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SYNTHESES OF (+)-AND (-)-2-METHOXY-4-(S-METHYL-N-[(4-METHYLPHENYL)-SULFONYL]-SULFONIMIDOYL)-BENZOIC ACIDS AND THEIR ABSOLUTE CONFIGURATIONS

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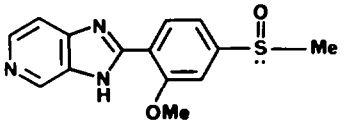
Summary: The synthesis of enantiomerically pure (+)- and (-)-2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-benzoic acid 4a was carried out. The chemical correlation of(+)-(S)-S-methyl-N-[(4-methylphenyl)-sulfonyl]-4-methyl-phenyl)-sulfoximide 13 with (+)-4a was undertaken. The absolute configuration was found to be (S). Since both antipodes of 4a have been used for the synthesis of the isomazole enantiomers, their absolute configuration was established as well.

Isomazole 1 is a new imidazo[4,5-c]pyridine derivative[1] presently under development as its racemate for the treatment of congestive heart failure jointly by E. Merck and Eli Lilly, USA.



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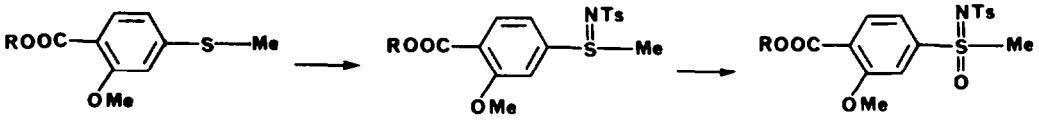
During the pharmacological evaluation of this new cardiotonic substance the pure enantiomers of isomazole were needed. Recently the resolution of the racemate with optically active mandelic acid and the synthesis by condensation of 3,4-diamino-pyridine with optically pure (+)- and (-)-2-methoxy-4-(S-methyl-N-[(4-methyl-phenyl)-sulfonyl]-sulfonimidoyl)-benzoic acid 4a and subsequent conversion into the target molecules was reported[2].

Here we disclose the synthesis of 4a (Scheme 1) and the determination of its absolute configuration by chemical correlation with the known (S)-(+)-S-methyl-N-[(4-methylphenyl)-sulfonyl]-(4-methylphenyl)-sulfoximide 12 (Scheme 2). The syntheses and pharmacological findings of some further chiral heterocyclic sulfoxides of the isomazole family will be the topics of a future publication[3].

In order to make use of E. Merck's know how in the field of chromatography we envisioned a chromatographic resolution of 4a or a suitable precursor. Therefore 2-methoxy-4-methylthiobenzoic acid 2a[4] was esterified with methanol to yield the methyl ester 2b. Subsequent treatment with Chloramine T led[5] to the sulfimino ester 3b which was converted by oxidation with potassium permanganate in pyridine[6] into the sulfoximino ester 4b. By saponification the corresponding carboxylic acids 3a

and 4a were obtained.

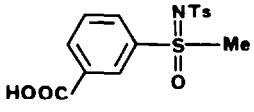


2 3 4

Scheme 1

When applied to a column packed with polycrystalline triacetyl cellulose[7] neither the methyl esters 3b and 4b nor the acids 3a and 4a could be resolved. Also the commercially available Bakerbond® column[8] with a covalently bound chiral phase did not work. As the only exception the antipodes of acid 3a and its ester 3b were separated on the new analytical Enantio-Pac® column[9]. But the use of this column could not seriously be considered as a means for the preparation of multigram quantities.

With the two racemic acids 3a and 4a at hand next the classical resolution of diastereoisomeric salts was attempted. The successful resolution of 3-[S-methyl-N-(benzenesulfonyl)-sulfonimidoyl]-benzoic acid 5 was reported by Kresze et al.[10] using optically active phenylethylamine.



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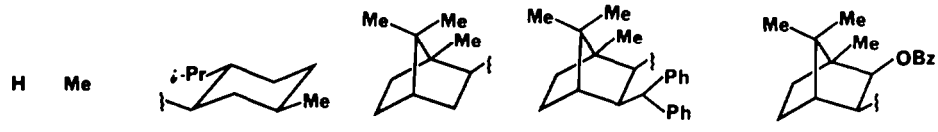
Under the same conditions the acids 3a and 4a formed the phenylethylammonium salts. But unfortunately neither of the salts could be resolved by repeated recrystallisations.

