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A General Approach to 3-*n*-Butyl-5-alkylindolizidines: Total Synthesis of (−)-Indolizidine 195B

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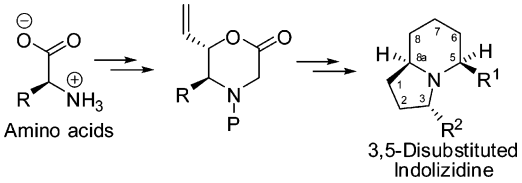

Indolizidine type alkaloids have been attractive synthetic targets due to their biological activity. The total synthesis of (−)-indolizidine 195B via a general route, which could potentially be used to prepare other indolizidine alkaloids such as (−)-gephyrotoxin 223AB and (−)-myrmicarin 237A, is described.

Introduction

Indolizidine type alkaloids produced by neotropical frogs and ants have been attractive synthetic targets[1] due to their potent biological activity.[2] Many of the indolizidine alkaloids are structurally similar, possessing a *cis*-orientation of hydrogens at C-5 and C-8a, and differ only in functionality at C-3 and C-5 as shown in Figure 1.

Many of the syntheses reported to date require rather dramatic changes in strategy and starting materials to prepare more than one of these indolizidines.[1b,g,3] The generality of the stereochemical structures of these indolizidines can be exploited to develop a general synthetic route to several natural products. A similar approach was undertaken by Somfai[1k,l,p] in the synthesis of indolizidine 195B, indolizidine 209D and 209B, as well as Monomorine I. We have previously shown that the silyl ketene acetals derived from *trans*-5-alkyl-6-alkenyl morpholinone **6** undergo a Claisen rearrangement at room temperature to afford *cis*-2,6-substituted pipecolic esters **8** with high stereo- and enantioselectivity (Scheme 1).[4] The stereochemical outcome of the Claisen rearrangement is consistent with the process proceeding through boat-like transition state **7**. Morpholinone **6** can in turn be derived from readily available α-amino acids **5** (Scheme 1).

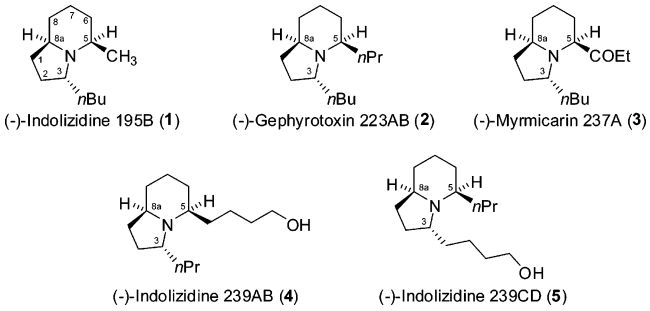

FIGURE 1. Structures of 3,5-disubstituted indolizidines.

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(1) (a) Hart, D. J.; Tsai, Y. M. *J. Org. Chem.* **1982**, *47*, 4403−4409. (b) Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *26*, 1515−1518. (c) Daly, J. W.; Spande, T. F.; Whittaker, N.; Highet, R. J.; Feigl, D.; Nishimori, N.; Tokuyama, T.; Myers, C. W. *J. Nat. Prod.* **1986**, *49*, 265−280. (d) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986**, *42*, 3453−3460. (e) Edwards, M. W.; Daly, J. W. *J. Nat. Prod.* **1988**, *51*, 1188−1197. (f) Machinaga, N.; Kibayashi, C. *J. Chem. Soc., Chem. Commun.* **1991**, 405−407. (g) Machinaga, N.; Kibayashi, C. *J. Org. Chem.* **1992**, *57*, 5178−5189. (h) Taber, D. F.; Deker, P. B.; Silverberg, L. J. *J. Org. Chem.* **1992**, *57*, 5990−5994. (i) Pilli, R. A.; Dias, L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717−722. (j) Fleurant, A.; Celerier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1429−1430. (k) Åhman, J.; Somfai, P. *Tetrahedron* **1995**, 9747−9756. (l) Åhman, J.; Somfai, P. *Tetrahedron* **1995**, 303−306. (m) Célimène, C.; Dhimane, H.; Saboureau, A.; Lhommet, G. *Tetrahedron: Asymmetry* **1996**, *7*, 1585−1588. (n) Thanh, G. V.; Celerier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2211−2212. (o) Solladie, G.; Chu, G. H. *Tetrahedron Lett.* **1996**, *37*, 111−114. (p) Somfai, P.; Jarevång, T.; Lindström, U. M.; Svensson, A. *Acta Chem. Scand.* **1997**, *51*, 1024−1029. (q) Thanh, G. V.; Celerier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1999**, *40*, 3713−3716. (r) Kiewel, K.; Tallant, M.; Sulikowski, G. A. *Tetrahedron Lett.* **2001**, *42*, 6621−6623. (s) Conchon, E.; Gelas-Mialhe, Y.; Remuson, R. *Tetrahedron: Asymmetry* **2006**, *17*, 1253−1257.

