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Optical Resolution of Chiral Sulfinyl Compounds via β-Cyclodextrin Inclusion Complexes[1,2]

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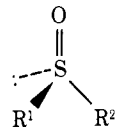
Abstract: Direct resolution of chiral sulfoxides, sulfinates, and thiosulfinate *S*-esters by stereospecific inclusion into β-cyclodextrin is described. Optical purities of the partially resolved alkyl aryl and alkyl benzyl sulfoxides do not exceed 15%. The highest stereospecificity of inclusion was observed for isopropyl methanesulfinate, which has been isolated after one inclusion process with 68% optical purity. For the first time simple, optically stable thiosulfinate *S*-esters containing *tert*-butyl groups have been obtained. The influence of steric hindrance on the optical stability of this class of compounds is discussed. The relationship between the chirality at sulfur and optical purity of sulfoxides and the structure of their inclusion complexes with β-cyclodextrin is considered.

The stability of pyramidal arrangement of ligands around the three-coordinate sulfur atom causes the existence of optical isomerism in a large group of suitably substituted sulfinyl compounds of general structure shown below.[3,4] Until now

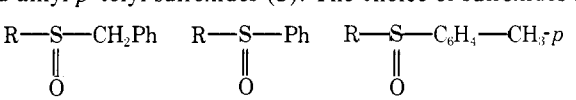


$R^1 \neq R^2$

sulfoxides,[5,6] sulfinates,[3] thiosulfinate *S*-esters,[7] sulfinamides,[8] unsymmetrical sulfites,[9] amido sulfites,[10] and amido thiosulfites[10] belonging to this group of compounds have been obtained in optically active forms. The majority have been prepared mainly by means of the reactions of diastereomeric sulfinates and sulfinamides with organometallic reagents.[6] Some of them have been synthesized by asymmetric oxidation of the corresponding sulfenyl compounds or by means of other asymmetric syntheses.[11]

We now report a novel nonclassical method of resolution of chiral sulfinyl compounds via β-cyclodextrin inclusion complexes.[12] Cyclodextrins (hosts) are optically active since they consist of optically active glucose molecules. Cyclodextrin inclusion compounds with chiral substances (guests) are mixtures of diastereomers which can be formed in unequal amounts, especially when an excess of the included chiral compounds is used. For this reason stereospecific inclusion into cyclodextrins can be applied as a method for resolution of racemic molecules. It is of advantage that it becomes possible to resolve compounds without acidic or basic functional groups which are necessary in the resolution of racemates by the classical method via diastereomeric salts with optically active acids or bases. The use of cyclodextrin as a resolving agent for some chiral carbon compounds was first reported by Cramer.[13] More recently Benschop and Van den Berg[14] described partial resolution of chiral *O*-alkyl alkylphosphonates, R(RO)P(O)H, via α- and β-cyclodextrin inclusion complexes. In the present paper we describe our studies on the resolution of chiral sulfoxides, sulfinates, and thiosulfinate *S*-esters. We should mention that until the present time 2,5-dithiaspiro[3,3]heptane 2,5-dioxide[15] and ethyl *p*-tolyl sulfoxide[16] were the only chiral sulfur compounds which have been resolved by the nonclassical method by forming diastereomeric metal complexes containing optically active ligands.

Resolution of Chiral Sulfoxides. During the first stage of our work on the resolution of chiral sulfinyl compounds via β-cyclodextrin inclusion compounds we attempted to resolve several alkyl benzyl sulfoxides (**1**), alkyl phenyl sulfoxides (**2**), and alkyl *p*-tolyl sulfoxides (**3**). The choice of sulfoxides for



1 **2** **3**

these preliminary studies was dictated by two facts. The first is that they are chemically and configurationally stable. Secondly, specific rotations and absolute configurations of enantiomeric sulfoxides are known[4] and for this reason stereospecificity of the inclusion of sulfoxides into β-cyclodextrin may be easily estimated.

Resolution of sulfoxides was carried out according to the standard procedure elaborated by Cramer.[13] The sulfoxides **1, 2,** and **3** in 5-molar excess were added to a 1.5% solution of β-cyclodextrin in water. The precipitated inclusion compounds were decomposed by trichloroethylene–water at 60 °C and the released, included sulfoxides isolated by column chromatography. The optical rotations, optical purities, and absolute configurations of the included sulfoxides are given in Table I.

