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Stereospecific synthesis and hydrolysis of optically active diaryl(acylamino)(acyloxy)spiro-λ^4-sulfanes and related cyclic diaryl(acylamino)sulfonium salts

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Abstract—The stereospecific synthesis of diaryl(acylamino)(acyloxy)spiro-λ^4-sulfanes (*S*)-(+)-**2**, (*R*)-(+)-**5**, (*S*)-(+)-**8**, and their conversion into related diaryl(acylamino)sulfonium tetrafluoroborates (*R*)-(+)-**3**, (*S*)-(+)-**6**, (*R*)-(+)-**9**, respectively, is described. The enantiomers of spiro-λ^4-sulfanes (*S*)-(+)-**2**, (*R*)-(+)-**5** and (*S*)-(+)-**8** were prepared by dehydration of the corresponding optically active sulfoxide–carboxylic acids (*R*)-(+)-**1**, (*R*)-(−)-**4** and (*S*)-(+)-**7**, respectively, which were obtained from the racemic forms by diastereoisomeric salt separation with homochiral organic bases. The stereomechanism of the hydrolysis reaction of spiro-λ^4-sulfanes and sulfonium tetrafluoroborates that depends on pH, the nature of the axial heteroatom, the size of the spiro rings and carboxyl neighbouring group participation is also discussed.

1. Introduction

Much effort is currently directed towards understanding the stereochemistry of compounds having trigonal bipyramidal (TBP) geometry with a central S(IV) atom.[1–7] As a starting point for our investigations in this direction, we reported the stereospecific synthesis of homochiral diaryl(alkoxy)(acyloxy)spiro-λ^4-sulfanes.[1] Absolute configurations were also determined by X-ray crystallography and a comparative analysis of CD spectra.[1,2] In a subsequent publication we described the stereospecific synthesis of monocyclic sulfonium salts having spiro-λ^4-sulfane-like TBP spatial arrangement of ligands about sulfur, which is stabilised by intramolecular S···O interaction in an O(alkoxy)–S^+···O(carbonyl) axial bonding system.[4] The stereomechanism of the hydrolysis reactions of the above optically active spiro-λ^4-sulfanes and related sulfonium salts depending on pH was also reported. Continuing with this work, we prepared homochiral spiro-λ^4-sulfanes **2**, **5** and **8** and cyclic sulfonium salts **3**, **6** and **9** having N(acylamino)–S–O(acyloxy) and N(acylamino)–S^+···O(carbonyl) bonding systems, respectively. Absolute configurations were determined by CD analyses.[5]

Herein, we report the stereospecific synthesis of the above compounds starting from homochiral sulfoxides, and the hydrolysis reactions leading back to sulfoxides with retention or inversion of sulfur configuration. The results provide additional information about the stereochemistry of the formation and ring opening of model compounds, which depends on structural parameters such as the nature of the Y heteroatom in the S–Y bond, the size of spiro rings and neighbouring group participation by the carboxyl functionality.

2. Results and discussion

The stereospecific syntheses of optically active diaryl-(acylamino)(acyloxy)spiro-λ^4-sulfanes **2**, **5** and **8** from the precursor diaryl sulfoxides **1**, **4** and **7**, respectively, are shown in Scheme 1 together with their conversion into optically active diaryl(acylamino)sulfonium salts **3**, **6** and **9**, respectively.

2.1. Resolution of sulfoxides

Racemic sulfoxides 2-[2-(*N*-methylcarbamoyl)phenylsulfinyl]benzoic acid **1**, 8-[2-(*N*-methylcarbamoyl)-phenylsulfinyl]naphthoic acid **4** and 2-[8-(*N*-methylcarbamoyl)-1-naphthylsulfinyl]benzoic acid **7** were prepared by known methods.[8] To the aqueous solution of

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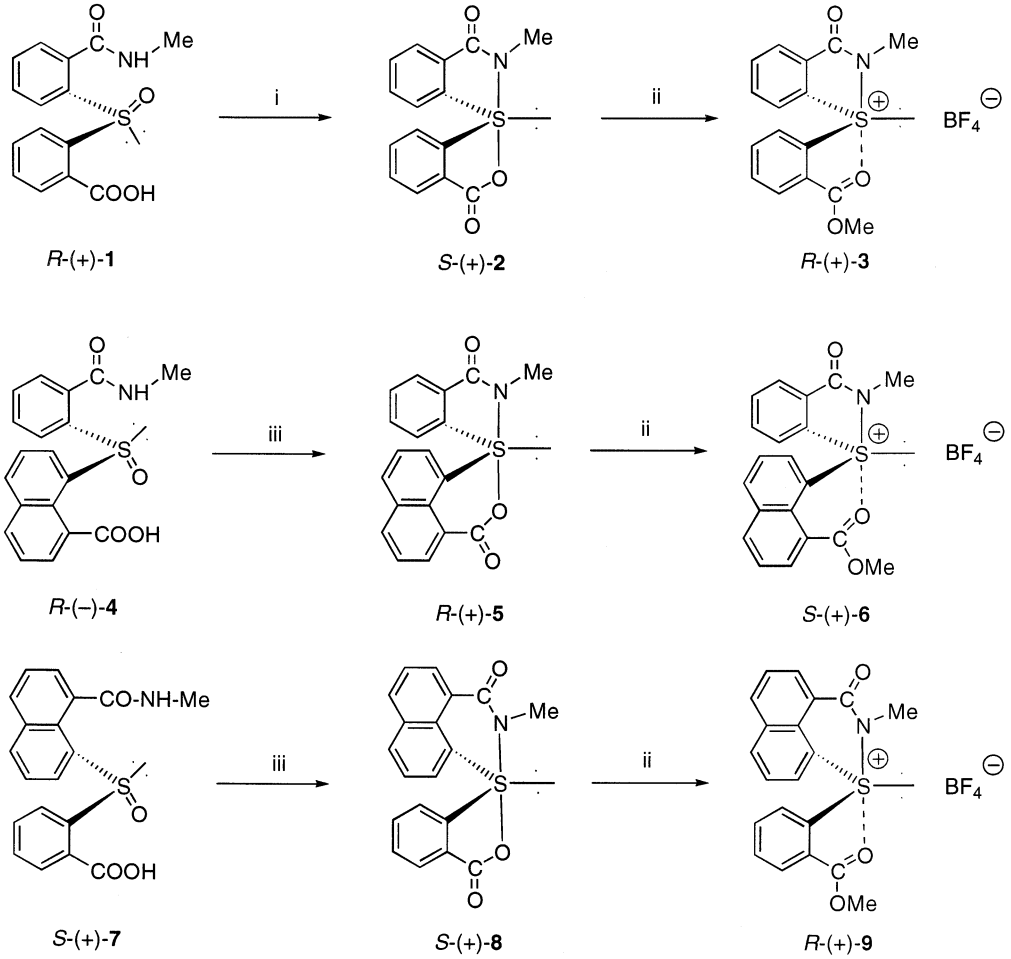


