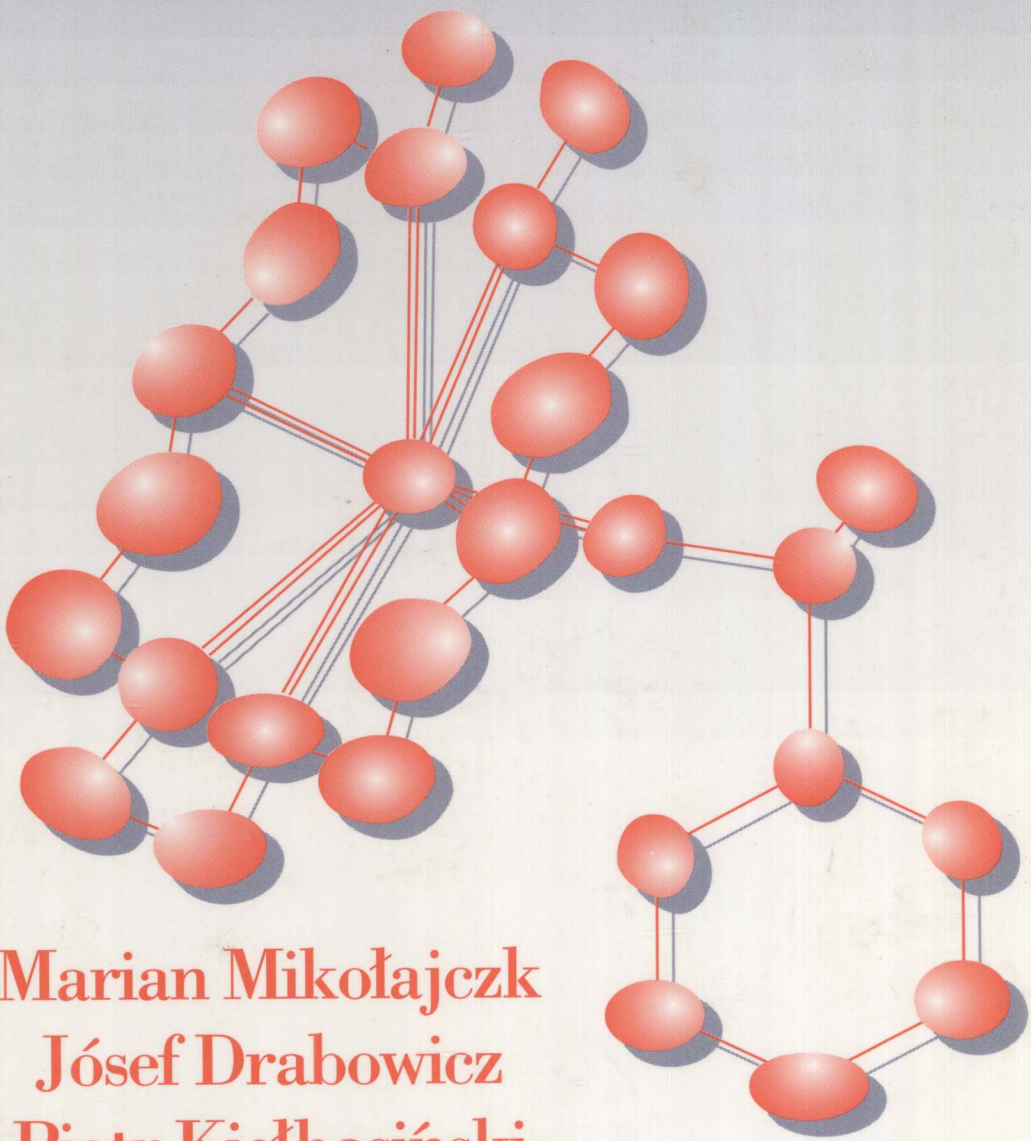
CHIRAL SULFUR REAGENTS

Applications in Asymmetric and Stereoselective Synthesis



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Preface

Although the first chiral organosulfur compounds were obtained at the beginning of this century, they have received more attention since the early 1960s. Initially, chiral sulfur compounds served as model compounds in studies on the mechanism and stereochemistry of nucleophilic substitution at sulfur's center. Quite soon, however, it was recognized that chiral sulfur compounds are of great value in asymmetric synthesis, since many reactions may be efficiently stereocontrolled by chiral sulfur auxiliaries which later are easily removable under mild conditions by reductive or eliminative methods. As a result, there has been a literature explosion in this field. On the one hand, over the last three decades more than 40 different classes of chiral sulfur compounds have been described in the chemical literature and a large number of useful procedures for the synthesis of enantiomerically pure sulfur compounds have been developed, especially of tri- and tetracoordinated sulfur structures. On the other hand, every year literature records dozens and dozens of diverse sulfur-mediated asymmetric syntheses applied in both academic and industrial laboratories for obtaining desirable chiral materials like natural products, drugs, or agrochemicals.

