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Enantioselective synthesis of 5-substituted pipecolic acids using an intramolecular allylsilane-iminium ion cyclization

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Abstract

The application of the intramolecular allylsilane-iminium ion cyclization reaction for the enantioselective synthesis of piperidine derivatives is described. The synthetic potential of this methodology is demonstrated by the enantioselective synthesis of 5-substituted pipecolic acids.

1. Introduction

The piperidine ring is a structural subunit found in a large number of naturally occurring alkaloids. The stereoselective synthesis of functionalized piperidines has received considerable attention due to the biological activities possessed by these compounds.[1–3] Substituted pipecolic acids are the subject of many current investigations.[1,2,4,5] They have been used as key intermediates in the synthesis of different types of piperidine-like natural products and, as constrained α-amino acids, they have been used as building blocks in the synthesis of peptidomimetics. We report herein the enantioselective synthesis of 5-substituted pipecolic acids via a short sequence of reactions, which should prove to be a general method for the synthesis of piperidine derivatives. The key reaction in the sequence is an intramolecular allylsilane-iminium ion addition. This type of Mannich intramolecular cyclization reaction has previously been used to prepare piperidines possessing unsaturation.[6–8] Our approach relies on chiral *N*-cyanomethyl-4-phenyloxazolidine **1**, which is efficiently prepared from (*R*)-(−)-phenylglycinol. Compound **1** represents a precursor of an iminium ion by opening of the oxazolidine ring whereas the cyano

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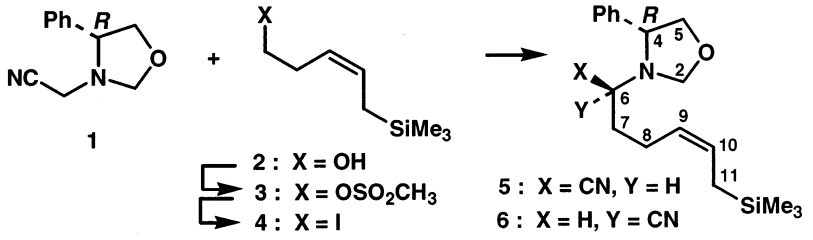
group can be transformed into a carboxylic acid function to obtain pipecolic acids. Furthermore, it provides the first stereogenic center used for the enantioselective elaboration of the piperidine ring.

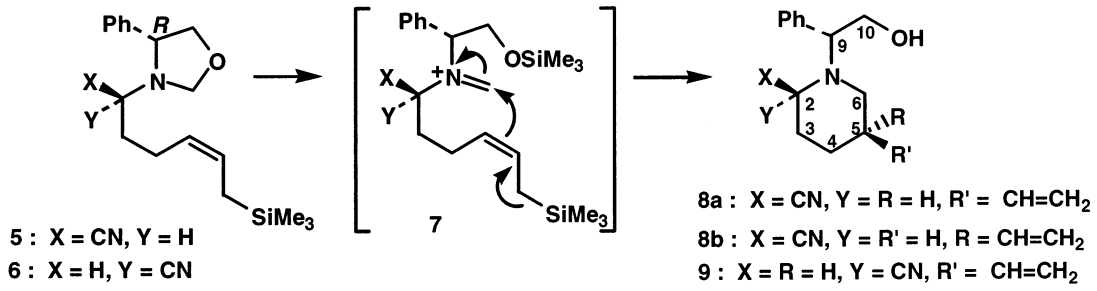
2. Synthesis and structural analysis

(*R*)-Cyanomethyloxazolidine **1** was prepared as previously described.[9] Nickel catalyzed coupling of trimethylsilylmethyl magnesium chloride with 2,3-dihydrofuran according to the methodology described[10,11] gave homoallylic alcohol **2**.[12] According to the literature procedure,[9] **1** was alkylated with iodide **4** to afford a 3:1 mixture of the allylsilyl diastereomers **5** and **6** in 75% yield (Scheme 1). These isomers were separated by flash chromatography. The (*S*) absolute configuration was assigned to the new stereogenic center (C-6) of the major isomer **5** on the basis of the chemical shift of H-6, by analogy with previous work.[12]



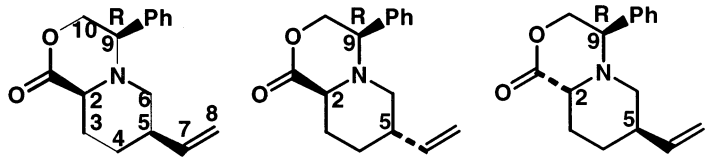
Scheme 1.

