Asymmetric Synthesis. 32.[1] A New Access to Enantiomerically Pure (S)-(−)-Pipecolic Acid and 2- or 6-Alkylated Derivatives

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Received January 4, 1994®

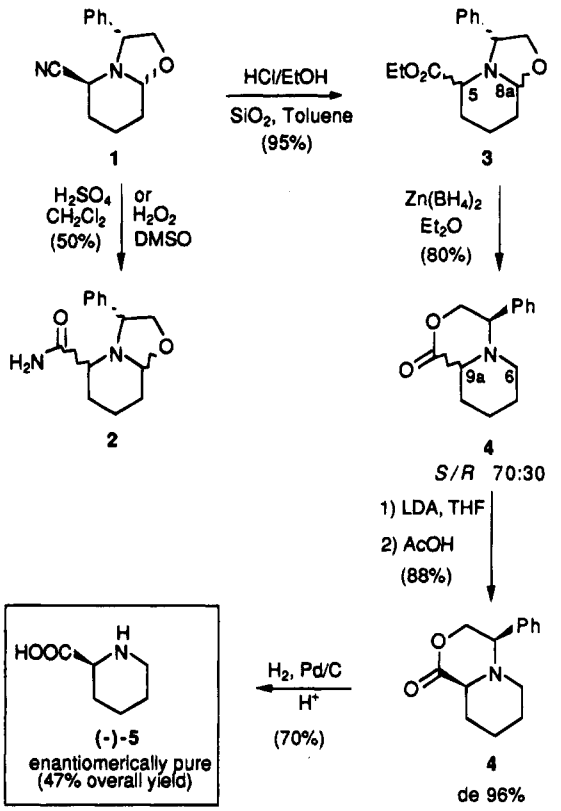
Enantiomerically pure (*S*)-(−)-pipecolic acid (**5**) was synthesized in four steps and 47% overall yield starting from 2-cyano-6-phenyloxazolopiperidine (**1**). A general strategy is described for preparing 2-alkylated and 6-alkylated pipecolic acid **7a–c** and **11a–c** using diastereoselective procedures.

(*S*)-(−)-Pipecolic acid (**5**), a widespread natural, but nonproteinogenic aminoacid, is of current interest both as a component of and a starting material for synthetic peptides,[2] potential enzyme inhibitors,[3] synthetic drugs,[4] and biologically-important natural products such as the immunosuppressant FK506[5a] and the antifungal antibiotic demethoxyrapamycin.[5b] These applications have stimulated considerable study of the stereoselective synthesis of pipecolic acid and its derivatives.

A limited number of asymmetric syntheses of (*S*)-(−)-pipecolic acid have been reported.[6] (*S*)-Lysine has often been used as a starting material.[6a–c] Key steps have involved regioselective diazotation, photoinduced oxidoreduction, and asymmetric aminocyclization.[6d–f] Some 2-alkylated pipecolic acids have been prepared starting from glycine derivatives with chiral auxiliaries, such as the Boc-BMI of Seebach[7] and the bislactim method of Schöllkopf.[8] Very recently, Wanner reported a new efficient synthetic approach to 2-alkylated pipecolic acids.[9] While several asymmetric syntheses of pipecolic acid derivatives have appeared,[10] to our knowledge only one paper has described the preparation of optically pure 6-substituted pipecolic acid.[11]

We report herein a general asymmetric synthesis of optically pure (*S*)-(−)-pipecolic acid (**5**) and its 2- and 6-alkyl derivatives **7a–c** and **11a–c** from the readily available intermediate **1**.

Scheme 1



(*S*)-(−)-Pipecolic Acid. In recent years, we have investigated the asymmetric synthesis of piperidine derivatives from the 2-cyano-6-phenyloxazolopiperidine synthon (**1**).[12] This synthon appeared to also be a good starting material for the synthesis of pipecolic acid since only a simple hydrolytic step would be required to transform the cyano group into a carboxylic acid function. But in fact, amide **2** (Scheme 1) could be obtained in 50% yield with H_2SO_4 in dichloromethane and ester **3** in only 8% yield with dry HCl in ethanol. In both cases epimerization at the C-5 center occurred. The yield for the latter conversion was dramatically improved when **1** was first adsorbed onto silica gel to prevent intermolecular reactions[13] between the carboxylic enol function and the iminium ion, formed in the acidic medium. Ester **3** could be isolated in 95% yield using this very simple modification but always with epimerization at the C-5 center.

® Abstract published in *Advance ACS Abstracts,* June 1, 1994.

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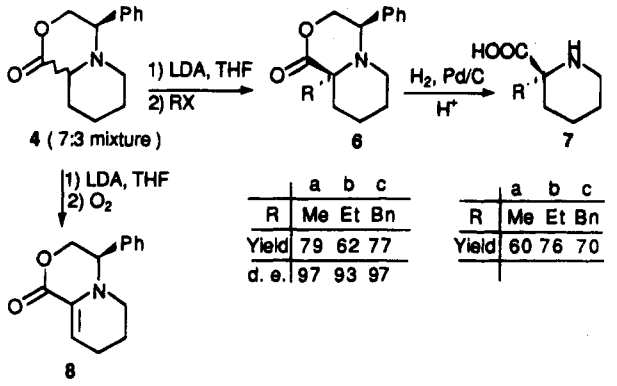
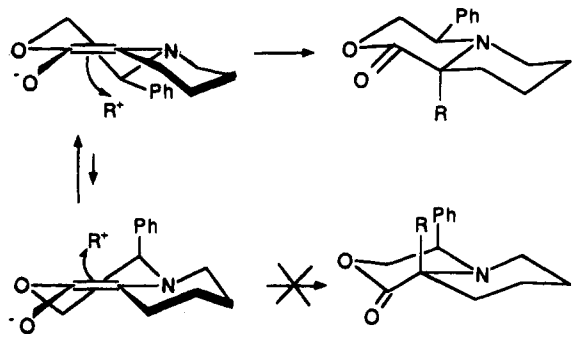
Scheme 2



