Asymmetric Syntheses of Enantiopure 4-Substituted Pipecolic Acid Derivatives

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(2*R*,4*R*)-4-Methylpipecolic acid and (2*S*,4*R*)-4-hydroxypipecolic acid, two biologically active amino acids, were synthesized using the same strategy. A third amino acid, obtained in a protected form, was also obtained in the same way. The key step of these syntheses involves an intramolecular ene-iminium cyclization which occurs with complete stereoselectivity. The resulting exocyclic double bond can react in a diastereoselective way to afford pure lactones, which can then be efficiently converted into the amino acids.

Introduction

4-Substituted pipecolic acid derivatives present very potent biological activities. Among other examples, (2*R*,4*R*)-4-methylpipecolic acid (**1**) and (2*S*,4*R*)-4-hydroxypipecolic acid (**2**) are valuable precursors for the syntheses of complex bioactive molecules (Figure 1). Compound **1** is a key component for the preparation of the very selective thrombin inhibitor (2*R*,4*R*)-MQPA or Argatroban®[1] (Figure 2). Compound **2**, a natural amino acid isolated from the leaves of *Calliandra pittieri* and *Strophantus scandeus*,[2] is a constituent of some cyclodepsipeptide antibiotics such as virginiamicin S2.[3] It has been used as a synthetic intermediate in the preparation of NMDA receptor antagonists[4] and as a building block in the synthesis of Palinavir[5] (Figure 2), a highly potent inhibitor of the immunodeficiency virus (HIV) protease. For these reasons, several racemic and enantioselective syntheses of these two compounds have been described.[6,7] In the course of our research on the synthesis of pipecolic acid derivatives,[8] we have developed a common strategy which provides a very efficient access to these amino acids from the β-amino alcohols **3** and *ent*-**3**.

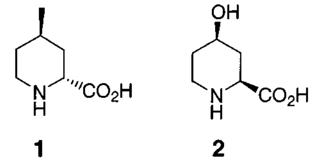

Figure 1

Results and Discussion

The synthesis of the pipecolic acid derivative **1** is described in Scheme 1. The β-amino alcohol **3**, derived from (*R*)-phenylglycinol,[9] was condensed with glyoxal to afford the hemiacetal **4**, which was then submitted to a Swern oxidation to produce the diastereoisomerically pure lactone **5**. Catalytic hydrogenation of the exocyclic double bond with palladium hydroxide or Raney nickel gave unsatisfactory results: amino acids and saturated lactones were obtained as inseparable mixtures. Reaction with hydrogen in the presence of palladium on carbon and one equivalent of hydrochloric acid in ethanol afforded a mixture of both diastereoisomers **6** and **7** in a 33:66 ratio, thus favoring the formation of the unsuitable isomer. Eventually, the use of platinum oxide in ethanol was found to afford a separable mixture of the two diastereoisomers **6** and **7** in a 75:25 ratio. Although the stereoselectivity was modest, platinum oxide turned out to be the best catalyst, in our hands, to perform this reduction.[10] Hydrogenolysis of the pure lactone **6** produced the amino acid **1** in a diastereoisomerically pure form.

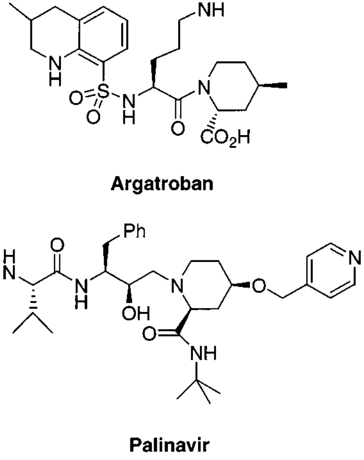

Figure 2

The synthesis of amino acid **2** commences from the β-amino alcohol *ent*-**3**, obtained from (*S*)-phenylglycinol (see Scheme 2). Cyclisation with glyoxal furnished the epimeric mixture of hemiacetals **8**. Oxidation of the double bond with osmium tetroxide and sodium periodate was followed

