Asymmetric Strecker Synthesis of α-Amino Acids via a Crystallization-Induced Asymmetric Transformation Using (R)-Phenylglycine Amide as Chiral Auxiliary

Boesten, Wilhelmus H.J.; Seerden, Jean-Paul G.; Lange, Ben de; Dielemans, Hubertus J.A.; Elsenberg, Henk L.M.; Kaptein, Bernard; Moody, Harold M.; Kellogg, Richard M.; Broxterman, Quirinus B.

Published in:
Organic Letters

DOI:
10.1021/ol007042c

Publication date:
2001

Supporting Information

Asymmetric Strecker Synthesis of α-Amino Acids via a Crystallization-Induced Asymmetric Transformation Using (*R*)-Phenylglycine Amide as Chiral Auxiliary

Wilhelmus H.J. Boesten,[†] Jean-Paul G. Seerden,[‡] Ben de Lange,*[,†] Hubertus J.A. Dielemans,[†] Henk L.M. Elsenberg,[†] Bernard Kaptein,[†] Harold M. Moody,[†] Richard M. Kellogg,[‡] Quirinus B. Broxterman,*[,†]

[†] *DSM Research Life Sciences-Organic Chemistry & Biocatalysis, PO Box 18, 6160 MD Geleen, The Netherlands*

[‡] *Syncom B.V., Kadijk 3, 9747 AT Groningen, The Netherlands*

Rinus.Broxterman@dsm-group.com

General. Reagents were purchased from Aldrich Chemical Company and were used without further purification. (*R*)-Phenylglycine amide **1** was available from DSM (Geleen, The Netherlands) NMR spectra were recorded on either a Varian VXR-300 spectrometer (300 MHz) or a Bruker Spectrometer (200 MHz). Chemical shifts are denoted in ppm and were referenced to residual solvent.

2-[1-(*S*)-cyano-2,2-dimethyl-propyl)amino]-2-(*R*)-phenyl-acetamide 3.
To a stirred suspension of (*R*)-phenylglycine amide **1** (60.3 g, 400 mmol) in H_2O (400 mL) was added pivaldehyde **2** (37.2 g, 419 mmol) at room temperature. Simultaneously, 30 % aqueous NaCN (68.8 g, 420 mmol) and glacial acetic acid (25.4 g, 423 mmol) were added in 30 minutes, whereby the temperature increased from 23 to 28ºC. The mixture was stirred for 2h at 30ºC, followed by stirring for 20 h at 70ºC. After cooling to 30ºC, the amino nitrile was isolated by filtration and washed with H_2O (500 mL). After drying the amino nitrile (*R*,*S*)-**3** was obtained as a nearly colorless solid (92.4%, dr > 99/1).

(*R*,*S*)-**3:** m.p. 141ºC. $[\alpha]^{20}_{589}$ = -32.8° (c = 1.0, $CHCl_3$).
^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38-7.46 (m, 5H), 5.55 (bs, 1H), 5.40 (bs, 1H), 4.49 (s, 1H), 2.87 (d, *J* = 12.7 Hz, 1H), 2.76 (d, *J* = 12.7 Hz, 1H), 1.05 (s, 9H).
^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 134.4, 126.9, 126.7, 126.0, 116.3, 62.0, 55.9, 31.7, 23.7.
(*R*,*R*)-**3**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.36-7.46 (m, 5H), 6.85 (bs, 1H), 6.15 (bs, 1H), 4.49

(s, 1H), 3.31 (d, *J* = 12.3 Hz, 1H), 1.89 (d, *J* = 12.3 Hz, 1H), 1.15 (s, 9H).

2-[1-(*S*)-aminocarbonyl-2,2-dimethyl-propyl)-amino]-2-(*R*)-phenyl-acetamide 5

A solution of (*R*,*S*)-amino nitrile **3** (940 mg, 4.0 mmol, dr 98/1) in CH_2Cl_2 (5.0 mL) was added slowly to conc. H_2SO_4 (5.6 mL, 96%), at such at rate that the temperature was 15-20°C. After the addition was complete, stirring is continued for 30 minutes at room temperature and then the mixture is stirred for 2h at 40°C. After cooling to 20°C, the mixture was poured on ice and neutralized with 25% aqueous NH_3 to pH = ~ 9. The oily product was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried on Na_2SO_4 and concentrated under vacuum to give 950 mg (94%) of diamide **5**.