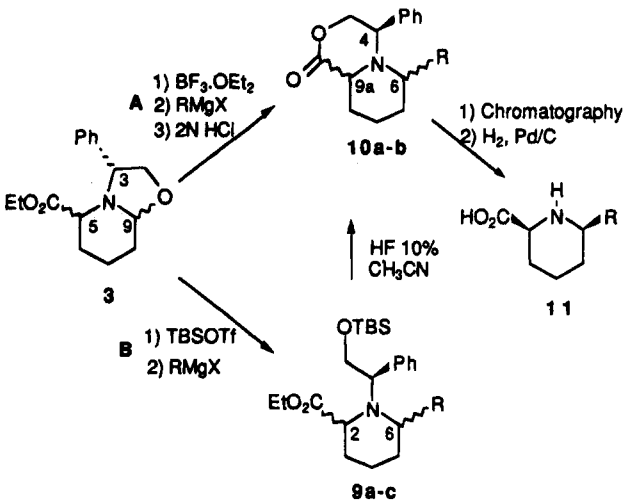
	a	b	c
R	Me	Et	Bn
Yield	79	62	77
d. e.	97	93	97

	a	b	c
R	Me	Et	Bn
Yield	60	76	70

Scheme 3



Scheme 4



a: R = Me; b: R = Pr; c: R = i-Pr

Nucleophilic and mild, basic conditions, such as H_2O_2 in DMSO with catalytic K_2CO_3,[14] gave the amide **2** without C-5 epimerization, but further transformation of the amide to the ester with Meerwein salt[15] afforded **3** in poor yield (27% from **1**). Similarly, hydrolysis of **1** with Na_2O_2 to give the carboxylic acid salt,[16] followed by esterification with ethyl bromide,[17] gave **3** in very poor yield (15%). Thus the silica gel method was prefered, even though **3** had to be used as a mixture of four diastereoisomers (5: 15:20:60 ratio as determined by ^1H NMR) which were difficult to separate by column chromatography or HPLC. The major isomer was assumed to have the (5*S*) configuration in accordance with the stereochemistry of the resulting (*S*)-pipecolic acid. The oxazolidine function of **3** was easily reduced by $Zn(BH_4)_2$ in ether at −10 °C followed by acidic workup, and lactones (9a*S*)-**4** and (9a*R*)-**4** were obtained in a 70:30 ratio and 77% yield (Scheme 1). Sequential deprotonation of lactones **4** with LDA (THF, −78 °C), followed by reprotonation (acetic acid, −78 °C), led to (9a*S*)-**4** in 96% de and 88% yield. Enantiomerically pure (9a*S*)-**4** was obtained after purification on silica gel or by crystallization and directly produced enantiomerically pure (*S*)-pipecolic acid (**5**) by simple hydrogenation on Pd/C in mild acidic medium (ethanol/acetic acid). A similar double O- and N-deprotection has already been reported by Harwood and coworkers[18] under similar conditions and was found to be general in our series for the obtention of 2- and 6-alkyl pipecolic derivatives **7a−c** and **11a−c** from **6a−c** and **9a−c** (*vide infra*).

2-Alkyl Derivatives. In order to access 2-alkyl pipecolic acids, lactone **4** (7:3 epimeric mixture) was alkylated as its enolate at −78 °C in THF with methyl, ethyl, and benzyl halides. Alkylated lactones **6a−c** were obtained in good yields with de ranging from 93 to 97% as determined by GC-MS (Scheme 2). The absolute configurations of the lactones **6a−c** were deduced with the help of known pipecolic acid derivatives **7a−c**. In all cases and as in the above epimerization, the major diastereoisomer resulted from an axial approach of the electrophile on the more stable enolate conformer bearing an equatorial phenyl group (Scheme 3). Alkylated lactones **6a−c** were obtained as pure diastereoisomers after purification by chromatography (crystallization for **6a**). It must be noted that the enolate derived from **4** was extremely oxygen sensitive and that strictly oxygen-free conditions were necessary to avoid the formation of **8**, presumably via the peroxo derivative at C-9a. Enamine **8** could be obtained almost quantitatively by bubbling O_2 at −78 °C into a THF solution of the enolate for a few minutes.[19] Pipecolic acids **7a−c**, substituted at the 2-position, were obtained by simultaneous O- and N-deprotection (H_2/Pd/C, MeOH, AcOH) from optically pure lactones **6a−c** in 60−76% yield.

6-Alkyl Derivatives. Ester **3** also offers access to 6-substituted pipecolic acids by reaction of Grignard reagents with the oxazolidine function. Initial attempts indicated that the reaction did not occur at temperatures lower than −20 °C in THF, and attack on the ester function was competive. In order to improve regioselectivity, iminium ions were preformed before addition of the nucleophile. Addition of $BF_3{\cdot}OEt_2$ or TBSOTf to the mixture of four diastereoisomers of **3** gave mixtures of two diastereoisomeric iminium ions as indicated by ^1H and ^{13}C NMR spectra. Addition of a Grignard reagent at −78 °C in THF and subsequent lactonization in acidic medium regioselectively produced 6-substituted lactones **10a−c** (Scheme 4) as a mixture of four diastereoisomers that could be separated by chromatography. The stereochemistry of each isolated diastereoisomer was studied by ^1H NMR analysis that included NOE studies and was assigned with confidence after a set of identical experiments that started from a pair of diastereoisomers **3** having the same major (5*S*) absolute configuration.

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Chart 1. Diastereoisomeric Ratio upon Alkylation of Diastereoisomeric Mixtures of Ester 3 Using Method A or B (according to Scheme 4)

(5S)-3 + (5R)-3 —B→ 9

	a	b	c
R	Me	Pr	i-Pr
Yield	77	66	20
ratio[1]	5 : 9 : 18 : 68[2]	28 : 32 : 40[3]	3 : 10 : 87[3]

(5S)-3 + (5R)-3 —A→ 10

	a	b
	Me	Pr
	88	90
	3 : 11 : 23 : 63	9 : 14 : 21 : 55[2]

(5S)-3 —B→ 9

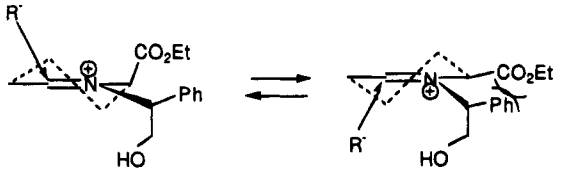
cis / trans ratio	93 : 7	52 : 48	>99 : 1

