An Efficient Access to Enantiomerically Pure Substituted Derivatives of Pipecolic Acid

Claude Agami, Sébastien Comesse, and Catherine Kadouri-Puchot*

Laboratoire de Synthèse Asymétrique (UMR CNRS 7611), Case courrier 47, Université P. et M. Curie, 4 place Jussieu, 75005 Paris, France

kadouri@ccr.jussieu.fr

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Pipecolic acid **1** and its numerous derivatives are attractive synthetic targets, since these cyclic β-amino acids are present in many biologically important compounds.[1] For example, (2*R*,4*R*)-methylpipecolic acid **2** is a key component for the preparation of a highly selective thrombin inhibitor,[2] and (2*S*,4*S*)-hydroxypipecolic acid **3** is a naturally occurring compound isolated from *Acacia* species.[3,4] The synthesis of trans-configured 6-alkyl substituted pipecolic acid derivatives is of current interest since they represent key precursors to antibiotics such as solenopsin A.[5] We now report a general method[6] for the preparation of 6-alkyl and 4,6-disubstituted derivatives of pipecolic acid **4**−**6**. All these compounds present a trans relation between the 6-substituent and the acid carboxylic moiety (Figure 1).

The general features of these syntheses are illustrated, in retrosynthetic format, in Scheme 1. It was projected to construct bicyclic intermediate **8** from a diastereoselective intramolecular attack of an allylsilane moiety onto an iminium ion.[7] A diastereoselective addition of an organometallic compound on oxazolidine **10** would furnish key intermediate **9** possessing the requisite allylsilane moiety.

Results

Synthesis of (2*S*,4*S*,6*R*)-4-Methyl-6-ethylpipecolic Acid 5. Chiral oxazolidine **12** was obtained quantitatively by reaction of (*S*)-phenylglycinol **11** with propionaldehyde. This heterocycle was reacted with [2-((trimethylsilyl)methyl)prop-2-enyl]lithium **16**.[8] The reactivity of simple organolithium compounds onto phenylglycinol-derived oxazolidines is well documented,[9] but to the best of our knowledge, no reaction of the more complex lithium reagent **16** onto oxazolidines has ever been described. In the event, oxazolidine **12** reacted with reagent **16** to afford β-amino alcohols **14** with 73% yield and a 95/5 diastereomeric ratio. Reaction between glyoxal and β-amino alcohol **14** gave quantitatively bicyclic compound **17** (Scheme 2). The creation of the stereocenter at the ring junction was totally diastereoselective. This material was an epimeric mixture at the hemiacetal

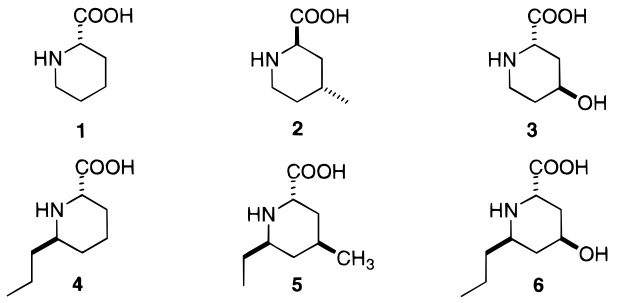
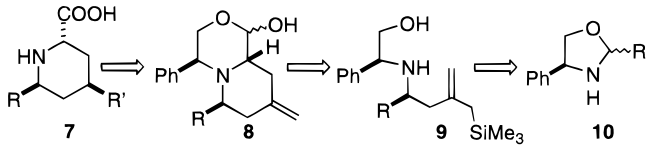
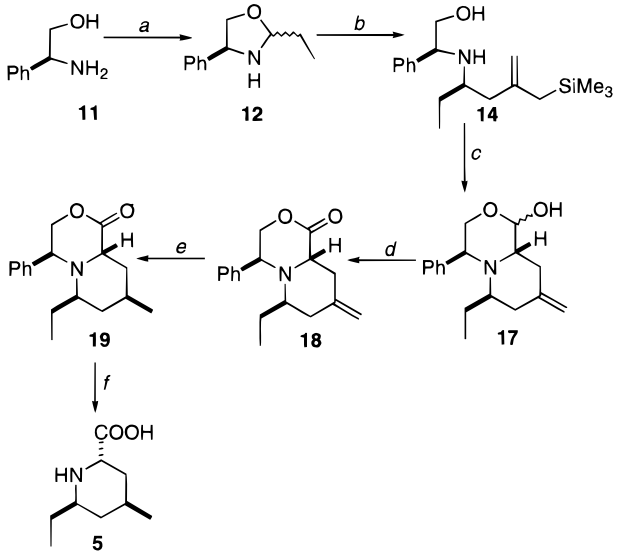


Figure 1.

Scheme 1



Scheme 2[a]



[a] Reaction conditions: (a) EtCHO, THF, $MgSO_4$, rt, 98%; (b) $TMSCH_2C(=CH_2)CH_2Li$ **16**, THF, −78 to −20 °C, 73%; (c) CHO-CHO, THF/H_2O, rt, 98%; (d) Me_2SO, $(COCl)_2$, NEt_3, −60 °C to room temperature, 91%; (e) H_2, PtO_2, 70%; (f) H_2, $Pd(OH)_2$, 95%.

* To whom correspondence should be addressed. Fax: (33) 01 44 27 26 20.

