Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 14, pp. 2403–2410, 1997

Printed in Great Britain
PII: S0957-4166(97)00244-9
0957-4166/97 $17.00 + 0.00

Resolution and absolute configuration of enantiomeric spiro-λ^4-sulfane-precursor diaryl sulfoxides

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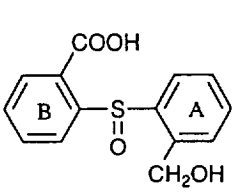
Abstract: The spiro-λ^4-sulfane (spirosulfurane) precursors 2-[(2-hydroxymethylphenyl)-sulfinyl]benzoic acid **1**, 8-[(2-hydroxymethylphenyl)sulfinyl]-1-naphthoic acid **2**, and 2-[(8-hydroxymethyl-1-naphthyl)sulfinyl]benzoic acid **3** were prepared from the corresponding sulfides by oxidation with chloramine-T. By using chiral organic bases racemic **1–3** were resolved to yield the enantiomers in high enantiomeric excess. The molecular structures of sulfoxides (+)-**1**, (+)-**2**, and (+)-**3** were determined by X-ray diffraction method, and the absolute configuration of the stereogenic sulfur atom was assigned as (*R*), (*S*), and (*S*), respectively. The actual conformations are discussed including effective S···O close contacts and the relative positions of aromatic rings. Relevant bond lengths, angles and CD spectra are also given. © 1997 Elsevier Science Ltd

Introduction

Diaryl sulfoxides (aryl=phenyl or 1-naphthyl) carrying two reactive groups (e.g. COOH, CH_2OH, CONHMe, SO_2NH_2) in *ortho* or *peri* positions can be easily dehydrated, and so they are appropriate precursors for preparing spiro-λ^4-sulfanes (spirosulfuranes) with O(acyl),[1,2] O(alkyl),[3,4] and N(acyl)[5,6] hetero atoms in axial positions. Because spiro-λ^4-sulfanes with more or less strong S–O(acyl), S–O(alkyl) or S–N(acyl) hypervalent bonds proved to be excellent models to study structure–reactivity relationship for sulfur(IV) compounds with trigonal–bipyramidal geometry,[7–9] we decided to investigate the stereochemistry of spiro-λ^4-sulfane formation starting from optically active diaryl sulfoxides. As a first part of this work we report now the synthesis and resolution of 2-[(2-hydroxymethylphenyl)sulfinyl]benzoic acid **1**, 8-[(2-hydroxymethylphenyl)sulfinyl]-1-naphthoic acid (**2**), and 2-[(8-hydroxymethyl-1-naphthyl)sulfinyl]benzoic acid **3** together with their X-ray structure determination including the elucidation of absolute configurations.



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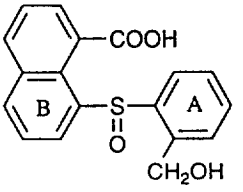

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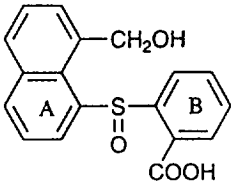

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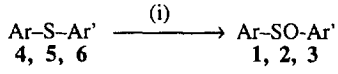
Results and discussion

Synthesis

The racemic mixtures of diaryl sulfoxides **1**, **2**, and **3** were prepared from the corresponding sulfides **4**, **5**, and **6**, respectively, by oxidation with chloramine-T (TsNClNa) in aqueous media, as shown in Scheme 1.



Scheme 1. Conversion of diaryl sulfides to diaryl sulfoxides. Ar=2-(hydroxymethyl)phenyl for **1**, **2**, **4**, and **5**; 8-(hydroxymethyl)-1-naphthyl for **3** and **6**. Ar'=2-carboxyphenyl for **1**, **3**, **4**, and **6**; 8-carboxy-1-naphthyl for **2** and **5**. *Reagents and conditions*: (i) TsNClNa, aq $KHCO_3$, 100°C, 1 h.