Because we were unable to resolve the acids and esters 3a,b and 4a,b by simple means we hoped the chromatographic separation of suitable diastereoisomeric esters on achiral phases would be more successful.

Acid 2a was esterified with different chiral alcohols[11,12] listed in the table. Subsequent conversion with Chloramine T and potassium permanganate led to the desired esters. It should be emphasised that ester 2e was formed with difficulty and could not be further transformed. Ester 2f on the other hand could only be converted into the corresponding sulfimine 3f.

Table



2	a	b	c	d	e	f
3	a	b	c	d	-	f
4	a	b	c	d	-	-

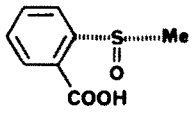
The chromatographic inspection of the diastereoisomeric esters 3 and 4 showed immediately that a preparative resolution on an achiral sorbent would not be feasible. Only in the case of ester 3f a certain degree of separation was achieved using analytical HPLC. But even in this case the resolution of the two peaks was not sufficient for the preparation of pure material. The chromatogram showed clearly the existence of the two diastereoisomers in a 1:1 ratio and only one conclusion can be drawn: even a fairly powerful enantiomeric discriminator as the 2-benzyloxy-bornyl group was unable to induce optical activity at the too remote thioether moiety of 2f.

Taking this fact into account one should not expect any asymmetric induction during the Chloramine T oxidation of menthyl ester 2c either and this proved to be the case. Very fortunately we were able to obtain some crystalline material from the mixture of the diastereoisomeric esters 4c. In analytical TLC the crystals and mother liquors showed the same RF-values. They could be differentiated by their staining behaviour against iodine vapour. But all attempts to improve the diastereoisomeric purity of this crystalline material by repeated recrystallisations failed however.

In order to obtain both enantiomers of 4a we saponified crystals and mother liquors of 4c separately. After three recrystallisations each from methanol the pure enantiomers were obtained.

The enantiomeric purity of (+)- and (-)-4a could be determined by two different ways: either indirectly by conversion into (+)- and (-)-isomazole or directly by chromatographic analysis using the Enantio-Pac® column. The purity turned out to be > 99 % e.e.[2].

The final task to be undertaken was the determination of the absolute configuration[13] of the acid (+)-4a. The configurations of the (-)-ortho- and (-)-meta-benzoic acids 6 and 7 have been assigned[14] to (S), but to our knowledge the configuration of the corresponding para-acid is not known.



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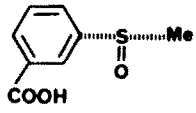

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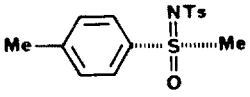
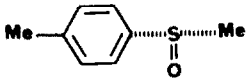
Since we did not want to rely on (admittedly feasible) plausibility arguments, we carried out the chemical correlation of (+)-4a with (S)-(+)-13 whose absolute configuration has been determined by Cram et al.[15] through correlation with the sulfoxide (S)-(-)-14.

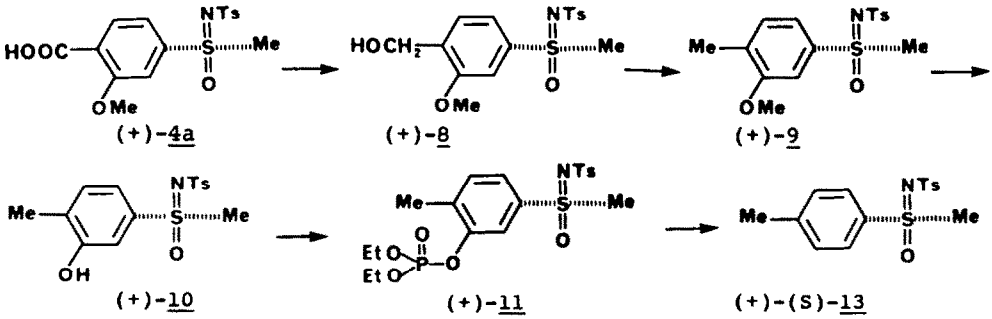


(S)-(+)-13



(S)-(-)-14

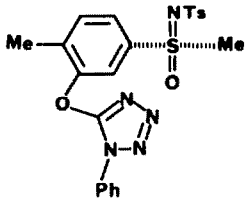
This in turn had been determined unambiguously: indirectly by X-ray crystallographic analysis of (-)-menthyl-(-)-p-iodobenzene sulfinate[16] and directly by anomal X-ray dispersion according to Bijvoet[17].