Many of these developments have received treatment in recent books and monographs on sulfur chemistry and organic synthesis, but no comprehensive text covering the whole area is available. The aim of this book, therefore, is to take a somewhat broader view, encompassing as many as possible of the chiral sulfur reagents, their preparation, and application in asymmetric and stereoselective synthesis. It does not seek to be totally comprehensive because compilation of such a text would entail a task of daunting proportions. Therefore, we apologize that many interesting contributions to this field which have been published could not be cited in this book.

As this is a practical book, the greater emphasis has been usually placed on describing the modern methodologies and procedures furnishing compounds with full or high enantiomeric purity. For the same reasons, some selected experimental data and examples of experimental procedures have been included which we felt were liable to be of greatest use both to students working for their first degree as well as to research chemists. However, some space has also been devoted to mechanistic aspects of the discussed asymmetric reactions.

Though the main purpose of this book is to demonstrate the great potential of enantiomerically pure sulfur reagents in transmitting chirality to other centers, the results obtained with racemic compounds are also discussed, particularly in cases where a high diastereoselectivity was observed. Such results can be easily transferred to enantiopure sulfur compounds, the only problem being the effective synthesis of the latter. Furthermore, several rather unsuccessful results (low extent of asymmetric induction, unsatisfactory yields) have also been mentioned to warn and prevent the reader from undertaking efforts which had already been made by others.

Finally, we believe that the scientific technological importance of chiral sulfur compounds justifies the conclusion that the subject of this book will be of interest to many chemists in many countries. We can only hope that our treatment of it has been adequate.

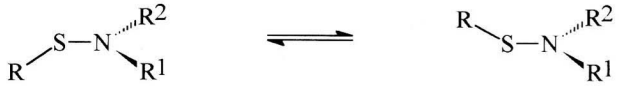
M. Mikołajczyk
J. Drabowicz
P. Kiełbasiński

Contents

Chapter 1

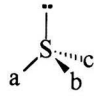
Structure-Chirality Relationship in Organic Sulfur Compounds

Sulfur forms a variety of organic compounds showing different structural and stereochemical properties. A very useful criterion to classify all the organosulfur compounds is the number (N) of ligands on sulfur.[1-3] Based on this criterion sulfur compounds are divided into six classes with ligand numbers N = 1 to 6. A limited number of monocoordinate (N = 1) sulfur compounds of linear structure are not interesting from the point of view of chirality at sulfur, since they are achiral compounds. Similarly, sulfur in dicoordinate (N = 2) compounds having angular structures cannot be a center of chirality. The only exception is the sulfenamide **1** which, due to the partial double bond character of the sulfur-nitrogen bond, shows, like allenes and carbodiimides, an axial chirality and may exist in two enantiomeric forms. This stereochemical feature of sulfenamides was first demonstrated by Kost and Raban[4] and then widely investigated.



1 ent - **1** (1.1)

Sulfur compounds with the ligand number N = 3 may adopt a trigonal planar or trigonal pyramidal structure. However, planar arrangement of three different substituents around sulfur is not a sufficient condition for chirality at sulfur. On the contrary, pyramidal sulfur compounds, of the general structure **2**, containing three different ligands and the lone electron pair occupying the fourth position of a distorted tetrahedron are chiral and configurationally stable. This is in contrast to isoelectronic amines and carbonium ions. A higher, configurational stability of this class of sulfur compounds is due to the higher amount of *s*-character and the longer bond lengths about the central sulfur atom.