Resolution by crystallization

The resolution of racemic sulfoxide **1** was carried out by a slight modification of a method published by us earlier.[3] To one eq of sulfoxide carboxylic acid **1** were added half–half eq of NaOH and (+)-cinchonine in water. One of the diastereomeric cinchonine salts separated in crystalline form from which, after recrystallization (2×EtOH–H_2O), the pure (+)-**1** was regenerated by aq H_2SO_4; $[\alpha]^{25}_{546}$=+173, c=0.47, DMF. By using (−)-cinchonidine dissolved in EtOH–H_2O the resolution of racemic sulfoxide **2** was performed in a similar way. To obtain the pure (+)-**2** the first crop of the cinchonidine salt was recrystallized (EtOH), then treated with aq NaOH and acidified by aq H_2SO_4; $[\alpha]^{25}_{546}$=+673, c=0.5, DMF. The resolution of racemic sulfoxide **3** was based on the different solubility of the diastereomeric salts prepared with (−)-brucine in ethanol. The first crop of the brucine salt was treated with aq NaOH, acidified by aq H_2SO_4, then the crude product obtained was recrystallized (EtOH) to yield the pure (−)-**3**; $[\alpha]^{25}_{546}$=−146, c=0.5, DMF.

The other enantiomers of the above optically active sulfoxides were prepared, in a more or less pure form, from the mother liquors obtained by filtering off the first crystalline crops of the alkaloid salts; $[\alpha]^{25}_{546}$=−161, −575, and +145 (c=0.49, 0.5, and 0.5, DMF) were measured for (−)-**1**, (−)-**2**, and (+)-**3**, respectively.

Enantiomeric excess

To measure the enantiomeric excess for the enantiomers obtained, samples of the optically active sulfoxides **1–3** were first converted to their methyl esters by diazomethane. By using chiral shift reagents, tris-[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III) for **1** and **3** and tris[3-heptafluoro-propylhydroxymethylene)-(+)-camphorato]praseodymium(III) for **2**, in $CDCl_3$, the methyl signs were separated in the NMR spectra. The following enantiomeric excess data were obtained: >99% for (+)-**1**, (+)-**2**, and (−)-**3**, whereas 93, 85, and >99% for the (−)-**1**, (−)-**2**, and (+)-**3** enantiomers, respectively. The CD spectra recorded for (*R*)-(+)-**1**, (*S*)-(+)-**2**, and (*S*)-(+)-**3** are shown in Figure 1.

Resolution by salting out selective extraction

Although the above sulfoxide enantiomers could be obtained by classical crystallization methods, we also tried to apply an extractive procedure,[10] which allows calculating the values of the absolute rotation $[\alpha]_{max}$. To a mixture of water and chloroform were added two eq of a racemic sulfoxide carboxylic acid (**1** or **2** or **3**), one eq of NaOH and one eq of a chiral organic base,[11] and the mixture was shaken until the partition equilibrium was reached, then the partially resolved carboxylic acids were isolated from both solvents (see details in Experimental part). After the first extraction step 23, 30, and 46%, while after the second step 40, 47, and 77% enantiomeric excess values were found for **1**, **2**, and **3**, respectively. The $[\alpha]_{max}$ values (181, 635, and 134) calculated by an equation given in Ref.[10] are in rather good agreement with those found experimentally (173, 673, and 145).

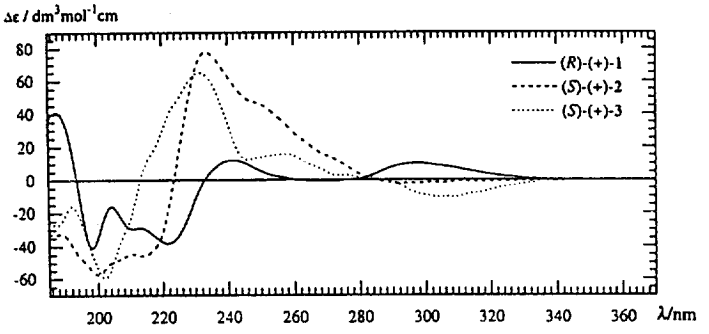


Figure 1. CD spectra obtained for sulfoxides (*R*)-(+)-**1**, (*S*)-(+)-**2**, and (*S*)-(+)-**3**, respectively (in acetonitrile).

Molecular structure and absolute configuration

The molecular structures of sulfoxides (*R*)-(+)-**1**, (*S*)-(+)-**2** and (*S*)-(+)-**3** as determined by single-crystal X-ray diffraction method are shown in Figs 2–4 together with selected interatomic distances and angles.