(1) See, for example: (a) Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914. (b) Jones, J. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157. (c) Sehgal, S. N.; Baker, H.; Eng, C. P.; Singh, K.; Véniza, C. *J. Antibiot.* **1983**, *36*, 351.

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(6) For a preliminary report, see: Agami, C.; Comesse, S.; Kadouri-Puchot, C.; Lusinchi, M. *Synlett* **1999**, 1094.

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(9) Bloch, R. *Chem. Rev.* **1998**, *98*, 1413.

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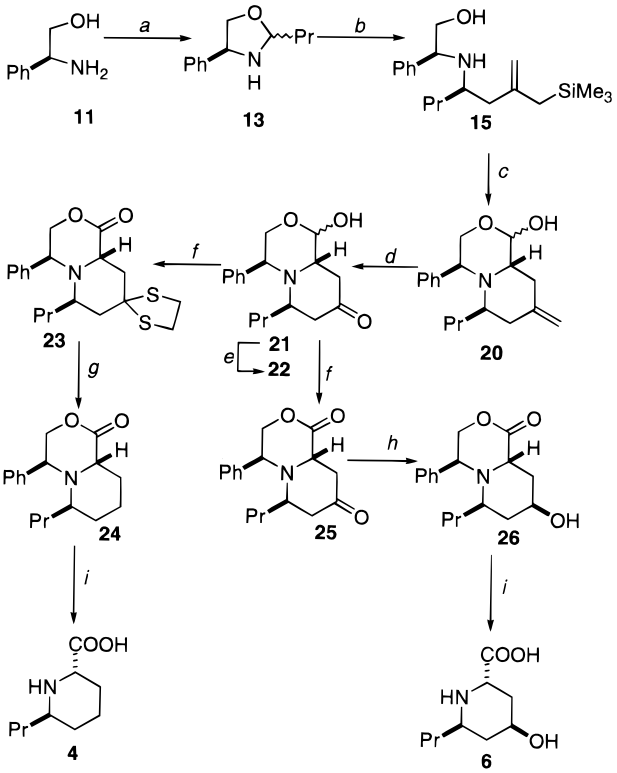
Scheme 3[a]



[a] Reaction conditions: (a) PrCHO, THF, $MgSO_4$, rt, 98%; (b) $TMSCH_2C(=CH_2)CH_2Li$ **16**, THF, −78 to −20 °C, 80%; (c) CHO-CHO, THF/H_2O, rt, 98%; (d) OsO_4, $NaIO_4$, THF, H_2O, rt, 75%; (e) $(CH_2SH)_2$, BF_3-Et_2O, $HCCl_3$, rt, 95%; (f) Me_2SO, $(COCl)_2$, NEt_3, CH_2Cl_2, −60 °C to room temperature, 77% from **22** and 90% from **21**; (g) H_2, Raney nickel, 45%; (h) K-Selectride, THF, −78 °C, 54%; (i) H_2, $Pd(OH)_2$, 98% from **24** and **26**.

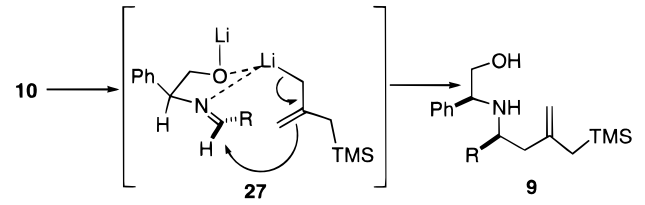
center. Swern oxidation of this hemiacetal function was followed by a diastereoselective hydrogenation of the ethylenic double bond. Two diastereomers (85/15 dr) resulted from this reduction. The stereochemistry of the three created asymmetric centers was determined from an X-ray analysis of the major compound **19**.[10] Finally, hydrogenolysis of lactone **19** afforded the enantiopure disubstituted derivative of pipecolic acid **5**.

Synthesis of (2*S*,6*R*)-6-Propylpipecolic Acid 4 and (2*S*,4*S*,6*R*)-4-Hydroxy-6-propylpipecolic Acid 6. Oxazolidine **13** obtained quantitatively from the condensation between butyraldehyde and (*S*)-phenylglycinol **11** was reacted with organolithium reagent **16** with 80% yield and 95/5 dr to afford amino alcohol **15**, which was transformed into the unsaturated hemiacetal **20**. Oxidative cleavage of the ethylenic double bond of compound **20** furnished ketone **21**, which reacted with ethane dithiol to give derivative **22**. Swern oxidation of compound **22** provided lactone **23**. Removal of the dithiane group by hydrogen in the presence of Raney nickel followed by a hydrogenolysis of lactone **24** resulted in the formation of the diastereomerically pure amino acid **4** (Scheme 3).

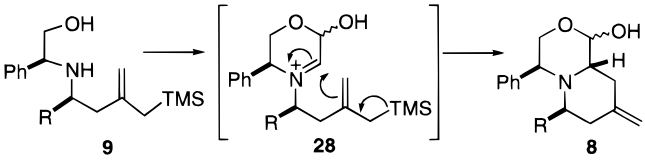
In another way, compound **21** was transformed into lactone **25** by Swern oxidation. A diastereoselective reduction of the keto group by K-selectride afforded alcohol **26** as a sole diastereomer. X-ray analysis was performed on this bicyclic alcohol[10] in order to determine

(10) The X-ray analysis were performed by Dr. J. Vaissermann at the Laboratoire de Chimie des Métaux de Transition (Université P. et M. Curie).