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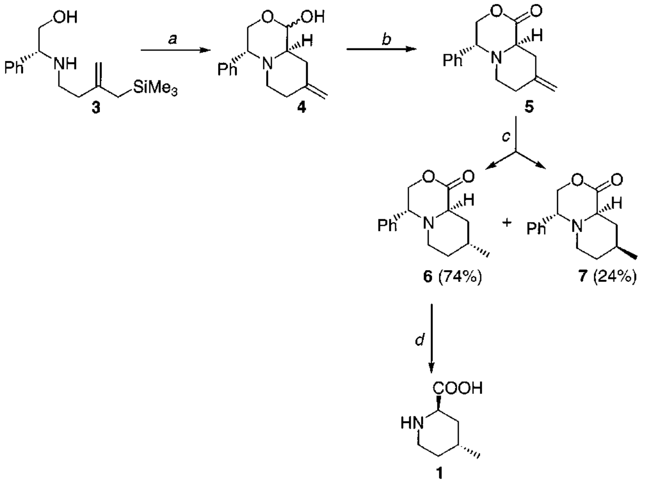
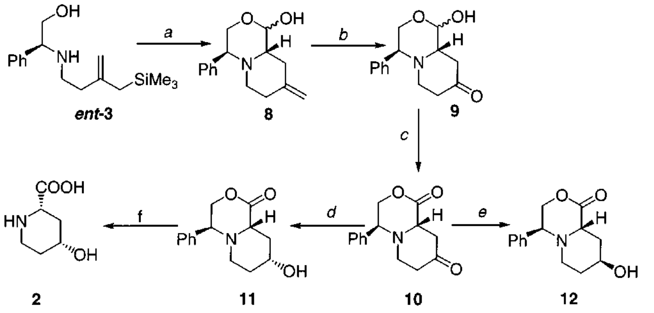


Scheme 1. Reagents and conditions: (a) CHOCHO, THF, H_2O, room temperature, 2.5 h, 97%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, −50 °C, 1 h, 85%; (c) H_2, PtO_2, AcOEt, 15 min.,74% for **6** and 24% for **7**; (d) H_2, $Pd(OH)_2$, EtOH, 98%



Scheme 2. Reagents and conditions: (a) CHOCHO, THF, H_2O, room temperature, 2.5 h, 97%; (b) OsO_4, $NaIO_4$, THF, H_2O, room temperature, 30 min., 70%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, −50 °C, 1 h, 78%; (d) BH_3-THF, THF, −60 °C, 20 min., 67%; (e) K-selectride, THF, −78 °C, 1.5 h, 49%; (f) H_2, $Pd(OH)_2$, EtOH, 95%

by Swern oxidation to give the pure ketolactone **10**. Reduction with K-selectride gave the undesired diastereoisomer **12**. Fortunately, a diastereoselective reduction of the keto group by diborane afforded the required diastereoisomerically pure alcohol **11**. This dramatic change of stereoselectivity according to the reducing agent can be ascribed to the bulkiness of K-selectride compared to borane. It is well known that sterically demanding hydrides add to cyclohexanone to produce preferentially the axial alcohols.[11] Finally, hydrogenolysis of compound **11** gave amino acid **2** quantitatively.

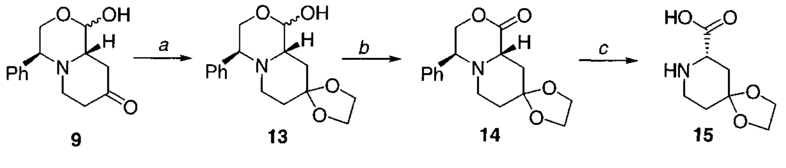
In order to check the versatility of our methodology, we explored the possibility of obtaining another amino acid, (2*S*)-4-oxopipecolic acid, in a form conveniently protected for peptide synthesis.[12] The hemiketal **9**, when treated with ethylene glycol, afforded the dioxolane **13**, which was then oxidized with the Swern reagent. The diastereoisomerically pure lactone **14** was debenzylated with palladium hydroxide to afford the amino acid **15** with the keto group protected as a dioxolane (Scheme 3).