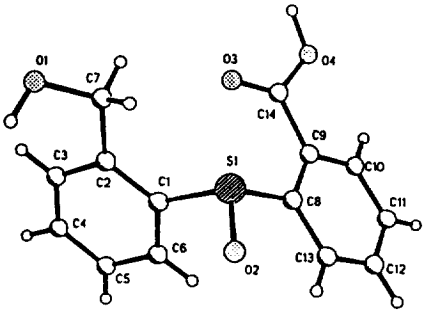


Figure 2. Perspective representation of sulfoxide (*R*)-(+)-**1** molecule. Selected bond lengths (Å) and angles (deg) are as follows: S(1)–O(2) 1.501(3), S(1)···O(3) 2.778(3), S(1)–C(1) 1.803(2), S(1)–C(8) 1.812(2), C(14)–O(3) 1.201(2), C(14)–O(4) 1.317(3). ϑ_1(O2–S1···O3) 176.1(1), ϑ_2(C1–S1–C8) 100.6(2), ϑ_3(C1–S1–O2) 105.1(2), ϑ_4(C8–S1–O2) 104.5(2), ϑ_5(C8–S1···O3) 74.1(1), ϑ_6(C1–S1···O3) 78.8(1). φ_1(O1–C7–C2–C1) −147.9 (3), φ_2(C2–C1–S1–C8) −136.7(2), φ_3(C2–C1–S1–O2) 115.0(3), φ_4(C1–S1–C8–C9) 81.3(3), φ_5(O2–S1–C8–C9) −169.9(3), φ_6(C8–C9–C14–O3) −11.0(3).

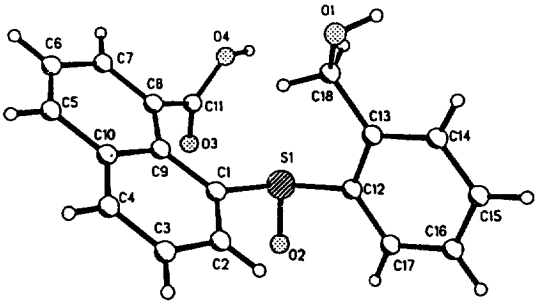


Figure 3. Perspective representation of sulfoxide (*S*)-(+)-**2** molecule. Selected bond lengths (Å) and angles (deg) are as follows: S(1)–O(2) 1.512(2), S(1)···O(3) 3.026(2), S(1)–C(1) 1.799(2), S(1)–C(12) 1.793(3), C(11)–O(3) 1.213(3), C(11)–O(4) 1.305(3). ϑ_1(O2–S1···O3) 84.7(1), ϑ_2(C1–S1–C12) 100.9(2), ϑ_3(C12–S1–O2) 106.0(1), ϑ_4(C1–S1–O2) 106.4(2), ϑ_5(C1–S1···O3) 87.5(2), ϑ_6(C12–S1···O3) 163.6(2). φ_1(O1–C18–C13–C12) 148.7(5), φ_2(C13–C12–S1–C1) −73.8(4), φ_3(C13–C12–S1–O2) 175.4(4), φ_4(C12–S1–C1–C9) 135.8(2), φ_5(O2–S1–C1–C9) −113.8(4), φ_6(C9–C8–C11–O3) 65.3(5).