Scheme 4



Scheme 5



the absolute configuration of the stereogenic centers. Finally, hydrogenolysis of the compound **26** gave quantitatively the enantiopure amino acid **6**.

Discussion

Asymmetric Induction during the Syntheses of *β*-Amino Alcohols 14 and 15. As described above, the addition of the lithium reagent **16** on the oxazolidines **12** and **13** gave, respectively, *β*-amino alcohols **14** and **15** with a 95/5 dr. This diastereofacial selectivity can be rationalized by assuming the formation of the chelated intermediate **27**. This intermediate undergoes an internal delivery of the nucleophile from the less hindered side of the chelate, i.e., the *Si* face of the imine moiety (Scheme 4). It is well-known[9,11a] that a primary amine-derived oxazolidine exists as an equilibrium mixture with its imine tautomer showing an *E* geometry.

This stereoselective course leads in both cases to an *R* configuration at the created stereogenic center. This result is in agreement with previously reported reactions between oxazolidines-derived from phenylglycinol and simple organolithium compounds such as MeLi[11] or PhLi.[12]

Asymmetric Induction during the Cyclization Step. The key step of our methodology is based on a totally stereoselective reaction between the allylsilane and the iminium ion moieties in intermediate **28** (Scheme 5).

The stereoselective formation of the stereocenter at the ring junction corresponds to what was already described on similar iminium ions:[7,13] chiral induction by the phenyl-bearing stereocenter leads the addition of the olefinic double bond to occur on the less encumbered face, i.e., the *Si* face of the cyclic iminium ion. It is worth noting that during this cyclization leading to compounds **8** the integrity of the stereogenic center bearing the R substituent was not altered. In connection with the huge amount of published works in this field,[14] this process

(11) See, for example: (a) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron Lett*. **1992**, *33*, 235. (b) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083. (c) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem*. **1991**, *56*, 1340.

(12) See, for example: Delorme, D.; Berthelette, C.; Lavoie, R.; Roberts, E. *Tetrahedron: Asymmetry* **1998**, *9*, 3963.

(13) Agami, C.; Couty, F.; Puchot-Kadouri, C. *Synlett* **1998**, 449.

(14) (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford 1991; Vol. 2, pp 975−1006.

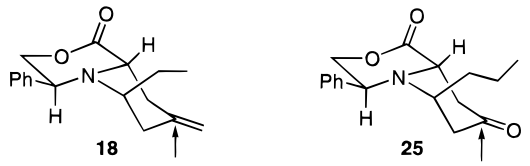


Figure 2.

can be viewed as a classical ene/iminium reaction since such a concerted one-step process should not affect this center. This fact seems to preclude the occurrence of a two-step process involving an aza-Cope rearrangement followed by an ene/iminium addition, which has recently been put forward by Mariano et al.[15] in order to explain their results.

Asymmetric Induction during the Reduction of Unsaturated Bonds. The attack of hydrogen on lactone **18** as well as the action of K-Selectride on ketone **25** follows the same stereochemical outcome. The major product resulting from the hydrogenation of the double bond corresponds to an approach on the *Re* face of bicyclic compound **18**. The same requirement is involved during the attack of K-Selectride on ketone **25**. Molecular modelization shows that the more stable conformation (Figure 2) of compounds **18** and **25** is a cis-bicyclic structure in which the phenyl and the alkyl substituents (Et in **18** and Pr in **25**) are respectively in an equatorial and axial geometry. The attack on the *Re* face can thus be rationalized on a steric basis.

In conclusion, diastereomerically pure amino acids **4**, **5**, and **6** were synthesized from (2*S*)-phenylglycinol in 18%, 43%, and 28% overall yield, respectively, via two stereoselective key steps: a nucleophilic addition of a silylated allyllithium reagent on an oxazolidine-derived imine and an ene−iminium cyclization involving an allylsilane moiety.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$ solutions unless otherwise stated) were carried out at 250 and 62.9 MHz. ^{1}H NMR and ^{13}C NMR spectra for lactone **18** were carried out at 400 and 100 MHz. Column chromatography was performed on silica gel 230−400 mesh with various mixtures of ethyl acetate (AcOEt) or diethyl ether (Et_2O) and petroleum ether (PE). Tetrahydrofuran was distilled from benzophenone ketyl. For X-ray analysis of compounds **19** and **26**, data were collected at room temperature. The program used was CRYSTALS. No significant variations were observed in the intensities of two checked reflections during data collection. The structure was solved by use of SHELXS86 program, G. M. Sheldrick, Program for Crystal Structure Solution, University of Göttingen, 1986, and refined by full-matrix least-squares analysis with anisotropic thermal parameters for all non hydrogen atoms. H atoms were introduced in calculated positions in the last refinement.

General Procedure for the Preparation of Oxazolidines 12 and 13. Propionaldehyde or butyraldehyde (5.85 mmol) was added dropwise to a solution of (2*S*)-phenylglycinol (800 mg, 5.85 mmol) in THF (12 mL) in the presence of $MgSO_4$. The mixture was stirred at room temperature for 1 h and filtered over Celite 545. The solution was concentrated under reduced pressure to afford a mixture of cis and trans oxazolidines in a quantitative yield. This mixture was engaged in the next step without further purification.

