Asymmetric Synthesis of (*R*)-(+)-β-Phenylalanine from (*S*)-(+)-Benzylidene-*p*-toluenesulfinamide. Regeneration of the Sulfinimine Precursor

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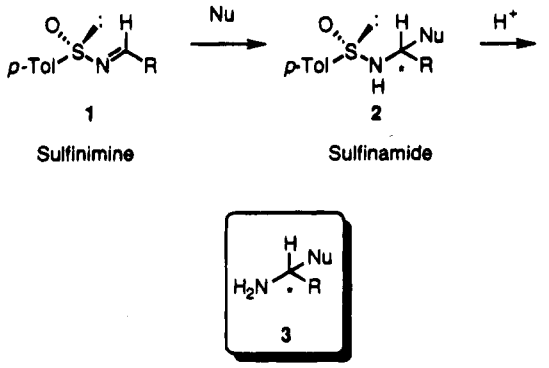
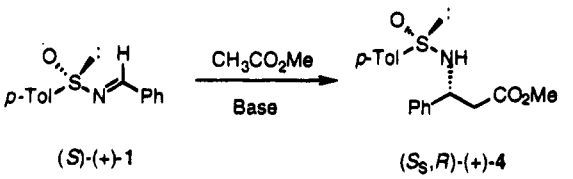
Enantiopure sulfinimines **1** are chiral ammonia imine building blocks; following nucleophilic addition across the C–N bond, cleavage of the resultant sulfinamide **2** furnishes primary amine **3** which contains a new stereogenic center (Scheme 1).[2–6] The application of **1**, derived from aliphatic and aromatic aldehydes, in highly diastereoselective asymmetric syntheses of α-amino acids,[7] *N*-sulfinyl *cis*-aziridine 2-carboxylic acids,[8,9] β-amino acids,[10,11] and the taxol C-13 side chain[11] and its fluorinated analog[12] has recently been described by us. In these syntheses the *N*-sulfinyl auxiliary in **1** not only activates the C–N bond toward nucleophilic addition but also acts as a powerful stereodirecting group. Another advantage of this "chiral auxiliary" based asymmetric synthesis is that the resulting diastereoisomers **2** are easily separable affording, after hydrolysis, the enantiomerically pure product. On the other hand a disadvantage of such a process is that the auxiliary needs to be introduced and eventually removed. However, if the auxiliary is recyclable or a precursor regenerated, these limitations are, to a large extent, mitigated. In this context we describe new methodology for the conversion of the *p*-tolylsulfinyl group in **2** into the Andersen reagent (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate (**7**), the precursor of **1**.[13] This new protocol is illustrated in the asymmetric synthesis of (*R*)-(+)-β-phenylalanine (**5**, (*R*)-(+)-methyl-β-amino-3-phenyl propanoate). β-Phenylalanine (**5**) is an important constituent of the antitumor cyclic peptide astins A–C,[10] the taxane alkaloids,[14] the alkaloid dihydroperiphylline,[15] and the peptide antibiotic andrimid[16] and is a precursor of the C-13 side chain of taxol[11] and its fluorinated analogue.[12]

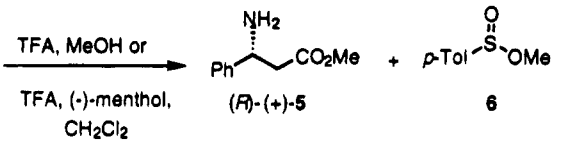
Scheme 1

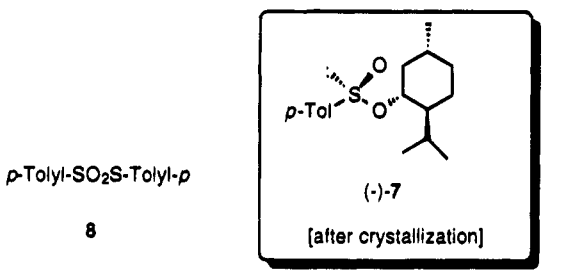


Scheme 2



base/solvent	% De	% Yield
LDA/THF	80	74
NaHMDS/THF	92	73
NaHMDS/Et_2O	>98	84





(*R*)-(+)-β-Phenylalanine (**5**) is prepared by addition of the metal enolate of methyl acetate to (*S*)-(+)-benzylidene-*p*-toluenesulfinimine (**1**) at −78 °C. After 5–7 h the reaction was quenched at −78 °C by addition of saturated NH_4Cl solution and the resultant (+)-**4** was purified by flash chromatography. Lower diastereoselectivities (80 to 92% de) were observed with the lithium and sodium enolates in THF (Scheme 2). Although the de's can be improved to >98% by crystallization of **4** from *n*-hexane, the sodium enolate in diethyl ether affords sulfinamide **4** in >98% de and 84% isolated yield. The *N*-sulfinyl auxiliary was removed by treatment of **4** with TFA in MeOH followed by removal of the solvent to dryness. The residue was treated with aqueous HCl and

