The Intriguing Reactivity of Functionalized β-Amino Alcohols with Glyoxal: Application to a New Expedient Enantioselective Synthesis of *trans*-6-Alkylpipecolic Acids

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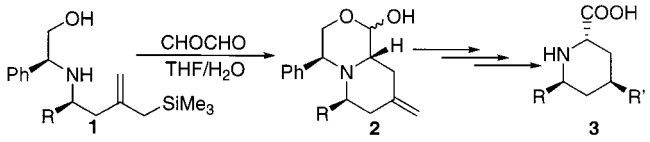
New β-amino alcohols possessing a vinylsilane moiety were reacted with glyoxal to produce lactones that were transformed in three steps in enantiopure pipecolic acid derivatives. The key step was a totally diastereoselective ene−iminium cyclization, whose mechanism can be viewed as a direct cyclization of the vinylsilane moiety onto the iminium ion. The reactivity of two β-amino alcohols having an allylsilane terminator was also examined. Their difference of reactivity toward glyoxal can be ascribed to the intervention of a carbocation, which presents a behavior that differs according to the position of the trimethylsilyl group.

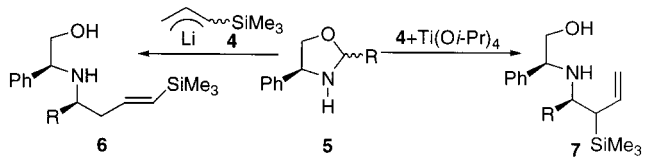
Intramolecular cyclizations between allyl or vinylsilane and iminium ion moieties serve as one of the most general methods for the synthesis of N-heterocyclic compounds. As demonstrated by the pioneer work of the Overman group,[1] these Mannich-type cyclizations have found considerable applications in the field of natural product synthesis.[2,3] Our group has developed a wide range of syntheses of enantiopure derivatives of pipecolic acid by using, in the key step, an ene−iminium cyclization between glyoxal and silylated β-amino alcohols.[4] For example, a spontaneous intramolecular cyclization occurred when β-amino alcohol **1** was mixed with glyoxal (Scheme 1). This quantitative and totally diastereoselective reaction forms bicyclic compound **2**, which is a valuable precursor for the synthesis of 4,6-disubstituted pipecolic acid derivatives.[5]

Our interest in the synthesis of pipecolic acid derivatives was significantly enhanced by the discovery of a new method to produce β-amino alcohols derived from phenylglycinol.[6,7] We have recently studied reactions between

Scheme 1



Scheme 2



the organolithium reagent derived from allyltrimethylsilane **4**[8] and oxazolidines **5**, which afforded β-amino alcohols **6** possessing an *E* vinylsilane moiety. A change of selectivity was observed when these reactions were performed in the presence of titanium isopropoxide,[9] thus producing compounds **7** (Scheme 2). The study of the reactivity of β-amino alcohols **6** and **7** toward glyoxal should constitute an obvious extension of the above-mentioned methodology.

This article describes (i) a novel synthetic application allowing a rapid access to diastereoisomerically pure pipecolic acid derivatives and (ii) a comparison between the reactivities of these β-amino alcohols toward the glyoxal.

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(1) (a) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. (b) Overman, L. E.; Ricca, D. J. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Trost, B. M., Flemming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1007.

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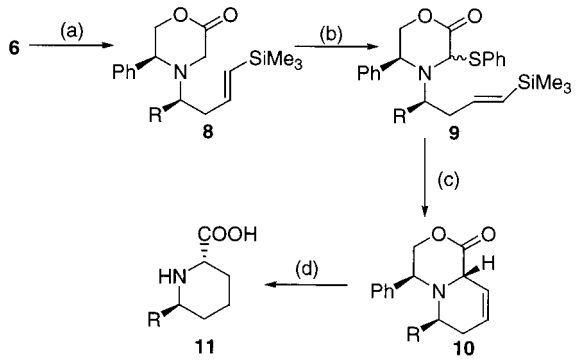
Results

The various steps needed to obtain pipecolic acid derivatives are described on Scheme 3. β-Amino alcohols **6** were treated with glyoxal in ethanol[10] to obtain lactones **8**, which were isolated as pure isomers in good yields. These compounds were then treated by diphenyl disulfide in the presence of lithium bis(trimethylsilyl)amide[11] in order to afford morpholinones **9** as a mixture of diastereoisomers relative to the stereogenic carbon bearing the thiophenyl group.[12] Treatment of these morpholinones with zinc chloride produced the bicyclic lactones **10** with an excellent diastereoselectivity (de > 95%) (cf. Table 1). Finally, action of hydrogen in the presence of palladium hydroxide gave trans 6-alkylated pipecolic acid **11a**−**c**.

An *S* absolute configuration of the created stereogenic center has been deduced from a correlation with the already described 6-propylpipecolic acid **11a**.[5] The lowest yield resulting from the cyclization of compound **9c** is due to the formation of byproduct **12**, whose configuration was established from a NOESY experiment (see Scheme 4).

Scheme 3[a]



[a] Reaction conditions: (a) CHOCHO, EtOH, reflux, 2 h; (b) LiHMDS,THF, −45 °C, 15 min, then, PhSSPh; (c) $ZnCl_2$, CH_2Cl_2, rt, 1 h 30; (d) H_2, $Pd(OH)_2$, EtOH.