Oxazolidine (12). ^{1}H NMR: 7.28−7.17 (m, 5H), 4.47−4.42 (m, 1H), 4.30−4.17 (two t, J = 7.4 and 7.5 Hz, 1H), 4.00 (t, J = 7.7 Hz, 0.5H), 3.62−3.55 (m, 1.5H), 2.28−2.05 (m, 1H), 1.72−1.64 (m, 2H), 1.02−0.93 (m, 3H). ^{13}C NMR: 142.5, 140.5, 129.0, 128.7, 128.0, 127.4, 127.3, 127.0, 126.5, 94.1, 93.7, 72.5, 71.5, 62.5, 60.6, 27.6, 27.2, 9.6, 9.5.

Oxazolidine (13). ^{1}H NMR: 7.29−7.13 (m, 5H), 4.49−4.38 (m, 1H), 4.30−4.15 (two t, J = 7.4 and 7.8 Hz, 1H), 4.00 (t, J = 7.6 Hz, 0.5H), 3.80−3.46 (m, 1.5H), 2.28−2.05 (m, 1H), 1.67−1.55 (m, 2H), 1.48−1.38 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR: 142.7, 140.6, 129.1, 128.8, 128.1, 127.5, 127.4, 127.1, 126.6, 93.2, 92.8, 72.7, 71.7, 62.8, 60.9, 37.0, 36.8, 19.1, 19.0, 14.4.

General Procedure for the Synthesis of β-Amino Alcohols. To a solution of organolithium compound **16**[8] (7.5 mmol) in THF (45 mL), stirred at −78 °C, was added a solution of freshly prepared oxazolidines (3 mmol) in THF (5 mL). Stirring was continued for 30 min at −78 °C. The solution was allowed to reach −20 °C over 45 min. The mixture was hydrolyzed with a saturated solution of ammonium chloride (25 mL), and the aqueous layer was extracted with diethyl ether. The combined organic layers were dried over K_2CO_3 and evaporated under reduced pressure to afford a diastereomeric mixture (diastereomeric ratios were determined by GC (GC OV17) analysis of crude material) of β-amino alcohols (95/5 dr) which was chromatographed (AcOEt/PE: 20/80). The minor diastereomer was eliminated during the chromatography step.

(1*R*,2*S*)-Phenyl-2-(1-ethyl-3-trimethylsilanylmethylbut-3-enylamino)ethanol (14). White solid (yield 73%). Mp: 58 °C. $[\alpha]^{20}_D$: +75 (*c* 0.9, $HCCl_3$). ^{1}H NMR: 7.36−7.22 (m, 5H), 4.61−4.58 (m, 2H), 3.83 (dd, J = 4.6, 8.3 Hz, 1H), 3.64 (dd, J = 4.6, 10.6 Hz, 1H), 3.46 (dd, J = 8.3, 10.6 Hz, 1H), 2.56−2.52 (m, 1H), 2.11 (dd, J = 6.4, 14.3 Hz, 1H), 1.95 (dd, J = 6.9 and 13.6 Hz, 1H), 1.80−1.60 (m, 2H), 1.44 (d, J = 3.2 Hz, 2H), 1.43−1.23 (m, 2H), 0.77 (t, J = 7.4 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR: 145.6, 142.0, 128.8, 127.8, 127.6, 110.1, 67.0, 62.5, 55.0, 43.8, 28.1, 26.8, 10.3, −0.9. IR ($CHCl_3$): 2900, 1820, 1750 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NOSi$: C, 70.76; H, 10.23; N, 4.58. Found: C, 70.77; H, 10.25; N, 4.52.

(1*R*,2*S*)-Phenyl-2-(1-propyl-3-trimethylsilanylmethylbut-3-enylamino)ethanol (15). White solid (yield: 80%). Mp: 58 °C. $[\alpha]^{20}_D$: +63 (*c* 0.9, $HCCl_3$). ^{1}H NMR: 7.36−7.21 (m, 5H), 4.60−4.57 (m, 2H), 3.85 (dd, J = 4.6, 8.3 Hz, 1H), 3.65 (dd, J = 4.6, 10.6 Hz, 1H), 3.47 (dd, J = 8.3, 10.5 Hz, 1H), 2.62−2.56 (m, 1H), 2.17−2.08 (m, 2H), 2.15 (dd, J = 6.0, 13.4 Hz, 1H), 1.92 (dd, J = 6.7, 13.5 Hz, 1H), 1.42 (d, J = 4.6 Hz, 2H), 1.40−1.10 (m, 4H), 0.75 (t, J = 6.8 Hz, 3H), 0.00 (s, 9H). ^{13}C NMR: 145.4, 141.8, 128.6, 127.6, 127.4, 109.8, 66.8, 62.2, 53.1, 44.1, 37.6, 26.7, 18.9, 14.2, −1.0. IR ($CHCl_3$): 2900, 1820, 1750 cm^{-1}. Anal. Calcd for $C_{19}H_{33}NOSi$: C, 71.41; H, 10.41; N, 4.38. Found: C, 71.45; H, 10.32; N, 4.28.