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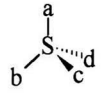

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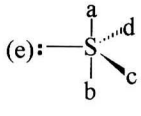

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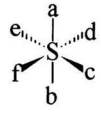

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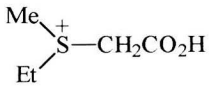
To the class of chiral tricoordinate sulfur compounds belong various sulfonium salts, $R^1R^2R^3S^+A^-$, sulfinyl compounds, $R^1R^2S{=}O$, and iminosulfinyl compounds, $R^1R^2S{=}NR$, which, in the majority of cases, are configurationally stable and have been obtained in optically active states. It is interesting to note that the first resolution of chiral sulfur compounds was reported in 1900 by Pope and Peachey[5] and by Smiles,[6] who resolved the sulfonium salts **6** and **7** via diastereomeric salts with chiral acids.



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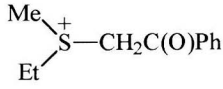

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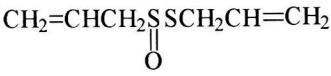
The isolation, around 1950, of many chiral sulfinyl compounds such as **8**, **9**, **10**, and **11** from natural sources resulted in intense activity in the preparation and study of new chiral tricoordinate sulfur structures.[7,8]



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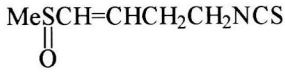

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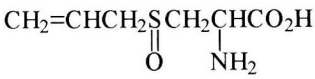

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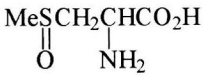

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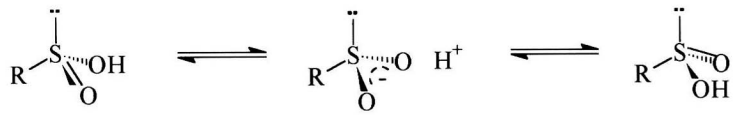
A great number of chiral tricoordinate sulfur compounds may be derived from sulfinic acids **12** which, however, are themselves effectively achiral. This is due to a fast proton exchange between two enantiomeric forms of **12** via the achiral sulfinic acid anion (Equation 1.2).



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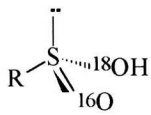
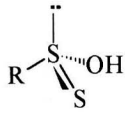


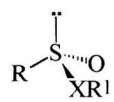
[^{16}O, ^{18}O]-**12**
R = p-Tol



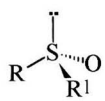
13
R = t-Bu, Adamantyl, Triptycenyl (1.2)

Replacement of one of the two ^{16}O oxygen atoms in **12** by ^{18}O or by sulfur leads to chiral structures of sulfinic acid [^{16}O, ^{18}O]-**12** and thiosulfinic acid **13**, respectively.[9] The former was recently obtained in optically active form by stereoselective synthesis.[10]

Other sulfinic acid derivatives such as sulfinates **14**, thiosulfinates **15**, sulfinamides **16**, sulfoxides **17**, and sulfoxonium salts **18** as well as their imino-analogs are chiral and have been obtained in enantiomeric forms.[2]



14, X = O
15, X = S
16, X = NR



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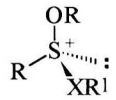
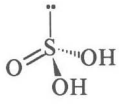


18, X = O, S, NR
XR^1 = alkyl, aryl

Another series of chiral tricoordinate sulfur compounds may be derived from achiral sulfurous acid **19** by replacement of the hydroxy groups by suitable substituents. Thus, sulfites, amidosulfites, and amidothiosulfites of the general structure **20** belong to this class of compounds. Although these chiral compounds have been obtained in enantiomeric or diastereomeric forms, they are not in common use.



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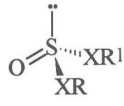
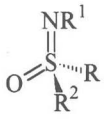


20, X = O, S, NR

The structure of sulfur compounds with four ligands (N = 4) and without a "stereochemically active" nonbonding electron pair is tetrahedral. If the four ligands are different as in **3**, such tetrahedral, tetracoordinate sulfur compounds are chiral and can be resolved or prepared in enantiomeric forms. Here, the situation is quite similar to the tetrahedral, sp^3-carbon compounds if one neglects the different bond order between some substituents and sulfur.

