Resolution of 4-Phenyl-2-pyrrolidinone: A Versatile Synthetic Intermediate

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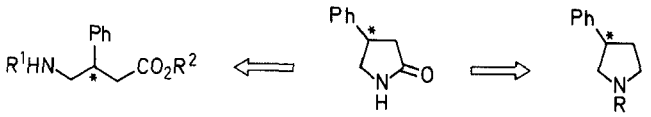
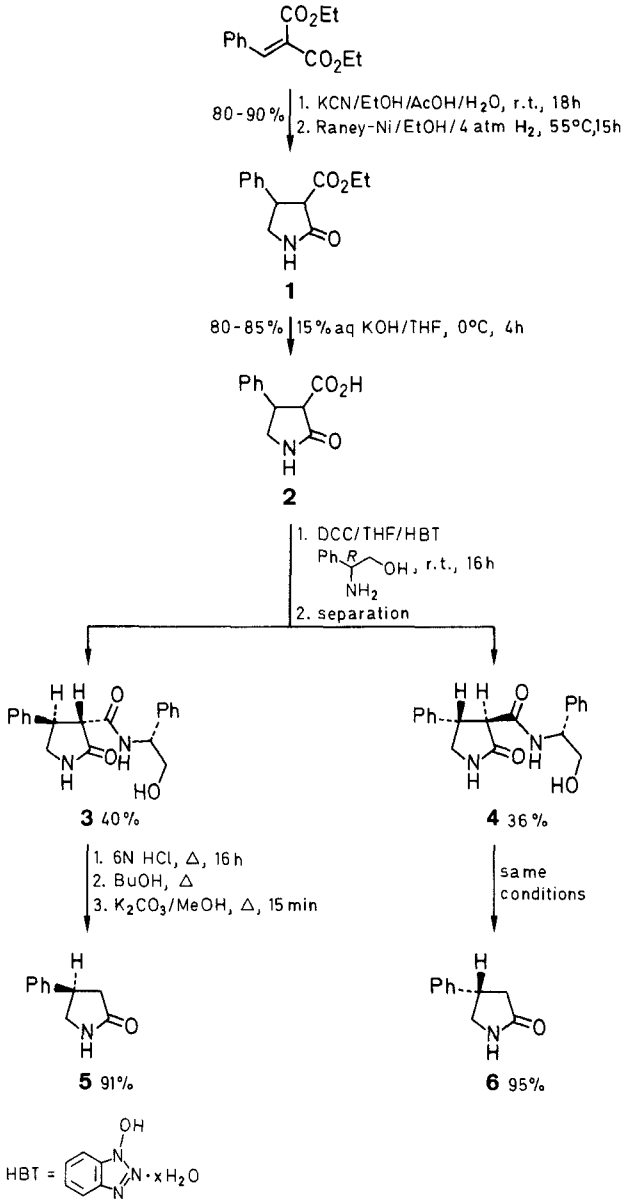
A resolution of 4-phenyl-2-pyrrolidinone is described. The resulting enantiomerically pure pyrrolidinones are exploited as precursor to 3-phenylpyrrolidines and 3-phenyl-γ-amino acids (4-amino-3-phenylbutanoic acid derivatives).

3-Phenylpyrrolidine and 3-phenyl-γ-aminobutanoic acid (GABA) and their derivatives are fairly common amongst natural products and compounds of pharmacological interest. Consequently, there is a need to obtain such substrates in enantiomeric form on a practical scale. The use of 4-phenyl-2-pyrrolidinone provides access into both of these structural types and is thus a logical target for synthesis in optically pure form.