(5S)-3 —A→ 10

97 : 3	85 : 15

(1)-underlined values correspond to (2S) or (9aS) configuration (for **9** or **10** respectively)
(2)-determined by GC and ^{13}C NMR
(3)-only trace amounts of a forth diastereoisomer has been detected

Scheme 5



Diastereoisomeric ratios were determined by GC-MS, with the aid of ^{13}C NMR in some cases (see Chart 1), on the silyl ethers **9a–c** and the lactones **10a–c** respectively, for the TBSOTf and BF_3·OEt_2 methods. From Chart 1 it can be seen that to the (*5S*) esters, addition of the Grignard reagent occurred with a good to excellent *cis* stereoselectivity with a *cis/trans* ratio ranging from 85:15 to >99:1, except in the case of **9b**. This stereoselectivity corresponded to a *cis* addition onto the more stable iminium ion as dictated by $A^{1,2}$ strain[20] and stereoelectronic control[21] (Scheme 5). The (*5R*)-**3** esters behaved quite differently indeed. In every case, the selectivity was lower, but the relative configuration was known with confidence only in the case of *n*-PrMgBr addition. Here it was found that the *trans* product predominated. Thus we can conclude that, at least in this case, two different factors are involved in determining the stereoselectivity: one is the stability of the iminium ions (as depicted in Scheme 5) and the other is probably related to the configuration at C-2, relative to the chiral appendage. Pipecolic acids **11a–c**, alkylated at the 6-position, were eventually obtained as above by simple hydrogenolysis from optically pure lactones **10a–c** in good yield.

Experimental Section

All melting points were determined on a hot-stage apparatus and are uncorrected. Chemical shifts for NMR spectra are quoted in ppm downfield from internal tetramethylsilane. Mass spectra were obtained in the chemical ionization (CI) or electron impact (EI) mode, as specified in the text. Diastereoisomeric ratios (dr) and excesses (de) were determined by GC-MS analysis of crude materials using a flame ionization detector adopted for quantification of the diastereoisomeric ratio. Column packing was DB-5 phase, and helium was used as the gas vector. TLC was performed on 0.2-mm aluminum-backed silica gel plates; components were visualized using ultraviolet light and developed with Draggendorf or ninhydrin (for amino acids) sprays. Column chromatography was performed as specified in the text, using silica gel 60 (230–400 mesh) under moderate pressure with an eluant that gave an R_f of 0.3 or an adsorbant resin HP-20SS. Passage through ion-exchange resin 50W X8 was used for purification of amino acids. Evaporation refers to the removal of the solvent under reduced pressure.

3-Phenylhexahydrooxazolo[3,2-*a*]pyridine-5-carboxylic Acid Amide (2). K_2CO_3 (170 mg, 1.23 mmol) was added to a solution of **1** (1.1 g, 4.82 mmol) in DMSO (2 mL). H_2O_2 (30%, 650 μL) was added cautiously over 15 min. The slurry was warmed for 15 min at 60 °C, cooled to 0 °C, diluted with brine (40 mL), and then extracted with CH_2Cl_2 (4 × 25 mL). Organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, and evaporated. The crude mixture was subjected to chromatography on silica gel (CH_2Cl_2:MeOH 95:5) to yield 895 mg of **2** (75%) as a solid consisting of a mixture of two epimers at the C-8a center. Pure (*3R,5S,8aR*)-**2** can be obtained by recrystallization from Et_2O.

(*3R,5S,8aR*)-**2** (major isomer): mp 122 °C (ether); MS (CI) *m/z* 247 (MH^+, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 1.2–2.2 (m, 6H), 3.37 (t, J = 4.2 Hz, 1H), 3.75 (t, J = 7.6 Hz, 1H), 4.14 (t, J = 7.6 Hz, 1H), 4.29 (t, J = 7.6 Hz, 1H), 4.93 (dd, J = 3.4, 7.9, 1H), 7.2–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.5, 28.5, 30.1, 55.6, 62.9, 71.7, 87.8, 127.8, 128.2, 128.9, 136.5, 175.4; IR (KBr) 3200, 1670.

(*3R,5S,8aS*)-**2** (minor isomer): MS (CI) *m/z* 247 (MH^+, 100); ^1H NMR (200 MHz, $CDCl_3$) δ 1.2–2.2 (m, 6H), 2.53 (d, J = 9.7 Hz, 1H), 4.12 (m, 1H), 4.21 (dd, J = 2.2, 8.3 Hz, 1H), 4.39 (t, J = 8.2 Hz, 1H), 4.64 (dd, J = 2.2, 8.3 Hz, 1H), 7.2–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.4, 29.8, 30.4, 60.5, 61.2, 70.8, 88.4, 127.6, 128.4, 128.9, 138.7, 175.6; IR (KBr) 3200, 1670.

3-Phenylhexahydrooxazolo[3,2-*a*]pyridine-5-carboxylic Acid Ethyl Ester (3). To solution of **1** (5g, 22 mmol) in toluene (150 mL) was added silica gel (50 g) followed by dry HCl in ethanol (50 mL 5 M, 250 mmol). The suspension was stirred for 2 h and then neutralized with aqueous K_2CO_3 solution and filtered. The filtrate was washed with water, dried over $MgSO_4$, and evaporated to give a yellow-brown oil. Further trituration with pentane, filtration through a Celite pad, and evaporation afforded 5.7 g of **3** as a colorless oil (95%). This crude mixture of four diastereoisomers (5:15:20:60 ratio) was used for further reaction without purification. A mixture of (*3R,5S,8aR*)-**3** and (*3R,5S,8aS*)-**3** (9:1) can be obtained by chromatography on silica gel eluting with heptane ether 2:1.

(*3R,5S,8aR*)-**3** (major isomer): MS (EI) *m/z* 275 (M^+, 8), 260 (7), 203 (48), 202 (100), 104 (34), 82 (41); ^1H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3 H), 1.3–2.1 (m, 6H), 3.58 (dd, J = 2.0, 5.9 Hz, 1H), 3.65 (t, J = 7.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 4.18 (t, J = 7.4 Hz, 1H), 4.35 (t, J = 7.4 Hz, 1H), 4.73 (dd, J = 3.1, 9.0 Hz, 1H), 7.2–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.4, 19.5, 27.8, 30.9, 55.3, 60.1, 62.2, 73.3, 87.7, 127.9, 128.6, 128.9, 139.8, 172.5; IR (neat) 1730; HRMS calcd for $C_{16}H_{22}NO_3$ 276.1600, found 276.1608.