Scheme 2

Reduction of (+)-4a gave the benzyl alcohol (+)-8, which was hydrogenated over 5 % palladised charcoal to yield (+)-9. The cleavage of the methoxy group was easily performed using boron tribromide. The final goal in this sequence was the replacement of a phenolic hydroxyl function by hydrogen. The method of choice for this transformation seemed to us Kenner's procedure[18]. Phenol (+)-10 was converted by reaction with diethyl phosphite in the presence of carbon tetrachloride and tri-

ethylamine into the phosphate ester (+)-11, which subsequently was treated with sodium metal in liquid ammonia. Instead of the desired benzene derivative we mainly obtained starting material and some 25 % of N-toluenesulfonylamide. Therefore we converted phenol (+)-10 by reaction with 1-chloro-2-phenyltetrazole into the phenol ether (+)-12. The following very smooth hydrogenolysis[19] led to pure (+)-(S)-13.



(+)-12

Starting with enantiomerically pure (+)-4a we obtained (+)-(S)-13 melting at 162 °C and with an optical rotation of $[\alpha]_D^{15}$ = + 140.2° (C = 1.105; acetone). We used reactions which should not attack the sulfur atom. The high consistency of the optical rotations and their signs in all intermediates supports the conclusion that indeed all reactions must have occurred with retention of configuration at the chiral sulfur atom[20]. This proves the (S)-configuration for (+)-4a and the (R)-configuration for (-)-4a.

And since the acids (S)-(+)-4a and (R)-(-)-4a have been used for the preparation of the isomazole enantiomers, their absolute configurations are known as well: (S)-(-)-isomazole and (R)-(+)-isomazole.

EXPERIMENTAL

All analytical data were obtained from the E. Merck central analytical department. NMR spectra were measured on a Bruker AC 200 or WM 250 instrument, IR spectra on a Bruker FT-IR spectrometer IFS 45 and mass spectra on a Varian MAT 711 or a Vaccum Generators VG 70-250 instrument. The melting points were determined with an automatic Mettler FP 61 instrument. Petroleum ether (40-60 °C fraction) is referred to as petrol and diethyl ether is referred to as ether. The chromatography was performed on E. Merck silica gel 60 (230-400 mesh) and all solvents used were of E. Merck grade.

Esterification of 2-methoxy-4-methylthiobenzoic acid (2a), general procedure: The acid 2a (12.5 mmol) is refluxed in 10 ml thionyl chloride for two hours. Then the reagent is removed by distillation and the residue is taken up in 20 ml of dry toluene. This solution is added dropwise to a mixture of the appropriate alcohol (12.5 mmol) and triethylamine (23 mmol) in 10 ml dry toluene. After a stirring period of 2 to 72 hours at reflux (TLC-control) the reaction mixture is chilled and washed with water. After drying the solvent is evaporated and the residue chromatographed over silica gel with dichloromethane as solvent.

2-methoxy-4-methylthiobenzoic acid methyl ester (2b): The pure fraction is taken up in ether. After trituration with petrol colourless crystals melting at 39 °C are collected in 80 % yield. IR: 1719, 1595, 1552, 1492, 1469, 1432, 1394, 1237, 1157, 1108, 1073, 1019, 884, 851, 817 and 771 cm^{-1}. MS: 91 (57), 155 (14), 181 (28), 212 (12), 226 (100), 287 (4), 302 (5), 362 (3) and 381 (M+,6). ^{1}H-NMR ($CDCl_3$): (ppm) = 2.36 (s, 3H, methyl-H), 2.88 (s, 3H, S-methyl-H), 3.85) (s. 3H, O-methyl-H), 3.90 (s, 3H, O-methyl-H), 7.0 - 7.35 (m, 4H, aromatic-H) and 7.6 - 7.85 (m, 3H, aromatic-H). Microanalysis: Calculated 56.6 C, 5.7 H. Found 56.3 C, 5,6 H %.

2-methoxy-4-methylthiobenzoic acid menthyl ester (2c): As the main fraction a 93 % yield of a pale yellow oil is obtained. IR: 1710, 1596, 1298, 1339, 1144, 1108, 1075, 1034, 909 and 734 cm^{-1}. MS: 84 (100), 119 (37), 198 (43) and 336 (M+,6).