Scheme 4

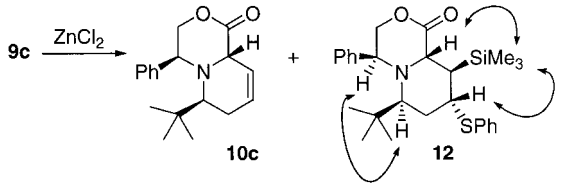
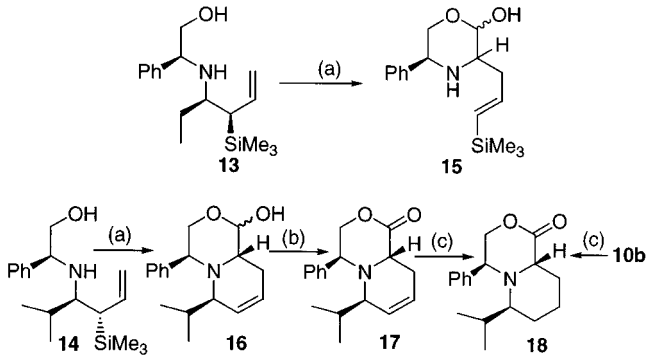


Table 1. Isolated Yields in the Synthesis of Lactones 10

6	lactone **8** (%)	aminothioether derivative **9** (%)	lactone **10** (%)
6a, R = Pr	78	66	79
6b, R = *i*-Pr	78	73	78
6c, R = *t*-Bu	74	55	62
6d, R = Ph	66	38	83

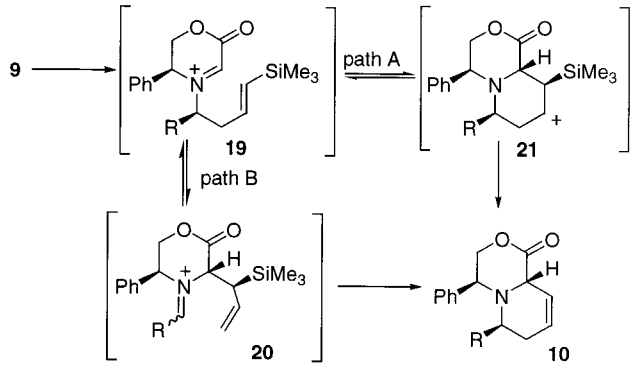
The reactivity of two β-amino alcohols **13** and **14** possessing an allylsilane function (Scheme 5) was then

Scheme 5[a]



[a] Reaction conditions: (a) CHOCHO, THF−H_2O, rt, 24 h for **15** or 48 h for **16**; (b) DMSO, $COCl_2$, NEt_3, −60 °C to rt; (c) H_2, PtO_2, Et_2O, rt, 2 h.

Scheme 6



studied.[13] Compound **13** treated with glyoxal afforded the cyclic amine **15** as a sole product. Under the same conditions, amino alcohol **14** gave the bicyclic derivative **16**. A Swern oxidation followed by a hydrogenation of the endocyclic double bond furnished the diastereoisomerically pure lactone **18**. This lactone was identical to the hydrogenated product resulting from lactone **10b**.

From a stereochemical point of view, all the cyclizations reported above show that the iminium ion undergoes an anti attack by the unsaturated silane moieties with respect to the phenyl group. This stereochemical outcome is consistent with previous observations.[4]

Discussion

To account for these transformations, an intricate component has to be addressed, i.e., the possible occurrence of an aza-Cope rearrangement which could take place prior to the cyclizations.

Cyclization of the Vinylsilane Derivatives 6. From a mechanistic point of view, the reactions described above can be viewed either as a simple reaction between the vinylsilane and the iminium moieties followed by elimination of the silyl group (path A, Scheme 6) or as the result of a tandem aza-Cope/allylsilane addition process in which the second step is rate determining (path B, Scheme 6).[14] This problem is crucial in asymmetric synthesis, and it has to be considered in relation to the conservation of the integrity of the stereocenters. In the

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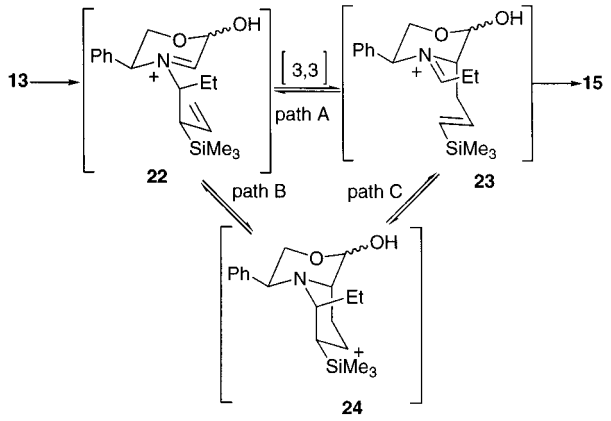
(11) (a) Bull, S. D.; Davies, S. G.; Fox, D. J.; Sellers, T. G. R. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1483. (b) Galland, J.-C.; Roland, S.; Malpart, J.; Savignac, M.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 621.