M.p. 69ºC. $[\alpha]^{20}_{589}$ = -139.5º (c = 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.40 (m, 5H), 6.51 (bs, 1H), 6.40 (bs, 2H), 6.35 (bs, 1H), 4.08 (s, 1H), 2.53 (bs, 1H), 2.46 (bs, 1H), 0.97 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 172.4, 135.6, 126.4, 125.9, 125.5, 66.0, 62.5, 30.9, 24.5.

(*S*)-2-amino-3,3-dimethylbutanamide 6 ((*S*)-*tert*-leucine amide)

The diamide **5** (0.90 g, 3.7 mmol) was dissolved in EtOH (96%, 25 mL) and 10% Pd/C (50 mg) was added. The mixture was shaken under pressurized H_2 (2 bar) for 20 h and then filtered through celite. The celite was washed with EtOH (3 x 10 mL). The combined filtrate and washings were concentrated and the crude reaction mixture was separated via SiO_2 chromatography with CH_2Cl_2/MeOH (9:1) as eluent to give first the side product phenylacetamide (R_f = 0.5) and then 0.49 g (90%) of pure (*S*)-*tert*-leucine amide **6** (R_f = 0.10).

M.p. 105ºC (lit.[1] 98-100ºC). $[\alpha]^{20}_{589}$ +47.1º (c =1.0, 5N HCl); (lit.[1] $[\alpha]^{20}_{589}$ = +41.0º)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50, (bs, 1H), 5.49 (bs, 1H), 3.07 (s, 1H), 1.48 (bs, 2H), 0.96 (s, 9H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 174.0, 61.9, 31.3, 24.1.

(*S*)-2-amino-3,3-dimethylbutanoic acid 7 ((*S*)-*tert*-leucine)

(*S*)-2-amino-3,3-dimethylbutanamide **6** (200 mg, 1.54 mmol) in 6N HCl (50 mL) was heated at 100ºC for 24 h, cooled to room temperature and applied to a Dowex 50 Wx8 ion-exchange column in the NH_4^+ -form. The column was washed with H_2O (25 mL), followed by elution with 10% aqueous NH_3 (40 mL). Concentration and drying gave 174 mg (86%) of pure (*S*)-*tert*-leucine **7** as a white solid.

M.p. 252-256ºC (lit.[1] 252-260ºC; sublimes). $[\alpha]^{20}_{589}$ = -10.0º (c = 1.0, H_2O), (lit.[1] $[\alpha]^{20}_{589}$ = -10.9º).

^{1}H NMR (300 MHz, D_2O) δ 3.44 (s, 1H), 1.06 (s, 9H).

^{13}C NMR (50 MHz, D_2O) δ 174.0, 61.9, 31.3, 24.1.

2-[2-(*S*)-cyano-(3,4-dimethoxyphenyl)propyl)-amino]-2-(*R*)-phenyl-acetamide 9.