The intramolecular cyclization reaction (Scheme 2) was performed by treating the oxazolidine with trimethylsilyl trifluoromethanesulfonate (TMSOTf). Treatment of allylsilyl substituted oxazolidine **5** with TMSOTf resulted in conversion to piperidine **8** in 96% yield via the iminium ion intermediate **7**. The ^{1}H NMR spectrum of **8** showed it to be a 9:1 mixture of two isomers (**8a** and **8b**, respectively), each displaying characteristic eight peak signals for the alkene hydrogen H-7 at δ 5.77 and 6.07 ppm. These diastereomers could not be separated by flash chromatography. Alkylation product **6** was also reacted with TMSOTf to give piperidine **9** in 62% isolated yield after flash chromatography. This intramolecular cyclization proceeded with excellent diastereoselectivity (>92%), as the C-5 diastereomer of **9** was only detected as a minor component in the crude reaction mixture. The small coupling constants exhibited by proton H-2 for the piperidines **8a**, **8b** and **9** are consistent with an axial disposition of the cyano group.



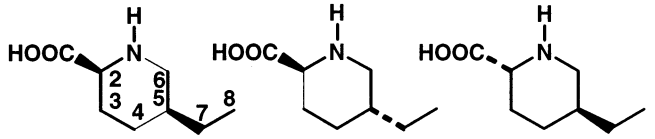
Scheme 2.

Stirring a solution of 2-cyanopiperidine **8** in a 1 M solution of HCl gas in ethyl acetate at room temperature for 24 h afforded a 4:1 mixture of lactones **10** and **11** in 77% yield, which were separated by flash chromatography. The 400 MHz ^{1}H NMR spectrum of **10** showed H-2 as a double doublet with $J=11.3$ and 2.7 Hz, indicative of an axial position of this atom. The two H-6 signals are indicative of an equatorial orientation of H-5 and hence of a *cis* stereochemistry of the 2,5-disubstituted piperidine ring, with a 2*S*,5*R* absolute configuration. The minor diastereomer **11** was assigned the *trans* stereochemistry, with a 2*S*,5*S* absolute configuration. This structural assignment followed from its ^{1}H NMR spectrum: Proton H-2 showed a large $J_{1,2}$ value (11.5 Hz) due to a *trans* diaxial coupling. The axial orientation of H-5 was inferred from the large *J* value due to geminal and *trans* diaxial coupling exhibited by the axial H-6 hydrogen. Similar reaction of **9** gave lactone **12** in 60% isolated yield. For this diastereomer the values of the coupling constants for H-2 and H-6 indicated an axial orientation for H-2 and H-5 and hence a *trans* stereochemistry of the piperidine ring, and a 2*R*,5*R* absolute configuration.



10 : (2S,5R) 11 : (2S,5S) 12 : (2R,5R)

Lactones **10**, **11** and **12** were quantitatively converted to the corresponding pipecolic acid derivatives **13**, **14** and **15** respectively, upon cleavage of the lactone ring and hydrogenolysis of the benzylic C–N bond in the presence of Pearlman's catalyst. The structural assignments of acids **13**, **14** and **15** were confirmed by their ^{1}H NMR spectra analysis.



