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

Robert E. Zelle
Division of Cardiovascular Research, D-47C, AP10 Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064 USA

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 12 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 diastereomically pure by 1H-NMR and HPLC analysis, 1H-NMR and 13C-NMR analysis of the Mosher amides of 7a and 7b confirmed the enantiomeric purity (> 98% ee, limits of 1H-NMR detection). Alternatively, treatment of the respective pyrrolidines with di-tert-butyl dicarbonate provided the N-tert-butyloxycarbonyl derivatives which are utilized as precursors to the GABA derivatives.

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.

1H-NMR (300 MHz, CDCl3): δ = 1.28 (t, 3H, J = 7.5 Hz, CH3), 3.44 (dd, 1H, J = 9.0, 10.5 Hz), 3.56 (dd, 1H, J = 9.0, 10.5 Hz), 3.83 (dd, 1H, J = 1.5, 9.0, 10.5 Hz), 4.12 (br, 1H, J = 9.0 Hz), 4.25 (ABq, 2H, J = 7.5 Hz, Δνav = 13.8 Hz, OCH2), 7.39−7.24 (m, 5H arom., 6.61 (br s, 1H, NH).

(E)-2-Oxo-4-phenylpyrroline-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 K2O (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 H2O (100 mL) and extracted with Et2O (2 × 75 mL). The aqueous phase is acidified with conc. 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 then taken-up into hot THF (125 mL – note: a solid impurity remained), allowed to cool, dried (MsSO4), filtered and concentrated in vacuo to provide 6.4 g (98%) of the desired acid as a white crystalline material. Recrystallization from THF/CH2Cl2/Et2O provides 5.4 g (83%) of pure acid 2; mp 151–152°C (evolution of gas) (Lit.: mp 151°C).

4H-NMR (300 MHz, DMSO-d6): δ = 3.22 (t, 1H, J = 10.5 Hz), 3.50 (d, 1H, J = 10.5 Hz), 3.62 (t, 1H, J = 9.0 Hz), 3.87 (dt, 1H, J = 9.0, 10.5 Hz), 7.23–7.35 (m, 5H arom., 8.08 (br s, 1H, NH), 12.55–12.83 (br s, 1H, CO2H).

(3R,4R)-(1R,2R)-hydroxy-1-phenethyl-2-oxo-4-phenylpyrroline-3-carboxamide (3) (3S,4S)-(1R,2R)-hydroxy-1-phenethyl-2-oxo-4-phenylpyrroline-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 CH2Cl2 (150 mL), washed with 5% HCl (50 mL), 1:1 H2O/brine solution (50 mL), 10% KOH (50 mL), brine (50 mL), dried (MsSO4), filtered and concentrated in vacuo to afford an off-white solid. Chromatography on silica gel (2% MeOH/CH2Cl2) gives 3 as a white solid; yield: 2.62 g (40%); mp 164–167°C; [α]D2 −186° (c = 1.14, MeOH).

C15H10N2O3 calc. C 70.35 H 6.21 N 8.64
(324.4) found 70.39 6.22 8.59
MS (DCI-NH3): m/z = 325 (M + 1).

IR (CDCl3): ν = 1705 cm−1

1H-NMR (300 MHz, CDCl3): δ = 2.40 (t, 1H, J = 9.0 Hz, OH), 3.40 (dd, 1H, J = 8.9, 9.1 Hz), 3.44 (dd, 1H, J = 9.0 Hz), 3.74 (t, 1H, J = 9.0 Hz), 3.84 (t, 2H, J = 6.0 Hz), 4.17 (q, 1H, J = 9.0 Hz), 5.07 (m, 1H), 6.03 (br s, 1H, NH), 7.23–7.40 (m, 10H arom.), 7.96 (br d, J = 7.5 Hz, NH).

In conclusion, the method described provides a facile access to enantiomerically pure 4-phenyl-2-pyrrolidones, 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-phenylpyrrolidones and 2-substituted 3-phenyl-GABA derivatives from 8 is presently under investigation.
Further elution with 5% MeOH/CH₂Cl₂ affords 4 as a white solid; yield: 2.35 g (36%); mp 197–199°C; [α]₂⁰D +44.89° (c = 0.92, MeOH).

C₇H₆N₂O₅ calc. C 70.35 H 6.21 N 8.64 (324.4) found 70.49 6.23 8.59

MS (DCI-NH₃); m/z = 325 (M + 1).

IR (CDCl₃); v = 1700 cm⁻¹.

1H-NMR (300 MHz, CDCl₃); δ = 1.54 (s, 9H), 2.83 (dq, 2H, J = 8.7, 18.0 Hz), 3.55 (quint, 1H, J = 9.0 Hz), 3.71 (dd, 1H, J = 9.0, 11.7 Hz), 4.17 (dd, 1H, J = 9.0, 11.7 Hz), 7.40–7.23 (m, 5H).