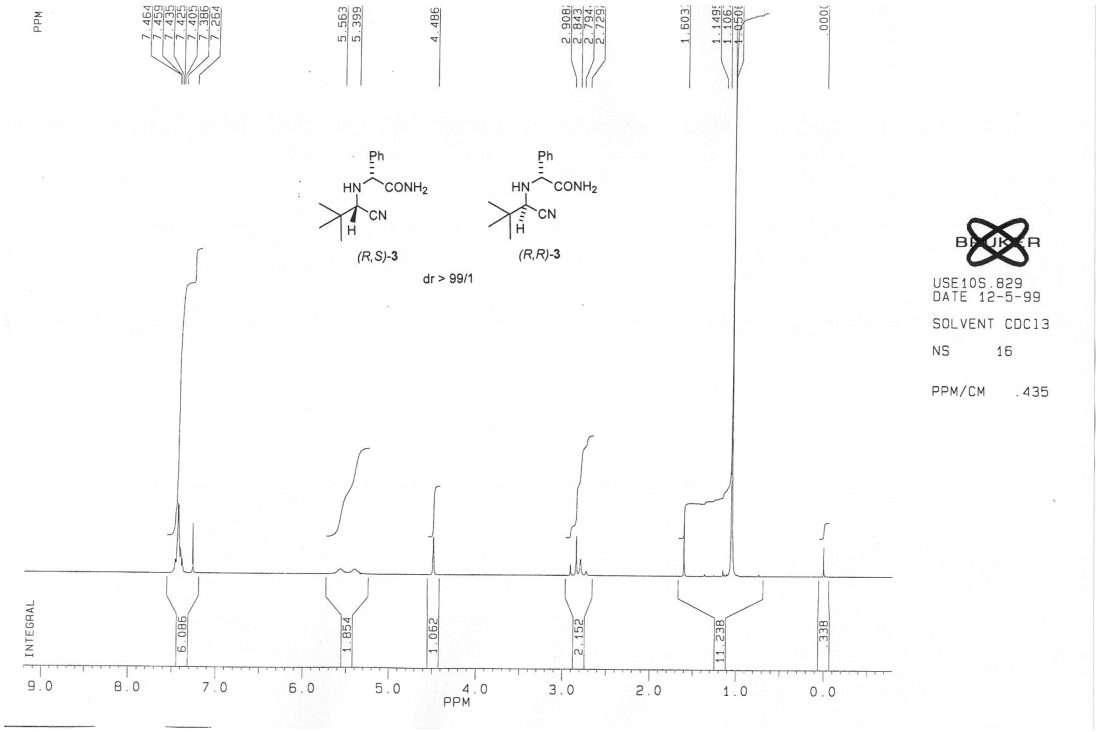
To a stirred suspension of (*R*)-phenylglycine amide **1**.HCl salt (18.6 g, 100 mmol) in MeOH (150 mL) and H_2O (25 mL) was added 3,4-dimethoxyphenylacetone **8** (19.3 g, 100 mmol) at room temperature. Then, 30 % aqueous NaCN (16.5 g, 100 mmol) was added and the now clear solution stirred for 96 h at room temperature. The precipitated amino nitrile (*R*,*S*)-**9** was isolated by filtration and washed with H_2O/MeOH (3 x 15 mL, v/v 70:30). After drying, the amino nitrile (*R*,*S*)-**9** was obtained as a nearly colorless solid (76% yield, dr >99/1).