It was found that the inclusion of sulfoxides **1**–**3** into β-

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Table I. Resolution of Chiral Sulfinyl Compounds, $R^1S(O)R^2$, via β-Cyclodextrin Inclusion Compounds

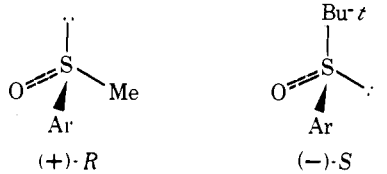
No.	R^1	R^2	$[\alpha]_{589}$	(*c*, solvent)	Optical purity,[b] %	Absolute configuration
1a	Bz[a]	Me	−8.50	(2.08, ethanol)	8.0	*R*
1b	Bz	Et	+5.00	(2.00, chloroform)	4.7	*R*
1c	Bz	Pr-*n*	+2.00	(1.20, ethanol)	3.6	*S*
1d	Bz	Pr-*i*	0.00			
1e	Bz	Bu-*n*	+1.96	(3.16, chloroform)	2.0	*R*
1f	Bz	Bu-*i*	+6.40	(3.82, chloroform)	5.8	*R*
1g	Bz	Bu-*t*	+45.00	(4.05, ethanol)	14.5	*R*
2a	Ph	Me	+6.50	(2.29, ethanol)	4.4	*R*
2b	Ph	Et	+16.10	(2.18, ethanol)	9.1	*R*
2c	Ph	Pr-*n*	0.00			
2d	Ph	Pr-*i*	+8.80	(5.60, acetone)	5.2	*R*
2e	Ph	Bu-*n*	+15.30	(5.14, ethanol)	9.2	*R*
2f	Ph	Bu-*i*	+4.90	(10.34, ethanol)	2.2	*R*
2g	Ph	Bu-*t*	−1.90	(5.66, ethanol)	1.1	*S*
3a	Tol[a]	Me	+11.50	(2.77, ethanol)	8.0	*R*
3b	Tol	Et	+11.10	(2.30, acetone)	5.3	*R*
3c	Tol	Pr-*i*	+3.45	(1.39, ethanol)	1.9	*R*
3d	Tol	Bu-*n*	+6.70	(1.18, acetone)	3.6	*R*
3e	Tol	Bu-*t*	−12.30	(0.77, ethanol)	6.4	*S*
5a	Me	OPr-*n*	+2.38	(3.30, ethanol)	1.4	*R*
5b	Me	OPr-*i*	−165.91	(2.50, ethanol)	68.2	*S*
5c	Me	OBu-*i*	+10.10	(4.90, ethanol)	8.7	*R*
5d	Me	OBu-*t*	−19.90	(1.00, ethanol)	12.4	*S*
5e	Me	OCp	+1.10	(10.40, ethanol)	0.4	*R*
5f	Me	ONp	+5.16	(3.90, ethanol)	4.2	*R*
6a	Pr-*i*	OMe	+14.40	(7.30, ethanol)	12.8	*R*
6b	Pr-*i*	OPr-*i*	−1.87	(10.20, ethanol)	2.1	*R*
8a	Bu-*t*	SBu-*t*	−21.10	(2.43, ethanol)	13.6	
8b	Bu-*t*	SMe	−3.04	(4.02, methanol)		
8c	*p*-Tol	SBu-*t*	+2.00	(4.00, methanol)	2.5	*R*

[a] Bz = $C_6H_5CH_2$; Tol = *p*-$CH_3C_6H_4$; Cp = cyclopentyl; Np = neopentyl. [b] Optical purity values were calculated based on the following data: $[\alpha]_D$ −106.08° (ethanol) for *R*-**1a**, $[\alpha]_D$ +106.6° (chloroform) for *R*-**1b**, $[\alpha]_D$ +115.3° (chloroform) for *R*-**1e**, and $[\alpha]_D$ +308.8° (ethanol) for *R*-**1g** from K. Mislow, M. M. Green, and M. Raban, *J. Am. Chem. Soc.*, **87**, 2761 (1965); $[\alpha]_D$ +149.0° (ethanol) for *R*-**2a** from J. Jacobus and K. Mislow, *J. Am. Chem. Soc.*, **89**, 5228 (1967); $[\alpha]_D$ +180.0° (ethanol) for *R*-**2f** from U. Folli, F. Montanari, and G. Torre, *J. Chem. Soc. C*, 1317 (1968); $[\alpha]_D$ +141.0° (ethanol) for *R*-**3a**, $[\alpha]_D$ +176.5° (ethanol) for *R*-**3b**, $[\alpha]_D$ +187.0° (acetone) for *R*-**3d**, and $[\alpha]_D$ +190.0° (ethanol) for *R*-**3e** from K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, and A. L. Ternay, *J. Am. Chem. Soc.*, **87**, 1958 (1965), $[\alpha]_D$ +55.0° (ethanol) for *S*-**1c** and $[\alpha]_D$ +110.0° (chloroform) for *R*-**1f** from this work; $[\alpha]_D$ +177.1° (ethanol) for *R*-**2e** and $[\alpha]_D$ +234.6° (ethanol) for *R*-**2f** from M. Mikołajczyk and J. Drabowicz, unpublished results.