4-Phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (4). To a mechanically stirred solution of **3** (1.05 g, 3.9 mmol) in anhydrous ether (65 mL) at −10 °C was added over 15 min a 0.1 M solution of $Zn(BH_4)_2$ in ether (20 mL, 2 mmol). After 1 h at −10 °C, excess reagent was destroyed with 1 N HCl (12 mL) and then decanted. The aqueous layer was extracted twice with CH_2Cl_2. The extracts were dried over $MgSO_4$ and treated with dry HCl in ether (1.5 equiv) and then silica gel (5 g), and the solvent was distilled off. The mixture was resuspended in ether (50 mL), neutralized with NH_4OH, and filtered. Evaporation gave 1.06 g of an oil which could be epimerized directly or separated by chromatography on silica gel eluting with heptane:ether 1:1 to give 750 mg of **4** (85%, 7:3 ratio).

(*4R,9aS*)-**4**: mp 94 °C (heptane); $[\alpha]^{20}_D$ −136.3 (*c* 1.09, MeOH); MS (CI) *m/z* 232 (MH^+, 100), 84 (27); ^1H NMR (250 MHz, $CDCl_3$) δ 1.2–1.7 (m, 5H), 1.85 (d, J = 12.2 Hz, 1H), 2.37 (dd, J = 1.0, 13.1 Hz, 1H), 2.74 (d, J = 11.3 Hz, 1H), 2.90 (dd, J = 1.0, 11.1 Hz, 1H), 3.52 (dd, J = 3.4, 10.7 Hz, 1H), 4.17 (dd, J = 3.8, 10.9 Hz, 1H), 4.28 (t, J = 10.8 Hz, 1H), 7.1–7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.7, 25.0, 28.3, 52.8, 64.8, 65.0, 72.9, 128.5, 128.7, 129.0, 135.6, 168.7; IR (neat) 1735.

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Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.05. Found: C, 72.51; H, 7.40; N, 5.98.

(4*R*,9a*R*)-4: oil, $[\alpha]^{20}_D$ −1.41 (*c* 0.8, MeOH); MS (EI) *m/z* 231 (M^+, 22), 187 (91), 172 (100), 104 (92), 83 (91), 55 (53); ^1H NMR (250 MHz, $CDCl_3$) δ 1.1−2.1 (m, 6H), 2.31 (ddd, *J* = 3.6, 9.6, 12.0 Hz, 1H), 2.7 (dt, *J* = 4.2, 11.9 Hz, 1H), 3.30 (dd, *J* = 3.5, 9.3 Hz, 1H), 3.97 (t, *J* = 5.0 Hz, 1H), 4.43 (dd, *J* = 5.3, 10.9 Hz, 1H), 4.67 (dd, *J* = 4.7, 10.9 Hz, 1H), 7.1−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.2, 24.7, 27.5, 52.5, 58.6, 60.9, 73.0, 129.0, 129.1, 129.5, 136.5, 171.0; IR (neat) 1740. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.05. Found: C, 72.50; H, 7.59; N, 5.92.

(4*R*,9a*S*)-4-Phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (4) from Diastereoisomeric Mixture. To an LDA solution prepared under argon from *n*-BuLi (2.5 mmol) and degassed anhydrous diisopropylamine (350 μL, 2.5 mmol) in THF (3 mL) at −78 °C was added a solution of the diastereoisomeric mixture of lactones **4** (385 mg, 1.67 mmol) in THF (2 mL). After 30 min of stirring at −78 °C, acetic acid (5 mmol) in THF (1 mL) was added, followed after 5 min with a saturated NH_4Cl solution (4 mL). The reaction mixture was extracted twice with CH_2Cl_2, and the organic extracts were washed with water, dried over $MgSO_4$, and evaporated to give 363 mg of a wax (de 96%). Pure (4*R*, 9a*S*)-**4** (323 mg, 84%) was obtained after chromatography on silica gel (heptane:ether 1:1).

General Procedure for Alkylation of 4. To an LDA solution prepared under argon from *n*-BuLi (1.5 equiv) and degassed anhydrous diisopropylamine (1.5 equiv) in THF (1.5 mL/mmol) at −78 °C was added a solution of the diastereoisomeric mixture of lactones **4** (1 equiv) in THF (1.5 mL/mmol). After 30 min of stirring, HMPA (2 equiv) and then electrophile (5 equiv) were added and the mixture was kept at −78 °C until the reaction was complete. The same workup as described for epimerization of **4** was followed. The crude alkylation mixture was submitted for GC-MS analysis and subjected to chromatography on silica gel (heptane:ether 2:1).

(4*R*,9a*S*)-9a-Methyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (6a). This compound was obtained by the general alkylation procedure using methyl iodide as the electrophile and a reaction time of 3 h on a 1.2-mmol scale (79%): mp 77 °C (heptane); $[\alpha]^{20}_D$ −120.7 (*c* 0.45, $CHCl_3$); MS (EI) *m/z* 245 (M^+, 7), 230 (11), 229 (86), 201 (100), 187 (36), 186 (32); ^1H NMR (250 MHz, $CDCl_3$) δ 1.46 (s, 3H), 1.3−1.75 (m, 4H), 1.86 (td, *J* = 4.2, 12.3 Hz, 1H), 2.1−2.3 (m, 2H), 2.42 (dt, *J* = 3.9, 11.9 Hz, 1H), 3.99 (dd, *J* = 5.2, 9.6 Hz, 1H), 4.2−4.4 (m, 2H), 7.2−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.5, 25.9, 35.1, 44.3, 58.8, 60.9, 73.7, 129.0, 129.6, 138.3, 174.3; IR (neat) 1737. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.71. Found: C, 73.43; H, 7.64; N, 5.67.

