Asymmetric Synthesis of (1*S*,2*R*)-(+)-2-Phenyl-1-Aminocyclopropane-1-Carboxylic Acid

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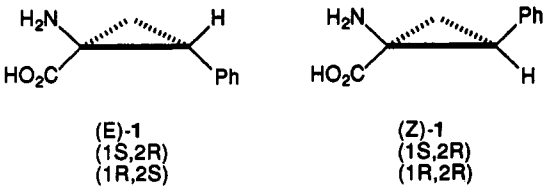
The synthesis of both the (*E*)- and (*Z*)-isomers of the unnatural amino acid, 2-phenyl-1-aminocyclopropane-1-carboxylic acid (cyclopropylPhe, Figure 1), has been accomplished in racemic fashion.[1] To date, only (*Z*)-cyclopropylPhe has been synthesized in diastereoenriched form;[2] (*E*)- and (*Z*)-cyclopropylPhe have been resolved via the agency of (−)-brucine,[3] and (−)-*O*,*O*-dibenzoyltartaric acid,[4] respectively. In recent years there has been considerable interest in the study of peptides that incorporate cyclopropylPhe as a conformationally restricted analog of phenylalanine.[5] This amino acid imposes conformational constraints and hydrolytic stability on the peptide structure, which may alter the chemical reactivity and molecular recognition properties of the peptide. Continued research in the areas of protein structure modification[6] and total synthesis[7] may ultimately reveal the full potential of cyclopropylPhe, as well as other ACC derivatives, in medicinal chemistry.

Recently we have described a method for the asymmetric synthesis of (*E*)-1-amino-1-cyclopropane-1-carboxylic acid (ACC) derivatives, including the naturally occurring coronamic and norcoronamic acids.[8] At that time we were unable to synthesize (1*S*,2*R*)-2-phenyl-1-aminocyclopropane-1-carboxylic acid (1), cyclopropylPhe (Figure 1), due to the inherent lability[9] of the α,β-cyclopropane bond bearing the phenyl group during reductive or oxidative deprotection sequences. In this earlier work we reported that we were unable to unmask cyclopropyl lactone (2)[8] (Scheme I) via dissolving metal reduction or the stepwise hydrolysis/periodate cleavage protocol first described by Weinges[10] on a related heterocycle and employed by this laboratory[11] in the synthesis of arylglycines from the α-aryloxazinones. Despite this temporary setback we continued to investigate an alternative stepwise deprotection method by replacing periodic acid with lead tetraacetate[12] for the removal of the chiral auxiliary. In this paper we wish to describe the first asymmetric synthesis of (*E*)-cyclopropylphenylalanine.



(E)-1 (1S,2R) (1R,2S) (Z)-1 (1S,2R) (1R,2R)

Figure 1.

Results and Discussion

The synthesis of (1*S*,2*R*)-2-phenyl-1-aminocyclopropane-1-carboxylic acid (1) began with the TFA-mediated deblocking of cyclopropyl lactone 2 to amine 3 in essentially quantitative yield, followed by basic hydrolysis of the lactone ring to provide amino acid derivative 4 in 85% yield (Scheme I). Protection of the carboxyl group using CH_2N_2 afforded methyl ester 5 in 89% yield. During ^1H NMR analysis of crude 5 we were able to detect the presence of approximately 3% of a minor cyclopropane diastereomer of undetermined relative stereochemistry. Since cyclopropyl lactone 2 is isomerically pure as previously determined,[8] the partial loss of stereochemical integrity is presumed to be a result of deprotonation of the amino proton of 3 during saponification, followed by cyclopropane ring opening and reclosure via the corresponding prochiral imine intermediate. A similar decomposition process has been documented in the literature for 1-methyl-2,2-diphenylcyclopropylamine.[13] Cleavage of the chiral auxiliary of 5 was accomplished by using a slight excess of $Pb(OAc)_4$ (LTA) in CH_2Cl_2/MeOH (2:1) at −15 °C (3 min) to produce the corresponding acid-sensitive benzaldehyde imine.

The crude imine was immediately converted to the diprotected amino acid 6[13,14] in 41% yield via a one-pot sequence that involved acidic hydrolysis followed by nitrogen protection using di-*tert*-butyl dicarbonate. It is our belief that the imine hydrolysis and nitrogen protection reactions of this three-step sequence occur in essentially quantitative yield and that the LTA-mediated cleavage reaction is the low-yielding step. This is supported by ^1H NMR analysis of both the crude imine and the corresponding cyclopropylPhe methyl ester hydrochloride salt (purified via C_{18} reverse-phase chromatography). The NMR spectrum of the latter intermediate clearly shows a major impurity that contains aromatic and olefinic proton resonances. Several trials of the LTA cleavage reaction were conducted wherein we altered reaction temperature and LTA stoichiometry. Nevertheless, we were unable to substantially increase the yield of this process.