13 : (2S,5S) 14 : (2S,5R) 15 : (2R,5S)

3. Conclusion

In conclusion, we have developed a concise method for the synthesis of enantiomerically pure 5-substituted pipecolic acids, starting from readily available materials. The key step in the synthesis is a stereoselective intramolecular cyclization which involves the formation of a C–C skeletal bond. The other steps are functional group transformations. The work described herein also provides a useful entry to enantiopure 5-substituted 2-cyanopiperidines which are considered to be valuable building blocks in the synthesis of 2-aminomethylpiperidines used in the preparation of several pharmaceuticals.[13–17]

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker AC 400 spectrometer operating at 400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR. Chemical shifts were recorded as δ values (ppm) and coupling constants were expressed in hertz (Hz). ^{1}H and ^{13}C NMR assignments were confirmed by 2D-COSY spectra. A Perkin–Elmer 377 instrument was used to effect IR spectra. TLC analyses were performed on Merck 60 F_{254} silica gel plates and were visualized using iodine. Flash column chromatography was carried out using Merck silica gel (grade 60, 230–400 mesh).

4.2. N-*(1-Cyano-6-trimethylsilylhex-4-enyl)-4-phenyloxazolidines* ***5*** *and* ***6***

A solution of cyanomethyloxazolidine **1**[9] (3.27 g, 0.017 mol) in THF (25 mL) was added to a stirring solution of LDA–HMPA (1:1, 1.25 equiv.) in THF (50 mL) under argon at −78°C and the stirring was continued for 30 min. Iodide **4** (5.1 g) was then added and the mixture was stirred at room temperature overnight. It was then hydrolyzed with saturated aqueous ammonium chloride and extracted with ether. The combined extracts were dried, concentrated and the residue chromatographed on silica gel (hexane–ethyl acetate 95:5 as eluent) to give 3.2 g of **5** and 1.05 g of **6** (75% overall yield).

Compound **5**: oil; $[\alpha]_D$ −162 (*c* 0.99, $CHCl_3$); IR (cm^{-1}) 1695, 2220; ^{1}H NMR ($CDCl_3$) 0.00 (9H, s, $SiMe_3$), 1.45 (2H, d, H-11, $J=8.7$), 1.75 (2H, q, H-7, $J=7.7$), 2.15 (2H, m, H-8), 3.62 (1H, t, H-6, $J=8.0$), 3.72 (1H, t, H-4, $J=8.3$), 4.01 (1H, dd, H-5, $J=7.4$, 8.3), 4.31 (1H, t, H-5, $J=7.4$), 4.49 (1H, d, H-2, $J=2.5$), 4.83 (1H, d, H-2, $J=2.5$), 5.13 (1H, m, H-9), 5.45 (1H, m, H-10), 7.30–7.40 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) −1.7, 18.9, 23.3, 32.9, 50.6, 65.4, 74.4, 82.4, 117.1, 124.2, 127.7, 128.1, 128.5, 128.9, 137.2; anal. calcd for $C_{19}H_{28}N_2OSi$: C, 69.46; H, 8.59; N, 8.53; Si, 8.55. Found: C, 69.52; H, 8.64; N, 8.58; Si, 8.25.

Compound **6**: oil; $[\alpha]_D$ −103 (*c* 0.9, $CHCl_3$); IR (cm^{-1}) 1645, 2220; ^{1}H NMR ($CDCl_3$) 0.00 (9H, s, $SiMe_3$), 1.43 (2H, m, H-11), 1.60 (2H, q, H-7, $J=7.3$), 2.02 (2H, m, H-8), 3.71 (1H, dd, H-4, $J=6.2$, 8.4), 3.81 (1H, t, H-6, $J=7.8$), 4.24 (1H, dd, H-5, $J=6.2$, 7.5), 4.42 (1H, t, H-5, $J=8.1$), 4.58 (1H, d, H-2, $J=4.4$), 4.78 (1H, d, H-2, $J=4.4$), 5.06 (1H, m, H-9), 5.48 (1H, m, H-10), 7.25–7.45 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) −1.7, 18.5, 23.0, 32.9, 53.8, 63.1, 75.1, 87.3, 118.8, 124.3, 126.8, 127.7, 128.2, 128.8, 141.8; anal. calcd for $C_{19}H_{28}N_2OSi$: C, 69.46; H, 8.59; N, 8.53; Si, 8.55. Found: C, 69.58; H, 8.88; N, 8.18; Si, 8.40.