Scheme 1.

the sodium salt of **1** was added 0.5 equivalents of (+)-cinchonine sulfate. One of the diastereomeric cinchonine salts separated in crystalline form was collected, dried and recrystallised twice from EtOH–H_2O. (+)-**1** was regenerated by treating the salt with aqueous NaOH and then with aqueous H_2SO_4. To obtain homochiral sulfoxide **4** a similar procedure was performed by using 0.5 equivalents of (–)-brucine sulfate. The diastereoisomeric salt which precipitated was treated with aqueous NaOH and acidified with aqueous H_2SO_4. The crude product obtained was recrystallised from EtOH–DMF to yield (+)-**4**. Racemic **7** was resolved through its sodium salt by diastereoisomeric salt formation with 0.5 equivalents of (–)-strychnine nitrate. The diastereomeric salt precipitated was filtered off and the sulfoxide was liberated by treatment with aqueous NaOH. After acidifying, the crude product was recrystallised twice from EtOH–DMF to give (–)-**7**.

The opposite enantiomers of the above sulfoxides were prepared by acidification of the filtration mother liquors (from the initial diastereoisomeric salt separation). The crude enantiomers obtained were purified by crystallisation from a suitable solvent (see Section 3) to afford enantiomerically pure (–)-**1**, (–)-**4** and (+)-**7**, respectively.

2.2. Synthesis of homochiral spiro-λ^4-sulfanes and sulfonium tetrafluoroborates

Sulfoxide (*R*)-(+)-**1** was treated with sulfopropionic anhydride[9] in dichloromethane at −78°C to give (*S*)-(+)-spiro[3*H*-2,1-benzoxathiol-3′-one-1,1′-3*H*-2,1-benzazathiol]-2-methyl-3-one (spiro-λ^4-sulfane (*S*)-(+)-**2**). In the synthesis of (*R*)-(+)-spiro[3*H*-2,1-benzazathiol-2′-methyl-3′-one-1,1′-naphtho-[1,8-*d*,*e*]-3*H*-2,1-oxathiin-3-one] (spiro-λ^4-sulfane (*R*)-(+)-**5**) and (*S*)-(+)spiro-[3*H*-2,1-benzoxathiol-3′-one-1,1′-naphtho-[1,8-*d*,*e*]-3*H*-1,2-thiazine-2-methyl-3-one] (spiro-λ^4-sulfane (*S*)-(+)-**8**), sulfoxides (*R*)-(–)-**4** and (*S*)-(+)-**7**, respectively, were dehydrated with DCC in dichloromethane. It should be mentioned that the dehydration procedure described earlier for the synthesis of racemic spiro-λ^4-sulfanes **2**, **5** and **8**, which involves heating the precursor sulfoxide with acetic anhydride at 100°C,[8] resulted in racemic products when starting from the optically active sulfoxides (+)-**1**, (+)-**4** and (+)-**7**.

Spiro-λ^4-sulfanes (*S*)-(+)-**2**, (*R*)-(+)-**5** and (*S*)-(+)-**8** were treated with trimethyloxonium tetrafluoroborate in dichloromethane at room temperature to yield (*R*)-(+)-2,3-dihydro-1-[2′-(methoxycarbonyl)phenyl]-2-methyl-3-oxo-1,2-benzisothiazol-1-ium tetrafluoroborate [sulfo-

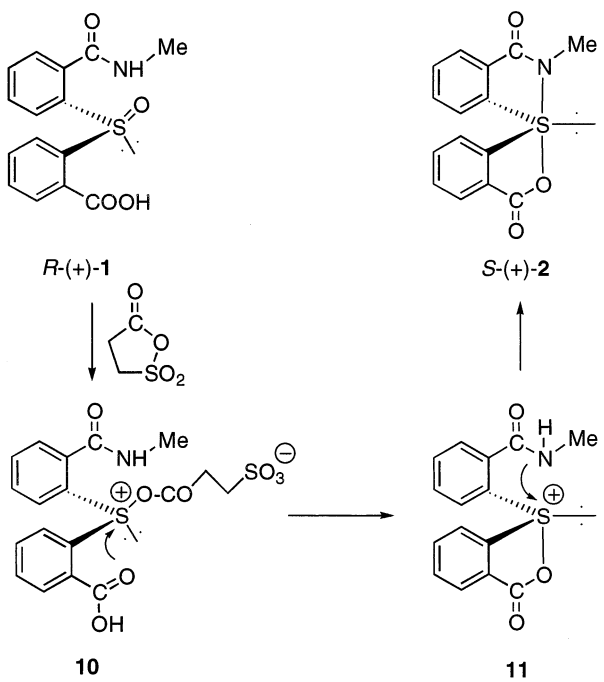
nium salt (*R*)-(+)-**3**], (*S*)-(+)-2,3-dihydro-1-[8′-(methoxycarbonyl)-1′-naphthyl]-2-methyl-3-oxo-1,2-benzisothiazol-1-ium tetrafluoroborate (sulfonium salt (*S*)-(+)-**6**) and (*R*)-(+)-2,3-dihydro-1-[2′-(methoxycarbonyl)-phenyl]-2-methyl-3-oxo-naphtho[1,8-*d*,*e*]-1,2-thiazin-1-ium tetrafluoroborate (sulfonium salt (*R*)-(+)-**9**), respectively.

2.3. Enantiomeric excess

To determine the e.e. of the sulfoxide enantiomers they were first converted to methyl esters with diazomethane. In the presence of chiral shift reagent tris[3-heptafluoro-butyryl-(+)-camphorato]praesodymium(III) in $CDCl_3$ the methyl signals of the enantiomers were separated in the NMR spectra. The following e.e. data were obtained: >99% for (−)-**1**, (+)-**1**, (+)-**4**, 97% for (−)-**4**, 89% for (−)-**7** and 86% for (+)-**7**.

The enantiomers of spiro-λ^4-sulfanes **2**, **5** and **8** were analysed by HPLC using a chiral stationary phase.[3] E.e. data obtained: >99% for (+)-**2**, 97% for (+)-**5** and (+)-**8**. The increased e.e. of (+)-**8** (97%) compared to the starting sulfoxide (+)-**7** (86%) may be attributed to the work-up procedure which involved crystallisation from acetone (see Section 3).

