56.4, 44.8, 43.1, 23.5, 23.3, 21.7, 10.6; IR (CCl_4) 3550, 2938, 1616, 1465, 1451, 1348, 1219, 1126, 885 cm^{-1}; MS (EI, 20 eV) m/z 278 (M^+, 100), 249 (20), 233 (20), 220 (18), 219 (12), 205 (58); HRMS calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1520.

(4b*S,8a*S**)-2,4-Dimethoxy-3-hydroxy-4b-methyl-4b,5,6,7,8,8a-hexahydro-9*H*-fluorene (44) and 1-[(3,5-Dimethoxy-4-hydroxyphenyl)methyl]-2-methyl-1-cyclohexene (45).** The same procedure described for the preparation of **36f** from **23** was carried out with alcohol **37** (103 mg, 0.560 mmol), 1-methylcyclohexene (2.7 mL of a 1.014 M solution in CH_2Cl_2, 2.74 mmol, 4.9 equiv), and $SnCl_4$ (0.08 mL, 0.684 mmol, 1.2 equiv). The reaction was carried out at 25 °C (95 min) rather than −78 °C. Flash chromatography (6:1 hexane/ethyl acetate) afforded 75.5 mg (51%) of **44** and 54.5 mg (37%) of **45** as clear oils. Spectral data for **44**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (s, 1 H, Ar), 5.45 (s, 1 H, OH), 3.91 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 2.78 (dd, J = 7.2, 15 Hz, 1 H, CHC*H*H), 2.60 (dd, J = 7.8, 15 Hz, 1 H, CHCH*H*), 2.06–1.98 (m, 1 H, C*H*CHH), 1.84–1.43 (m, 8 H, $CCH_2CH_2CH_2CH_2CH$), 1.40 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 144.1, 137.0, 136.4, 133.1, 103.5, 77.2, 60.4, 56.2, 48.5, 35.9, 34.8, 26.3, 25.1, 22.7, 22.0; IR (CCl_4) 3551, 2928, 1613, 1471, 1447, 1233, 887 cm^{-1}; MS (EI, 20 eV) m/z 262 (M^+, 69), 247 (100), 219 (49); HRMS calcd for $C_{19}H_{22}O_3$ 262.1569, found 262.1573. Spectral data for **45**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.39 (s, 2 H, Ar), 5.39 (s, 1 H, OH), 3.88 (s, 6 H, OCH_3), 3.28 (s, 2 H, CH_2Ar), 2.32–1.20 (m, 11 H, $CH_3C{=}C$, $CH_2CH_2CH_2CH_2$); IR (CCl_4) 3559, 2931, 1618, 1515, 1463, 1213 cm^{-1}; MS (EI, 20 eV) m/z 262 (M^+, 100), 247 (10), 167 (42).

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Supplementary Material Available: ^1H NMR spectra for the following compounds: **14, 15, 21, 22, 23, 24, 25, 26a, 26b, 32, 35a/36a, 35b/36b, 35c/36c, 35d/36d, 35e/36e, 36f, 36g, 36i, 36j, 36k, 40, 42, 43a, 43b, 44,** and **45** (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

An Efficient Stereoselective Synthesis of $\Delta^{4,5}$-Pipecolic Esters

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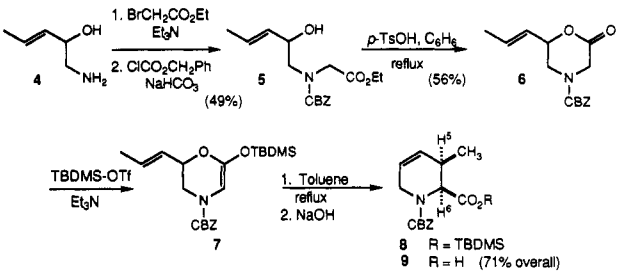
The synthesis of racemic and enantiomerically homogeneous pipecolic esters from 1-amino-3-buten-2-ols is reported. The synthesis of enantiomerically homogeneous *N*-methylpipecolic esters requires four chemical steps from *N*-*t*-BOC-protected amino esters. The key step of the sequence is a conformationally restricted Claisen rearrangement. The method affords complete control of the absolute and relative stereochemistry of all three stereogenic centers in pipecolic ester **22** which is obtained in 33% overall yield from *N*-*t*-BOC-L-alanine ethyl ester **16a**.

Introduction

The piperidine ring is a structural subunit found in a large number of naturally occurring alkaloids.[1] Due to the broad range of biological activity possessed by these compounds[1] and their versatility as key synthetic intermediates, the stereoselective synthesis of highly functionalized piperidines has received considerable attention.[2,3] As a part of our program to develop general routes

Scheme I



to piperidine-containing natural products, we report here a general method for the synthesis of 1,2,5,6-tetrahydro-

(1) (a) Glasby, J. S. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975, Vols. 1 and 2; 1977, Vol. 3; 1983, Vol. 4. (b) For naturally occurring pipecolic acid derivatives, see: Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816 and references cited therein.

(2) For recent examples and leading references on the synthesis of tetrahydropyridines, see: (a) Flann, C.; Malone, T. C.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 6097. (b) Bailey, P. D.; McLay, N. R. *Tetrahedron Lett.* **1991**, *32*, 3895. (c) Bosch, J.; Rubiralta, M.; Bolos, J. *Tetrahedron* **1987**, *43*, 391. (d) Kuriharra, T.; Matsubara, Y.; Osaki, H.; Harusawa, S.; Yoneda, R. *Heterocycles* **1990**, *30*, 885. (e) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781. (f) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672. (g) Shono, T.; Matsumura, Y.; Onomura, O.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 4073. (h) Wuts, P. G. M.; Jung, Y.-W. *J. Org. Chem.* **1988**, *53*, 5989. (i) Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth.* **1991**, *70*, 54. (j) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382. (k) Royer, J.; Husson, H.-P. *J. Org. Chem.* **1985**, *50*, 670. (l) Wang, C. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341. (m) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889. (n) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. (o) Comins, D. L.; Morgan, L. A. *Tetrahedron Lett.* **1991**, *32*, 5919. (p) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976.

(3) For recent examples and leading references on the synthesis of pipecolic acids and their derivatives, see: (a) Bailey, P. D.; Bryans, J. S. *Tetrahedron Lett.* **1988**, *29*, 2231. (b) Kurihara, T.; Matsubara, Y.; Osaki, H.; Harusawa, S.; Yoneda, R. *Heterocycles* **1990**, *30*, 885. (c) Adams, D. R.; Carruthers, W.; Williams, M. J.; Crowley, P. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1507. (d) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1990**, *31*, 759. (e) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (f) Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751. (g) Esch, P. M.; Boska, I. M.; Hiemstra, H.; Speckamp, W. N. *Syn. Lett.* **1989**, 38. (h) Shuman, R. T.; Ornstein, P. L.; Paschal, J. W.; Gesellchen, P. D. *J. Org. Chem.* **1990**, *55*, 738. (i) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068. (j) Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239. (k) Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 3882.

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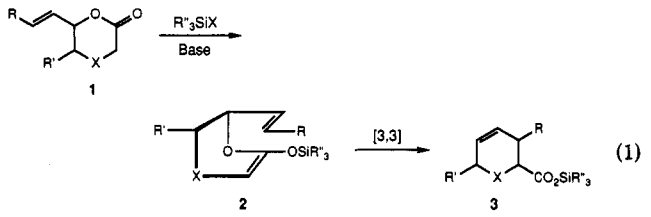
pyridines from 1-amino-3-buten-2-ols. The enantiospecific synthesis of *N*-methyl-$\Delta^{4,5}$-pipecolic acids has been accomplished from optically active *t*-BOC-protected α-amino esters in four steps.

The goal of the work described here is to prepare $\Delta^{4,5}$-pipecolic acid derivatives in an efficient manner that allows control of the relative and absolute stereochemistry at all potential stereogenic centers throughout the tetrahydropyridine ring. The key step of the sequence is a conformationally restricted Claisen rearrangement analogous to that used by Danishefsky[4] (X = CH_2), Burke[5] (X = O), and others[6,7] (eq 1). Due to the constrained nature



1 2 3 (1)

of the boat-like transition state (**2**) in the rearrangement, the relative orientation of new stereogenic centers in the products can be predicted with certainty,[4-6] making this a potentially valuable method in the synthesis of complex tetrahydropyridine-containing alkaloids.[2,3]

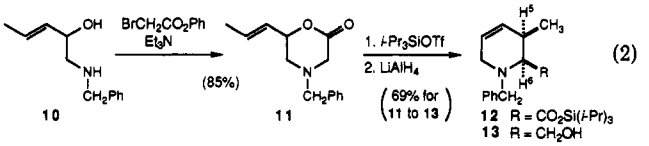
Results and Discussion

Synthesis of Racemic Pipecolic Acids. We chose to first explore the viability of this Claisen rearrangement (X = N, eq 1) in a readily available system. Amino alcohol **4**[8] was alkylated with ethyl bromoacetate, and the resulting secondary amine was protected as the (carbobenzyloxy)-carbamate to afford hydroxy ester **5** in 49% yield (Scheme I). Heating a benzene solution of **5** with a catalytic amount of *p*-toluenesulfonic acid gave lactone **6** in 27% overall yield from **4**.

Treatment of lactone **6** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMS-OTf) in the presence of triethylamine resulted in smooth conversion to ketene acetal **7**. This extremely sensitive compound was purified by chromatographic filtration through silylated silica gel.[9] The 200-MHz ^{1}H NMR spectrum of **7** showed it to be a mixture of carbamate isomers at room temperature, each displaying a characteristic singlet for the new alkene hydrogen (δ 6.5 and δ 6.2, 23 °C).

Heating a toluene solution of purified **7** at reflux for 18 h followed by hydrolysis of the silyl ester afforded acid **9** in 71% overall yield from lactone **6**. The 300-MHz ^{1}H NMR spectrum (65 °C) of **9** showed H(6) as a 6-Hz doublet indicative of the assigned cis stereochemistry. This stereochemical outcome is also consistent with the predicted boat-like transition state for the sigmatropic rearrangement.[4-6] The observed coupling constant is also consistent with an alternative diastereomer in which the methyl and acid groups are both pseudoaxial. The acid substituent in **9** might show a strong tendency for an axial orientation due to an $A^{1,3}$ interaction with the planar *N*-CBZ carbamate.[10] The stereochemical assignment was confirmed with the preparation and characterization of **13** (vide infra).

We next explored a substrate with a benzyl protecting group on nitrogen. Using a modification of a method recently reported by Dellaria and Santarsiero, amino alcohol **10**[10] was treated with triethylamine and phenyl α-bromoacetate to afford lactone **11** in 85% yield (eq 2).[11]

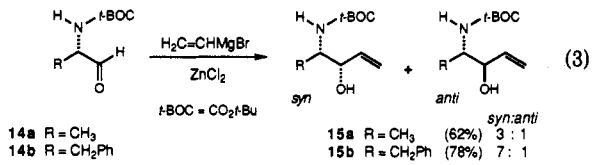


10 11 (2)

Many other methods were examined; however, the mild conditions and high yield make this the method of choice for carrying out the lactonization.[12] Lactone **11** was converted to the corresponding silyl ketene acetal by addition of triisopropylsilyl triflate in the presence of triethylamine. Claisen rearrangement was effected by heating the above reaction mixture to 80 °C (2-h reaction time, ^{1}H NMR monitoring). The product, silyl ester **12**, was observed by ^{1}H NMR analysis; however, it was not isolated. Reduction of crude **12** with $LiAlH_4$ afforded amino alcohol **13** in 69% overall yield from lactone **11**. The assigned cis orientation of the methyl and hydroxymethyl substituents is predicted by the required boat-like transition state and is consistent with the observed coupling constant between H(6) and H(5) of 5.7 Hz in the ^{1}H NMR spectrum of **13**.