(4*R*,9a*S*)-9a-Ethyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (6b). This compound was obtained by the general alkylation procedure using ethyl iodide as the electrophile, and a reaction time of 6 h on a 1.4-mmol scale (62%): oil, $[\alpha]^{20}_D$ −90.7 (*c* 0.97, $CHCl_3$); MS (EI) *m/z* 259 (M^+, 2), 230 (100), 215 (10), 111 (7), 82 (8); ^1H NMR (250 MHz, $CDCl_3$) δ 1.0 (t, *J* = 7.4 Hz, 3H), 1.4−2.0 (m, 6H), 2.0−2.25 (m, 2H), 2.3−2.5 (m, 2H), 4.19 (t, *J* = 7.0 Hz, 1H), 4.41 (d, *J* = 7.0 Hz, 1H), 7.2−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 8.5, 19.9, 20.2, 25.2, 30.4, 44.0, 56.7, 63.1, 71.8, 127.8, 128.0, 128.7, 138.8, 172.1; IR (neat) 1737. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.93; H, 7.87; N, 5.43.

(4*R*,9a*R*)-9a-Benzyl-4-phenylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (6c). This compound was obtained by the general alkylation procedure using benzyl bromide as electrophile and a reaction time of 3 h on a 0.9-mmol scale (77%): oil, $[\alpha]^{20}_D$ −143.7 (*c* 0.48, $CHCl_3$); MS (CI) *m/z* 322 (MH^+, 100), 230 (5), 214 (3), 104 (7), 73 (15); ^1H NMR (250 MHz, $CDCl_3$) δ 1.3−2.2 (m, 6H), 2.53 (dt, *J* = 3.9, 11.7 Hz, 1H), 2.67 (td, *J* = 3.1, 11.7 Hz, 1H), 3.28 (d, *J* = 13.6 Hz, 1H), 3.42 (d, *J* = 13.6 Hz, 1H), 4.08 (t, *J* = 7.0 Hz, 1H), 4.28 (d, 2H), 7.2−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.2, 25.3, 32.2, 33.7, 44.0, 57.5, 64.7, 72.5, 126.7, 128.0, 128.2, 128.7, 130.2, 136.9, 138.7, 171.7; IR (neat) 1750. Anal. Calcd for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.35. Found: C, 78.40; H, 7.43; N, 4.37.

(4*R*)-4-Phenyl-4,6,7,8-tetrahydro-3*H*-pyrido[2,1-*c*][1,4]oxazin-1-one (8). This compound was prepared by the general alkylation procedure by bubbling dry O_2 through the reaction mixture for 1 min (88%): oil, $[\alpha]^{20}_D$ −10.8 (*c* 3.8, $CHCl_3$); MS (EI) *m/z* 229 (M^+, 65), 198 (6), 170 (23), 152 (13), 143 (11), 104 (100), 91 (36); ^1H NMR (300 MHz, $CDCl_3$) δ 1.8−2.0 (m, 2H), 2.2−2.35 (m, 2H), 2.54 (dt, *J* = 4.1, 11.1 Hz, 1H), 2.93 (td, *J* = 3.9, 11.1 Hz, 1H), 4.08 (t, *J* = 5.6 Hz, 1H), 4.3−4.4 (m, 2H), 6.28 (t, *J* = 4.2 Hz, 1H), 7.2−7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.1, 46.6, 60.4, 71.6, 115.1, 127.7, 128.7, 129.0, 133.9, 136.6, 161.7; IR (neat) 1731, 1618. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.04; H, 6.45; N, 5.93.

General Procedure for Alkylation of 3. Method A. To a solution of **3** (1 equiv) in anhydrous THF (8 mL/mmol) under argon was added boron trifluoride etherate (1.2 equiv) at −10 °C. After 15 min of stirring, the solution was cooled to −78 °C and the Grignard reagent (1.2 equiv) was added over 10 min. The reaction was quenched with 2 N HCl after 5 min, allowed to warm to rt, neutralized with saturated $NaHCO_3$, and then extracted twice with CH_2Cl_2. Organic extracts were washed with water, dried over $MgSO_4$, and evaporated to give an oil which was submitted to GC-MS analysis and purified by chromatography on silica gel to give **10a,b**.

General Procedure for Alkylation of 3. Method B. To a solution of **3** (1 equiv) in CH_2Cl_2 (1 mL/mmol) under argon was added at rt *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.2 equiv). After 30 min, the reaction mixture was diluted with anhydrous THF (4 mL/mmol) and cooled at −78 °C and then the Grignard reagent (1.2 equiv) was added over 10 min. After 5 min, the reaction was quenched with aqueous NH_4Cl and extracted twice with CH_2Cl_2. The organic extracts were washed with water, dried under $MgSO_4$, and evaporated to give an oil which was submitted to GC-MS analysis and chromatography on silica gel (heptane:ether 95:5) to obtain **9a−c** or to effect desilylation[22] before purification by chromatography on silica gel to give **10a−c**.

1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-phenylethyl]-6-methylpiperidine-2-carboxylic Acid Ethyl Ester (9a). (**2*S*,6*S*,1′*R*)-9a** (major isomer): MS (CI) *m/z* 406 (MH^+, 100), 332 (4), 260 (6), 172 (32); ^1H NMR (250 MHz, $CDCl_3$) δ −0.06 (s, 3H), −0.03 (s, 3H), 0.81 (s, 9H), 1.08 (d, *J* = 6.3 Hz, 3H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.3−1.9 (m, 6H), 3.55−3.6 (m, 1H), 3.65−3.8 (m, 1H), 3.88 (dd, *J* = 7.7, 10.5 Hz, 1H), 3.96 (dd, *J* = 4.3, 10.5 Hz, 1H), 4.10 (q, *J* = 7.4 Hz, 2H), 4.29 (dd, *J* = 4.2, 7.7 Hz, 1H), 7.1−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.5, 14.3, 16.8, 17.2, 25.9, 28.6, 32.2, 49.1, 56.3, 60.0, 66.2, 66.5, 126.9, 127.9, 128.7, 142.5, 176.1; IR (neat) 1728; HRMS calcd for $C_{23}H_{40}NO_3Si$ 406.2778, found 406.2793.

