Studies toward the Synthesis of (+)-Palustrine: The First Asymmetric Synthesis of (−)-Methyl Palustramate

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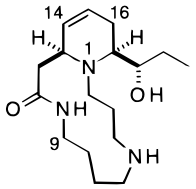
The stereoselective synthesis of (−)-methyl palustramate, a possible intermediate for the synthesis of (+)-palustrine, is described. The key step of the synthesis is a conformationally restricted Claisen rearrangement to afford the highly functionalized 1-benzylpipecolic ester **10**. In addition, a new procedure for debenzylation of 1-benzylpiperidines (Li, $(NH_2CH_2)_2$, Et_3N, THF) was used to remove the benzyl protecting group where traditional methods failed.

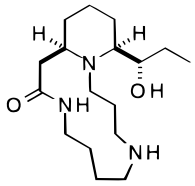
Palustrine, a piperidine alkaloid, is a toxic component of the horsetail plant *Equisetum paluster* L., found in the moist meadows of Europe.[1] If ingested, the horsetail plant has deleterious effects on grazing animals, particularly cows. The major biological effects of this alkaloid are a loss of appetite, weight loss, and decreased milk secretion.[2]

Palustrine was isolated by Eugster and co-workers in 1948.[1] The structure was tentatively assigned with the alkene at the C(15)−C(16) position, rather than at the C(14)−C(15) position, on the basis of spectroscopic data.[3] The correct position of the alkene became apparent when Natsume[4] and Wasserman[5] independently reported the racemic synthesis of the ΔC(15)−C(16) alkene isomer, which was not identical with the natural product. Hydrogenation of natural palustrine and the synthetic ΔC(15)−C(16) alkene isomer afforded the structurally identical product dihydropalustrine, indicative of the isomeric nature of the alkene in the two compounds.[4,5] Natsume and Ogawa then confirmed the structure with the synthesis of (±)-palustrine.[6]

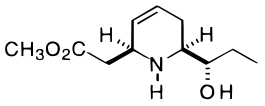
To date there has been a single synthesis of (−)-methyl dihydropalustramate (**4**),[7] a degradation product of palustrine.[3c] Compound **4** has been reported to be a possible intermediate for the synthesis of dihydropalustrine.[8] We viewed the previously unknown (−)-methyl palustramate (**3**) as a possible intermediate for the synthesis of palustrine and as a compound that might be easily prepared via our conformationally restricted Claisen rearrangement methodology.[8,9]



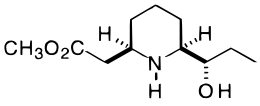
(+)-Palustrine, **1**



(+)-Dihydropalustrine, **2**



(-)-Methyl Palustramate, **3**



(-)-Methyl Dihydro-Palustramate, **4**

A key part of our analysis relied on the ready availability of the known L-homoserine lactone **5** (Scheme 1). We hoped the lactone would be compatible with the DIBAl-H−Grignard addition to esters of α-amino acids that had proven successful in our previous work.[9] In addition, the lactone would, in effect, be a protecting group for the latent primary alcohol.

Lactone **5**,[10] prepared from L-methionine, was treated sequentially[9] with DIBAl-H and freshly prepared vinylmagnesium chloride[11] to afford the amino alcohol **6** as an 11:1 mixture of diastereomers (^{1}H NMR) in 71% yield (Scheme 1).[12] Reduction of the benzamide with lithium aluminum hydride afforded benzylamine **7** in 89% yield. This material was then recrystallized to afford **7** as a 32:1 mixture of diastereomers in 76% yield from **6**. Alkylation of the amine with phenyl α-bromoacetate,[13] followed by stirring at room temperature for 66 h, led to selective lactonization onto the secondary alcohol, affording the six-membered-ring lactone **8** in 71% yield. Treatment of

(1) For the isolation see: Karrer, Von P.; Eugster, C. *Helv. Chim. Acta* **1948**, *31*, 1062−1066.
(2) Eugster, C. H. *Heterocycles* **1976**, *4*, 51−105.
(3) (a) Eugster, C. H.; Walchli, P. C. *Helv. Chim. Acta* **1978**, *61*, 885−898. (b) Eugster, C. H.; Ruedi, P. *Helv. Chim. Acta* **1978**, *61*, 899−904. (c) Eugster, C. H.; Walchli, P. C.; Trueb, W.; Green, C. L.; Mayer, C. *Helv. Chim. Acta* **1978**, *61*, 905−920. (d) Eugster, C. H.; Walchli, P. C.; Muller, G. M. *Helv. Chim. Acta* **1978**, *61*, 921−927. (e) Eugster, C. H.; Schaer-Walchli, M. *Helv. Chim. Acta* **1978**, *61*, 928−935.
(4) (a) Natsume, M.; Ogawa, M.; Yoda, I.; Shiro, M. *Chem. Pharm. Bull.* **1984**, *32*, 812−814.
(5) Wasserman, H. H.; Leadbetter, M. R.; Kopka, I. E. *Tetrahedron Lett.* **1984**, *25*, 2391−2394.
(6) Natsume, M.; Ogawa, M. *Chem. Pharm. Bull.* **1984**, *32*, 3789−3791.
(7) Muraoka, O.; Zheng, B.-Z.; Okumura, K.; Tanabe, G.; Momose, T.; Eugster, C. H. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1567−1576.
(8) For leading references to synthesis approaches to palustrine and palustramic acid see: (a) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776−777. (b) Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573−7580.
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(10) (a) Natelson, S.; Natelson, E. A. *Microchem. J.* **1989**, *40*, 226−232. (b) Seela, F., Cramer, F.; *Chem. Ber.* **1976**, *109*, 82−89.
(11) Commercial vinylmagnesium chloride was inferior to freshly prepared reagent: Ramsden, H. E.; Leebrick, J. R.; Sanders, D.; Rosenberg, S. D.; Miller, E. H.; Walburn, J. J.; Balint, A. E.; Cserr, R. *J. Org. Chem.* **1957**, *22*, 1602−1607.
(12) Ratios of diastereomers were determined by integration of ^{1}H NMR spectra; see the Supporting Information for details.
(13) Dellaria, J. F., Jr.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916−3926.

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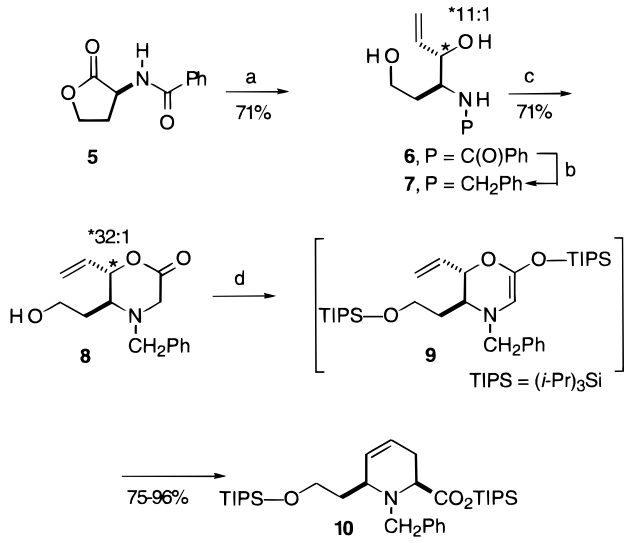
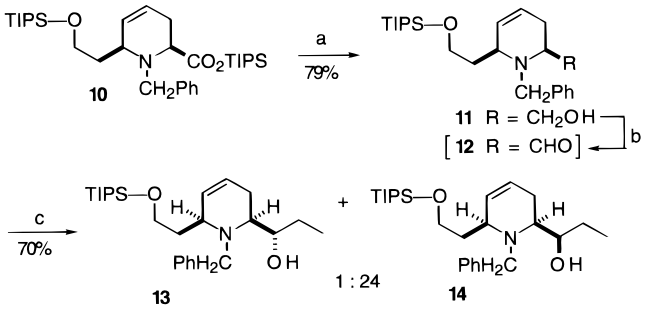
Scheme 1[a]



[a] Legend: (a) DIBAL-H; $H_2O{=}CHMgCl$, 71%; (b) $LiAlH_4$, 89%; (c) $BrCH_2CO_2Ph$, $EtN(i\text{-}Pr)_2$, 71%; (d) $(i\text{-}Pr)_3SiOTf$, Et_3N, 96%.

Scheme 2[a]

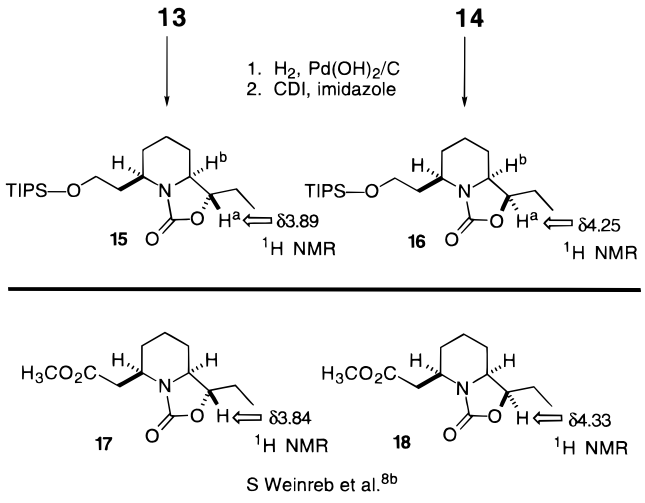


[a] Legend: (a) DIBAL-H 79%; (b) Swern oxidation; (c) EtMgBr, 70% from **11**.

lactone **8** with 2.1 equiv of TIPS-OTf effected formation of the silyl ketene acetal as well as protection of the primary alcohol to afford **9** (^{1}H NMR analysis). The silyl ketene acetal **9** was not isolated; simply stirring the above reaction mixture at room temperature afforded pipecolic ester **10** in 96% yield. This material was used without purification in subsequent reactions but could be purified by flash chromatography to afford analytically pure silyl ester **10** in 75−96% yield.