The most common chiral, tetracoordinate sulfur compounds are sulfoximines **21** which formally arise from achiral, unsymmetrical sulfones by replacement of one of the two oxygen atoms by the imino nitrogen. Consequently, replacement of both oxygen atoms in unsymmetrical sulfones by different imino groups leads to other chiral, tetracoordinate structures, namely sulfodiimides **22**. Of interest is that chiral, optically active sulfonimidoyl chlorides **23** have also been obtained. Due to the presence of a good leaving group, these chlorides are excellent substrates for nucleophilic substitution reaction and afford in a highly stereoselective way the corresponding esters and amides **24**.[2,11]



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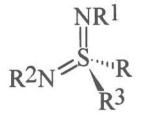

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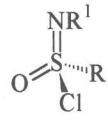

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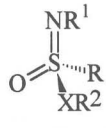
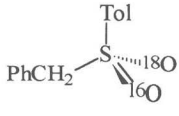


24, X = O, NH

As in the case of sulfinic acids, the chirality at sulfur in unsymmetrical sulfones may be generated by isotopic substitution. The first example of such a chiral sulfone, i.e., (–)-benzyl p-tolyl [^{16}O, ^{18}O]-sulfone **25** was described by Stirling[12] as early as 1963. A few years later, Sabol and Andersen[13] prepared diastereomerically pure (–)-menthyl [^{16}O, ^{18}O]-phenylmethanesulfonate **26**. The list of the tetracoordinate sulfur compounds chiral by virtue of isotopic oxygen substitution was recently extended by the synthesis of the lithium salt of chiral [^{16}O, ^{18}O]-p-toluenethiosulfonic acid **27**.[10]



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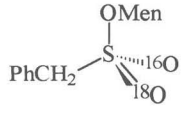

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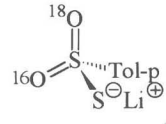

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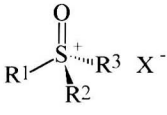
Oxosulfonium salts of the general formula **28** belong to the group of tetrahedral tetracoordinate sulfur compounds with four different ligands (N = 4). Therefore, they are chiral at sulfur and can exist in enantiomeric forms. Thus far, however, methylethylphenyloxosulfonium perchlorate **29** is the only compound of this type whose enantiomers have been isolated.[14]



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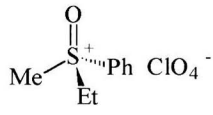
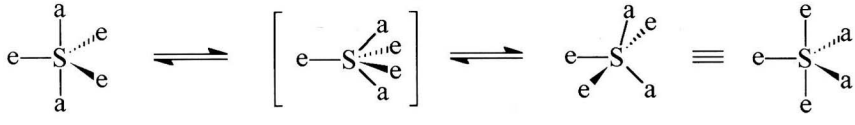


29

Tetracoordinate sulfur compounds (N = 4), which contain the lone electron pair as a phantom ligand, as well as pentacoordinate sulfur compounds (N = 5) possess a trigonal bipyramidal structure exemplified by **4**. A common name, sulfurane, is generally accepted for this type of high-coordinated compounds.[15]

In the present brief account at least three significant features of sulfuranes should be mentioned. The first concerns the positions of substituents in a trigonal bipyramidal structure. In such a structure two substituents occupy apical positions while the remaining three are placed in a basal plane in equatorial positions. This nonequivalence of ligand positions is preserved even in the case of the same substituents connected with the central sulfur atom. The tendency of a substituent to occupy an apical position is defined as apicophilicity. In the first approximation apicophilicity is related to electronegativity, i.e., the more electronegative the ligand the greater its apicophilicity. Ring strain, steric bulk, and electronic effects are the other factors affecting the apicophilicity order in sulfuranes.

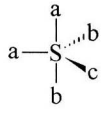
Secondly, the most interesting phenomenon observed in sulfuranes as well as in other valency-shell expanded compounds is the internal ligand reorganization changing the relative positions of ligands in a trigonal bipyramidal structure. This process is commonly called pseudorotation. A single process of pseudorotation according to the Berry mechanism is visualized below (Equation 1.3).



(1.3)

Since the energy required for pseudorotation is usually very low, this process may have an important influence on the stereochemical properties of sulfuranes.

Finally, it should be emphasized that sulfuranes may be chiral. However, the number of optically active isomers is dependent on the nature of substituents connected with sulfur, their apicophilicity, and the energy for pseudorotation. In this context, it is interesting to note that acyclic sulfuranes with five different ligands like **4** should exist in twenty isomeric chiral forms. However, in the case of sulfuranes, all structures containing at least three different ligands can be chiral. Thus, the sulfurane structure **30** is chiral in contrast to the more symmetrical **31**, which is achiral. Moreover, considering the topological properties of such trigonal bipyramidal molecules, it should be pointed out that, after incorporation of cyclic ligands into this structure, chirality may still appear in the more symmetrical spiro system **32**.



