THE SYNTHESIS OF BICYCLIC PIPERAZINE-2-CARBOXYLIC ACIDS FROM L-PROLINE

Stephen Hanessian* and Raman Sharma

Department of Chemistry, Université de Montréal, C.P. 6128, Succ. Centre-ville,
Montréal, QC, H3C 3J7, Canada

Abstract - The sterically controlled synthesis of two diastereomeric bicyclic
piperazine-2-carboxylic acids from L-proline is described.

The piperazine ring figures prominently in a large number of biologically active molecules, particularly with regard to effects on the cardiovascular and central nervous systems. Piperazine itself has anthelmintic properties. Perhaps one of the more noteworthy occurrences of a piperazine ring, as the 2-carboxylic acid, can be found in the structure of the HIV protease inhibitor, Indinavir. With the great advances in receptor mapping and discovery of subtypes, the number of bioactive piperazines with substituents has increased substantially in recent years.

Bicyclic piperazines have been used to study catalytic asymmetric reactions and as building blocks in the synthesis of analogs of HIV protease inhibitors. The closely related diketopiperazines, which are often precursors to the corresponding piperazines, are also components of natural products.

We report herein the synthesis of bicyclic piperazine-2-carboxylic acids in enantiopure form starting with L-proline as an amino acid chiron (Scheme 1). Thus, the readily available N-Cbz L-proline (1) was transformed into the corresponding α-diazoketone (2), and the latter converted to the corresponding methyl ester (3), essentially according to a published method. Formation of the enolate with NaHMDS and quenching with trisyl azide afforded the enantiopure α-azido ester (4) in excellent yield. It was important to conduct the reaction at -100 °C, since the enolate undergoes a ring opening by a β-elimination and reclosure to a partially racemized precursor (3). Reduction of the azido group with triphenylphosphine, followed by acylation with chloroacetic anhydride afforded the N-chloroacetyl derivative (5). The formation of the desired lactam was envisaged to occur through a cyclization of

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the pyrrolidine intermediate (6). In the event, hydrogenolysis of the N-Cbz group in 5 and cyclization afforded the bicyclic lactam (7) in good overall yield. Its structure and stereochemistry were corroborated by a single crystal X-Ray analysis. Since it was not possible to reduce the lactam directly to the desired piperazine in the presence of the ester, we chose to adopt an indirect route. It was possible to convert the lactam (7) into the thiolactam (8) with Lawesson’s reagent,\textsuperscript{11} albeit in modest yield. Desulfurization with Raney nickel in ethanol afforded the corresponding bicyclic piperazine derivative (9). In order to avoid racemization, the ester group was cleaved with porcine liver esterase\textsuperscript{12} to afford the desired amino acid (10).

Having ready access to intermediate (2), it was possible to hydroxylate the corresponding sodium enolate with the Davis oxaziridine reagent\textsuperscript{13} in a stereoselective manner, to give the α-hydroxy ester (11) (Scheme 2). Treatment with diphenylphosphoryl azide afforded the corresponding α-azido derivative (12) with inversion of configuration. The transformation of 12 to the lactam (14) followed the same course as with the diastereomeric series shown in Scheme 1.

In addition to their utility as constrained amino acids,\textsuperscript{14} and applications in the synthesis of peptidomimetics,\textsuperscript{15} the bicyclic piperazines and lactams described in this paper could also be of interest as catalysts for asymmetric reactions.\textsuperscript{7,16–18}
EXPERIMENTAL

Melting points are uncorrected. $^1$H NMR spectra were recorded at 300 and 400 MHz, and $^{13}$C spectra at 75 MHz. Optical rotations were recorded at 25 °C.