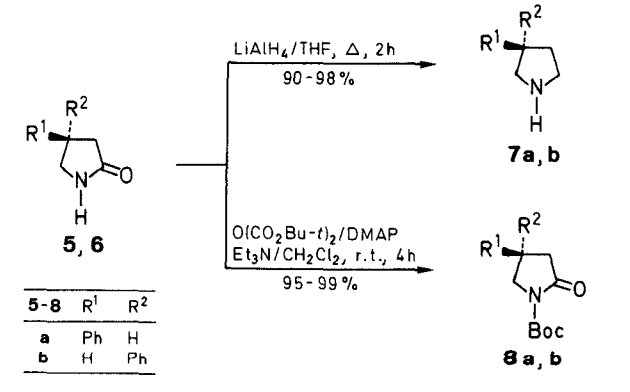


Early methods to resolve 4-phenyl-2-pyrrolidinone relied on classical resolution techniques such as fractional crystallization of diastereomeric salts.[1,2] Such resolutions suffer from the uncertainty of the final enantiomeric purity and most importantly the possibility of low overall yield of resolved material. Amino acid precursors have also been employed as a source of chirality,[3] but this type of method is usually lengthy and lacks the ability to provide both enantiomers. Pirkle et al.[4] has recently reported on the chromatographic separation of diastereomeric ureido lactam derivatives, derived from a butyrolactam and an enantiomerically pure isocyanate. This methodology works well with 3- or 5-phenyl-2-pyrrolidinones, but the chromatographic separation of the diastereomers becomes more difficult as the phenyl substituent becomes more remote from the nitrogen. In fact, it appears that only the (*R*)-1-naphthylethyl carboxamide derivative of 4-phenyl-2-pyrrolidinone is amenable to separation and unfortunately the employed isocyanate derivative is too costly for large scale preparations.

This paper describes a facile synthesis and resolution of 4-phenyl-2-pyrrolidinone and its use as a versatile precursor to 3-phenyl-γ-aminobutanoic acid and 3-phenylpyrrolidine derivatives. The synthesis commences with the addition of cyanide to commercially available diethyl benzylidenemalonate followed by Raney-nickel reduction of the resulting adduct to provide the pyrrolidinone **1**[2] in 85% overall yield (Scheme **1**). Hydrolysis of **1** sets the stage for the coupling of the resulting acid **2** with (*R*)-(−)-phenylglycinol(2-amino-2-phenylethanol)[5] to provide a diastereomeric mixture of amides **3** and **4**. Separation of the resulting amides by chromatography (flash or Prep-500 MPLC) gives rise to the diastereomerically pure amides **3** and **4**. One pot hydrolysis and decarboxylation of **3** and **4** provided enantiomerically pure **5** (91%) and **6** (95%), respectively.



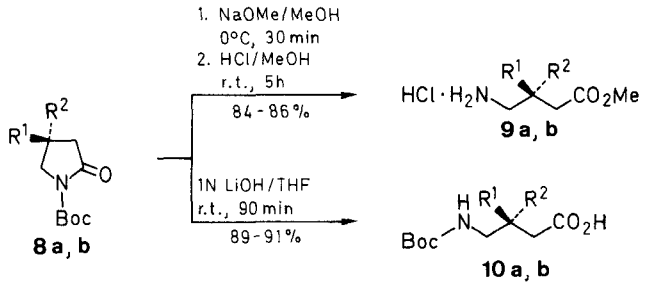
Scheme 1



Scheme 2

Reduction of **5** and **6** with lithium aluminum hydride provided the pyrrolidines **7a** and **7b** respectively, Scheme **2**. Although the amides **3** and **4** were determined to be diastereomerically pure by ^{1}H-NMR and HPLC analysis, ^{1}H-NMR and ^{19}F-NMR analysis of the Mosher amides[6] of **7a** and **7b** reconfirmed the enantiomeric purity (> 98% ee, limits of ^{1}H-NMR detection). Alternatively, treatment of the respective pyrrolidinones with di-*tert*-butyl dicarbonate provided the *N*-*tert*-butoxycarbonyl derivatives which are utilized as precursors to the GABA derivatives.[7]

Treatment of **8** with sodium methoxide in methanol followed by methanolic hydrogen chloride, provided the desired γ-amino acid methyl ester **9** in good yield, Scheme **3**. Alternative the corresponding acids **10** were obtained by treatment of **8** with lithium hydroxide.



8-10	R^1	R^2
a	Ph	H
b	H	Ph

Scheme 3

In conclusion, the method described provides a facile access to enantiomerically pure 4-phenyl-2-pyrrolidinones, 3-phenylpyrrolidines and 3-phenyl-GABA derivatives on a practical scale in good overall yield. The chiral auxiliary employed is both inexpensive and recyclable. Since the starting diethyl benzylidenemalonate is the Knoevenagel product of benzaldehyde and diethyl malonate, this procedure could in principle provide easy entry into a variety of aryl substituted pyrrolidines. The synthesis of 3-substituted 4-phenylpyrrolidines and 2-substituted 3-phenyl-GABA derivatives from **8** is presently under investigation.