Synthesis of Enantiomerically Pure Pipecolic Esters. With an efficient method to convert amino alcohols such as **4** to pipecolic esters, the synthesis of enantiomerically pure amino alcohols from α-amino acids was examined.

While either diastereomer of ketene acetal **2** is predicted to undergo a [3,3] sigmatropic rearrangement,[5] we elected to first examine the diastereomer having the alkenyl and alkyl (R′) groups in a trans orientation. The desired amino alcohol (*syn*-**15**) is the product of a chelation-controlled (cyclic Cram) addition to the aldehyde **14** derived from the corresponding protected amino acid (eq 3). To facilitate



(3)

formation of *syn*-**15a**, an ether solution of **14a**[13] was added to a solution of $ZnCl_2$ and vinylmagnesium bromide to afford **15a** in 62% yield as a 3:1 mixture of syn/anti diastereomers (^{1}H NMR).[14] The diastereomers were inse-

(4) (a) Danishefsky, S. J.; Funk, R. L.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 6889. (b) Danishefsky, S. J.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6891. (c) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371.

(5) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320. (b) Burke, S. D.; Schoenen, J. F.; Murtiashaw, C. W. *Tetrahedron Lett.* **1986**, *27*, 449.

(6) (a) Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4559. (b) Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126. (c) Kinney, W. A.; Coghlan, J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868 and references cited therein. (d) Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252.

(7) Angle, S. R.; Arnaiz, D. O. *Tetrahedron Lett.* **1989**, *30*, 515.

(8) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.

(9) Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021.

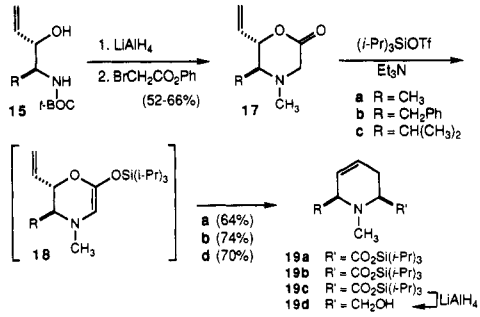
(10) For an example of this type of allylic strain, see: Callens, R. E. A.; Anterinis, M. J. O.; Reyniers, F. *Bull. Soc. Chim. Belg.* **1982**, *91*, 713. For an excellent discussion of the conformation and stereochemical assignments in similar systems, see: Sugg, E. E.; Griffin, J. F.; Portoghese, P. S. *J. Org. Chem.* **1985**, *50*, 5032. For a reviews on allylic strain, see: (a) Johnson, F. *Chem. Rev.* **1968**, *64*, 375. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(11) (a) Dellaria, J. F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916. (b) Dellaria, J. F.; Nordeen, C.; Sweet, L. R. *Synth. Commun.* **1986**, *16*, 1043.

(12) For a detailed account of methods attempted to prepare the lactones, see: Arnaiz, D. O. Ph.D. Dissertation, University of California, Riverside, 1991.

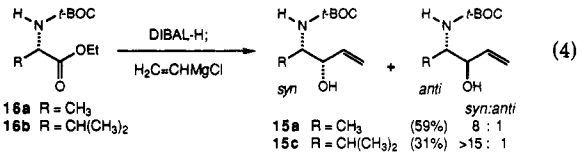
(13) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399; the stereochemistry of **15b** was assigned.

Scheme II



parable by HPLC. Addition of phenylalanine-derived aldehyde **14b** to $ZnCl_2$/vinylmagnesium bromide afforded **15b** in 78% yield as a 7:1 mixture of syn/anti diastereomers (^{1}H NMR).[13]

During the course of this work, Yamamoto and coworkers reported the transformation of *N*-*t*-BOC-alanine ethyl ester **16a** to amino alcohol **15a** in a single operation upon the sequential addition of DIBAL-H and vinylmagnesium chloride.[15a,b] This procedure provided **15a** as an 8:1 mixture of syn/anti diastereomers in 59% overall yield (eq 4).[15c] The valine-derived ester **16b** afforded **15c**



(4)

as a single diastereomer (^{1}H NMR) in 31% yield. This one-pot procedure is the method of choice for selectively preparing amino alcohols of this type with syn selectivity. The subsequent chemistry was performed on mixtures of diastereomers to show that separation at this point is not necessary for the synthesis of enantiomerically and diastereomerically pure pipecolic esters.

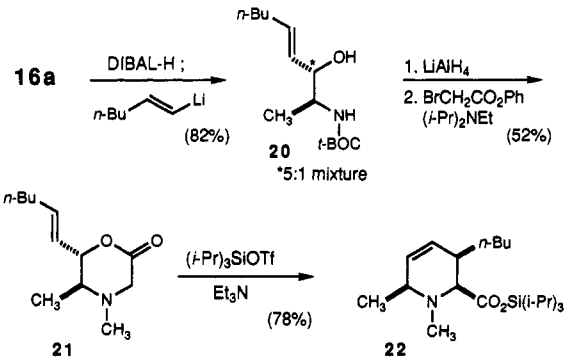
N-*t*-BOC-amino alcohols **15** were reduced with $LiAlH_4$ to afford the corresponding methylamines. The crude amines were then treated with phenyl α-bromoacetate[11] and diisopropylethylamine to afford lactones **17** in 52–66% yield from **15** (Scheme II). Treatment of lactone **17a** (8:1 mixture of diastereomers, ^{1}H NMR) with triisopropylsilyl triflate in the presence of triethylamine afforded silyl ketene acetal **18** within 2 min (^{1}H NMR monitoring) at room temperature. At longer reaction times, 10–20 min, the Claisen rearrangement of the *trans*-silyl ketene acetal to pipecolic ester **19a** could be observed. The Claisen rearrangement was complete within 6 h at room temperature, affording **19a** in 64% yield after HPLC purification. The cis isomer of **17a**, derived from diastereomeric amino alcohol *anti*-**15a**, failed to undergo rearrangement even when heated to 80 °C for 24 h. Pipecolic ester **19a** is the only diastereomer obtained, thus showing a diastereomeric mixture of lactones is compatible with the sequence.[16]

Treatment of lactone **17b** (7:1 mixture of diastereomers, ^{1}H NMR) with triisopropylsilyl triflate as above, followed by reaction at room temperature for 1 h, afforded pipecolic ester **19b** in 74% yield (Scheme II). Again, none of the *cis*-ketene acetal (derived from *anti*-**15b**) underwent rearrangement. Treatment of lactone **17c** with triisopropylsilyl triflate, followed by reaction at room temperature for 40 min, afforded **19c**. Silyl ester **19c** could not be obtained analytically pure by HPLC due to silicon-containing impurities with identical retention time. Reduction of **19c** with $LiAlH_4$ followed by flash chromatography afforded analytically pure alcohol **19d** in 70% yield from **17c**.[17]

Table I. $J_{H(5)-H(6)}$ vs Reaction Time

ketene acetal	R	$J_{H(5)-H(6)}$	time (25 °C)
18a	CH_3	5.7 Hz	6 h
18b	CH_2Ph	3.8 Hz	1 h
18c	$CH(CH_3)_2$	0.5 Hz	40 min

Scheme III



The mild conditions of this conformationally restricted Claisen rearrangement of the silyl ketene acetals derived from lactones **17** are noteworthy. These types of rearrangements normally require heating at temperatures in excess of 100 °C for several hours.[4-6] Indeed, we found that *N*-(acyloxy)silyl ketene acetal **7** required heating at 111 °C for several hours to effect the rearrangement.[7] It is likely that the origin of this rate enhancement is due to the ease of obtaining the boat conformation (required for rearrangement) with a pyramidal nitrogen in the lactone ring. It was observed that the reaction time for the Claisen rearrangement of **18a–c** decreases with increasing steric bulk of the C(2) substituent. MMX calculations[18] showed that as the steric bulk of this substituent increases, there is an increasing preference for the boat conformation. The boat conformers of the silyl ketene acetals **18** are calculated to have a H(5)–H(6) dihedral angle near 90° and a $J_{H(5)-H(6)}$ of 0.5 Hz. Table I shows that the value of the H(5)–H(6) coupling constant decreases as the steric bulk of the C(2) substituent increases. This is consistent with a decrease in the H(5)–H(6) dihedral angle and thus a larger population of the boat conformer. This trend is consistent with the rate of the reaction being dependent upon the ease of obtaining the boat transition state required for rearrangement.

The methodology is also applicable to the synthesis of a pipecolic ester with three stereogenic centers. Treatment of *N*-*t*-BOC-L-alanine ethyl ester **16a** with DIBAL-H followed by (*E*)-1-lithio-1-hexene afforded alcohols **20** in 82% yield as a 5:1 mixture of diastereomers by ^{1}H NMR analysis (Scheme III). Treatment of this mixture of diastereomers with $LiAlH_4$ followed by phenyl α-bromoacetate[11] and diisopropylethylamine afforded lactone **21**

(14) Thompson, W. J.; Tucker, T. J.; Schwering, J. E.; Barnes, J. L. *Tetrahedron Lett.* **1990**, *31*, 6819.

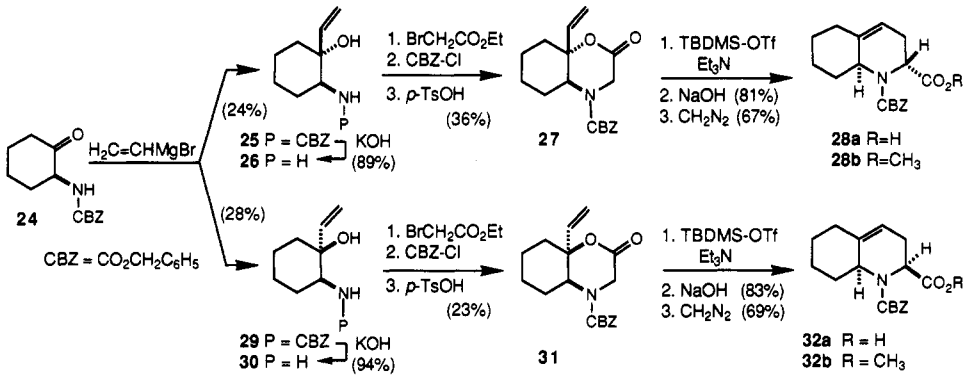
(15) (a) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370. (b) DIBAL-H/vinyl Grignard additions to other amino esters where reported by Shue, Y.-K.; Carrera, G. M.; Tufano, M. D.; Nadzan, A. M. *J. Org. Chem.* **1991**, *56*, 2107. (c) Yamamoto reports a 15:1 ratio of diastereomers. We feel that this reaction may be sensitive to the source of Grignard reagent.

(16) The unrearranged lactone diastereomer was easily separated from the tetrahydropyridine product by flash chromatography.

(17) Flash chromatography and HPLC failed to remove impurities with peaks in the aliphatic region of the ^{1}H NMR spectrum of silyl ester **19c**. The purity of **19c** was estimated to be >90% by ^{1}H NMR.