(2) Daly, J. W.; Brown, G. B.; Mensahdwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163−188.

(3) (a) Célimène, C.; Dhimane, H.; Lhommet, G. *Tetrahedron* **1998**, *54*, 10457−10468. (b) Francke, W.; Schroder, F.; Walter, F.; Sinnwell, V.; Baumann, H.; Kaib, M. *Liebigs Ann.* **1995**, 965−977. (c) Royer, J.; Husson, H. P. *J. Org. Chem.* **1985**, *50*, 670−673.

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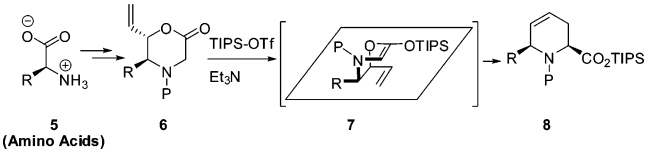
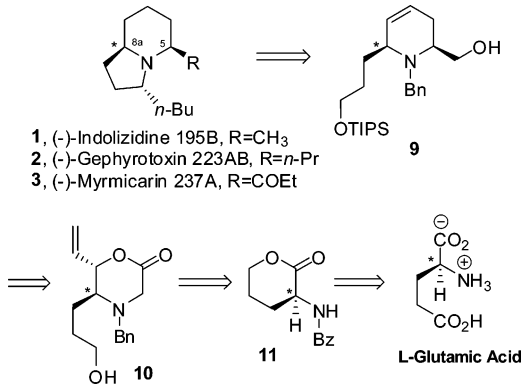
SCHEME 1. Morpholinone Variation of the Claisen Rearrangement



5 (Amino Acids) 6 7 8

SCHEME 2. The Retrosynthesis of Indolizidines 1−3



1, (-)-Indolizidine 195B, R=CH_3
2, (-)-Gephyrotoxin 223AB, R=*n*-Pr
3, (-)-Myrmicarin 237A, R=COEt

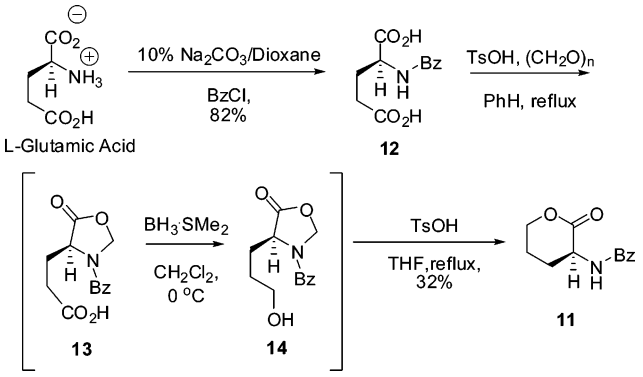
9 **10** **11** **L-Glutamic Acid**

We report here a synthetic strategy where several different indolizidines might be available from a common advanced intermediate. We chose to illustrate the validity of our general route with the synthesis of (−)-indolizidine 195B, **1**, but the 3-*n*-butyl indolizidines such as (−)-gephyrotoxin 223AB (**2**) and (−)-myrmicarin 237A (**3**), as well as other indolizidines, should be easily prepared from a common intermediate using similar chemistry.