Sulfonium salts (+)-**3**, (+)-**6** and (+)-**9** can be hydrolysed to form compounds (−)-**12**, (−)-**13** and (+)-**14** (which are methyl ester derivatives of (−)-**1**, (−)-**4** and (+)-**7**), and then their optical activity measured. Because the hydrolysis is stereospecific and the e.e. of the pure methyl esters is known, the e.e. of the starting sulfonium salts can be calculated. Taking into account that sulfoxides may undergo racemisation under the conditions employed for the hydrolysis, the following e.e. data were obtained: 94% for (+)-**3**, 96% for (+)-**6** and 95% for (+)-**9**.



Scheme 2.

2.4. Absolute configurations and stereomechanism

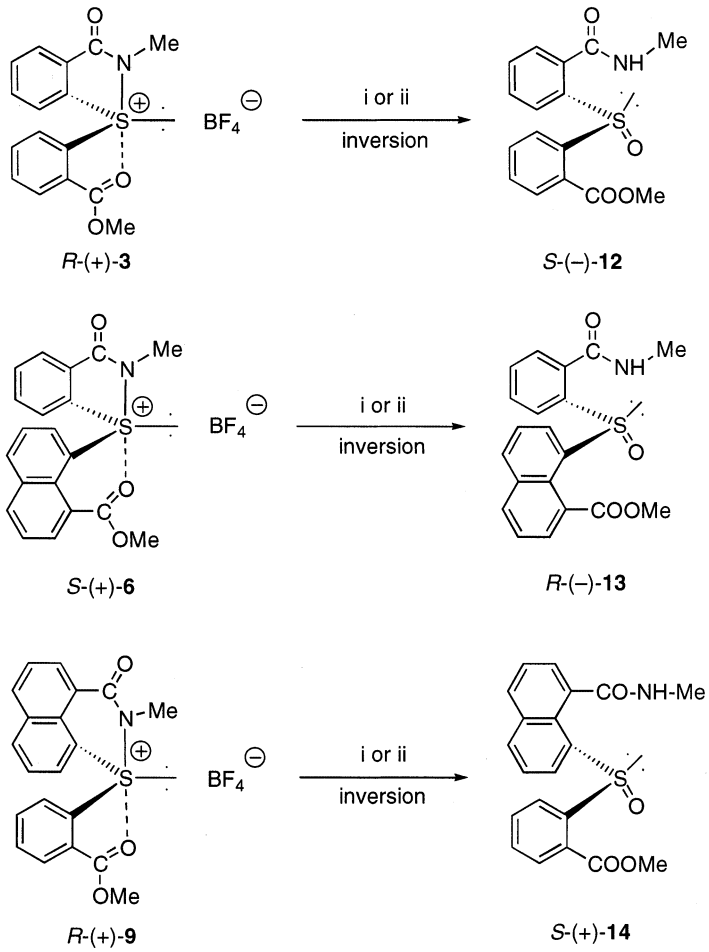
The absolute configuration of compounds shown in Scheme 1, as determined on the basis of CD analyses, has been reported recently by us.[5] Earlier we described the stereomechanism of the formation of spiro-λ^4-sulfanes having alkoxy and acyloxy ligands in axial positions.[1] Molecular structure determination revealed that the stereospecific dehydration of the corresponding sulfoxide with acetyl chloride or DCC proceeds with retention of configuration at sulfur, i.e. (*R*)-sulfoxides are converted into (*R*)-spiro-λ^4-sulfanes (for the convention for the designation of spiro-λ^4-sulfanes, see Ref. 10). As was expected, the dehydration of sulfoxides (*R*)-(−)-**4** and (*S*)-(+)-**7** occurred with retention (path iii in Scheme 1). In contrast, the reaction of sulfoxide (*R*)-(+)-**1** with sulfopropionic anhydride (path i in Scheme 1) takes place with inversion at sulfur, yielding the (*S*)-enantiomer of spiro-λ^4-sulfane **2**. We presumed that the latter reaction proceeds through the intermediates **10** and **11** (Scheme 2). To verify this assumption we isolated the intermediate **10** and identified its structure by IR spectroscopy {3600–2400 cm^{-1} (O–H), 1720, 1660 cm^{-1} (C=O), 1195, 1168 cm^{-1} (SO_3^-)}.

Sulfonium methyl esters (*R*)-(+)-**3**, (*S*)-(+)-**6** and (*R*)-(+)-**9** were prepared from spiro-λ^4-sulfanes (*S*)-(+)-**2**, (*R*)-(+)-**5** and (*S*)-(+)-**8**, respectively, by methylation of the negatively polarised oxygen, built in a weak S—O(acyloxy) hypervalent bond[8,11] according to the analogous reaction of (alkoxy)(acyloxy)spiro-λ^4-sulfanes.[4] Despite the structural analogy, corresponding spiro-λ^4-sulfanes and sulfonium salts are designated by opposite stereodescriptors, owing to the different conventions applied to these compounds.

2.5. Hydrolysis; neighbouring group participation of COOH group

Previously we described the hydrolysis of spiro-λ^4-sulfanes having an axial O(alkoxy)–S–O(acyloxy) moiety and cyclic sulfonium salts having an axial O(alkoxy)–$S^+\cdots$O(carbonyl) moiety.[4] It has also been reported that the reaction is stereospecific, following different pathways in alkaline (1 M $KHCO_3$) and acidic (1 M H_2SO_4) solutions. We performed the hydrolysis in basic and acidic media of optically active spiro-λ^4-sulfanes **2**, **5** and **8** and sulfonium salts **3**, **6** and **9** bearing an N–O(acylamino) function.

Alkaline hydrolysis of the spiro-λ^4-sulfanes **2**, **5** and **8** occurred with retention of configuration at sulfur. The same results were obtained for the analogous O(alkoxy) compounds (with a CH_2O moiety instead of CONMe[4]). Similarly, the hydrolysis of (acylamino)sulfonium salts **3**, **6** and **9** proceeded by the same inversion mechanism as that of (alkoxy)sulfonium salts,[4] both in basic and acidic media (Scheme 3).



Scheme 3.