4.3. N-*(1-Phenyl-2-hydroxyethyl)-2-cyano-5-vinylpiperidines* ***8*** *and* ***9***

Trimethylsilyl trifluoromethanesulfonate (1.2 equiv., 71 μL) was added to a stirred 0.3 M solution of oxazolidine **5** (0.1 g, 0.30 mmol) in anhydrous methylene chloride (1 mL) at −40°C under argon. The solution was stirred for 30 min at −40°C and for 3 h at room temperature. After concentration, the residue was chromatographed over silica gel (eluted with ethyl acetate–hexane 5:5) to give 0.075 g (96% yield) of a mixture of piperidines **8a** and **8b** (**8a**/**8b** 9:1): oil; $[\alpha]_D$ −83 (*c* 0.21, $CHCl_3$); IR (cm^{-1}) 3630, 3610, 3500, 2230, 1650, 1620; anal. calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93; O, 6.24. Found: C, 74.56; H, 8.12; N, 10.25; O, 6.76.

Compound **8a**: ^{1}H NMR ($CDCl_3$) δ 1.40–1.60 (1H, m, H-4), 1.70–1.90 (3H, m, H-3a, H-3e, H-4), 2.30–2.40 (2H, m, H-5, H-6), 3.21 (1H, m, H-6), 3.57 (1H, dd, H-9, $J=5.3$, 4.1), 3.62 (1H,

t, H-2, $J=3.3$), 3.82 (1H, dd, H-10, $J=11.5$, 4.1), 3.92 (1H, dd, H-10, $J=11.5$, 5.3), 5.04 (1H, d, H-8, $J=10.4$), 5.10 (1H, d, H-8, $J=17.1$), 5.77 (1H, ddd, H-7, $J=17.1$, 10.4, 6.3), 7.25–7.50 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) 26.6 (C-4), 28.5 (C-3), 40.1 (C-5), 51.0 (C-2), 51.9 (C-6), 64.0 (C-10), 69.5 (C-9), 115.2 (C-8), 116.9 (CN), 128.3, 128.4, 129.0 and 140.0 (Ph), 140.3 (C-7).

Compound **8b**: ^{1}H NMR ($CDCl_3$) δ 2.55 (1H, dd, $J=12.2$, 3.1), 2.65 (1H, d, $J=12.2$), 4.33 (1H, broad s, H-2), 6.03 (1H, ddd, H-7, $J=17.2$, 10.5, 6.4); ^{13}C NMR ($CDCl_3$) 25.6 (C-4), 26.6 (C-3), 36.9 (C-5), 51.5 (C-2), 51.6 (C-6), 64.2 (C-10), 69.8 (C-9), 115.3 (C-8), 117.2 (CN), 128.3, 128.7, 128.8 and 140.0 (Ph), 140.3 (C-7).

Compound **9** was prepared as described for **8**. Oxazolidine **6** (0.3 g, 0.91 mmol) in anhydrous methylene chloride (3 mL) gave 0.145 g of pure piperidine **9** (62% yield): mp 58–60°C; $[\alpha]_D$ −47 (*c* 0.78, $CHCl_3$); IR (cm^{-1}) 3600, 3480, 2220, 1640, 1610; ^{1}H NMR ($CDCl_3$) δ 1.45 (1H, qd, H-4a, $J=13.0$, 4.3), 1.80 (1H, broad d, H-4e, $J=13.0$), 1.90–2.10 (3H, m, H-3a, H-3e, H-6), 2.12–2.22 (1H, m, H-5), 2.66 (1H, dd, H-6, $J=11.7$, 3.0), 3.58 (1H, t, H-9, $J=5.0$), 3.78 (1H, dd, H-10, $J=12.0$, 5.0), 3.88, (1H, dd, H-10, $J=12.0$, 4.0), 4.36 (1H, broad s, H-2), 4.93 (1H, d, H-8, $J=10.0$), 4.97 (1H, d, H-8, $J=17.0$), 5.58 (1H, ddd, H-7, $J=17.0$, 10.5, 6.7), 7.30–7.50 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) 26.5 (C-4), 28.7 (C-3), 39.8 (C-5), 50.2 (C-2), 52.1 (C-6), 64.2 (C-10), 69.3 (C-9), 114.5 (C-8), 117.2 (CN), 127.9, 128.4, 128.8 and 138.9 (Ph), 139.7 (C-7).