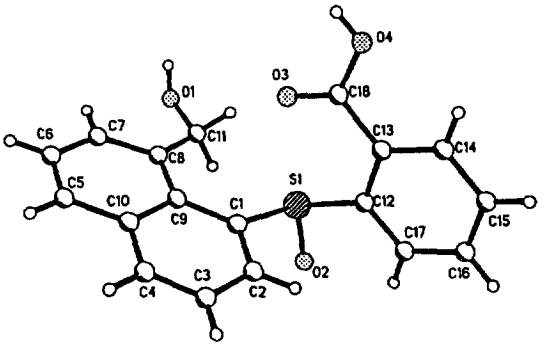


Figure 4. Perspective representation of sulfoxide (*S*)-(+)-**3** molecule. Selected bond lengths (Å) and angles (deg): S(1)–O(2) 1.500(1), S(1)···O(3) 2.720(2), S(1)–C(1) 1.812(2), S(1)–C(12) 1.805(2), C(18)–O(3) 1.214(2), C(18)–O(4) 1.305(2). ϑ_1(O2–S1···O3) 177.5(1), ϑ_2(C1–S1–C12) 100.8(1), ϑ_3(C1–S1–O2) 104.6(2), ϑ_4(C12–S1–O2) 103.1(1), ϑ_5(C1–S1···O3) 77.0(1), ϑ_6(C12–S1···O3) 74.7(1). φ_1(O1–C11–C8–C9) 176.8 (4), φ_2(C9–C1–S1–C12) 142.2(2), φ_3(C9–C1–S1–O2) −111.0(3), φ_4(C1–S1–C12–C13) −77.8(2), φ_5(O2–S1–C12–C13) 174.3(3), φ_6(C12–C13–C18–O3) 4.5 (3).

Sulfur configuration

Following the Cahn–Ingold–Prelog convention the configuration of the stereogenic sulfur atom in sulfoxides (+)-**1**, (+)-**2**, and (+)-**3** may be assigned as (*R*), (*S*) and (*S*), respectively. Owing to an S···O close contact between the central sulfur and the carbonyl-oxygen atom of the *ortho*-carboxyl group in **1** and **3** (2.78 and 2.72 Å, respectively), these compounds exhibit sulfurane-like trigonal–bipyramidal geometry about sulfur with an almost linear arrangement of the 'axial' O(2) and O(3) atoms (ϑ_1=176° and 177°); the C('equatorial')–S–O('axial') angles are nearly perpendicular (ϑ_5=74–77°). As is known, a fully conjugated planar five-membered ring (φ_{max}=13° for **1** and 6° for **3**) which is closed by near-lying sulfur and oxygen atoms, as well as a linear O=S···O arrangement of the hetero atoms both assist the existence of an attractive S···O nonbonded interaction (see details in Ref.[12]). In contrast, the analogous nonplanar six-membered ring in sulfoxide **2** is unfavourable for an effective S···O interaction, as clearly shown by an elongated S···O distance (3.02 Å) as well as by ϑ_1=85° and φ_6=65° angles. The geometries of sulfoxides **1**, **2** and **3** may be compared with those of dimethyl 2,2′-sulfinyldibenzoate (**VI** in Ref.[13]) and methyl 2-(2-nitrophenylsulfinyl)phenylacetate (**IX** in Ref.[13]): S···O=2.73 and 3.62 Å, ϑ_1(O=S–O)=174° and 91°,φ_{max}=6° and 75° (in close-contact ring), for **VI** and **IX**, respectively; ϑ_5=82° for **VI**.

Bond lengths and angles

The S(IV)–O=1.50–1.51, S(IV)–C(ar)=1.79–1.81, C(sp^2)–O(sp^2)=1.20–1.21, C(sp^2)–O(sp^3)=1.30–1.32, and C(sp^3)–O(sp^3)=1.40–1.41 Å bond lengths, as well as the C(ar)–S–C(ar)=101°, C(ar)–S–O=103–106° bond angles obtained for compounds **1–3** agree well with those found in diaryl sulfoxides carrying e.g. an *ortho*-alkoxycarbonyl substituent (see Ref.[13]; the corresponding data of **VI** are: 1.49, 1.83, 1.20, 1.32 Å, 97° and 104°, respectively).

Conformations

Compounds **1** and **3** like *o,o′*-disubstituted diaryl sulfoxides (e.g. dimethyl 2,2′-sulfinyldibenzoate; see **VI** in Ref.[13]) assume a twist-axial conformation, i.e. the ring A with a CH_2OH group lies in an intermediate position between being coplanar with or perpendicular to the C(ar)–S–C(ar) plane (φ_2=−137°, 142° and −132° for **1**, **3** and **VI**, respectively), whereas ring B carrying a COOH group is perpendicular to the same plane (φ_4=81°, −78°, and −84° for **1**, **3** and **VI**, respectively). The perpendicular position of ring B gives rise to both an effective S···O close contact and a conjugative interaction between the aryl ring and S=O bond lying in the same plane. In compound **2** exhibiting less effective S···O interaction the positions of ring A (axial) and ring B (twist) are changed (φ_2=−74°,

φ_4=136°). As is expected (cf. Ref.[12]) hydroxy-oxygen atoms do not compete with the carbonyl-oxygen in approaching the central sulfur atom (S1···O1=4.38, 4.41, and 4.32 Å, S1···O4=4.44, 3.41, and 4.44 Å, φ_1=−148°, 149°, and 177° for **1**, **2**, and **3**, respectively).