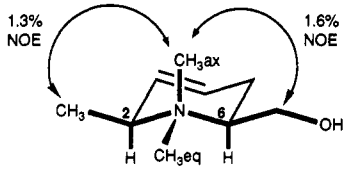
(18) PC Model (Serena Software) was used to perform the calculations.

Scheme IV



in 52% overall yield. Treatment of lactone **21** with triisopropylsilyl triflate in the presence of triethylamine (3 h, 25 °C) afforded pipecolic ester **22** in 78% yield after purification by HPLC.

The relative stereochemistry assigned to pipecolic esters **19a–c** and **22** is mandated by a concerted [3,3] sigmatropic rearrangement and well precedented in this type of conformationally restricted reaction.[4–6] Confirmation of the stereochemical assignment is complicated by the presence of the C(3)–C(4) alkene which makes the C(2)-hydrogen–C(3)-hydrogen coupling constant of marginal value in assigning stereochemistry. The cis orientation of the 2,6-substituents was confirmed by difference NOE experiments on ammonium salt **23**. Reduction of ester **19a** with



23

$LiAlH_4$, followed by treatment with CH_3I, afforded **23** in 74% overall yield. Homonuclear decoupling experiments allowed the assignment of the 500-MHz ^1H NMR spectrum of **23**.[19] In a difference NOE experiment, irradiation of the signal for the axial *N*-methyl (CH_3^{ax})[20] hydrogens caused a 1.6% enhancement of the signal for one of the hydrogens of the methylene group on C(6), a 1.3% enhancement of the signal for the hydrogens of the methyl group on C(2), and no enhancement of the signal for the C(2) and C(6) methine hydrogens. Irradiation of the signal for the equatorial *N*-methyl (CH_3^{eq})[20] hydrogens showed enhancement of the signal for one of the hydrogens of the methylene group on C(6) (4.2%), the hydrogens of the methyl group on C(2) (1.6%), the C(2) methine hydrogen (6.3%), and the C(6) methine hydrogen (2.4%). The results of the NOE experiments are only consistent with the assigned cis orientation of the C(2)- and C(6)-alkyl substituents in **23** and thus **19a** must also have a cis orientation between the C(2)- and C(6)-alkyl substituents.

The enantiomeric purities of the pipecolic esters were shown to be >95% by chiral shift ^1H NMR experiments. Pipecolic esters **19a** and **19b** were prepared in racemic form from racemic amino acids. Addition of $Eu(hfc)_2$ to the pipecolic esters prepared from racemic amino acids showed two sets of resonances for the alkene hydrogens, whereas those prepared from optically pure amino acids showed a single set of resonances for these hydrogens with the same quantity of shift reagent.

Annulation of a Tetrahydropyridine onto an α-Amino Ketone. The viability of this sequence as a general method for the annulation of a tetrahydropyridine onto an α-amino ketone was also examined. Treatment of α-amino ketone **24**[21] with vinylmagnesium bromide afforded a 1:1 mixture of diastereomeric alcohols **25** and **29** in 24% and 28% yields, respectively (Scheme IV). Each diastereomer was separately hydrolyzed to afford amino alcohols **26** and **30** (89% and 94% yields). The relative stereochemistry of **26** and **30** has been assigned previously.[7]

Each diastereomer was then carried through the sequence of alkylation with ethyl bromoacetate, protection with benzyl chloroformate, and lactonization to give **27** and **31** in 36% and 23% yields, respectively. Treatment of **27** with TBDMS-OTf in the presence of triethylamine (111 °C, 2 h) followed by hydrolysis of the silyl ester and base extraction afforded acid **28a** as a single diastereomer by ^1H NMR spectroscopy (65 °C) in 81% yield from lactone **27**. Treatment of **28a** with CH_2N_2 afforded methyl ester **28b** for characterization. Treatment of lactone **31** as above afforded acid **32a** in 83% yield. Treatment of **32a** with CH_2N_2 afforded methyl ester **32b** in 69% yield. The stereochemical assignments of **28b** and **32b** are based upon the required boat topology in the Claisen rearrangement.[5,6] These two examples show that the stereochemistry about the tetrahydropyridine can easily be controlled by establishing the required relative orientation of the amino and alcohol functionalities in the starting amino alcohols, **26** and **30**.

Conclusion

In conclusion, we have developed a concise method for the conversion of amino acids to enantiomerically homogeneous pipecolic esters. Work is in progress to exploit the methodology in the synthesis of naturally occurring alkaloids.

Experimental Section

General Information. NMR spectra were recorded on a JEOL FX-200, a General Electric QE-300 NMR, or a GE GN-500 NMR; shifts reported are relative to internal tetramethylsilane; coupling constants, *J*, are reported in hertz and refer to apparent peak multiplicities and not true coupling constants; abbreviations used are as follows: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, p = pentuplet. Mass spectra were recorded at the UCR-MS facility on a VG-7070EHF or a VG-ZAB1FHF

(19) See supplementary material for details. The numbering system used for **23** reflects tetrahydropyridine nomenclature, not pipecolic acid nomenclature.

(20) The methyl singlets were assigned on the basis of chemical shift. The downfield signal being attributed to the equatorial methyl and the upfield signal being attributed to the axial methyl: Rubiralta, M.; Giralt, E.; Diez, A. *Piperidine*; Elsevier: New York, 1991; pp 57–58.

(21) A known compound: Driguez, H.; Vermes, J.-P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119.

and are reported as percent relative intensity to the base peak. IR spectra were recorded on a Nicolet-5DX FT-IR. Microanalysis were performed by Desert Analytics, Tucson, AZ. Flash chromatography was done on E. Merck silica gel 60, 230–400 mesh, and analytical TLC was performed on E. Merck glass-backed silica gel 60 plates, 0.250-mm thickness, with a 254-nm fluorescent indicator. HPLC was carried out on a Rainin HPLC system with HPX pumps and a Knauer Model 198 RI detector using a 25-cm column (1-cm i.d.) packed with 8-μm silica gel at a flow rate of 1 mL/min. THF and ether were distilled from sodium/benzophenone. Acetonitrile and CH_2Cl_2 were distilled from CaH_2. Solvents for chromatography and recrystallization were distilled prior to use. Silyl triflates were purchased from Aldrich Chemicals and used as received. Unless stated otherwise, all reactions were run under an atmosphere of nitrogen or argon in oven-dried glassware. The molarities indicated for alkyllithiums were established by titration with 2,5-dimethoxybenzyl alcohol.[22a] The molarities indicated for Grignard reagents were established by titration with *sec*-butyl alcohol and 2,2′-dipyridyl.[22b] Melting points are uncorrected. In cases where synthetic intermediates or products were isolated by "aqueous workup (organic solvent, drying agent)", the procedure was to dilute with water and the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic extracts over the drying agent, and concentrate the reaction mixture. "Concentration" in the experimental refers to isolation of product(s) from a solvent/product mixture by removal of the solvent under reduced pressure (water aspirator) with a Rotavapor. Bulb-to-bulb distillations were performed with a Büchi GKR-50 microdistillation apparatus. The temperature reported is that of the oven.

(±)-(*E*)-1-[*N*-(Benzyloxycarbonyl)-*N*-[(ethoxycarbonyl)methyl]amino]-2-hydroxy-3-pentene (5). Triethylamine (2.00 mL, 14.4 mmol) and ethyl bromoacetate (1.10 mL, 9.90 mmol) were sequentially added to a stirred solution of amino alcohol 4[8] (0.96 g, 9.5 mmol) and THF (50 mL) at room temperature. After 2 h, H_2O (50 mL) was added. Aqueous workup (ethyl acetate, Na_2SO_4) afforded 1.67 g (84%) of (*E*)-1-[*N*-[(ethoxycarbonyl)methyl]amino]-2-hydroxy-3-pentene as a yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.80–5.60 (m, 1 H, HC=C*H*CH_3), 5.43 (dd, 1 H, *H*C=CHCH$_3$), 4.15 (q, 2 H, CH_2CH$_3$), 3.60–3.40 (m, 2 H, NCH_2CO$_2$), 2.80–2.60 (m, 3 H, C*H*OH, NCH_2CHOH), 1.71 (d, 3 H, HC=CHCH_3), 1.2 (t, 3 H, CH$_2$CH_3). Benzyl chloroformate (1.42 mL, 9.9 mmol) was added dropwise to a stirred two phase mixture of (*E*)-1-[*N*-[(ethoxycarbonyl)-methyl]amino]-2-hydroxy-3-pentene (1.67 g, 9.00 mmol), saturated $NaHCO_3$ (30 mL), and CH_2Cl_2 (40 mL). The mixture was stirred for 3 h. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded crude product as a yellow oil. Flash chromatography (3:1 hexane/ethyl acetate) afforded 1.74 g (58%) of **5** as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$, mixture of carbamate isomers) δ 7.30 (d, 5 H, Ar), 5.85–5.60 (m, 1 H, HC=C*H*CH$_3$), 5.50–5.40 (m, 1 H, *H*C=CHCH$_3$), 5.15–5.00 (m, 3 H, CH_2Ph, C*H*OH), 4.40–4.00 (m, 2 H, CH_2CH$_3$), 3.70–3.20 (m, 4 H, NCH_2CO$_2$, NCH_2CHOH), 1.70 (m, 3 H, HC=CHCH_3), 1.20 (t, 3 H, CH$_2$CH_3).

(±)-(*E*)-*N*-(Benzyloxycarbonyl)-6-(1-propenyl)-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (6). A solution of carbamate **5** (890 mg, 2.76 mmol), benzene (14 mL), and *p*-toluenesulfonic acid (2 mg, 0.01 mmol) was heated to 100 °C in a flask equipped with a Dean–Stark trap. During the course of the reaction additional *p*-TsOH (5 mg) and benzene were added. After 2 h, the solution was cooled to room temperature and concentrated. MPLC (4:1 hexane/ethyl acetate) afforded 0.43 g (56%) of **6** as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.37 (s, 5 H, Ar), 5.90 (m, 1 H, HC=C*H*CH$_3$), 5.48 (dd, 1 H, J = 6, 15 Hz, *H*C=CHCH$_3$), 5.16 (s, 2 H, CH_2Ph), 4.87 (br s, 1 H, C*H*OH), 4.24 (AB q, 2 H, J = 20 Hz, $\Delta\nu$ = 20 Hz, NCH_2CO$_2$), 3.90 (m, 1 H, NC*H*HCHOH), 3.30 (m, 1 H, NCH*H*CHOH), 1.72 (d, 3 H, J = 6.5 Hz, HC=CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 154.3, 135.8, 132.5, 128.8, 128.6, 128.4, 128.1, 125.8, 125.0, 67.8, 60.3, 53.4, 45.2, 17.8; IR (CCl_4) 1770, 1725 cm^{-1}; MS (EI, 70 eV) m/z 275 (M$^+$, 18), 230 (59), 205 (27), 186 (52), 140 (28), 91 (100); HRMS for $C_{15}H_{17}NO_4$ calcd 275.1158, found 275.1158.