We next addressed homologation about the silyl ester and introduction of the secondary alcohol in the correct relative orientation to the existing stereocenters. Relying on the easy access to the corresponding aldehyde,[9a] we reduced **10** with DIBAl-H to afford the corresponding primary alcohol **11** in 79% yield (Scheme 2). Swern oxidation[14] afforded aldehyde **12**, which was immediately treated with excess ethylmagnesium bromide to afford alcohols **13** and **14** in an unoptimized yield of 70% and a 1:24 ratio (**13**:**14**, based on isolated yields).[15] As we had predicted on the basis of Felkin−Ahn addition to the aldehyde, the major diastereomer turned out to be **14**,

Scheme 3



the undesired diastereomer.[16] While this route afforded primarily the incorrect diastereomer **14**, it did serve the desired purpose of providing samples of both diastereomers to allow their stereochemical assignment.[16]

The stereochemistry of **13** and **14** was assigned by conversion to cyclic carbamates that were similar to compounds of known relative stereochemistry. Hydrogenation/hydrogenolysis of **13** and **14** followed by treatment with carbonyldiimidazole afforded cyclic carbamates **15** and **16**. The $H^a{-}H^b$ coupling constants for the two diastereomers (see Scheme 3 for a/b labels) were extremely close and not diagnostic. However, the chemical shift of hydrogens H^a differed by over 0.35 ppm for the two diastereomers. Comparison of the chemical shifts of these hydrogens with those for similar compounds of known relative stereochemistry, **17** and **18**, showed a strong correlation and allowed the assignment of the relative stereochemistry in **13** and **14**.[8b]

We hoped to exploit the high preference for addition to the aldehyde carbonyl by reversing the order of the reduction and ethyl addition steps. This strategy required conversion of silyl ester **10** to an ethyl ketone followed by reduction. Direct conversion of the TIPS ester to the ketone failed; ester **10** was inert to excess ethyl Grignard and alkyllithium reagents. Thus, the hindered TIPS ester was converted to a Weinreb amide,[17] as outlined below (Scheme 4). Hydrolysis of silyl ester **10** with potassium carbonate in ethanol/THF/water (3:1:1) afforded the carboxylic acid, which was treated with carbonyldiimidazole to give the acyl imidazole. This activated ester was then treated with additional imidazole (3 equiv) and methoxymethylamine hydrochloride (4 equiv, room temperature, 12 h) to afford Weinreb amide **19** in 76% overall yield from lactone **8**. Treatment of **19** with excess ethylmagnesium bromide gave ketone **20**, which was immediately reduced with lithium borohydride[16] in CH_3OH to afford alcohols **13** and **14** in 81% yield and a 32:1 ratio, respectively.

The completion of the synthesis of (−)-methyl palustramate was accomplished via the route shown in Scheme 5. Protection of the secondary alcohol **13** as the MOM ether followed by treatment of the resulting ether **21**,

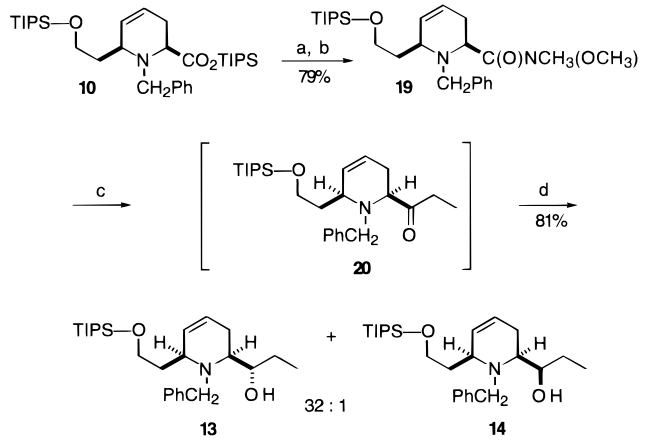
(14) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.

(15) The stereochemistry of **13** and **14** was tentatively assigned by correlation with similar compounds reported in the literature, as shown in the text. The ultimate proof of the assignment was provided by correlation of the spectral data for **4** with those in the literature; see the Supporting Information for details.

(16) Natsume, M.; Ogawa, M. *Chem. Pharm. Bull.* **1982**, *30*, 3442−3445.

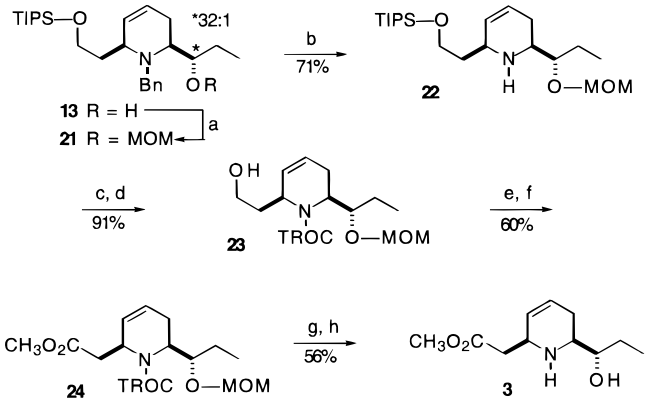
(17) Weinreb, S. M.; Lipton, M. F.; Basha, A. *Org. Synth.* **1980**, *59*, 49−53.

Scheme 4[a]



[a] Legend: (a) K_2CO_3, EtOH/THF/H_2O 3:1:1; (b) CDI, H_2NCH_3-$(OCH_3)Cl$, 79%; (c) EtMgBr, THF; (d) $LiBH_4$, 81% from **15**.

Scheme 5[a]



[a] Legend: (a) CH_3OCH_2Br, Et_3N, 83%; (b) Li, $(NH_2CH_2)_2$, Et_3N, THF, 71%; (c) $Cl_3CH_2COC(O)Cl$, pyridine, 93%; (d) HF−pyridine, 98%; (e) PDC, DMF, 85%; (f) CDI; CH3OH, 70%; (g) Zn, 74%; (h) BuSH, $MgBr_2$, 76%.

under standard dissolving-metal conditions with sodium[18] or lithium[19] in ammonia, resulted in poor yields of secondary amine **22** (Scheme 5). Using 2−20 equiv of sodium or lithium afforded mainly starting material, and employing a large excess of metal (100−2000 equiv) resulted in poor mass recovery (<50%) and the products isolated were apparently derived from Birch reduction (^{1}H NMR analysis), with negligible cleavage of the benzyl group. A survey of classic conditions[18−20] to effect this transformation failed to afford **22** in acceptable yield. Hydrogenolysis conditions were not acceptable due to the presence of the alkene in the piperidine ring, and chloroformate dealkylation reactions failed to afford any of the desired products. Benkeser and co-workers investigated dissolving-metal reductions and found that the reducing ability of the system was attenuated by addition of ethylenediamine.[21] After some experimentation, we found that treatment of **21** with lithium (50 equiv) using a solvent mixture of ethylenediamine, triethylamine, and THF (1:10:5) afforded **22** in 71% yield. This reaction was carried out at room temperature (2.3 h) and completely avoided the use of liquid ammonia. If the percentage of ethylenediamine was increased, reduction of the alkene was competitive with debenzylation. This dissolving-metal reduction, which appears to be quite general for 2,6-disubstituted-1-benzylpiperidines, offers an attractive alternative to traditional procedures which involve liquid ammonia as the solvent. A similar procedure for the debenzylation of amides was recently reported by Garst and co-workers.[22]

Attempts to oxidize silyl ether **22** or the corresponding alcohol with Jones reagent to the carboxylic acid afforded products in poor yield and low purity. Even when the amine was pretreated with sulfuric acid, many of the problems appeared to result from the presence of this functionality. Accordingly, amine **22** was protected as the TROC carbamate[23] and the TIPS ether was removed by treatment with HF−pyridine to afford alcohol **23** in 91% overall yield (Scheme 5). Oxidation of primary alcohol **23** with PDC in DMF[24] afforded the acid, which was esterified by sequential treatment with carbonyldiimidazole and methanol to afford **24** in 55% yield from primary amine **22**. Completion of the synthesis required only removal of the protecting groups. Reductive cleavage of the TROC carbamate[23] with zinc afforded the secondary amine. Removal of the MOM ether using Kim's transketylization conditions[25] with butanethiol and magnesium bromide afforded (−)-methyl palustramate (**3**) in 56% yield from **24**. The structure of **3** was proven by hydrogenation to (−)-methyl dihydropalustramate (**4**) and comparison of the spectral data and optical rotation of **4** with those reported in the literature.[3,7,12]

The first asymmetric synthesis of (−)-methyl palustramate has been achieved using a conformationally restricted Claisen rearrangement and a novel debenzylation reaction as the key steps. The application of the methodology to the synthesis of (+)-palustrine is currently under investigation.