4.4. 4-Phenyl-7-vinylhexahydropyrido[2,1c][1,4]oxazin-1-one ***10***, ***11*** *and* ***12***

A mixture of piperidines **8a** and **8b** (0.6 g, 0.23 mmol) was dissolved in a 1 M solution of HCl gas in ethyl acetate (18.7 mL) and SiO_2 (6 g) was added.[18] The mixture was stirred for 24 h, neutralized with saturated aqueous K_2CO_3, filtered and extracted with ethyl acetate. The combined extracts were dried and concentrated to give a 4:1 mixture of lactones **10** and **11** (0.46 g, 77% yield) which were separated by chromatography on silica gel (hexane–ethyl acetate 8:2 as eluent).

Compound **10**: white solid, mp 148°C; $[\alpha]_D$ −114 (*c* 0.355, $CHCl_3$); IR (cm^{-1}) 1760, 1640; ^{1}H NMR ($CDCl_3$) δ 1.60–1.70 (1H, m, H-4), 1.85–1.95 (2H, m, H-3, H-4), 2.0 (1H, dd, H-6a, $J=11.4$, 3.8), 2.20–2.35 (2H, m, H-3, H-5), 2.76 (1H, dd, H-6e, $J=11.4$, 2.2), 3.00 (1H, dd, H-2a, $J=11.3$, 2.7), 3.57 (1H, dd, H-9, $J=11.1$, 3.8), 4.23 (1H, dd, H-10, $J=11.1$, 3.8), 4.33 (1H, t, H-10, $J=10.8$), 5.05 (1H, d, H-8, $J=17.3$), 5.09 (1H, d, H-8, $J=10.5$), 6.15 (1H, ddd, H-7, $J=6.8$, 10.5, 17.3); ^{13}C NMR ($CDCl_3$) δ 23.9 (C-3), 29.2 (C-4), 36.4 (C-5), 56.4 (C-6), 64.2 (C-9), 64.7 (C-2), 72.7 (C-10), 114.5 ((C-8), 128.3, 128.5, 128.8 and 136.2 (Ph), 140.4 (C-7), 169.2 (C=O); anal. calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44; O, 12.44. Found: C, 74.54; H, 7.12; N, 5.76; O, 12.02.

Compound **11**: oil; $[\alpha]_D$ −70 (*c* 1.89, $CHCl_3$); IR (cm^{-1}) 1760, 1640; ^{1}H NMR ($CDCl_3$) δ 1.10 (1H, tdd, H-4a, $J=13.0$, 11.9, 4.0), 1.75 (1H, tdd, H-3a, $J=13.0$, 11.5, 3.9), 1.85–1.92 (1H, m, H-4e), 1.97 (1H, t, H-6a, $J=11.6$), 2.15–2.30 (2H, m, H-3e, H-5a), 2.82 (1H, ddd, H-6e, $J=11.6$, 3.8, 1.8), 3.12 (1H, dd, H-2a, $J=11.5$, 3.2), 4.0 (1H, t, H-9, $J=4.0$), 4.51 (1H, dd, H-10, $J=11.0$, 4.0), 4.69 (1H, dd, H-10, $J=11.0$, 4.0), 4.91 (1H, ddd, H-8, $J=10.3$, 1.5, 1.3), 4.94 (1H, ddd, H-8, $J=17.2$, 1.5, 1.3), 5.54 (1H, ddd, H-7, $J=17.2$, 10.3, 6.8), 7.40–7.80 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 26.8 (C-3), 30.2 (C-4), 38.0 (C-5), 56.2 (C-6), 58.4 (C-2), 59.1 (C-9), 73.1 (C-10), 114.5 (C-8), 128.5, 128.8 and 134.5 (Ph), 140.1 (C-7), 170.2 (C=O).