Experimental

General procedure for preparations of racemic sulfoxides 1–3

The sulfide **4**[14] or **5**[4] or **6**[14] (0.1 mol) was dissolved in a solution of $KHCO_3$ (11.0 g, 0.11 mol) in water (500 mL) by heating on a steam bath, then chloramine-T ($TsNClNa \cdot 3H_2O$, 31 g, 0.11 mol) was added to the mixture. After heating at 100°C for 1 h, the mixture was cooled to room temperature, and the precipitate ($TsNH_2$) was filtered off. The filtrate was extracted with EtOAc (3×80 mL) then acidified (pH 1) with concd aq HCl. The precipitate was filtered off, washed with water and dried to give sulfoxides **1**, **2**, and **3** (yield: 73, 82, and 81%), respectively. Selected data for **1**: mp 217–219°C (212°C in Ref.[3]); IR ν_{max} (KBr)/cm^{-1} 3238s (alcohol OH), 3100–2300br (carboxyl OH), 1700vs (C=O), 1012vs (S=O) (cf. Ref.[3]); ^{1}H-NMR (80 MHz, DMSO) δ 5.02 (d, 1H, J=14.0 Hz), 5.23 (d, 1H, J=14.0 Hz), 6.8–8.5 (m, 8H, ArH); for **2**: mp 189–192°C; IR ν_{max} (KBr)/cm^{-1} 3435s (alcohol OH), 3120–2200br (carboxyl OH), 1673vs (C=O), 981vs (S=O); ^{1}H-NMR (80 MHz, DMSO) δ 3.88 (d, 1H, J=14.9 Hz), 4.65 (d, 1H, J=14.9 Hz), 7.3–8.6 (m, 10H, ArH) (cf. Ref.[4]); for **3**: mp 196–198°C; IR ν_{max} (KBr)/cm^{-1} 3130s (alcohol OH), 2950–2100br (carboxyl OH), 1692vs (C=O), 992vs (S=O); ^{1}H-NMR (80 MHz, DMSO) δ 5.59 (d, 1H, J=14.2 Hz), 5.73 (d, 1H, J=14.2 Hz), 7.2–8.6 (m, 10H, ArH).

(R)-(+)- and (S)-(−)-2-[(2-Hydroxymethylphenyl)sulfinyl]benzoic acid 1

To a hot solution of racemic sulfoxide **1** (55.2 g, 0.2 mol) and NaOH (8 g, 0.2 mol) in water (2 L) were added a solution of (+)-cinchonine (29.4 g, 0.1 mol) in 1 L of 0.05 M H_2SO_4 and 1.5 L of water. The mixture was allowed to cool and stand at room temperature for a night. The white crystals precipitated were filtered off, washed with water and dried to give the cinchonine salt of (+)-**1**, (43.0 g; $[\alpha]^{25}_{546}$=+192, c=0.63, DMF, mp 183–187°C), which was recrystallized twice from EtOH–H_2O (30.0 g, $[\alpha]^{25}_{546}$=+173, c=0.33, DMF, mp 167–171°C). The cold solution of the recrystallized cinchonine salt (30.0 g) in EtOH (500 mL) was acidified by adding 0.05 M H_2SO_4 (pH 2) and allowed to stand at 4°C for 3 days. The precipitate was filtered off, washed with water and dried to afford the sulfoxide (*R*)-(+)-**1** (7.7 g, $[\alpha]^{25}_{546}$=+173, c=0.47, DMF, mp 160–161°C, enantiomeric excess >99%).