Experimental Section

α-L-Benzamido-γ-butyrolactone (5).[26] L-Methionine (30.0 g, 0.201 mol) was added to a solution of H_2O (120 mL), 2-propanol (120 mL), and glacial acetic acid (48 mL). The solution was stirred until homogeneous; then bromoacetic acid (28.0 g, 0.202 mol; *caution*! this compound is highly toxic and a severe irritant) was added and the reaction mixture refluxed for 2 h. The reaction mixture was then cooled to room temperature and concentrated to a viscous orange oil. A solution of 2-propanol and toluene (1:1, v/v, 100 mL) was added, and the reaction mixture was stirred until homoge-

(18) Vigneaud, V. D.; Behrens, K. O. *J. Biol. Chem*. **1937**, *117*, 27−36.

(19) Smith, H. *Organic Reactions in Liquid Ammonia*; Interscience Publishers: New York, 1963; Vol. 2, Part 2.

(20) (a) Calcium metal in reductions: Benkeser, R. A.; Belmonte, F. G.; Kang, J. *J. Org. Chem*. **1983**, *48*, 2796−2802. (b) Pandey, G.; Rani, K. S. *Tetrahedron Lett*. **1984**, *29*, 4157−4158. (c) Kaiser, E. M. *Synthesis* **1972**, 391−415.

(21) (a) Benkeser, R. A.; Robinson, R. E.; Landesman, H. *J. Am. Chem. Soc*. **1952**, *74*, 5699−5701. (b) Benkeser, R. A.; Robinson, R. E.; Sauve, D. M.; Thomas, O. W. *J. Am. Chem. Soc*. **1955**, *77*, 3230−3233.

(22) Garst, M. E.; Dolby, L. J.; Esfandiari, S.; Chamberlain, N. C.; Fedoruk, N. *Abstracts of Papers*, 213th National Meeting of the American Chemical Society, San Francisco, CA, April 13−17 1997, American Chemical Society: Washington, DC, 1997; ORG-290.

(23) (a) Carson, J. F. *Synthesis* **1981**, 268−270. (b) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett*. **1967**, 2555−2557.

(24) Corey, E. J.; Schmidt, G. *Tetrahedron Lett*. **1979**, *5*, 399−402.

(25) Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *SYNLETT*, **1991**, 183−184.

(26) General information: Capillary GC was carried out using an FID detector on a 25 m HP-102 (methyl silicone) column. The following standard GC parameters were used: flow rate 60 mL/min; injector temperature 200 °C; detector temperature 280 °C; temperature program 40−280 °C at 8 °C/min; initial time 1 min.

neous. Concentration (90 °C, bath temperature) afforded an orange oil. A solution of dioxane (80 mL) and concentrated HCl (40 mL) was then added to the orange oil, and the resulting solution was heated to 50 °C for 10 min. The heating bath was then removed, the mixture was stirred for 12 h, and the reaction flask was then placed in an ice bath for 4 h without stirring to precipitate an orange solid. The orange solid was then filtered and rinsed with cold 2-propanol (50 mL, −78 °C) until the rinsings were colorless. The resulting white solid was then dried (0.5 mmHg) to afford the product, homoserine lactone hydrobromide (21 g, 57%): mp 229−231 °C (lit.[10a] mp 234−236 °C); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.79 (bs, 3H), 4.30 (m, 3H), 2.50−2.46 (m, 1H), 2.32−2.18 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.2, 66.2, 47.7, 27.0; IR (KBr) 2300−4000 (br), 1774 cm^{-1}; $[\alpha]_D^{25} = -24.4°$ (c = 0.087, H_2O), lit.[10a] $[\alpha]_D^{25} = -26.5°$ (c = 0.130, H_2O). Homoserine lactone hydrobromide (10.0 g, 54.9 mmol) was added to H_2O and CH_2Cl_2 (1:1, v/v, 120 mL), and this mixture was then cooled to 0 °C. K_2CO_3 (23.0 g, 165 mmol) was then added and the resulting mixture stirred for 5 min. Benzoyl chloride (7.0 mL, 61 mmol) was added dropwise, and the resulting mixture was warmed to room temperature and stirred for 20 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and the aqueous layer extracted with ethyl acetate (4 × 60 mL) followed by $CHCl_3$ (4 × 60 mL). The combined organic extracts were then dried (Na_2SO_4) and concentrated to afford the crude product as a yellow solid. The crude product was then rinsed with ethyl acetate (−78 °C) until the rinsings were colorless and the solid was white. The solid was then dried (0.5 mmHg) for 1 h to yield the product **5** (10.0 g, 89%): mp 145−147 °C (lit.[10b] mp 140−141 °C);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (m, 2H), 7.49 (m, 1H), 7.39 (m, 2H), 7.09 (br d, J = 5.2 Hz, 1H), 4.80 (m, 1H), 4.49 (dt, J = 10.0, 0.9 Hz, 1H), 4.32 (m, 1H), 2.87 (m, 1H), 2.29 (dq, J = 20.4, 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 167.7, 132.9, 132.0, 128.6, 127.1, 66.2, 49.6, 30.3; IR (CCl_4) 1786, 1677 cm^{-1}; $[\alpha]_D^{25} = -28.6°$ (c = 0.0198, EtOH abs) lit.[10b] $[\alpha]_D^{20} = -29.6°$ (c = 1.2, ethanol).

(3*S*,4*S*)-3-[(Phenylcarbonyl)amino]-5-hexene-1,4-diol (6). A solution of DIBAl-H (1.8 mL, 9.9 mmol) in hexanes (0.4 mL) was added dropwise over 10 min to a mechanically stirred solution of lactone **5** (1.01 g, 4.93 mmol) in CH_2Cl_2 (45 mL) at −78 °C. The rate of addition was adjusted as needed to maintain a temperature of <−75 °C. The resulting solution was stirred for 20 min. Vinylmagnesium chloride (9.5 mL of a 1.55 M solution in THF, 14.8 mmol) was then added slowly, again continuously adjusting the rate of addition to maintain a temperature of <−75 °C. Immediately after the addition was complete, the reaction flask was placed in a 0 °C ice bath, slowly warmed to room temperature, and stirred for 13 h. The mixture was then slowly poured into stirred 1 N HCl (50 mL) at 0 °C and stirred for 10 min. The aqueous layer was then extracted with ether (2 × 50 mL) and $CHCl_3$ (5 × 40 mL), and the combined organic extracts were dried (K_2CO_3) and concentrated to afford 1.33 g of crude product as a yellow oil. Flash chromatography (silica gel, 5.5:3.5:1 ethyl acetate/hexanes/2-propanol) afforded diol **6** (0.824 g, 71%; 11:1 mixture of diastereomers, determined by ^{1}H NMR integration of NH's at δ 6.76 major (3*S*,4*S*) and δ 6.91 minor (3*S*,4*R*)) as a white solid: mp 68−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 7.77 (d, J = 7.8 Hz, 2H), 7.47 (m, 3H), 6.76 (br d, J = 7.6 Hz, 1H), 5.94 (ddd, J = 16.1, 10.0, 4.2 Hz, 1H), 5.37 (d, J = 16.2 Hz, 1H), 5.21 (d, J = 10.4 Hz, 1H), 4.43 (m, 2H), 3.84 (bs, 1H), 3.80−3.60 (m, 2H), 3.11 (bs, 1H), 2.04−1.95 (m, 1H), 1.87−1.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 138.1, 133.8, 131.8, 128.6, 127.0, 116.3, 74.1, 58.6, 50.8, 35.5; IR (neat) 3421−3284 (br), 2955, 2882, 1637, 1537 cm^{-1}; MS (CI, NH_3) m/z 236 (MH^+, 100), 218 (4), 178 (9), 122 (13), 105 (26), 74 (11); HRMS calcd for $C_{13}H_{18}NO_3$ (MH^+) 236.1287, found 236.1283; $[\alpha]_D^{25} = -38.6°$ (c = 0.0825, $CHCl_3$); GC major t_R = 41.16 min, minor t_R = 41.47 min.

(3*S*,4*S*)-3-(Benzylamino)-5-hexene-1,4-diol (7). A solution of benzamide **6** (7.44 g, 31.7 mmol) in THF (75 mL) was added dropwise to a suspension of lithium aluminum hydride (5.0 g, 0.13 mol) in THF (225 mL) at 0 °C. The resulting suspension was warmed to room temperature, heated to reflux for 4 h, and then cooled to 0 °C. H_2O (5 mL), 15% NaOH (5 mL), and H_2O (15 mL) were sequentially added, and the resulting suspension was warmed to room temperature and stirred overnight. Filtration through Celite, followed by concentration, afforded the crude product (6.5 g) as a yellow oil. Flash chromatography (silica gel, 4.5:3.0:2.5:0.4 ethyl acetate/hexanes/2-propanol/triethylamine) afforded **7** (∼11:1 ratio of diastereomers, ^{1}H NMR) (6.20 g, 89%) as a clear oil. This oil was then crystallized by the addition of ether (20 mL, −50 °C, 1 week). Filtration afforded the diastereomerically enriched **7** as colorless crystals (5.3 g, 76%; ∼30:1; 3*S*,4*S* and 3*S*,4*R*) as determined by ^{1}H NMR integration of C*H*OH signals at δ 4.18 (major, 3*R*,4*S*) and 4.41 (minor, 3*R*,4*R*): mp 56−57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 5H), 5.84 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.31 (d, J = 17.1 Hz, 1H), 5.20 (d, J = 10.3 Hz, 1H), 4.14 (t, J = 6.4 Hz, 1H), 3.89−3.74 (m, 4H), 3.53 (bs, 3H), 2.83 (dt, J = 6.5, 4.1 Hz, 1H), 1.91−1.83 (m, 1H), 1.63−1.55 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.6, 138.4, 128.5, 128.2, 127.2, 117.2, 73.7, 61.3, 61.1, 51.4, 31.0; IR (neat) 3353−3303 (br), 2928, 2865, 1455 cm^{-1}; MS (CI, NH_3) m/z 222 (MH^+, 100), 164 (42), 106 (11), 91 (39); HRMS calcd for $C_{13}H_{20}NO_2$ (MH^+) 222.1494, found 222.1492; $[\alpha]_D^{25} = -20.8°$ (c = 0.048, $CHCl_3$); GC major t_R = 28.33.