Compound **12** was prepared from **9** (0.145 g, 0.566 mmol) as described previously. The crude product was purified by chromatography on silica gel (hexane–ethyl acetate 8:2 as eluent) to give piperidinolactone **12** (0.087 g, 60% yield): oil; $[\alpha]_D$ −118 (*c* 1.485, $CHCl_3$); IR (cm^{-1}) 1760, 1640;

^{1}H NMR ($CDCl_3$) δ 1.20 (1H, qd, H-4a, J=13.0, 4.1 Hz), 1.49 (1H, t, H-6a, J=11.2), 1.69 (1H, tdd, H-3a, J=13.1, 11.4, 3.8), 1.89 (1H, d large, H-4e, J=12.7), 2.10–2.22 (1H, m, H-5a), 2.41 (1H, d large, H-3e, J=13.1), 2.72 (1H, ddd, H-6e, J=11.2, 3.7, 1.5), 2.88 (1H, dd, H-2a, J=11.4, 2.5), 3.57 (1H, dd, H-9, J=10.6, 3.8), 4.15 (1H, dd, H-10, J=11.1, 3.8), 4.22 (1H, t, H-10, J=10.9), 4.82 (IH, d, H-8, J=11.5Hz), 4.88 (1H, d, H-8, J=17.5Hz), 5.49 (1H, ddd, H-7, J=17.2, 10.6, 6.8), 7.20–7.45 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 27.6 (C-3), 30.2 (C-4), 39.2 (C-5), 57.2 (C-6), 64.1 (C-2), 64.3 (C-9), 72.7 (C-10), 114.1 (C-8), 128.5, 128.6, 128.9 and 136.1 (Ph), 139.9 (C-7), 169.1 (C=O).

4.5. (2S,5S)-5-Ethylpipecolic acid ***13***

The piperidinolactone **10** (54 mg, 0.21 mmol) was dissolved in ethanol (14 mL), acetic acid (0.35 mL) and water (1.4 mL) and Pearlman's catalyst (80 mg) was added. The resultant mixture was stirred under 4 atm of hydrogen at room temperature for 48 h in a Parr apparatus. Removal of the catalyst by filtration through a Celite pad followed by evaporation of the solvent in vacuo furnished the free amino acid in a quantitative yield: white solid, mp 205–210°C; $[\alpha]_D$ −13 (*c* 1.3, H_2O); ^{1}H NMR (D_2O) δ 0.96 (3H, t, H-8, J=7.4), 1.20–1.34 (1H, m, H-4), 1.35–1.50 (2H, m, H-7), 1.65–1.80 (1H, m, H-5), 1.82–1.94 (1H, m, H-4), 1.95–2.05 (1H, m, H-3), 2.22–2.40 (1H, m, H-3), 3.08 (1H, dd, H-6a, J=10.2, 12.7), 3.32 (1H, dd, H-6e, J=3.8, 12.7), 3.95 (1H, t, H-2, J=4.6); ^{13}C NMR (D_2O) δ 12.8 (C-8), 26.6 (C-3), 27.8 (C-7), 27.9 (C-4), 36.2 (C-5), 48.8 (C-6), 59.2 (C-2), 176.4 (C=O); anal. calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.56; H, 9.21; N, 8.58.