In contrast, the acidic hydrolysis of spiro-λ^4-sulfanes proceeds in an unusual way, depending on the axial heteroatoms and the size of the spiro rings. Whereas (alkoxy)spiro-λ^4-sulfanes hydrolysed with inversion, racemisation and inversion, respectively, the analogous (acylamino)spiro-λ^4-sulfanes **2**, **5** and **8** converted with retention, retention and inversion, respectively (Scheme 4).[4]

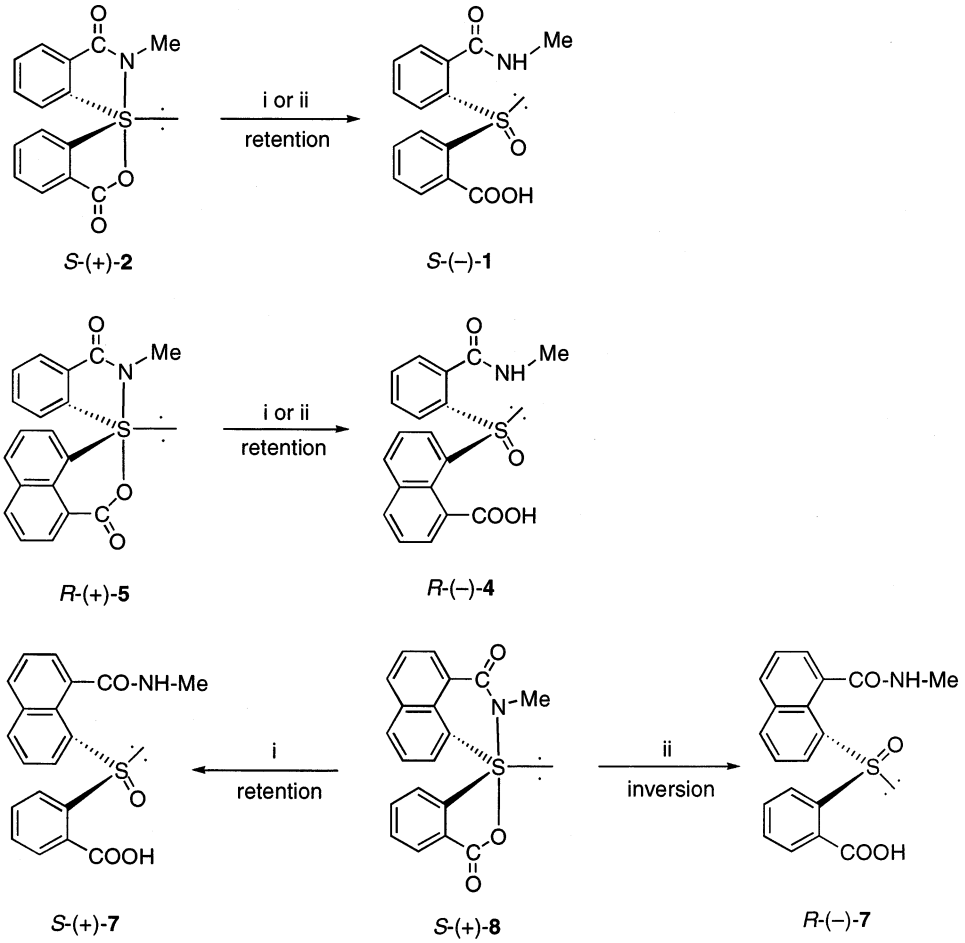
In Schemes 5–7 the reaction pathways a–c, which are more detailed and partly modified as compared to those suggested earlier,[4,7,12–14] are proposed.

a) The hydrolysis of non-symmetrical spiro-λ^4-sulfanes (**15** in Scheme 5) in basic (1 M $KHCO_3$) media starts with an equilibrium cleavage of the weak S–O hypervalent bond. The sulfonium centre of **16** is then attacked by H_2O or OH^- opposite to the cyclic S^+–Y bond yielding the monocyclic λ^4-sulfane intermediate **17**, from which the sulfoxide–carboxylic acid **18** is formed with the retention of configuration at sulfur.

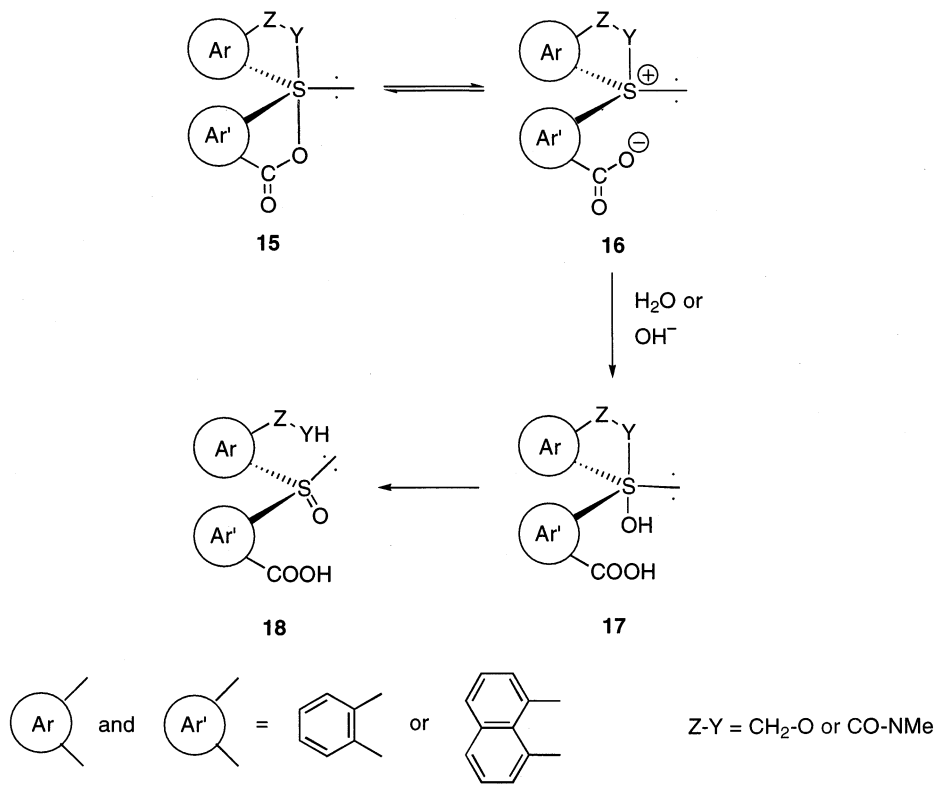
b) In basic or acidic media the hydrolysis of sulfonium tetrafluoroborates **19** (Scheme 6) takes place by a similar mechanism involving the nucleophilic attack of H_2O or OH^- on the sulfonium centre of **20**. The reaction proceeds with the inversion of sulfur configuration.

c) The mechanisms suggested for the acidic hydrolysis of non-symmetrical spiro-λ^4-sulfanes (**15** in Scheme 7) are based on both the present stereochemical findings and some kinetic results obtained earlier:[12–14] (i) Under similar conditions the S–O(alkoxy) bond is cleaved more slowly than the S–N(acylamino) bond when the sulfur atom is attacked by water. (ii) Spiro-λ^4-sulfanes with six-membered N(acylamino)- or O(alkoxy)-containing spiro rings are less reactive towards nucleophiles than their five-membered analogues. (iii) Carboxyl as a neighbouring group is more effective in forming a five-membered than a six-membered ring. (iv) (Acyloxy)sulfonium salts are unstable and are susceptible to attack even by poor nucleophiles such as water, leading to ready hydrolysis.