(+)-(R)-1-tert-Butyloxycarbonyl-4-phenyl-2-pyrrolidinone (8b): 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; [α]₂⁰D +0.39° (c = 1.02, MeOH).

C₁₇H₁₈N₂O₄ calc. C 68.94 H 7.33 N 5.36 (261.3) found 69.02 7.59 5.33

Methyl (±)-(S)-4-Amino-3-phenylbutananoate 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 NaOEt/MeOH solution (663 μL) upon which a solution is immediately formed. After 30 min at 0°C, the reaction is poured into brine and extracted with EtO (3 x 5 mL). The organic phases are combined, dried (MgSO₄) 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; [α]₂⁰D +5.24° (c = 1.03, MeOH).

C₁₁H₁₆C₂NO₂ calc. C 57.52 H 7.02 N 6.10 (229.7) found 57.32 7.15 6.08

MS (DCI-NH₃); m/z = 211 (M + NH₄), 194 (M + H).

IR (CDCl₃); v = 3450, 1735 cm⁻¹.

1H-NMR (300 MHz, DMSO-d₆); δ = 2.68 (d, 1H, J = 10.5, 15.0 Hz), 2.93–3.04 (m, 1H), 3.12 (dd, 1H, J = 7.5, 13.0 Hz), 3.38 (m, 1H), 3.48 (s, 3H), 7.25–7.38 (m, 5H, arom.), 8.05 (br s, 2H, NH).

Methyl (±)-(R)-4-Amino-3-phenylbutananoate 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; [α]₂⁰D +5.26° (c = 1.04, MeOH).

C₁₁H₁₆C₂NO₂ calc. C 57.52 H 7.02 N 6.10 (229.7) found 57.72 6.88 6.10

(−)-(−)-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; [α]₂⁰D −37.8° (c = 0.95, MeOH); [α]₂⁰D −45.7° (c = 1.24, CH₂Cl₂) (Lit. 5 mp 99–100°C; [α]₂⁰D −42.6° (c = 0.3, MeOH)).

(+)-(S)-3-Phenylpyrrolidine (7b): To a suspension of LiAlH₄ (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 H₂O (710 mL), 10% KOH (710 mL) and an additional 2.1 mL of H₂O. After stirring for 30 min, the reaction is dried (MgSO₄), filtered and concentrated. Bulb-to-bulb distillation under reduced pressure provides 7b as a colorless liquid; yield: 1.32 g (96%); [α]₂⁰D +22.0° (c = 0.47, EtOH) [Lit. 6 [α]₂⁰D +22.7° (c = 2.36, EtOH)].

(−)-(−)-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%); [α]₂⁰D −22.4° (c = 0.46, EtOH).

(−)-(−)-1-tert-Butyloxycarbonyl-4-phenyl-2-pyrrolidinone (8b): To a solution of 6 (856 mg, 5.32 mmol) in dry CH₂Cl₂ (3 mL) containing Et₃N (740 μL, 5.32 mmol) and 4-dimethylaminopyridine (DMAP, 650 mg, 5.32 mmol) is added di-tert-butyl dicarboxylate (2.44 mL, 10.64 mmol). After 4 h at rt, the reaction is directly chromatographed on silica gel (20% EtO/hexane) to provide 8b as white crystalline needles; yield: 1.38 g (99%); mp 101.5–102.5°C; [α]₂⁰D −0.32° (c = 1.23, MeOH).

C₁₉H₂₄N₂O₄ calc. C 68.94 H 7.33 N 5.36 (261.3) found 69.13 7.35 5.33

MS (DCI-NH₃); m/z = 279 (M + NH₄).

IR (CDCl₃); v = 1780, 1745, 1715 cm⁻¹.

1H-NMR (300 MHz, CDCl₃); δ = 1.54 (s, 9H), 2.83 (dq, 2H, J = 8.7, 18.0 Hz), 3.55 (quint, 1H, J = 9.0 Hz), 3.71 (dd, 1H, J = 9.0, 11.7 Hz), 4.17 (dd, 1H, J = 9.0, 11.7 Hz), 7.40–7.23 (m, 5H).

I wish to acknowledge Jim Leonard for conducting the MPLC separations, Lou Seif for conducting catalytic hydrogenations and Bill Mc Clellan for technical assistance.

Received: 22 April 1991; revised: 8 July 1991.
(1) Bettoni, G.; Cellucci, C.; Tortorella, V. J. Heterocycl. Chem. 1976, 13, 1053.


(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/CH₂Cl₂, flow rate 200 mL/min provides 3 and further elution with 12% i-PrOH/CH₂Cl₂, flow rate 500 mL/min provides 4.