4.6. (2S,5R)-5-Ethylpipecolic acid ***14***

The piperidinolactone **11** (52 mg, 0.20 mmol) was dissolved in ethanol (5 mL) and Pearlman's catalyst (80 mg) was added. The resultant mixture was stirred under 4 atm of hydrogen at room temperature for 48 h in a Parr apparatus. Removal of the catalyst by filtration through a Celite pad followed by evaporation of the solvent in vacuo furnished the free amino acid (29 mg, 92% yield): oil; $[\alpha]_D$ +18 (*c* 1.35, H_2O); ^{1}H NMR (D_2O) δ 1.00 (3H, t, H-8, J=7.4), 1.22–1.50 (3H, m, H-7, H-4e), 1.62–1.80 (2H, m, H-3a, H-5a), 2.00 (1H, d large, H-4e, J=13.2), 2.35 (1H, dq, H-3e, J=3.2, 14.3), 2.75 (1H, t, H-6a, J=12.5), 3.50 (1H, dd, H-6e, J=2.8, 12.5), 3.70 (1H, dd, H-2a, J=3.2, 12.8); ^{13}C NMR (D_2O)) δ 12.8 (C-8), 28.3 (C-7), 29.3 (C-3), 31.1 (C-4), 37.1 (C-5), 50.8 (C-6), 62.1 (C-2), 177.4 (C=O); anal. calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62. Found: C, 61.42; H, 10.06.

4.7. (2R,5S)-5-Ethylpipecolic acid ***15***

Hydrogenolysis of the piperidinolactone **12** (80 mg, 0.31 mmol) was performed as described above to furnish the free amino acid in a quantitative yield: oil; $[\alpha]_D$ −17 (*c* 2.0, H_2O); ^{1}H NMR (D_2O) δ 1.00 (3H, t, H-8, J=7.4), 1.22–1.50 (3H, m, H-7, H-4e), 1.62–1.80 (2H, m, H-3a, H-5a), 2.00 (1H, d large, H-4e, J=13.2), 2.35 (1H, dq, H-3e, J=3.2, 14.3), 2.75 (1H, t, H-6a, J=12.5), 3.50 (1H, dd, H-6e, J=2.8, 12.5), 3.70 (1H, dd, H-2a, J=3.2, 12.8); ^{13}C NMR (D_2O) δ 12.8 (C-8), 28.3 (C-7), 29.3 (C-3), 31.1 (C-4), 37.1 (C-5), 50.8 (C-6), 62.1 (C-2) 177.4 (C=O); anal. calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.68; H, 9.28; N, 8.60.

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References

1. Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed. Pyridine and Piperidine alkaloids. Academic Press: New York, 1985; Vol. 26, pp. 89.
2. Angle, S. R.; Breitenbucher, J. G. In *Studies in Natural Products*; Atta-ur-Rahman, Ed. Recent Progress in the Synthesis of Piperidine and Indolizidine Alkaloids. Elsevier Science: Amsterdam, 1995; Vol. 16, pp. 453.
3. Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633–640.
4. Couty, F. *Amino Acids* **1999**, *16*, 297–320.
5. Zaparucha, A.; Danjoux, M.; Chiaroni, A.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1999**, *40*, 3699–3700.
6. Grieco, P. A.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 5067–5070.
7. Agami, C.; Bihan, D.; Morgentin, R.; Puchot-Kadouri, C. *Synlett* **1997**, 799–800.
8. Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org.Chem.* **1998**, *63*, 841–859.
9. Marco, J. L.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 3567–3570.
10. Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M. *J. Org. Chem.* **1984**, *49*, 4894–4899.
11. Kocienski, P. J.; Pritchard, M.; Wadman, S. N.; Whitby, R. J.; Yeates, C. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3419–3429.
12. Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014–4020.
13. Perumattam, J.; Shearer, B. G.; Confer, W. L.; Mathew, R. M. *Tetrahedron Lett.* **1991**, *32*, 7183–7186.
14. Compernolle, F.; Saleh, M.-A.; Toppet, S.; Hoonaert, G. *J. Org. Chem.* **1991**, *56*, 5192–5196.
15. Murray, P. J.; Starkey, I. D. *Tetrahedron Lett.* **1996**, *37*, 1875–1878.
16. Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 6700–6705.
17. Nazabadioko, S.; Perez, R. J.; Brieva, R.; Gotor, V. *Tetrahedron: Asymmetry* **1998**, *9*, 1597–1604.
18. Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* **1996**, *37*, 4001–4002.