Diastereoselective Synthesis of (*S*)- and (*R*)-α-Phenylserine by a Sulfinimine-Mediated Strecker Reaction

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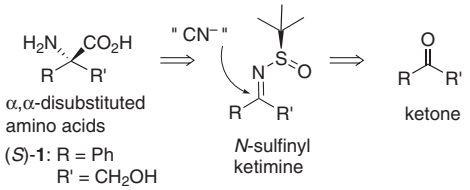
Abstract: A straightforward and efficient diastereoselective synthesis of (*S*)- and (*R*)-α-phenylserine is reported. The key step involves an asymmetric Strecker reaction of a chiral *N*-sulfinyl ketimine, which was obtained from the commercially available 2-hydroxyacetophenone.

Key words: amino acids, asymmetric synthesis, imines, nitriles, nucleophilic addition

Enantiomerically pure α,α-disubstituted amino acids are important building blocks for pharmaceutical and artificially designed peptides.[1] One of the most direct methods to synthesize such amino acids is the so-called Strecker reaction.[2] In recent years sulfinyl imines have proven to be extremely effective substrates for the 1,2-addition of a wide range of nucleophiles. Moreover, these imines serve as chiral directing groups and are straightforward to remove under mild conditions.[3] In this sense, several α-amino acids have been obtained from *N*-sulfinyl aldimines. However, it is important to note that the application of this methodology to the synthesis of α,α-disubstituted amino acids involves the use of ketimines, which are generally more difficult to obtain and give poorer selectivities than aldimines[4] (Scheme 1).



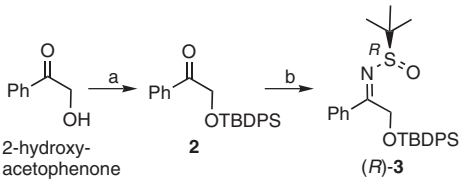
Scheme 1 Retrosynthesis of α,α-disubstituted amino acids using the sulfinimine-mediated asymmetric Strecker reaction.

In an effort to combine the two aforementioned processes, and in connection with our research into the asymmetric synthesis of conformationally restricted amino acids,[5] we focused our attention on α-phenylserine (**1**), an α,α-disubstituted β-hydroxy-α-amino acid. Compound **1** has previously been described in racemic form[6] but to the best of our knowledge, there is only one method in the literature for the diastereoselective synthesis of this amino acid.[7]

The key step in our synthesis of α-phenylserine (*S*)-**1** involves the stereoselective addition of 'CN$^-$' to a chiral *N*-sulfinyl ketimine derived from the appropriately protected 2-hydroxyacetophenone (Scheme 1).

The first step in the synthesis of (*S*)-**1** was to protect the hydroxyl group of commercially available 2-hydroxyacetophenone with *tert*-butyldiphenylsilyl chloride (TBDPSCl) to give compound **2** in 95% yield (Scheme 2).

Following Ellman's procedure, standard $Ti(OEt)_4$ mediated condensation of (*R*)-*tert*-butanesulfinamide[8] with derivative **2** gave *N*-sulfinyl ketimine (*R*)-**3** in 65% yield (Scheme 2). The ^{1}H NMR spectrum of this compound revealed that the *Z* isomer was obtained exclusively in the reaction. This isomer was unequivocally identified because the methylene proton signals of C*H*$_2$OTBDPS appear at high field ($\delta > 4.9$ ppm) due to the proximity of the oxygen of the sulfinimine group.



Scheme 2 a) TBDPSCl, imidazole, DMAP, CH_2Cl_2, 25 °C, 95%; b) (*R*)-*tert*-butanesulfinamide, $Ti(OEt)_4$, THF, reflux, 65%.

Compound (*R*)-**3** was treated with ethylaluminium cyanoisopropoxide [EtAl(O-*i*-Pr)CN], which was generated in situ by addition of *i*-PrOH to diethylaluminium cyanide (Et_2AlCN).[9] Interestingly, the cyanide addition to derivative (*R*)-**3** at –20 °C gave moderate diastereoselectivity [(*R*,*R*)-**4a**/(*R*,*S*)-**4b** = 81:19] in favor of α-amino nitrile (*R*,*R*)-**4a** (Scheme 3). The diastereoselectivity of this reaction could be easily determined by HPLC.[10] In an effort to improve the stereoselectivity, we decided to decrease the reaction temperature. However, all attempts to carry out the reaction at temperatures lower than –20 °C were unsuccessful. Diastereomerically pure (*R*,*R*)-**4a** could be obtained by simple column chromatography.