(12) We have not determined the stereochemistry of the center bearing the thiophenyl group, because the stereogenic character of this carbon disappear in the generation of iminum ion in the following step.

(13) The configuration of compounds **13** and **14** are respectively described in ref 6a,b.

(14) (a) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (b) McCann, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6107.

Scheme 7



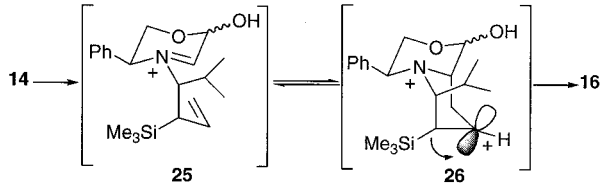
case of a sigmatropic rearrangement, the fast equilibrium between iminium ions **19** and **20** should produce at least a partial racemization of the stereocenters.

As described above, no loss of the stereochemical integrity of the stereogenic center bearing the R group was observed during the cyclization of the vinylsilane derivative **6** (Scheme 3). It is interesting to note that Mariano et al.[3b] stated that this fact should preclude the occurrence of an aza-Cope rearrangement. Actually, they reported such an epimerization during their works on oxidative Mannich cyclization of allylsilanes. On these grounds, the fact that no epimerization took place in the present cyclizations should discard the alternative process featuring an aza-Cope rearrangement.[15]

Cyclization of Allylsilane Derivatives 13 and 14. In regard to the cyclizations involving the allylsilane derivatives, the mechanism seems strongly dependent on the substrate, which comes into play since compounds **13** and **14**, which essentially differ by their relative configuration, present different behaviors. The reaction between β-amino alcohol **13** and glyoxal affords compound **15**, which clearly results from the hydrolysis of the iminium moiety in intermediate **23**. This intermediate can be produced either by an aza-Cope rearrangement (path A in Scheme 7) or via a cyclization yielding carbocation **24** (path B in Scheme 7) capable of undergoing a Grob fragmentation (path C in Scheme 7).[16]

What happens in the case of β-amino alcohol **14** may give a clue in order to discriminate between these two putative mechanisms. Actually, in this case, no product derived from a hydrolysis of a rearranged iminium ion was produced. Most probably, the cyclization leading to compound **16** involves the silyl-stabilized cation **26** analogous to cation **24**. However, cation **26** presents a silyl substituent in an axial geometry, thus favoring the elimination of this group[17] (cf. Scheme 8). This phenomenon has already been invoked to explain the difference of reactivity between *Z* and *E* isomers of vinylsilanes in an ene−iminium cyclization.[2c,18] Therefore, there is a great temptation to assume that both cations **24** and **26** are operating in the case of these cyclizations involving allylsilane derivatives.[19]

Scheme 8



In conclusion, these various β-amino alcohols possessing an unsaturated silyl moiety can be considered as valuable substrates for the stereoselective synthesis of pipecolic acid derivatives. The fact that these compounds exhibit different reactivities is incentive to clear up the mechanistic aspects of these reactions. The results reported here extend the various parameters that control the ene-iminium cyclizations. As regards our own results, it appears that there is no need to invoke any aza-Cope rearrangement to account for what was observed. However, it is worth noting that many authors have already underscored the complexity of this problem, and so far, no general conclusions have been reached.

Experimental Section

General Methods. ^{1}H and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were, respectively, recorded on a Bruker ARX 250 spectrometer at 250 and 62.9 MHz. Optical rotations were determined with a Perkin-Elmer 141 instrument. All reactions were carried out under argon exept those performed in aqueous medium. Column chromatography was performed on silica gel, 230−400 mesh by using various mixtures of diethyl ether (Et_2O) and petroleum ether (PE). Melting points are uncorrected. THF was distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Compositions of stereoisomeric mixtures were determined by NMR analysis on crude products before any purification.

General Procedure for the Syntheses of Lactones 8. Glyoxal (0.32 mL, 40% weight, 2.6 mmol) was added to a solution of β-amino alcohols (1.7 mmol) in EtOH (11 mL). The mixture was stirred for 2 h. at reflux, and the solvent was evaporated at reduced pressure to afford a residue that was chromatographed to give lactone.

[4(1*R*),5*S*]-4-(1-Propyl-4-trimethylsilanylbut-3-enyl)-5-phenylmorpholin-2-one (8a). Oil (Et_2O/PE 10/90). Yield: 78%. $[\alpha]^{20}_D$: +53 (*c* 3, $CHCl_3$).^{1}H NMR: 7.40−7.27 (m, 5H), 5.78−5.66 (m, 1H), 5.57 (d, J = 18.5 Hz, 1H), 4.26−4.23 (m, 2H), 4.06 (dd, J = 8.2 and 5.7 Hz, 1H), 3.77 (AB, J = 17.5 Hz, 1H), 3.51 (AB, J = 17.5 Hz, 1H), 2.63−2.52 (m, 1H), 2.41−2.32 (m, 1H), 2.00−1.89 (m, 1H), 1.55−1.39 (m, 1H), 1.37−1.06 (m, 3H), 0.78 (t, J = 7.2 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR: 169.7, 143.8, 137.1, 132.9, 128.8, 128.5, 128.4, 72.8, 60.4, 57.4, 46.3, 35.6, 33.7, 19.5, 14.0, −1.3. Anal. Calcd for $C_{20}H_{31}NO_2Si$: C, 69.52; H, 9.04; N, 4.05. Found: C, 69.48; H, 9.19; N, 3.99.