The crucial step of our methodology is the spontaneous cyclization of β-amino alcohols **3** and *ent*-**3** with glyoxal. As already described,[8,13] this very efficient reaction is completely stereoselective: the attack of the allylsilane moiety onto the intermediate iminium ion **16** occurs on the less-encumbered face i.e. in an *anti* position relative to the phenyl group (Scheme 4).

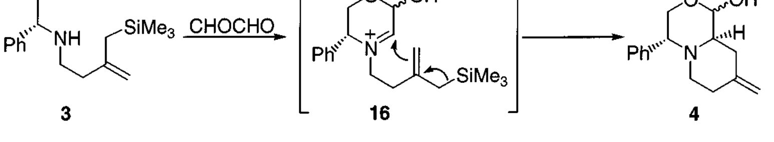
The exocyclic double bond included in the bicyclic structure of compounds **4** and **8** is of the highest importance. As a matter of fact, this function can be transformed into an alkyl or an alcohol group, allowing an access to various substituted amino acids that are found in many biologically active molecules. In conclusion, our methodology is very convenient for the rapid and efficient enantioselective syntheses of 4-substituted pipecolic acid derivatives.

Experimental Section

General Comments: ^1H and ^{13}C NMR spectra ($CDCl_3$ solution) were recorded on a Bruker ARX 250 spectrometer at 250 and 62.5 MHz, respectively; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin−Elmer 141 instrument. IR Spectra were recorded on a Nicolet Avatar 320 FTIR spectrometer (characteristic absorptions are given in cm^{-1}). All reactions were carried out under an argon atmosphere except those performed in an aqueous medium. THF was distilled from sodium/benzophenone ketyl, and dichloromethane over CaH_2 be-



Scheme 3. Reagents and conditions: (a) $(CH_2OH)_2$, BF_3-Et_2O, $CHCl_3$, 3 days, 83%; (b) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, −50 °C, 1 h, 84%; (c) H_2, $Pd(OH)_2$, EtOH, 95%



Scheme 4

fore use. Column chromatography was performed on silica gel, 230−400 mesh with various mixtures of diethyl ether (Et_2O) or ethyl acetate (AcOEt) and petroleum ether (PE). HRMS was measured in the EI mode with an ionization potential of 70 eV; the accurate measurements were done with a resolving power of 10,000.

(4*R*,10*R*)-8-Methylene-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazin-1-ol (4) and (4*S*,10*S*)-8-methylene-4-phenyloctahydropyrido[2,1-*c*][1,4]oxazin-1-ol (8): Glyoxal (40% weight 0.72 mL, 6.3 mmol) was added to a solution of the silylated amino alcohol **3** or *ent*-**3** (1.16 g, 4.2 mmol) in a THF/H_2O mixture (1:1 v/v, 10 mL). This mixture was stirred for 2.5 h at room temperature and then poured into water (14 mL). The aqueous layer was extracted with Et_2O (3 × 14 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was then evaporated under reduced pressure. Chromatography on silica gel (Et_2O/PE, 35:65) afforded the hemiacetals **4** (from **3**) or **8** (from *ent*-**3**) (1 g, 97%) as a mixture of two diastereoisomers at C-1. Only the characteristic peaks (for a 35:65 mixture of the two diastereoisomers) are given: − ^1H NMR: $\delta = 7.39-7.18$ (m, 5 H, H_{Ph}), 5.06 (d, $J = 2.5$ Hz, 0.35 H, H_1), 4.78 (d, $J = 6.2$ Hz, 0.65 H, H_1), 4.65−4.58 (m, 2 H, H_{11}), 4.07−3.93 (m, 2 H, H_3), 3.78 (dd, $J = 2.5$ and 10.2 Hz, 0.65 H, H_4), 3.59 (dd, $J = 7.2$ and 11 Hz, 0.35 H, H_4). − ^{13}C NMR: $\delta = 146.2-145.7$ (C_8), 138.6−138.4−129.3−129.2−128.9−128.3 (C_{Ph}), 108.8−108.6 (C_{11}), 95.4−94.6 (C_1), 68.9, 66.4, 61.2, 60.0, 58.2, 51.8, 51.5, 33.4, 30.9, 30.7, 29.5. − IR: $\tilde{\nu} = 3250$, 1656, 1056 cm^{-1}.