1-Carbobenzyloxy-2S-pyrrolidinyl diazomethyl ketone (2)

To the stirred suspension of 1-carbobenzyloxy-L-proline (1) (6 g, 24 mmol) in 50 mL of dry ether at -15 °C was added Et$_3$N (3.36 mL, 24 mmol) dropwise. After 5 min isobutyl chloroformate (3.12 mL, 24.1 mmol) was added slowly, and 25 min later, diazomethane (∼75 mmol) in 150 mL of ether was cannulated at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, excess diazomethane was destroyed with glacial acetic acid, 50 mL of water was added and the organic layer was washed with 80 mL of saturated NaHCO$_3$ solution, water (80 mL X 3), dried over MgSO$_4$ and concentrated. The product (2) was separated from the small ester by flash chromatography using 40% ethyl acetate in hexane, (yield 5.89 g, 89%) as a pale yellow oil; Rf = 0.42 (40% ethyl acetate in hexane); [α]$_D$ = -131.8° (c 1.1, CHCl$_3$); IR (CHCl$_3$) 2130, 1710, 1650; $^1$H NMR 1.75–2.25 (m, 4H), 3.40–3.60 (m, 2H), 4.30 (m, 1H), 5.00–5.20 (m, 2H), 5.25 and 5.46 (s, CHN$_2$ rotamers), 7.26–7.33 (m, 5H); $^{13}$C NMR 23.4(24.2), 29.6(31.1), 46.8(47.2), 52.6(53.2), 63.9, 67.0, 127.8–136.4 (Ar-C), 154.4(155.1), 194.3(195.1); HRMS calcd for C$_9$H$_{10}$N$_2$O$_3$(MH$^+$) 274.1192, found 274.1182.

Methyl 1-carbobenzyloxy-2S-pyrrolidinylacetate (3)

To a suspension of 2 (5 g, 18.4 mmol) and silver benzoate (27 mg) in 21.5 mL of methanol was added 242 μL (1.70 mmole) of Et$_3$N dropwise and the suspension was stirred for 40 min in the dark. Activated carbon (100 mg) was added and reaction mixture was heated near to boiling for 10 min., the solids were filtered through Celite and the filtrate was concentrated. The residue was dissolved in ether (100 mL),
washed with 20 mL of saturated NaHCO₃, H₂O (50 mL X 3), brine (50 mL), dried over MgSO₄ and concentrated to give a pale yellow oil that was purified by flash chromatography using 50% ethyl acetate in hexane; yield 4.74 g (92%) as a colorless oil; RF = 0.56 (40% ethyl acetate in hexane); [α]₀ = -31.6⁰ (c 1.33, CHCl₃); IR (CHCl₃) 2980, 2900, 1740, 1700; ¹H NMR 1.70–2.20 (m, 4H), 2.30–2.45 (m, 1H), 2.80 and 3.00 (m, 1H rotamers), 3.40–3.50 (m, 2H), 3.66 (s, OCH₃), 4.25 (m, 1H), 5.15 (s, 2H), 7.20–7.40 (m, 5H); ¹³C NMR 22.7(23.5), 30.5(31.3), 38.1(39.0), 46.4(46.7), 51.5, 53.9(54.5), 66.5(66.7), 154.6, 171.6(171.8); HRMS calcd for C₁₃H₂₀O₄N (MH⁺) 278.1392, found 278.1387.

Methyl 1-carbonyloxy-2S-pyrroldinyl-αS-azidoacetate (4)
To a stirred solution of 3 (4.59 g, 16.6 mmol) in 60 mL of dry THF was added 1M NaHMDS (24.9 mL, 24.9 mmol) at -100 °C. After 1 h, a precooled solution of trisyl azide (10.26 g, 33 mmol) in 116 mL THF was cannulated at -100 °C. The reaction mixture was stirred for 5 min and quenched by rapid addition of 4.61 mL (80.5 mmol) of glacial acetic acid. After stirring the white slurry at ambient temperature for 1.5 h it was diluted with 250 mL of CH₂Cl₂, washed successively with dilute brine, 10% NaHCO₃, dried over Na₂SO₄, concentrated, and chromatographed using hexane/ethyl acetate/CH₂Cl₂ (7:2:1) to give 80% of 4 and 4% of a 1:1 mixture of diastereoisomers. Major diastereoisomer (4), colorless oil; RF = 0.33 (hexane/ethyl acetate/CH₂Cl₂, 7:2:1); [α]₀ = -101.4⁰ (c 1.03, CHCl₃); FTIR (CHCl₃) 2114, 1745, 1694; ¹H NMR 1.70–2.10 (m, 4H), 3.30–3.70 (m, 2H), 3.80 (s, OCH₃), 4.20–4.40 (m, 1H), 4.63 and 5.00 (br signal, 1H rotamers) 5.20 (s, 2H), 7.25–7.45 (m, 5H); ¹³C NMR (23.4)24.0, 26.3(27.3), 47.1(47.5), 52.6, (58.0)58.7, 62.8(64.3), 66.9, 127.8–136.6 (Ar-C), (154.2)154.8, (168.8)169.1; HRMS calcd for C₁₅H₁₉N₂O₄(MH⁺) 319.1406, found 319.1424.