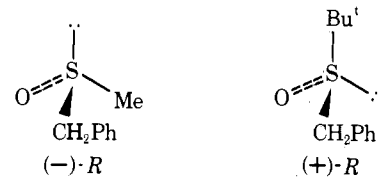
cyclodextrin was stereospecific in almost all the cases, with the exception of isopropyl benzyl sulfoxide (**1d**) and *n*-propyl phenyl sulfoxide (**2c**) which could not be resolved by this method. However, the optical purities of the partially resolved sulfoxides were not very high. They could be increased by repeating the inclusion process. Thus, after the second inclusion procedure the optical rotation of methyl *p*-tolyl sulfoxide (**3a**), $[\alpha]_{589}$ +11.5° (optical purity 8.1%), was increased to $[\alpha]_{589}$ +16.1°, which corresponds to an optical purity of 11.4%. The optical purity of this sulfoxide could also be increased by crystallization. Four crystallizations of **3a**, $[\alpha]_{589}$ +11.5°, from light petroleum (bp 60–80 °C) gave a sample having $[\alpha]_{589}$ +100.8° (optical purity 71.5%).

The formation of the inclusion compounds by cyclodextrin with nonpolar substances depends largely on steric size of the "guest" molecule. Thus, β-cyclodextrin does not form inclusion complexes with chlorine, whereas complexes with the larger bromine and iodine molecules are well known.[12a] The formation of inclusion compounds with strongly polar compounds in aqueous solution depends not only on steric factors but also on various other factors such as the possibility of hydrogen bond formation and dipole–dipole interactions.[12c] Furthermore, it may be expected that in the case of inclusion complexes of a homologous series of racemic compounds the stereospecificity of inclusion should also depend on steric requirements and arrangement of substituents bonded to an asymmetric atom.

An inspection of the data in Table I shows that there is a pronounced relation between the stereospecificity of inclusion of sulfoxides into β-cyclodextrin and steric bulk and spatial arrangement of substituents connected with the chiral sulfur atom. It is of special interest that (+)-methyl phenyl sulfoxide (**2a**) and (+)-methyl *p*-tolyl sulfoxide (**3a**) recovered from the inclusion compounds with β-cyclodextrin had configuration *R* whereas the chirality at sulfur in (−)-*tert*-butyl phenyl sulfoxide (**2g**) and (−)-*tert*-butyl *p*-tolyl sulfoxide (**3e**) included into β-cyclodextrin was *S*. Although (−)-methyl benzyl



sulfoxide (**1a**) and (+)-*tert*-butyl benzyl sulfoxide (**1g**) isolated from the β-cyclodextrin inclusion complexes had the same configuration *R* according to the Cahn, Ingold, and Prelog



rules,[17] this agreement was only a result of formal requirements of this nomenclature. In fact, the arrangements of the benzyl, methyl, and benzyl *tert*-butyl groups with respect to the other two substituents in these sulfoxides are opposite.

It appears reasonable to assume that preferential inclusion of sulfoxides with the opposite configurations at sulfur on passing from the methyl to *tert*-butyl series is connected with the fact that the steric requirements of the methyl group are smaller than those of the phenyl and benzyl groups which in turn are smaller than those of the *tert*-butyl group.

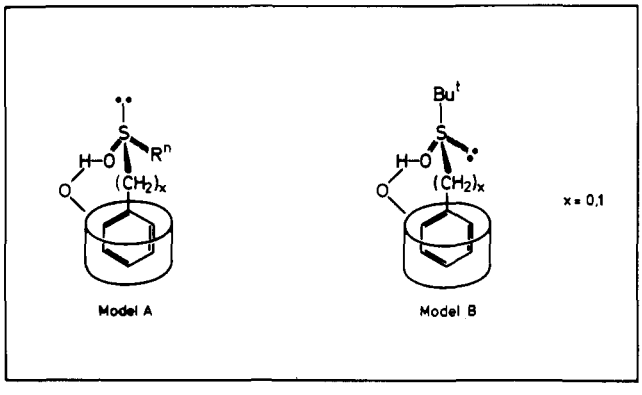
Analysis of the optical purity values of the partially resolved sulfoxides **1** and **3** provides additional evidence supporting this view. In the series of alkyl benzyl sulfoxides (**1**) the highest optical purity was observed for methyl benzyl sulfoxide (**1a**) and *tert*-butyl benzyl sulfoxide (**1g**), i.e., 8.0 and 14.5%, respectively. In other cases the optical purities were much lower. Thus, it may be assumed that the greatest differences between the steric size of substituents which are observed in the cases of the benzyl and methyl groups and benzyl and *tert*-butyl groups correspond to the highest stereospecificity of inclusion. Similar relationships were also observed for the sulfoxides **3**.

Taking into account the results which have hitherto been obtained concerning the structure of the cyclodextrin inclusion compounds formed with aromatic compounds[18] one may suppose that the inclusion of the sulfoxides **1**, **2**, and **3** consists in incorporation of the aromatic ring into the cyclodextrin cavity. The resulting adduct can be further stabilized by hydrogen bonding between the cyclodextrin hydroxy groups situated on the rim of the ring-shaped cyclodextrin molecule and the sulfinyl oxygen atom.

