catalyzed[10b] oxidation procedures resulted in moderate *ee* and yield (run 3 and 4). In the course of this investigation, we examined both [(3,3-dimethoxycamphoryl)sulfonyl]oxaziridine **8**[11a] and *N*-(phenylsulfonyl)-(3,3-dichlorocamphoryl)oxaziridine **9**[11b], two Davis reagents which have been reported to be useful for asymmetric sulfoxidation (runs 5–8). These oxidations were carried out by treating the sulfide **5** with an equivalent amount of the oxaziridines in the appropriate solvent at 25°C. In particular, *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine **9** yielded much better *ee*s than the other reagents. A screening of appropriate solvents for oxidation showed a dramatic solvent effect, and the best solvents

were dichloromethane and toluene. The major advantages of these stoichiometric reagents are that they can oxidize substrates under neutral, aprotic conditions, and that they can be recycled as chiral species. Recrystallization of the resulting *N*-Boc-(*S*)-**1** (94–96% *ee*) from diisopropyl ether gave *N*-Boc-(*S*)-**1** of 99.8% *ee* as white crystals (mp 129.0–130.5°C), $[\alpha]_D^{24}$ +57.1 (*c* 1, MeOH). Following deprotection of the Boc group with 4 N HCl/dioxane in ethanol, recrystallization from a mixture of methanol:diethyl ether (1:2) gave (*S*)-**1** HCl salt in quantitative yield (mp 209.5–210.5°C, $[\alpha]_D^{24}$ +63.8 (*c* 1, MeOH)).

In conclusion, the methods described above greatly simplify the preparation of **1** in both enantiomeric forms with high enantiomeric purity.

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4. All new compounds are fully characterized by their spectroscopic and analytical data.
5. Crystal data: $C_{22}H_{22}NO_3F_3S$, MW=437.5, T=298 K, CuKα radiation, λ=1.5418 Å; monoclinic, space group $P2_1$, *a*=9.994(2) Å, *b*=10.870(1) Å, *c*=20.569(1) Å, β=103.24(1)°, *V*=2175.0(5) Å^3, *Z*=4, *Dc*=1.34g/cm^3, *R*=0.066. Full X-ray crystallographic data will be deposited with the Cambridge Crystallographic Data Centre.
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