Indolizidine alkaloids **1**, **2**, and **3** should be available from common intermediate **9** (Scheme 2). Our choice of starting material for the synthesis of **9** was L-glutamic acid, with a three-carbon side chain that could be used to form the five-membered ring of the indolizidine using Husson's methodology.[1b] The stereocenter of the amino acid should be preserved throughout the synthesis to introduce C-8a of the indolizidine in the correct absolute configuration. The stereochemistry of C-5 in the final products will be controlled via the conformationally restricted Claisen rearrangement of the silyl ketene acetal derived from morpholinone **10** (Scheme 2).

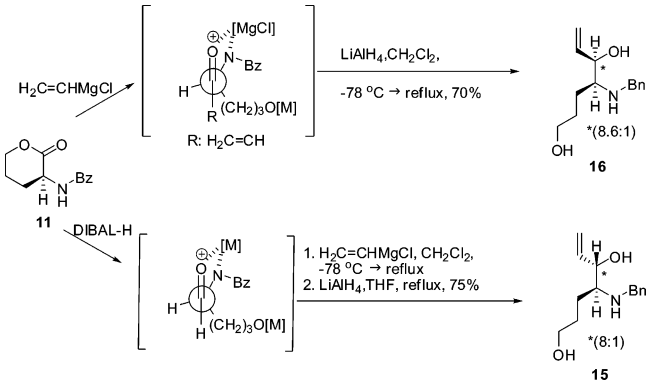
There are only a few reported syntheses of α-amino-*δ*-lactones such as **11**.[5] Thus, our first goal was to develop an efficient synthesis of compound **11**. Using a modification of Miller's procedure,[5b] the amino group of L-glutamic acid was protected with benzoyl chloride to afford benzamide **12** (Scheme 3). Treatment of **12** with paraformaldehyde afforded **13**, which was then reduced with $BH_3{\cdot}SMe_2$ to give **14**. Without isolation, compound **14** was refluxed in THF with a catalytic amount of TsOH to afford lactone **11** in 26% overall yield from L-glutamic acid.

SCHEME 3. Synthesis of Lactone 11



12 **13** **14** **11**

SCHEME 4. Synthesis of Amino Alcohols 15 and 16



11 **16** **15**

Lactone **11** was treated with DIBAL-H and vinyl magnesium chloride[4d,6] followed by reduction of the amide with $LiAlH_4$ to afford the desired amino alcohol **15** in 75% overall yield as an 8:1 mixture of diastereomers (^{1}H NMR analysis; Scheme 4). Interestingly, changing the order of addition of the hydride and Grignard reagent reversed the stereoselectivity. Addition of vinyl Grignard at 0 °C, followed by addition of hydride ($LiAlH_4$), afforded **16** in 70% yield as an 8.6:1 mixture of diastereomers (^{1}H NMR analysis).

Amino alcohols **15** and **16** are presumably both formed via a chelation-controlled addition of a nucleophile (vinyl or hydride) to an aldehyde/ketone type intermediate.[4d,6] Reversing the order of addition of vinyl and hydride nucleophiles led to a reversal of the stereochemical outcome for the reaction.

Amino alcohol **15** was treated with phenyl bromoacetate and Hünig's base to afford morpholinone **10** in 68% yield (Scheme 5).[4d,1] Treatment of **10** with TIPS-OTf and Et_3N gave the corresponding ketene acetal, which underwent a Claisen rearrangement at room temperature to afford TIPS ester **17**. Without further purification, crude TIPS ester **17** was reduced with DIBAL-H to afford piperidine **9** in 56% overall yield from **10**.