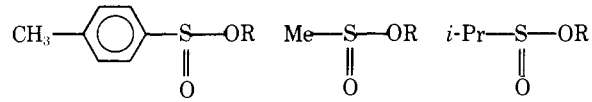
If one assumes this it is reasonable to consider that the stereospecificity of inclusion of sulfoxides into β-cyclodextrin should be determined by the interactions between the sulfoxide alkyl groups and the cyclodextrin ring. When the sulfoxide **1**, **2**, and **3** contains one *n*-alkyl group, the enantiomer with the *R* chirality at sulfur is preferably included into β-cyclodextrin (model A).[19] In the case of the *tert*-butyl analogues the steric repulsions between the *tert*-butyl and the β-cyclodextrin ring favor the formation of the inclusion compounds with the sulfoxide having the spatial arrangement of substituents around the sulfur atom as shown in model B [the configuration *R* for *tert*-butyl benzyl sulfoxide (**1g**) and *S* for *tert*-butyl phenyl and *tert*-butyl *p*-tolyl sulfoxides (**2g** and **3e**)]. The decrease of the degree of stereospecificity of inclusion with increasing size of *n*- and isoalkyl groups, as it is seen in the series of benzyl sulfoxides **1**, is probably due to the increasing amount of the inclusion complex formed according to model B.

Although the explanation given above makes it possible to understand the observed dependence between the chirality and optical purity of included sulfoxides and the structure of their β-cyclodextrin inclusion complexes, it is necessary to provide further evidence supporting the nature of the cyclodextrin-sulfoxide binding.

Scheme I



Resolution of Alkyl Alkanesulfinates. Optically active alkyl *p*-toluenesulfinates (**4**) were obtained for the first time by Philips[3] in 1925 from (−)-menthyl *p*-toluenesulfinate by transesterification and then by Fava[7c] by asymmetric oxidation of methyl *p*-toluenesulfinate with (+)-monopercamphoric acid. However, their optical purity was extremely low (about 3%) and for this reason they were unsuitable for further stereochemical studies. It is interesting to note that aliphatic analogues of optically active sulfinic esters were not known until the present time.[20,23]



4, R = Me, Et, Bu-*n* **5** **6**

Our successful attempts to resolve chiral sulfoxides via β-cyclodextrin inclusion compounds prompted us to extend this method for resolution of simple alkyl alkanesulfinates **5** and **6** with the sulfur atom as a sole chirality center. Since sulfinic acid esters are slowly hydrolyzed in water and it is well known that cyclodextrins act effectively as a hydrolysis catalysts,[12] the resolution of sulfinates could not be carried out in aqueous solution by the procedure used for sulfoxides. Therefore, the resolution of **5** and **6** was performed, according to the modified procedure described by Benschop[14] in which β-cyclodextrin hydrate was used.

β-Cyclodextrin inclusion compounds were prepared by grinding β-cyclodextrin hydrate (12 mol of water per 1 mol of β-cyclodextrin) with a 4–5 molar excess of sulfinate. After several hours the mixture was treated with ether and filtered to give the inclusion complexes which were in turn decomposed in a methylene chloride-water mixture (20:1) to give optically active sulfinates. The nonincluded sulfinates having the opposite rotation sign were recovered from the ether filtrate. Optical rotations, purities, and absolute configurations of sulfinates **5** and **6** resolved by this method are collected in Table I.

These data indicate that the inclusion of sulfinic acid esters into β-cyclodextrin is always stereospecific. The highest degree of resolution was achieved in the case of isopropyl methanesulfinate (**5b**). The included ester recovered from the complex had $[\alpha]_{589}$ −165.91°, which corresponds to 68.2% optical

(−)-*S*-**5b** (−)-*S*-**7**

purity. The nonincluded ester has been isolated with $[\alpha]_{589}$ +18.52° (optical purity 7.8%). Also in this case the optical purity of the nonincluded ester **5b** may be increased by repetition of the inclusion processes. Thus, the samples of the nonincluded **5b** having $[\alpha]_{589}$ +47.20, +62.00, and +76.50° were obtained after three successive inclusions.

It is of interest that Benschop[14] observed the highest stereospecificity of inclusion in the case of *O*-isopropyl methylphosphonate (**7**), which has a spatial structure very similar to that of isopropyl methanesulfinate (**5b**). In both cases the enantiomer having the configuration *S* was preferred in the formation of the inclusion compound with β-cyclodextrin.