^{1}H-NMR spectra of $CDCl_3$ or DMSO-d_6 solutions (TMS in internal standard) were recorded on a General Electric QE-300 (300 MHz) spectrometer. Mass spectra were obtained with a Hewlett-Packard HP5985. IR spectra were determined on a Nicolet IR 80 spectrometer. Elemental analyses and the above determinations were preformed by the Analytical Research Department, Abbott Laboratories, Abbott Park and North Chicago. Melting points were determined on a Thomas-Hoover capaillary apparatus and are uncorrected. A Perkin-Elmer 141 polarimeter was used to determine observed rotations. All reactions were run in flame-dried glassware under dry N_2. Reagents were obtained from Aldrich Chemical Co. and used directly. Reagent quality solvents were used without further purification. Preparative column chromatography was carried out with silica gel 60 (E. Merck 9285, 230–400 mesh).

Ethyl (*E*)-2-oxo-4-phenylpyrrolidine-3-carboxylate (1):
A solution of KCN (2.37 g, 48.38 mmol) in H_2O (6 mL) is diluted with EtOH (30 mL) and treated with AcOH (2.76 mL, 48.38 mmol). To the resulting solution is added a solution of diethyl benzylidenemalonate (10.0 g, 40.32 mmol) in EtOH (30 mL) and the resulting solution allowed to stir for 18 h. The EtOH is removed in vacuo. The residue is taken up into a mixture of CH_2Cl_2 (100 mL) and 10% $NaHCO_3$ (50 mL). The layers are separated and the aqueous phase re-extracted with CH_2Cl_2 (100 mL). The extracts are combined, dried ($MgSO_4$), filtered and concentrated in vacuo to provide 10.38 g of a faint yellow oil which crystallizes upon standing. This material is used directly in the next reaction without further purification.

The above material is reduced under H_2 (4 atm) at 55°C in abs. EtOH (200 mL) in the presence of Raney-Ni W-28 (25 g). The reaction is filtered and the catalyst washed with EtOH. The washes are combined and concentratd in vacuo. The residue is taken up into EtOAc (150 mL) and filtered through Celite. The filtrate is washed with a 5% HCl solution (50 mL) and the aqueous phase re-extracted with EtOAc (75 mL). The extracts are combined, dried ($MgSO_4$), filtered and concentrated in vacuo to afford 8.02 g (85% overall yield) of **1** as a white crystalline material: mp 121.5–122.5°C (Lit.[2] mp 119–120°C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, J = 7.5 Hz, CH_3), 3.44 (dd, 1 H, J = 9.0, 10.5 Hz), 3.56 (d, 1 H, J = 10.5 Hz), 3.83 (ddd, 1 H, J = 1.5, 9.0, 10.5 Hz), 4.12 (br q, 1 H, J = 9.0 Hz), 4.25 (ABq, 2 H, J = 7.5 Hz, $\Delta\nu_{AB}$ = 13.8 Hz, OCH_2), 7.39–7.24 (m, 5 H_{arom}), 6.61 (br s, 1 H, NH).

(*E*)-2-Oxo-4-phenylpyrrolidine-3-carboxylic Acid (2):
To a suspension of ester **1** (7.5 g, 31.91 mmol) in THF (70 mL) at 0°C is added 15% aq KOH (35 mL) upon which a solution is obtained. After 1 h, a precipitate forms. After additional 3 h at 0°C, the reaction is diluted with H_2O (100 mL) and extracted with Et_2O (2 × 75 mL). The aqueous phase is acidified with con. HCl upon which a white precipitate forms. The mixture is cooled in an ice bath to induce further precipitation. The solid is collected and air dried. The moist solid is than taken-up into hot THF (125 mL – note: a solid impurity remained), allowed to cool, dried ($MgSO_4$), filtered and concentrated in vacuo to provide 6.4 g (98%) of the desired acid as a white crystalline material. Recrystallization from $THF/CH_2Cl_2/Et_2O$ provides 5.4 g (83%) of pure acid **2**; mp 151–152°C (evolution of gas) (Lit.[2] mp 151°C).

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.22 (t, 1 H, J = 10.5 Hz), 3.50 (d, 1 H, J = 10.5 Hz), 3.62 (t, 1 H, J = 9.0 Hz), 3.87 (dt, 1 H, J = 9.0, 10.5 Hz), 7.23–7.35 (m, 5 H_{arom}), 8.08 (br s, 1 H, NH), 12.55–12.83 (br s, 1 H, CO_2H).