In order to confirm unambiguously the absolute configuration of (*R*,*R*)-**4a**, it was transformed into alcohol (*R*,*R*)-**5** by treatment with HF in pyridine. This reaction selectively removed the TBDPS group[11] to give alcohol (*R*,*R*)-**5** in good yield (Scheme 4). Fortunately, we were able to obtain single crystals of (*R*,*R*)-**5** by slow evaporation at low temperature (approximately –20 °C) of a solution in

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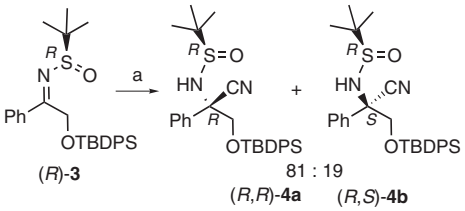
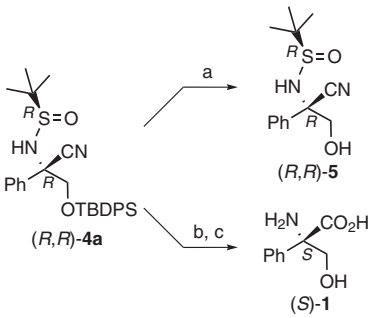


Scheme 3 a) Et_2AlCN, *i*-PrOH, THF, –20 °C, 52%.

hexane and CH_2Cl_2. The new stereogenic center was found to have the (*R*)-configuration. This situation is shown in the ORTEP diagram obtained from the X-ray analysis of these monocrystals (Figure 1).[12]



Scheme 4 a) 14% HF/pyridine, THF, 25 °C, 93%; b) 12 N HCl, reflux; c) propylene oxide, EtOH, reflux, 93%.

The acid-catalyzed hydrolysis of diastereomerically pure (*R*,*R*)-**4a** not only removed the sulfinyl auxiliary and the silyl group, but also hydrolyzed the nitrile group (Scheme 4).

Liberation of the amino acid from its hydrochloride salt was achieved by treatment with propylene oxide in EtOH under reflux to give (*S*)-**1** in high yield (Scheme 4).

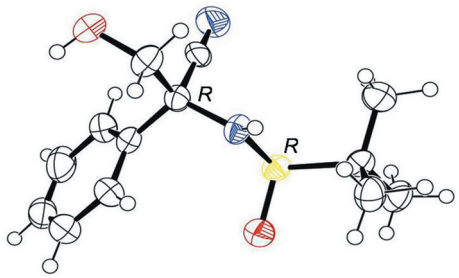


Figure 1 ORTEP drawing of the molecular structure of compound **5**.

Finally, (*R*)-α-phenylserine [(*R*)-**1**] was obtained using the same strategy as described above for its enantiomer (*S*)-**1**, but starting from sulfinimine (*S*)-**3**. The spectroscopic data and the optical activity of (*R*)-**1** was found to be similar to those previously reported.[7]

In summary, we have developed a straightforward and efficient diastereoselective synthesis of (*S*)- and (*R*)-α-phenylserine in which the key step is an asymmetric Strecker reaction of a *N*-sulfinyl ketimine derived from the commercially available 2-hydroxyacetophenone.

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in D_2O with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants, selective ^{1}H–^{1}H homonuclear decoupling experiments, ^{1}H–^{1}H COSY experiments and ^{1}H–^{13}C HETCOR experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter in 1.0 dm and 0.5 dm cells of 1.0 mL and 3.4 mL capacity, respectively. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values. Mass spectra were obtained by electrospray ionization (ESI) technique on a HP 5989B mass spectrometer.

2-(*tert*-Butyldiphenylsilyloxy)acetophenone (2)

To a stirred solution of 2-hydroxyacetophenone (0.75 g, 5.51 mmol), imidazole (0.47 g, 6.89 mmol) and DMAP (0.17 g, 1.39 mmol) in anhyd CH_2Cl_2 (15 mL) at 0 °C under an inert atmosphere was added TBDPSCl (1.89 g, 6.89 mmol) dropwise. The reaction mixture was stirred at r.t. for 12 h and then H_2O (10 mL) was added. The phases were separated and the organic layer was dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane–EtOAc, 9.5:0.5) to give **2** in 95% yield (1.96 g, 5.23 mmol) as a white solid; mp 58–59 °C.

^{1}H NMR ($CDCl_3$): δ = 1.13 [s, 9 H, $(CH_3)_3CSi$], 4.94 (s, 2 H, CH_2O), 7.38–7.83 (m, 15 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 19.3 [$(CH_3)_3CSi$], 26.7 [$(CH_3)_3CSi$], 67.5 (CH_2O), 127.8, 128.5, 129.9, 130.4, 132.9, 133.2, 135.3, 135.6 (Ph), 196.7 (Ph*C*O).

ESI$^+$: *m*/*z* = 375.

Anal. Calcd for $C_{24}H_{26}O_2Si$: C, 76.96; H, 7.00. Found: C, 76.77; H, 7.15.