Finally, saponification of methyl ester 6 with LiOH (97%) followed by deblocking of 7 with anhydrous HCl in

(1) (a) King, S. W.; Riordan, J. M.; Holt, E. M.; Stammer, C. H. *J. Org. Chem.* **1982**, *47*, 3270. (b) Arenal, I.; Bernabe, M.; Fernandez-Alvarez, E.; Izquierdo, M. L.; Penades, S. *J. Heterocycl. Chem.* **1983**, *20*, 607. (c) Arenal, I.; Bernabe, M.; Fernandez-Alvarez, E.; Penades, S. *Synthesis* **1985**, 773. (d) Izquierdo, M. L.; Arenal, I.; Bernabe, M.; Fernandez-Alvarez, E. *Tetrahedron* **1985**, *41*, 215.

(2) Fernandez, D.; de Frutos, P.; Marco, J. L.; Fernandez-Alvarez, E.; Bernabe, M. *Tetrahedron Lett.* **1989**, *30*, 3101.

(3) Stammer, C. H.; Kimura, H. *J. Org. Chem.* **1983**, *48*, 2440.

(4) Mapelli, C.; Kimura, H.; Stammer, C. H. *Int. J. Pept. Protein Res.* **1986**, 347.

(5) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231 and refs cited therein.

(6) Ellman, J. A.; Mendel, D.; Schultz, P. G. *Science* **1992**, *255*, 197.

(7) Wentland, M. P.; Perni, R. B.; Dorff, P. H.; Rake, J. B. *J. Med. Chem.* **1988**, *31*, 1694.

(8) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796.

(9) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, 165.

(10) Weinges, K.; Brachmann, H.; Stahnecker, P.; Rodewald, H.; Nixdorf, M.; Irngartinger, H. *Liebigs Ann. Chem.* **1985**, 566.

(11) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723.

(12) (a) Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002. (b) Inaba, T.; Kozono, I.; Fujita, M.; Ogura, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2359.

(13) Walborsky, H. M.; Ronman, P. E. *J. Org. Chem.* **1973**, *38*, 4231.

(14) We attempted to isolate and subsequently saponify the amino acid methyl ester derived directly from the acid hydrolysis reaction of the crude imine. However, we were unable to isolate the title compound in this fashion which supports work published by Stammer and co-workers (ref 1). Therefore, it is essential that the nitrogen atom be protected prior to ester saponification.

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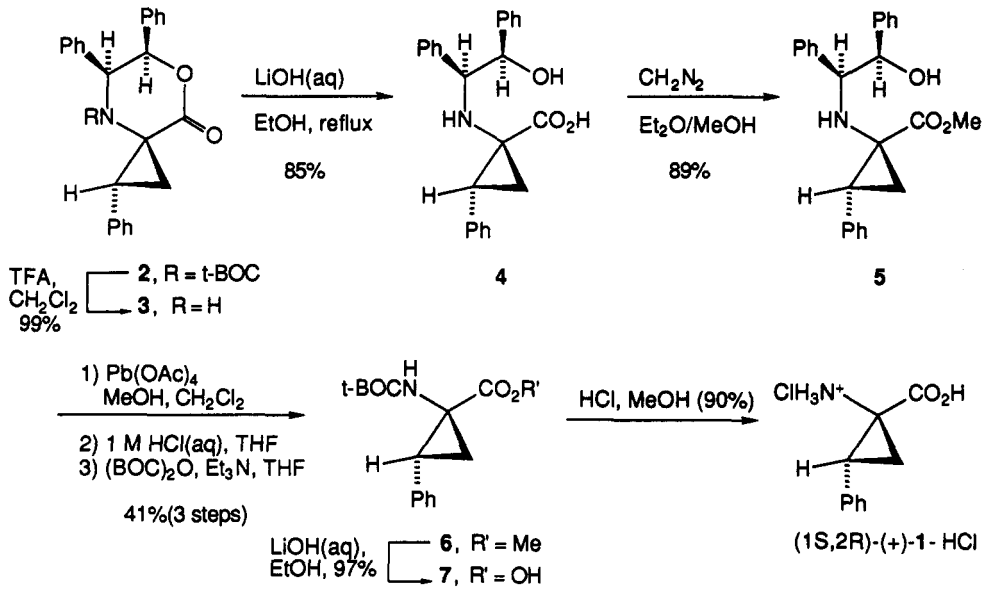
Scheme I