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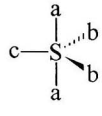

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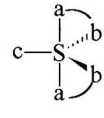

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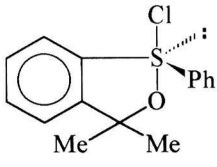
The first example of an optically active sulfurane was the dextrorotatory chlorosulfurane **33** prepared by Martin and Balthazor.[16] All other sulfuranes **34–38**, which have been till now prepared[17,18] as optically active species, belong to the group of spiro derivatives and are shown below.



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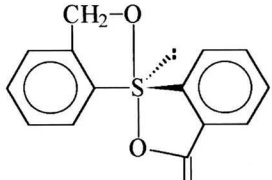

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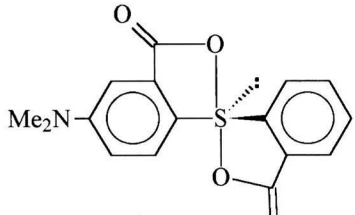

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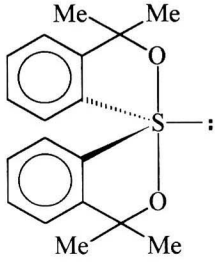

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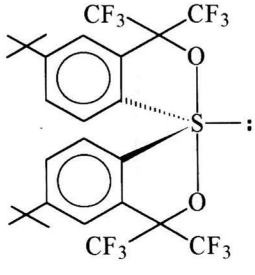

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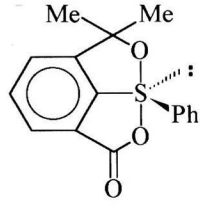

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For hexacoordinate sulfur compounds (N = 6) the octahedral arrangement of ligands is characteristic as pictured in **5**. In spite of the fact that such compounds are known their stereochemistry has yet to begin. Till now, no optically active compounds of this type have been described in the literature.

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Chapter 2

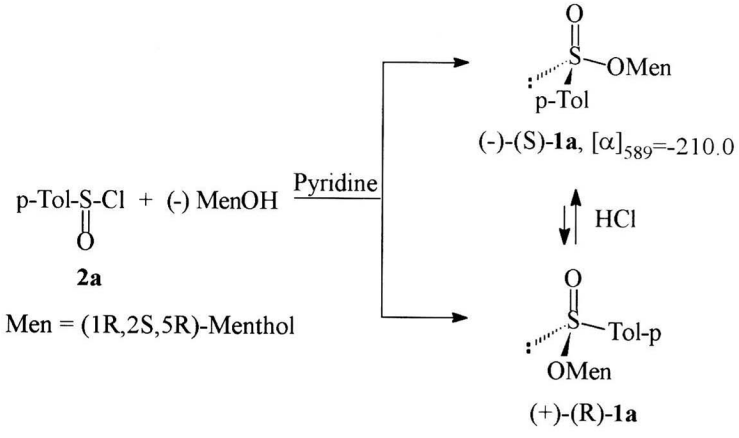
Chiral Sulfinic Acid Derivatives

2.1 SULFINIC ESTERS

Sulfinic esters of the general structure R-S(O)OR^1 belong to the oldest group of chiral organosulfur derivatives prepared as optically active species.[1] Depending on the nature of a substituent R^1, they can be obtained as enantiomers (if R^1 is achiral) or as diastereomeric mixtures (if R^1 contains at least one chiral center). A high stability of the pyramidal structure around the central sulfur atom[1,2] allows the synthesis of a rich family of stable, optically active sulfinic esters. Their importance as substrates in the synthesis of optically active sulfinyl derivatives and in establishing the absolute configuration of three- and tetracoordinated sulfur compounds is well recognized.[1,3] A presentation of synthetic routes reported for the preparation of the most important diastereomeric and enantiomeric sulfinic esters as well as their synthetic applications will follow these introductory remarks. A comprehensive review on the synthesis of sulfinates can be found in Reference 3.