(3*R*,4*R*)-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-4-phenylpyrrolidine-3-carboxamide (3) and (3*S*,4*S*)-*N*-[(1*R*)-2-hydroxy-1-phenylethyl]-2-oxo-4-phenylpyrrolidine-3-carboxamide (4):
To a solution of acid **2** (4.15 g, 20.24 mmol) and 1-hydroxybenzotriazole hydrate (6.0 g, 44.52 mmol) in THF (200 mL) is added the (*R*)-(−)-2-phenylglycinol (2.77 g, 20.24 mmol) upon which a white precipitate forms. The reaction is treated with dicyclohexylcarbodiimide (DCC, 4.59 g, 22.26 mmol) and the mixture allowed to stir overnight (16 h). The reaction is filtered and concentrated in vacuo. The residue is taken up into CH_2Cl_2 (150 mL), washed with 5% HCl (50 mL), a 1:1 H_2O/brine solution (50 mL), 10% KOH (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford an off-white solid. Chromatography[8] on silica gel (2% $MeOH/CH_2Cl_2$) gives **3** as a white solid; yield: 2.62 g (40%); mp 164–167°C; $[\alpha]_D^{22}$ −186° (c = 1.14, MeOH).

$C_{19}H_{20}N_2O_3$	calc.	C 70.35	H 6.21	N 8.64
(324.4)	found	70.39	6.22	8.59

MS (DCI-NH_3): m/z = 325 (M + 1).

IR ($CDCl_3$): ν = 1705 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.40 (t, 1 H, J = 9.0 Hz, OH), 3.40 (dd, 1 H, J = 8.9, 9.1 Hz), 3.44 (d, 1 H, J = 9.0 Hz), 3.74 (t, 1 H, J = 9.0 Hz), 3.84 (t, 2 H, J = 6.0 Hz), 4.17 (q, 1 H, J = 9.0 Hz), 5.07 (m, 1 H), 6.03 (br s, 1 H, NH), 7.23–7.40 (m, 10 H_{arom}), 7.96 (br d, J = 7.5 Hz, NH).

Further elution with 5% MeOH/CH_2Cl_2 affords **4** as a white solid; yield: 2.35 g (36%); mp 197–199°C; $[\alpha]_D^{22}$ +44.89° (*c* = 0.92, MeOH).

$C_{19}H_{20}N_2O_3$	calc.	C 70.35	H 6.21	N 8.64
(324.4)	found	70.49	6.23	8.59

MS (DCI-NH_3): *m/z* = 325 (M + 1).

IR ($CDCl_3$): ν = 1700 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.96 (dd, 1 H, *J* = 6.0, 7.5 Hz, OH), 3.47 (dd, 1 H, *J* = 8.9, 9.0 Hz), 3.79–3.96 (m, 3 H), 4.28 (q, 1 H, *J* = 9.0 Hz), 5.13 (m, 1 H), 5.89 (br s, 1 H, NH), 7.23–7.37 (m, 10 H_{arom}), 7.52 (br d, 1 H, *J* = 9.0 Hz, NH).

(+)-(*S*)-4-Phenyl-2-pyrrolidinone (6):
A suspension of **4** (2.74 g, 8.45 mmol) in 6N HCl (80 mL) is heated to reflux upon which a solution is obtained. After 16 h, the reaction is diluted with BuOH (80 mL) and heated under azeotropic conditions until complete removal of H_2O from the mixture is achieved. The reaction is than cooled and concentrated under reduced pressure. The residue is taken up into MeOH, treated with K_2CO_3 until basic and heated to reflux. After 15 min, the reaction is cooled and concentrated in vacuo. The residue is taken up into H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extracts are combined, washed with 5% HCl (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to provide a crystalline material. Chromatography on silica gel (EtOAc) provides pure **6** as colorless plates; yield: 1.29 g (95%); mp 96.5–97.5°C; $[\alpha]_D^{22}$ +37.5° (*c* = 0.83, MeOH) $[\alpha]_D^{22}$ +45.3° (*c* = 1.1, benzene); Lit.[2] mp 100–101°C; $[\alpha]_D^{20}$ +40.1° (*c* = 1.0, MeOH); Lit.[3] mp 101–104°C; $[\alpha]_D^{20}$ +45.6° (*c* = 0.366, benzene)].

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.62 (dd, 1 H, *J* = 9.0, 18.0 Hz), 2.75 (dd, 1 H, *J* = 9.0, 18.0 Hz), 3.41–3.46 (m, 1 H), 3.71 (quint, 1 H, *J* = 9.0 Hz), 3.74–3.83 (m, 1 H), 6.41 (br s, 1 H, NH), 7.23–7.38 (m, 5 H_{arom}).