[4(1*S*),5*S*]-4-(1-Isopropyl-4-trimethylsilanylbut-3-enyl)-5-phenylmorpholin-2-one (8b). Oil (Et_2O/PE 10/90). Yield: 78%. $[\alpha]^{20}_D$: +36 (*c* 1.7, $CHCl_3$). ^{1}H NMR: 7.41−7.28 (m, 5H), 5.89 (dt, J = 18.5, 6.0 Hz, 1H), 5.66 (m, 1H), 4.31−4.18 (m, 2H), 4.14 (dd, J = 9.5, 4.0 Hz, 1H), 3.78 (AB, J = 17.7 Hz, 1H), 3.60 (AB, J = 17.7 Hz, 1H), 2.42−2.22 (m, 3H), 1.71−1.62 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H), 0.79 (d, J = 6.5 Hz, 3H), 0.04 (s, 9H). ^{13}C NMR: 169.9, 145.3, 137.4, 132.3, 128.7,

(15) A reviewer has rightly noticed that this observation indeed makes the aza-Cope pathway unlikely but does not definitely rule it out. For example, if the cyclization rate of one of the isomer of intermediate **20** is significantly greater than the other, then only one isomer of compound **10** will be observed.

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(18) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739.

(19) Substrates **13** and **14** differ essentially by their relative configurations, which are responsible of the equatorial geometry of the silyl group in **22** whereas it occupies an axial position in intermediate **25**. It could be noted that those compounds differ also by the nature of the alkyl group (ethyl or isopropyl) in an α-position with respect to the silyl moiety. However, it seems unlikely that the opposite behavior of cations **22** and **25** could be due to any steric difference between the ethyl and isopropyl group.

127.5, 72.7, 63.6, 60.9, 47.1, 35.3, 31.3, 20.8, 20.7, −2.3. Anal. Calcd for $C_{20}H_{31}NO_2Si$: C, 69.52; H, 9.04; N, 4.05. Found: C, 69.34; H, 8.92; N, 4.00.

[4(1*S*),5*S*]-4-(1-*tert*-Butyl-4-trimethylsilanylbut-3-enyl)-5-phenylmorpholin-2-one (8c). Oil (Et_2O/PE 10/90). Yield: 74%. $[\alpha]^{20}_D$: −10 (*c* 0.6, $CHCl_3$). ^{1}H NMR: 7.28−7.15 (m, 5H), 6.00−5.87 (m, 1H), 5.71−5.64 (m, 1H), 4.23−4.02 (m, 3H), 3.82 (AB, *J* = 17.5 Hz, 1H), 3.69 (AB, *J* = 17.5 Hz, 1H), 2.41−2.23 (m, 3H), 0.68 (s, 9H), 0,03 (s, 9H). ^{13}C NMR: 170.7, 146.7, 138.3, 132.6, 129.0, 128.5, 71.7, 67.2, 62.8, 48.9, 36.0, 34.0, 28.8, −1.3. Anal. Calcd for $C_{21}H_{33}NO_2Si$: C, 70.14; H, 9.25; N, 3.90. Found: C, 70.14; H, 9.44; N, 3.73.

[4(1*S*),5*S*]-5-Phenyl-4-(1-phenyl-4-trimethylsilanylbut-3-enyl)morpholin-2-one (8d). Oil (Et_2O/PE 10/90). Yield: 66%. $[\alpha]^{20}_D$: +9 (*c* 1.8, $CHCl_3$). ^{1}H NMR: 7.53−7.44 (m, 5H), 7.39−7.33 (m, 5H), 5.80 (dt, *J* = 18.5, 5.5 Hz, 1H), 5.68 (d, *J* = 18.5 Hz, 1H), 4.44−4.38 (m, 2H), 4.30 (m, 1H), 3.93 (dd, *J* = 6.5, 7.5 Hz, 1H), 3.62 (s, 2H), 2.78−2.72 (m, 2H), 0.00 (s, 9H). ^{13}C NMR: 169.5, 142.8, 139.6, 137.3, 133.6, 129.1, 128.7, 128.5, 128.4, 127.5, 72.5, 62.1, 59.9, 47.7, 33.7, −1.3. Anal. Calcd for $C_{23}H_{29}NO_2Si$: C, 72.78; H, 7.70; N, 3.69. Found: C, 72.50; H, 8.05; N, 3.38.

General Procedure for Thiophenylation of Lactones 9. Lithium bis(trimethylsilyl)amide (2.66 mL, 2.66 mmol, 1 M in THF) was added at −45 °C to a solution of lactone (1.33 mmol) in THF (11 mL). After the solution was stirred at this temperature for 15 min, a solution of diphenyl disulfide (0.511 g, 2.34 mmol) in THF (4 mL) was added dropwise, and the mixture was allowed to reach slowly 0 °C and hydrolyzed with NH_4Cl (15 mL). The aqueous layer was extracted twice with Et_2O, and the organic layers were dried over $MgSO_4$ and evaporated. The residue was chromatographed to afford corresponding lactones as a various mixture of diastereoisomers at C-3.