MeOH gave (1*S*,2*R*)-2-phenyl-1-aminocyclopropane-1-carboxylic acid hydrochloride salt (**1·HCl**) in 90% yield ($[\alpha]_D^{25}$ (obsd) = +72.7° (*c* = 1.0, H_2O); $[\alpha]_D^{25}$ (lit.)[3] = +74.4° (*c* = 1.0, H_2O). Subsequent ^{19}F NMR analysis of the Mosher[15] amide of **1** showed that the enantiomeric excess of the final product to be 95%.

In summary, this note describes the first asymmetric synthesis of (*E*)-cyclopropylphenylalanine in high diastereomeric excess.

Experimental Section

^1H NMR spectra were obtained on a Bruker AC 300-MHz spectrometer and chemical shifts are reported in parts per million downfield from the internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 Series FT-IR and are reported as λ_{max} in cm^{-1}. Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter at a wavelength of 589 nm (sodium "D" line) with a 1.0-dm cell with a volume of 1 mL. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at the specified temperature and the concentration (*c*) given in grams per 100 mL in the specified solvent. Elemental analyses are accurate to within ±0.4% of the calculated values. High-resolution mass spectra are accurate to within ±3 millimass units. Column chromatography was performed with Merck silica gel grade 60, 230–400 mesh, 60 Å. Reagents and solvents were dried or purified in the following way. Dichloromethane and triethylamine were each distilled from CaH_2. Methanol and tetrahydrofuran were distilled from Na and sodium benzophenone ketyl, respectively. Lead tetraacetate was recrystallized from glacial acetic acid and stored under argon at 0 °C. All other reagents were used in commercial grade form.

(1*S*,3*S*,5*S*,6*R*)-1,5,6-Triphenyl-7-oxa-4-azaspiro[2.5]octan-8-one (3). To a 0 °C solution containing **2** (398 mg, 0.87 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added TFA (1.35 mL, 17.47 mmol, 20.0 equiv). The reaction was slowly warmed to room temperature and stirred an additional 17 h. The solvent and excess TFA were removed in vacuo and the crude residue was redissolved in CH_2Cl_2 (15 mL) and washed with dilute $NaHCO_3$ (aqueous). The layers were separated, and the aqueous layer was extracted with 2 × 5 mL of CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated to provide 307 mg (99%) of **3** as a light-yellow solid. The crude product can be carried on without further purification: ^1H NMR (300 MHz) ($CDCl_3$, TMS) δ 1.68 (1H, dd, J_{gem} = 9.5 Hz, J_{vic} = 3.9 Hz), 2.35 (1H, dd, J_{gem} = 8.3 Hz, J_{vic} = 2.7 Hz), 2.55 (1H, broad s), 2.80 (1H, apparent t, *J* = 8.9 Hz), 4.86 (1H, d, *J* = 4.1 Hz), 5.81 (1H, d, *J* = 4.1 Hz), 6.81–6.84 (2H, m), 6.90–6.94 (2H, m), 7.12–7.33 (11H, m); IR (KBr) ν 3357, 3085, 3063, 3030, 2965, 2921, 2889, 1959, 1889, 1736, 1605, 1496, 1453, 1316, 1251, 1213, 1142, 1082, 1049 cm^{-1}; $[\alpha]_D^{25}$ = +299.5° (*c* = 1.0, CH_2Cl_2); mp = 165–166 °C. Anal. (recrystallized from EtOH) Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.95; N, 3.94. Found: C, 80.87; H, 5.77; N, 3.94.