Optical purities and absolute configurations of optically active sulfinates **5** and **6** obtained in the present work were determined chemically by means of their stereospecific con-

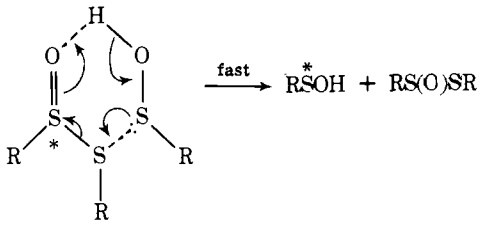
version into known sulfoxides (methyl *n*-propyl sulfoxide and methyl isopropyl sulfoxide) assuming that the Grignard reaction proceeds with full inversion of configuration at the sulfur atom.[5,6] The results of these determinations are shown in Table II.[38]

As the mechanism of formation and the structure of β-cyclodextrin inclusion complexes with aliphatic compounds is not clear, it is now not possible to rationalize the observed relation between the stereospecificity of inclusion and the chirality at sulfur in sulfinates.

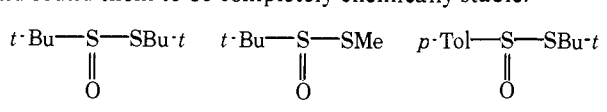
Resolution of Thiosulfinate S-Esters. Organic thiosulfinate *S*-esters (**8**) possessing labile S(O)S grouping are very interesting as model compounds for mechanistic and stereochemical studies.[25] The attack of a nucleophilic reagent may be directed on a sulfinyl and/or sulfenyl sulfur. The latter is preferred by the so-called "soft" nucleophilic reagents whereas the strongly electronegative and nonpolarizable "hard" nucleophiles tend to react on the sulfinyl sulfur atom.

$$RS(O)N + RS^- \xleftarrow{N^-} \underset{\mathbf{8}}{RS(O)SR} \xrightarrow{N^-} RS^-{=}O + RSN$$

Although the cleavage of the sulfur–sulfur bond in these compounds has been investigated in detail, stereochemical studies are practically limited to the synthesis and racemization of optically active thiosulfinates **8**. It is worthy of mention that in contrast to other sulfinyl compounds, simple, optically active esters **8** so far prepared are optically unstable and undergo readily thermal and acid- and nucleophile-catalyzed racemization. There is no doubt that the racemization of **8** caused by acids and bases is connected with the scission of the sulfur–sulfur bond and the formation of achiral sulfenic acid or its anion as an intermediate.[26] In order to explain the unusually rapid thermal racemization of optically active arenethiosulfinates Fava[27] has advanced the view that an internal displacement at sulfenyl sulfur rather than pyramidal inversion at sulfinyl sulfur may be involved. However, Block and O'Connor[28] based on the results obtained on the thiosulfinate scrambling process recently gave an alternative explanation for the unusually low optical stability of optically active **8** which consists in their facile reaction with traces of sulfenic acid, a reaction which takes place via the concerted transition state shown below.



Considering the observations reported above one may suppose that the chemical and optical instability of thiosulfinates **8** is due to the ease of a nucleophilic attack on the sulfenyl sulfur atom. Therefore, introduction of steric hindrance around one or both sulfur atoms should lead to a considerable increase of chemical and consequently optical stability of these compounds. With this in mind we prepared the sterically hindered thiosulfinates **8a, 8b,** and **8c** containing the *tert*-butyl group and found them to be completely chemically stable.

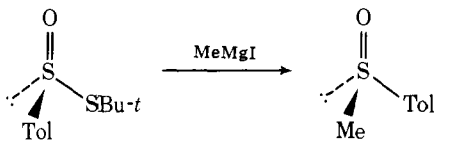


8a **8b** **8c**

Anticipating that these esters would be also optically stable we carried out their optical resolution via inclusion compounds with β-cyclodextrin.[29] It was found that partial resolution of racemic thiosulfinates **8** took place under the conditions analogous to those used in the resolution of sulfinates. The results of these studies are shown in Table I. When the inclusion process was repeated the optical rotation of the nonincluded thiosulfinate **8a,** $[\alpha]_{589}$ −3.02°, could be increased. Thus, the samples of the nonincluded **8a** having $[\alpha]_{589}$ −9.38, −12.24, and −15.73° were obtained after three consecutive inclusions.

As expected, *S-tert*-butyl *tert*-butanethiosulfinate (**8a**), which is the first example of an optically active dialkyl thiosulfinate, exhibited a very high optical stability. When the sample of **8a,** $[\alpha]_{589}$ +21.05°, was heated for 8 h in boiling benzene, its optical rotation remained unchanged. Also in pyridine solution at room temperature the racemization of **8a** did not take place. It occurred, however, over 90 °C at a measurable rate but it was accompanied by considerable decomposition of the ester.

The optical purity and chirality at sulfur in *S-tert*-butyl *p*-toluenethiosulfinate (**8c**) was determined chemically by means of its conversion into *p*-tolyl methyl sulfoxide (**3b**) using methylmagnesium iodide. It was assumed that this reaction is completely stereospecific and proceeds with inversion of configuration at the sulfinyl sulfur atom.