(4*R*,10*R*)-8-Methylene-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (5): Dimethyl sulfoxide (0.60 mL, 8.6 mmol) was added dropwise to a solution of oxalyl chloride (0.40 mL, 4.7 mmol) in dry dichloromethane (10 mL) at −60 °C. The mixture was stirred for 5 minutes and a solution of hemiacetal **4** (950 mg, 3.9 mmol) in dichloromethane (8 mL) was added. After 60 min. at −50 °C, triethylamine (2.7 mL, 19.6 mmol) was added and the mixture was allowed to warm to room temperature in 1.5 h. Addition of water (25 mL) and extraction of the aqueous layer with dichloromethane (3 × 15 mL) gave a residue, after evaporation of the solvent, which was chromatographed (AcOEt/PE, 45:55) to afford lactone **5**. (800 mg, 85%). − $[\alpha]_D^{20} = -39$ ($c = 1$, $CHCl_3$). − ^1H NMR: $\delta = 7.32-7.19$ (m, 5 H, H_{Ph}), 4.70 (d, $J = 1.1$ Hz, 1 H, H_{11}), 4.64−4.57 (m, 2 H, H_{11} and H_3), 4.44 (dd, $J = 5.4$ and 11 Hz, 1 H, H_3), 4.05 (t, $J = 5.1$ Hz, 1 H, H_4), 3.25 (dd, $J = 6.9$ and 10.8 Hz, 1 H, H_{10}), 2.86−2.75 (m, 1 H, H_6), 2.64 (dd, $J = 3.7$ and 13.6 Hz, 1 H, H_9), 2.43 (t, $J = 12.3$ Hz, 1 H, H_9), 2.25−1.90 (m, 3 H, H_6 and H_7). − ^{13}C NMR: $\delta = 169.9$ (C_1), 143.5 (C_8), 135.1, 128.9, 128.6 (C_{Ph}), 110.0 (C_{11}), 72.9 (C_3), 59.3 (C_{10}), 58.5 (C_4), 51.6 (C_6), 35.2 (C_9), 32.3 (C_7). − HRMS ($C_{15}H_{17}NO_2$): calcd. 243.125927; found 243.125823. − IR: $\tilde{\nu} = 1730$, 1655 cm^{-1}.

(4*R*,8*R*,10*R*)-8-Methyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (6) and (4*R*,8*S*,10*R*)-8-methyl-4-phenylhexahydropyrido-[2,1-*c*][1,4]oxazin-1-one (7): A solution of lactone **5** (50 mg, 0.21 mmol) in ethyl acetate (2 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of platinum oxide (10 mg) in ethyl acetate (1 mL). The hydrogenation was complete in 15 min. The mixture was then filtered through Celite 545 and the residue washed with ethyl acetate. The filtrate was evaporated to dryness, leaving the crude methylated derivative as a diastereomeric mixture (75:25 at C_8, 98%). Chromatography on silica gel furnished compounds **6** (major diastereoisomer) and **7** (minor diastereoisomer).