[4(1*R*),5*S*]-5-Phenyl-3-phenylsulfanyl-4-(1-propyl-4-trimethylsilanylbut-3-enyl)morpholin-2-one (9a). Solid (Et_2O/PE 3/97). Yield: 66%. ^{1}H NMR: 7.59−7.56 (m, 2H), 7.47−7.35 (m, 8H), 5.89 (dt, *J* = 6.5, 18.5 Hz, 1H), 5.67 (d, *J* = 18.5 Hz, 1H), 5.06 (s, 1H), 4.80 (t, *J* = 11.5 Hz, 1H), 4.30 (dd, *J* = 4.2, 11.5 Hz, 1H), 4.20 (dd, *J* = 4.2, 11.5 Hz, 1H), 2.73−2.62 (m, 1H), 2.39−2.28 (m, 1H), 2.18−2.07 (m, 1H), 1.66−1.44 (m, 2H), 1.38−1.26 (m, 1H), 1.20−1.08 (m, 1H), 0.72 (t, *J* = 7.0 Hz, 3H), 0.03 (s, 9H). ^{13}C NMR: 166.0, 143.1, 137.6, 134.5, 134.3, 132.7, 129.3, 129.0, 128.7, 128.9, 128.4, 69.9, 66.9, 60.8, 59.2, 39.2, 35.4, 20.1, 13.9, −1.3. Anal. Calcd for $C_{26}H_{35}NO_2SSi$: C, 68.83; H, 7.78; N, 3.09. Found: C, 68.81; H, 7.94; N, 2.93.

[4(1*S*),5*S*]-4-(1-Isopropyl-4-trimethylsilanylbut-3-enyl)-5-phenyl-3-phenylsulfanylmorpholin-2-one (9b). Solid (Et_2O/PE 3/97). Yield: 73%. ^{1}H NMR: 7.55−7.45 (m, 2H), 7.35−7.28 (m, 8H), 6.01 (ddd, *J* = 18.5, 7.4, 5.5 Hz, 1H), 5.76−5.68 (m, 1H), 5.08 (s, 1H), 4.91 (t, *J* = 11.7 Hz, 1H), 4.32 (dd, *J* = 11.7, 4.0 Hz, 1H), 4.18 (dd, *J* = 11.7, 4.3 Hz, 1H), 2.62−2.42 (m, 3H), 1.83−1.67 (m, 1H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.5 Hz, 3H), 0.07 (s, 9H). ^{13}C NMR: 165.9, 144.0, 137.5, 134.5, 134.1, 132.6, 129.4, 129.0, 128.9, 128.8, 69.7, 67.9, 66.2, 62.0, 37.8, 32.0, 21.5, 20.5, −1.3. HRMS: calcd for $C_{26}H_{36}NO_2SSi$ (M + H^+) *m*/*z* = 454.2236, obsd *m*/*z* = 454.2239.

[4(1*S*),5*S*]-4-(1-*tert*-Butyl-4-trimethylsilanylbut-3-enyl)-5-phenyl-3-phenylsulfanylmorpholin −2-one (9c). Solid (Et_2O/PE: 3/97). Yield: 55%. ^{1}H NMR: 7.48−7.44 (m, 2H), 7.31−7.24 (m, 8H), 6.00 (ddd, *J* = 18.5, 7.8, 5.2 Hz, 1H), 5.68 (d, *J* = 18.5 Hz, 1H), 5.01 (s, 1H), 5.01 (t, *J* = 12.0 Hz, 1H), 4.22 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.04 (dd, *J* = 12.0, 4.5 Hz, 1H), 2.45 (dd, *J* = 9.5, 3.5 Hz, 1H), 2.40−2.25 (m, 2H), 0.76 (s, 9H), 0.01 (s, 9H). ^{13}C NMR: 165.9, 144.9, 137.6, 134.6, 134.2, 132.0, 129.4, 129.3, 129.1, 128.9, 128.7, 69.8, 69.2, 68.2, 63.4, 35.9, 28.4, −1.3. HRMS: calcd for $C_{27}H_{38}NO_2SSi$ (M + H^+) *m*/*z* = 468.2393, obsd *m*/*z* = 468.2390.

[4(1*S*),5*S*]-5-Phenyl-3-phenylsulfanyl-4-(1-phenyl-4-trimethylsilanylbut-3-enyl)morpholin-2-one (9d). Oil (Et_2O/PE 3/97). Yield: 38% (mixture of two inseparable diastereoisomers at the C-3 center in a 65/35 ratio). ^{1}H NMR: 7.62−7.18 (m, 15 H), 6.00−5.71 (m, 2H), 5.18 (s, 0.35H), 5.13 (dd, *J* = 4.7, 12.2 Hz, 0.35H), 5.01 (s, 0.65H), 4.82 (t, *J* = 11.7 Hz, 0.65H), 4.52 (dd, *J* = 4.2, 5.7 Hz, 0.65H), 4.33−4.22 (m, 1.70H), 4.06 (m, 0.65H), 3.02−2.90 (m, 0.65H), 2.87−2.65 (m, 1.35H), 0.08 (s, 9H). ^{13}C NMR: 166.9 (maj), 165.9, 143.2, 142.6, 141.2, 138.8, 137.8, 137.4, 134.8, 134.4, 134.0, 133.7, 132.3, 129.4, 128.4, 71.8, 70.6, 69.9 (maj), 67.7 (maj), 63.5, 62.6 (maj), 60.4 (maj), 58.0, 38.5, 36.1 (maj), −1.3. HRMS: calcd for $C_{29}H_{34}NO_2SSi$ (M + H^+) *m*/*z* = 488.2080, obsd *m*/*z* = 488.2083.