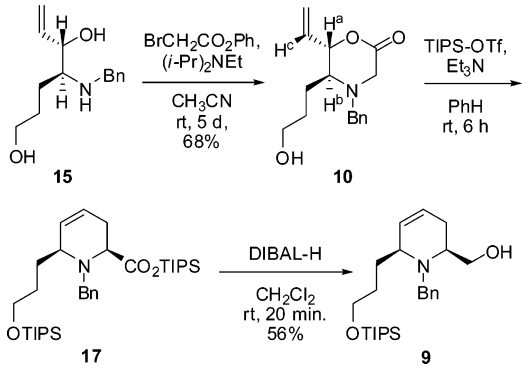
Amino alcohol **16** was converted to *cis*-morpholinone **18** in 32% yield (Scheme 6). The comparison of morpholinone **18** with **10** supports the stereochemical assignment of **15** and **16**. Morpholinone **18** (Scheme 6, from amino alcohol **16**) shows a smaller coupling constant (J_{a-b} = 3.1 Hz) than **10** (J_{a-b} = 7.0 Hz), suggesting a *cis*-orientation of the two hydrogens and supporting the assigned relative stereochemistry of **16**. The coupling constant J_{a-b} of **18** was determined from a decoupling study where irradiation of H^c collapsed H^a to an apparent doublet with a coupling constant of 3.1 Hz.

(4) (a) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1998**, *63*, 7490−7497. (b) Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1997**, *62*, 8549−8552. (c) Angle, S. R.; Breitenbucher, J. G. *Tetrahedron Lett.* **1993**, *34*, 3985−3988. (d) Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947−5955. (e) Angle, S. R.; Arnaiz, D. O. *Tetrahedron Lett.* **1989**, *30*, 515−518.

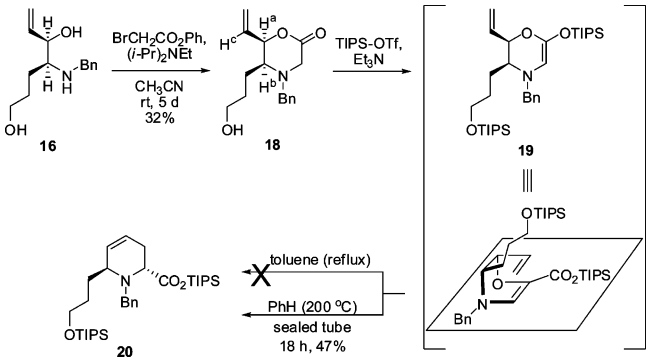
(5) (a) Kanai, F.; Isshiki, K.; Umezawa, Y.; Morishima, H.; Naganawa, H.; Takita, T.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1985**, *38*, 31−38. (b) Lee, B. H.; Miller, M. J. *Tetrahedron Lett.* **1984**, *25*, 927−930. (c) Kim, Y. B.; Park, S. J.; Keum, G.; Jang, M. S.; Kang, S. B.; Lee, D. H.; Kim, Y. *Bull. Korean Chem. Soc.* **2002**, *23*, 1277−1284.

(6) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370−4382.

SCHEME 5. Synthesis of Key Intermediate 9



SCHEME 6. The Claisen Rearrangement of *cis*-Morpholinone 20



We expected the conversion of **18** to **20** to be more difficult than that of **10** to **17** due to the *cis*-orientation of the substituents on the morpholinone. Examination of the boat-like transition state required for Claisen rearrangement of silyl ketene acetal **19** shows a significant steric interaction between the alkyl and alkenyl substituents, and thus the temperature required for rearrangement is expected to be higher. Indeed, Burke found the same to be true for pyranones similar to our morpholinones.[7] Treatment of **18** with TIPS-OTf and Et_3N in refluxing toluene failed to provide the desired *trans*-pipecolic ester **20**. However, when **18** was heated to 200 °C (sealed tube), the desired *trans*-pipecolic ester **20** was formed in 47% yield (Scheme 6).

