Synthesis of Racemic *cis*- and *trans*-3-Phenylazetidine-2-Carboxylic Acids as Conformationally Restricted Analogs of Phenylalanine

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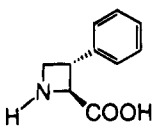
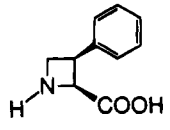
In this report we present the synthesis of two novel, conformationally restricted phenylalanine analogs **1** and **2**. These azetidine-based analogs have structural features that may prove useful when incorporated into peptides as phenylalanine mimics.[1a] For example they should have improved metabolic stability since tertiary amide bonds are resistant to proteolysis.[1b,c] Also there is the possibility of enhanced or altered selectivity as a consequence of the reduced conformational space available to the side chain phenyl group.[2,3] The conformationally restricted analogs **1** or **2** may also be useful in the design of novel peptide-based enzyme inhibitors.[1d]



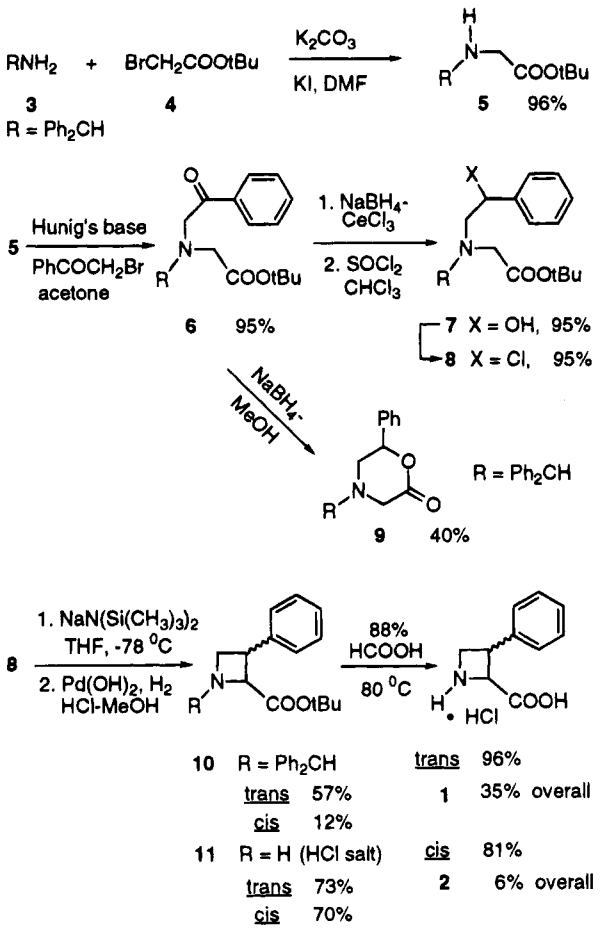
1



2

To explore the potential of *cis*- and *trans*-3-phenylazetidine-2-carboxylic acids in drug design, we needed a versatile method for their preparation. However, only a very limited number of effective methods are available for the preparation of azetidine-2-carboxylic acids in general and 3-phenylazetidine-2-carboxylic acid itself is unknown. The synthesis of the parent azetidine-2-carboxylic acid was reported by Rodebaugh and Cromwell[4] from γ-butyrolactone and further modified by Wasserman and co-workers.[5] However, in their reports the methods were applied only to the unsubstituted γ-butyrolactone. It was not practical to apply these methods to the synthesis of 3-phenylazetidine-2-carboxylic acid since β-phenyl-γ-butyrolactone was not readily available and the bromination conditions employed in their preparation were quite drastic and might produce over-brominated products. In view of these potential problems, we developed an easy, efficient method for the preparation of this ring system. The synthesis is outlined in Scheme 1. Alkylation of benzhydrylamine (**3**) (R = Ph_2CH) with *tert*-butyl bromoacetate (**4**) gave a 96% yield of **5** which was then alkylated with 2-bromoacetophenone to provide the ketone **6** in 95% yield. Reduction of **6** with $NaBH_4$ in methanol gave a 50% yield of alcohol **7** and a 40% yield of the lactone byproduct **9**. The yield of **7** was improved by reduction of **6** with the less basic $NaBH_4$/$CeCl_3$ complex[6] which prevented intramolecular cyclization to the lactone **9** and gave the desired alcohol **7** in 95% yield. Reaction of **7** with thionyl chloride furnished the chloride **8** in 95% yield. Formation of the anion of **8** with sodium bis(trimethylsilyl)amide in THF at −78 °C and subsequent cyclization at −40 °C formed a racemic mixture of *cis*- and *trans*-**10**. Separation by short-path chromatography using TLC grade silica gel gave 57% *trans*-**10** and 12% *cis*-**10** respectively, from **8**.