Neutralization of the acidic aqueous wash with KOH and extraction with CH_2Cl_2 (3 × 25 mL) provides a 95% recovery of (*R*)-(−)-phenylglycinol.

(−)-(*R*)-4-Phenyl-2-pyrrolidinone (5):
Reaction of **3** (2.98 g, 9.20 mmol) as above provides pure **5** as a colorless crystalline material; yield: 1.35 g (91%); mp 96–97°C; $[\alpha]_D^{25}$ −37.8° (*c* = 0.95, MeOH); $[\alpha]_D^{25}$ −45.7° (*c* = 1.24, C_6H_6) (Lit.[2] mp 99–100°C; $[\alpha]_D^{20}$ −42.6° (*c* = 0.3, MeOH)).

(+)-(*S*)-3-Phenylpyrrolidine (7b):
To a suspension of $LiAlH_4$ (708 mg, 18.64 mmol) in dry THF (35 mL) is added dropwise a solution of **6** (1.5 g, 9.32 mmol) in THF (15 mL). After the addition is complete, the reaction is heated to reflux and stirred for 2 h. The reaction is cooled in an ice bath and quenched by the dropwise addition of H_2O (710 µL), 10% KOH (710 µL) and an additional 2.1 mL of H_2O. After stirring for 30 min, the reaction is dried ($MgSO_4$), filtered and concentrated. Bulb-to-bulb distillation under reduced pressure provides **7b** as a colorless liquid; yield: 1.32 g (96%); $[\alpha]_D^{22}$ +22.0° (*c* = 0.47, EtOH) [Lit.[3] $[\alpha]_D^{20}$ +22.7° (*c* = 2.36, EtOH)].

(−)-(*R*)-3-Phenylpyrrolidine (7a):
Reaction of **5** (1.5 g, 9.32 mmol) as described above provides **7a** as a colorless liquid; yield: 1.35 g (98%); $[\alpha]_D^{22}$ −22.4° (*c* = 0.46, EtOH).

(−)-(*S*)-1-*tert*-Butoxycarbonyl-4-phenyl-2-pyrrolidinone (8b):
To a solution of **6** (856 mg, 5.32 mmol) in dry CH_2Cl_2 (3 mL) containing Et_3N (740 µL, 5.32 mmol) and 4-dimethylaminopyridine (DMAP, 650 mg, 5.32 mmol) is added di-*tert*-butyl dicarbonate (2.44 mL, 10.64 mmol). After 4 h at r.t., the reaction is directly chromatographed on silica gel (20% Et_2O/hexane) to provide **8b** as white crystalline needles; yield: 1.38 g (99%); mp 101.5–102.5°C; $[\alpha]_D^{22}$ −0.32° (*c* = 1.23, MeOH)

$C_{15}H_{19}NO_3$	calc.	C 68.94	H 7.33	N 5.36
(261.3)	found	69.13	7.35	5.33

MS (DCI-NH_3): *m/z* = 279 (M + NH_4).

IR ($CDCl_3$): ν = 1780, 1745, 1715 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.54 (s, 9 H), 2.83 (dq, 2 H, *J* = 8.7, 18.0 Hz), 3.55 (quint, 1 H, *J* = 9.0 Hz), 3.71 (dd, 1 H, *J* = 9.0, 11.7 Hz9, 4.17 (dd, 1 H, *J* = 9.0, 11.7 Hz), 7.40–7.23 (m, 5 H).

(+)-(*R*)-1-*tert*-Butoxycarbonyl-4-phenyl-2-pyrrolidinone (8a):
Reaction of **5** (1.03 g, 6.39 mmol) as described above provides **8a** as a crystalline solid; yield: 1.46 g (87%); mp 102–103°C; $[\alpha]_D^{22}$ +0.39° (*c* = 1.02, MeOH).

$C_{15}H_{19}NO_3$	calc.	C 68.94	H 7.33	N 5.36
(261.3)	found	69.02	7.59	5.33

Methyl (−)-(*S*)-4-Amino-3-phenylbutanoate Hydrochloride (9b):
To a suspension of **8b** (300 mg, 1.5 mmol) in MeOH (1.0 mL) at 0°C is added a solution of 2.0 M NaOMe/MeOH solution (633 µL)upon which a solution is immediately formed. After 30 min at 0°C, the reaction is poured into brine and extracted with Et_2O (3 × 5 mL). The organic phases are combined, dried ($MgSO_4$) and concentrated to provide 327 mg (97%) Boc-amino ester as a colorless oil which crystallizes upon standing. This material is dissolved in sat. methanolic HCl (2 mL) and stirred for 5 h. The reaction is concentrated and the resulting solid recrystallized from MeOH/THF to provide amine hydrochloride **9b** as needles; yield: 227 mg (86%); mp 169–170°C; $[\alpha]_D^{22}$ −5.24° (*c* = 1.03, MeOH).