(−)-*S*-**8c**, $[\alpha]_{589}$ −2.75° (+)-*S*-**3a**, $[\alpha]_{589}$ +2.00°

However, this approach failed for the ester **8a,** most probably owing to the steric hindrance exerted by the two bulky *tert*-butyl groups. The reaction of **8a** with Grignard reagents (methylmagnesium iodide and *p*-tolylmagnesium bromide) even on prolonged heating in tetrahydrofuran solution gave after the usual workup the unreacted thiosulfinate **8a** with unchanged optical rotation. For this reason its optical purity was estimated by an NMR technique using the chiral shift reagent tris[3-(trifluoromethylhydroxymethylene)(+)-camphorato]europium (TFMC).[31]

The ^{1}H NMR spectrum of the racemic thiosulfinate **8a** consists of two singlets at 1.32 and 1.55 ppm which can be ascribed to the *tert*-butyl group bonded to the sulfinyl and sulfenyl sulfur atom, respectively.[32] In the spectrum of the optically active **8a,** $[\alpha]_{589}$ +21.1°, obtained in the presence of TFMC we observed four signals of unequal intensity at 2.07, 2.33, 2.80, and 3.30 ppm. The enantiomeric content in the sample studied determined by integration of the above discussed signals corresponds to 13.6% of optical purity. Hence, the specific rotation of the pure enantiomers of **8a** is, within the limits of error of the NMR method, ±154.9°.

Experimental Section

All boiling and melting points are uncorrected. ^{1}H NMR spectra were obtained on a JEOL-JNM-C-60 or Perkin-Elmer R-20 spectrometer in carbon tetrachloride solution. Chemical shifts are reported on the δ scale relative to Me_4Si. IR spectra were recorded on a Perkin-Elmer 137 Infracord spectrophotometer for liquid films or KBr disks. Optical rotations were measured on a Perkin-Elmer 141 photopolarimeter.

Materials and Purification Procedures. Trichloroethylene was purified by successive washings with concentrated sulfuric acid, aqueous sodium carbonate, aqueous sodium bicarbonate and water. After drying over calcium chloride, trichloroethylene was distilled from P_2O_5. Other solvents were purified by standard methods.

Most of racemic sulfoxides **1, 2,** and **3** were prepared by oxidation of the corresponding sulfides with 30% hydrogen peroxide in acetone solution. Sulfoxides **3c, 3d,** and **3f** were obtained from methyl *p*-toluenesulfinate and alkylmagnesium halides. Physical properties of sulfoxides were in good agreement with the literature data.[33]

Sulfinates **5** and **6** were prepared by the method of Douglas[34] from sulfinyl chlorides and appropriate alcohols in the presence of pyridine. Physical constants, elemental analyses, and some ^{1}H NMR and IR data for new sulfinates **5** and **6** are given in Tables III and IV.[38]

S-tert-Butyl *tert*-butanethiosulfinate (**8a**) was prepared by oxidation of *tert*-butyl disulfide with 30% hydrogen peroxide in acetone solution: bp 70–71 °C (1.7 mmHg); n^{21}D 1.5050; yield 82% (lit.[35] bp 55 °C (0.05 mmHg); n^{21}D 1.5060); IR 1080 cm^{-1} (S=O); ^{1}H NMR (CCl_4) δ 1.32 (s, 9 H, $(CH_3)_3CSO$), 1.55 (s, 9 H, $(CH_3)_3CS$).

Thiosulfinates **8b** and **8c** were obtained from the corresponding sulfinyl chlorides and thiols according to the method described by Block and O'Connor.[36] Their structures were confirmed by the ^{1}H NMR spectra. **8b:** δ 1.30 (s, 9 H, $(CH_3)_3CSO$), 2.46 (s, 3 H, CH_3S). **8c:** δ 1.60 (s, 9 H, $(CH_3)_3CSO$), 2.49 (s, 3 H, $CH_3C_6H_4$), 7.33–7.78 (distorted AB system, 4 H, aromatic).

Resolution of Methyl Benzyl Sulfoxide (1a) via β-Cyclodextrin Inclusion Complexes. To a solution of β-cyclodextrin (6 g, 0.0055 mol) in water (400 mL) methyl benzyl sulfoxide (**1a**, 4 g, 0.026 mol) was added. After 72 h the precipitated inclusion compound was filtered off, dried, and analyzed.

In the next step, the inclusion compound (8.4 g) was dissolved in water (200 mL) at 60 °C and trichloroethylene (200 mL) was added. After addition of trichloroethylene stirring at ca. 0 ° C was continued for 2 h. The organic layer was then separated and the water solution was extracted twice with chloroform (50 mL). The combined organic solutions were dried over $MgSO_4$ and evaporated to give the crude sulfoxide (**1a**) (0.6 g). Column chromatography on silica gel using chloroform as eluent gave the analytically pure sulfoxide (**1a**): $[\alpha]_D$ −8.50° (c 2.08, ethanol); mp 52–55 °C. Its IR spectrum was identical with that of a racemic sample.