(±)-(2*S,3*R**)-1-(Benzyloxycarbonyl)-2-carboxy-3-methyl-1,2,5,6-tetrahydropyridine (9).** Triethylamine (0.072 mL, 0.52 mmol) and *tert*-butyldimethylsilyl triflate (0.12 mL, 0.52 mmol) were sequentially added to a solution of morpholinone **6** (130 mg, 0.47 mmol) and C_6D_6 (0.5 mL) in a 5-mm NMR tube. After 10 min the reaction was complete (^{1}H NMR). Filtration (silanized silica gel,[9] ethyl acetate) and concentration afforded ketene acetal **7**: ^{1}H NMR (200 MHz, C_6D_6, mixture of carbamate isomers) δ 7.38–7.16 (m, 5 H, Ar), 6.50 (s, 1 H, NC*H*=C), 6.18 (s, 1 H, NC*H*=C), 5.64–5.45 (m, 1 H, HC=C*H*CH$_3$), 5.39–5.26 (m, 1 H, *H*C=CHCH$_3$), 5.23 (s, 2 H, CH_2Ph), 4.23–4.15 (m, 1 H, NC*H*H), 3.89–3.73 (m, 1 H, NCH*H*), 3.16–2.95 (m, 1 H, C*H*O), 1.42 (d, J = 5 Hz, 3 H, HC=CHCH_3), 1.03 (s, 9 H, SiC(CH_3)), 0.30 (s, 6 H, SiCH_3). Ketene acetal **7** was diluted with toluene (4 mL), and the resulting solution was refluxed for 18 h at 111 °C. After cooling to room temperature, the reaction mixture containing **8** was poured into a stirred two-phase mixture of ether (10 mL) and NaOH (10 mL of a 2 N solution). After 2 h the reaction mixture was diluted with ether (10 mL) and acidified to pH 3 by addition of $NaHSO_4$. Aqueous workup (ether, $MgSO_4$) afforded 91.4 mg (71%) of acid **9** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.60 (br s, 1 H, CO$_2$*H*), 7.47 (s, 5 H, Ar), 5.85–5.77 (m, 1 H, CH$_2$*H*C=CH), 5.67 (d, 1 H, J = 9 Hz, CH$_2$HC=C*H*CH), 5.30 (q, 2 H, J = 12 Hz, CH_2Ph), 5.12 (d, 1 H, J = 6 Hz, NC*H*), 4.30–4.08 (m, 2 H, NCH_2), 2.89 (bs, 1 H, C*H*CH$_3$), 1.34 (d, 3 H, J = 6.6 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.5, 156.0, 155.0, 136.3, 128.5, 128.1, 127.8, 127.2, 123.5, 123.1, 67.6, 56.3, 55.9, 42.5, 42.4, 31.5, 17.3; IR (CCl_4) 3300, 2800, 1710 cm^{-1}; MS (CI, NH_3) m/z 293 (MNH$_4^+$), 276 (MH$^+$, 90), 232 (100), 186 (28), 142 (75), 108 (17), 91 (53); HRMS for $C_{15}H_{17}NO_4$ calcd 275.1158, found 275.1168.

(±)-(*E*)-*N*-Benzyl-6-(1-propenyl)-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (11). A solution of phenyl α-bromoacetate[11] (675 mg, 3.14 mmol) in THF (10 mL) was added dropwise at 0 °C to a solution of amino alcohol 10[8] (600 mg, 3.14 mmol) and triethylamine (953 mg, 9.42 mmol) in dry THF (30 mL). The resulting solution was allowed to warm to room temperature and stirred for 4 h. Aqueous workup (ethyl acetate, K_2CO_3) followed by flash chromatography (1:1 hexane/ethyl acetate) afforded 620 mg (85%) of **11** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H, Ar*H*), 5.83 (dq, J = 15.0, 6.3 Hz, 1 H, CH$_3$C*H*=CHR), 5.50 (dd, J = 15.0, 7.2 Hz, 1 H, CH$_3$CH=C*H*CH), 4.87 (m, 1 H, C*H*OR), 3.55 (AB q, J = 15.9 Hz, $\Delta\nu$ = 16.8 Hz, 2 H, NCH_2Ar) 3.53 (dd, J = 17.4, 1.5 Hz, 1 H, RO$_2$CC*H*HN), 3.05 (d, J = 17.4, 1 H, RO$_2$CCH*H*N), 2.87 (ddd, J = 12.6, 3.6, 1.5 Hz, 1 H, CHC*H*HN), 2.31 (dd, J = 12.6, 9.3 Hz, 1 H, CHCH*H*N), 1.71 (dd, J = 6.3, 1.2 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168, 136, 131, 129, 128, 127, 126, 81, 62, 55, 54, 18; IR ($CHCl_3$) 3034, 2944, 2923, 2809, 2768, 1752, 1557, 1455, 1243 cm^{-1}; MS (EI, 20 eV) m/z 231 (M$^+$, 43), 187 (35), 172 (16), 134 (12), 133 (100), 91 (51); HRMS for $C_{14}H_{17}NO_2$ calcd 231.1259, found 231.1260.

(±)-(2*S,3*R**)-*N*-Benzyl-6-(hydroxymethyl)-5-methyl-1,2,5,6-tetrahydropyridine (13).** Triisopropylsilyl triflate (477 mg, 1.56 mmol) was added to an NMR tube containing lactone **11** (300 mg, 1.3 mmol), triethylamine (197 mg, 1.95 mmol), and $CDCl_3$ (2.0 mL). The NMR tube was sealed and heated to 75 °C for 2.5 h. The solvent was removed by rotary evaporation; the crude product was then redissolved in ethyl acetate and filtered through a 1-in. plug of silica gel to afford 490 mg of crude silyl ester **12**. The silyl ester, which could not be purified by HPLC, was reduced to the alcohol. Crude silyl ester **12** (490 mg) was added to a suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in THF (5.0 mL) at 0 °C. The reaction mixture was heated to reflux for 3 h, cooled to 0 °C, and quenched by the sequential addition of H_2O (100 μL), 15% NaOH (100 μL), and H_2O (300 μL). The resulting suspension was stirred for 3 h at room temperature, filtered, and concentrated. Flash chromatography (2:1 hexane/ethyl acetate) afforded 200 mg (69%) of alcohol **13** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5 H, ArH), 5.59 (s, 2 H, CH$_2$C*H*=CHR), 3.82 (AB q, J = 13.2 Hz, $\Delta\nu$ = 20.4 Hz, 2 H, ArCH_2N), 3.58 (dd, J = 10.5, 5.4 Hz, 1 H, CHR$_2$C*H*HOH), 3.49 (t, J = 10.5 Hz, 1 H, CH*H*OH), 3.26 (dd, J = 18.6, 4.2 Hz, 1 H, C*H*HN), 3.00 (m, 1 H, C*H*N), 2.86 (d, J = 18.6 Hz, 1 H, CH*H*N), 2.70 (m, 1 H, CH$_3$C*H*N), 0.91 (d, J = 7.5 Hz, 3 H, CH_3); ^{13}C NMR (75 MHz,

(22) (a) Alkyllithium titration: Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87. (b) Grignard titration: Ellison, R. A.; Griffin, R.; Kotsonis, F. N. *J. Organomet. Chem.* **1972**, *36*, 209.

$CDCl_3$) δ 139.6, 130.1, 129.2, 128.9, 127.7, 124.5, 61.1, 58.8, 58.3, 44.2, 26.1, 16.4; IR ($CDCl_3$) 3417, 3027, 2949, 2935, 2892, 1058, 1045, 890 cm^{-1}; MS (FAB) *m/z* 218 (M^+, 69), 216 (65), 204 (17), 200 (11), 187 (28), 186 (100), 184 (13), 164 (22); HRMS for $C_{14}H_{20}NO$ calcd 218.1545, found 218.1537.

(2*S*,3*S*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-hydroxy-4-pentene (15a). From 14a. Using a modification of the procedure by Tucker,[14] $ZnCl_2$ (50.0 mL of a 1.0 M solution in ether, 50 mmol) was added to a solution of vinylmagnesium bromide (61.0 mL of a 0.82 M solution in THF, 50 mmol) at −20 °C. The solution was stirred at −20 °C for 30 min, and then a solution of *N*-*t*-BOC-L-alaninal[13] **14a** (3.46 g, 20.0 mmol) in ether (50 mL) was added. The reaction mixture was allowed to warm to 0 °C and stirred for 3 h. The resulting solution was then poured into aqueous citric acid (5% w/v, 150 mL). Aqueous workup (ether, K_2CO_3) afforded 4.05 g of crude **15a**. Bulb-to-bulb distillation (110–150 °C, 0.10 mmHg) afforded 2.50 g (62%) of **15a** as a 3:1 mixture of syn and anti diastereomers (^1H NMR).

From 16a. Using a modification of the procedure by Ibuka, Fujii, and Yamamoto,[15a] DIBAL-H (23.5 mL of a 1.7 M solution in hexane, 40 mmol) was added to a solution of *N*-*t*-BOC-alanine ethyl ester **16a** (4.11 g, 20 mmol) in CH_2Cl_2 (20 mL) in such a manner as to keep the temperature of the solution below −70 °C. The resulting solution was then stirred at −78 °C for 3 h, warmed to −20 °C for 30 min, and recooled to −78 °C. Vinylmagnesium chloride (30.6 mL of a 1.3 M solution in THF, 40 mmol) was added dropwise to the mixture. The solution was then allowed to warm to 0 °C and stirred for 3 h. The solution was poured into an ice-cold solution of 1 N HCl (160 mL) and stirred for 1 h. Aqueous workup (ether, $MgSO_4$) afforded 2.50 g of crude **15a**. Flash chromatography (4:1 hexane/ethyl acetate) afforded 2.2 g (59%) of **15a** as an 8:1 mixture of syn and anti diastereomers (^1H NMR). The diastereomers could not be separated by HPLC and a mixture was used in the subsequent chemistry. The ^1H NMR of this mixture matched that reported by Yamamoto et al.[15a] for the 15:1 mixture of diastereomers. Major diastereomer, **15a**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (m, 1 H, CH_2=C*H*R), 5.31 (d, *J* = 16.2 Hz, 1 H, C*H*H=CHR), 5.20 (d, *J* = 10.5 Hz, 1 H, CH*H*=CHR), 4.65 (br s, 1 H, N*H*), 4.00 (m, 1 H, C*H*OH), 3.68 (m, 1 H, CH_3CH), 2.44 (br s, 1 H, O*H*), 1.44 (s, 9 H, *t*-Bu), 1.16 (d, *J* = 6.9 Hz, 3 H, CH_3).

(2*S*,3*S*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-hydroxy-1-phenyl-4-pentene (15b). The same procedure used for the preparation of **15a** from **14a** was carried out with *N*-*t*-BOC-phenylalaninal **14b**[13] (2.02 g, 8.1 mmol) to afford 2.01 g of crude **15b**. Flash chromatography (4:1 hexane/ethyl acetate) afforded 1.76 g (78%) of **15b** as a white solid (7:1 ratio of syn and anti diastereomers, ^1H NMR). A portion of **15b** was purified by HPLC (4:1 hexane/ethyl acetate; (*syn*-**15b** t_R = 8.8 min; *anti*-**15b** t_R = 10.5 min) to afford alcohol *syn*-**15b** as a white crystalline solid: mp 95–96 °C (lit.[13] mp 102–103 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.18 (m, 5 H, Ar*H*), 5.89 (m, 1 H, CH_2=C*H*), 5.27 (d, *J* = 17.1 Hz, 1 H, C*H*H=CH), 5.18 (d, *J* = 10.5 Hz, 1 H, CH*H*=CH), 4.82 (br d, *J* = 8.7 Hz, 1 H, CO_2NH), 4.11 (br s, 1 H, C*H*OH), 3.80 (m, 1 H, NC*H*), 3.00–2.80 (m, 2 H, $PhCH_2$), 2.43 (br s, 1 H, O*H*), 1.38 (s, 9 H, *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 138.3, 129.3, 128.5, 126.4, 116.1, 79.4, 72.7, 56.0, 37.9, 28.3; IR ($CDCl_3$) 3443, 2982, 2931, 1706, 1502, 1368, 1167 cm^{-1}; MS (EI, 20 eV) *m/z* 220 (14, M^+ − *t*-Bu), 186 (17), 164 (41), 130 (21), 120 (70), 91 (12), 86 (54), 57 (100); $[\alpha]^{25}_D$ −51.7° ($CHCl_3$, *c* = 0.00290) (lit.[13] $[\alpha]^{25}_D$ −53°). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.35. Found: C, 69.04; H, 8.23.