Lactone **6** (Et_2O/PE, 30:70), white solid (38 mg, 74%), m.p. 111 °C. − $[\alpha]_D^{20} = +125$ ($c = 1$, $CHCl_3$). − ^1H NMR: $\delta = 7.34-7.18$ (m, 5 H, C_{Ph}), 4.47 (dd, $J = 6$ and 12 Hz, 1 H, H_3), 4.14 (t, $J = 10.2$ Hz, 1 H, H_3), 3.83−3.77 (m, 2 H, H_4 and H_{10}), 2.75 (dt, $J = 3.9$ and 11.3 Hz, 1 H, H_6), 2.50 (dt, $J = 2.8$ and 11.3 Hz, 1 H, H_6), 2.17−2.11 (m, 1 H, H_9), 1.80−1.71 (m, 1 H, H_8), 1.57−1.45 (m, 1 H, H_9), 1.22−1.15 (m, 2 H, H_7), 0.88 (d, $J = 6.5$ Hz, 3 H, C_{Me}). − ^{13}C NMR: $\delta = 172.8$ (C_1), 138.6, 128.9, 128.1, 127.2 (C_{Ph}), 70.2 (C_3), 63.7 (C_4), 54.0 (C_{10}), 52.9 (C_6), 33.9, 32.9 (C_3 and C_7), 26.3 (C_8), 21.6 (C_{Me}). − HRMS ($C_{15}H_{20}NO_2$ [M + H^+]): calcd. 246.1494; found 246.1495.

Lactone **7** (Et_2O/PE, 35:65), oil (12 mg, 24%). − $[\alpha]_D^{20} = +30$ ($c = 2.2$, $CHCl_3$). − ^1H NMR: $\delta = 7.32-7.19$ (m, 5 H, H_{Ph}), 4.62 (dd, $J = 4.2$ and 10.8 Hz, 1 H, H_3), 4.45 (dd, $J = 4.2$ and 10.9 Hz, 1 H, H_3), 3.97 (t, $J = 4.2$ Hz, 1 H, H_4), 3.15 (dd, $J = 2.9$ and 11 Hz, 1 H, H_{10}), 2.80 (tdd, $J = 2.1$, 3.7 and 12.3 Hz, 1 H, H_6), 2.18 (td, $J = 2.4$ and 12.2 Hz, 1 H, H_6), 2.09−2.04 (m, 1 H, H_7), 1.39−1.24 (m, 4 H, H_9, H_8 and H_7), 0.86 (d, $J = 5.6$ Hz, 3 H, H_{Me}). − ^{13}C NMR: $\delta = 167.8$ (C_1), 132.2, 126.4, 126.2, 125.9 (C_{Ph}), 70.7 (C_3), 56.4, 55.8 (C_4 and C_{10}), 48.2 (C_6), 32.8 (C_7), 29.1 (C_9), 28.9 (C_8), 19.6 (C_{Me}).

(4*S*,10*S*)-1-Hydroxy-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-8-one (9): A solution of osmium tetroxide (0.8 mL, 0.12 mmol, 4.5% solution in water) was added at room temp. to a solution of hemiacetals **8** (590 mg, 2.4 mmol) in a mixture of THF/H_2O (1:1, 30 mL). Sodium periodate (2.4 g, 12 mmol) was then added over 30 min. At the end of the addition the mixture was hydrolyzed by addition of an aqueous sodium thiosulfate solution (7.5% weight, 20 mL) and extracted with Et_2O. The organic layers were dried over $MgSO_4$ and the solvents evaporated. The black residue was chromatographed (AcOEt/PE, 30:70) to afford a mixture (70:30) of hemiacetals **9** (420 mg, 70%). Only the peaks of the major isomer are given. − ^1H NMR: $\delta = 7.40-7.21$ (m, 5 H, H_{Ph}), 4.07−3.87 (m, 3 H, H_3 and H_4), 3.67−3.53 (m, 1 H, H_{10}), 3.27−2.82 (m, 2 H, H_6), 2.82−2.43 (m, 4 H, H_7 and H_9). − ^{13}C NMR: $\delta = 210.2$ (C_8), 137.9, 129.4, 129.2, 128.8 (C_{Ph}), 94.4 (C_1), 65.7 (C_3), 60.8 (C_{10}), 57.6 (C_4), 49.9 (C_6), 37.9 (C_9), 36.2 (C_7). − IR: $\tilde{\nu} = 3346$, 1685 cm^{-1}.