^{1}H-NMR ($CDCl_3$): (ppm) = 0.7-2.2 (m, 18H, menthyl-H), 2.51 (2, 3H, S-methyl-H), 3.89 (s, 3H, O-methyl-H), 4,87 (2t, 1H, O-methine-H), 6.77 (m, 2H, aromatic-H) and 7.7 (m, 1H, aromatic-H). $[\alpha]_D^{20}$ = -22.5° (c = 1, methanol). Microanalyis: Calculated 67.9 C, 8.3 H. Found 66.8 C, 7.98 H %.

2-methoxy-4-methylthiobenzoic acid bornyl ester (2d): From the pure main fraction slowly a 91 % yield of colourless crystals with mp. 60 °C deposits. IR: 1713, 1594, 1558, 1398, 1260, 11655, 1105 and 1071 cm^{-1}. MS: 181 (100, 198 (5) and 334 (M+,8). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.8-2.55 (m, 16H, bornyl-H), 2.55 (s, 3H, S-methyl-H), 3.92 (s, 3H, O-methyl-H), 5.10 (m, 1H, O-methine-H), 6.84 (m, 2H, aromatic-H) and 8.82 (d,1H,aromatic-H). $[\alpha]_D^{20}$ = -29.2° (c = 1.035, chloroform). Microanalysis: Calculated 68.2 C, 7.8 H. Found 67.2 C, 7.58 H %.

2-methoxy-4-methylthiobenzoic acid exo-3'-diphenylmethyl-2'-bornyl ester (2e): The main fraction solidified. Pure colourless crystals are obtained with mp. 156-157 °C in 65 % yield. IR: 1727, 1594, 1583, 1494, 1390, 1279, 1245, 1154, 1104, 1070, 1031, 893 and 765 cm^{-1}. MS: 167 (22), 181 (100), 206 (15), 302 (18) and 500 (M+). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.77 (s, 3H, methyl-H), 0.84 (s, 3H, methyl-H), 1.0-1.8 (m, 7H, bornyl-H), 2.48 (s. 3H, S-methyl-H), 2.89 (m, 1H, bornyl-methine-H), 3.82 (s, 3H, O-methyl-H), 4.31 (d, 1H, O-methine-H), 5.43 (d, 1H, methine-H) and 6.6-7.3 (m, 13H, aromatic-H). $[\alpha]_D^{20}$ = -12.6° (c = 1.065, chloroform). Microanalysis: Calculated 76.8 C, 7.2 H. Found 76.3 C, 7.1 H %.

2-methoxy-4-methylthiobenzoic acid exo-2'-benzyloxy-3'-bornyl ester (2f): The pure fraction consists of a 62 % yield of a pale yellow oil. IR: 1720, 1595, 1557, 1491, 1482, 1401, 1290, 1247, 1142, 1110, 1076, 1029, 888, 827, 774, 738 and 711 cm^{-1}. MS: 91 (52), 136 (88), 181 (100), 198 (25), 199 (21), 242 (9) and 400 (M+,3). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.85 (m, 15H, methyl-H), 0.96 (s, 3H, methyl-H), 1.0-1.95 (m, 15H, bornyl-H), 2.49 (s, 3H, s-methyl-H), 3.52 (d, 1H, methine-H), 3,78 (s, 3H, O-methyl-H), 4.46 (dd, 2H, O-benzyl-H), 5.02 (d, 1H, O-methine-H) and 6.6 - 7.7 (m, 8H, aromatic-H). $[\alpha]_D^{20}$ = -15.4° (c = 1.005, chloroform). Microanalysis: Calculated 70.9 C, 7.3 H. Found 69.2 C, 7.05 H %.

Oxidation with Chloramin T trihydrate, general procedure: Chloramine T trihydrate (10 mmol) is added in portions to the ester 2b-e (10 mmol) dissolved in 20 ml tetrahydrofuran. (A mild exothermic reaction is observed.) After reflux for one hour the mixture is chilled and filtered over Celite. The solvent is removed and the residue chromatographed or crystallised.

2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfiminyl)-benzoic acid methyl ester (3b): The crude reaction mixture is taken up in the minimum amount of dichloromethane. After trituration with ether a colourless solid with mp. 123 °C is obtained in 78 % yield. IR: 1735, 1592, 1572, 1494, 1428, 1393, 1295, 1256, 1141, 1089, 1023, 930, 826 and 757 cm^{-1}. MS: 91 (57), 155 (14), 166 (10), 181 (28), 212 (12), 226 (100), 287 (4) and 381 (M+,6). ^{1}H-NMR ($CDCl_3$): (ppm) = 2.36 (s, 3H, methyl-H), 2.88 (s, 3H, S-methyl-H), 3.85 (s, 3H, O-methyl-H), 3.90 (s, 3H, O-methyl-H), 7.0-7.35 and 7.6-7.85 (m, 7H, aromatic-H). Microanalysis: Calculated 53.5 C, 5.03 H, 3.67 N. Found 53.7 C, 5.12 H, 3.9 N %.