General Procedure for the Cyclization of Lactones (10). A solution of aminothioether (0.44 mmol) and zinc chloride (0.2 g, 0.88 mmol) in CH_2Cl_2 (9 mL) was stirred for 1 h 30 at room temperature. The mixture was then poured into water (20 mL) and extracted with CH_2Cl_2. The organic layers were dried on $MgSO_4$, evaporated, and chromatographed to give the corresponding bicyclic compounds.

(4*S*,6*R*,9a*S*)-4-Phenyl-6-propyl-3,4,7,9a-tetrahydro-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-one (10a). Oil (Et_2O/PE 10/90). Yield: 79%. $[\alpha]^{20}_D$: −93 (*c* 0.6, $CHCl_3$). ^{1}H NMR: 7.34−7.27 (m, 5H), 5.92−5.84 (m, 1H), 5.70−5.64 (m, 1H), 4.47−4.42 (m, 1H), 4.23 (t, *J* = 10.7 Hz, 1H), 4.10 (dd, *J* = 10.7, 3.2 Hz, 1H), 4.02 (dd, *J* = 10.7, 3.2 Hz, 1H), 2.70−2.62 (m, 1H), 2.14−2.02 (m, 1H), 1.57−1.48 (m, 1H), 1.44−1.06 (m, 4H), 0.77 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: 170.2, 136.5, 128.9, 128.7, 128.6, 127.1, 123.6, 74.0, 57.4, 55.6, 50.5, 34.1, 22.9, 19.3, 14.2. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.37; H, 7.96; N, 4.98.

(4*S*,6*S*,9a*S*)-4-Phenyl-6-isopropyl-3,4,7,9a-tetrahydro-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-one (10b). Solid (Et_2O/PE 8/92). Yield: 78%. Mp: 75 °C. $[\alpha]^{20}_D$: −69 (*c* 1.2, $CHCl_3$). ^{1}H NMR: 7.39−7.32 (m, 5H), 5.94−5.90 (m, 1H), 5.74−5.68 (m, 1H), 4.45−4.40 (m, 1H), 4.24 (t, *J* = 10.5 Hz, 1H), 4.08 (dd, *J* = 10.7, 3.2 Hz, 1H), 4.04 (dd, *J* = 10.5, 3.2 Hz, 1H), 2.17 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.11−1.92 (m, 1H), 1.80−1.67 (m, 2H), 0.96 (d, *J* = 6.5 Hz, 3H), 0.66 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR: 170.1, 136.5, 128.9, 128.7, 127.0, 124.1, 74.0, 57.5, 57.4, 55.8, 27.2, 20.6, 20.2, 19.3. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.12; H, 7.80; N, 5.09.

(4*S*,6*S*,9a*S*)-6-*tert*-Butyl-4-phenyl-3,4,7,9a-tetrahydro-6*H*-pyrido[2,1-*c*][1,4]oxazin-1-one (10c) and (4*S*,6*S*,8*R*,9*R*,-9a*S*)-6-*tert*-Butyl-4-phenyl-8-phenylsulfanyl-9-trimethylsilanylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (12). Compound 10c. Oil (Et_2O/PE 10/90). Yield: 62%. $[\alpha]^{20}_D$: −110 (*c* 0.5, $CHCl_3$). ^{1}H NMR: 7.29−7.22 (m, 5H), 5.98−5.91 (m, 1H), 5.68−5.62 (m, 1H), 4.57−4.52 (m, 1H), 4.27 (t, *J* = 10.7 Hz, 1H), 4.06 (dd, *J* = 10.7, 3.2 Hz, 1H), 3.94 (dd, *J* = 10.7, 3.2 Hz, 1H), 2.27 (d, *J* = 7.7 Hz, 1H), 2.02−1.89 (m, 1H), 1.75−1.63 (m, 1H), 0.78 (s, 9H). ^{13}C NMR: 170.5, 137.0, 129.0, 128.8, 128.7, 123.8, 73.9, 58.6, 58.3, 57.5, 34.9, 28.5, 18.6. HRMS: calcd for $C_{18}H_{24}NO_2$ (M + H^+) *m*/*z* = 286.1807, obsd *m*/*z* = 286.1805.