Methyl 1-carbonyloxy-2S-pyrroldinyl-αS-(chloroacetylamino)acetate (5)
Azido ester (4) (3.94 g, 12.6 mmol) in 110 mL of THF was reacted with triphenylphosphine (4.19 g, 16 mmol) for 24 h, subsequently 8 mL of H₂O was added and the mixture was stirred vigorously for 36 h. Volatiles were removed under vacuum and crude product was purified by chromatography with 2% methanol in ethyl acetate to give the α-amino derivative as a colorless oil (3.56 g, 98%); RF = 0.33 (2% MeOH in ethyl acetate); [α]₀ = -19.6⁰ (c 1.04, CHCl₃); IR (CHCl₃) 3420, 3360, 1745, 1700; ¹H NMR 1.41 (s, 2H rotamers), 1.60–2.00 (m, 4H), 3.25–3.40 (m, 1H), 3.61 (s, OCH₃), 3.95 and 4.20 (m, 2H), 5.00–5.15 (br signal, OCH₂Ph), 7.20–7.40 (m, 5H); ¹³C NMR (23.6)24.1, 25.9(26.6), 47.3(47.7), 51.8, 54.8(55.8), (59.7)60.3, 66.5(66.7), 127.6, 127.8, 128.3, (136.6)136.8, 154.8, (173.7)174.1; HRMS calcd for C₁₃H₁₉N₂O₄(MH⁺) 293.1502, found 293.1488.

The amino ester (3.56 g, 12.38 mmol) in 90 mL of CH₂Cl₂ was treated with chloroacetic anhydride (2.51 g, 14.7 mmol). After 2 h, solvent was removed and the residue was purified by chromatography using 40% ethyl acetate in hexane to give 5 (3.46 g, 75%) as a colorless oil; RF = 0.27 (50% ethyl acetate in hexane); [α]₀ = -30.7⁰ (c 1.01, CHCl₃); IR (CHCl₃) 3420, 3310, 1745, 1690; ¹H NMR 1.70–2.25 (m, 4H), 3.25–3.40 (m, 1H), 3.50–3.65 (m, 1H), 3.66 and 3.69 (s, OCH₃ rotamers), 3.96–4.06 (m, CH₂Cl rotamers), 4.17–4.30 (m, 1H), 4.77 and 5.10 (m, αH rotamers), 5.10–5.30 (m, 2H), 7.10–7.50 (m, 5H),
8.45–8.60 (m, NHCO); $^{13}$C NMR (23.1) 23.8, (28.4) 28.9, 42.3, 47.2, 52.4 (52.5), (54.6) 56.0, (58.9) 59.8, 67.2 (67.3), 127.8, 127.9, 128.1, 128.4, 136.4, (154.5) 156.2, (165.9) 166.4, 169.9 (170.0); HRMS calcd for C$_7$H$_{12}$N$_2$O$_3$Cl (MH$^+$) 369.1272, found 369.1234.