(1*S*,2*R*,1′*S*,2′*R*)-1-[*N*-(1′,2′-Diphenyl-2′-hydroxyethyl)amino]-2-phenylcyclopropane-1-carboxylic Acid (4). A mixture containing **3** (340 mg, 0.96 mmol, 1.0 equiv), LiOH·H_2O (52 mg, 1.24 mmol, 1.3 equiv), EtOH (5 mL), and H_2O (5 mL) was heated to reflux for 0.5 h. The reaction was cooled to room temperature and 2 M HCl (aqueous) was added until a thick white precipitate formed. The crude product was collected via Buchner filtration and washed thoroughly with H_2O, providing 302 mg (85%) **4** as a white amorphous solid: ^1H NMR (300 MHz) (DMSO-d_6, TMS) δ 1.33 (1H, dd, J_{gem} = 9.4 Hz, J_{vic} = 4.8 Hz), 1.70 (1H, dd, J_{gem} = 8.0 Hz, J_{vic} = 4.7 Hz), 2.32 (1H, apparent t, *J* = 8.7 Hz), 4.12 (1H, d, *J* = 4.8 Hz), 4.90 (1H, d, *J* = 4.8 Hz), 6.96 (2H, d, *J* = 6.9 Hz), 7.07–7.25 (13H, m); IR (KBr) ν 3424, 3268, 3089, 3062, 3029, 2873, 2780, 1952, 1886, 1630, 1604, 1569, 1498, 1454, 1390, 1353, 1327, 1190, 1099, 1066 cm^{-1}; $[\alpha]_D^{25}$ = +82.4° (*c* = 0.5, 1 M NaOH); mp = 201–202 °C. Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 76.93; H, 6.31; N, 3.61.

(1*S*,2*R*,1′*S*,2′*R*)-Methyl 1-[*N*-(1′,2′-Diphenyl-2′-hydroxyethyl)amino]-2-phenylcyclopropane-1-carboxylate (5). To a 0 °C slurry containing MNNG (440 mg, 3.0 mmol, 6.0 equiv) and Et_2O (6 mL) was added approximately 1 mL of 5 N NaOH. The mixture was stirred for 20 min at which time the ethereal CH_2N_2 solution was separated and added to a room temperature suspension of **4** (186 mg, 0.50 mmol, 1.0 equiv) in MeOH (2 mL). The reaction was allowed to stir overnight in an open flask and the crude ester was concentrated to dryness and purified via flash silica chromatography (10 g silica, 1:5 EtOAc/hexanes) providing 171 mg (89%) of **5** as a white solid: ^1H NMR (300 MHz) ($CDCl_3$, TMS) δ 1.41 (1H, dd, J_{gem} = 9.6 Hz, J_{vic} = 4.5 Hz), 1.98 (1H, dd, J_{gem} = 7.9 Hz, J_{vic} = 2.7 Hz), 2.57 (1H, apparent t, *J* = 8.8 Hz), 2.69 (1H, s), 3.14 (3H, s), 3.60 (1H, d, *J* = 3.9 Hz), 4.28 (1H, d, *J* = 5.0 Hz), 4.97 (1H, t, *J* = 4.5 Hz), 6.99–7.01 (2H, m), 7.07–7.26 (13H, m); IR (KBr) ν 3426, 3339, 3236, 3086, 3063, 3029, 2956, 2918, 1734, 1452, 1319, 1215, 1199, 1154, 1061 cm^{-1}; $[\alpha]_D^{25}$ = +128.4° (*c* = 1.0, CH_2Cl_2); mp = 142–143 °C. Anal. (recrystallized from EtOH) Calcd for $C_{25}H_{25}NO_3$: C, 77.49; H, 6.50; N, 3.61. Found: C, 77.31; H, 6.41; N, 3.65.

(1*S*,2*R*)-Methyl 1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-phenylcyclopropane-1-carboxylate (6). To a −15 °C solution

(15) Mosher, H. S.; Dale, J. A.; Dull, D. L. *J. Org. Chem.* **1969**, *34*, 2543.

containing **5** (62 mg, 0.16 mmol, 1.0 equiv) and a 1:2 mixture of MeOH/CH_2Cl_2 (3 mL) was added $Pb(OAc)_4$ (78 mg, 0.18 mmol, 1.1 equiv). The reaction was complete in 2 min and subsequently quenched with saturated $NaHCO_3$ (5 mL) at −15 °C. A heavy white precipitate formed and was removed via Buchner filtration. The filter cake was washed thoroughly with CH_2Cl_2 (10 mL), and the filtrate layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL), and the organic fractions were combined, dried over Na_2SO_4, filtered, and concentrated. Crude yield of the acid-sensitive imine was 51 mg (>100%, contaminated by benzaldehyde and minor impurities) isolated as a clear oil. This material was directly used for the subsequent transformation without additional purification or handling: ^1H NMR (300 MHz) ($CDCl_3$, TMS) δ 1.82–1.87 (1H, m), 2.41–2.46 (1H, m), 2.94 (1H, apparent t, J = 8.8 Hz), 3.39 (3H, s), 7.19–7.44 (10H, m), 8.48 (1H, s).