$C_{11}Hd_{16}ClNO_2$	calc.	C 57.52	H 7.02	N 6.10
(229.7)	found	57.32	7.15	6.08

MS (DCI-NH_3): *m/z* = 211 (M + NH_4), 194 (M + H).

IR ($CDCl_3$): ν = 3450, 1735 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d_6: δ = 2.68 (d, 1 H, *J* = 10.5, 15.0 Hz), 2.93–3.04 (m, 2 H), 3.12 (dd, 1 H, *J* = 7.5, 13.0 Hz), 3.38 (m, 1 H), 3.48 (s, 3 H), 7.25–7.38 (m, 5 H_{arom}), 8.05 (br s, 2 H, NH).

Methyl (+)-(*R*)-4-Amino-3-phenylbutanoate Hydrochloride (9a):
Reaction of **8a** (1.5 g, 9.32 mmol) as described above provides **9a** as colorless needles; yield: 1.35 g (98%); mp 170–171°C; $[\alpha]_D^{22}$ +5.26° (*c* = 1.04, MeOH).

$C_{11}H_{16}ClNO_2$	calc.	C 57.52	H 7.02	N 6.10
(229.7)	found	57.72	6.88	6.10

(−)-(*S*)-4-(*tert*-Butoxycarbonylamino)-3-phenylbutanoic Acid (10b):
To a solution of **8b** (300 mg, 1.15 mmol) in THF (6 mL) is added 1N LiOH (3.45 mL, 3.45 mmol) and the heterogeneous mixture stirred for 1.5 h. The THF is removed in vacuo and the resulting aqueous phase acidified with 10% acetic acid. The aqueous phase is extracted with Et_2O (3 × 15 mL). The extracts are combined dried ($MgSO_4$), filtered and concentrated. The resulting oil is co-concentrated with CCl_4(2 ×) to remove residual acetic acid. The resulting oil is triturated with Et_2O to provide 318 mg (99%) of **10b** as a white crystalline material. Recrystallization from Et_2O/pentane provides analytically pure **10b**; yield: 290 mg (91%); mp 95–96°C; $[\alpha]_D^{22}$ −7.60° (*c* = 1.04, MeOH).

$C_{15}H_{21}NO_4$	calc.	C 64.50	H 7.58	N 5.01
(279.3)	found	64.56	7.57	5.01

MS (DCI-NH_3): *m/z* = 297 (M + NH_4), 280 (M + H).

IR ($CDCl_3$): ν = 1710 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.34 (br, s, 9 H), 2.44 (dd, 1 H, *J* = 10.0, 16.0 Hz), 2.63 (dd, 1 H, *J* = 6.0, 16.0 Hz), 3.05–3.22 (m, 3 H), 6.84 (br t, 1 H, *J* = 6.0 Hz, NH), 7.16–7.31 (m, 5 H_{arom}), 11.98 (br s, 1 H, CO_2H).

(+)-(*R*)-4-(*tert*-Butoxycarbonylamino)-3-phenylbutanoic Acid (10a):
Reaction of **8a** (300 mg, 1.15 mmol) as described above provides analytically pure **10a**; yield: 285 mg (89%); mp 106–107°C; $[\alpha]_D^{22}$ +7.78° (*c* = 1.08, MeOH).

$C_{15}H_{21}NO_4$	calc.	C 64.50	H 7.58	N 5.01
(279.3)	found	64.47	7.55	4.93

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(8) Chromatography is conducted using silica gel 60 (E. Merck 9285, 230–400 mesh) on a 4.5 cm column. The ratio of silica gel to compound by weight is approximately 12:1. Alternatively the two amides can be separated on a Waters Prep MPLC/System 550A, using two Prep PAK-500 silica cartridges (57 mm × 30 cm) Elution with 7.5% *i*-PrOH/CH_2Cl_2, flow rate 200 mL/min provides **3** and further elution with 12% *i*-PrOH/CH_2Cl_2, flow rate 500 mL/min provides **4**.