Compound 12. Oil (Et_2O/PE 10/90). Yield: 18%. $[\alpha]^{20}_D$: −23 (*c* 0.8, $CHCl_3$). ^{1}H NMR: 7.47−7.43 (m, 2H), 7.31−7.11 (m, 8H), 5.16 (dd, *J* = 4.2, 11.2 Hz, 1H), 4.38 (dd, *J* = 2.2, 4.0 Hz, 1H), 4.28 (dd, *J* = 2.2, 11.5 Hz, 1H), 4.04 (d, *J* = 11.7 Hz, 1H), 3.77−3.74 (m, 1H), 2.86 (dd, *J* = 6.5, 11.5 Hz, 1H), 1.80 (ddd, *J* = 4.0, 6.0, 14.5 Hz, 1H), 1.56 (ddd, *J* = 3.5, 11.5, 15.0 Hz, 1H), 1.41 (d, *J* = 11.0 Hz, 1H), 0.45 (s, 9H), 0.00 (s, 9H). ^{13}C NMR: 171.4, 144.1, 134.6, 133.6, 129.2, 129.0, 128.3, 128.1, 127.7, 127.3, 72.3, 66.2, 64.0, 56.5, 44.7, 36.1, 29.9, 26.8, 25.8, −2.2. Anal. Calcd for $C_{27}H_{37}NO_2SSi$: C, 69.33; H, 7.97; N, 2.99. Found: C, 69.38; H, 8.07; N, 3.01.

(4*S*,6*S*,9a*S*)-4,6-Diphenyl-3,4,7,9a-tetrahydro-6*H*-pyrido-[2,1-*c*][1,4]oxazin-1-one (10d). Oil (Et_2O/PE 20/80). Yield: 83%. $[\alpha]^{20}_D$: −70 (*c* 2.4, $CHCl_3$). ^{1}H NMR: 7.35−7.15 (m, 10H), 6.06 (ddd, *J* = 3.7, 6.7, 10.2 Hz, 1H), 5.77 (ddd, *J* = 2.2, 5.0, 10.2 Hz, 1H), 4.35 (dd, *J* = 9.0, 11.0 Hz, 1H), 4.27 (dd, *J* = 4.0, 11.0 Hz, 1H), 4.12−4.04 (m, 2H), 3.84 (t, *J* = 4.7 Hz, 1H), 2.28−2.19 (m, 2H). ^{13}C NMR: 170.3, 140.5, 137.4, 129.0, 128.5, 128.4, 128.1, 128.0, 127.6, 127.2, 124.4, 71.8, 57.8, 56.6, 55.9, 25.6. HRMS: calcd for $C_{20}H_{20}NO_2$ (M + H^+) *m*/*z* = 306.1494, obsd *m*/*z* = 306.1492.

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-Isopropylpiperidinecarboxylic acid (11b). White solid (yield: 98% from lactone **10b**). Mp: 230 °C dec. ^{1}H NMR (D_2O): 3.98−3.96 (m, 1H), 3.22−3.13 (m, 1H), 2.27−2.20 (m, 1H), 1.96−1.72 (m, 4H), 1.50−1.32 (m, 2H), 0.95 (t, J = 7.2 Hz, 6H). ^{13}C NMR (D_2O): 173.1, 59.7, 56.5, 30.1, 24.7, 24.2, 19.2, 17.3, 17.1. HRMS: calcd for $C_9H_{18}NO_2$ (M + H^+) m/z = 172.1338, obsd m/z = 172.1340.

(2S,6*R*)-6-*tert*-Butylpiperidinecarboxylic Acid (11c). White solid (yield: 98% from lactone **10c**). Mp: 230 °C dec. $[\alpha]^{20}_D$: +9 (*c* 0.6, MeOH). ^{1}H NMR (D_2O): 4.23 (d, J = 5.0 Hz, 1H), 3.01 (dd, J = 2.5, 12 Hz, 1H), 2.29−2.16 (m, 1H), 1.99−1.77 (m, 3H), 1.51−1.31 (m, 2H), 1.01 (s, 9H). ^{13}C NMR (D_2O): 172.3, 64.9, 57.0, 33.1, 27.7, 24.4, 23.8, 20.4. HRMS: calcd for $C_{10}H_{20}NO_2$ (M + H^+) m/z = 186.1494, obsd m/z = 186.1490.

5-Phenyl-3-(3-trimethylsilanylallyl)morpholin-2-ol (15). Glyoxal (35 μL, 0.26 mmol, 40% weight in water) was added to a solution of amino alcohol **13** (72 mg, 0.236 mmol) in THF/H_2O (3 mL, 1/1). The mixture was stirred for 1 day at rt and evaporated under reduced pressure. Chromatography of the residue afforded amine **15** as a mixture of two epimers (60/40) at C-2. Gum (Et_2O/PE 25/75). Yield: 42%. ^{1}H NMR: 7.38−7.22 (m, 5H), 5.99−5.62 (m, 2H), 4.98 (d, J = 2.2 Hz, 0.4H), 4.83 (d, J = 1.7 Hz, 0.6H), 4.20−4.12 (m, 1H), 3.98−3.90 (m, 0.6H), 3.82 (dd, J = 5.5, 11.5 Hz, 0.4H), 3.62 (dd, J = 3.6, 11.5 Hz, 1H), 2.98−2.94 (m, 1H), 2.51−2.20 (m, 4H), 0.05 (s, 9H).^{13}C NMR: 142.1, 135.0, 128.8, 128.1, 127.3, 92.1, 65.1, 55.9, 52.6, 37.1, −1.1. HRMS: calcd for $C_{16}H_{26}NO_2Si$ (M + H^+) m/z = 292.1733, obsd m/z = 292.1725.