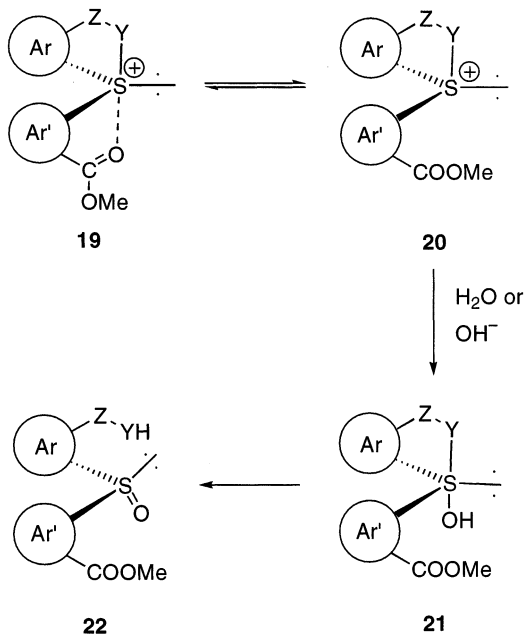
As shown in Scheme 7, the S–O(acyloxy) bond in **15** may split and the subsequent addition of two protons leads to the intermediate **24**. The back-side nucleophilic attack of water gives the protonated monocyclic (hydroxy)-λ^4-sulfane intermediate **25** (path 1), which converts into the sulfoxide enantiomer **18a** having the same configuration at sulfur as the starting spiro-λ^4-sulfane. This mechanism may operate if the



Scheme 4.



Scheme 5.



Scheme 6.

S–Y bond is relatively weak, e.g. in compounds **2** and **5**, which contain the S–N bond in a five-membered ring.

Another mechanism (path 2) occurs in the acidic hydrolysis of non-symmetrical spiro-λ^4-sulfanes having both an axial acyloxy group in a five-membered ring and a strong S–O(alkoxy) bond (Z–Y = CH_2O, Ar = 1,2-phenylene or 1,8-naphthylene, Ar′ = 1,2-phenylene in Scheme 7[†]) or an axial S–N(acylamino) bond in a six-membered ring, e.g. **8**. Instead of attack by water, the *ortho*-carboxyl, an effective neighbouring group, attacks the sulfonium centre of **24** and the (acyloxy)sulfonium ion **26** produced hydrolyses rapidly into sulfoxide **18b** (the enantiomer of **18a**) via intermediate **27**.

If the S^+–OH^+(alkoxy) bond in intermediate **24** is relatively strong, the neighbouring carboxyl group should form a less favoured six-membered acyloxy ring (see Scheme 7 with Z–Y = CH_2–O, Ar = 1,2-phenylene, Ar′ = 1,8-naphthylene[‡]) and hydrolysis can take place by two parallel mechanisms resulting in the formation of a near racemic product.

Because the methyl ester group cannot participate in the formation of an (acyloxy)sulfonium salt intermediate of the type **26**, attack of water on (alkoxy)- and (acylamino)sulfonium tetrafluoroborates is always opposite to the S–Y bond, causing inversion of configuration at sulfur during hydrolysis (see Scheme 6). Neighbouring group participation in the hydrolysis of monocyclic chloro-λ^4-sulfanes and related (acylamino)sulfonium chlorides has been investigated in detail in our laboratory.[15]

In control experiments sulfoxide enantiomers were treated under the conditions as employed for hydrolysis. By stirring sulfoxides **1** with aqueous H_2SO_4 and **13** with aqueous solutions of H_2SO_4 or aq. $KHCO_3$, ca. 20% racemisation was observed. In other cases racemisation occurred to a lesser extent (0–4%) (for racemisation of sulfoxides see Ref. 16).

3. Experimental

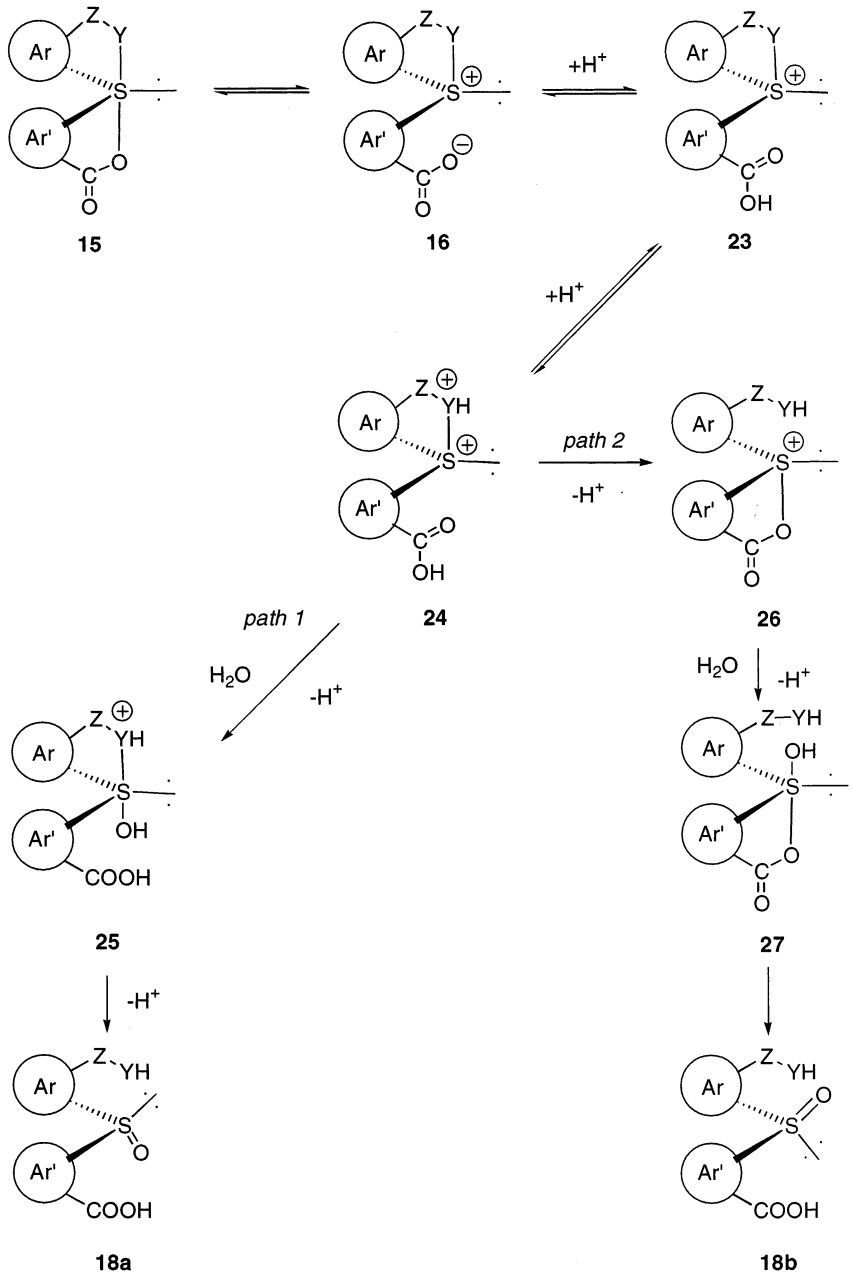
3.1. (*R*)-(+)- and (*S*)-(−)-2-[2-(*N*-Methylcarbamoyl)-phenylsulfinyl]benzoic acid 1