This procedure is typical for the resolution of sulfoxides **1**, **2**, and **3** via β-cyclodextrin inclusion compounds. Some experimental data concerning resolved sulfoxides are given in Table I. In Table V elemental analyses and molar ratio of the complexes between sulfoxides and β-cyclodextrin are summarized.[38]

Resolution of Isopropyl Methanesulfinate (5b) via β-Cyclodextrin Inclusion Complexes. β-Cyclodextrin (6.8 g, 0.006 mol) was mixed with 3.8 mL of water and then sulfinate **5b** (4.7 g, 0.04 mol) was added. The mixture was well ground for 0.5 h. After 3 h ether (30 mL) was added and the inclusion compound formed (7 g) was filtered off, dried, and analyzed. The ether solution was washed with 5% aqueous potassium bicarbonate and water, dried, and evaporated to give (3.8 g) optically active sulfinate **5b**, n^{20}D 1.4285, $[\alpha]_{589}$ +18.52° (c 3.3, ethanol). IR and NMR spectra of this sample were identical with those of racemic ester.

The isolated inclusion compound (7.0 g) was ground three times with a mixture of methylene chloride (20 mL) and water (2 mL) in order to recover the included sulfinate ester. The combined organic solutions were washed with 5% aqueous potassium carbonate and water and then dried over $MgSO_4$. Evaporation of the solvent yielded (0.3 g) optically active sulfinate **5b**, n^{21}D 1.4288, having optical rotation $[\alpha]_{589}$ −165.91° (c 2.5, ethanol). Its physical and spectroscopic properties were identical with those of a racemic sample.

According to the procedure described above we have resolved other sulfinates **5** and **6**. Their optical rotations, optical purities, and absolute configurations are collected in Table I. Elemental analyses and molar ratio between sulfinates and β-cyclodextrin in the inclusion complexes are given in Table VI.[38]

Resolution of *S-tert*-Butyl *tert*-Butanesulfinate (8a) via β-Cyclodextrin Inclusion Complexes. To a β-cyclodextrin hydrate prepared from β-cyclodextrin (3.8 g, 0.003 mol) and water (1.8 g) thiosulfinate **8a** (3.0 g, 0.015 mol) was added. The mixture was well ground for 1 h and then ether (30 mL) was added. The inclusion compound (4.0 g) was filtered off, dried, and analyzed.

The ether solution was washed with 5% aqueous potassium carbonate and water. After drying over $MgSO_4$ and evaporation 3.1 g of thiosulfinate **8a** was obtained, n^{21}D 1.5048, $[\alpha]_{589}$ −3.02° (c 6.05, ethanol).

The inclusion compound obtained (4.0 g) was ground three times with a mixture of methylene chloride (20 mL) and water (2 mL). The organic layer was dried and evaporated to give 0.1 g of thiosulfinate **8a**, n^{21}D 1.5050, $[\alpha]_{589}$ +21.07° (c 2.43, ethanol), which was spectrally identical with racemic material.

In a similar manner we were able to resolve thiosulfinates **8b** and **8c**. Elemental analyses of the inclusion compounds between thiosulfinates **8** and β-cyclodextrin are summarized in Table VII.[38]

Preparation of (+)-Benzyl *n*-Propyl Sulfoxide (1c). To a solution of *n*-propylmagnesium bromide [prepared from 4.9 g (0.04 mol) of *n*-propyl bromide and magnesium (0.96 g, 0.04 mol)] in ether (30 mL) a solution of (+)-menthyl phenylmethanesulfinate[37] [4.57 g, 0.016 mol, $[\alpha]_{589}$ +123.3° (c 0.18, ethanol)] in ether (10 mL) was added. After 1 h the reaction mixture was worked up by quenching with saturated aqueous ammonium chloride solution (35 mL). The water solution was extracted with chloroform (4 × 20 mL). The combined organic solutions were dried over magnesium sulfate and evaporated to give sulfoxide **1c**, which was chromatographed on silica gel using a mixture of ethyl acetate–benzene (4:1) as eluent: mp 42–43 °C; $[\alpha]_{589}$ +55.0° (c 0.67, ethanol); ^{1}H NMR δ 1.05 (t, 3 H, $CH_3CH_2CH_2$), 1.75 (sextet, 2 H, $CH_3CH_2CH_2$), 2.45 (t, $CH_3CH_2CH_2$), 3.85 (s, 2 H, $PhCH_2$), 7.35 (m, 5 H, aromatic).

Anal. Calcd for $C_{10}H_{14}OS$: C, 65.93; H, 7.69. Found: C, 65.86; H, 7.92.