The silyl ketene acetal derived from *trans*-morpholinone **10** rearranged at room temperature to give *cis*-pipecolic ester **17** and was converted to (−)-indolizidine 195B as described in Scheme 7. This effectively proves the stereochemistry of both **10** and **18**. The *cis*-morpholinone **18** only rearranged under high temperatures (200 °C, sealed tube) to give **20**, which has the identical mass and carbon connectivity (based on proton assignments on the carbon backbone by gCOSY) as **17**. With only two stereocenters in the molecule, **20** must have a *trans*-orientation of substituents.

To complete the synthesis of (−)-indolizidine 195B, alcohol **9** was treated with MsCl, followed by $LiAlH_4$, to afford **21** in 76% yield. TIPS ether **21** was treated with TBAF followed by Swern oxidation to give aldehyde **23** in 63% overall yield (Scheme 7). Aldehyde **23** was then protected as the dimethyl acetal to give **24** in 90% yield. Hydrogenation/hydrogenolysis

SCHEME 7. Total Synthesis of (−)-Indolizidine 195B

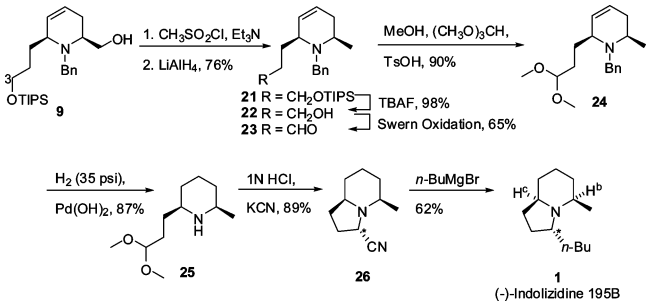
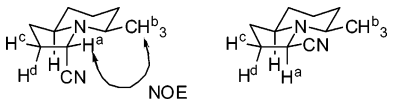


TABLE 1. Stereochemical Confirmation of 26



26 (*trans*) **26'** (*cis*)

MMX calcd	**26** (trans)	**26′** (cis)
H^a-H^c	$J = 7.5$ Hz	$J = 9.8$ Hz
H^a-H^d	$J = 1.1$ Hz	$J = 7.3$ Hz
	H^a (exp); δ 4.15 d, $J = 8.3$ Hz	

of **24** with Perlman's catalyst afforded **25** in an 87% yield.[1b] Amine **25** was treated with 1 N HCl and potassium cyanide to give **26** in 89% yield as a single diastereomer.[1b]

Using Husson's methodology, amino nitrile **26** was then treated with *n*-BuMgBr[1b] to afford (−)-indolizidine 195B and its C-3 epimer in 62% yield as a 2:1 mixture of diastereomers at C-3. The diastereomer ratio of **1** was determined on a purified sample (flash chromatography, SiO_2, 55:35:10 hexanes/ethyl acetate/*i*-PrOH, 2% Et_3N) by integration of the ^1H NMR signals for H^b and H^c appearing at δ 2.61−2.36 (m, 2H) and δ 2.34−1.97 [C-3 epimer, (−)-monomorine, lit.[1p] δ 2.20 (m, 1H) and δ 2.10 (m, 1H)]. Purification of the mixture of diastereomers by preparative TLC (Al_2O_3, 3:1 hexanes/CH_2Cl_2) afforded (−)-indolizidine 195B in 37% yield. Comparison of spectral data with those in the literature confirmed the success of the structural assignments.

The stereochemistry assigned to **26** is based upon an NOE experiment (Table 1) and examination of H−H coupling constants for H^a. MMX calculation showed that **26** was more stable than its C-3 epimer (**26′**) (nitrile *cis* to the methyl) by 0.8 kcal/mol. The coupling constants of H^a closely matched the calculated values for the *trans*-isomer.