To a hot solution of racemic sulfoxide **1**[8] (72.8 g, 0.24 mol) and NaOH (9.6 g, 0.24 mol) in water (2.4 L) was added a hot solution of (+)-cinchonine (35.3 g, 0.12 mol) in H_2SO_4 (1 M, 60 mL) and water (1.35 L). The mixture was allowed to cool and stand at room temperature for a night. The crystals which precipitated were collected by filtration, washed with water and dried, then recrystallised twice from EtOH–H_2O to give the cinchonine salt of (+)-**1** (29.8 g); $[\alpha]_{546}^{25} = +153$ ($c = 0.5$, DMF); mp 150–154°C.

The recrystallised cinchonine salt (29.6 g), NaOH (2.16 g, 54 mmol) in H_2O (200 mL), chloroform (60 mL) and amyl alcohol (230 mL) were stirred at 45°C for 5 h. Chloroform (140 mL) was added to the mixture and the alkaline solution was separated and acidified with cold 1 M H_2SO_4 (pH 2). The precipitate was collected by filtration and dried to afford the sulfoxide (*R*)-(+)-**1** (10.0 g); $[\alpha]_{546}^{25} = +42.1$ ($c = 0.5$, DMF); e.e. >99%, mp 88–96°C. IR ν_{max} (KBr)/cm^{-1} 3600–2200br (OH), 3275m (NH), 1700vs (C=O carboxyl), 1640vs, 1545vs (amide), 965vs (S=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 2.76 (d, 3H, $J = 4.2$ Hz), 5.15 (s, br, 1H), 7.42–8.03 (m, ArH), 8.11 (q, 1H, $J = 4.2$ Hz).

To prepare the (−)-enantiomer of **1** the aqueous mother liquor obtained from filtration of the crude cinchonine salt of (+)-**1** was evaporated to 1 L then acidified with 1 M H_2SO_4 (pH 2) and extracted with a mixture of dichloromethane (300 mL) and methanol (40 mL) (three extractions). The organic phase was dried with $MgSO_4$ and evaporated to dryness to give crude (−)-**1**. The crude product was crystallised from MeOH. The resultant crystals were removed by filtration and the filtrate was evaporated to dryness. The evaporation residue was crystallised from dichloromethane–pentane. This procedure was repeated twice yielding the sulfoxide (*S*)-(−)-**1** with an e.e. of >99% (12.0 g); $[\alpha]_{546}^{25} = -42.2$ ($c = 0.5$, DMF).

[†] Compounds **1** and **5** in Ref. 4.
[‡] Compound **3** in Ref. 4.



Ar, Ar', Z-Y see Scheme 5

Scheme 7.

3.2. (*R*)-(−)- and (*S*)-(+)-8-[2-(*N*-Methylcarbamoyl)-phenylsulfinyl)-1-naphthoic acid 4

To a hot solution of racemic sulfoxide **4**[8] (60.1 g, 0.17 mol) and Na_2CO_3 (9.0 g, 0.085 mol) in water (460 mL) was added (−)-brucine sulfate ($B_2{\times}H_2SO_4{\times}7H_2O$, 43.1 g, 0.0425 mol) in hot water (360 mL). After standing overnight at 20°C the crystals separated were collected by filtration and dried to afford the brucine salt of (+)-**4** (55.3 g); $[\alpha]_{546}^{25}=+165$ ($c=0.5$, DMF); mp 229–231°C. To liberate the sulfoxide (+)-**4** NaOH (1 M, 80 mL) was added dropwise to the stirred solution of the brucine salt (55.3 g in 500 mL of water) at 0°C. The stirring was continued for 2 h at room temperature. Brucine was removed by extraction with dichloromethane (300 mL). The alkaline solution was acidified with 1 M H_2SO_4 (pH 2), the precipitate was filtered off, washed with water and dried, then crystallised twice from EtOH–DMF to afford the sulfoxide *S*-(+)-**4** (5.3 g); $[\alpha]_{546}^{25}=+555$ ($c=0.5$, DMF); e.e. >99%, mp 219–223°C. IR ν_{max} (KBr)/cm^{-1} 3650–2400br (OH), 3290m (NH), 1705vs (C=O carboxyl), 1695vs, 1650vs (amide), 995vs (S=O). ^{1}H NMR (80 MHz, DMSO-d_6) δ 2.09 (d, 3H, $J=4.1$ Hz), 3.32 (s, br, 1H), 7.33–8.28 (m, ArH).

To prepare the (−)-enantiomer of **4** the mother liquor obtained by filtering off the brucine salt of (+)-**4** was washed with dichloromethane (3×150 mL) then acid-

ified with 1 M H_2SO_4 (pH 2). The precipitate was filtered off, washed with water, dried and crystallised from EtOH–DMF to yield sulfoxide (−)-**4** (13.2 g); $[\alpha]_{546}^{25}=-541$ ($c=0.5$, DMF); e.e. >97%.

3.3. (*R*)-(−)- and (*S*)-(+)-2-[8-(*N*-Methylcarbamoyl)-1-naphthylsulfinyl]benzoic acid 7

To a hot solution of racemic sulfoxide **7**[8] (60.1 g, 0.17 mol) and Na_2CO_3 (9.0 g, 0.085 mol) in water (510 mL) was added (−)-strychnine nitrate (33.8 g, 0.085 mol) in hot water (340 mL). After standing for 4 days at room temperature crystals which precipitated were collected by filtration and dried, then recrystallised from water to give the strychnine salt of (−)-**7** (33.6 g); $[\alpha]_{546}^{25}=-255$ ($c=0.5$, DMF); mp 207–221°C.

A solution of the strychnine salt of (−)-**7** (33.0 g) in water (170 mL) with 1 M NaOH (53 mL) and dichloromethane (200 mL) was stirred for 1 h at room temperature. The aqueous phase was separated, washed with dichloromethane (50 mL) and acidified with 1 M H_2SO_4 (pH 2). The precipitated (−)-enantiomer of **7** was collected by filtration, washed with water and dried (16.1 g); $[\alpha]_{546}^{25}=-501$ ($c=0.5$, DMF); e.e. >89%; mp 224–227°C; IR ν_{max} (KBr)/cm^{-1} 3160–2200br (OH), 3285m (NH), 1705vs (C=O carboxyl), 1600vs, 1545vs (amide), 1025vs (S=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 2.62 (d, 3H, $J=4.2$ Hz), 7.0–8.3 (m, ArH).