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extracted with ether, and the aqueous layer was brought to pH 7.5 and washed with methylene chloride to give the β-amino acid (*R*)-(+)-**5** in 92% isolated yield and >98% ee.

Concentration of the ether extracts gives methyl *p*-toluenesulfinate (**6**), in nearly quantitative yield. On the basis of its optical rotation, **6** has the (*S*)-configuration which is consistent with the inversion of configuration at the sulfinyl sulfur during the TFA/MeOH hydrolysis. However, its enantiomeric purity was only 64%.[17] The acid-catalyzed epimerization of sulfinate esters is well established.[18]

Although, in principle, **6** can be transesterified with menthol to the Andersen reagent **7**, it was thought that replacing MeOH with menthol in the deprotection step might give this key sulfinimine precursor directly. Indeed, treatment of **4** with 3 equiv of TFA and 1.2 equiv of (1*R*,2*S*,5*R*)-(−)-menthol in anhydrous CH_2Cl_2 followed by extraction with water to separate the trifluoroacetate salt of **5** afforded **7** contaminated with about 5−10% of *p*-tolyl *p*-toluenethiosulfonate (**8**).[19,20] Significantly, under these conditions the methyl ester in **5** is not affected. Attempts to crystallize the crude Andersen reagent **7** from acetone/HCl according to the Posner/Solladie protocol were unsuccessful.[21b] Flash chromatography of the crude reaction mixture through silica gel easily separated **7** from the other contaminants in 74% yield with a diastereomeric purity about 10% enriched in the (*S*)-isomer. Crystallization afforded the diastereomerically pure product in 50−60% yield.[21] In THF, hydrolysis of the auxiliary was slower, but yields were comparable. When methylene chloride was not predried, the thiosulfonate byproduct **8** increased to about 20% and probably results from disproportionation of *p*-toluenesulfinic acid formed in the hydrolysis of **7**.[20]

(*R*)-(+)-β-Phenylalanine (**5**) was separated from its TFA salt by treatment with base and isolated in 86% yield (>98% ee).

In summary, the *N*-sulfinyl auxiliary in sulfinamide **4** is easily removed without epimerization of the product and readily recycled into the Andersen reagent (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (**7**). The Andersen reagent is a common precursor of most enantiopure sulfinyl compounds,[21] including sulfinimines **1**.[2] This makes practical the employment of **1** as a chiral ammonia imine builiding block for the asymmetric synthesis of amine derivatives on a large scale. Furthermore, both Andersen reagents (+)-**7** and (−)-**7** are readily available by choice of the antipodal menthol.

Experimental Section

General Procedure. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh) purchased from Aldrich Chemical Co. Analytical thin layer chromatography was performed on precoated silica gel plates (250) purchased from Analtech Inc. THF and ether were freshly distilled under nitrogen from a purple solution of sodium and benzophenone, and CH_2Cl_2 was dried over CaH_2. Reagents and solvents were purchased from Aldrich Chemical Co. and were used without further purification unless otherwise noted.