2.1.1 Diastereomeric Sulfinic Esters

The oldest and up to now the most common procedure for the preparation of diastereomeric sulfinic esters involves condensation of sulfinyl chlorides with the appropriately selected enantiomerically or diastereomerically pure alcohols carried out in the presence of an organic or inorganic base. This method was for the first time used by Phillips[4] for obtaining O-menthyl p-toluenesulfinate **1a**. Thus, in the reaction between p-toluenesulfinyl chloride **2a** and (–)-(1R,2S,5R)-menthol in the presence of pyridine a mixture of the diastereomeric O-menthyl p-toluenesulfinates **1a** was formed (Scheme 2.1.1), from which Phillips was able to isolate a pure, solid, diastereomer (–)-(S)-O-menthyl p-toluenesulfinate **1a** by crystallization from acetone.

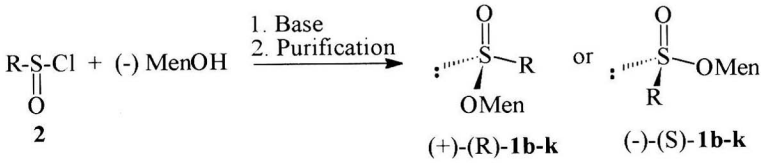


Scheme 2.1.1

Because of the importance of (–)-(S)-**1a** as a substrate in the synthesis of other optically active sulfinyl derivatives, a considerable effort has been devoted to improve its synthesis. The most important improvement is based on the observation reported by Herbrandson and Dickerson[5] as early as 1959 that the addition of hydrogen chloride gas to a mixture of diastereomeric **1a** causes epimerization of the liquid diastereomer (+)-(R)-**1a** to its crystalline epimer (–)-(S)-**1a**. Mioskowski and Solladie[6], by modifying the conditions of Herbrandson and Dickerson under which diastereomeric sulfinates **1a** undergo epimerization in favor of the less soluble (–)-(S)-**1a** isomer, were able to isolate it in 90% yield. In our laboratory,[7a] the above-discussed isomerization procedures did not always give fully reproducible results. It has been found that the more consistent results of epimerization of the sulfinates **1a** are observed when the solid diastereomer, once formed, is dissolved in the mother liquid and the crystallization process is repeated. Another modification of the reaction between p-toluenesulfinyl chloride and (–)-menthol, which allows the isolation of the solid (–)-(S)-**1a** diastereomer in a high yield, involves a very rapid addition of the reaction components.[8]

It is obvious that the use of (+)-(1S,2R,5S)-menthol leads to the formation of (+)-(R)-O-menthyl p-toluenesulfinate. Both sulfinates **1a** with the opposite configuration at the sulfinyl sulfur atom are now commercially available.

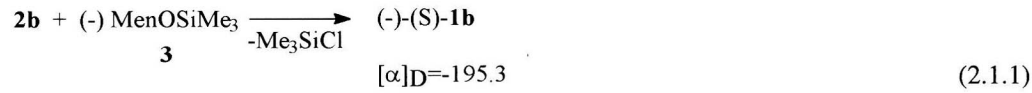
The Phillips approach to the synthesis of diastereomeric O-menthyl sulfinates is general in scope and a great number of other diastereomeric sulfinates **1b–k** were prepared in a similar way starting from the appropriate sulfinyl chlorides **2b–2k** (Scheme 2.1.2).



Sulfinyl chloride **2**		Sulfinic ester **1**				
No	R	No	$[\alpha]_{589}$	Abs.conf.	de	Ref.
b	Ph	**b**	–206.1	S	100	9
c	p-$MeOC_6H_4$	**c**	–189.1	S	100	10
d	p-ClC_6H_4	**d**	–181.1	S	100	2,11
e	p-IC_6H_4	**e**	–145.8	S	100	12
f	1-$C_{10}H_7$	**f**	–433.2	S	100	10a
g	$PhCH_2$	**g**	+105.0	R	90.5	13
g	$PhCH_2$	**g**	+123.0	R	100	14
h	Me	**h**	–99.1	R	13	10b
i	n-Bu	**i**	+50.0	R	47	12
k	2-MeO-$C_{10}H_6$	**k**	–183.0	S	100	18

Scheme 2.1.2

It should be noted that (–)-(S)-O-menthyl benzenesulfinate-**1b** was also prepared from benzenesulfinyl chloride **2b** and 1-menthoxytrimethylsilane **3** in 91% yield (Equation 2.1.1).[15]



(2.1.1)

The *in situ* reduction of commonly available sulfonyl chlorides **4** with trimethyl phosphite in the presence of (–)-menthol was found to be a simple method for the preparation of diastereomeric O-menthyl sulfinates **1**, especially those for which there are no readily available sulfinyl chloride