**Methyl 2S-pyrrolidinyl-$\alpha$S-(chloroacetylamino)acetate formate salt (6)**

To a stirred solution of (2.02 g, 5.48 mmol) in 77 mL of methanol and 9.15 mL of 88% HCO$_2$H was added 5% Pd-C (612 mg). The progress of reaction was carefully monitored by passage of evolved CO$_2$ into saturated Ba(OH)$_2$ solution, whereupon decarboxynyloxylation was complete in 20 - 25 min. The catalyst was filtered through Celite and washed with methanol (10 mL X 2). The combined organic extracts were concentrated to yield 6 as a pure product by NMR and was used as such without any purification and storage; colorless oil; [\(\alpha\)]$_D$ = -21.8° (c 1.16, CHCl$_3$); $^1$H NMR (CD$_2$OD) 1.70–2.25 (m, 4H), 3.30–3.40 (m, 2H), 3.78 (s, OCH$_3$), 3.95–4.10 (m, 1H), 4.13 (s, 2H), 4.76 (dd, 1H), 8.45 (br hump, 1H); $^{13}$C NMR (CD$_2$OD) 26.0, 30.5, 44.7, 48.9, 55.4, 56.0, 62.4, 170.0, 171.6, 172.6.

**Methyl 3-oxooctahydro-9S-pyrrolo[1,2-a]pyrazine-1S-carboxylate (7)**

To a stirred solution of 6 (1.54 g, 5.48 mmol) in 80 mL of CH$_2$Cl$_2$ were added Et$_3$N (3.8 mL, 27.4 mmol), a catalytic amount of DMAP, and Bu$_4$NI (404 mg, 1.1 mmol) and the mixture was refluxed for 18 h. Volatiles were removed and crude product was purified by chromatography using 8% methanol in ethyl acetate to give 761 mg (70%) of 7 as a white solid, mp 79-81 °C; RF = 0.26 (8% MeOH in ethyl acetate); [\(\alpha\)]$_D$ = +120.8° (c 1.01, CHCl$_3$); FTIR (CHCl$_3$) 3406, 1746, 1679; $^1$H NMR 1.70–2.00 (m, 4H), 2.25–2.40 (m, 1H), 2.90–3.05 (m, 1H), 3.05 (d, 1H), 3.04–3.10 (m, 1H), 3.64 (d, 1H), 3.78 (s, OCH$_3$), 4.17 (t, 1H), 6.54 (s, 1H); $^{13}$C NMR 22.2, 25.6, 52.3, 54.3, 56.3, 56.33, 60.4, 170.2, 170.5; HRMS calcd for C$_9$H$_{14}$N$_2$O$_3$ (MH$^+$) 199.1083, found 199.1091; Anal. Calcd for C$_9$H$_{14}$N$_2$O$_3$: C, 54.55; H, 7.07; N, 14.14. Found, C, 54.50; H, 7.22; N, 14.02. An X-Ray structure of the hydrate was obtained.

**Methyl 3-thiooctahydro-9S-pyrrolo[1,2-a]pyrazine-1S-carboxylate (8)**

To a solution of 7 (328 mg, 1.66 mmol) in 10 mL of dry dioxane was added Lawesson's reagent (0.369 g, 0.912 mmol), and the mixture was heated to 95 °C for 1.5 h. Removal of solvent gave a pale yellow crude product which was flash chromatographed using 5% methanol in ethyl acetate to give 142 mg (40%) of 8 as a pale yellow viscous oil; RF = 0.34 (85% MeOH in ethyl acetate); [\(\alpha\)]$_D$ = -180.5° (c 1.12, CHCl$_3$); FTIR (CHCl$_3$) 3357, 1741, 1513; $^1$H NMR 1.70–2.10 (m, 3H), 2.15 (m, 1H), 2.74 (m, 1H), 3.71 (s, OCH$_3$), 3.70–3.95 (m, 3H), 3.87 (d, 1H), 4.05 (d, 1H), 4.13 (d, 1H); $^{13}$C NMR 21.3, 28.6, 52.1, 53.4, 55.8, 60.0, 170.6, 194.1; HRMS calcd for C$_{9}$H$_{14}$N$_2$O$_3$ (MH$^+$) 215.0854, found 215.0859.