(3*S*,4*S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4-hydroxy-2-methyl-5-hexene (15c). The same procedure used for the preparation of **15a** from **16a** was carried out with *N*-*t*-BOC-valine methyl ester **16b** (2.38 g, 10 mmol) to afford 2.0 g of crude **15c**. Flash chromatography (4:1 hexane/ethyl acetate) afforded 700 mg (31%) of **15c** as a single diastereomer (^1H NMR): ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1 H, CH_2=C*H*R), 5.28 (d, *J* = 17.1 Hz, 1 H, C*H*H=CHR), 5.17 (d, *J* = 11.7 Hz, 1 H, CH*H*=CHR), 4.78 (br d, *J* = 7.8 Hz, 1 H, N*H*), 4.25 (m, 1 H, C*H*OH), 3.26 (m, 1 H, NHC*H*R), 2.21 (br s, 1 H, O*H*), 1.90 (m, 1 H, $(CH_3)_2CH$), 1.42 (s, 9 H, *t*-Bu), 0.98 (d, J = 6.6 Hz, 3 H, CH_3CH), 0.93 (d, *J* = 6.9 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 138.9, 115.6, 79.1, 72.7, 60.1, 29.5, 28.3, 20.0, 18.6; IR ($CDCl_3$) 3445, 2979, 2933, 2903, 1710, 1499, 1472, 1365, 1222 cm^{-1}; $[\alpha]^{25}_D$ −19.6° ($CHCl_3$, *c* = 0.00289). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.10. Found: C, 63.14; H, 10.00.

(5*S*,6*S*)-4,5-Dimethyl-6-ethenyl-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (17a). *N*-*t*-BOC-amino alcohol **15a** (0.92 g, 4.5 mmol; 8:1 mixture of diastereomers, ^1H NMR) was added to a suspension of $LiAlH_4$ (0.60 g, 23 mmol) and THF (50 mL). The resulting suspension was refluxed for 16 h, cooled to 0 °C, and quenched by the sequential addition of H_2O (0.6 mL), 15% NaOH (0.6 mL), and H_2O (1.8 mL). The resulting suspension was warmed to room temperature and stirred for 3 h, filtered through Celite, and concentrated to afford 490 mg of crude amine. Bulb-to-bulb distillation (50 °C, 0.5 mmHg) afforded 390 mg (78%) of (2*S*,3*S*)-3-hydroxy-2-(*N*-methylamino)-4-pentene (8:1 mixture of diastereomers, ^1H NMR) as a yellow oil. A solution of the above amino alcohol, CH_3CN (10 mL), and diisopropylethylamine (1.10 g, 8.50 mmol) was added to a solution of freshly distilled phenyl α-bromoacetate (0.77 g, 3.6 mmol) and CH_3CN (10 mL). The resulting solution was stirred at room temperature for 4 h, concentrated, diluted with ethyl acetate (50 mL), and then filtered through Celite. Flash chromatography (1:1 hexane/ethyl acetate) afforded 390 mg of **17a** (59% overall from **15a**) as an 8:1 mixture of lactone diastereomers (clear oil). HPLC (1:1 hexane/ethyl acetate; t_R cis, 17.8 min; t_R trans, 21.5 min) afforded an analytical sample of the trans diastereomer of **17a**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.1, 11.4, 8.1 Hz, 1 H, CHH=C*H*), 5.40 (d, *J* = 17.1 Hz, 1 H, C*H*H=CH), 5.35 (d, *J* = 11.4 Hz, 1 H, C*H*H=CH), 4.49 (dd, *J* = 8.7, 8.1 Hz, 1 H, =CHC*H*O), 3.23 (AB q, *J* = 17.7 Hz, Δν = 90 Hz, 2 H, C*HH*N), 2.30 (m, 1 H, CH_3CH), 2.29 (s, 3 H, NCH_3), 1.12 (d, *J* = 6.3 Hz, 3 H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 133.9, 120.6, 85.6, 58.1, 56.6, 40.9, 13.9; IR ($CHCl_3$) 3016, 2977, 1735, 1522, 1424, 1262, 1220, 1030 cm^{-1}; MS (EI, 20 eV) *m/z* 155 (M^+, 20), 71 (100), 56 (27), 43 (11); HRMS for $C_8H_{13}NO_2$ calcd 155.0946, found 155.0947; $[\alpha]^{25}_D$ −9.2° ($CHCl_3$, *c* = 0.0153).

(5*S*,6*S*)-6-Ethenyl-4-methyl-5-(phenylmethyl)-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (17b). The same procedure used for the reduction of **15a** to the *N*-methylamine was carried out with *N*-*t*-BOC-amino alcohol **15b** (700 mg, 2.53 mmol; 7:1 mixture of diastereomers, ^1H NMR) to afford 410 mg (86%) of crude (2*S*,3*S*)-3-hydroxy-2-(*N*-methylamino)-1-phenyl-4-pentene. Phenyl α-bromoacetate (540 mg, 2.50 mmol) was added to a solution of the above crude amino alcohol (410 mg), THF (20 mL) and triethylamine (640 mg, 6.3 mmol). The resulting solution was stirred for 4 h at room temperature. Aqueous workup (ethyl acetate, K_2CO_3) afforded 350 mg of crude **17b**. Flash chromatography (2:1 hexane/ethyl acetate) afforded 335 mg (52% from **15b**) of **17b** (clear oil) as a 7:1 mixture of diastereomers (^1H NMR). HPLC (2:1 hexane/ethyl acetate; t_R trans = 7.7 min; t_R cis = 9.8 min) of a portion of this material afforded an analytical sample of the trans diastereomer of **17b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5 H, Ar*H*), 5.90 (m, 1 H, CH_2=C*H*), 5.28 (d, *J* = 17.1 Hz, 1 H, C*H*H=CH), 5.27 (d, *J* = 11.1 Hz, 1 H, CH*H*=CH), 4.66 (dd, *J* = 6.0 Hz, *J* = 4.8 Hz, 1 H, CH_2=CHC*H*), 3.44 (AB q, *J* = 18.0 Hz, Δν = 18.1 Hz, 2 H, NCH_2CO_2), 2.90–2.72 (m, 3 H, $PhCH_2$, NC*H*), 2.43 (s, 3 H, NCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 137.8, 135.1, 129.3, 128.7, 126.6, 119.1, 80.6, 63.0, 53.4, 41.6, 31.2; IR ($CDCl_3$) 2958, 2927, 1738, 1216, 922 cm^{-1}; MS (CI, NH_3) *m/z* 232 (MH^+, 100), 140 (3); HRMS for $C_{14}H_{18}NO_2$ (MH^+) calcd 232.1337, found 232.1331; $[\alpha]^{25}_D$ −32.5° ($CHCl_3$, *c* = 0.0081).

(5*S*,6*S*)-6-Ethenyl-4-methyl-5-(1-methylethyl)-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (17c). The same procedure used for the preparation of **17a** from **15a** was carried out with *N*-*t*-BOC-amino alcohol **15c** (600 mg, 2.6 mmol) to afford 400 mg (98%) of (3*S*,4*S*)-3-hydroxy-2-methyl-4-(*N*-methylamino)-1-hexene which was treated with phenyl α-bromoacetate (660 mg, 3.07 mmol) as was described for the preparation of **17a** to afford 330 mg of **17c** (66% from **15c**) as a single diastereomer by ^1H NMR (clear oil): ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1 H, CH_2=C*H*R), 5.37 (d, *J* = 19.2 Hz, 1 H, C*H*H=CHR), 5.33 (d, *J* = 13.2 Hz, 1 H, CH*H*=CHR), 4.62 (t, *J* = 8.1 Hz, 1 H, C*H*OR), 3.37 (AB q, *J* = 16.5 Hz, Δν = 81.6 Hz, 2 H, C*HH*N), 2.45 (s, 3 H, NCH_3), 2.28 (dd, *J* = 3.0, 9.0 Hz, 1 H, NC*H*), 1.83 (dq, *J* = 3.3, 6.9 Hz, $(CH_3)_2CH$), 0.98 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 0.93 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 134.6, 119.5, 79.7, 67.7, 54.0, 46.5, 29.1, 20.3, 16.8; IR ($CDCl_3$) 2964,

2934, 2902, 1754, 1470, 1382, 1095, 988, 914 cm^{-1}; MS (EI, 20 eV) m/z 183 (79, M$^+$), 140 (100), 112 (82), 99 (50), 84 (84); HRMS for $C_{10}H_{17}NO_2$ calcd 183.1259, found 183.1257; $[\alpha]^{25}_D$ -200.3° ($CHCl_3$, c = 0.0238).

(2*S*,6*S*)-1,2-Dimethyl-6-[[(triisopropylsilyl)oxy]carbonyl]-1,2,5,6-tetrahydropyridine (19a). The same procedure used for the preparation of **13** was carried out with lactone **17a** (101 mg, 0.64 mmol; 8:1 mixture of diastereomers by ^{1}H NMR) [6 h, room temperature] to afford 160 mg of crude **19a**. HPLC (5:1 hexane/ethyl acetate; t_R 5.0 min) afforded 127 mg (64%) of **19a** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (m, 1 H, CH=C*H*CH$_2$), 5.47 (br d, J = 10.2 Hz, 1 H, C*H*=CHCH$_2$), 3.17 (dd, J = 4.5, 10.2 Hz, 1 H, NC*H*CO$_2$), 2.89 (m, 1 H, CH$_3$C*H*N), 2.50–2.20 (m, 2 H, =CHC*H*$_2$), 2.36 (s, 3 H, NC*H*$_3$), 1.30 (septet, J = 7.5 Hz, 3 H, SiC*H*(CH$_3$)$_2$), 1.20 (d, J = 6.6 Hz, 3 H, CHC*H*$_3$), 1.08 (d, J = 7.5 Hz, 18 H, SiCH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 131.2, 122.2, 65.1, 57.3, 39.5, 29.5, 20.0, 17.8, 11.9; IR ($CDCl_3$), 3022, 2975, 1720, 1523, 1424, 1225, 1047 cm^{-1}; MS (CI, CH_4) m/z 312 (100, MH$^+$), 296 (7), 268 (52), 231 (8), 110 (66); HRMS (CI, NH_3) for $C_{17}H_{34}NO_2Si$ (MH$^+$) calcd 312.2359, found 312.2343; $[\alpha]^{25}_D$ -19.4° ($CHCl_3$, c = 0.0127).