To prepare the (+)-enantiomer of **7**, the mother liquor obtained from the crude strychnine salt of (−)-**7** was evaporated to 500 mL then acidified with 1 M H_2SO_4 (pH 2). The precipitate was filtered off, washed with water and dried. To the hot solution of the above crude **7** (29.5 g) in water (250 mL) was added (−)-strychnine nitrate (16.6 g, 0.042 mol) in hot water (170 mL). After standing overnight at 20°C, the aqueous phase was separated from the precipitate and the residue was crystallised from EtOH to afford the strychnine salt of (+)-**7** (9.8 g). Sulfoxide (+)-**7** was liberated by stirring the above salt (9.8 g) with aq. NaOH (1.12 g in 100 mL of water) for 5 h. Strychnine was filtered off and the filtrate was acidified with 1 M H_2SO_4 (pH 2). The crystals were filtered off, washed with water and dried to give (*S*)-(+)-**7** (4.8 g). E.e. = 86%, $[\alpha]_{546}^{25}=+485$ ($c=0.5$, DMF).

3.4. Selected data for methyl esters of (+)-1, (−)-4 and (+)-7

3.4.1. Methyl (*R*)-(+)-2-[2-(*N*-methylcarbamoyl)phenylsulfinyl]benzoate. Mp 124–133°C; $[\alpha]_{546}^{25}=+81$ ($c=0.5$, DMF); e.e. >99%; IR ν_{max} (KBr)/cm^{-1} 3260m (NH), 1727vs, 1712vs, 1670vs, 1642vs (C=O), 1600vs, 1010vs (S=O).

3.4.2. Methyl (*R*)-(−)-8-[2-(*N*-methylcarbamoyl)phenylsulfinyl)-1-naphthoate. Mp 182–197°C; $[\alpha]_{546}^{25}=-469$ ($c=0.5$, DMF); e.e. >97%; IR ν_{max} (KBr)/cm^{-1} 3275m (NH), 1640vs, 1720vs, (C=O), 1010vs (S=O).

3.4.3. Methyl (*S*)-(+)-2-[8-(*N*-methylcarbamoyl)-1-naphthylsulfinyl]benzoate. Mp 262–273°C; $[\alpha]_{546}^{25}=+437$ ($c=0.1$, DMF); e.e. >86%; IR ν_{max} (KBr)/cm^{-1} 3300m (NH), 1715vs, 1633vs, (C=O), 1033vs (S=O).

3.5. (*S*)-(+)-Spiro[3*H*-2,1-benzoxathiol-3′-one-1,1′-3*H*-2,1-benzazathiol]-2-methyl-3-one (*S*)-(+)-2

To a stirred solution of sulfoxide (*R*)-(+)-**1** (1.82 g, 6 mmol, $[\alpha]_{546}^{25}=+42.1$ ($c=0.5$, DMF)) in dichloromethane (60 mL) was added sulfopropionic acid[9] (1.39 g, 10.2 mmol) at −78°C. Stirring was continued for 1 h at −78°C, then for 12 h at room temperature. Dichloromethane was removed then cold water (5 mL) was added to the residue. The crystals separated were collected by filtration, washed with EtOH and diethylether, dried and crystallised from pyridine–ether to give (*S*)-(+)-**2** (0.95 g, 55%); $[\alpha]_{546}^{25}=+181$ ($c=0.5$, DMF); e.e. >99%, mp 299–301°C; IR ν_{max} (KBr)/cm^{-1} 1700vs, 1650vs (C=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 3.30 (s, 3H), 7.37–8.42 (m, ArH).

3.6. (*R*)-(+)-Spiro[3*H*-2,1-benzazathiol-2′-methyl-3′-one-1,1′-naphtho-[1,8-*d*,*e*]-3*H*-2,1-oxathiin-3-one] (*R*)-(+)-5

To a solution of sulfoxide (*R*)-(−)-**4** (4.72 g, 14.1 mmol, $[\alpha]_{546}^{25}=-541$ ($c=0.5$, DMF)) in dichloromethane (150 mL) was added DCC (6.8 g, 32.4 mmol) and the mixture stirred for 72 h at room temperature. DCU was filtered off and the filtrate was evaporated to 20 mL, then mixed with pentane (150 mL). After standing overnight the crystals separated were collected by filtration, dried and crystallised from acetone to give (*R*)-(+)-**5** (1.0 g, 21%); mp 198–199°C, $[\alpha]_{546}^{25}=+623$ ($c=0.5$, DMF); e.e. >97%; IR ν_{max} (KBr)/cm^{-1} 1700vs, 1630vs (C=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 2.78 (s, 3H), 7.40–8.80 (m, ArH).

3.7. (*S*)-(+)-Spiro[3*H*-2,1-benzoxathiol-3′-one-1,1′-naphtho-[1,8-*d*,*e*]-3*H*-1,2-thiazine-2-methyl-3-one] (*S*)-(+)-8

To a solution of sulfoxide (*S*)-(+)-**7** (4.53 g, 12.8 mmol, $[\alpha]_{546}^{25}=+485$ ($c=0.5$, DMF)) in dichloromethane (100 mL) DCC was added (2.25 g, 25.4 mmol) and the mixture was stirred for 2 days. Additional DCC (2.25 g, 25.4 mmol) was added and the stirring was continued for 2 days. DCU precipitated was filtered off, the filtrate was evaporated to 5 mL and pentane (150 mL) was poured into the residue. The precipitate was filtered off, dried and crystallised from acetone to afford (*S*)-(+)-**8** (2.0 g, 47%); mp 258–262°C, $[\alpha]_{546}^{25}=161$ ($c=0.5$, DMF); e.e. >97%; IR ν_{max} (KBr)/cm^{-1} 1645vs, 1640vs (C=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 3.54 (s, 3H), 7.42–8.05 (m, ArH).

3.8. General procedure for the preparation of sulfonium tetrafluoroborates (*R*)-(+)-3, (*S*)-(+)-6 and (*R*)-(+)-9

To a stirred solution of spiro-λ^4-sulfanes (*S*)-(+)-**2**, (*R*)-(+)-**5** and (*S*)-(+)-**8** (3 mmol) in dichloromethane (30 mL) was added trimethyloxonium tetrafluoroborate (0.46 g, 3.03 mmol). After stirring for 4 h at 20°C ether was poured into the mixture. The crystals formed were collected by filtration, washed with ether and dried.