To a room temperature solution of the crude imine (45 mg based on theoretical yield, 0.16 mmol, 1.0 equiv) in THF (5 mL) was added 1 M $HCl_{(aq)}$ (5 mL). After stirring for 15 min the reaction was concentrated to dryness and thoroughly dried under high vacuum overnight. To the crude hydrochloride salt in THF (5 mL) at room temperature was added Et_3N (33 μL, 0.24 mmol, 1.5 equiv). Immediately a fine white suspension formed and the slurry was cooled to 0 °C followed by the addition of di-*tert*-butyl dicarbonate (38 mg, 0.18 mmol, 1.1 equiv). The reaction was warmed to room temperature and stirred for 24 h. At this time EtOAc (5 mL) was added to the reaction followed by washing of the solution with H_2O. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification via preparative thin-layer chromatography (96:4 CH_2Cl_2/MeOH) provided 19 mg (41% from **5**) of **6** as a clear viscous oil: ^1H NMR (300 MHz) ($CDCl_3$, TMS) δ 1.49 (9H, s), 1.61 (1H, dd, J_{gem} = 9.6 Hz, J_{vic} = 4.2 Hz), 2.18 (1H, dd, J_{gem} = 8.4 Hz, J_{vic} = 2.9 Hz), 3.35 (3H, s), 5.33 (1H, broad s), 7.18–7.33 (5H, m); IR (NaCl/neat) ν 3358, 3062, 3029, 3004, 2977, 2952, 2933, 1724, 1497, 1367, 1333, 1249, 1214, 1160, 1059 cm^{-1}; $[\alpha]^{25}_D$ = +74.8° (c = 1.10, CH_2Cl_2); HRMS (FAB) calcd for $C_{16}H_{21}NO_4$ ($[M + H]^+$) 292, 1549, obsd ($[M + H]^+$) 292.1561.

(1*S*,2*R*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-phenylcyclopropane-1-carboxylic Acid (7). A mixture of **6** (44 mg, 0.15 mmol, 1.0 equiv), LiOH·H_2O (63 mg, 1.50 mmol, 10.0 equiv), MeOH (4.0 mL), and H_2O (2.0 mL) was refluxed for 2.5 h. The reaction was cooled to room temperature and acidified to pH ≈ 2.5, and the product was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. Evaporation of the solvent provided 40 mg (97%) of **7** as a clear oil: ^1H NMR (300 MHz) ($CDCl_3$, TMS) δ 1.47 (9H, s), 1.57 (1H, broad s), 2.14 (1H, broad s), 2.82 (1H, apparent t, J = 9.1 Hz), 5.33 (1H, broad s, amide), 7.19–7.28 (5H, m); IR (NaCl/neat) ν 3559–2205 (broad), 3313, 3248, 3091, 3063, 3029, 2981, 2933, 2718, 2598, 1706 (broad), 1497, 1453, 1393, 1368, 1251, 1221, 1164, 1063 cm^{-1}; $[\alpha]^{25}_D$ = +86.5° (c = 1.32, CH_2Cl_2); HRMS (FAB) calcd for $C_{15}H_{19}NO_4$ ($[M + H]^+$) 278.1392, obsd ($[M + H]^+$) 278.1389.

(1*S*,2*R*)-(+)-2-Phenyl-1-amino-1-cyclopropane-1-carboxylic Acid (1). A −15 °C solution of anhydrous 1 N HCl in MeOH (6.0 mL, 6.00 mmol, 40 equiv) was added to **7** (40 mg, 0.15 mmol, 1.0 equiv) as a neat oil and the resulting mixture stirred for 4 h at −15 °C and 1 h at room temperature. The reaction was concentrated to dryness and the crude amino acid hydrochloride salt was purified by aqueous elution on a C_{18} reverse phase Sep-pack cartridge, providing 28 mg (90%) of **1**·HCl as a white crystalline solid: ^1H NMR (300 MHz) (D_2O, δ HOD at 4.64) 1.75 (1H, dd, J_{gem} = 10.0 Hz, J_{vic} = 2.7 Hz), 2.01 (1H, apparent t, J = 7.8 Hz), 2.98 (1H, apparent t, J = 9.5 Hz), 7.20 (5H, s); IR (KBr) ν 3665–2000 (broad), 3435, 3004, 1712, 1594, 1498, 1267, 1183 cm^{-1}; $[\alpha]^{25}_D$ = +72.7° (c = 1.0, H_2O); $[\alpha]^{25}_D$ (lit.) = +74.4° (c = 1.0, H_2O).

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