Preparation of (−)-Benzyl Isobutyl Sulfoxide (1f). By a similar procedure from (+)-menthyl phenylmethanesulfinate (2.94 g, 0.01 mol) and isobutylmagnesium bromide prepared from isobutyl bromide (2.74 g, 0.02 mol) and magnesium (0.48 g, 0.02 mol) sulfoxide **1f** was prepared: mp 66–67 °C $[\alpha]_{589}$ −110.0° (c 0.90, chloroform); ^{1}H NMR δ 1.05 (d, 6 H, $(CH_3)_2CHCH_2$), 1.015–2.55 (m, 3 H, $(CH_3)_2CHCH_2$), 3.82 (s, 2 H, $PhCH_2$), 7.3 (s, 5 H, aromatic).

Anal. Calcd for $C_{11}H_{16}OS$: C, 67.35; H, 8.16. Found: C, 67.41; H, 8.23.

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Supplementary Material Available: Tables II–VII including physical properties of new sulfinates **5** and **6** and elemental analyses and molar ratio of the complexes between sulfoxides, sulfinates, and thiosulfinates and β-cyclodextrin (6 pages). Ordering information is given on any current masthead page.

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Glycocinnamoylspermidines, a New Class of Antibiotics. 3. The Structures of LL-BM123β, γ1, and γ2

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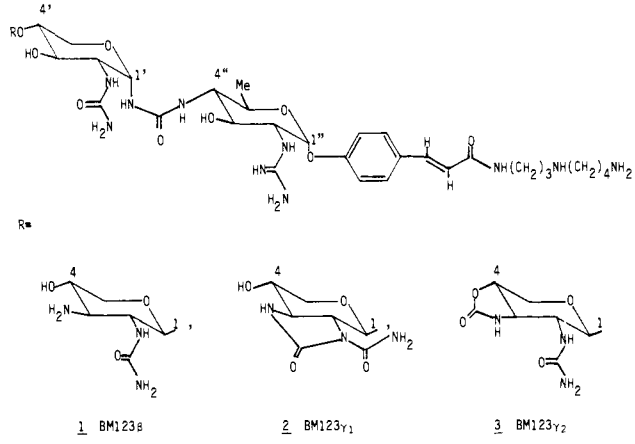
Abstract: On the basis of hydrolytic experiments in conjunction with ^{1}H NMR, ^{13}C NMR, and x-ray analysis, the structures of three novel broad-spectrum antibiotics called LL-BM123β, γ1, and γ2 have been determined.

LL-BM123β, γ1, and γ2 are three new broad-spectrum antibiotics which were recently isolated in these laboratories from fermentations of an unidentified species of *Nocardia*.[1,2] The γ1 and γ2 components are of special interest because of their broad-spectrum activity against gram-negative organisms and their protective effects against infections produced in mice.[2]

Initial attempts at structural characterization of these antibiotics centered on a possible x-ray solution. Although considerable effort was made to prepare a crystalline heavy-atom derivative, this approach was not successful. However, from the results of hydrolytic experiments and identification of the degradation products by spectral and, where possible, single-crystal x-ray analysis, we propose structures **1, 2,** and **3** for LL-BM123β, γ1, and γ2, respectively. These antibiotics contain several unusual structural features including the glycosylurea linkage and substituted 2,3-dideoxy-2,3-diaminoxylopyranoside moieties. The 2,4,6-trideoxy-2,4-diaminohexopyranoside has been observed only once before in nature as the 4-*N*-acetamide from mild acid hydrolysis of a polysaccharide from *Bacillus lichenformis*.[3] Also of interest is the 1′-*N*-carbamoylimidazolidone unit in **2** reminiscent of the 1′-*N*-carboxylimidazolidone portion of the biotin derivative postulated to be involved in biotin-dependent carboxylase systems.[4]

All three antibiotics are amorphous and strongly basic compounds. They are positive to ninhydrin and Sakaguchi tests and also to Ehrlich's reagent[5] for ureido groupings. Although elemental and mass spectral (including field desorption) analyses were of little value in obtaining molecular formulas,



^{13}C NMR experiments[6] indicate clearly the presence of 37 carbons in **2** and **3**, and 36 in **1**. These spectra also suggest a close relationship between the three antibiotics. Indeed, mild basic hydrolysis of **2** and **3** provided **1**, the loss of one carbonyl grouping being the only significant change as indicated by the ^{13}C NMR data. The *trans*-*p*-coumaroyl moiety is common to all three antibiotics as indicated by the UV maximum at 286 nm and the very characteristic ^{1}H NMR (220 MHz in D_2O) signals at δ 6.2 and 7.0 (1 H d's, J = 15.5 Hz) and 6.8 and 7.2 (1 H d's, J = 8.0 Hz). Other prominent ^{1}H NMR signals common to all three metabolites are those assigned to the secondary *C*-methyl at δ 1.4 (J = 6.0 Hz), the spermidine

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