Scheme 1



The structural assignment of *cis*-**10** was based on the chemical shift of the C-2 proton (δ 4.18, d, J = 7.5 Hz) and the NOE observed between the C-2 and C-3 protons. No such NOE was observed for *trans*-**10**.

Sequential removal of the protecting groups, first with Pearlman's catalyst, gave the amines, *trans*-**11** (73%) and *cis*-**11** (70%) and then with hot formic acid furnished the free amino acids **1** (96%) and **2** (81%) as their hydrochloride salts. The overall yield from *tert*-butyl bromoacetate (**4**) for the *trans* isomer **1** was 35% and for the *cis* isomer **2** was 6%.

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In this seven-step sequence, only one chromatographic purification was needed and most of the individual steps were simple, high-yielding reactions which could be performed on a large scale. Our useful method for the preparation of *cis*- and *trans*-3-phenylazetidine-2-carboxylic acid should also be applicable for the synthesis of similar conformationally restricted analogs of other amino acids, such as tryptophan, tyrosine, methionine, lysine, leucine, and histidine.

Experimental Section

General Procedures. All solvents except for chromatographic use were Aldrich Sure-Seal anhydrous quality. Thin-layer chromatography was performed on Analtech Uniplate silica gel GF plates (5 × 20 cm, 250 μm). Short-path column chromatography was performed on Kieselgel 60 (EM Reagents, 230–400 mesh). Melting points are uncorrected. FAB mass spectra were recorded on a Varian MAT-312. CI mass spectra were recorded on an Extrel ELQ 400. Proton NMR spectra were obtained on a Gemini-XL-300 instrument. All shifts are reported in ppm relative to TMS. Elemental analyses were performed on a 440 CHN-O/S elemental analyzer except for the chlorine analyses, performed by Microlit Laboratories, West Caldwell, NJ.

***N*-(Diphenylmethyl)glycine, 1,1-Dimethylethyl Ester (5).** Aminodiphenylmethane (**3**) (110 g, 545.7 mmol), KI (99.65 g, 600.2 mmol), and K_2CO_3 (82.96 g, 600.2 mmol) were stirred together in DMF (2 L) under a N_2 atmosphere. To the amber-colored suspension was added dropwise *tert*-butyl bromoacetate (**4**) (89.9 mL, 545.7 mmol). A white precipitate formed almost immediately. After 2 h, the solids were removed by filtration and were washed with CH_2Cl_2. The solvent was removed *in vacuo*. The residue was dissolved in Et_2O which was washed with water (300 mL × 3), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to afford **5** (164 g, 96%) as an orange solid which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$)δ 1.5 (s, 9H), 1.9–2.3 (br, 1H), 3.3 (s, 2H), 4.9 (s, 1H), 7.2–7.5 (m, 10H); CIMS *m/z* 298 (M + 1), 240, 195, 182.

***N*-(Diphenylmethyl)-*N*-(2-oxo-2-phenylethyl)glycine, 1,1-Dimethylethyl Ester (6).** *N*-(Diphenylmethyl)glycine, 1,1-dimethylethyl ester (**5**) (164 g, 545.7 mmol) was dissolved in acetone (730 mL) and chilled in a dry ice/acetone bath. *N,N*-diisopropylethylamine (Hunig's Base) (97 mL, 545.7 mmol) was added first and followed by the dropwise addition of 2-bromoacetophenone (110.8 g, 545.7 mmol) in acetone (365 mL) over 30 min. The reaction was stirred under N_2 and allowed to warm to room temperature overnight. The reaction was then heated to reflux. After 2 h, the reaction was cooled and an additional 5% of Hunig's Base was added, followed by the dropwise addition of 2-bromoacetophenone (5.5 g, 27.8 mmol) in acetone (60 mL), over 10 min at room temperature. The solution was refluxed overnight. After cooling to room temperature, Et_2O was added and the mixture was filtered, the solid was washed with Et_2O, and the combined organic solution was evaporated. The residue was dissolved in Et_2O, washed with brine (300 mL × 3), dried ($MgSO_4$), filtered, and evaporated *in vacuo* to afford **6** (416 g, 95%) as a yellowish solid which was used without further purification. A small amount was crystallized from hexane to afford an off-white solid that was used for characterization: ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H), 3.56 (s, 2H), 4.35 (s, 2H), 5.58 (s, 1H), 7.2 (m, 15H); CIMS *m/z* 416 (M + 1), 360, 310, 296. Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.04; N, 3.37. Found: C, 78.43; H, 7.18; N, 3.30.