(2*S*,6*S*)-1-Methyl-2-(phenylmethyl)-6-[[(triisopropylsilyl)oxy]carbonyl]-1,2,5,6-tetrahydropyridine (19b). The same procedure used for the preparation of **13** was carried out with lactone **17b** (100 mg, 0.43 mmol; 7:1 mixture of diastereomers by ^{1}H NMR) [1 h, room temperature] to afford 131 mg of crude **19b**. HPLC (9:1 hexane/ethyl acetate; t_R 4.5 min) afforded 123 mg (74%) of **19b** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (m, 5 H, Ph*H*), 5.69 (m, 1 H, C*H*=CHCH$_2$), 5.46 (br d, J = 10.2 Hz, 1 H, CH=C*H*CH$_2$), 3.27–3.10 (m, 3 H, NC*H*CO$_2$, PhC*H*H, NC*H*CH), 2.61 (dd, J = 9.0, 12.9 Hz, 1 H, PhCH*H*), 2.51 (s, 3 H, NC*H*$_3$), 2.30 (m, 2 H, =CHC*H*$_2$), 1.32 (septet, J = 7.5 Hz, 3 H, SiC*H*(CH$_3$)$_2$), 1.04 (d, J = 7.5 Hz, 18 H, SiCH(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 139.1, 129.7, 128.2, 127.9, 126.1, 122.8, 64.8, 63.5, 40.0, 28.7, 17.8, 17.7, 11.9; IR ($CDCl_3$) 2985, 2947, 2902, 1793, 1473, 1386, 1096 cm^{-1}; MS (Cl, CH_4) m/z 388 (91, MH$^+$), 344 (39), 296 (100), 186 (27); HRMS (CI, CH_4) for $C_{23}H_{38}NO_2Si$ (MH$^+$) calcd 388.2672, found 388.2686; $[\alpha]^{25}_D$ +19.4° ($CHCl_3$, c = 0.0187).

(2*S*,6*S*)-6-(Hydroxymethyl)-*N*-methyl-2-(1-methylethyl)-1,2,5,6-tetrahydropyridine (19d). The same procedure used for the preparation of **13** was carried out with lactone **17c** (75 mg, 0.41 mmol) [40 min, room temperature] to afford 140 mg of crude tetrahydropyridine **19c** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 1 H, CH$_2$C*H*=CH), 5.55 (d, J = 9.9 Hz, 1 H, CHC*H*=CH), 3.10 (dd, J = 2.7, 9.8 Hz, C*H*CO$_2$), 2.65 (m, 1 H, CH=CHC*H*), 2.31 (s, 3 H, NC*H*$_3$), 2.4–2.0 (m, 3 H, (CH$_3$)$_2$C*H* and CH=CHC*H*$_2$), 1.35 (m, 3 H, SiC*H*(CH$_3$)$_2$), 1.19 (d, 18 H, J = 6.7 Hz, SiCH(C*H*$_3$)$_2$), 0.95 (d, J = 6.6 Hz, 3 H, C*H*$_3$CH), 0.85 (d, J = 6.6 Hz, 3 H, C*H*$_3$CH). Attempts to purify the silyl ester by HPLC failed to afford analytically pure material. The crude ester was added to $LiAlH_4$ (85 mg, 1.62 mmol) in THF (10 mL) and refluxed for 2 h, cooled to 0 °C, and quenched by sequential addition of H_2O (0.8 mL), 15% NaOH (0.8 mL), and H_2O (2.4 mL). The resulting suspension was stirred for 4 h, filtered through Celite, and concentrated, affording 60 mg of crude alcohol. Flash chromatography (2:1 hexane/ethyl acetate) afforded 48 mg (70%) of alcohol **19d** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (m, 1 H, CHCH=C*H*CH$_2$), 5.56 (br d, J = 10.2 Hz, 1 H, CHC*H*=CHCH$_2$), 3.72 (dd, J = 4.2, 10.8 Hz, 1 H, C*H*HOH), 3.36 (dd, J = 4.8, 10.8 Hz, 1 H, CH*H*OH), 3.10 (br s, 1 H, O*H*), 2.72 (m, 1 H, NC*H*CH$_2$OH), 2.64 (m, 1 H, NC*H*CH=CH), 2.27 (s, 3 H, NC*H*$_3$), 2.20–2.05 (m, 1 H, CH=CHC*H*H), 1.94 (m, 1 H, CH=CHCH*H*), 1.83 (m, 1 H, (CH$_3$)$_2$C*H*), 0.95 (d, J = 6.9 Hz, 3 H, C*H*$_3$CH), 0.83 (d, J = 6.9 Hz, 3 H, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.4, 67.1, 62.5, 59.3, 37.2, 30.4, 25.8, 20.0, 17.6; IR ($CDCl_3$) 2964, 2933, 2902, 1468, 1383, 923, 908 cm^{-1}; MS (CI, CH_4) m/z 170 (12, MH$^+$), 138 (13), 126 (100), 94 (27); HRMS (CI, CH_4), for $C_{10}H_{20}NO$ (MH$^+$) calcd 170.1545, found 170.1539; $[\alpha]^{25}_D$ +51.2° ($CHCl_3$, c = 0.0474). Anal. Calcd for $C_{10}H_{19}NO$: C, 70.95; H, 11.31. Found: C, 70.37; H, 11.25.

(2*S*,3*S*,4*E*)-2-[*N*-(*tert*-Butyloxycarbonyl)amino]-3-hydroxy-4-nonene (20). DIBAL-H (2.13 g, 15 mmol, in hexane, 20 mL) was added to a solution of *N*-*t*-BOC-alanine ethyl ester **16a** (1.54 g, 7.5 mmol) in CH_2Cl_2 (20 mL) in such a manner as to keep the internal temperature below -70 °C. The resulting solution was stirred at -78 °C for 3 h. In a second flask *tert*-butyllithium (42.5 mL, of a 1.6 M solution in pentane, 68 mmol) was added to a solution of (*E*)-1-hexenyl iodide[23] (8.4 g, 40 mmol) and hexanes (50 mL) at -78 °C. The resulting solution was warmed to 0 °C and stirred for 1 h. The vinyllithium solution was then added to the DIBAL-H adduct via cannula. The resulting solution was allowed to warm to room temperature over 12 h and then poured into 1 N HCl (200 mL) and stirred for 1 h. Aqueous workup (ether, K_2CO_3) afforded 2.5 g of crude **20**. Flash chromatography (4:1 hexane/ethyl acetate) afforded 2.2 g (82%) of **20** as a 5:1 mixture of diastereomers (^{1}H NMR). The diastereomers could not be separated by HPLC and were taken onto the next step as a 5:1 mixture. Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (dt, J = 15.3, 6.6 Hz, 1 H, CH$_2$C*H*=CHCH), 5.44 (dd, J = 15.3, 6.9 Hz, 1 H, CH$_2$CH=C*H*CH), 4.70 (br s, 1 H, N*H*), 3.92 (t, 1 H, J = 5.4 Hz, CH=CHC*H*), 3.62 (m, 1 H, CH$_3$C*H*), 2.03 (m, 2 H, C*H*$_2$CH=CH), 1.43 (s, 9 H, *t*-Bu), 1.37–1.28 (m, 4 H, CH$_2$C*H*$_2$), 1.13 (d, J = 6.9 Hz, 3 H, C*H*$_3$CH), 0.88 (t, J = 6.9 Hz, 3 H CH$_2$C*H*$_3$). Anal. Calcd for $C_{14}H_{27}NO_3$ (mixture of diastereomers): C, 65.33; H, 10.57. Found: C, 65.02; H, 10.25.

(5*S*,6*S*,1*E*)-4,5-Dimethyl-6-(1-hexenyl)-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (21). *N*-*t*-BOC-amino alcohol **20** (400 mg, 1.55 mmol; 5:1 mixture of diastereomers, ^{1}H NMR) was added to a rapidly stirred suspension of $LiAlH_4$ (413 mg, 10.9 mmol) and THF (30 mL). The solution was refluxed for 16 h, cooled to 0 °C, and quenched by sequential addition of H_2O (0.41 mL), 15% NaOH (0.41 mL), and H_2O (1.23 mL). The resulting suspension was stirred at room temperature for 3 h, filtered through Celite, and concentrated to afford 260 mg of crude amino alcohol. Bulb-to-bulb distillation (125–145 °C, 0.5 mmHg) afforded 220 mg (84%) of amino alcohol. A solution of the amino alcohol (220 mg, 1.3 mmol) CH_3CN (10 mL) and diisopropylethylamine (418 mg, 3.23 mmol) was added slowly to a solution of freshly distilled phenyl α-bromoacetate (536 mg, 2.5 mmol) and CH_3CN (10 mL). The resulting solution was stirred for 4 h at room temperature. The reaction mixture was concentrated, diluted with ethyl acetate (20 mL), and filtered through Celite. Flash chromatography (2:1 hexane/ethyl acetate) afforded 170 mg (52% from **20**) of lactone **21** as a 5:1 mixture of diastereomers (^{1}H NMR). HPLC (2:1 hexane/ethyl acetate) afforded an analytical sample of *trans*-lactone **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (dt, J = 6.9, 15.3 Hz, 1 H, CH$_2$C*H*=CH), 5.39 (dd, J = 8.4, 15.3 Hz, 1 H, CH$_2$CH=C*H*), 4.41 (dd, J = 8.7, 8.4 Hz, 1 H, =CHC*H*O), 3.29 (AB q, J = 17.4 Hz, $\Delta\nu$ = 18.1 Hz, 2 H, NC*H*$_2$CO$_2$), 3.02 (d, J = 17.4 Hz, 1 H, O$_2$CCH*H*N), 2.25 (s, 3 H, NC*H*$_3$), 2.21 (m, 1 H, CH$_3$C*H*N), 2.05 (m, 2 H, C*H*$_2$CH), 1.40–1.20 (m, 4 H, C*H*$_2$C*H*$_2$), 1.06 (d, J = 6.3 Hz, 3 H, CHC*H*$_3$), 0.86 (t, J = 4.2 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 138.4, 125.6, 86.0, 58.4, 56.7, 40.9, 31.8, 30.8, 22.1, 14.3, 13.8; IR ($CDCl_3$) 2984, 2962, 1733, 1472, 1375, 1250, 1046 cm^{-1}; MS (EI, 70 eV) m/z 211 (5, M$^+$), 168 (1), 116 (1), 81 (1), 71 (100), 56 (7); HRMS (EI, 70 eV) for $C_{12}H_{21}NO_2$ calcd 211.1572, found 211.1572; $[\alpha]^{25}_D$ -24.6° ($CHCl_3$, c = 0.0156).

(2*S*,5*R*,6*S*)-3-Butyl-1,2-dimethyl-6-[[(triisopropylsilyl)oxy]carbonyl]-1,2,5,6-tetrahydropyridine (22). The same procedure used for the preparation of **13** was carried out with lactone **21** (90 mg, 0.43 mmol; 5:1 mixture of diastereomers by ^{1}H NMR) [2.0 h, room temperature] to afford 170 mg of crude **22**. HPLC (9:1 hexane/ethyl acetate; t_R 4.4 min) afforded 147 mg (78%) of **22** as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (ddd, J = 2.1, 5.4, 9.9 Hz, 1 H, CHC*H*=CHCHN), 5.47 (dd, J = 2.1, 9.9 Hz, 1 H, NCHC*H*=CH), 3.22 (d, J = 3.6 Hz, 1 H, O$_2$CC*H*), 2.77 (m, 1 H, CH$_3$C*H*N), 2.40 (s, 3 H, NC*H*$_3$), 2.33 (m, 1 H, =CHC*H*), 1.20–1.60 (m, 9 H, 3 C*H*$_2$ and SiC*H*(CH$_3$)$_2$), 1.19 (d, J = 6.6 Hz, 3 H, C*H*$_3$CHN), 1.08 (d, J = 6.9 Hz, 18 H, SiCHC*H*$_3$), 0.86 (t, J = 7.2 Hz, 3 H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 130.4, 127.0, 68.9, 58.5, 41.5, 38.1, 32.2, 29.5, 22.9, 20.6, 17.8, 14.1, 11.9; IR ($CDCl_3$), 2975, 2948, 2869, 1725, 1472, 1379, 1095 cm^{-1}; MS (CI, NH_3) m/z 368 (48, MH$^+$), 212 (3), 166 (100), 150 (5), 108 (3), 94 (5); HRMS (CI, NH_3) for $C_{21}H_{42}NO_2Si$ (MH$^+$) calcd 368.2985, found 368.2968; $[\alpha]^{25}_D$ -95.1° ($CHCl_3$, c = 0.0111).