(*S*)-(+)-Benzylidene-*p*-toluenesulfinamide (1). In a 500 mL single-necked, round bottom flask equipped with a magnetic stir bar, rubber septum, and argon inlet was placed 14.7 g (50.0 mmol) of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (**7**) (Andersen reagent)[21b] [also commercially available from Aldrich Chemical Co.] dissolved in 250 mL of freshly distilled THF, and the solution was cooled to −78 °C. A solution of 75.0 mL of LiHMDS (1.0 M solution in THF) was added dropwise via syringe, and after 15 min the reaction mixture was allowed to warm to rt with stirring. After 5.5 h the reaction mixture was cooled to 0 °C, and 10.9 mL (100.0 mmol) of benzaldehyde was added via syringe followed by addition of 11.4 g (75.0 mmol) of powdered CsF (99.9%). After stirring overnight at rt, the reaction was quenched with saturated NH_4Cl (20 mL), and the mixture was diluted with ethyl acetate (200 mL) and water (100 mL). The organic layer was separated and extracted with ethyl acetate (100 mL), and the combined organic extracts were washed with brine (80 mL). After drying ($MgSO_4$), concentration afforded a slightly yellow solid which was purified by flash chromatography on silica gel (5−10% EtOAc/*n*-pentane) to give the product which was contaminated with menthol. Crystallization of the residue from *n*-hexane afford 9.26 g (two crops) of (*S*)-(+)-benzylidene-*p*-toluenesulfinamide (**1**) in 76% yield: mp 77−78 °C; $[\alpha]^{20}_D$ +119.3° (*c* 1.77, $CHCl_3$); IR (KBr) 3050, 1607, 1574, 1449, 1104, 1072, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 7.32 (d, 2 H, *J* = 8.0 Hz), 7.41−7.51 (m, 3 H), 7.64 (d, 2 H, *J* = 8.0 Hz), 7.83−7.86 (m, 2 H), 8.76 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 160.5, 141.6, 133.7, 132.5, 129.7, 129.5, 128.8, 124.7, 21.5. Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.11; H, 5.38; N, 5.76. Found: C, 69.34; H, 5.14; N, 5.76.

(S_s,*R*)-(+)-Methyl *N*-(*p*-Tolylsulfinyl)-3-amino-3-phenylpropanoate (4). In a 250 mL dry two-necked round bottom flask fitted with magnetic stir bar, argon inlet, and rubber septum were placed 80 mL of anhydrous ether and 1.52 mL (18.9 mmol, 1.5 equiv) of anhydrous methyl acetate, and the solution was cooled to −78 °C. Sodium bis(trimethylsilyl)amide (NaHMDS, 1.0 M solution in THF) (19.0 mL 19.0 mmol, 1.5 equiv) was added at −78 °C, and the solution was stirred for 40 min. A solution of 3.08 g (12.66 mmol) of (*S*)-(+)-**1** in 35 mL of ether was added dropwise at −78 °C, the mixture was stirred for 7 h, the reaction was quenched with a saturated NH_4Cl solution (4 mL) at −78 °C, and the mixture was allowed to warm to rt. The mixture was diluted with ethyl acetate (100 mL) and washed with water (30 mL), and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), and concentrated to give the crude product which was purified by silica gel column chromatography (25% ethyl acetate/*n*-hexane) to afford 3.37 g (84%) of (+)-(S_s,*R*)-**4** in >98% de: $[\alpha]^{20}_D$ +116.84° (*c* 1.74, $CHCl_3$); mp 85−86 °C; IR (KBr) 3155, 1737, 1436, 1295, 1170, 1044, 804, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (s, 3 H), 2.86 (d, 2 H, *J* = 6.3 Hz), 3.60 (s, 3 H), 4.90 (q, 1 H, *J* = 5.7 Hz), 5.01 (d, 1 H, *J* = 5.4 Hz), 7.28−7.41 (m, 7 H), 7.60 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.1, 142.1, 141.3, 140.3, 129.4, 128.6, 127.9, 127.1, 125.3, 54.7, 51.7, 41.9, 21.2; MS *m*/*z* 317 (M^+), 269, 196, 178, 139, 121, 104, 91, 77. Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.01; H, 6.37; N, 4.68.

Hydrolysis of (S_s,*R*)-(+)-Methyl *N*-(*p*-Tolylsulfinyl)-3-amino-3-phenylpropanoate (4): Isolation of (*R*)-(+)-β-Phenylalanine (5) and (*S*)-Methyl *p*-Toluenesulfinate (6). In a 250 mL dry single-necked round bottom flask fitted with a magnetic stir bar, argon inlet, and rubber septum was placed 6.9 g (21.8 mmol) of (S_s,*R*)-(+)-methyl *N*-(*p*-tolylsulfinyl)-3-amino-3-phenylpropanoate (**4**) in 80 mL of dry methanol, and the reaction mixture was cooled to 0 °C in an ice bath. Trifluoroacetic acid (3.34 mL, 43.6 mmol, 2.0 equiv) was added at 0 °C, and the reaction mixture was stirred for 2 h at which time the solvent was removed to dryness below 35 °C. The residue was dissolved in 200 mL of ether and extracted with 15% aqueous HCl (2 × 75 mL), the combined aqueous layer was cooled to 5 °C, and 100 mL of CH_2Cl_2 was added. The resulting biphasic solution was carefully neutralized to pH 7.5 with solid $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water (30 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated to give 3.6 g

