Enantiomerically pure \(\alpha,\alpha\)-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 \(\alpha\)-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 \(\alpha,\alpha\)-disubstituted amino acids involves the use of ketimines, which are generally more difficult to obtain and give poorer selectivities than aldmines\(^4\) (Scheme 1).

![Scheme 1](image)

The key step in our synthesis of \(\alpha\)-phenylserine (\(S\))-1 involves the stereoselective addition of \(\text{CN}^-\) to a chiral \(N\)-sulfinyl ketimine derived from the appropriately protected 2-hydroxyacetophenone. The first step in the synthesis of \((S)\)-1 was to protect the hydroxyl group of commercially available 2-hydroxyacetophenone with \(\text{CN}^-\) to give compound 2 in 95% yield (Scheme 2).

Following Ellman’s procedure, standard \(\text{Ti(OEt)}_4\) mediated condensation of (\(R\))-\(\text{tert-butanesulfinamide}\)\(^8\) with derivative 2 gave \(N\)-sulfinyl ketimine (\(R\))-3 in 65% yield (Scheme 2). The \(^1\text{H}\) 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 \(\text{CH}_2\text{OTBDPS}\) appear at high field (\(\delta > 4.9 \text{ ppm}\)) due to the proximity of the oxygen of the sulfinimine group.

Compound (\(R\))-3 was treated with ethylaluminium cyanoisopropoxide \([\text{EtAl(O-i-Pr)}\text{CN}]\), which was generated in situ by addition of \(i\)-\(\text{PrOH}\) to diethylaluminium cyanide (\(\text{Et}_2\text{AlCN}\)).\(^{9}\) Interestingly, the cyanide addition to derivative (\(R\))-3 at \(-20 \text{ °C}\) gave moderate diastereoselectivity ([\((R,R)\)-4a]/[(\(R,S\))-4b] = 81:19) in favor of \(\alpha\)-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 \(-20 \text{ °C}\) 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 \(-20 \text{ °C}\)) of a solution in

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

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**Abstract:** A straightforward and efficient diastereoselective synthesis of (\(S\))- and (\(R\))-\(\alpha\)-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

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hexane and CH₂Cl₂. 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

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-pen-
Compound (R)-3
1H NMR (CDCl\textsubscript{3}): δ = 0.89 [s, 9 H, (CH\textsubscript{3})\textsubscript{3}Si], 1.23 [s, 9 H, (CH\textsubscript{3})\textsubscript{3}CSi], 4.96 (d, J = 14.7 Hz, 1 H, CH\textsubscript{2}O), 5.18 (d, J = 14.7 Hz, 1 H, CH\textsubscript{2}O), 7.36–7.72 (m, 15 H, Ph).

Compound (R,R)-4a
\[ [\alpha]\textsubscript{D}\textsubscript{25} = +3.5 (c = 0.88, MeOH).

1H NMR (CDCl\textsubscript{3}): δ = 1.08 [s, 9 H, (CH\textsubscript{3})\textsubscript{3}Si], 1.31 [s, 9 H, (CH\textsubscript{3})\textsubscript{3}CSi], 3.87 (s, J = 9.9 Hz, 1 H, CH\textsubscript{2}O), 3.97 (d, J = 9.9 Hz, 1 H, CH\textsubscript{2}O), 4.99 (br s, 1 H, NH), 7.37–7.45 (m, 10 H, Ph), 7.56–7.68 (m, 6 H, Ph).

13C NMR (CDCl\textsubscript{3}): δ = 19.2 [(CH\textsubscript{3})\textsubscript{3}CSi], 22.4 [(CH\textsubscript{3})\textsubscript{3}CSi], 52.7, 64.3 [PhCNH, (CH\textsubscript{3})\textsubscript{3}CSi], 71.0 (CH\textsubscript{2}O), 119.6 (CN), 127.4, 128.8, 128.9, 129.8, 130.2, 131.4, 135.4, 135.7, 135.9 (Ph).

ESI\textsuperscript{+}: \[ m/z = 505. \]

Anal. Calcd for C\textsubscript{33}H\textsubscript{39}NO\textsubscript{3}SSi: C, 59.99; H, 6.49; N, 7.61. Found: C, 60.06; H, 6.45; N, 7.56.

Compound (R,S)-4b
\[ [\alpha]\textsubscript{D}\textsubscript{25} = -38.0 (c = 1.41, MeOH).

1H NMR (CDCl\textsubscript{3}): δ = 1.10 [s, 9 H, (CH\textsubscript{3})\textsubscript{3}Si], 1.24 [s, 9 H, (CH\textsubscript{3})\textsubscript{3}CSi], 3.88 (s, 2 H, CH\textsubscript{2}O), 4.69 (br s, 1 H, NH), 7.37–7.68 (m, 15 H, Ph).

13C NMR (CDCl\textsubscript{3}): δ = 19.3 [(CH\textsubscript{3})\textsubscript{3}CSi], 22.4 [(CH\textsubscript{3})\textsubscript{3}CSi], 56.8, 62.5 [PhCNH, (CH\textsubscript{3})\textsubscript{3}CSi], 71.6 (CH\textsubscript{2}O), 118.9 (CN), 127.4, 128.0, 128.9, 129.7, 130.1, 131.4, 135.4, 135.7 (Ph).

ESI\textsuperscript{+}: \[ m/z = 505. \]

Anal. Calcd for C\textsubscript{33}H\textsubscript{39}NO\textsubscript{3}SSi: C, 60.01; H, 7.19; N, 5.55. Found: C, 60.06; 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 of the solvent, solution was stirred at r.t. for 24 h. The reaction was quenched with polypropylene flask was added 14% HF–pyridine (1.0 mL) and the reaction was quenched with (S)-4a was obtained from compound [(S,S)-4a]– was obtained from compound (S,S)-4a (282 mg, 52% overall yield) from 2 (500 mg, 1.33 mmol); \[ [\alpha]\textsubscript{D}\textsubscript{25} = -3.6 (c = 0.89, MeOH).

ESI\textsuperscript{+}: \[ m/z = 505. \]

Anal. Calcd for C\textsubscript{33}H\textsubscript{39}NO\textsubscript{3}SSi: C, 60.01; H, 7.19; N, 5.55. Found: C, 60.06; H, 7.28; N, 5.41.

(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]\textsubscript{D}\textsubscript{25} = +27.1 (c = 0.59, H\textsubscript{2}O).

ESI\textsuperscript{+}: \[ m/z = 180. \]

Anal. Calcd for C\textsubscript{33}H\textsubscript{39}NO\textsubscript{3}SSi: 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.


(12) (a) Crystal data of compound 1: C₃₉H₅₄N₆O₆S₃, Mᵣ = 799.06, colorless prism of 0.30 × 0.12 × 0.10 mm, T = 173 K, orthorhombic, space group *P* 2₁ 2₁ 2₁, Z = 4, α = 12.5430 (10) Å, β = 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) Å³, d_cali = 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 (SHELXL97¹²b), 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.