(23) Brown, H. C.; Hamaoka, T.; Ravindran, N. J. *J. Am. Chem. Soc.* **1973**, *95*, 5786.

(2S,6S)-6-(Hydroxymethyl)-N,N,2-trimethyl-1,2,5,6-tetrahydropyridinium Iodide (23). Silyl ester **19a** (800 mg, 2.56 mmol) in THF (5 mL) was added dropwise to a rapidly stirred suspension of $LiAlH_4$ (500 mg, 13.0 mmol) and THF (20 mL). The resulting suspension was refluxed for 3 h, cooled to 0 °C, and quenched by the sequential addition of H_2O (0.5 mL), NaOH 15% (0.5 mL), and H_2O (1.5 mL). The resulting suspension was stirred at room temperature for 3 h and then filtered through Celite. Concentration afforded 380 mg of crude amino alcohol. Flash chromatography (2:1 hexane/ethyl acetate) afforded 333 mg (92%) of (2S,6S)-N,2-dimethyl-6-(hydroxymethyl)-1,2,5,6-tetrahydropyridine as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1 H, CH_2CH=CH), 5.43 (dd, J = 8.1, 1.8 Hz, 1 H, CH_2CH=CHCH), 3.74 (dd, J = 4.2, 10.8 Hz, 1 H, HOCHH), 3.47 (dd, J = 5.4, 10.8 Hz, 1 H, HOCHH), 3.06 (m, 1 H, CH_3CH), 2.66 (m, 1 H, OCH_2CH), 2.28 (s, 3 H, NCH_3), 2.16 (m, 1 H, =CHCHH), 1.92 (m, 1 H, =CHCHH), 1.17 (d, J = 6.6 Hz, 3 H, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 130.3, 123.7, 62.7, 59.8, 56.9, 35.4, 26.0, 20.5. IR ($CDCl_3$) 3156, 3070, 3019, 2980, 1475, 1383, 1217, 1096 cm^{-1}; MS (CI, CH_4), 142 (MH^+, 80), 140 (23), 124 (18), 110 (28), 102 (23), 74 (100); HRMS (CI, CH_4) for $C_8H_{16}NO$ (MH^+) calcd 142.1231, found 142.1228; $[\alpha]^{25}_D$ +13.9° ($CHCl_3$, c = 0.0176). Methyl iodide (100 mg, 0.70 mmol) was added dropwise to a rapidly stirred solution of the above amino alcohol (50 mg, 0.35 mmol) and ether (2 mL). A white precipitate formed immediately. The precipitate was collected by vacuum filtration and washed with ether (3 × 5 mL). Recrystallization (ether/chloroform) afforded 80 mg (80%) of **23** as white needles: mp 200–203 °C dec; ^1H NMR (300 MHz, $CDCl_3$) δ 6.06 (m, 1 H, CH_2CH=CH), 5.44 (br d, J = 10.2 Hz, 1 H, CH_2CH=CHCH), 4.53 (m, 1 H, CH_3CH), 4.41 (dd, J = 14.1, 1.0 Hz, 1 H, HOCHH), 4.08 (m, 1 H, OCH_2CH), 3.97 (dd, J = 14.1, 1.2 Hz, 1 H, HOCHH), 3.56 (s, 3 H, NCH_3(eq)), 3.01 (s, 3 H, NCH_3(ax)), 2.73 (m, 1 H, =CHCHH), 2.47 (m, 1 H, =CHCHH), 1.49 (d, J = 6.9 Hz, 3 H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.7, 124.7, 70.9, 68.6, 59.6, 49.7, 39.5, 25.6, 15.0; IR ($CDCl_3$) 3155, 2985, 1472, 1382, 1095 cm^{-1}; MS (FAB, nitrobenzyl alcohol), 156 (MH^+, 100); HRMS (FAB, nitrobenzyl alcohol) for $C_9H_{18}NO$ calcd 156.1388, found 156.1386; $[\alpha]^{25}_D$ −7° ($CHCl_3$, c = 0.0176).

(±)-2-[N-(Benzyloxycarbonyl)amino]cyclohexanone (24).[21] Using the general procedure of Swern and co-workers,[24] DMSO (3.75 mL, 52.8 mmol) was added to a stirred solution of oxalyl chloride (2.5 mL, 29 mmol) and CH_2Cl_2 (150 mL) at −78 °C. After 20 min, a solution 2-[N-(benzyloxycarbonyl)amino]cyclohexanol[21] (5.98 g, 24 mmol) in CH_2Cl_2 (35 mL) was added dropwise over 10 min. The resulting solution was stirred for 25 min, and then triethylamine (17.5 mL, 126 mmol) was added. After 15 min, the reaction solution was allowed to warm to room temperature and stirred for 45 min. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded crude ketone as a yellow oil. Flash chromatography (3:1 hexane/ethyl acetate) afforded 4.76 g (80%) of **24**[21] as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 5 H, ArH), 5.88 (br s, 1 H, NH), 5.20 (s, 2 H, $ArCH_2$), 4.40 (dd, J = 6.0, 12.0 Hz, 1 H, NHCH), 2.8–1.4 (m, 8 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.1, 155.6, 136.3, 128.4, 128.3, 128.0, 66.7, 59.4, 41.0, 35.7, 27.8, 24.0; IR (CCl_4) 1740, 1715 cm^{-1}; MS (EI, 70 eV) m/z 247 (M^+, 4), 117 (14), 108 (58), 98 (17), 91 (100), 84 (48); HRMS for $C_{14}H_{17}NO_3$ calcd 247.1208, found 247.1205.

(±)-(1S*,2S*)- and (1R*,2S*)-2-[N-(Benzyloxycarbonyl)amino]-1-ethenyl-1-cyclohexanol [25 (1R*,2S*) and 29 (1S*,2S*)]. Vinylmagnesium bromide (47 mL of a 1 M solution in THF, 47 mmol) was added dropwise to a stirred solution of ketone **24** (3.95 g, 15.9 mmol) and THF (80 mL) at −78 °C. After the addition, the reaction mixture was slowly allowed to warm to room temperature. After 3 h the reaction mixture was cooled to 0 °C, and 1 N HCl (80 mL) was added. Aqueous workup (ethyl acetate, $MgSO_4$) followed by MPLC (4:1 hexane/ethyl acetate) purification afforded 1.23 g (28%) of **29** (1S*,2S*) as a white solid, mp 57–58 °C, and 1.04 g (24%) of **25** (1R*,2S*) as a white solid mp 68–69 °C. High R_f diastereomer **29** (1S*,2S*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 5 H, ArH), 5.89 (dd, J = 10.8, 17.0 Hz, 1 H, CH=CH_2), 5.30–5.00 (m, 4 H, $ArCH_2$, HC=CH_2), 3.52 (m, 1 H, NCH), 2.00–1.20 (m, 8 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 143.6, 136.6, 128.3, 127.9, 112.9, 74.0, 66.5, 55.0, 37.6, 28.5, 24.6, 20.4; IR (CCl_4) 3620, 3450, 1725 cm^{-1}; MS (EI, 20 eV) m/z 275 (M^+, 3), 140 (60), 123 (9), 91 (100), 84 (6), 55 (34); HRMS for $C_{16}H_{21}NO_3$ calcd 275.1521, found 275.1518. Low R_f diastereomer **25** (1R*,2S*): ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 5 H, ArH), 6.24 (dd, J = 10.8, 17.1 Hz, 1 H, HC=CHH), 5.56 (dd, J = 1.0, 17.1 Hz, 1 H, HC=CHH), 5.37 (dd, J = 1.0, 10.8 Hz, 1 H, HC=CHH), 5.17 (q, J = 12.2 Hz, 2 H, $ArCH_2$), 4.88 (d, 1 H, NH), 3.79–3.71 (m, 1 H, NHCH), 3.18 (br s, 1 H, OH), 2.00–1.25 (m, 8 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 137.3, 136.2, 128.4, 128.2, 128.0, 116.2, 74.4, 66.8, 58.2, 38.8, 30.2, 24.5, 22.5; IR (CCl_4) 3535, 3390, 1720 cm^{-1}; MS (EI, 20 eV) m/z 275 (M^+, 3), 140 (36), 91 (100), 55 (25); HRMS or $C_{16}H_{21}NO_3$ calcd 275.1521, found 275.1515.

(1R*,2S*)-2-Amino-1-ethenyl-1-cyclohexanol (26). A rapid stream of N_2 was bubbled into a solution of carbamate **25** (433 mg, 1.57 mmol), MeOH (42.4 mL), and H_2O (3.4 mL) for 20 min. After degassing, KOH (34.2 g, 0.61 mol) was added and the resulting mixture was refluxed for 20 h. The resulting solution was then cooled to room temperature, and H_2O (10 mL) was added. The reaction mixture was extracted with ether (2 × 40 mL). The combined organic layers were then extracted with 1 N HCl (2 × 40 mL). The aqueous layer was saturated with NaOH. Aqueous workup (ether, K_2CO_3) afforded 198 mg (89%) of amine **26** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (dd, J = 10.9, 17.2 Hz, 1 H, HC=CHH), 5.37 (dd, J = 1.7, 17.2 Hz, 1 H, HC=CHH), 5.23 (dd, J = 1.7, 10.9 Hz, 1 H, HC=CHH), 2.57 (dd, J = 3.7, 11.4 Hz, 1 H, NH_2CH), 1.80–1.00 (m, 8 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 115.5, 74.7, 58.1, 38.1, 32.9, 24.9, 22.8; IR (CCl_4) 3620, 3510, 3380, 2940, 2860, 990 cm^{-1}; MS (EI, 20 eV) m/z 142 (M^+, 100), 124 (82), 114 (5), 107 (4), 96 (3), 84 (4), 69 (71), 56 (32); HRMS for $C_8H_{15}NO$ calcd 141.1154, found 141.1151.