3.8.1. Selected data for sulfonium tetrafluoroborates

3.8.1.1. (*R*)-(+)-2,3-Dihydro-1-[2′-(methoxycarbonyl)-phenyl]-2-methyl-3-oxo-1,2-benzisothiazol-1-ium tetrafluoroborate (*R*)-(+)-3. Yield: 85%; mp 244–248°C; $[\alpha]_{546}^{25}=+293$ ($c=0.5$, DMF); e.e. >94%; IR ν_{max} (KBr)/cm^{-1} 1745vs, 1680vs (C=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 3.43 (s, 3H), 4.23 (s, 3H) 7.60–8.38 (m, ArH).

3.8.1.2. (*S*)-(+)-2,3-Dihydro-1-[8′-(methoxycarbonyl)-1′-naphthyl]-2-methyl-3-oxo-1,2-benzisothiazol-1-ium tetrafluoroborate (*S*)-(+)-6. Yield: 35%; mp 280–284°C; $[\alpha]_{546}^{25}=+398$ ($c=0.5$, DMF); e.e. >96%; IR ν_{max} (KBr)/cm^{-1} 1720vs, 1660vs (C=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 3.09 (s, 3H), 4.18 (s, 3H) 7.70–8.78 (m, ArH).

3.8.1.3. (*R*)-(+)-2,3-Dihydro-1-[2′-(methoxycarbonyl)-phenyl]-2-methyl-3-oxo-naphtho[1,8-*d*,*e*]-1,2-thiazin-1-ium tetrafluoroborate (*R*)-(+)-9. Yield: 89%; mp 108–111°C; $[\alpha]_{546}^{25}=+323$ ($c=0.5$, DMF); e.e. >95%; IR ν_{max} (KBr)/cm^{-1} 1700vs (C=O); ^{1}H NMR (80 MHz, DMSO-d_6) δ 3.60 (s, 3H), 4.14 (s, 3H) 7.50–8.95 (m, ArH).

3.9. General procedure for the hydrolysis of spiro-λ^4-sulfanes (*S*)-(+)-2, (*R*)-(+)-5 and (*S*)-(+)-8

(A) To a solution of spiro-λ^4-sulfane (0.2 mmol) in dichloromethane (2 mL) aqueous $KHCO_3$ (1 M, 2 mL) was added and the mixture was stirred (20 min at 25°C for **2**, 20 min at 0°C for **5** and 20 h at 25°C for **8**). Dichloromethane was removed in vacuo and the residual aqueous phase was acidified with 4 M H_2SO_4 (pH 2), then the crystals formed were collected by filtration, washed with water and dried. Yields: 76, 86 and 88% for sulfoxides (*S*)-(−)-**1**, (*R*)-(−)-**4** and (*S*)-(+)-**7**, respectively.

(B) To a solution of spiro-λ^4-sulfane (0.2 mmol) in dichloromethane (2 mL), H_2SO_4 (1 M, 2 mL) was added and the mixture was stirred (5 h at 25°C for **2**, 1 h at 0°C for **5** and 20 h at 25°C for **8**). Dichloromethane was removed and the crystals separated were collected by filtration, washed with water and dried. Yields: 38, 69 and 61% for sulfoxides (*S*)-(−)-**1**, (*R*)-(−)-**4** and (*R*)-(−)-**7**, respectively.

3.10. General procedure for the hydrolysis of sulfonium tetrafluoroborates (*R*)-(+)-3, (*S*)-(+)-6 and (*R*)-(+)-9

(A) To a solution of sulfonium salt (0.1 mmol) in dichloromethane (2 mL) was added 1 M $KHCO_3$ (2 mL) and the mixture was stirred (15 min at 0°C for **3**, 20 h at 25°C for **6** and **9**). The organic phase was separated, dried and the solvent was removed in vacuo. Yields: 99, 82 and 85% for sulfoxide-methyl esters (*S*)-(−)-**12**, (*R*)-(−)-**13** and (*S*)-(+)-**14**, respectively.

(B) To a solution of sulfonium salt (0.1 mmol) in dichloromethane (2 mL) was added H_2SO_4 (1 M, 2 mL), then the mixture was stirred (5 h at 0°C for **3**, 20 h at 25°C for **6** and **9**). Dichloromethane was removed in vacuo and the crystals were collected by filtration, washed with water and dried. Yields: 75, 42 and 66% for sulfoxide-methyl esters (*S*)-(−)-**12**, (*R*)-(−)-**13** and (*S*)-(+)-**14**, respectively.

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References

1. Szabó, D.; Szendeffy, Sz.; Kapovits, I.; Kucsman, Á.; Czugler, M.; Kálmán, A.; Nagy, P. *Tetrahedron: Asymmetry* **1997**, *8*, 2411.
2. Szendeffy, Sz.; Szarvas, Sz.; Szabó, D.; Kapovits, I.; Hollósi, M. *Enantiomer* **1998**, *3*, 323.
3. Szókán, Gy.; Szarvas, Sz.; Majer, Zs.; Hollósi, M.; Szabó, D.; Kapovits, I. *J. Liq. Chromatogr.* **1999**, *22*, 993.
4. Szabó, D.; Varga, J.; Csámpai, A.; Kapovits, I. *Tetrahedron: Asymmetry* **2000**, *11*, 1303.
5. Varga, J.; Szabó, D.; Hollósi, M. *Enantiomer* **2000**, *5*, 513.
6. Drabowitz, J.; Martin, J. C. *Pure Appl. Chem.* **1996**, *4*, 951.
7. Zhang, J.; Saito, S.; Koizumi, T. *J. Am. Chem. Soc.* **1998**, *120*, 1631.
8. Szabó, D.; Kapovits, I.; Kucsman, Á.; Huszthy, P.; Argay, Gy.; Czugler, M.; Fülöp, V.; Kálmán, A.; Koritsánszky, T.; Párkányi, L. *J. Mol. Struct.* **1993**, *300*, 123.
9. Karash, M. S.; Chao, T. H.; Brown, H. C. *J. Am. Chem. Soc.* **1940**, *62*, 2393.
10. Martin, J. C.; Balthazor, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 152.
11. Pauling, L. *The Nature of the Chemical Bond*, 3rd ed.; Cornell University Press: Ithaca, NY, 1960; p. 221.
12. Vass, E.; Ruff, F.; Kapovits, I.; Rábai, J.; Szabó, D. *J. Chem. Soc., Perkin Trans. 2* **1993**, 855.
13. Vass, E.; Ruff, F.; Kapovits, I.; Szabó, D.; Kucsman, Á. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2061.
14. Ádám, T.; Ruff, F.; Kapovits, I.; Szabó, D.; Kucsman, Á. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1269.
15. Nagy, P.; Csámpai, A.; Szabó, D.; Varga, J.; Harmat, V.; Ruff, F.; Kucsmann, Á. *J. Chem. Soc., Perkin Trans. 2* **2001**, 339.
16. Tillett, J. G. *Chem. Rev.* **1976**, *6*, 747.