2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfiminyl)-benzoic acid menthyl ester (3c): Chromatography over silica gel with ethyl acetate as solvent gives a 89 % yield of a pale oil. IR: 1725, 1596, 1493, 1485, 1401, 1291, 1255, 1144, 1091, 1075, 1022, 1000, 952, 815, 77, 658, 573 and 545 cm^{-1}. MS 91 (26), 155 (8), 171 (8), 195 (9) and 253 (56). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.76-2.23 (m, 18H, menthyl-H), 2.40 (s, 3H, methyl-H), 2.90 (s, 3H, S-methyl-H), 3,86 (s, 3H, O-methyl-H), 4.93 (m, 1H, O-methine-H) and 7.1-7.8 (m, 7H, aromatic-H). $[\alpha]_D^{20}$ = -27.9° (c = 1, methanol). Microanalysis: Calculated 61.8 C, 6.9 H, 2.8 N. Found 61.3 C,

6.93 H, 3.0 N %.

2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfiminyl)-benzoic acid bornyl ester (3d): The crude reaction mixture is chromatographed over silica gel with dichloromethane containing 1 % methanol. The resulting pure fraction crystallises from ether. A 77 % yield of a colourless solid of mp. 152 °C is obtained. IR: 1707, 1598, 1401, 1298, 1278, 1255, 1140, 1090, 1019 and 947 cm^{-1}. MS: 91 (29), 155 (14), 167 (23), 181 (100), 334 (22) and 384 (M+, 18). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.7-2.55 (m, 16H, bornyl-H). 2.38 (s, 3H, methyl-H), 288 (s, 3H, S-methyl-H), 2.88 (s, 3H, S-methyl-H), 3.86 (s, 3H, O-methyl-H), 5.12 (m, 1H, O-methine-H) and 7.1-7.9 (m, 7H, aromatic-H). $[\alpha]_D^{20}$ = -5.2° (c = 1.045, chloroform). Microanalysis: Calculated 62.0 C, 6.6 H, 2.8 N. Found 62.3 C, 6.52 H, 2.9 N %.

2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfiminyl)-benzoic acid 2'-benzyloxy-3'-bornyl ester (3f): The crude reaction mixture is chromatographed over silica gel with dichloromethane containing 25 % ethyl acetate to give a pale oil in 53 % yield. IR: 1727, 1595, 1493, 1462, 1401, 1292, 1257, 1143, 1090, 1020, 999 and 948 cm^{-1}. MS: 91 (100), 131 (37), 155 (20), 167 (22), 181 (17), 185 (14), 195 (10), 350 (18) and 368 (8). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.85 (s, 3H, methyl-H), 0.98 (s, 3H, methyl-H), 1.06-1.95 (m, 7H, bornyl-H), 2.32 (s, 3H, methyl-H), 2.82 (s, 3H, S-methyl-H), 3.56 (d, 1H, O-methine-H), 3.68 (s, 3H, O-methyl-H), 4.46 (s, 2H, benzyl-H), 4.98 (d, 1H, O-methine-H) and 6.82-7.75 (m, 12 H, aromatic-H). $[\alpha]_D^{20}$ = + 6.2° (c = 1.055, chloroform). Microanalysis: Calculated 65.0 C, 6.4 H, 2.3 N. Found 64.2 C, 6. 31 H, 2.35 N %.

Oxidation with potassium permanganate, general procedure: The sulfiminoester 3b-e (15 mmol) in 50 ml pyridine is treated portionwise with potassium permanganate (55 mmol). A temperature of 50 to 60 °C should not be exceeded. The mixture is stirred for another six hours at the same temperature (eventually some cooling is necessary). When the reaction is finished (TLC-control) the cold solution is filtered over Celite. The residue is washed thoroughly with dichloromethane. After evaporation the dark oil is taken up in dichloromethane and washed successively with bicarbonate solution and water. After drying and evaporation of the solvent the residue is either chromatographed or recrystallised.