(*R*,*R*)-*tert*-Butanesulfinic Acid [2-(*tert*-Butyldiphenylsilyloxy)-1-cyano-1-phenylethyl]amide [(*R*,*R*)-4a]

$Ti(OEt)_4$ (0.69 mL, 3.33 mmol) and (*R*)-*tert*-butanesulfinamide (200 mg, 1.65 mmol) were added to a stirred solution of **2** (620 mg, 1.65 mmol) in THF (20 mL) under an inert atmosphere. The reaction mixture was heated under reflux for 12 h. The solvent was removed and the crude product was purified by flash chromatography (hexane–EtOAc, 9:1) to give *N*-sulfinyl ketimine (*R*)-**3** (520 mg, 65%), which was dissolved in THF (5 mL) at –20 °C. In a separate round-bottomed flask, 1 M Et_2AlCN in toluene (1.62 mL, 1.62 mmol) was added to a solution of *i*-PrOH (64.7 μL, 1.08 mmol) in THF (5 mL) and the mixture was stirred at r.t. for 30 min. This mixture was transferred to the solution of (*R*)-**3** at –20 °C. After 3 d at –20 °C, the reaction was quenched with 0.05 M aq HCl (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane–EtOAc, 7:3) to give (*R*,*R*)-**4a** in 42% yield (350 mg, 0.69 mmol) and (*R*,*S*)-**4b** (82 mg, 0.17 mmol), both as colorless oils; overall yield: 52%.

Compound (*R*)-3

^{1}H NMR ($CDCl_3$): δ = 0.89 [s, 9 H, $(CH_3)_3CSi$], 1.23 [s, 9 H, $(CH_3)_3CSO$], 4.96 (d, *J* = 14.7 Hz, 1 H, CH_2O), 5.18 (d, *J* = 14.7 Hz, 1 H, CH_2O), 7.36–7.72 (m, 15 H, Ph).

Compound (*R*,*R*)-4a

$[\alpha]^{25}_D$ +3.5 (*c* = 0.88, MeOH).

^{1}H NMR ($CDCl_3$): δ = 1.08 [s, 9 H, $(CH_3)_3CSi$], 1.31 [s, 9 H, $(CH_3)_3CSO$], 3.87 (d, *J* = 9.9 Hz, 1 H, CH_2O), 3.97 (d, *J* = 9.9 Hz, 1 H, CH_2O), 4.99 (br s, 1 H, NH), 7.37–7.45 (m, 10 H, Ph), 7.56–7.66 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 19.2 [$(CH_3)_3CSi$], 22.4 [$(CH_3)_3CSi$], 26.6 [$(CH_3)_3CSO$], 57.2, 64.3 [Ph*C*NH, $(CH_3)_3CSO$], 71.0 (CH_2O), 119.6 (CN), 127.4, 128.8, 128.9, 129.8, 130.2, 131.4, 135.4, 135.6 (Ph).

ESI$^+$: *m*/*z* =505.

Anal. Calcd for $C_{29}H_{36}N_2O_2SSi$: C, 69.01; H, 7.19; N, 5.55. Found: C, 68.85; H, 7.25; N, 5.38.

Compound (*R*,*S*)-4b

$[\alpha]^{25}_D$ –38.0 (*c* = 1.41, MeOH).

^{1}H NMR ($CDCl_3$): δ = 1.10 [s, 9 H, $(CH_3)_3CSi$], 1.24 [s, 9 H, $(CH_3)_3CSO$], 3.88 (s, 2 H, CH_2O), 4.69 (br s, 1 H, NH), 7.37–7.68 (m, 15 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 19.3 [$(CH_3)_3CSi$], 22.4 [$(CH_3)_3CSi$], 26.6 [$(CH_3)_3CSO$], 56.8, 62.5 [Ph*C*NH, $(CH_3)_3CSO$], 71.6 (CH_2O), 118.9 (CN), 127.4, 128.0, 128.9, 129.7, 130.1, 131.4, 135.4, 135.7 (Ph).

ESI$^+$: *m*/*z* = 505.

Anal. Calcd for $C_{29}H_{36}N_2O_2SSi$: C, 69.01; H, 7.19; N, 5.55. Found: C, 68.83; H, 7.28; N, 5.41.

(*S*)-α-Phenylserine [(*S*)-1]

A suspension of (*R*,*R*)-**4a** (300 mg, 0.59 mmol) in 12 N aq HCl solution (7 mL) was heated under reflux for 12 h to give, after removal of the solvent, α-phenylserine hydrochloride as a white solid. This compound was dissolved in EtOH–propylene oxide (3:1, 4 mL) and the mixture was heated under reflux for 2 h. The α-phenylserine (*S*)-**1** partially precipitated as a white solid (75 mg). The filtrate was concentrated and the residue was dissolved in H_2O and eluted through a C_{18} reverse-phase Sep-pak cartridge to give, after removal of the H_2O, (*S*)-**1** (25 mg) as a white solid; total amount: 100 mg, 0.55 mmol; yield: 93%; $[\alpha]^{25}_D$ –26.9 (*c* = 0.60, H_2O).