(5*S*,6*S*)-6-Ethenyl-5-(hydroxyethyl)-4-(phenylmethyl)-3,4,5,6-tetrahydro-2*H*-1,4-oxazin-2-one (8). Solid phenyl α-bromoacetate (892 mg, 4.14 mmol) was dissolved in CH_3CN (13 mL) and this solution then added via cannula over 30 min to a stirred solution of benzylamine **7** (865 mg, 3.92 mmol) and diisopropylethylamine (3.5 mL, 20 mmol) in CH_3CN (13 mL) at 0 °C. The resulting solution was slowly warmed to room temperature and stirred for 66 h. The solution was then concentrated using a rotary evaporator, followed by high vacuum (0.3 mmHg) for 30 min. Addition of ethyl acetate (30 mL) with continuous stirring resulted in the precipitation of amine salts. Washing of the precipitate with ethyl acetate (5 × 30 mL), followed by concentration of the ethyl acetate washings, afforded the crude product as a gold oil. Flash chromatography (silica gel, 25:75 hexanes/ethyl acetate) afforded lactone **8** (0.731 g, 71%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5H), 5.92 (ddd, J = 17.1, 10.3, 6.8 Hz, 1H), 5.40 (d, J = 17.1 Hz, 1H), 5.35 (d, J = 10.7 Hz, 1H), 4.70 (t, J = 7.2 Hz, 1H), 3.77 (m, 2H), 3.73 (s, 2H), 3.38 (AB q, J = 17.4 Hz, $\Delta\nu$ = 30.6 Hz, 2H), 2.99 (m, 2H), 1.85−1.67 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 136.5, 134.0, 129.1, 128.6, 127.8, 119.7, 81.5, 60.2, 59.1, 58.4, 49.8, 29.5; IR (neat) 3487−3387 (br), 2937, 1736 cm^{-1}; MS (CI, NH_3) m/z 262 (MH^+, 100), 172 (11), 120 (7), 106 (9), 91 (21); HRMS calcd for $C_{15}H_{20}NO_3$ (MH^+) 262.1443, found 262.1440; $[\alpha]_D^{25} = -85.0°$ (c = 0.0456, $CHCl_3$); GC major t_R = 74.12 min.

(2*S*,6*S*)-1-(Phenylmethyl)-6-[[(triisopropylsilyl)oxy]carbonyl]-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (10). Triisopropylsilyl triflate (2.2 mL, 8.3 mmol) was added to a stirred solution of lactone **8** (1.03 g, 3.93 mmol) and triethylamine (2.7 mL, 20 mmol) in benzene (35 mL) at 5 °C. The resulting suspension was stirred for 4 h at room temperature and then concentrated to 3 mL. Immediately following partial concentration, filtration (silica gel, 95:5:0.5 hexanes/ethyl acetate/triethylamine) afforded the crude pipecolic ester **10** (2.17 g, 96%) as a light yellow oil that was used without further purification. Flash chromatography of a similar sample afforded an analytical sample as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, J = 7.0 Hz, 2H), 7.26 (m, 3H), 5.81−5.73 (m, 2H), 4.00 (m, 2H), 3.87−3.80 (m, 1H), 3.74−3.65 (m, 1H), 3.49 (m, 2H), 2.46−2.35 (dm, J = 16.4 Hz, 1H), 2.33−2.25 (dm, J = 16.0 Hz, 1H), 2.00−1.90 (m, 1H), 1.74−1.62 (m, 1H), 1.28 (m, 3H), 1.08−1.02 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 139.1, 129.9, 128.8, 128.1, 126.8, 122.6, 60.7, 58.2, 57.5, 55.0, 36.7, 25.9, 18.1, 17.9, 12.0, 12.0; IR (neat) 2944, 2867, 1718 cm^{-1}; MS (FAB$^+$, ether, NBA/PEG) m/z 574 (MH^+, 21), 530 (9), 372 (100), 370 (21), 328 (15), 172 (31), 170 (55); HRMS calcd for $C_{33}H_{60}NO_3Si_2$ (MH^+) 574.4112, found 574.4134; $[\alpha]_D^{25} = -8.27°$ (c = 0.114, $CHCl_3$).

(2*S*,6*S*)-6-(Hydroxymethyl)-1-(phenylmethyl)-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (11). TIPS ester **10** (244 mg, 0.449 mmol) was dissolved in CH_2Cl_2 (20 mL), and the solution was then cooled to 0 °C. DIBAl-H (0.179 mL, 0.915 mmol) was slowly added to the reaction mixture. After the addition was complete, the cooling bath was removed and the reaction mixture was warmed to room temperature and stirred for 20 min. The reaction mixture was then recooled to 0 °C and poured into a stirred 0 °C solution of pH 7.5 phosphate buffer (25 mL). The resulting solution was stirred for 10 min at room temperature; then the aqueous layer was extracted with ether (4 × 25 mL). The combined organic extracts were washed with H_2O (25 mL) and brine (25 mL) and dried (K_2CO_3) to afford the crude material (244 mg) as a yellow oil. Flash chromatography (silica gel, 80:20 hexanes/ethyl acetate) afforded alcohol **11** (135 mg, 79%) as a light yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 3H), 7.24 (m, 2H), 5.77 (m, 1H), 5.71 (dm, J = 11.0 Hz, 1H), 3.84 (AB q, J = 13.6 Hz, $\Delta\nu$ = 10.0 Hz, 2H), 3.72 (m, 2H), 3.44 (t, J = 10.3 Hz, 1H), 3.34 (m, 2H), 3.04 (ddd, J = 12.2, 8.1, 2.2 Hz, 1H), 2.95−2.75 (vbr s, 1H), 2.33 (d sextet, J = 17.9, 2.4 Hz, 1H), 1.77−1.62 (m, 3H), 1.02 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 128.8, 128.4, 127.2, 122.6, 62.8, 60.8, 60.4, 55.6, 54.1, 39.8, 21.7, 18.1, 12.0; IR (neat) 3600−3200, 2942, 2891, 1463 cm^{-1}; $[\alpha]_D^{25}$ = +41.1° (c = 0.0233, CH_2Cl_2).

(1′*S*,2*S*,6*S*)-6-(1′-Hydroxypropyl)-1-(phenylmethyl)-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (13). Reduction of Ketone 20 with $LiBH_4$. Crude ketone **20** (from 0.779 g, 1.69 mmol of amide **19**) was immediately dissolved in methanol (12.5 mL) and the solution cooled to 0 °C. $LiBH_4$ (1.8 mL of a 2.0 M solution in THF, 3.6 mmol) was then added, the cooling bath was removed, and the mixture was stirred at room temperature for 12 h. The reaction mixture was then concentrated, diluted with CH_2Cl_2 (30 mL), and poured into saturated aqueous $NaHCO_3$ (30 mL). The resulting mixture was stirred for 15 min. Extraction of the aqueous layer with CH_2Cl_2 (3 × 30 mL), followed by washing of the combined organic extracts with H_2O (75 mL) and drying (K_2CO_3), afforded the crude material (597 mg) as a yellow oil. Flash chromatography (silica gel, 90:10 hexanes/ethyl acetate) afforded **13** (567 mg, R_f 0.42, clear oil) and **14** (17.6 mg, R_f 0.24, clear oil) in a 32:1 ratio and an 81% combined yield: ^{1}H NMR (**13** major diastereomer, 300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 5.75 (s, 2H), 4.21 (s, 1H), 3.87−3.77 (AB q, J = 13.4 Hz, $\Delta\nu$ = 10.3 Hz, 2H), 3.70 (t, J = 5.8 Hz, 2H), 3.42 (m, 1H), 3.35 (m, 1H), 2.64 (dt, J = 7.8, 1.4 Hz, 1H), 2.33−2.24 (m, 1H), 1.90−1.72 (m, 2H), 1.69−1.49 (m, 2H), 1.16 (m, 1H), 1.00 (s, 21H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (**13** major diastereomer, 75 MHz, $CDCl_3$) δ 139.7, 129.2, 128.9, 128.4, 127.2, 122.5, 70.4, 60.6, 60.0, 54.0, 39.6, 27.2, 19.9, 18.0, 11.9, 10.0; IR (neat) 3380, 2942, 2924, 1463 cm^{-1}; MS (CI, NH_3) m/z 432 (MH^+, 46), 372 (38), 247 (76), 148 (20), 91 (100); HRMS calcd for $C_{26}H_{46}NO_2Si$ (MH^+) 432.3298, found 432.3289: $[\alpha]_D^{25}$ = +36.4° (c = 0.0213, $CHCl_3$); GC t_R = 44.57 min.