(4*S*,10*S*)-4-Phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1,8-dione (10): The Swern oxidation procedure described above was applied to hemiacetal **9** (330 mg, 1.33 mmol) to afford lactone **10** as a solid (260 mg, 78%), m.p: 106 °C. − $[\alpha]_D^{20} = +1$ and $[\alpha]_{436}^{20} = -18$ ($c = 1$, $CHCl_3$). − ^1H NMR: $\delta = 7.36-7.28$ (m, 5 H, H_{Ph}), 4.55 (dd, $J = 4.2$ and 11.2 Hz, 1 H, H_3), 4.40 (dd, $J = 7$ and 11.2 Hz, 1 H, H_3), 4.11 (dd, $J = 4.2$ and 7 Hz, 1 H, H_4), 3.78 (dd, $J = 6.5$ and 9 Hz, 1 H, H_{10}), 3.09 (ddd, $J = 4.6$, 5.5 and 12.5 Hz, 1 H, H_6), 2.77−2.69 (m, 2 H, H_9), 2.66−2.55 (m, 1 H, H_6), 2.47−2.34 (m, 1 H, H_7), 2.27−2.18 (dt, $J = 4$ and 15 Hz, 1 H, H_7). − ^{13}C NMR: $\delta = 205.5$ (C_8), 168.9 (C_1), 134.8, 129.2, 129.1, 128.3 (C_{Ph}), 72.7 (C_3), 59.0 (C_4), 57.6 (C_{10}), 49.0 (C_6), 41.2 (C_9), 39.6 (C_7). − $C_{14}H_{15}NO_3$ (245.28): calcd. C 68.55, H 6.16, N 5.71; found C 68.46, H 6.28, N 5.54. − IR: $\tilde{\nu} = 1743$, 1731 cm^{-1}.

(4*S*,8*R*,10*S*)-8-Hydroxy-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (11): A solution of diborane (1 M in THF, 1.4 mL, 1.4 mmol) was added at −60 °C to a solution of the ketolactone **10** (171 mg, 0.7 mmol) in THF (4 mL). The mixture was stirred for 20 min. and hydrolyzed by addition of a saturated aqueous solution of ammonium chloride (4 mL). After extraction with dichloromethane, the organic layers were combined and the solvent was evaporated. The residue was chromatographed on silica gel (AcOEt/PE, 60:40) to afford compound **11** as a single diastereoisomer (116 mg, 67%), m.p.103 °C. − $[\alpha]_D^{20} = +24$ ($c = 1$, $CHCl_3$). − ^1H NMR: $\delta = 7.32-7.19$ (m, 5 H, H_{Ph}), 4.54 (dd, $J = 4.2$ and 11 Hz, 1 H, H_3), 4.39 (dd, $J = 5.7$ and 11 Hz, 1 H, H_3), 3.99 (dd, $J = 4.5$ and 5.7 Hz, 1 H, H_4), 3.64−3.52 (m, 1 H, H_8), 3.32 (dd, $J = 3.5$ and 10.8 Hz, 1 H, H_{10}), 2.87 (dt, *J* = 4 and 12.8 Hz, 1 H, H_6), 2.37−2.20 (m, 3 H, H_6, H_9 and OH), 1.77−1.62 (m, 2 H, H_7 and H_9), 1.50−1.37 (m, 1 H, H_7). − ^{13}C NMR: δ = 170.8 (C_1), 135.3, 129.3, 129.0, 1283.9 (C_{Ph}), 73.4 (C_3), 68.2 (C_8), 58.7 (C_4), 57.2 (C_{10}), 48.4 (C_6), 35.2 (C_9), 32.1 (C_7). − HRMS ($C_{14}H_{18}NO_3$ [M + H^+]): calcd. 248.1287; found 248.1286. − IR: $\tilde{\nu}$ = 3460, 1730 cm^{-1}.