2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-benzoic acid methyl ester (4b): The crude material is chromatographed over silica gel with ethyl acetate as solvent. Crystallisation from methanol gives a 25 % yield of a colourless solid with mp. 135 °C. IR: 1724, 1595, 1576, 1489, 1470, 1429, 1398, 1314, 1236, 1153, 1081, 1054, 1017, 860 and 742 cm^{-1} . MS: 91 (72), 110 (28), 139 (100), 151 (45), 181 (19), 214 (15), 244 (15), 382 (69) and 397 (M+,5). ^{1}H-NMR ($CDCl_3$): (ppm) = 2.19 (s, 3H, methyl-H), 3.21 (s, 3H, S-methyl-H), 3.97 (s, 3H, O-methyl-H), 3.99 (s, 3H, O-methyl-H) and 7.2-8.0 (m, 7H, aromatic-H). Microanalysis: Calculated 51.4 C, 4,83 H, 3.52 N. Found 51.4 C, 4.86 H, 3.81 N %.

2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-benzoic acid menthyl ester (4c): Viscous, pale oil. Yield: 64 %. The oil is taken up in the same volume of dichloromethane and triturated with petrol until turbidity persists. After standing overnight colourless crystals of mp. 132 °C are formed. Yield: 23 %. IR: 1724, 1491, 1395, 1313, 1248, 1153, 1072, 1024, 988 and 724 cm^{-1}. MS: 139 (62), 151 (28), 155 (13), 169 (5), 185 (14), 197 (8), 213 (30), 253 (100), 384 (58) and 506 (32). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.78-2.25 (m, 18H, methyl-H), 2.42 (s, 3H, methyl-H), 3.41 (s, 3H, S-methyl-H), 3.98 (s, 3H, O-methyl-H), 4.95 (dt, 1H, O-methine-H) and 7.2-7.9 (m, 7H, aromatic-H). $[\alpha]_D^{20}$ = -143.8° (c = 1, chloroform). Microanalysis: Calculated 59.9 C, 6.7 H, 2.7 N. Found 59.9 C, 6.7 H, 3.0 % N. From the mother liquors is obtained after evaporation an amorphous foam in 40 %

yield. $[\alpha]_D^{20}$ = +56.6° (c = 1, chloroform).

2-methyl-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-benzoic acid bornyl ester (4d): The crude reaction product is taken up in ether and triturated with petrol. After some time colourless crystals melting at 175 °C are collected with 87 % yield. IR: 1722, 1599, 1402, 1301, 1289, 1240, 1161 and 738 cm^{-1}. MS: 91 (100), 155 (35), 167 (53), 183 (32), 198 (10), 213 (17), 304 (20), 324 (59), 338 (21), 366 (39), 384 (24), 410 (16), 504 (42), 519 (M+,7). ^{1}H-NMR ($CDCl_3$): (ppm) = 0.85-2.55 (m, 16H, bornyl-H), 2.42 (s, 3H, methyl-H), 3.42 (s, 3H, S-methyl-H), 3.98 (s, 3H, O-methyl-H), 5.14 (m, 1H, O-methine-H) and 7.2-8.0 (m, 7H, aromatic-H). $[\alpha]_D^{20}$ = -11.7° (c = 1.14, chloroform). Microanalysis: Calculated 60.1 C, 6.4, 2.7 N. Found 60.0 C, 6.27 H, 2.7 N %.

Hydrolysis of esters 3b, c and 4b, c: The ester (0.1 mol) is refluxed with sodium hydroxide (0.35 mol) in methanol for one hour. Then the solvent is removed and the residue taken up in 100 ml water. After extraction with dichloromethane the aqueous phase is acidified and the acid extracted with dichloromethane. The optically active acids (+)- and (-)- 4a are recrystallised from methanol until enantiomerically pure (usually tree times is sufficient). The enantiomerically pure acid (+)-4a is collected as a colourless solid of mp. 187 °C. Yield: 50 %. IR: 3462, 3253, 1724, 1601, 1411, 1316, 1233, 1153, 1067, 1011, 989, 739 and 703 cm^{-1}. MS: 91 (100), 139 (82), 155 (22), 171 (9), 199 (8), 213 (8), 230 (5), 276 (5), 368 (39) and 382 (M+-1,8). ^{1}H-NMR (DMSO-d_6): (ppm) = 2.35 (s, 3H, methyl-H), 3.64 (s, 3H, S-methyl-H), 3.81 (s, 3H, O-methyl-H) and 7.15-7.8 (m, 7H, aromatic-H). $[\alpha]_D^{20}$ = +157° (c = 1, acetone). Microanalysis: Calculated 50.1 C, 4.4 H, 3.7 N. Found 49.9 C, 4.46 H, 4.0 N %. (-)- 4a correspondingly with mp. 187 °C and $[\alpha]_D^{20}$ = -157° (c = 1, acetone). Racemic 4a melts at 153 °C.