(1′*R*,2*S*,6*S*)-6-(1′-Hydroxypropyl)-1-(phenylmethyl)-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (14). Reaction of Aldehyde 11 with Ethyl Grignard. A solution of dimethyl sulfoxide (1.22 mL, 15.1 mmol) in CH_2Cl_2 (5 mL) was slowly added to a stirred solution of oxalyl chloride (0.75 mL, 8.6 mmol) in CH_2Cl_2 (5 mL) at −62 °C ($CHCl_3/CO_2$) over 5 min. A solution of **11** (692 mg, 1.72 mmol) in CH_2Cl_2 (25 mL) was added to the reaction mixture, and the resulting solution was stirred for 20 min at −62 °C. Triethylamine (3.2 mL, 22.6 mmol) in CH_2Cl_2 (10 mL) was then added, and the reaction mixture was stirred for 15 min at −62 °C and then slowly warmed to room temperature over 75 min. The reaction mixture was then poured into stirred pH 7 phosphate buffer (50 mL). The aqueous layer was extracted with ether (4 × 40 mL), and the combined organic extracts were washed with H_2O (40 mL) and brine (40 mL) and dried (K_2CO_3), and concentrated. The resulting aldehyde **12** (dark yellow oil) was then immediately diluted with dry ether (10 mL) and added dropwise to a stirred −78 °C solution of ethylmagnesium bromide (13.1 mL of a 2.3 M solution in THF, 30.2 mmol) in ether (100 mL). The reaction mixture was kept in the cooling bath and slowly warmed to room temperature over 16 h. The reaction mixture was then poured into 1 N HCl (50 mL) at 0 °C, the cooling bath was removed, and the resulting mixture was stirred at room temperature for 15 min. The pH of the resulting solution was then adjusted to 10 (pH paper) with solid Na_2CO_3 (60 g). The aqueous layer was extracted with ether (3 × 50 mL) and $CHCl_3$ (3 × 50 mL). The combined organic extracts were then washed with H_2O (200 mL) and brine (200 mL), dried (K_2CO_3), and concentrated to afford the crude material (790 mg) as a yellow oil. Flash chromatography (silica gel, 90:10 hexanes/ethyl acetate) afforded **14** (undesired diastereomer, 497 mg, 67%; a single diastereomer by ^{1}H and ^{13}C NMR, GC t_R = 45.23 min; R_f 0.24; 90:10 hexanes/ethyl acetate) as a colorless oil. A second column (silica gel, 95:5 hexanes/ethyl acetate) of the less polar material from above afforded **13** (desired diastereomer, 21 mg, 2.8%; a single diastereomer by ^{1}H and ^{13}C NMR, GC, t_R = 44.57 min; R_f 0.31; 95:5 hexanes/ethyl acetate) as a colorless oil. Major diastereomer **14:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 3H) 7.23 (m, 2H), 5.85 (m, 1H), 5.78 (dm, J = 5.8 Hz, 1H), 3.82 (m, 2H), 3.68 (m, 3H), 3.40 (m, 1H), 2.64 (dt, J = 7.6, 5.0 Hz, 1H), 2.18 (dm, J = 14.8 Hz, 1H), 2.04 (dm, J = 17.0 Hz, 1H), 1.74 (m, 1H) 1.59 (m, 2H), 1.38 (m, 1H), 1.02 (m, 21H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.2, 129.5, 128.6, 128.3, 126.9, 124.3, 71.7, 60.6, 60.4, 58.7, 55.9, 39.9, 26.0, 21.1, 18.0, 12.0, 10.5; IR (neat) 3600−3200 (br), 2943, 2865, 1463 cm^{-1}; $[\alpha]_D^{25}$ = +26.5° (c = 0.0099, $CHCl_3$); MS (CI, NH_3) m/z 432 (MH^+, 100), 372 (47), 172 (10), 91 (2); HRMS calcd for $C_{26}H_{46}NO_2Si$ (MH^+) 432.3298, found 432.3305.

(1*S*,5*R*,9*S*)-1-Ethyl-4,5,6,7,8,9-hexahydro-3-oxo-5-[2-[(triisopropylsilyl)oxy]ethyl]-3*H*-oxazolo[3,4-a]pyridine (15). The benzyl-protected amine **13** (56.6 mg, 0.131 mmol) was dissolved in absolute ethanol (1 mL) and hydrogenated using a Parr hydrogenator (35 psi of H_2, 30 mg of $Pd(OH)_2$) for 90 min at 50 °C. The reaction mixture was then cooled to room temperature and diluted with $CHCl_3$ (5 mL). The $Pd(OH)_2$ was then filtered from the reaction mixture and rinsed with $CHCl_3$ (4 × 10 mL). The combined organic rinsings were dried (K_2CO_3) and then concentrated to afford (1′*S*,2*S*,6*R*)-2-(1-hydroxypropyl)-6-[2-[(triisopropylsilyl)oxy]ethyl]piperidine (42.8 mg, 96%) as a light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (m, 2H), 3.19 (dt, J = 3.4, 7.7 Hz, 1H), 2.67 (m, 1H), 2.40 (tm, J = 9.0 Hz, 1H), 1.82 (dm, J = 13.1 Hz, 1H), 1.70−1.50 (m, 5H), 1.43−1.21 (m, 3H), 1.05 (m, 24 H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.8, 60.9, 60.8, 54.1, 40.2, 32.8, 29.0, 26.6, 24.6, 18.0, 12.0, 10.0; IR (neat) 3500−3000 (br), 2940, 2866, 1463 cm^{-1}; MS (CI, NH_3) m/z 344 (MH^+, 100), 284 (23), 58 (23); HRMS calcd for $C_{19}H_{42}NO_2Si$ (MH^+) 344.2985, found 344.2984; $[\alpha]_D^{25}$ = −8.5° (c = 0.0192, CH_2Cl_2). Carbonyldiimidazole (12 mg, 0.07 mmol) was carefully added to a solution of the above amino alcohol (15.4 mg, 0.045 mmol) in CH_3CN (0.15 mL) at 0 °C. The resulting solution was stirred and gradually warmed (while in cooling bath) to room temperature over 10 h. The reaction mixture was then concentrated to afford 21.4 mg of crude product. Flash chromatography (silica gel, 85:15 ethyl acetate/hexanes) afforded cyclic carbamate **15** (6.8 mg, 40%, unoptimized) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (m, 3H), 3.35 (m, 1H), 3.18 (apparent dt, J = 11.6, 4.2 Hz, 1H), 2.77 (dm, J = 5.0 Hz, 1H), 1.98−1.78 (m, 2H), 1.78−1.56 (m, 4H), 1.54−1.30 (m, 3H), 1.04 (bs, 21H), 0.99 (t, J = 7.4 Hz, 3H); ^{1}H NMR (300 MHz, C_6D_6) δ 3.94 (m, 1H), 3.82 (m, 1H), 3.32 (dt, J = 7.3, 5.1 Hz, 1H), 3.15 (m, 1H), 3.03 (m, 1H), 2.54 (dt, J = 11.0, 4.4 Hz, 1H), 1.87 (m, 1H), 1.31 (m, 3H), 1.78−0.78 (m, 26 H), 0.67 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 80.3, 62.2, 60.4, 54.0, 34.7, 31.4, 30.6, 26.8, 23.8, 18.1, 12.0, 9.2; IR (neat) 2941, 2866, 1750, 1458 cm^{-1}; MS (CI, NH_3) m/z 370 (MH^+, 100), 326 (36); HRMS calcd for $C_{20}H_{40}NO_3Si$ (MH^+) 370.2778, found 370.2778; $[\alpha]_D^{25}$ = −32.0° (c = 0.0083, CH_2Cl_2).

(1*R*,5*R*,9*S*)-1-Ethyl-4,5,6,7,8,9-hexahydro-3-oxo-5-[2-[(triisopropylsilyl)oxy]ethyl]-3*H*-oxazolo[3,4-a]pyridine (16). A suspension of benzyl-protected amine **14** (68.4 mg, 0.158