To prepare the (−)-enantiomer of **1** the aqueous mother liquor obtained by filtering off the crude cinchonine salt of (+)-**1** was evaporated to 2 L then acidified with cold 1 M H_2SO_4 (pH 2). The crystals separated were filtered off, washed with water and dried to give the sulfoxide (−)-**1** as a crude product (28.0 g, $[\alpha]^{25}_{546}$=−105, c=0.53, DMF, mp 172–175°C) which was purified by crystallization from MeOH–H_2O. The resulted crystals (racemic **1**) were filtered off, and (−)-**1** was obtained by evaporation of the filtrate. This procedure was repeated twice yielding the sulfoxide (*S*)-(−)-**1** in enantiomeric excess of 93% (8.2 g, $[\alpha]^{25}_{546}$=−161, c=0.49, DMF, mp 170–172°C).

(S)-(+)- and (R)-(−)-8-[(2-Hydroxymethylphenyl)sulfinyl]-1-naphthoic acid 2

To a hot solution of (−)-cinchonidine (14.7 g, 0.05 mol), EtOH (200 mL) and 1 M HCl (50 mL) was added a solution of racemic sulfoxide **2** (32.6 g, 0.1 mol) and Na_2CO_3 (5.3 g, 0.05 mol) in water (400 mL). After standing overnight at 20°C the crystals separated were filtered off, dried and recrystallized from EtOH to yield the cinchonidine salt of (+)-**2** (16.8 g, $[\alpha]^{25}_{546}$=+293, c=0.5, DMF). To liberate the sulfoxide (+)-**2**, the cinchonidine salt (15.6 g, 0.025 mol) was added to a solution of NaOH (1.12 g, 0.028 mol) in water (30 mL), which was stirred for 2 h at room temperature, then cinchonidine was removed by extraction with chloroform (150 mL). The alkaline solution was acidified with cold 1 M H_2SO_4 (pH 2), the precipitate was filtered off, washed with water and dried to afford the sulfoxide (*S*)-(+)-**2** (6.9 g, $[\alpha]^{25}_{546}$=+673, c=0.5, DMF, mp 171–178°C, enantiomeric excess >99%).

To prepare the (−)-enantiomer of **2** the mother liquor obtained by filtering off the crude cinchonidine salt of (+)-**2** was evaporated to 100 mL then acidified with 1 M H_2SO_4 (pH 2). The precipitate was filtered off, washed with water and dried to give the sulfoxide (−)-**2** as a crude product (17.2 g, $[\alpha]^{25}_{546}$=−479, c=0.5, DMF, mp 160–174°C). The above product was dissolved in a warm (80°C) solution of Na_2CO_3 (2.9 g, 0.027 mol) in water (200 mL), then (−)-cinchonidine (7.9 g, 0.027 mol), EtOH (100 mL) and 1 M HCl (27 mL) was added to the hot mixture. The separated crystals of the cinchonidine salt were filtered off (the sulfoxide liberated from this salt weighed 3.97 g; $[\alpha]^{25}_{546}$=−430, c=0.5, DMF), then the mother liquor was evaporated to 50 mL and acidified with 1 M H_2SO_4 (pH 2). The precipitate was filtered off, washed with water, then dried and crystallized from EtOH to yield the sulfoxide (*R*)-(−)-**2** in enantiomeric excess of 85% (3.8 g, $[\alpha]^{25}_{546}$=−575, c=0.5, DMF, mp 174–176°C).

(R)-(−)- and (S)-(+)-2-[(8-Hydroxymethyl-1-naphthyl)sulfinyl]benzoic acid 3

Racemic sulfoxide **3** (40.0 g, 0.122 mol) and (−)-brucine (48.3 g, 0.122 mol) was dissolved in hot EtOH (450 mL) then the solution was allowed to cool to room temperature and stand overnight. The precipitate was filtered off and dried to yield the brucine salt of (−)-**3** (42.7 g, $[\alpha]^{25}_{546}$=−50.5, c=0.5, DMF). The mixture of the above salt (33.7 g, 0.047 mol), a solution of NaOH (2 g, 0.05 mol) in water (450 mL) and dichloromethane (200 mL) was stirred at 0°C for 1 h. The aqueous phase was separated and acidified with 1 M H_2SO_4 (pH 2). The (−)-enantiomer of **3** precipitated as a crude product was filtered off, washed with water, dried, then recrystallized from EtOH to afford the sulfoxide (*R*)-(−)-**3** (7.4 g, $[\alpha]^{25}_{546}$=−146, c=0.5, DMF, mp 181–184°C, enantiomeric excess >99%).