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(92%) of pure β-amino ester (+)-**5**[11,22] as a thick oil: $[\alpha]^{20}_D$ +22.3° (*c* 2.17 $CHCl_3$); IR (neat) 3378, 3026, 2950, 1734, 1603, 1436, 1171, 1020, 762, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (br s, 2 H, exchangeable with D_2O), 2.66 (d, 2 H, J = 6.9 Hz), 3.68 (s, 3 H), 4.42 (t, 1 H, J = 6.7 Hz), 7.25–7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 144.6, 128.5, 127.3, 126.1, 52.5, 51.5, 43.9; HRMS calcd for $C_{10}H_{13}NO_2$ (M + 1) 180.1025, found 180.1022.

The ether layer was washed with saturated $NaHCO_3$ (30 mL), dried ($MgSO_4$), and concentrated to give 3.5 g (95% yield) of (*S*)-(−)-methyl *p*-toluenesulfinate (**6**) as a thick oil: $[\alpha]^{20}_D$ −140.0° (*c* 1.3, EtOH), ee 64% [lit.[17] $[\alpha]_D$ -218.9° (EtOH) for (*S*)-**6**]; IR (neat) 1596, 1492, 1453, 1133, 963, cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3 H) 3.47 (s, 3 H), 7.34 (d, 2 H, J = 8.3 Hz), 7.59 (d, 2 H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 142.8, 140.8, 129.6, 125.3, 49.3, 21.4; MS *m*/*z* 170 (M^+), 139, 91, 84, 65; HRMS calcd for $C_8H_{10}SO_2$ (M + 1) 171.0479, found 171.0456.

Hydrolysis of (*S*ₛ,*R*)-(+)-Methyl *N*-(*p*-Tolylsulfinyl)-3-amino-3-phenylpropanoate (4): Isolation of (*R*)-(+)-β-Phenylalanine (5) and (1*R*,2*S*,5*R*)-(−)-Menthyl (*S*)-*p*-Toluenesulfinate (7). In a 500 mL round bottom flask equipped with a magnetic stir bar and argon inlet were placed 4.68 g (14.8 mmol) of (*S*ₛ,*R*)-sulfinamide **4**, 2.76 g (17.6 mmol) of (−)-menthol (1.2 equiv) and 150 mL of dry CH_2Cl_2, and the solution was cooled to 0 °C. Trifluoroacetic acid, 3.42 mL (3.0 equiv) was added, and the mixture was stirred at rt until the reaction was complete as monitored by TLC (4 h). The reaction mixture was diluted with CH_2Cl_2 (80 mL) and extracted with water (3 × 40 mL), and the organic layer was dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (5–10% EtOAc–petroleum ether) to afford 3.22 g (74%) of **7** enriched in (*S*)-diastereomer (10% de) and 5–10% *p*-tolyl *p*-toluenethiosulfonate (**8**). Crystallization of the diastereomeric mixture of **7** in acetone–HCl according to the literature procedure[21b] afforded optically pure (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate (**7**) in 50–60% yield.

***p*-Tolyl *p*-toluenethiosulfonate (8)**: colorless solid; mp 74–75 °C [lit.[20] mp 76 °C]; IR (neat) 1593, 1489, 1326, 1303, 1142, 1078, 1016, 809 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 2.42 (s, 3 H), 7.12–7.26 (m, 6 H), 7.45 (d, 2 H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 21.4, 21.5, 124.6, 127.4, 129.3, 130.1, 136.3, 140.2, 142.0, 145.5; MS *m*/*z* 278 (M^+), 246, 172, 139, 123, 91. Anal. Calcd for $C_{14}H_{14}O_2S_2$: C, 60.60; H, 5.07. Found: C, 60.44; H, 5.14.

The aqueous layer was basified to pH 7.5 with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated to afford 2.28 g (86%) of (+)-(*R*)-methyl β-amino-3-phenylpropanoate (**5**);[11] ee >98%, $[\alpha]^{20}_D$ +22.9° (*c* 1.8, $CHCl_3$).

(22) For (*S*)-methyl β-amino-3-phenylpropanoate hydrochloride, see: Paris, M.; Sarfati, R.; Jarreau, F.-X. *Bull Soc. Chim. Fr.* **1973**, 331.

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