The total synthesis of (−)-indolizidine 195B was achieved in 9 isolated steps and 3.5% overall yield from morpholinone **10** and in 13 steps from L-glutamic acid. Comparison of NMR data and optical rotation with literature data confirmed the stereochemistry of the final product.[1b] The synthesis of other indolizidine natural products from piperidine **9** should be easily accomplished.[8]

Experimental Section

(2*S*,6*S*)-[1-Benzyl-6-(3-triisopropylsilanyloxypropyl)-1,2,3,6-[tetrahydropyridin-2-yl]methanol (9). DIBAL-H (0.352 mL, 1.91 mmol) was slowly added to a stirred 0 °C solution of TIPS ester

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(8) For discussion and progress toward the synthesis of other indolizidine natural products, see: Kim, M. Ph.D. Dissertation, University of California, Riverside, 2002.

17 (0.562 g, 0.955 mmol) in CH_2Cl_2 (47 mL). After the addition was complete, the cooling bath was removed and the reaction mixture was allowed to warm to rt and stirred for 20 min. The reaction mixture was then cooled to 0 °C and poured into a stirring 0 °C solution of pH 7.5 buffer (30 mL). The resulting mixture was stirred for 10 min at rt, then the aqueous layer was extracted with ether (4 × 30 mL). The combined organic extracts were washed with H_2O (3 × 30 mL) and brine (30 mL), dried (K_2CO_3), and concentrated to afford crude product (0.481 g) as a yellow oil. Flash chromatography (5:1 hexanes/ethyl acetate, 2% triethylamine) afforded alcohol **9** (0.234 g, 56% from **10**) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31−7.21 (m, 5H,), 5.71 (dm, J = 10.5 Hz, 1H), 5.68 (br d, J = 10.5 Hz, 1H), 3.80 (s, 2H), 3.55 (m, 2H), 3.42 (m, 2H), 3.05 (m, 2H), 2.68 (br s, 1H), 2.31 (dsextet, J = 17.6, 2.6 Hz, 1H), 1.76 (dm, J = 18.0 Hz, 1H), 1.64−1.43 (m, 4H), 1.04 (m, 21H); ^{13}C (75 MHz, $CDCl_3$) δ 140.0, 128.8, 128.7, 128.4, 127.2, 122.8, 63.1, 60.1, 57.3, 56.5, 32.7, 30.2, 22.2, 18.0, 11.9; IR (CH_2Cl_2) 3456, 3028, 2847, cm^{-1}; MS (DCI/NH_3) m/z 418 (MH^+, 100), 386 (4), 294 (2), 220 (4), 202 (4), 106 (2); HRMS calcd for $C_{25}H_{44}NO_2Si$ (MH^+) 418.3141, found 418.3146; $[\alpha]^{25}_D$ = +41.53 (c 5.24, CH_2Cl_2).