To prepare the (+)-enantiomer of **3** the mother liquor obtained by filtering off the crude brucine salt of (−)-**3** was evaporated and the residual brucine salt of (+)-**3** (43.3 g) was decomposed by stirring with a mixture of aq NaOH (2.6 g, 65 mmol in 550 mL of water) and dichloromethane (200 mL) at 20°C for 2 h. After acidification of the aqueous phase with 1 M H_2SO_4 (pH 2) crude (+)-**3** was filtered off, dried, then recrystallized (2×EtOH) to give (*S*)-(+)-**3** in enantiomeric excess of >99% (12.2 g, $[\alpha]^{25}_{546}$=+145, c=0.5, DMF, mp 178–181°C).

Selected physical data for methyl esters of (+)-1, (+)-2, and (+)-3

Methyl R-(+)-2-[2-(hydroxymethylphenyl)sulfinyl]benzoate

mp 147–150°C; $[\alpha]^{25}_{546}$=+152 (c=0.49, DMF); IR ν_{max} (KBr)/cm^{-1} 3330s (OH), 1710vs (C=O), 1000vs (S=O); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.79 (s, 3H, CH_3), 4.83 (d, 1H, J=12.7 Hz), 5.47 (d, 1H, J=12.7 Hz), 6.9–8.3 (m, 8H, ArH).

Methyl S-(+)-8-[(2-hydroxymethylphenyl)sulfinyl]-1-naphthoate

mp 125–146°C; $[\alpha]^{25}_{546}$=+543 (c=0.5, DMF); IR ν_{max} (KBr)/cm^{-1} 3340s (OH), 1701vs (C=O), 1005vs (S=O); ^{1}H-NMR (80 MHz, DMSO) δ 3.94 (s, 3H, CH_3), 3.79 (d, 1H, J=14.7 Hz), 4.49 (d, 1H, J=14.7 Hz), 7.4–8.3 (m, 10H, ArH).

Methyl S-(+)-2-[(8-hydroxymethyl-1-naphthyl)sulfinyl]benzoate

mp 218–220°C; $[\alpha]^{25}_{546}$=+151, c=0.5, DMF; IR ν_{max} (KBr)/cm^{-1} 3400s (OH), 1718vs (C=O), 1012vs (S=O); ^{1}H-NMR (80 MHz, $CDCl_3$) δ 3.52 (s, 3H, CH_3), 5.52 (d, 1H, J=13.4 Hz), 5.79 (d, 1H, J=13.4 Hz), 7.2–8.6 (m, 10H, ArH).

General procedure for resolution by extraction

To the solution of a racemic sulfoxide (**1–3**, 5 mmol) in 0.1 M NaOH (50 mL) was added (+)-cinchonine hydrochloride (for **1**; 0.92 g, 2.5 mmol), or (−) optochin-hydrochloride (for **2** and **3**; 0.94 g, 2.5 mmol) and chloroform (100 mL), and the mixture was shaken at 20°C for 1 h. The two phases were separated, then the aqueous phase was acidified with cold 0.5 M H_2SO_4 (pH 2), the precipitate formed was filtered off, washed with water and dried. The organic phase was extracted with 0.25 M NaOH (3×20 mL), then the alkaline solution was acidified, and the precipitate formed was isolated

as described above. Starting from racemic samples we obtained 0.60, 0.85, and 0.87 g of partially resolved **1**, **2**, and **3** with $[\alpha_1]^{25}_{546}$=−39.8, −166.1, and −67.2 (c=0.5, DMF) from the aqueous phase, while the organic phase gave 0.62, 0.56, and 0.73 g of the same compounds with $[\alpha_1{*}]^{25}_{546}$=+40.6, +200.7, and +67.2 (c=0.5, DMF), respectively. Starting from the partially resolved samples of **1**, **2**, and **3** (1.38 g, 5 mmol; 0.85 g, 2.6 mmol; and 0.66 g, 2.02 mmol with $[\alpha_2]^{25}_{546}$=−33.4, −166.1, and −58.2, c=0.5, DMF) the aqueous phase gave 0.57, 0.42, and 0.27 g of the better resolved samples with $[\alpha_2]^{25}_{546}$=−69.6, −316.9, and −111.5 (c=0.5, DMF), while the organic phase gave 0.69, 0.33, and 0.27 g with $[\alpha_2{*}]^{25}_{546}$=+8.4, +29.8, −12.3 (c=0.5, DMF), respectively.