**Methyl octahydro-9S-pyrrolo[1,2-a]pyrazine-1S-carboxylate (9)**

Raney nickel (∼ 1 g) prewashed with isopropyl alcohol, was suspended in 50 mL of isopropyl alcohol in a Parr apparatus and stirred under the H$_2$ pressure (32 psi) for 1 h. Subsequently the thiolactam (8) (70.8 mg, 0.33 mmol) in 10 mL of isopropyl alcohol was added and the mixture was stirred for 30 min at 32 psi. Filtration over Celite, washing the catalyst with isopropyl alcohol (10mL X 2) and usual processing
gave 9 as a pale yellow oil; yield 48.7 mg (80%); Rf = 0.34 (50% CHCl₃ in MeOH); [α]₀ = +8.08° (c 0.73, CH₂OH); FTIR (CHCl₃) 3346 (br and weak), 1737, 1672; ¹H NMR (CD₂OD) 1.63–1.91 (m, 4H), 2.22–2.32 (m, 1H), 2.34–2.46 (m, 1H), 2.61–2.80 (m, 3H), 2.89–3.00 (m, 1H), 3.17–3.28 (m, 1H), 3.70 (s, OCH₃), 3.80 (s, 1H); ¹³C NMR 23.1, 26.3, 44.9, 53.0, 53.8, 57.2, 60.1, 65.0, 174.9; HRMS calcd for C₁₀H₁₅N₂O₂ (MH⁺) 185.1290, found 185.1294.

Octahydro-9S-pyrrolo[1,2-a]pyrazine-1S-carboxylic acid (10)
A solution containing 9 (40 mg, 0.21 mmole) in 4 mL phosphate buffer (pH 7.2), was added porcine liver esterase (10 mg). After stirring for 4 d, the solution was acidified to pH 4 at 0°C, lyophylized and the residue was passed through a Dowex-50 (H⁺) column. Elution with 1% ammonium hydroxide, and evaporation of the desired fractions gave the title compound as an amorphous powder, (23 mg, 62%), mp 170 °C (decomp), Rf = 0.17 (CHCl₃/MeOH/30% aq. NH₄OH, 4:4:1) [α]₀ = -41.6° (c 0.51, H₂O); FTIR (KBr pellet) 3436, 1618; ¹H NMR (D₂O) 1.90–2.30 (m, 4H), 2.90–3.10 (m, 2H), 3.10–3.21 (m, 1H), 3.21–3.46 (m, 3H), 3.65–3.83 (m, 1H), 3.87 (d, 1H); ¹³C NMR 19.7, 21.2, 41.5, 46.8, 54.7, 57.9, 61.9, 175.0; HRMS calcd for C₁₀H₁₅N₂O₂ (MH⁺) 171.1134, found 171.1131.

Methyl 1-carbobenzyloxy-2S-pyrrolidinyl-αS-hydroxyacetate (11)
To the stirred solution of methyl ester (3) (1.7 g, 6.14 mmol) and Davis’s reagent (2.4 g, 9.2 mmol) in 30 mL of THF was added a precooled solution of NaHMDS (12.25 mL, 12.25 mmol) in 20 mL of THF at −78 °C by cannula. After stirring for 1 h, a solution of camphorsulfonic acid (6.14 g, 26.4 mmol) in 26 mL of THF was added at −78 °C. The mixture was diluted with 150 mL of ethyl acetate, washed with 10% HCl (50 mL X 2), 5% NaHCO₃ (50 mL X 2), brine and dried over MgSO₄, concentrated, then chromatographed using 40% ethyl acetate in hexane to give 1.33 g (74%) of 11 as a colorless oil; Rf = 0.15 (40% ethyl acetate in hexane); [α]₀ = -35.1° (c 1.1, CHCl₃); IR (CHCl₃) 3550, 3360 (br), 1740, 1700; ¹H NMR (CD₂OD) 1.70–2.10 (m, 4H), 3.32–3.57 (m, 2H), 3.68 (s, OCH₃), 4.07–4.23 (m, 1H), 4.56 and 4.65 (d, 1H rotamers), 5.10 and 5.14 (s, 1H rotamers), 7.20–7.45 (m, 5H); ¹³C NMR (24.6) 25.2, 26.8(27.4), 48.3(48.6), 52.6, (61.0) 61.6, 68.0(68.2), 71.6(72.5), 127.1, 128.9, 129.1, 129.6, 130.0, 133.2, 138.0, 138.2, 145.1, (156.5)156.7, (174.5)174.7; HRMS calcd for C₁₃H₁₅NO₃ (MH⁺) 294.1342, found 294.1332.