***N*-(Diphenylmethyl)-*N*-(2-hydroxy-2-phenylethyl)glycine, 1,1-Dimethylethyl Ester (7).** Crude *N*-(diphenylmethyl)-*N*-(2-oxo-2-phenylethyl)glycine, 1,1-dimethylethyl ester (**6**) (50 g, 415.5 mmol) was dissolved in anhydrous MeOH/THF (2 L, 1:1) and cooled to −23 °C, and cerium(III) chloride heptahydrate (29.14 g, 78.21 mmol) was added. The mixture was stirred until homogeneous and then $NaBH_4$ (11.83 g, 312.86 mmol) was added slowly via a solid addition funnel. Gas was evolved immediately (caution). The reaction was followed by TLC (hexane/CH_2Cl_2/EtOAc, 5:4:1) and was complete in 10 min. The reaction was poured into brine and extracted with CH_2Cl_2 (300 mL × 3), dried ($MgSO_4$), filtered, and evaporated to afford **7** (418 g, 95%) as a dark amber oil. The product was used without purification: ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H), 2.72 (dd, 1H, J = 10.5, 13.5 Hz), 2.92 (dd, 1H, J = 3, 13.5 Hz), 3.4 (s, 2H), 4.64 (dd, 1H, J = 3, 10.5 Hz), 4.8 (s, 1H), 5.2 (s, 1H), 7.2–7.5 (m, 15H); CIMS *m/z* 418 (M + 1), 360, 310.

***N*-(Diphenylmethyl)-*N*-(2-chloro-2-phenylethyl)glycine, 1,1-Dimethylethyl Ester (8).** *N*-(Diphenylmethyl)-*N*-(2-hydroxy-2-phenylethyl)glycine, 1,1-dimethylethyl ester (**7**) (50.24 g, 120.33 mmol) was dissolved in $CHCl_3$ (270 mL) and chilled in an ice/water bath. Thionyl chloride (50.24 mL, 258.9 mmol) was added dropwise. After 0.5 h, solvents were removed *in vacuo* to afford **8** (52 g, 95%) as a beige solid which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H), 3.6–3.78 (m, 2H), 4.15–4.25 (m, 2H), 6.0 (s, 1H), 6.4 (t, 1H), 7.3–8.2 (m, 15H).

1-(Diphenylmethyl)-3-phenyl-2-azetidine Carboxylic Acid, 1,1-Dimethylethyl Ester, *trans*-(10) and *cis*-(10). *N*-(Diphenylmethyl)-*N*-(2-chloro-2-phenylethyl)glycine, 1,1-dimethylethyl ester (**8**) (52.46 g, 120.33 mmol) was dissolved in anhydrous THF (850 mL) and chilled in a dry ice/acetone bath. Sodium bis(trimethylsilyl)amide (264.7 mL of 1 mmol/mL THF solution) was added dropwise over 45 min. After completion, the reaction was neutralized with AcOH. The solids were filtered off and washed with EtOAc, and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (300 mL) and washed with brine (150 mL × 3). It was dried ($MgSO_4$), filtered, and evaporated to give a dark semisolid. The 300 MHz ($CDCl_3$) NMR showed the desired product in a ratio of approximately 5:1. The *cis* and *trans* isomers were separated by short-path column chromatography (Kieselgel 60, 1 g of compound/11 g of silica gel, hexane/CH_2Cl_2/Et_2OAc 50:49:0.5) and crystallized from hexane: yield 57% *trans*-**10** and 12% *cis*-**10**. Racemic *trans*-(2*S**,3*S**)-**10:** mp 93–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 3.1–3.2 (m, 1H), 3.7–3.9 (m, 3H), 4.5 (s, 1H), 7.15–7.6 (m, 15H); CIMS *m/z* 400 (M + 1), 386, 344, 298. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.00; H, 7.20; N, 3.50. Racemic *cis*-(2*S**,3*R**)-**10**: mp 126–128 °C; ^{1}H NMR ($CDCl_3$) δ 0.85 (s, 9H), 3.28 (t, 1H, J = 7.5, Hz), 3.7 (dd, 1H, J = 7.5, 4.5), 3.87 (sextet, 1H, J = 7.5, 4.5 Hz), 4.18 (d, 1H, J = 7.5), 4.73 (s, 1H), 7.1–7.6 (m, 15H); FAB (NBA–DMSO) MS *m/z* 400 (M + 1), 398, 344, 298. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32;N, 3.51. Found: C, 81.23; H, 7.09; N, 3.20.