mmol), Pd/C (60 mg), and anhydrous K_2CO_3 (41 mg) in ether was stirred for 2 h. The solids were removed by filtration and rinsed with $CHCl_3$ (5 × 5 mL), and the combined rinsings were concentrated. The above process was repeated one additional time. The benzyl-protected amine was then diluted with absolute ethanol (1.2 mL) and hydrogenated using a Parr hydrogenator (35 psi of H_2, 34 mg of $Pd(OH)_2$) for 90 min at 50 °C. The reaction mixture was then cooled, anhydrous K_2CO_3 (20 mg) was added, followed by $CHCl_3$ (5 mL). The solids were then removed by filtration and rinsed with $CHCl_3$ (4 × 10 mL). The combined organic rinsings were dried (K_2CO_3) and concentrated to afford the crude product as a light yellow oil. Flash chromatography (silica gel, 60:40 ethyl acetate/hexanes) afforded (1′*R*,2*S*,6*R*)-2-(1′-hydroxypropyl)-6-[2-[(triisopropylsilyl)oxy]ethyl]piperidine (46.6 mg, 86%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (m, 4H), 3.58 (m, 1H), 2.90 (m, 1H), 2.72 (m, 1H), 1.86−1.17 (m, 10H), 1.05 (m, 21H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.6, 61.2, 60.6, 55.9, 38.7, 31.6, 25.6, 23.8, 23.4, 18.0, 11.9, 10.6; IR (neat) 3382−3354 (br), 2940, 1462 cm^{-1}; MS (CI, CH_4) *m*/*z* 344 (MH^+, 53), 300 (33), 284 (100); HRMS calcd for $C_{19}H_{42}NO_2Si$ (MH^+) 344.2985, found 344.2999; $[\alpha]_D^{25}$ = −8.1° (*c* = 0.036, $CHCl_3$). Carbonyldiimidazole (16 mg, 0.16 mmol) was carefully added to a solution of the above amino alcohol (35 mg, 0.10 mmol) in CH_3CN (0.2 mL) at 0 °C. The resulting solution was stirred and slowly warmed to room temperature over 10 h. The reaction mixture was then concentrated to afford crude product. Flash chromatography (silica gel, 15:85 ethyl acetate/hexanes) afforded the cyclic carbamate **16** (23 mg, 61%, unoptimized) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (dt, J = 8.7, 6.1 Hz, 1H), 3.80 (m, 2H), 3.43 (m, 2H), 2.68 (m, 1H), 1.97 (m, 1H), 1.86−1.79 (ddd, J = 8.6, 5.4, 2.6 Hz, 1H), 1.76−1.69 (m, 1H), 1.66 (dd, J = 13.4, 2.9 Hz, 1H, C*H*), 1.59−1.36 (m, 5H), 1.08−1.03 (21H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 77.9, 61.2, 60.2, 54.4, 34.9, 30.8, 24.3, 24.0, 21.7, 18.0, 12.0, 10.2; ^{1}H NMR (300 MHz, C_6D_6) δ 3.92 (m, 1H), 3.80 (m, 1H), 3.73 (partially obscured dt, J = 8.5, 6.0 Hz, 1H), 3.21 (m, 1H), 2.97 (apparent octet, J = 4.6 Hz, 1H), 2.71 (m, 1H), 1.86 (ddd, J = 8.5, 5.2, 2.1 Hz, 1H), 1.45−0.8 (m, 29 H), 0.65 (t, J = 7.4 Hz, 3H); IR (neat) 2941, 2866, 1754 cm^{-1}; MS (CI, CH_4) *m*/*z* 370 (MH^+, 14), 327 (24), 326 (100), 196 (38); HRMS calcd for $C_{20}H_{40}NO_3Si$ (MH^+) 370.2778, found 370.2793; $[\alpha]_D^{25}$ = −36.1° (*c* = 0.0160, CH_2Cl_2).

(2*S*,6*S*)-6-[[(Methoxymethyl)amino]carbonyl]-1-(phenylmethyl)-2-[2-[(2-triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (19). Crude pipecolic ester **10** from above (2.17 g, 3.79 mmol) was dissolved in absolute ethanol (15 mL), THF (5 mL), and H_2O (5 mL). Solid K_2CO_3 (10 g) was then added and the resulting suspension stirred at room temperature for 5 h. The solids were then rinsed with EtOH and the combined organic rinsings concentrated. The resulting oil was then diluted with CH_2Cl_2 (20 mL) and poured into stirred pH 7 buffer/CH_2Cl_2 (1:1, v/v, 100 mL). The aqueous layer was then extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and then concentrated to yield the crude product (2*S*,6*S*)-1-(phenylmethyl)-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine-6-carboxylic acid (2.27 g) as a yellow oil (containing silanol) that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.33 (m, 3H), 6.75−6.45 (bs, 1H), 5.94 (m, 1H), 5.76 (dm, J = 10.1 Hz, 1H), 4.18 (AB q, J = 13.5 Hz, $\Delta\nu$ = 67.6 Hz, 2H), 3.86 (m, 1H), 3.75 (m, 2H), 3.56 (t, J = 6.0 Hz, 1H), 2.68 (dm, J = 17.7 Hz, 1H), 2.42 (dm, J = 17.6 Hz, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.04 (m, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 139.2, 129.9, 128.8, 128.1, 126.8, 122.6, 60.7, 58.2, 57.6, 55.0, 36.7, 25.8, 18.0, 17.9, 12.0, 12.0; IR (neat) 3600−2400 (br), 2866, 1653 cm^{-1}; MS (DCI, NH_3) *m*/*z* 418 (MH^+, 100), 216 (50), 148 (55), 131 (18); HRMS calcd for $C_{24}H_{40}NO_3Si$ (MH^+) 418.2777, found 418.2776; $[\alpha]_D^{25}$ = +21.6° (*c* = 0.0231, CH_2Cl_2). Carbonyldiimidazole (2.64 g, 16.3 mmol) was carefully added to a stirred solution of the above crude acid (2.27 g, 5.44 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The resulting solution was stirred for 1 h at room temperature, and then imidazole (1.11 g, 16.3 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.12 g, 21.7 mmol) were added sequentially. The mixture was stirred at room temperature for 12 h and then poured into a stirred solution of ether/pH 6 buffer (1:1, v/v, 30 mL). The aqueous layer was extracted with ether (3 × 40 mL), and then the combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated to afford crude product **19** (2.82 g) as a light yellow oil. Flash chromatography (silica gel, 75:25:3 hexanes/ethyl acetate/triethylamine) afforded product **19** (1.38 g, 76% from lactone **8**) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 6.9 Hz, 2H), 7.25 (m, 3H), 5.86 (bd, J = 8.8 Hz, 1H), 5.71 (d, J = 9.8 Hz, 1H), 3.85 (bs, 3H), 3.68 (m, 2H), 3.56 (bs, 3H), 3.58−3.45 (bm, 1H), 3.13 (bs, 3H), 2.45−2.30 (bs, 1H), 2.19 (dd, J = 15.1, 2.2 Hz, 1H), 1.82 (m, 1H), 1.64 (m, 1H), 1.01 (bs, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140 (br), 129.1, 128.5, 128.0, 126.8, 123.4, 61 (br), 60.6, 57.3, 56.1, 37.4, 33 (br), 24 (br), 18.0, 17.7, 12.3, 12.0; IR (neat) 2958, 1672, 1463 cm^{-1}; $[\alpha]_D^{25}$ = +28.6° (*c* = 0.0180, CH_2Cl_2).

(2*S*,6*S*)-1-(Phenylmethyl)-6-(1-oxopropyl)-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (20). Ethylmagnesium bromide (5.6 mL of a 2.13 M solution in THF, 11.8 mmol) was slowly added to a solution of amide **19** (0.779 g, 1.69 mmol) in THF (13 mL) at 0 °C. The resulting solution was carefully maintained at 0 °C and stirred for 6 h. The reaction mixture was then poured into pH 7 buffer (20 mL) at 0 °C and the aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were then washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated to afford the unstable ketone **20** as a yellow oil, which was immediately used in the next step. An analytical sample was obtained by concentration of a similar reaction mixture to afford **20** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (m, 2H), 7.29 (m, 3H), 5.87 (dm, J = 10.3 Hz, 1H), 5.64 (dm, J = 10.3 Hz, 1H), 3.86 (s, 2H), 3.84−3.65 (m, 2H), 3.38−3.32 (m, 2H), 2.94−2.80 (dq, J = 17.6, 7.4 Hz, 1H), 2.41−2.32 (m, 1H), 2.30−2.24 (q, J = 7.3 Hz, 1H), 2.14−2.04 (dm, 1H), 1.62−1.41 (m, 2H), 1.02 (bs, 21H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 139.4, 129.1, 128.3, 127.2, 123.4, 62.6, 60.5, 55.5, 38.3, 32.1, 19.5, 18.0, 12.0, 8.0; IR (neat) 2866, 1719, 1462 cm^{-1}; $[\alpha]_D^{25}$ = +15.1° (*c* = 0.0351, CH_2Cl_2).

(1′*S*,2*S*,6*S*)-6-[1′-(Methoxymethoxy)propyl]-1-(phenylmethyl)-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (21). Bromomethyl methyl ether (0.40 mL, 4.9 mmol) was added dropwise to a 0 °C solution of the secondary alcohol **13** (1.33 g, 3.08 mmol) and *N*,*N*-diisopropylethylamine (1.2 mL, 6.6 mmol) in CH_2Cl_2 (10 mL). The mixture was then warmed to room temperature and stirred for 4 h. An additional portion of bromomethyl methyl ether (0.26 mL, 3.2 mmol) was then subsequently added and the mixture stirred for an additional 3 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and poured into a stirred solution of saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL); then the combined organic extracts were washed with H_2O (35 mL), dried (Na_2SO_4), and concentrated to afford the crude product (1.51 g) as a dark oil. Flash chromatography (silica gel, 9:1:0.2 hexanes/ethyl acetate/triethylamine) afforded the MOM ether **21** as a colorless oil (1.21 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 7.25 (m, 3H), 5.84 (m, 1H), 5.73 (dm, J = 9.9 Hz, 1H), 4.57 (AB q, J = 6.8 Hz, $\Delta\nu$ = 19.0 Hz, 2H), 3.82 (partially obscured AB q, J = 15.4 Hz, $\Delta\nu$ = 31.4 Hz, 2H), 3.72 (m, 2H), 3.56 (m, 1H), 3.36 (partially obscured bs, 1H), 3.36 (s, 3H), 2.95 (m, 1H), 2.08 (m, 2H), 1.86 (m, 1H), 1.65 (m, 2H), 1.28 (m, 1H), 1.03 (s, 21H), 0.68 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 129.7, 128.4, 128.0, 126.5, 124.6, 96.6, 81.3, 60.8, 60.4, 57.8, 57.5, 55.6, 38.6, 23.4, 23.3, 18.0, 12.0, 10.2; IR (neat) 2942, 2866, 1457 cm^{-1}; MS (CI, NH_3) *m*/*z* 476 (MH^+, 100), 372 (31), 359 (15), 299 (17), 91 (22); HRMS calcd for $C_{28}H_{50}NO_3Si$ (MH^+) 476.3560, found 476.3562; $[\alpha]_D^{25}$ = +16.8° (*c* = 0.0498, $CHCl_3$).