2-methoxy-4-(S-methyl-N-[(4-methylbenzyl)-sulfonyl]-sulfiminyl-benzoic acid (3a): Colourless solid of mp.: 166 °C. Yield: 95 %. IR: 1735, 1595, 1577, 1495, 1467, 1406, 1261, 1228, 1131, 1083, 1025, 1000, 970, 828, 751 and 685 cm^{-1}. MS: 91 (100), 155 (43), 171 (35), 181 (18), 199 (75), 214 (42), 228 (3), 267 (4), 302 (4) and 334 (3). ^{1}H-NMR (DMSO-d_6): (ppm) = 2.34 (s, 4H, methyl-H), 3.03 (s, 3H, S-methyl-H), 3.80 (s, 3H, O-methyl-H), 72.-7.8 (m, 7H, aromatic-H) and 13.1 (br, 1H, acid-H). Microanalyis: Calculated 52.3 C, 4.67 H, 3.81 N. Found 52.1 C, 4.8 H, 3.4 N %.

(+)-2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl-benzyl alcohol (8): (+)-4a (13 mmol) is reduced with lithium aluminium hydride (13 mmol) in 130 ml absolute tetrahydrofuran. After the reaction has ceased (TLC-control) excess reducing agent is destroyed by careful addition of water. The reaction mixture is acidified with dilute hydrochloric acid and extracted with dichloromethane. The pale oil obtained after drying and evaporation is chromatographed over silica gel. Yield: 52 %. IR: 3504, 1598, 1494, 1402, 1302, 1288, 1151, 1089 and 1071 cm^{-1}. MS: 369 (M+). ^{1}H-NMR ($CDCl_3$): (ppm) = 2.41 (s, 3H, methyl-H), 3.43 (s, 3H, methyl-H), 3.95 (3H, S, methyl-H), 4.77 (2H, s, methylene-H) and 7.2-7.9 (7H, m, aromatic-H). $[\alpha]_D^{20}$ = +127.6°; (c = 1, methanol). Microanalysis: Calculated 52.0 C, 5.2 H, 3.8 N. Found 51.9 C, 5.56 H, 3.5 N %.

(+)-2-methoxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-toluene (9): (+)-8 (5 mmol) is hydrogenated in methanol over 5 % palladised charcoal (0.3 g). After twenty hours the catalyst is filtered off and the solvent evaporated. The remaining residue is taken up in the minimum amount of methanol and crystallised after trituration with ether and petrol. A colourless solid with mp. 69 °C is collected in 72 % yield. IR: 1593, 1496, 1397, 1313, 1246, 1233, 1153, 1069 and 735 cm^{-1}. Ms: 137 (100), 169 (14), 200 (24), 338 (28) and 353 (M+,4). ^{1}H-NMR ($CDCl_3$): (ppm) = 2.28 (s, 3H, O-methyl-H); 7.15-7,85 (m,7H, aromaticH). $[\alpha]_D^{20}$ =

+138.2° (c = 1, methanol). Microanalysis: Calculated 54.4 C; 5.4 H; 4.0 N. Found 54.7 C; 5.38 H; 4,0 N %.

(+)-2-hydroxy-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-toluene (10): Boron tribromide (40 mmol) dissolved in 20 ml dichloromethane is added dropwise to a stirred solution of (+)-9 (40 mmol) in 50 ml dichloromethane. During the addition the temperature is kept at 0 °C. After two hours at ambient temperature the reaction mixture is poured on ca. 100 g chipped ice. After extraction with dichloromethane, drying and evaporating a pale, viscous oil is obtained. After crystallisation from dichloromethane/ether/petrol a colourless solid with mp. 164 °C is obtained. Yield: 86 %. IR: 3351, 1598, 1413, 1308, 1300, 1242, 1146, 1086 and 741 cm^{-1}. Ms: 92 (71), 124 (64), 140 (66), 150 (100), 156 (30), 187 (18), 324 (38) and 339 (M+,8). ^{1}H-NMR (DMSO-d_6): (ppm) = 2.29 (s, 3H, methyl-H), 2.35 (s, 3H, methyl-H), 3,48 (s, 3H, S-methyl-H) and 7.15-7.65 (m, 7H, aromatic-H). $[\alpha]_D^{20}$ = +129° (c = 1, methanol). Microanalysis: Calculated 53.1 C, 5.0 H, 4.1 N. Found 53.6 C, 4.93 H, 4.1 N %.