General Procedure for the Formation of Hemiacetals. Glyoxal (40% weight, 1.1 mL) was added to a solution of amino alcohol **14** or **15** (1.66 mmol) in THF/H_2O (v/v: 1/1, 6.6 mL). The mixture was stirred for 5 h at room temperature, and water (6 mL) was added. Extraction with CH_2Cl_2 was followed by drying the organic layers on $MgSO_4$. After evaporation under reduced pressure, chromatography on silica gel (AcOEt/PE: 20/80) gave the corresponding hemiacetals (yield: 98%) as a mixture (50/50 for **17** and 70/30 for **20**) of diastereomers at C-1.

(4*S*,6*R*,9*S*)-8-Methylene-4-phenyl-6-ethyloctahydropyrido-[2,1-*c*][1,4]oxazin-1-ol (17). Only the characteristic peaks are given. ^{1}H NMR: 7.23−7.10 (m, 5H), 4.87 (d, J = 2.7 Hz, 0.5H), 4.75 (s, 0.5H), 4.65−4.63 (m, 1H), 4.51−4.49 (m, 1H), 4.22 (dd, J = 4.1, 11 Hz, 0.5H), 4.06 (dd, J = 3.8, 10.5 Hz, 0.5H), 3.76 (t, J = 11.5 Hz, 0.5H), 3.67 (dd, J = 3.8, 11.4 Hz, 0.5H), 1.42−0.85 (m, 4H), 0.65 (two t, J = 6.7 Hz, 3H). ^{13}C NMR: 144.5, 143.8, 139.4, 129.1, 128.9, 128.7, 128.5, 128.4, 128.2, 110.1, 109.8, 96.0, 93.6, 72.3, 65.3, 60.8, 57.6, 57.4, 56.4, 56.2, 55.4, 54.5, 32.8, 32.5, 31.6, 26.3, 23.8, 21.5, 14.6, 11.3. IR ($CHCl_3$): 3324, 2910, 1689, 1635, 1430 cm^{-1}.

(4*S*,6*R*,9a*S*)-8-Methylene-4-phenyl-6-propyloctahydropyrido[2,1-*c*][1,4]oxazin-1-ol (20). ^{1}H NMR: 7.24−7.12 (m, 5H), 4.86 (d, J = 2.9 Hz, 0.3H), 4.76 (s, 0.7H), 4.66−4.63 (m, 1H), 4.52−4.47 (m, 1H), 4.20 (dd, J = 4.0, 11.1 Hz, 0.7H), 4.05 (dd, J = 3.7, 10.4 Hz, 0.3H), 3.77 (t, J = 11.7 Hz, 0.7H), 3.66 (dd, J = 3.7, 11.5 Hz, 0.3H), 1.43−0.80 (m, 4H), 0.64 and 0.63 (two t, J = 6.7 Hz, 3H). ^{13}C NMR: 144.3, 143.6, 139.3, 139.1, 128.8, 128.6, 128.5, 128.3, 128.1, 127.9, 109.9, 109.6, 95.8, 93.3,

(15) Wu, X.-D.; Khim, S.-K.; Zhang, X.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 841.

71.9, 64.9, 57.3, 57.1, 55.1, 54.6, 54.3, 33.1, 32.7, 32.4, 31.3, 29.8, 26.0, 19.6, 19.5, 14.3(CH_3). IR ($CHCl_3$): 3324, 2910, 1689, 1635, 1430 cm^{-1}.

(4*S*,6*R*,9a*S*)-1-Hydroxy-4-phenyl-6-propylhexahydropyrido[2,1-*c*][1,4]oxazin-8-one (21). Osmium tetraoxide (800 μL, 4% solution in H_2O, 0.12 mmol) was added to a solution of hemiacetal **20** (510 mg, 1.78 mmol) in THF/H_2O (1/1, v/v, 24 mL) at room temperature. Stirring was continued for 5 min, and $NaIO_4$ (1.9 g, 8.9 mmol) was added by fraction over 30 min. After the end of addition, stirring was maintained for an additional 15 min. The mixture was hydrolyzed with an aqueous solution of $Na_2S_2O_3$ (7.5%, 15 mL). The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over $MgSO_4$. After evaporation, the residue was chromatographed (AcOEt/PE: 30/70) to afford ketone **21** (385 mg, 75%) as a mixture (60/40) of two diastereomers at C-1. ^{1}H NMR: 7.32−7.19 (m, 5H), 5.09 (bs, 0.6H), 4.85 (bs, 0.4H), 4.17 (dd, J = 3.6 and 10.7 Hz, 0.4H), 4.07−3.93 (m, 1H), 3.83 (dd, J = 3.7 and 11.7 Hz, 1H), 3.65−3.29 (m, 2.6H), 3.07−2.57 (m, 3H), 2.40−2.28 (m, 0.6H), 2.15−2.08 (m, 0.4H), 1.93−1.84 (m, 1H), 1.40−1.20 (m, 2H), 1.19−1.08 (m, 2H), 0.76−0.68 (m, 3H). ^{13}C NMR: 210.2, 208.8, 138.6, 129.0, 128.9, 128.6, 128.4, 128.2, 94.9, 92.8, 71.5, 64.7, 57.7, 57.4, 56.6, 56.4, 55.0, 54.6, 41.2, 40.9, 39.7, 34.8, 34.6, 19.3, 19.2, 14.0. IR ($CHCl_3$): 3370, 2720, 1709, 1470 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.44; H, 8.17; N, 4.78.