3-Phenyl-2-azetidinecarboxylic Acid, 1,1-Dimethylethyl Ester, Hydrochloride, *trans*-(11) and *cis*-(11). 1-(Diphenylmethyl)-3-phenyl-2-azetidinecarboxylic acid, 1,1-dimethylethyl ester *trans*-(**10**) (9.57 g, 23.96 mmol) was dissolved in MeOH (135 mL, anhydrous) and 20% anhydrous methanolic HCl (5.47 mmol/mL, 4.4 mL) with the aid of sonication. Palladium hydroxide on carbon (10% by weight, 0.957 g, 1.36 mmol) was added and the mixture was hydrogenated at 60 psi. After 4 h, 5% more of the catalyst was added to bring the reaction to completion. The catalyst was removed by filtration and solvents evaporated *in vacuo* to afford 3.4 g (73%) of *trans*-**11** as a hydrochloride salt which was triturated with hexane to give a white solid. A similar procedure was applied to obtain *cis*-**11** as a hydrochloride salt from *cis*-**10** in 70% yield. Racemic *trans*-(2*S**,3*S**): mp 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 1.5 (s, 9H), 4.2–4.32 (m, 2H), 4.35–4.45 (m, 1H), 5.01–5.03 (m, 1H), 7.3–7.5 (m, 5H); CIMS 234 (M + 1), 206, 178, 148. Anal. Calcd for $C_{14}H_{19}NO_2$·HCl: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.65; H, 7.47; N, 5.18; Cl, 12.75. Racemic *cis*-(2*S**,3*R**): mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 1.1 (s, 9H), 4.4–4.5 (m, 2H), 4.5–4.6 (m, 1H), 5.25–5.35 (m, 1H), 7.3–7.4 (m, 5H); CI MS 234 (M + 1), 218, 206, 178. Anal. Calcd for $C_{14}H_{19}NO_2$·HCl: C, 62.33; H, 7.47; N, 5.19; Cl, 13.14. Found: C, 62.43; H, 7.44; N, 5.14; Cl, 13.10.

3-Phenyl-2-azetidinecarboxylic Acid Hydrochloride (1 and 2). 3-Phenyl-2-azetidinecarboxylic acid, 1,1-dimethylethyl ester hydrochloride (*trans*-**11**) (3.5 g, 12.97 mmol) was dissolved in 88% formic acid (35 mL) and heated for 4 h at 80 °C. After removal of the solvents *in vacuo* the residue was triturated with CH_2Cl_2 and filtered to afford **1** as a white solid in 96% yield. The overall yield of **1** was 35% from **4**. A similar procedure was applied to obtain compound **2** from compound *cis*-**11** with an 81% yield. The overall yield of **2** was 6% from **4**. Racemic *trans*-(2*S**,3*S**)-**1:** mp 193–194 °C; ^{1}H NMR (D_2O) δ 4.25–4.40 (m,

3H), 5.15 (d, 1H, J = 8.3), 7.4–7.5 (m, 5H); CI MS 178 (M + 1), 132, 104. Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 56.60; H, 5.54; N, 6.43; Cl, 16.38. Racemic *cis*-(2*S**,3*R**)-**2**: mp 224–226 °C; ^{1}H NMR (300 MHz, D_2O) δ 4.38–4.56 (m, 3H), 5.2–5.3 (m, 1H), 7.4–7.5 (m, 5H, Ph); FAB MS 178 (M + 1), 133, 132. Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 56.34; H, 5.67; N, 6.60; Cl, 14.99.

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