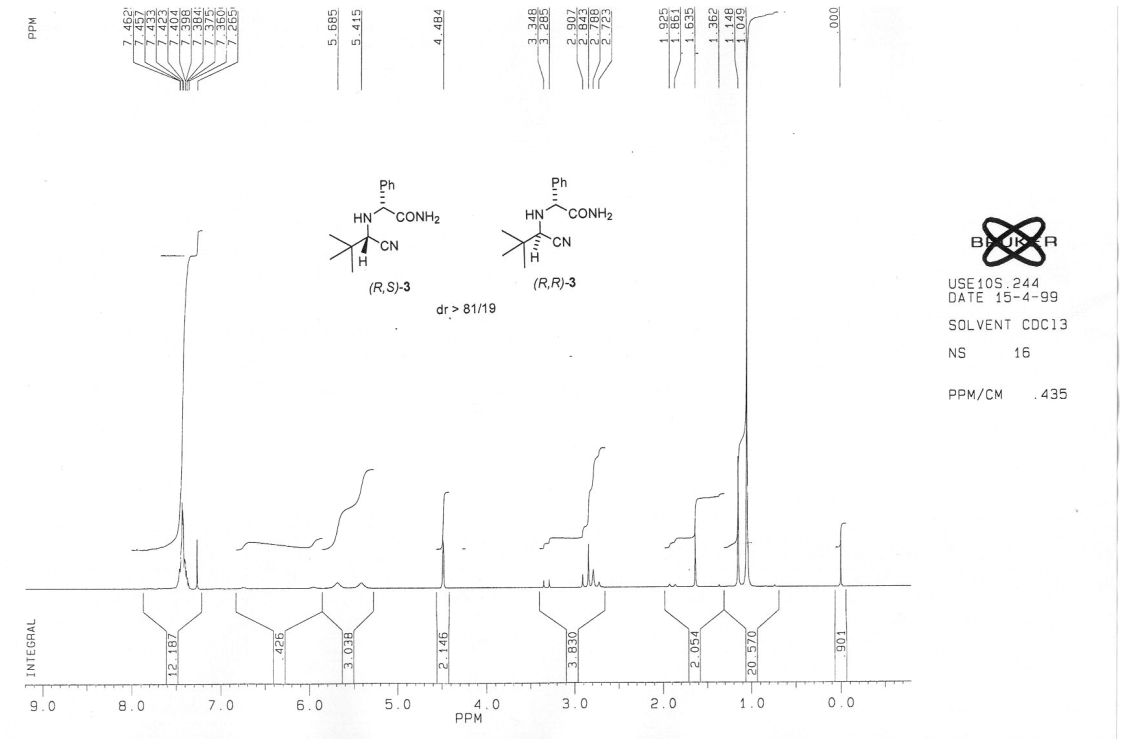
(*R*,*S*)-**9**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26-7.38 (m, 5H), 6.79 (s, 3H), 6.58 (bs, 1H), 5.70 (bs, 1H), 4.49 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.85 (s, 2H), 2.56 (s, 1H), 1.50 (s, 3H).

(*R*,*R*)-**9**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.26-7.43 (m, 5H), 6.78-6.91 (m, 3H), 6.64 (bs, 1H), 5.78 (bs, 1H), 4.49 (s, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 2.85-2.98 (m, 2H), 1.15 (s, 3H). NH could not be assigned

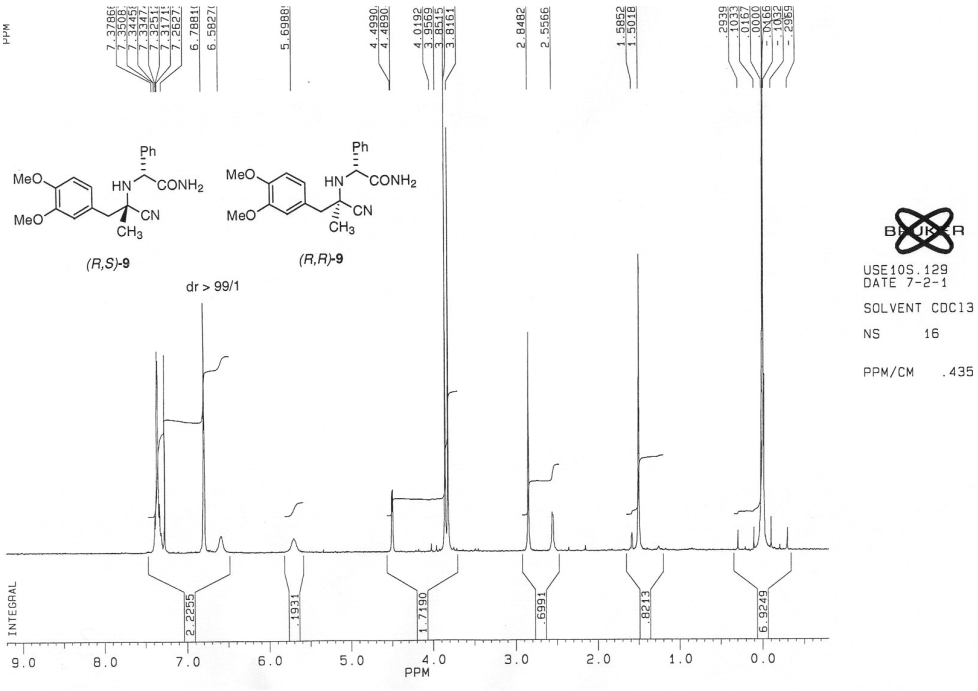
NMR spectrum of (*R*,*R*)-**9** also contains the imine