(4*S*,8*S*,10*S*)-8-Hydroxy-4-phenylhexahydropyrido[2,1-c][1,4]oxazin-1-one (12): A solution of K-selectride (1 M in THF, 0.39 mL, 0.39 mmol) was added slowly at −78 °C to a solution of lactone **10** (95 mg, 0.39 mmol) in THF (4 mL). The mixture was stirred for 1.5 h and then hydrolyzed by addition of a saturated aqueous solution of ammonium chloride (4 mL). After extraction with dichloromethane, the organic layers were combined, dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on silica gel to afford compound **12** (47 mg, 49%). − ^{1}H NMR: δ = 7.33−7.25 (m, 5 H, H_{Ph}), 4.56 (dd, *J* = 5.0 and 12.5 Hz, 1 H, 1 H, H_3), 4.31 (dd, *J* = 6.5 and 12.5 Hz, 1 H, H_3), 4.06−4.02 (m, 1 H, H_8), 3.90 (dd, *J* = 5 and 6.5 Hz, 1 H, H_4), 3.74 (dd, *J* = 5 and 7.5 Hz, 1 H, H_{10}), 2.76−2.66 (m, 1 H, H_6), 2.59−2.50 (m, 1 H, H_6), 2.12−2.07 (m, 2 H, H_9 and OH), 1.97−1.90 (m, 1 H, H_9), 1.80−1.69 (m, 2 H, H_7). − ^{13}C NMR: δ = 171.8 (C_1), 136.4, 129.1, 128.6, 128.2 (C_{Ph}), 7.2 (C_3), 64.7 (C_8), 60.8 (C_4), 53.9 (C_{10}), 47.6 (C_6), 34.3 (C_9), 32.0 (C_7).

Dioxolane Derivative 13: A solution of BF_3/Et_2O (0.62 mL, 4.9 mmol) was added at −10 °C to a solution of compound **9** (303 mg, 1.23 mmol) and ethylene glycol (2.4 mL, 43 mmol) in chloroform (13 mL). After 15 min. at −10 °C, the mixture was stirred for 3 days at room temp. and then hydrolyzed by addition of a saturated aqueous solution of sodium bicarbonate. After extraction with dichloromethane, the organic layers were combined and the solvent was evaporated. The residue was chromatographed on silica gel (AcOEt/PE, 70:30) to afford compound **13** (295 mg, 83%) as a mixture of two diastereoisomers (70:30). Only the characteristic peaks are given. − ^{1}H NMR: δ = 7.38−7.19 (m, 5 H, H_{Ph}), 5.04 (d, *J* = 2.5 Hz, 0.3 H, H_{1major}), 4.74 (d, *J* = 2.5 Hz, 0.7 H, H_{1minor}), 3.94−3.80 [m, CH_2O and $O(CH_2)_2O$]. − ^{13}C NMR: δ = 138.6, 128.9, 128.3 (C_{Ph}), 107.9 (OCO), 94.9 (C_1), 66.0 (C_3), 64.7, 64.6 [$O(CH_2)_2O$], 58.2, 57.3 (C_4 and C_{10}), 47.7 (C_9), 36.2 (C_7). − IR: $\tilde{\nu}$ = 3346, 1685 cm^{-1}.

Lactone 14: The Swern oxidation procedure described above was applied to hemiacetal **13** (225 mg, 0.77 mmol) to afford lactone **14** (186 mg, 84%). − $[\alpha]_D^{20}$ = +37 (*c* = 0.9, $CHCl_3$). − ^{1}H NMR: δ = 7.34−7.21 (m, 5 H, H_{Ph}), 4.54 (dd, *J* = 4 and 10.8 Hz, 1 H, H_3), 4.41 (dd, *J* = 5.3 and 10.8 Hz, 1 H, H_3), 4.01 (m, 1 H, H_4), 3.88−3.80 (m, 4 H, $O(CH_2)_2O$), 3.48 (dd, *J* = 3.3 and 12.0 Hz, 1 H, H_{10}), 2.78 (ddd, *J* = 2.8, 4.8 and 12.8 Hz, 1 H), 2.44 (td, *J* = 3.0 and 12.8 Hz, 1 H), 2.08 (dt, *J* = 3.3 and 13.3 Hz, 1 H), 1.89 (m, 1 H), 1.69 (td, *J* = 4.8 and 13.0 Hz, 1 H), 1.39 (m, 1 H). − ^{13}C NMR: δ = 170.0 (C_1), 134.9, 129.1, 128.9, 128.8 (C_{Ph}), 106.8 (C_8), 73.4 (C_3), 64.6 [$O(CH_2)_2O$], 57.5, 57.1 (C_4 and C_{10}), 47.7 (C_6), 35.6, 32.6 (C_7 and C_9).