(1′*S*,2*S*,6*S*)-6-[1′-(Methoxymethoxy)propyl]-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (22). Lithium (0.875 g, 127 mmol) was added to a stirred, room-

temperature solution of benzyl-protected amine **21** (1.21 g, 2.54 mmol) and triethylamine (20 mL) in THF (10 mL). Ethylenediamine (2.0 mL) was then added dropwise. After 140 min, the dark brown solution was cooled in an ice bath to 0 °C. The reaction mixture was then carefully quenched with saturated aqueous NH_4Cl (30 mL), followed by dilution with H_2O (30 mL) and $CHCl_3$ (30 mL). After it was stirred for 10 min at room temperature, the mixture was basified with Na_2CO_3 (3 g) until a pH of 10 was achieved (pH paper). The aqueous layer was then extracted with $CHCl_3$ (5 × 50 mL). The combined organic extracts were dried (K_2CO_3) and concentrated to yield the crude product (1.07 g) as a light yellow oil. Flash chromatography (silica gel, gradient 90:10 to 65:35 hexanes/ethyl acetate) afforded **22** as a colorless oil (698 mg, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (m, 1H), 5.62 (dm, J = 10.0 Hz, 1H), 4.70 (AB q, J = 6.7 Hz, $\Delta\nu$ = 5.9 Hz, 2H), 3.83 (t, J = 5.9 Hz, 2H), 3.57 (bm, 1H), 3.40 (partially obscured m, 1H), 3.40 (s, 3H), 2.87 (m, 1H), 2.15−1.85 (bs, 3H), 1.80−1.58 (m, 3H), 1.55−1.41 (m, 1H), 1.06 (s, 21H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.2, 124.5, 96.5, 82.9, 60.4, 55.8, 55.1, 52.0, 39.4, 28.5, 22.9, 18.4, 12.0, 8.6; IR (neat) 2942, 2866, 1464 cm^{-1}; MS (CI, NH_3) m/z 386 (MH^+, 100), 282 (18), 108 (4); HRMS calcd for $C_{21}H_{44}NO_3Si$ (MH^+) 386.3084, found 386.3090; $[\alpha]_D^{25}$ = −13.2° (c = 0.0093, CH_2Cl_2).

(1′*S*,2*S*,6*S*)-2-(2-Hydroxyethyl)-6-[1′-(methoxymethoxy)-propyl]-1-[[(2″,2″,2″-trichloroethyl)oxy]carbonyl]-1,2,5,6-tetrahydropyridine (23). Amine **23** (698 mg, 1.81 mmol) was dissolved in pyridine (15 mL) and the resulting solution cooled to 0 °C. TROC-Cl (1.24 mL, 9.03 mmol) was added, and the mixture was stirred at room temperature for 4.25 h. The mixture was then poured into a stirred solution of ether and saturated aqueous Na_2CO_3 (1:1, v/v, 25 mL). The aqueous layer was then extracted with $CHCl_3$ (3 × 30 mL), and the combined organic extracts were washed with H_2O (100 mL), dried (K_2CO_3), and concentrated to afford the crude material (1.63 g) as a dark oil. Flash chromatography (silica gel, 90:10 hexanes/ethyl acetate) afforded the product (1′*S*,2*S*,6*S*)-6-[1′-(methoxymethoxy)propyl]-1-[[(2″,2″,2″-trichloroethyl)-oxy]carbonyl]-2-[2-[(triisopropylsilyl)oxy]ethyl]-1,2,5,6-tetrahydropyridine (945 mg, 93%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (dt, J = 10.4, 2.9 Hz, 1H), 5.72 (bm, 1H), 4.90−4.67 (m, 2H), 4.64 (s, 2H), 4.57 (t, J = 7.2 Hz, 1H), 4.46 (m, 1H), 3.88 (m, 2H), 3.60 (dt, J = 12.2, 4.6 Hz, 1H), 3.52 (s, 3H), 2.39 (bd, J = 15.3 Hz, 1H), 2.12 (dd, J = 17.3, 6.0 Hz, 2H), 1.93−1.73 (bm, 2H), 1.48 (m, 1H), 1.05 (s, 21H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) mixture of rotational isomers δ 154.4, 127.8 (br), 121.0, 96.7, 95.9, 80.7 (br), 75.3, 62.1, 56.0, 51.3, 50.8, 39.0, 25.2, 24.4, 18.1, 12.1, 9.1 (br); IR (neat) 2943, 2867, 1711, 1034 cm^{-1}; MS (CI, NH_3) m/z 562 (MH^+, 100), 560 (MH^+, 96), 528 (21), 520 (19), 518 (54), 516 (52), 458 (17), 256 (18); HRMS calcd for $C_{24}H_{45}NO_5SiCl_3$ (MH^+) 560.2133, found 560.2116; $[\alpha]_D^{25}$ = +27.1° (c = 0.0379, $CHCl_3$). The above TIPS ether (945 mg, 1.68 mmol) was dissolved in THF (6.0 mL) and cooled to 0 °C. HF−pyridine (1.6 mL of a solution containing ∼30% HF and ∼70% pyridine, Aldrich Chemical Co.) was added dropwise and the mixture stirred at room temperature for 3 h. The mixture was then diluted with CH_2Cl_2 and poured into a stirred solution of saturated aqueous Na_2CO_3 and CH_2Cl_2 (1:1, v/v, 20 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (4 × 40 mL), and then the combined organic extracts were washed with H_2O (75 mL), dried (K_2CO_3), and concentrated to afford crude material (676 mg) as a light yellow oil. Flash chromatography (silica gel, 50:50 hexanes/ethyl acetate) afforded alcohol **23** (663 mg, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (m, 1H), 5.67 (m, 1H), 4.82 (partially obscured AB q, J = 11.8 Hz, $\Delta\nu$ = 63.1 Hz, 2H), 4.62 (m, 4H), 3.78−3.58 (m, 4H), 3.36 (s, 3H), 2.39 (dm, J = 17.6 Hz, 1H), 2.10 (dd, J = 17.6, 5.7 Hz, 1H), 1.95−1.65 (m, 3H), 1.55−1.42 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 45 °C) δ 155.7, 127.9, 121.6, 96.6, 95.6, 79.5, 75.3, 58.8, 56.1, 50.6, 49.3, 38.6, 25.2, 24.2, 7.6; IR (neat) 3650−3180 (br), 2951, 2885, 1708 cm^{-1}; MS (CI, NH_3) m/z 406 (MH^+, 91), 404 (MH^+, 100), 374 (62), 372 (70), 192 (22), 120 (27); HRMS calcd for $C_{15}H_{25}NO_5Cl_3$ (MH^+) 404.0798, found 404.0788; $[\alpha]_D^{25}$ = +40.1° (c = 0.0352, CH_2Cl_2).

(1′*S*,2*S*,6*S*)-2-{(Carbomethoxy)methyl]-6-[1′-(methoxymethoxy)propyl]-1-[[(2″,2″,2″-trichloroethyl)oxy]carbonyl]-1,2,5,6-tetrahydropyridine (24). Primary alcohol **23** (113 mg, 0.278 mmol) was dissolved in DMF (1.5 mL) at room temperature. Pyridinium dichromate (PDC; 523 mg, 1.39 mmol) was then added, and the mixture was stirred for 30 h and then concentrated. $NaHSO_3$ (1 g), pH 7 buffer, and CH_2Cl_2 (1:2, v/v, 30 mL) were sequentially added, and the mixture was stirred for 10 min. The aqueous layer was then extracted with CH_2Cl_2 (4 × 25 mL), and the combined organic extracts were dried (Na_2SO_4). Filtration of the solids through Celite, followed by concentration, afforded crude (1′*S*,2*S*,6*S*)-2-(carboxymethyl)-6-[1′-(methoxymethoxy)propyl]-1-[[(2″,2″,2″-trichloroethyl)oxy]carbonyl]-1,2,5,6-tetrahydropyridine (997 mg, 85%) as a yellow oil that was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotational isomers) δ 10.00−8.00 (vb, 1H), 5.78 (bm, 2H), 4.88 (bm, 3H), 4.62 (m, 3H), 3.53 (m, 1H), 3.36 (s, 3H), 3.00 (m, 1H), 2.86 (m, 1H), 2.42 (m, 1H), 2.14 (dd, J = 17.2, 3.5 Hz, 1H), 1.65 (m, 1H), 1.46 (m, 1H), 0.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotational isomers) δ 176.5, 154.3, 125.9, 125.1, 122.8, 122.6, 122.4, 96.2, 96.0, 95.4, 81.6, 80.1, 75.1, 56.1, 50.2, 49.9, 48.8, 48.3, 39.5, 38.7, 25.7, 25.5, 24.3, 9.0, 8.1; IR (neat) 3400−2900 (br), 2942, 1708 cm^{-1}; $[\alpha]_D^{25}$ = +61.9° (c = 0.0163, CH_2Cl_2). Carbonyldiimidazole (CDI; 841 mg, 5.18 mmol) was carefully added to a stirred solution of the above crude acid (435 mg, 1.04 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The solution was warmed to room temperature and stirred for 2 h. Imidazole (141 mg, 2.07 mmol) and methanol (0.84 mL, 21 mmol) were then added sequentially. The mixture was then stirred at room temperature for 19 h, concentrated, and dried *in vacuo* (0.3 mmHg, 1 h). The solid residue was diluted with ethyl acetate (10 mL) and then poured into a stirred solution of ethyl acetate and pH 7 buffer (1:1, v/v, 30 mL) at room temperature. The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic extracts were washed with H_2O (40 mL), dried (K_2CO_3), and concentrated to afford the crude product (525 mg) as a yellow oil. Flash chromatography (silica gel, 85:15 hexanes/ethyl acetate) afforded ester **20** (315 mg, 70%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotational isomers) δ 5.83−5.69 (m, 2H), 4.99−4.72 (m, 2H), 4.62 (apparent q, J = 7.0 Hz, 2H), 4.62 (obscured m, 2H), 3.69 (s, 3H), 3.53 (m, 1H), 3.36 (s, 3H), 3.01−2.50 (m, 2H), 2.51−2.08 (m, 2H), 1.85−1.60 (m, 1H), 1.55−1.40 (m, 1H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotational isomers) δ 171.6, 154.2, 126.1, 125.3, 122.4, 96.4, 96.3, 81.4, 80.1, 75.1, 56.1, 51.5, 50.2, 50.0, 49.0, 48.5, 39.6, 38.6, 25.7, 24.3, 8.9, 8.1; IR (neat) 2952, 1738, 1711 cm^{-1}; MS (DCI, NH_3) m/z 434 (MH^+, 20), 432 (MH^+, 21) 402 (100), 400 (99), 258 (33), 256 (16), 254 (14); HRMS calcd for $C_{16}H_{25}NO_6Cl_3$ (MH^+) 432.0748, found 432.0734; $[\alpha]_D^{25}$ = +69.0° (c = 0.0148, CH_2Cl_2).