^{1}H NMR (D_2O): δ = 4.26 (d, *J* = 11.7 Hz, 1 H, CH_2), 4.39 (d, *J* = 11.7 Hz, 1 H, CH_2), 7.49 (m, 5 H, Ph).

^{13}C NMR (D_2O): δ = 63.6 (CNH_2), 67.7 (CH_2OH), 125.9, 129.3, 129.4, 134.7 (Ph), 173.4 (CO_2H).

ESI$^-$: *m*/*z* = 180.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.49; H, 6.33; N, 7.62.

(*R*,*R*)-*tert*-Butanesulfinic Acid (1-Cyano-2-hydroxy-1-phenylethyl)amide (5)

To a solution of (*R*,*R*)-**4a** (100 mg, 0.20 mmol) in THF (5 mL) in a polypropylene flask was added 14% HF–pyridine (1.0 mL) and the solution was stirred at r.t. for 24 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo and purified by column chromatography (hexane–EtOAc, 3:7) to give (*R*,*R*)-**5** (49 mg, 0.19 mmol) as a white solid; yield: 93%; mp 147–148 °C; $[\alpha]^{25}_D$ –14.4 (*c* = 0.93, MeOH).

^{1}H NMR ($CDCl_3$): δ = 1.27 [s, 9 H, $(CH_3)_3CSO$], 3.85–4.20 (m, 3 H, CH_2O, OH), 4.93 (br s, 1 H, NH), 7.35–7.49 (m, 3 H, Ph), 7.60–7.68 (m, 2 H, Ph).

^{13}C NMR ($CDCl_3$): δ = 22.4 [$(CH_3)_3CSO$], 57.5, 64.1 [Ph*C*NH, $(CH_3)_3CSO$], 69.2 (CH_2O), 119.5 (CN), 127.2, 129.1, 129.8, 134.0 (Ph).

ESI$^+$: *m*/*z* = 267.

Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.86; H, 6.75; N, 10.40.

(*S*,*S*)-*tert*-Butanesulfinic Acid [2-(*tert*-Butyldiphenylsilyloxy)-1-cyano-1-phenylethyl]amide [(*S*,*S*)-4a]

As described for (*R*,*R*)-**4a** but using (*S*)-*tert*-butanesulfinamide, the enantiomer (*S*,*S*)-**4a** was obtained (282 mg, 52% overall yield) from **2** (500 mg, 1.33 mmol); $[\alpha]^{25}_D$ –3.6 (*c* = 0.89, MeOH).

ESI$^+$: *m*/*z* = 505.

Anal. Calcd for $C_{29}H_{36}N_2O_2SSi$: C, 69.01; H, 7.19; N, 5.55. Found: C, 68.80; H, 7.24; N, 5.36.

(*R*)-α-Phenylserine [(*R*)-1]

As described for enantiomer (*S*)-**1**, compound (*R*)-**1** (132 mg, 92%) was obtained from compound (*S*,*S*)-**4a** (400 mg, 0.79 mmol); $[\alpha]^{25}_D$ +27.1 (*c* = 0.59, H_2O).

ESI$^-$: *m*/*z* = 180.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.50; H, 6.29; N, 7.78.

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(10) HPLC conditions: Lichrospher Si (5 μm, 250 × 4.6 mm), hexane–MTBE = 70:30, 0.6 mL/min, 265 nm, 25 °C.
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(12) (a) Crystal data of compound **1**: $C_{39}H_{54}N_6O_6S_3$, M_w = 799.06, colorless prism of 0.30 × 0.12 × 0.10 mm, T = 173 K, orthorhombic, space group $P\,2_1\,2_1\,2_1$, Z = 4, a = 12.5430 (10) Å, b = 18.4770 (10) Å, c = 18.5730 (10) Å, α = 90.000(10), β = 90.000(10), γ = 90.000(10)°, V = 4304.4 (5) Å^3, d_{calc} = 1.233 g cm^{-3}, F(000) = 1704, λ = 0.71073 Å (Mo, Kα), μ = 0.086 mm^{-1}, Nonius kappa CCD diffractometer, c range 1.55–25.01°, 7270 collected reflections, 7241 unique, full-matrix least-squares (SHELXL97[12b]), $R1$ = 0.0586, $wR2$ = 0.1142, ($R1$ = 0.1026, $wR2$ = 0.1304 all data), goodness of fit = 1.029, residual electron density between 0.254 and –0.263 e Å^{-3}. Hydrogen atoms fitted at theoretical positions. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number 246445. (b) Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, **1997**.