General Procedure for Swern Oxidation. Dimethyl sulfoxide (0.52 mL, 7.39 mmol) was added dropwise to a solution of oxalyl chloride (0.27 mL, 3.06 mmol) in dichloromethane (6 mL) at −60 °C. The mixture was stirred for 10 min, and a solution of hemiacetal **17**, **21** or **22** (2.55 mmol) in dichloromethane (5 mL) was introduced. After 30 min at −60 °C, triethylamine (1.77 mL, 12.7 mmol) was added, and the mixture was allowed to warm to room temperature in 1 h. Addition of water (15 mL) and extraction with dichloromethane gave after evaporation of the combined organic layers a residue that was chromatographed to afford corresponding lactone.

(4*S*,6*R*,9a*S*)-8-Methylene-4-phenyl-6-ethyloctahydropyrido[2,1-*c*][1,4]oxazin-1-one (18). Oil (AcOEt/PE: 20/80) (yield: 91%). $[\alpha]_D$: +81 (*c* 1.0, $HCCl_3$). ^{1}H NMR (400 MHz): 7.38−7.36 (m, 5H), 4.86 (d, J = 1.6 Hz, 1H), 4.70 (d, J = 1.6 Hz, 1H), 4.44 (dd, J = 4.5, 9.7 Hz, 1H), 4.33−4.24 (m, 2H), 4.02 (dd, J = 3.8, 12.0 Hz, 1H), 2.72 (dd, J = 12.0, 13.9 Hz, 1H), 2.68−2.61 (m, 1H), 2.43 (dd, J = 3.8, 14.1 Hz, 1H), 2.29 (dd, J = 4.3, 13.6 Hz, 1H), 1.70 (d, J = 13.6 Hz, 1H), 1.55−1.45 (m, 1H), 1.25−1.13 (m, 1H), 0.81 (t, J = 7.4 Hz, 3H). ^{13}C NMR (400 MHz): 170.5, 141.3, 136.4, 129.1, 128.8, 128.6, 110.8, 73.8, 56.0, 55.9, 55.7, 33.1, 32.8, 23.5, 10.8. IR ($CHCl_3$): 3320, 2980, 2920, 1750, 1465 cm^{-1}. HRMS: calcd for $C_{17}H_{21}NO_2$ ($M + H^+$) m/z = 272.1651, obsd m/z = 272.1648.

Lactone (23). Oil (AcOEt/PE: 20/80) (yield: 77%). $[\alpha]^{20}_D$: +93 (*c* 1.7, $HCCl_3$). ^{1}H NMR: 7.34−7.28 (m, 5H), 4.30−4.21 (m, 3H), 4.17 (dd, J = 3.3, 11.4 Hz, 1H), 3.35−3.28 (m, 2H), 3.26−3.20 (m, 2H), 2.70−2.66 (m, 1H), 2.52 (dd, J = 11.4, 13.9 Hz, 1H), 2.17 (dd, J = 5.6, 14.5 Hz, 1H), 2.13−2.08 (m, 1H), 1.77−1.65 (m, 2H), 1.36−1.12 (m, 3H), 0.76 (t, J = 7.1 Hz, 3H). ^{13}C NMR: 170.6, 136.1, 129.0, 128.8, 128.5, 73.0, 64.5, 55.8, 55.1, 54.0, 40.3, 40.0, 37.3, 36.7, 34.6, 20.1, 14.0. IR ($CHCl_3$): 2990, 1720, 1460, 736 cm^{-1}. HRMS: calcd for $C_{19}H_{26}NO_2S_2$ ($M + H^+$) m/z = 364.1405, obsd m/z = 364.1402.

(4*S*,6*R*,9a*S*)-4-Phenyl-6-propylhexahydropyrido[2,1-*c*][1,4]oxazine-1,8-dione (25). Solid (AcOEt/PE: 30/70) (yield: 90%). Mp: 104 °C. $[\alpha]^{20}_D$: +71 (*c* 0.5, $HCCl_3$). ^{1}H NMR: 7.37−7.31 (m, 5H), 4.34−4.23 (m, 2H), 4.26 (t, J = 4.7 Hz,1H), 4.19 (dd, J = 4.3, 11.7 Hz, 1H), 3.08−3.00 (m, 1H), 2.80 (dd, J = 11.7, 14.5 Hz, 1H), 2.55 (ddd, J = 2.0, 4.3, 14.6 Hz, 1H), 2.45 (dd, J = 5.9, 14.1 Hz, 1H), 1.91 (dt, J = 2.1, 14.1 Hz, 1H), 1.39−1.24 (m, 2H), 1.20−1.08 (m, 2H), 0.74 (t, J = 6.9 Hz, 3H).^{13}C NMR: 205.4, 168.7, 135.2, 129.3, 128.5, 73.6, 56.3, 56.1, 55.8, 41.6, 40.1, 34.4, 19.1, 13.8. IR ($CHCl_3$): 2990, 2650, 1720, 1450 cm^{-1}. HRMS: calcd for $C_{17}H_{22}NO_3$ ($M + H^+$) m/z = 288.1600, obsd m/z = 288.1600.