(−)-Methyl Palustramate (3). Zinc (300 mg, excess) and aqueous KH_2PO_4 (0.1 mL, 1 M solution) were added to a stirred solution of **24** (41.6 mg, 0.097 mmol) in THF (0.20 mL). The reaction mixture was then stirred for 15 h at room temperature. It was then diluted with $CHCl_3$ and saturated aqueous Na_2CO_3 (1:1, v/v, 5 mL). The aqueous layer was extracted with $CHCl_3$ (4 × 10 mL), and the combined organic extracts were washed with H_2O (30 mL), dried (K_2CO_3), and concentrated to afford the crude product (37.2 mg) as a light yellow oil. Flash chromatography (neutral alumina, 96:4 hexanes/ethyl acetate) afforded (1′*S*,2*S*,6*S*)-2-[(carbomethoxy)methyl]-6-[(1′-methoxymethoxy)propyl]-1,2,5,6-tetrahydropyridine (18.3 mg, 74%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.51 (dm, J = 9.9 Hz, 1H), 4.70 (AB q, J = 6.7 Hz, $\Delta\nu$ = 11.0 Hz, 2H), 3.81 (bm, 1H), 3.68 (s, 3H), 3.41 (s, 3H), 3.37 (partially obscured m, 1H), 2.89 (m, 1H), 2.47 (m, 2H), 1.91 (m, 3H), 1.73 (m, 1H), 1.50 (m, 1H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 129.3, 125.9, 96.5, 82.5, 55.9, 54.8, 51.5, 51.4, 40.9, 28.3, 22.9, 8.6; IR (neat) 2933, 1738, 1438 cm^{-1}; MS (DCI, NH_3) m/z 258 (MH^+, 100), 154 (38), 80 (35); HRMS calcd for $C_{13}H_{24}NO_4$ (MH^+) 258.1705, found 258.1704; $[\alpha]_D^{25}$ =

−26.6° (c = 0.0044, CH_2Cl_2). $MgBr_2$ (55 mg, 0.30 mmol) and butanethiol (0.27 mL, 0.23 mmol) were sequentially added to a solution of the above amine (17.2 mg, 0.067 mmol) in ether (0.5 mL). The reaction mixture was stirred for 39 h at room temperature and then diluted with ether (3 mL) and saturated aqueous Na_2CO_3 (3 mL). It was then extracted with $CHCl_3$ (4 × 5 mL), and the combined organic extracts were dried (K_2CO_3) and concentrated to afford the crude material (24.9 mg) as a yellow oil. Flash chromatography (neutral alumina, 80:20 hexanes/ethyl acetate) afforded (−)-methyl palustramate (**3**; 11 mg, 76%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.60 (dt, J = 9.3, 2.0 Hz, 1H), 3.76 (bs, 1H), 3.68 (s, 3H), 3.25 (dt, J = 3.3, 8.1 Hz, 1H), 2.96 (bs, 1H), 2.68 (ddd, J = 11.6, 8.0, 4.2 Hz, 1H), 2.50 (dd, J = 15.7, 5.4 Hz, 1H), 2.44 (dd, J = 15.7, 8.3 Hz, 1H), 2.03−1.93 (dm, J = 18.3 Hz, 1H), 1.90−1.68 (m, 2H), 1.66−1.57 (dp, J = 7.6, 3.3 Hz, 1H), 1.43−1.35 (sept, J = 7.4 Hz, 1H), 0.99 (t, J = 7.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.3, 129.8, 126.3, 75.6, 57.3, 51.6, 51.4, 40.5, 28.0, 26.0, 9.7; ^{1}H NMR (500 MHz, C_6D_6) δ 5.58 (m, 1H), 5.42 (m, 1H), 3.68 (m, 1H), 3.29 (s, 3H), 3.06 (dt, J = 8.0, 3.2 Hz, 1H), 2.52 (dd, J = 14.5, 7.7 Hz, 1H), 2.28 (dd, J = 15.7, 7.7 Hz, 1H), 2.18 (dd, J = 15.7, 5.0 Hz, 1H), 1.61 (m, 2H), 1.37 (d sextet, J = 7.6, 3.2 Hz, 1H), 1.24 (septet, J = 7.3 Hz, 1H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.8, 130.2, 126.4, 75.6, 57.7, 51.8, 50.9, 40.8, 28.3, 26.5, 9.9; IR (neat) 3315, 3309, 2959 1734 cm^{-1}; MS (CI, NH_3) m/z 214 (MH^+, 100), 154 (22), 140 (8), 80 (26); HRMS calcd for $C_{11}H_{20}NO_3$ (MH^+) 214.1443, found 214.1445; $[\alpha]_D^{25} = -18.2°$ (c = 0.0044, CH_2Cl_2).

(−)-Methyl Dihydropalustramate (4). (−)-Methyl palustramate (**3**; 10 mg, 0.046 mmol) was added to CD_3OD (0.7 mL) and the reaction mixture hydrogenated using a Parr hydrogenator (16 psi of H_2, 5 mg of $Pd(OH)_2$) for 35 min. The reaction mixture was then diluted with CH_2Cl_2 (2 mL), and K_2CO_3 (15 mg) was added. The solids were rinsed with CH_2Cl_2 (6 × 5 mL) and the combined organic rinsings concentrated to afford crude material (4.5 mg, 45%; unoptimized) as a light yellow oil. Flash chromatography (silica gel, 9:1 $CHCl_3$/CH_3OH) afforded an analytical sample of (−)-methyl dihydropalustramate (**4**) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H, OCH_3), 3.26 (dt, J = 3.7, 10.2 Hz, 1H), 2.97 (m, 1H), 2.52 (m, 1H), 2.44 (d, J = 6.6 Hz, 2H), 2.20−1.70 (partially obscured vb, 2H), 1.85 (dt, J = 13.2, 3.1 Hz, 2H), 1.65 (bd, J = 14.0 Hz, 1H), 1.61−1.50 (m, 1H), 1.51−1.30 (m, 2H), 1.27−1.06 (dp, J = 12.0, 3.4 Hz, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 75.8, 60.5, 53.1, 51.5, 41.5, 32.2, 28.4, 26.6, 24.2, 9.9; ^{1}H NMR (300 MHz, C_6D_6) δ 3.25 (s, 3H), 3.08 (dt, J = 8.5, 3.6 Hz, 1H), 2.74 (m, 1H), 2.95−2.18 (dd, J = 15.8, 8.2 Hz, 1H), 2.23 (obscured m, 1H), 2.16−2.08 (dd, J = 15.7, 5.1 Hz, 1H), 1.55−0.75 (m, 10H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ 172.3, 75.6, 61.1, 53.3, 51.0, 41.5, 32.4, 28.8, 27.1, 24.6, 10.4; IR (neat) 3700−3050 (br), 2933, 1736 cm^{-1}; MS (CI, NH_3) m/z 216 (MH^+, 100), 198 (6), 156 (27); HRMS calcd for $C_{11}H_{22}NO_3$ (MH^+) 216.1600, found 216.1598; $[\alpha]_D^{25} = -26.4°$ (c = 0.0014, CH_3OH); lit.[7] $[\alpha]_D^{16} = -22.1°$ (c = 0.8 mg/mL, CH_3OH); lit.[3d] $[\alpha]_D^{22} = -23°$ (c = 2.45 mg/mL, CH_3OH).

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Supporting Information Available: Figures giving NMR spectra and a tabular comparison of spectral data for our synthetic **4** with those in the literature (59 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.

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