(2*R*,6*R*,1′*R*)-9a: $[\alpha]^{20}_D$ +56.8 (*c* 0.46, $CHCl_3$); MS (CI) *m/z* 406 (MH^+, 100); ^1H NMR (250 MHz, $CDCl_3$) δ −0.09 (s, 3H), −0.08 (s, 3H), 0.82 (s, 9H), 1.07 (d, *J* = 6.4 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 0.9−2.1 (m, 6H), 3.3−3.45 (m, 2H), 3.82 (dd, *J* = 5.2, 10.6 Hz, 1H), 3.90 (dd, *J* = 5.3, 10.6 Hz, 1H), 4.0−4.1 (m, 2H), 4.38 (t, *J* = 5.3 Hz, 1H), 7.2−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −0.1, 14.3, 20.9, 21.7, 25.9, 29.6, 35.9, 49.3, 55.9, 59.8, 61.7, 62.7, 126.2, 127.6, 128.7, 142.6, 176.1; HRMS calcd for $C_{23}H_{40}NO_3Si$ 406.2778, found 406.2784.

1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-phenylethyl]-6-propylpiperidine-2-carboxylic Acid Ethyl Ester (9b). This compound was obtained by method B on a 1.92-mmol scale (66%, 40:32:28 ratio). (**2*S*,6*S*,1′*R*)-9b** (major isomer): oil, $[\alpha]^{20}_D$ −58.9 (*c* 1.2, $CHCl_3$); MS (CI) *m/z* 434 (MH^+, 100), 302 (2), 288 (2), 200 (5); ^1H NMR (250 MHz, $CDCl_3$) δ −0.12 (s, 3H), −0.10 (s, 3H), 0.7−0.9 (m, 12H), 1.1−2.0 (m, 13H), 3.0−3.1 (m, 1H), 3.41 (dd, *J* = 2.7, 5.3 Hz, 1H), 3.78 (dd, *J* = 5.0, 10.6 Hz, 1H), 3.85 (dd, *J* = 5.1, 10.6 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 4.34 (t, *J* = 5.0 Hz, 1H), 7.15−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.5, 14.3, 14.5, 16.6, 18.3, 20.9, 26.0, 26.5, 27.0, 32.1, 54.0, 55.4, 60.0, 66.2, 67.0, 126.9, 127.9, 128.7, 143.0, 176.4; IR (neat) 1725; HRMS calcd for $C_{25}H_{44}NO_3Si$ 434.3090, found 434.3078.

(22) Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, *21*, 3981.

(2S,6R,1'R)-9b: oil, $[\alpha]^{20}_D$ −53.4 (*c* 1.1, $CHCl_3$); MS (CI) *m/z* 434 (MH^+, 100), 302 (8), 288 (2), 251 (10); ^1H NMR (250 MHz, $CDCl_3$) δ −0.08 (s, 3H), −0.07 (s, 3H), 0.74 (s, 9H), 0.82 (t, *J* = 7.1 Hz, 3H), 1.0 (t, *J* = 7.1 Hz, 3H), 1.1−1.8 (m, 10H), 3.3−3.4 (m, 1H), 3.55−3.7 (m, 3H), 3.85 (d, *J* = 6.5 Hz, 2H), 4.18 (t, *J* = 6.5 Hz, 1H), 7.05−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.5, 14.2, 14.6, 18.3, 19.4, 20.7, 26.0, 28.5, 30.6, 35.8, 54.1, 57.0, 59.8, 61.6, 64.8, 126.5, 127.6, 128.2, 141.2, 175.0; IR (neat) 1737; HRMS calcd for $C_{25}H_{44}NO_3Si$ 434.3090, found 434.3070.

(2R,6S,1'R)-9b (minor isomer): oil; MS (CI) *m/z* 434 (MH^+, 100), 302 (11), 288 (3), 200 (12); ^1H NMR (250 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.83 (s, 9H), 0.92 (t, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.3−1.8 (m, 10H), 3.5−3.6 (m, 2H), 3.90 (dd, *J* = 8.7, 10.4 Hz, 1H), 4.02 (dd, *J* = 4.2, 10.4 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 2H), 4.29 (dd, *J* = 4.2, 8.5 Hz, 1H), 7.15−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.3, 14.3, 14.6, 19.0, 20.9, 26.0, 29.0, 31.2, 35.9, 53.6, 56.5, 59.9, 62.1, 62.2, 126.4, 127.8, 128.9, 142.0, 176.0; IR (neat) 1737; HRMS calcd for $C_{25}H_{44}NO_3Si$ 434.3090, found 434.3093.

1-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-phenylethyl]-6-(1-methylethyl)piperidine-2-carboxylic Acid Ethyl Ester (9c). This compound was obtained by method B on a 3.24-mmol scale (20%, 87:10:3:<0.1 ratio). **(2S,6S,1'R)-9c** (major isomer): oil, $[\alpha]^{20}_D$ −37.4 (*c* 1.6, $CHCl_3$); MS (CI) *m/z* 434 (MH^+, 100), 302 (1); ^1H NMR (250 MHz, $CDCl_3$) δ −0.10 (s, 3H), −0.09 (s, 3H), 0.61 (d, *J* = 6.5 Hz, 3H), 0.73 (s, 9H), 0.76 (d, *J* = 7.3 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H), 1.2−1.9 (m, 6H), 2.15−2.25 (m, 1H), 3.70−3.80 (m, 2H), 3.85−4.05 (m, 5H), 7.05−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −5.5, 14.1, 15.7, 18.2, 19.9, 21.5, 22.3, 24.3, 25.9, 28.7, 55.8, 60.3, 62.0, 65.7, 68.8, 127.1, 127.9, 129.0, 142.2, 176.3; IR (neat) 1725; HRMS calcd for $C_{25}H_{44}NO_3Si$ 434.3090, found 434.3117.

6-Methyl-4-phenylhexahydropyrido[2,1-c][1,4]oxazin-1-one (10a). This compound was obtained by general procedures with methylmagnesium chloride, 22% w/v, in THF. Elution with CH_2Cl_2 gave 88% on a 0.36-mmol scale with method A and 55% of (*4R,6S,9aS*)-**10a** and 75% on a 2.0-mmol scale with method B and 56% of (*4R,6S,9aS*)-**10a**. **(4R,6S,9aS)-10a**: mp 107 °C (heptane); $[\alpha]^{20}_D$ −126.3 (*c* 1.33, $CHCl_3$); MS (EI) *m/z* 245 (M^+, 13), 229 (22), 201 (80), 186 (43), 104 (100), 97 (100); ^1H NMR (250 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.2 Hz, 3H), 1.1−1.9 (m, 5H), 2.1−2.2 (m, 1H), 2.68 (dqd, *J* = 2.8, 6.1, 9.6 Hz, 1H), 3.39 (dd, *J* = 2.7, 10.7 Hz, 1H), 4.03 (d, *J* = 4.3 Hz, 1H), 4.20 (d, *J* = 11.6 Hz, 1H), 4.69 (dd, *J* = 4.3, 11.6 Hz, 1H), 7.2−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.2, 27.9, 35.2, 58.2, 59.7, 60.3, 69.7, 126.9, 127.1, 128.3, 144.6, 172.6; IR (KBr) 1755. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.80; N, 5.71. Found: C, 73.44; H, 7.77; N, 5.31.