(4*S*,6*R*,8*S*,9a*S*)-8-Methyl-4-phenyl-6-ethyloctahydropyrido[2,1-*c*][1,4]oxazin-1-one (19). A solution of lactone **18** (100 mg, 0.369 mmol) in benzene/acetone (1/1, 2 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of PtO_2 (15 mg) in benzene/acetone (1/1, 1 mL). The hydrogenation was complete into 30 min. The mixture was filtered through Celite 545 and the residue washed with acetone. The filtrate was evaporated to dryness, leaving the corresponding crude methylated derivative as a diastereomeric mixture (85/15 at C-8; 95%) that was recrystallized with pentane to afford compound **19** as white crystals. Mp: 147 °C. $[\alpha]^{20}_D$: −150 (*c* 1.2, $HCCl_3$). ^{1}H NMR: 7.45−7.25 (m, 5H), 4.34 (dd, J = 2.6, 8.3 Hz, 1H), 4.20−4.07 (m, 2H), 3.99 (dd, J = 2.2, 5.1 Hz, 1H), 2.49−2.39 (m, 1H), 2.28−2.19 (m, 1H), 1.93−1.77 (m, 1H), 1.75−1.66 (m, 1H), 1.55−1.32 (m, 2H), 1.20−1.05 (m, 1H), 1.00 (d, J = 6.2 Hz, 3H), 1.00−0.88 (m, 1H), 0.72 (t, J = 7.4 Hz, 3H). ^{13}C NMR: 172.9, 140.4, 128.7, 127.6, 126.7, 69.7, 62.4, 61.0, 54.4, 39.4, 33.1, 27.1, 25.5, 22.2, 9.3. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.79; H, 8.48; N, 5.12. Found: C, 74.67; H, 8.54; N, 5.19.

Crystal data: $C_{17}H_{23}NO_2$, orthorhombic, no centrosymmetric $P2_1$ space group, Z = 4, D_c = 1.18 g cm^{-3}, μ(Mo Kα) = 0.72 cm^{-1}, a = 7.650(2) Å, b = 10.114(1) Å, c = 19.857(2) Å, β = 90°, V = 1536.3(5) Å^3. The final refinement of 200 parameters using 1032 reflections (with $(F_o)^2 > 3\sigma(F_o)^2$) were used to solve and refine the structure to R = 0.0388 and R_w = 0.0491.

Compound 22. Ethane dithiol (320 μL, 3.82 mmol) was added slowly at −10 °C to a solution of hemiacetal **21** (54 mg, 0.19 mmol) and BF_3·Et_2O (94 μL, 0.74 mmol) in $CHCl_3$ (1.8 mL) under inert atmosphere. The mixture was stirred at −10 °C for 2 h and then allowed to reach rt in 2 h. Addition of a solution of $NaHCO_3$ (10 mL) was followed by extraction with CH_2Cl_2. The organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatographed (AcOEt/EP: 20/80) to afford compound **22** (65 mg, 95%) as a mixture of diastereomers in a ratio of 70/30. ^{1}H NMR: 7.27−7.19 (m, 5H), 4.92 (s, 0.3H), 4.84 (bs, 0.7H), 4.15 (dd, J = 4.1, 11 Hz, 0.7H), 4.12−3.83 (m, 0.3H), 3.95−3.60 (m, 1H), 3.45 (dd, J = 4.1, 11.7 Hz,1H), 3.32−3.20 (m, 4H), 2.71−2.20 (m, 4H), 1.72−1.66 (m, 2H), 1.34−1.13 (m, 4H), 0.72 (2t, J = 7.1 Hz, 3H).^{13}C NMR: 138.0, 126.8, 126.3, 91.3, 63.5, 62.9, 55.5, 52.8, 52.1, 38.5, 36.7, 35.5, 34.3, 32.5, 18.6, 12.2. IR ($CHCl_3$): 3324, 2920, 1450 cm^{-1}. HRMS: calcd for $C_{19}H_{28}NO_2S_2$ ($M + H^+$) m/z = 366.1561, obsd m/z = 366.1551.

(4*S*,6*R*,9a*S*)-4-Phenyl-6-propylhexahydropyrido[2,1-*c*]-[1,4]oxazin-1-one (24). To a solution of compound **23** (77 mg, 0.212 mmol) in MeOH (2 mL) was added a suspension of Raney nickel in MeOH (2 mL). The mixture was hydrogenated for 2 h, filtered on Celite 545, and evaporated under reduced pressure. The crude residue was chromatographed (Et_2O/EP: 25/75) to afford lactone **24** as a white solid (26 mg, 45%). Mp: 81 °C. $[\alpha]^{20}_D$: −26 (*c* 1, $HCCl_3$). ^{1}H NMR: 7.39−7.27 (m, 5H), 4.39−4.16 (m, 3H), 4.05 (dd, J = 3.5, 9.5 Hz, 1H), 2.57−2.54 (m, 1H), 2.18−1.98 (m, 1H), 1.76−1.62 (m, 5H), 1.30−1.12 (m, 4H), 0.77 (t, J = 7.2 Hz, 3H).^{13}C NMR: 172.1, 138.1, 128.7, 128.5, 128.3, 72.8, 57.8, 55.3, 55.0, 34.1, 29.9, 25.3, 19.7, 19.5, 14.1. HRMS: calcd for $C_{17}H_{24}NO_2$ ($M + H^+$) m/z = 274.1807, obsd m/z = 274.1802.