(+)-2-diethylphosphato-4-(S-methyl-N[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-toluene (11): To a solution of (+)-10 (32.4 mmol) in 10 ml tetrahydrofuran and 50 ml carbon tetrachloride diethyl phosphite (37 mmol) is added. With stirring triethylamine (10 mmol) is added dropwise. After the exothermic reaction has ceased it is stirred another two hours at ambient temperature. The mixture is treated successively with dilute hydrochloric acid and water. After drying and evaporation of the solvent a quantitative yield of a colourless oil is obtained. IR: 1487, 1397, 1317, 1303, 1241, 1154, 1087, 1031 and 955 cm^{-1}. Ms: 139 (40), 203 (24), 259 (23), 460 (15) and 475 (M+,17). ^{1}H-NMR ($CDCl_3$): (ppm) = 1.2-1.4 (2t, 6H, methyl-H), 2.30 (s, 3H, methyl-H), 2.32 (s, 3H, methyl-H), 3.38 (s, 3H, S-methyl-H), 4.1-4.35 (2q, 4H, methylene-H), and 7.15-7.86 (m, 7H, aromatic-H). $[\alpha]_D^{20}$ = +108.9° (c = 1, methanol).

(+)-2-[5-(1-phenyl)-tetrazolo]-4-(S-methyl-N-[(4-methylphenyl)-sulfonyl]-sulfonimidoyl)-toluene (12): The stirred solution of (+)-10 (12.9 mmol) and 1-phenyl-5-chlorotetrazole (12.9 mmol) in 50 ml absolute acetone is refluxed for eighteen hours in the presence of finely powdered potassium carbonate (30 mmol). The cooled reaction mixture is filtered and the acetone distilled off. The remaining oil is chromatographed over silica gel using ethyl acetate/dichloromethane = 8/2. An amorphous solid is obtained. Yield: 64.5 %. IR: 1597, 1504, 1490, 1397, 1320, 1302, 1248, 1180, 1152, 1080, 978 and 909 cm^{-1}. Ms: 91 (100), 118 (20), 123 (20), 139 (34), 155 (30), 171 (24), 223 (8), 239 (7), 324 (15), 455 (9) and 483 (5,M+). ^{1}H-NMR ($CDCl_3$): (ppm) = 2.29 (s, 6H, methyl-), 343 (s, 3H, S-methyl-H) and 7.15-8.05 (m, 12H, aromatic-H). $[\alpha]_D^{20}$ = +139.4° (c = 1.03, chloroform). Microanalysis: Calculated 54.7 C, 4.4 H, 14.5 N. Found 53.7 C, 4.5 H, 13.9 N %.

(+)-(S)-4-(S-methyl)-N-[(4-methylphenyl)-sulfonyl]-4-methylphenyl)-sulfoximide (13): (+)-12 (7.5 mmol) is hydrogenated in 30 ml methanol over 5 % palladised charcoal (0.3 g). After 30 minutes the theoretical amount of hydrogen is consumed. The catalyst is filtered off and the solvent evaporated. The residue is chromatographed over silica gel using ethyl acetate/dichloromethane = 2/8. A 75 % yield of a colourless solid is obtained melting at 162 °C after recrystallisation from acetone. IR: 3029, 2933, 1591, 1320, 1312, 1231, 1151, 1098, 1089, 1060, 1014, 814 and 741 cm^{-1}. ^{1}H-NMR ($CDCl_3$): (ppm) = 2.41 (s, 3H, methyl-H), 2.47 (s, 3H, methyl-H), 3.40 (s, 3H, S-methyl-H), 7.15-7.4 and 7.7-7.9 (m, 8H, aromatic-H). $[\alpha]_D^{20}$ = +143.6° and $[\alpha]_D^{25}$ = +140.2° (c = 1.105, acetone). Microanalysis: Calculated 55.7 C, 5.3 H, 4.3 N. Found 54.95 C, 4.97 H, 4.3 N %.

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