6-Propyl-4-phenylhexahydropyrido[2,1-c][1,4]oxazin-1-one (10b). This compound was obtained with 1-propylmagnesium bromide (2 M in THF prepared with 1-propylbromide and Mg). Elution with CH_2Cl_2 gave 90% on a 1.35-mmol scale with method A and 39% of (*4R,9aS,6S*)-**10b** and 74% on a 0.94-mmol scale with method B and 30% of (*4R,9aS,6S*)-**10b**.

(4R,6S,9aS)-10b: mp 98 °C (heptane); $[\alpha]^{20}_D$ −92.4 (*c* 0.37, $CHCl_3$); MS (EI) *m/z* 273 (M^+, 2), 230 (100), 104 (10), 82 (15); ^1H NMR (300 MHz, $CDCl_3$) δ 0.58 (t, *J* = 7.1 Hz, 3H), 0.8−1.5 (m, 6H), 1.6−1.8 (m, 2H), 1.89 (dt, *J* = 3.3, 12.7 Hz, 1H), 2.14 (dquint, *J* = 3.0, 13.4 Hz, 1H), 2.56 (ddt, *J* = 3.0, 7.9, 10.6 Hz, 1H), 3.39 (dd, *J* = 2.7, 10.8 Hz, 1H), 4.05 (d, *J* = 4.1 Hz, 1H), 4.20 (dd, *J* = 0.6, 11.7 Hz, 1H), 4.70 (dd, *J* = 3.9, 11.7 Hz, 1H), 7.2−7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.6, 23.2, 27.8, 31.5, 36.4, 58.6, 60.2, 64.2, 69.7, 126.9, 127.1, 128.3, 144.3, 172.8; IR (KBr) 1737. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.65; H, 8.46; N, 5.38.

(4R,6R,9aR)-10b: oil; MS (EI) *m/z* 273 (M^+, 10), 230 (100), 229 (10), 104 (19), 82 (60); ^1H NMR (300 MHz, $CDCl_3$) δ 0.5−1.8 (m, 12H), 2.3−2.4 (m, 1H), 2.73 (dq, *J* = 2.8, 10.9 Hz, 1H), 3.52 (dd, *J* = 2.7, 10.7 Hz, 1H), 3.95 (dd, *J* = 3.5, 10.1 Hz, 1H), 4.17 (dd, *J* = 3.5, 10.7 Hz, 1H), 4.29 (t, *J* = 10.4 Hz, 1H), 7.3−7.5 (m, 5H); ^{13}C NMR δ ($CDCl_3$) 14.1, 19.3, 20.0, 23.1, 26.9, 29.6, 53.7, 56.9, 60.1, 73.2, 128.6, 128.7, 128.9, 136.4, 170.5; IR (NaCl) 1743; HRMS calcd for $C_{25}H_{44}NO_3Si$ 273.1729, found 273.1738.

(4R,6S,9aR)-10b: mp 72 °C (heptane); MS (EI) *m/z* 273 (M^+, 33), 230 (100), 214 (14), 104 (13), 82 (12); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J* = 7.1 Hz, 3H), 1.0−1.9 (m, 9H), 2.0−2.2 (m, 1H), 2.5−2.6 (m, 1H), 4.05 (dd, *J* = 3.4, 8.9 Hz, 1H), 4.21 (t, *J* = 10.8 Hz, 1H), 4.29 (dd, *J* = 4.4, 11.1 Hz, 1H), 4.35 (dd, *J* = 4.35, 10.7 Hz, 1H), 7.3−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.3, 19.6, 24.5, 25.4, 34.1, 54.9, 55.3, 57.8, 72.7, 128.1, 128.4, 128.9, 138.0, 171.5; IR (NaCl) 1743; HRMS calcd for $C_{25}H_{44}NO_3Si$ 273.1729, found 273.1721.

6-(1-Methylethyl)-4-phenylhexahydropyrido[2,1-c][1,4]-oxazin-1-one (10c). This compound was obtained with method B on a 0.3-mmol scale with 2-propylmagnesium bromide (2 M) in THF prepared with 2-propylbromide and Mg. Elution with heptane:ether 1:1 gave 11% of (9a*S*,6*R*)-**10c**. **(4R,6R,9aS)-10c**: mp 174 °C (heptane); $[\alpha]^{20}_D$ −105.8 (*c* 1.66, $CHCl_3$); MS (EI) *m/z* 273 (M^+, 1), 231 (48), 230 (100), 104 (22), 82 (98); ^1H NMR (300 MHz, $CDCl_3$) δ 0.26 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 1.2−1.5 (m, 2H), 1.5−1.8 (m, 2H), 1.8−2.0 (m, 3H), 2.14 (dquint, *J* = 2.8, 13.2 Hz, 1H), 2.46 (dt, *J* = 2.4, 10.5 Hz, 1H), 3.41 (dd, *J* = 2.7, 10.9 Hz, 1H), 4.04 (d, *J* = 4.2 Hz, 1H), 4.12 (d, *J* = 11.8 Hz, 1H), 4.70 (dd, *J* = 4.1, 11.7 Hz, 1H), 7.1−7.3 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.3, 20.6, 23.1, 24.2, 27.9, 28.5, 59.3, 60.7, 69.6, 70.1, 127.1, 127.2, 128.3, 144.0, 172.9; IR (KBr) 1756. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.31; H, 8.25; N, 5.13.