(4aS*,8aR*)-4-(Benzyloxycarbonyl)-8a-ethenyl-2-oxo-3,4,4a,5,6,7,8,8a-octahydro-2H-1,4-benzoxazine (27). Triethylamine (0.33 mL, 2.4 mmol) and ethyl α-bromoacetate (0.16 mL, 1.4 mmol) were sequentially added to a stirred solution of amine **26** (164.5 mg, 1.17 mmol) and THF (7 mL) at room temperature. After 5 h, the reaction mixture was poured into ethyl acetate (10 mL) and H_2O (10 mL). Aqueous workup (ethyl acetate, K_2CO_3) afforded 210 mg (81%) of crude amine as a yellow oil. To a mixture of the above amine (215 mg, 0.95 mmol), saturated $NaHCO_3$ (4 mL), and CH_2Cl_2 (4.8 mL) was added benzyl chloroformate (0.16 mL, 1.12 mmol). The resulting two-phase mixture was stirred for 5 h. Aqueous workup (CH_2Cl_2, $MgSO_4$) afforded crude product as a yellow oil. Flash chromatography (3:1 hexane/ethyl acetate) afforded 242.1 mg (71%) of (1R*,2S*)-[N-(benzyloxycarbonyl)-N-[(ethoxycarbonyl)methyl]amino]-1-ethenyl-1-cyclohexanol as a clear oil: ^1H NMR (300 MHz, $CDCl_3$, mixture of carbamate isomers) δ 7.40 (m, 5 H, ArH), 6.20–6.00 (m, 1 H, HC=CH_2), 5.50–5.00 (m, 4 H, $ArCH_2$, HC=CH_2), 4.40–4.00 (m, 2 H, OCH_2CH_3), 3.90 (d, 1 H, $NCHHCO_2$), 3.40 (d, 1 H, $NCHHCO_2$), 2.90 (dd, 1 H, NCH), 2.00–1.40 (m, 2 H, CH_2), 1.50–1.20 (m, 3 H, OCH_2CH_3). A solution of the above carbamate (321 mg, 0.89 mmol), benzene (45 mL), and p-toluenesulfonic acid (11.9 mg, 0.060 mmol) was heated to 100 °C for 4 h in a flask equipped with a Dean–Stark trap. During the course of the reaction additional p-toluenesulfonic acid (13 mg) and benzene were added. After being cooled to room temperature the reaction mixture was concentrated and purified by MPLC (4:1 hexane/ethyl acetate) to afford 173 mg (62%) of **27** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 5 H, ArH), 6.46 (dd, J = 9.0, 15 Hz, 1 H, HC=CHH), 5.55 (d, J = 18 Hz, 1 H, HC=CHH), 5.45 (d, J = 15 Hz, 1 H, HC=CHH), 5.21 (s, 2 H, $ArCH_2$), 4.42 (AB q, J = 21.0 Hz, Δν = 30 Hz, 2 H, NCH_2), 3.55 (dd, J = 3.0, 12 Hz, 1 H, NCH), 2.80 (d, J = 12.0 Hz, 1 H, CHH), 2.20–1.40 (m, 7 H, CH_2, CHH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 155.2, 136.1, 135.7, 128.8, 128.6, 128.5, 128.3, 118.8, 83.8, 67.6, 61.9, 48.5, 39.0, 27.7, 25.0, 22.5; IR (CCl_4) 1760, 1720, 1450, 1395 cm^{-1}; MS (EI, 20 eV) m/z 315 (M^+, 4) 152 (11), 108 (12), 91 (100); HRMS for $C_{18}H_{21}NO_4$ calcd 315.1470, found 315.1478.

(2R*,8aS*)-1-(Benzyloxycarbonyl)-2-(methoxycarbonyl)-1,2,3,5,6,7,8,8a-octahydroquinoline (28b). To a solution of lactone **27** (19.4 mg, 0.062 mmol) and C_6D_6 (0.5 mL) in an NMR tube was added triethylamine (0.02 mL, 0.144 mmol) and *tert*-butyldimethylsilyl triflate (0.016 mL, 0.07 mmol). After 30 min the NMR tube was sealed and heated to 125 °C. After

(24) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

1.5 h the reaction mixture was cooled to room temperature. The reaction mixture was poured into THF (20 mL) and NaOH (10 mL, 10 M). After 1 h, ether (10 mL) was added, and the aqueous layer was acidified to pH 3 with $NaHSO_4$. Aqueous workup (ether, $MgSO_4$) afforded 15.7 mg (81%) of acid **28a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5 H, Ar*H*), 5.48–5.44 (m, 1 H, C=C*H*CH_2), 5.24–5.17 (m, 2 H, CH_2Ph), 4.87–4.80 (m, 1 H, NC*H*CO_2H), 4.04 (d, J = 6.0 Hz, 1 H, NC*H*), 2.74–2.57 (m, 1 H, CH=CHC*H*H), 2.56–2.37 (m, 1 H, CH=CHCH*H*), 2.37–0.53 (m, 8 H, CH_2); IR (CCl_4) 1735, 1715 cm^{-1}; MS (EI, 20 eV) m/z 315 (M^+, 38), 271 (8), 226 (74), 180 (63), 134 (27), 91 (100); HRMS for $C_{18}H_{21}NO_4$ calcd 315.1471, found 315.1475. To a solution of acid **28a** (27.5 mg, 0.09 mmol, prepared in a different run) and ether (2 mL) was added diazomethane (9 mL of a 0.2 M solution, 1.7 mmol). After 30 min, a stream of N_2 was passed through the solution to remove unreacted diazomethane; concentration afforded crude ester **28b**. Flash chromatography (20:1 hexane/ethyl acetate) afforded 19.4 mg (67%) of ester **28b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H, Ar*H*), 5.38 (d, J = 4.2 Hz, 1 H, ArCH*H*), 5.23 (m, 1 H, *H*C=C), 5.10 (m, 1 H, ArC*H*H), 4.73 (dd, J = 2.9, 5.7 Hz, 1 H, NC*H*CO_2), 3.56 (d, J = 20.5 Hz, 1 H, NC*H*), 3.10 (br s, 3 H, CO_2CH_3), 2.90–0.90 (m, 8 H, CH_2); IR (CCl_4) 1750, 1715 cm^{-1}; MS (EI, 20 eV) m/z 329 (M^+, 11), 270 (10), 226 (50), 194 (39), 136 (28), 91 (100); HRMS for $C_{19}H_{23}NO_4$ calcd 329.1628, found 329.1615.

(1*S,2*S**)-2-Amino-1-ethenyl-1-cyclohexanol (30).** The procedure described for the preparation of **26** was carried out with carbamate **29** (460 mg, 1.70 mmol), MeOH (42.4 mL), H_2O (4.2 mL), and KOH (36.2 g, 0.65 mol) to afford 164.5 mg (68%) of **30** as a yellow oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (dd, J = 10.6, 17.2 Hz, 1 H, *H*C=CHH), 5.32 (d, J = 17.2 Hz, 1 H, HC=C*H*H), 5.09 (d, J = 10.6 Hz, HC=CH*H*), 2.68 (m, 1 H, C*H*NH_2), 2.00–1.00 (m, 8 H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 113.2, 76.2, 54.0, 35.7, 30.0, 24.6, 20.7; IR (CCl_4) 3610, 3470, 2930, 1020 cm^{-1}; MS (EI, 20 eV) m/z 141 (M^+, 26), 124 (31), 107 (49), 69 (100), 56 (56); HRMS for $C_8H_{15}NO$ calcd 141.1154, found 141.1150.

(4a*S,8a*S**)-4-(Benzyloxycarbonyl)-8a-ethenyl-2-oxo-3,4,4a,5,6,7,8,8a-octahydro-2*H*-1,4-benzoxazine (31).** The same procedure described for the preparation of **27** was carried out with amine **30** (200 mg, 1.4 mmol), triethylamine (0.39 mL, 2.8 mmol), and ethyl α-bromoacetate (0.19 mL, 1.71 mmol) to afford 243.9 mg (77%) of crude amine as a yellow oil. The above amine (243.9 mg, 1.1 mmol) was submitted to the same conditions as used for the synthesis of **27**, saturated $NaHCO_3$ (5 mL), CH_2Cl_2 (5.5 mL), and benzyl chloroformate (0.19 mL, 1.33 mmol) to afford a yellow oil. Flash chromatography (3:1 hexane/ethyl acetate) afforded 295.7 mg (76%) of (1*S**,2*S**)-[*N*-(benzyloxycarbonyl)-*N*-[(ethoxycarbonyl)methyl]amino]-1-ethenyl-1-cyclohexanol as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (m, 5 H, Ar*H*), 6.50 (m, 1 H, *H*C=CH_2), 5.70 (m, 2 H, HC=CH_2), 4.20 (dd, 1 H, *H*CN), 3.90 (m, 2 H, NCH_2), 2.00–1.00 (m, 8 H, CH_2). A solution of the above carbamate (125 mg, 0.35 mmol), benzene (20 mL), and *p*-toluenesulfonic acid (4.1 mg, 0.022 mmol) was heated to 100 °C for 4 h in a flask equipped with a Dean–Stark trap. During the course of the reaction additional *p*-toluenesulfonic acid (5.0 mg) and benzene were added. After cooling to room temperature the reaction mixture was concentrated and flash chromatographed (6:1 hexane/ethyl acetate) to afford 42.4 mg (39%) of **31** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 5 H, Ar*H*), 5.87 (dd, J = 11.0, 17.0 Hz, *H*C=CH_2), 5.45–5.25 (m, 4 H, HC=CH_2, ArCH_2), 4.38–4.18 (m, 3 H, NCH_2, NC*H*), 2.18–1.28 (m, 8 H, CH_2); IR (CCl_4) 1745, 1700 cm^{-1}; MS (EI, 20 eV) m/z 315 (M^+, 8), 152 (18), 91 (100), 65 (11); HRMS for $C_{18}H_{21}NO_4$ calcd 315.1471, found 315.1475.

(2*S,8a*S**)-1-(Benzyloxycarbonyl)-2-carbomethoxy-1,2,3,5,6,7,8,8a-octahydroquinoline (32b).** The same procedure described for the preparation of **28b** was carried out with lactone **31** (19 mg, 0.06 mmol) to afford 15.7 mg (83%) of acid **32a** as a yellow oil [IR (CCl_4) 1725, 1705 cm^{-1}]. Esterification with CH_2N_2 (6 mL of a 0.2 M solution, 1.1 mmol) afforded crude ester **32b**. Flash chromatography (20:1 hexane/ethyl acetate) afforded 11.4 mg (69%) of ester **32b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5 H, Ar*H*), 5.44 (br s, 1 H, C=C*H*), 5.23 (br s, 3 H, ArCH_2, NC*H*CO_2), 4.15 (br s, 1 H, NC*H*), 3.68 (s, 3 H, CO_2CH_3), 2.70–0.80 (m, 10 H, CH_2); IR (CCl_4) 1745, 1705 cm^{-1}; MS (EI, 20 eV) m/z 329 (M^+, 15), 270 (14), 226 (81), 194 (83), 134 (20), 91 (100); HRMS for $C_{19}H_{23}NO_4$ calcd 329.1627, found 329.1617.

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Supplementary Material Available: Summary of NOE and decoupling data and ^1H and ^{13}C NMR spectra of new compounds (49 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Synthesis and Properties of Dihydrocyclobuta[*e*]pyrene and Tetrahydrodicyclobuta[*e*,*l*]pyrene

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Dihydrocyclobuta[*e*]pyrene and tetrahydrodicyclobuta[*e*,*l*]pyrene were prepared by the sequence of photocycloaddition of stryene derivatives, transannulation, and aromatization through lithiation. They reacted with dienophiles at 180 °C to afford Diels–Alder adducts in excellent yields.

Introduction

Since the synthesis of benzocyclobutene (1) and its Diels–Alder reaction were reported by Cava in 1956,[1a] its homologs such as **2–8** have attracted much attention.[1,2] Syntheses of related compounds having substituents and/or multiple cyclobutene rings have been investigated. Their structures were examined thoroughly by spectroscopic and X-ray crystallographic methods.[3] These com-

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