(4*S*,6*R*,8*S*,9a*S*)-8-Hydroxy-4-phenyl-6-propylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (26). A 1 M solution of K-Selectride in THF (425 μL, 0.42 mmol) was added at −78 °C to a solution of compound **25** (122 mg, 0.42 mmol) in THF (4.2 mL). The mixture was stirred at −78 °C for 80 min and then hydrolyzed by addition of a saturated aqueous solution of ammonium chloride (5 mL), and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The crude residue was chromatographed on silica gel (AcOEt/EP: 25/75) to furnish compound **26** as a single diastereomer (67 mg, 54%). White solid. Mp: 137 °C. $[\alpha]^{20}_D$: −114 (*c* 0.5, $HCCl_3$). ^{1}H NMR: 7.35−7.19 (m, 5H), 4.37−4.33 (m, 1H), 4.13−4.00 (m, 4H), 2.49−2.37 (m, 2H), 1.97−1.83 (m, 2H), 1.70−1.59 (m, 1H), 1.44−1.35 (m, 1H), 1.30−1.08 (m, 4H), 0.57 (t, J = 7.1 Hz, 3H). ^{13}C NMR: 172.5, 139.4, 128.9, 127.9, 127.0, 70.5, 64.5, 60.4, 59.0, 54.0, 38.7, 36.3, 33.5, 18.2, 14.1. IR ($CHCl_3$): 2817, 1720, 1450 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.51; H, 8.08; N, 4.70.

Crystal data: $C_{17}H_{23}NO_3$, monoclinic, no centrosymmetric $C2$ space group, Z = 4, D_c = 1.21 g cm^{-3}, μ(Mo Kα) = 0.77 cm^{-1}, a = 15.554(17) Å, b = 6.222(3) Å, c = 16.784(12) Å, β =102.81-(7)°, V = 1536.3(5) Å^3. The final refinement of 200 parameters using 1298 reflections (with $(F_o)^2 > 3\sigma(F_o)^2$) were used to solve and refine the structure to R = 0.0596 and R_w = 0.0694.

General Procedure for the Hydrogenolysis of Bicyclic Lactones. A solution of lactone (0.15 mmol) in absolute ethanol

(1.5 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of 20% $Pd(OH)_2/C$ (Pearlman catalyst) (0.04 g) in absolute ethanol (1.5 mL). The hydrogenation was complete in 4−6 h. The mixture was filtered through Celite 545 and the residue washed with ethanol to give after evaporation the corresponding amino acid.

(2S,6*R*)-6-Propylpiperidinecarboxylic Acid (4). White solid (yield: 98% from lactone **24**). Mp: 240 °C dec. $[\alpha]^{20}_D$: +44 (*c* 0.8, H_2O). ^1H NMR (D_2O): 3.92 (t, J = 4.7 Hz, 1H), 3.46−3.43 (m, 1H), 2.09−2.08 (m, 1H), 1.93−1.58 (m, 5H), 1.48−1.37 (m, 4H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C NMR (D_2O): 174.1, 56.2, 53.9, 34.2−27.5−25.3, 19.1−18.2, 13.2. HRMS: calcd for $C_9H_{18}NO_2$ ($M + H^+$) m/z = 172.1338, obsd m/z = 172.1342.

(2*S*,4*S*,6*R*)-4-Methyl-6-ethylpiperidinecarboxylic Acid (5). White solid (yield: 95% from lactone **19**). Mp: 220 °C dec. $[\alpha]^{20}_D$: +19 (*c* 0.5, H_2O). ^1H NMR (D_2O): 3.87−3.85 (m, 1H), 3.22−3.16 (m, 1H), 2.16−2.11 (m, 1H), 1.83−1.78 (m, 1H), 1.59−1.27 (m, 4H), 0.94−0.79 (m, 7H). ^{13}C NMR (D_2O): 174.6, 57.9, 56.7, 37.1, 33.6, 27.5, 27.3, 21.9, 9.9. HRMS: calcd for $C_9H_{18}NO_2$ ($M + H^+$) m/z = 172.1338, obsd m/z = 172.1337.

(2*S*,4*S*,6*R*)-4-Hydroxy-6-propylpiperidinecarboxylic acid (6). White solid (yield: 98% from lactone **26**). Mp: 220 °C dec. $[\alpha]^{20}_D$: +15 (*c* 0.6, H_2O). ^1H NMR (D_2O): 4.09 (dd, J = 2.5, 5.7 Hz, 1H), 3.82−3.70 (m, 1H), 3.57−3.45 (m, 1H), 2.57−2.49 (m, 1H), 2.22−2.13 (m, 1H), 1.79−1.57 (m, 3H), 1.50−1.33 (m, 3H), 0.92 (t, J = 7.25 Hz, 3H). ^{13}C NMR (D_2O): 171.7, 62.7, 54.9, 51.9, 35.7, 34.0, 32.0, 16.9, 12. HRMS: calcd for $C_9H_{18}NO_3$ ($M + H^+$) m/z = 188.1287, obsd m/z = 188.1290.

MO Calculations. The geometries of the conformations of compounds **18** and **25** were optimized by using the Davidson−Fletcher−Powel algorithm (FLEPO procedure), minimizing the energy with respect to all internal coordinates.[16]

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Supporting Information Available: Spectrometric information (^1H NMR) for compounds **4**−**6**, **18**, **19**, and **22**−**26** and two ORTEP drawings (X-ray analysis of compounds **19** and **26**). This material is available free of charge via the Internet at http://pubs.acs.org.

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