(4*S*,6*R*,9a*S*)-4-Phenyl-6-isopropyl-1,3,4,6,9,9a-hexahydropyrido[2,1-*c*][1,4]oxazin-1-ol (16). Glyoxal (40 μL, 0.35 mmol, 40% weight in water) was added to a solution of amino alcohol **14** (94 mg, 0.308 mmol) in THF/H_2O (3 mL, 1/1). The mixture was stirred for 48 h at rt. After extraction and evaporation of the organic layers, the residue was chromatographed to afford hemiketal **16** as a mixture of two epimers (75/25) at C-1. Gum (Et_2O/PE 25/75). Yield: 71%. ^{1}H NMR: 7.34−7.28 (m, 5H), 5.92−5.35 (m, 1H), 5.74−5.67 (m, 1H), 5.09 (d, J = 2.2 Hz, 0.25H), 4.97 (s, 0.75H), 4.62 (bs, 1H), 4.03−3.91 (m, 1.52H), 3.85−3.75 (m, 0.48H), 3.61 (dd, J = 10.0, 2.1 Hz, 0.25H), 3.53 (d, J = 7.7 Hz, 0.75H), 3.41−3.36 (m, 0.25H), 3.30−3.24 (m, 0.75H), 2.71−2.58 (m, 1H), 2.38−2.33 (m, 1H), 1.92−1.65 (m, 2H), 0.99−0.94 (m, 3H), 0.80−0.75 (m, 3H). ^{13}C NMR (for the major diastereoisomer): 139.3, 128.7, 128.4, 127.9, 124.2, 92.5, 65.0, 60.9, 58.5, 52.1, 32.3, 21.7, 21.1, 19.9. HRMS: calcd for $C_{17}H_{24}NO_2$ (M + H^+) m/z = 274.1807, obsd m/z = 274.1805.

(4*S*,6*R*,9a*S*)-4-Phenyl-6-isopropyl-3,4,9,9a-tetrahydropyrido[2,1-*c*][1,4]oxazin-1-one (17). Dimethyl sulfoxide (150 μL, 2.12 mmol) was added dropwise to a solution of oxalyl chloride (77 μL, 0.88 mmol) in dichloromethane (6 mL) at −60 °C. The mixture was stirred for 10 min, and a solution of hemiacetal **16** (0.2 g, 0.73 mmol) in dichloromethane (4 mL) was introduced. After 30 min at −60 °C, triethylamine (510 μL, 3.66 mmol) was added, and the mixture was allowed to warm to rt 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 **17** as a solid (Et_2O/PE 8/92). Yield: 70%. Mp: 68 °C. $[\alpha]^{20}_D$: −54 (*c* 1.6, $CHCl_3$). ^{1}H NMR: 7.46−7.36 (m, 5H), 5.98−5.91 (m, 1H), 5.76 (dq, J = 10.5, 2.0 Hz, 1H), 4.47−4.19 (m, 4H), 2.71−2.58 (m, 2H), 2.46−2.35 (m, 1H), 1.83−1.71 (m, 1H), 1.02 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.7 Hz, 3H). ^{13}C NMR: 171.0, 137.1, 128.8, 128.5, 128.4, 127.2, 123.3, 73.0, 59.9, 57.8, 52.9, 32.1, 23.1, 20.5, 18.7. IR (CCl_4): 3033, 2959, 1753 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.09; H, 7.93; N, 5.09.

(4*S*,6*R*,9a*S*)-4-Phenyl-6-isopropylhexahydropyrido[2,1-*c*][1,4]oxazin-1-one (18). A solution of lactone **17** or **10b** (40 mg, 0.147 mmol) in Et_2O (2 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of PtO_2 (15 mg) in Et_2O (1 mL). The hydrogenation was complete in 2 h. The mixture was filtered through Celite 545 and the residue washed with Et_2O. The filtrate was evaporated to dryness, leaving the corresponding hydrogenated lactone. After chromatography, lactone **18** was isolated as a solid (Et_2O/PE 20/80). Mp: 114 °C from **17** and 115 °C from **10b**. Yield: 90% from **17** and **10b**. $[\alpha]^{20}_D$: +18 (*c* 1.6, $CHCl_3$). ^{1}H NMR: 7.47−7.41 (m, 5H); 4.49 (dd, J = 8.2, 6.5 Hz, 1H), 4.37−4.34 (m, 2H), 4.16−4.10 (m, 2H), 2.72−2.12 (m, 3H), 1.87−1.73 (m, 3H), 1.67−1.53 (m, 1H), 1.44−1.35 (m, 1H), 1.04 (d, J = 6.2 Hz, 3H), 0.74 (d, J = 6.2 Hz, 3H).^{13}C NMR: 169.8, 137.3, 128.9, 128.5, 73.1, 60.5, 57.0, 55.3, 26.0, 24.2, 20.5, 20.0, 19.4, 18.9. IR (CCl_4): 2957, 2869, 1744 cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.57; H, 8.63; N, 5.00.

Supporting Information Available: Spectra of obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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