Single crystal X-ray diffraction analysis

X-Ray data were recorded on an Enraf–Nonius CAD-4 diffractometer with graphite monochromated Cu Kα (λ=1.54184 Å) radiation using ϖ–2Θ scan in the range 3.5°<Θ<77.0°. Cell constants for each crystal were determined by least squares refinement of diffractometer angles for 25 automatically centred reflections. For each crystal three standard reflections were monitored every hour. No decay correction was applied in either case. Intensities were corrected for Lorentz and polarization effects. The phase problems were solved by direct methods, using the program SHELXS86.[15] Full matrix least-squares refinement minimized $\Sigma w(\Delta F^2)^2$ for the all unique reflections by the program SHELXL93[16] with the weighting scheme: $w=1/[\sigma^2(F_o^2)^2+(aP)^2+bP]$ (where $P=[Max(F_o^2,0)+2F_c^2]/3$, while *a* and *b* varied for each data set). In each case, the fractional coordinates of the hydrogen atoms were generated from assumed geometries and were constrained to the corresponding heavy atoms with isotropic displacement parameters. Since compounds crystallized with a polar space group Flack parameter[17] was refined with good result.

*(R)-(+)-**1***

$C_{14}H_{12}O_4S$, M_t=276.30, orthorhombic, space group $P2_12_12_1$, a=8.133(1), b=8.289(1), c=19.081(1) Å, V=1286.4(2) Å^3, Z=4, D_c=1.427 Mg.m^{-3}, F(000)=576, μ=2.317 mm^{-1}. Crystal (mm): 0.30×0.25×0.20. 2674 independent reflections [R(int)=0.0118] measured. Final R=0.028, wR=0.074 for 2645 reflections applied in the refinement, R′=0.030 and wR′=0.088 for all observations, GOF=0.8892. Extinction coeff: 0.0526(14), absolute structure parameter 0.004(14).

*(S)-(+)-**2***

$C_{18}H_{14}O_4S$, M_t=326.35, orthorhombic, space group $P2_12_12_1$, a=8.066(1), b=8.231(1), c=23.182(1) Å, V=1539.0(3) Å^3, Z=4, D_c=1.408 Mg.m^{-3}, F(000)=680, μ=2.031 mm^{-1}. Crystal (mm): 0.25×0.15×0.12 (from EtOH). 3185 independent reflections [R(int)=0.023] measured. Final R=0.044, wR=0.114 for 3077 reflections applied in the refinement, R′=0.063 and wR′=0.249 for all observations, GOF=1.183. Extinction coeff: 0.0061(7), absolute structure parameter 0.02(2).

*(S)-(+)-**3***

$C_{18}H_{14}O_4S\cdot 1/2C_6H_{12}$, M_t=368.43, trigonal, space group $P3_22_1$, a=9.787(1), c=33.041(7) Å, V=2740.8(7) Å^3, Z=6, D_c=1.339 Mg.m^{-3}, F(000)=1164, μ=1.770 mm^{-1}. Crystal (mm): 0.50×0.45×0.27 (from CH_2Cl_2–DMF–cyclohexane). 3829 independent reflections [R(int)=0.028] measured. Final R=0.039, wR=0.118 for 3800 reflections applied in the refinement, R′=0.040 and wR′=0.119 for all observations, GOF=1.092. Extinction coeff: 0.0017(3), absolute structure parameter 0.02(2).

Supplementary data for the X-ray crystallographic studies on (*R*)-(+)-**1**, (*S*)-(+)-**2**, and (*S*)-(+)-**3** including bond lengths and angles have been deposited with the director of the Cambridge X-ray Crystallographic Database and they are available on request.

Acknowledgements

This work was supported by the Hungarian Scientific Research Foundation (OTKA, Nos. T017187 and T017233). The authors thank for Dr A. Csámpai for ^{1}H NMR spectral analyses.

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(Received in UK 20 May 1997)