Methyl 1-carbobenzyloxy-2S-pyrrolidinyl-αR-azidoacetate (12)
A solution of triphenylphosphine (2.13 g, 8.12 mmol) and diethyl azidocarboxylate (1.28 mL, 8.12 mL) in 44 mL of THF was stirred for 30 min at 0°C, then treated with 12 (1.19 g, 4.06 mmol) in 44 mL of THF by cannula. After 10 min, diphenylphosphoryl azide (1.75 mL, 8.12 mmol) was added over a period of 10 min, and the reaction mixture was stirred for 1 h at 0°C, then overnight at rt. Usual workup gave a crude oil which was chromatographed using 30% ethyl acetate in hexane to give 0.756 g (58%) of 12 as a colorless oil; Rf = 0.29 (hexane/ethyl acetate/CH₂Cl₂ 7:2:1); [α]₀ = -54.6° (c, 1.0, CHCl₃); FTIR (CHCl₃) 2114, 1744, 1697; ¹H NMR 1.75–2.25 (m, 4H), 3.30–3.50 (m, 1H), 3.50–3.70 (m, 1H), 3.60 and 3.80 (s, OCH₃ rotamers), 4.03 and 4.12 (br s, 1H rotamers), 4.20–4.45 (m, 1H), 4.90–5.35 (m, 2H), 7.20–7.45 (m,
5H); $^{13}$C NMR (23.0)23.9, 28.8(29.6), 47.1(47.4), (52.4)52.7, (58.3)59.1, 63.1(63.6), 66.9(67.2), 127.7, 127.9, 128.0, 128.4, 136.3, 136.6, (154.5)155.2, 169.5; HRMS calcd for $C_{15}H_{19}N_4O_4$ (MH$^+$) 319.1406, found 319.1388.

**Methyl 1-carbonyloxy-2S-pyrroldinyl-$\alpha R$-(chloroacetamido)acetate (13)**

To the solution of azido ester (12) (0.615 g, 1.93 mmol) in 17 mL of THF was added, triphenylphosphine (0.615 g, 2.35 mmol). After stirring for 14 h, water (0.815 mL, 45.2 mmol) was added and stirring was continued for 20 h. Usual workup and purification by chromatography using 2% MeOH in ethyl acetate resulted in 0.535g (95%) of the corresponding $\alpha$-amino ester as a colorless oil; Rf = 0.29 (2% MeOH in ethyl acetate); [$\alpha]_D = -70.6^\circ$ (c, 1.2, CHCl$_3$); IR (CHCl$_3$) 3400(weak), 3325(weak), 1740, 1700; $^1$H NMR 1.66 (s, NH$_2$), 1.75–2.20 (m, 4H), 3.36 (m, 1H), 3.45–3.90 (m, 5H), 4.10–4.35 (m, 1H), 4.95–5.30 (m, 2H), 7.20–7.45 (m, 5H); $^{13}$C NMR (23.1)23.9, 28.2(29.0), 47.3(47.7), (51.9)52.1, 56.5, (60.1)60.8, 66.7, 127.7, 127.8, 128.4, 136.7, (155.0)155.5, 174.8. HRMS calcd for $C_{15}H_{22}N_4O_4$ (MH$^+$) 293.1502, found 293.1488.