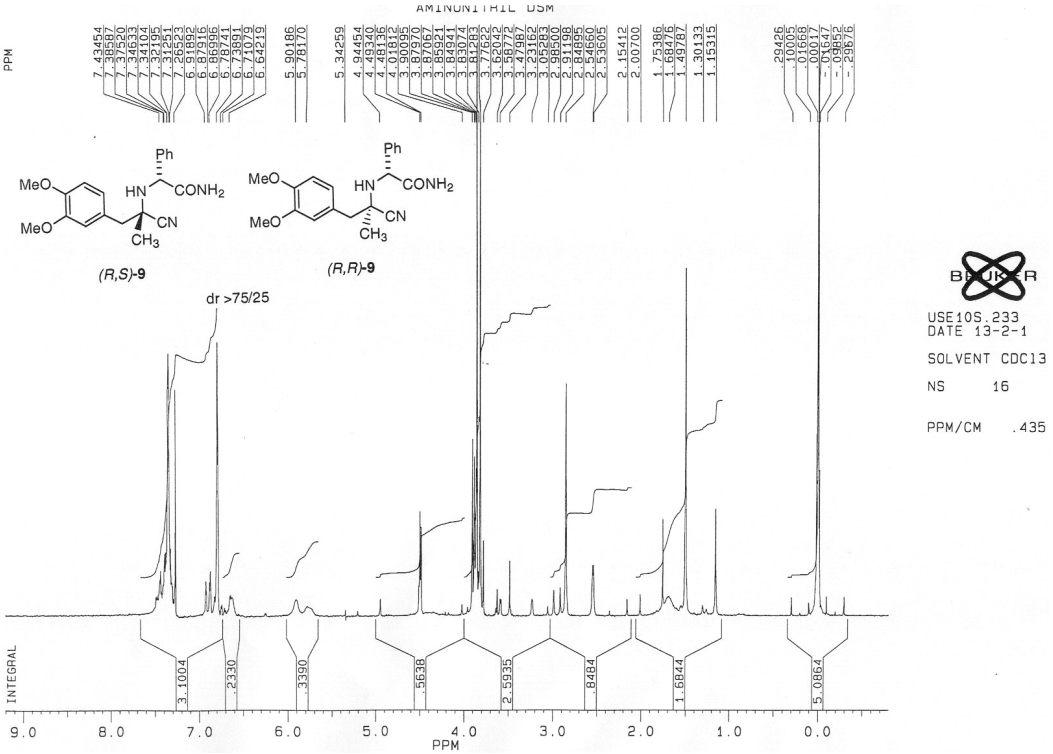
[1] Speelman, J.C.; Talma, A.G.; Kellogg, R.M.; Meetsma, A.; de Boer, A.; Beurskens, P.T.; Bosman, W.P. *J. Org. Chem.* **1989**, *54*, 1055.





The diastereomeric ratio of (*R*,*S*)-**3** and (*R*,*R*)-**3** is based on the integration of the tert-butyl signals at 1.05 ppm and 1.15 ppm in the spectrum shown. A ratio of 81/19 is calculated.





The spectrum of the mixture of (*R*,*S*)-**9** and (*R*,*R*)-**9** is contaminated with several peaks, which most probably can be attributed to the intermediate imine. During the crystallization-induced asymmetric transformation, crystallization of (*R*,*S*)-**9** and (*R*,*R*)-**9** occurs combined with the imine. This solid is isolated and the NMR measured.

During stirring, this mixture is transformed to the nearly diastereomerically pure (*R*,*S*)-**9** (dr 99/1).

The diastereomeric ratio of (*R*,*S*)-**9** and (*R*,*R*)-**9** can be calculated from this spectrum by integration of the peaks for the CH_2 group (singlet for (*R*,*S*)-**9** at 2.85 ppm, multiplet for (*R*,*R*)-**9** at 2.85-2.98 ppm). A ratio of 75/25 is calculated.