General Procedure for Hydrogenolysis. A hydrogenation flask was charged with a solution of substrate in a mixture of ethanol:acetic acid 2:1 (30 mL/mmol). After addition of 10% Pd/C (90 mg/mmol), the apparatus was charged with hydrogen. The reaction was complete within 30 min to 1 h under vigorous stirring. The slurry was filtered, evaporated to dryness using a toluene azeotrope, and submitted to adsorption chromatography using HP-20 SS resin (except for **6c**) eluting with a step gradient of water−1% acetic acid and methanol. Further purification was effected by recrystallization.

(S)-2-Piperidinecarboxylic Acid (5). This compound was obtained by the general hydrogenolysis procedure on a 0.86-mmol scale. The resin was eluted with water (70% yield): mp >250 °C dec (water); $[\alpha]^{20}_D$ −26.0 (*c* 2.9, H_2O), lit. −27.0 (0.2, H_2O),[6a] −26 (5, H_2O).[6b] Anal. Calcd for $C_6H_{11}NO_2$: C, 55.79; H, 8.58; N, 10.84. Found: C, 55.61; H, 8.32; N, 10.78.

(S)-2-Methyl-2-piperidinecarboxylic Acid (7a). This compound was obtained by the general hydrogenolysis procedure on a 0.41-mmol scale. The resin was eluted with 1% methanol (60% yield). Spectral data were in complete agreement with literature:[7,8] mp >250 °C dec (methanol:acetone 1:2); $[\alpha]^{20}_D$ −3.6 (*c* 0.7, H_2O), lit. −3.7 (*c* 0.2, H_2O),[9] −3.7 (*c* 2, H_2O),[23] −4 (*c* 0.97, H_2O);[7] ^{13}C NMR (D_2O, dioxane) δ 20.1, 22.1, 23.6, 32.6, 42.7, 63.4, 176.7. Anal. Calcd for $C_7H_{13}NO_3$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.85; H, 8.93; N, 9.82.

(S)-2-Ethyl-2-piperidinecarboxylic Acid (7b). This compound was obtained by the general hydrogenolysis procedure on a 0.19-mmol scale. The resin was eluted with water (76% yield). Spectral data were in complete agreement with literature:[7] mp >250 °C dec (methanol ether 3:1); $[\alpha]^{20}_D$ −12.4 (*c* 0.8, H_2O), lit.[7] −12 (*c* 1.1, H_2O); ^{13}C NMR (D_2O, dioxane) δ 7.9, 20.3, 22.4, 31.3, 31.8, 43.0, 66.5, 174.6. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.83; H, 9.46; N, 8.76.

(R)-2-Benzyl-2-piperidinecarboxylic Acid (7c). This compound was obtained by the general hydrogenolysis procedure on a 0.28-mmol scale. Because of its low solubility as zwiterion, **6c** was purified as its hydrochloride using ion exchange resine Dowex 50W-X8[9] (70% yield). Since the elemental analysis of the sample thus obtained was in poor agreement with the calculated values, $[\alpha]_D$ data may not be reliable: mp >250 °C dec (water); $[\alpha]^{20}_D$ −3.3° (*c* 0.6, H_2O), lit.[9] −3.0 (*c* 0.2, H_2O); ^{13}C NMR (D_2O, MeOH, NH_4OH) δ 22.1, 24.5, 34.1, 43.2, 47.1, 65.4, 126.9, 128.4, 130.6, 137.2, 175.2.

(2S,6S)-6-Methyl-2-piperidinecarboxylic Acid (11a). This compound was obtained by the general hydrogenolysis procedure on a 1.13-mmol scale. The resin was eluted with water (59% yield): mp >250 °C dec (methanol:ether 1:2); $[\alpha]^{20}_D$ −33.2 (*c* 1.2, H_2O); ^1H NMR data were in agreement with

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literature;[24] MS (EI) *m/z* 143 (M^+, 4), 128 (9), 98 (100), 82 (12), 70 (16), 55 (21); ^{13}C NMR ($CDCl_3$) δ 19.3, 23.2, 26.9, 30.3, 53.4, 60.6, 174.6; IR (KBr) 3090, 2990, 2610, 1622, 1405, 1363, 1180, 1024, 1001, 782. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.61; H, 9.38; N, 9.78.

(2*S*,6*S*)-6-Propyl-2-piperidinecarboxylic Acid (11b). This compound was obtained by the general hydrogenolysis procedure on a 0.36-mmol scale. The resin was eluted with 4% methanol (64% yield): mp >250 °C dec (methanol ether 1:4); $[\alpha]^{20}_D$ −22.8 (*c* 0.36, H_2O); MS (EI) *m/z* 171 (M^+, 8), 170 (6), 129 (30), 128 (100), 126 (100), 82 (93), 55 (47); ^1H NMR (300 MHz, DMSO-d_6) δ 0.97 (t, J = 7.2 Hz, 3H), 1.2−1.65 (m, 6H), 1.65−1.9 (m, 3H), 2.1−2.2 (m, 1H), 2.8−3.0 (m, 1H), 3.15 (dd, J = 2.3, 10.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 19.5, 24.1, 28.0, 28.9, 36.7, 57.7, 61.8, 176.2; IR (KBr) 2950, 1643, 1600, 1412. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 63.29; H, 9.88; N, 8.38.

(2*S*,6*R*)-6-(1-Methylethyl)-2-piperidinecarboxylic Acid (11c). This compound was obtained by the general hydrogenolysis procedure on a 0.16-mmol scale. The resin was eluted with 6% methanol (74% yield): mp >250 °C dec (methanol:ether 1:5); $[\alpha]^{20}_D$ −31.7 (*c* 0.3, H_2O); MS (EI) *m/z* 171 (M^+, 1), 170 (2), 129 (31), 128 (100), 126 (45), 82 (97), 55 (73); ^1H NMR (300 MHz, DMSO-d_6) δ 0.93 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 1.2−1.4 (m, 1H), 1.45−1.65 (m, 2H), 1.9−2.0 (m, 3H), 2.2−2.3 (m, 1H), 2.83 (ddd, J = 2.6, 6.5, 12.1 Hz, 1H), 3.42 (dd, J = 3.1, 12.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 19.5, 24.2, 25.8, 27.8, 32.3, 62.4, 63.5, 175.6; IR (KBr) 2964, 1622, 1600, 1403. Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.69; H, 9.52; N, 8.18.

Acknowledgment. We are indebted to Mrs. M.-A. Billion for GC-MS analysis.

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