A solution of amino ester (0.431 g, 1.47 mmol) and chloroacetic anhydride (0.303 g, 1.77 mmol) in 10 mL of dry CH$_2$Cl$_2$ was stirred for 7 h. After removal of solvent, the crude oil was chromatographed using 40% ethyl acetate in hexane to give 13 (0.52 g, 96%) as a colorless oil; Rf = 0.34 (50% MeOH in ethyl acetate); [$\alpha]_D = -39.9^\circ$ (c 1.1, CHCl$_3$); IR (CHCl$_3$) 3430, 3330, 1750, 1690; $^1$H NMR 1.75–2.25 (m, 4H), 3.30–3.55 (m, 2H), 3.59 and 3.77 (s, OCH$_3$ rotomers), 3.93 and 3.98 (s, CH$_2$Cl rotomers), 4.25–4.75 (m, 2H), 4.90–5.40 (m, 2H), 7.05–7.50 (m, 5H), 7.93 (s, 1H, NHCO); $^{13}$C NMR (22.8)23.6, 28.5(29.9), (40.8)42.1, 46.9(47.4), 52.5, (55.2)57.1, 58.2, 67.3, 127.9, 128.1, 128.4, 136.3, 156.6, (166.1)166.7, (168.5)170.4; HRMS calcd for $C_{15}H_{22}N_2O_3Cl$ (MH$^+$) 369.1217, found 369.1226.

**Methyl 3-oxo-octahydro-9S-pyrrolo[1,2-a]pyrazine-$\alpha R$-carboxylate (14)**

Nitrogen was bubbled through a flask containing 13 (0.347 g, 0.94 mmol), 88% formic acid (1.7 mL) and 5% Pd-C (105 mg) in 13 mL of methanol. Progress of the reaction and selective decarboxyloxylation was monitored by bubbling evolved CO$_2$ into a saturated solution of Ba(OH)$_2$. After 25 min, the catalyst was filtered through Celite and washed with methanol. The combined filtrates were concentrated to give the amine as a colorless oil, which was used for the subsequent reaction without purification; [$\alpha]_D = +25.6^\circ$ (c 0.43, MeOH); $^1$H NMR (CD$_3$OD) 1.75–2.30 (m, 4H), 3.15–3.35 (m, 2H), 3.77 (s, OCH$_3$), 4.00–4.15 (m, 1H), 4.16 (s, 2H), 4.73 (d, 1H), 8.23 (br s, 1H).

To a solution of the amine (0.264 g, 0.94 mmol) and Bu$_4$NI (70 mg, 0.19 mmol) in 13.6 mL of CH$_2$Cl$_2$ was added Et$_3$N (0.654 mL, 4.7 mmol), a catalytic amount of DMAP, and the mixture was refluxed for 28 h. Usual processing gave a crude mixture which was purified by chromatography using 10% methanol in ethyl acetate to give in 43 mg (23%) of 14 as a white solid, mp 109–110 °C (ethyl acetate and hexane); Rf = 0.21 (8% MeOH in ethyl acetate); [$\alpha]_D = +22.8^\circ$ (c 0.43, CHCl$_3$); IR (CHCl$_3$) 3420, 1750, 1680; $^1$H NMR 1.70–2.08 (m, 4H), 2.11–2.26 (m, 2H), 2.39 (m, 1H), 2.93 (d, 1H), 3.17 (m, 1H), 3.67 (d, 1H), 3.80 (s, OCH$_3$), 3.99 (d, 1H), 6.23 (s, 1H); $^{13}$C NMR 22.0, 28.6, 52.7, 53.7, 55.7, 59.4, 61.1,
168.4, 169.5; HRMS calcd for C_{13}H_{15}N_{2}O_{3} (MH^+) 199.1083, found 199.1089; Anal. Calcd for C_{13}H_{15}N_{2}O_{3} C, 54.55; H, 7.07; N, 14.14. Found C, 54.75; H, 7.48; N, 13.73.

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