General Procedure for the Hydrogenolysis of Bicyclic Lactones: A solution of lactone (0.16 mmol) in absolute ethanol (2 mL) was injected into a hydrogenation flask containing a suspension of palladium hydroxide (40 mg) in absolute ethanol (2 mL). The hydrogenation was complete in 2 h. The mixture was filtered through Celite 545 and the residue washed with ethanol. After evaporation of the solvent, the resulting solid was washed with pentane and dried to afford the corresponding amino acid.

(2*R*,4*R*)-4-Methylpiperidinecarboxylic Acid (1): Yield: 98%. − $[\alpha]_D^{20}$ = −20 (*c* = 0.3, 2 N HCl) {ref.[1a] $[\alpha]_D^{20}$ = −18 (*c* = 1, 2 N HCl)}. − ^{1}H NMR (D_2O): δ = 3.78 (dd, *J* = 3.1 and 4.7 Hz, 1 H, H_2), 3.14−3.10 (m, 2 H, H_6), 2.02−1.94 (m, 1 H, H_3), 1.76−1.28 (m, 4 H, H_3, H_4 and H_5), 0.89 (d, *J* = 6.4 Hz, H_{Me}). − ^{13}C NMR (D_2O): δ = 175.4 (CO_2H), 56.7 (C_2), 41.9 (C_6), 33.8 (C_3), 30.2, 26.5 (C_4 and C_5), 20.2 (C_{Me}).

(2*S*,4*R*)-4-Hydroxypiperidinecarboxylic Acid (2): Yield: 95%. − $[\alpha]_D^{20}$ = −17 (*c* = 0.5, H_2O) {ref.[7f] $[\alpha]_D^{20}$ = −17.2 (*c* = 1.05, H_2O); ref.[7g] $[\alpha]_D^{20}$ = −20.7 (*c* = 0.3, H_2O)}. − ^{1}H NMR (D_2O): δ = 3.87−3.69 (m, 1 H, H_4), 3.51(dd, *J* = 3.2 and 12.7 Hz, 1 H, H_2), 3.48−3.35 (m, 1 H, H_6), 2.96 (dt, *J* = 13.3 and 3 Hz, 1 H, H_6), 2.48−2.38 (m, 1 H, H_3), 2.13−2.05 (m, 1 H, H_5), 1.83−1.66 (m, 2 H, H_3 and H_5). − ^{13}C NMR (D_2O): δ = 173.8 (COOH), 65.9 (C_4), 58.2 (C_2), 41.8 (C_6), 35.1 (C_3), 30.3 (C_5). − HRMS ($C_6H_{12}NO_3$ [M + H^+]): calcd. 146.0817; found 146.0820.

7*S*-(1,4)-Dioxa-8-azaspiro[4.5]decane-7-carboxylic acid (15): Yield: 95%. − $[\alpha]_D^{20}$ = +11 (*c* = 1.3, MeOH). − ^{1}H NMR (D_2O): 4.13−4.05 (m, 4 H, $O(CH_2)_2O$), 3.77 (dd, *J* = 3.7 and 12.2 Hz, 1 H, H_7), 3.51 (td, *J* = 4.2 and 12.7 Hz, 1 H, H_9), 3.21−3.09 (m, 1 H, H_9), 2.37−2.25 (m, 1 H, H_6), 2.04−1.87 (m, 3 H, H_6 and H_7). − ^{13}C NMR (D_2O): δ = 173.4 (COOH), 105.2 (C_5), 65.0, 64.9 (C_2 and C_3), 57.7 (C_7), 41.4 (C_9), 35.1, 31.1 (C_6 and C_{10}). − HRMS: calcd. for $C_8H_{14}NO_4$ [M + H^+] 188.0923, found 188.0926.

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