(5*S*,6*S*)-4-Benzyl-5-[(3-hydroxy)propyl]-6-vinylmorpholin-2-one (10). A solution of phenyl bromoacetate (1.54 g, 7.17 mmol) in CH_3CN(10 mL) was added dropwise to a stirred 0 °C solution of amino alcohol **15** (1.41 g, 5.98 mmol), CH_3CN (60 mL), and *N*,*N*-diisopropylethylamine (3.1 mL, 17.9 mmol). The resulting solution was warmed to rt then stirred for 5 days. The solution was concentrated to dryness, ethyl acetate (20 mL) was added, and the mixture was stirred for 1 h at rt. Filtration, followed by concentration, afforded crude product (2.79 g) as a yellow oil. Flash chromatography (1:1 hexanes/ethyl acetate, 2% triethylamine) afforded lactone **10** (1.13 g, 68%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5H), 5.93 (ddd, J = 17.1, 10.1, 6.8 Hz, 1H), 5.39 (d, J = 17.1 Hz, 1H), 5.33 (d, J = 10.1 Hz, 1H), 4.70 (t, J = 7.0 Hz, 1H), 3.68 (ABq, J = 13.2 Hz, $\Delta\nu$ = 20.2 Hz, 2H), 3.62 (m, 2H), 3.34 (ABq, J = 18.0 Hz, $\Delta\nu$ = 32.5 Hz, 2H), 2.75 (br m, 1H), 2.34 (br s, 1H), 1.66 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 168.7, 136.8, 134.5, 128.8, 128.5, 127.6, 119.3, 81.6, 62.2, 59.8, 57.2 50.6, 28.6, 23.1; IR (CH_2Cl_2) 3684, 3615, 3074, 1740, 1604 cm^{-1}; MS (DCI/NH_3) m/z 276 (MH^+, 100), 258 (13), 191 (3); HRMS calcd for $C_{16}H_{22}NO_3$ (MH^+) 276.1600, found 276.1602; $[\alpha]^{25}_D$ = −73.46 (c 5.93, CH_2Cl_2).

(3*S*)-*N*-(2-Oxotetrahydropyran-3-yl)benzamide (11). A stirring solution of *N*-benzoyl-L-glutamic acid **12** (20.0 g, 79.6 mmol), paraformaldehyde (7.10 g, 238 mmol), and *p*-toluenesulfonic acid (TsOH) (3.0 g, 15.9 mmol) in benzene (700 mL) was refluxed for 3 h using a Dean−Stark apparatus to remove water. Two additional portions of paraformaldehyde (2 × 7.10 g, 2 × 238 mmol) were added on the hour. The resulting solution was filtered through glass wool while warm and concentrated to afford crude **13** (19.0 g, 72.3 mmol) as a white, cotton-candy-like solid. The crude product was then dissolved in dry THF (270 mL), cooled to 0 °C, and BH_3·SMe_2 (8.7 mL of 10 M solution in SMe_2, 86.7 mmol) was added. After warming to rt, the reaction mixture was stirred for 5 h. The resulting suspension was cooled to 0 °C, then 1 N HCl (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give crude **14** (12.6 g, 51.0 mmol) as a thick oil. Without purification, **14** was dissolved in THF (250 mL) and refluxed with TsOH (1.9 g, 10.2 mmol) for 8 h. After cooling to 0 °C, saturated $NaHCO_3$ (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed with H_2O (150 mL) and brine (150 mL), dried ($MgSO_4$), and concentrated to afford crude lactone (6.9 g) as a dark yellow oil. The crude product was recrystallized from ethyl acetate to give lactone **11** (5.6 g, 32% overall) as white solid: mp = 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (br d, J = 6.6 Hz, 2H), 7.56−7.43 (m, 3H), 7.07 (br s, 1H), 4.84 (m, 1H), 4.34 (t, J = 6.2 Hz, 2H), 2.84 (m, 1H), 2.09 (m, 2H), 1.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 167.1, 133.4, 131.9, 128.6, 127.1, 67.4, 48.6, 25.1, 20.9; IR (KBr) 3345,3310, 2904, 1736, 1647 cm^{-1}; MS (DEI) m/z 219 (M^+, 10), 147 (14), 105 (100), 77 (39), 51 (15); HRMS calcd for $C_{12}H_{13}NO_3$ (M^+) 219.0895, found 219.0892; $[\alpha]^{25}_D$ = +102.9 (c 10.1, CH_2Cl_2).

(2*S*)-2-(Benzoylamino)pentanedioic acid [*N*-benzoyl-L-glutamic acid] (12).[9] A solution of 10% (w/v) Na_2CO_3 (360 mL, 340 mmol) and benzoyl chloride (15.8 mL in 140 mL of 1,4-dioxane, 136 mmol) was slowly added to a stirred solution of L-glutamic acid (20 g, 136 mmol) in 1,4-dioxane (400 mL) at 0 °C. The resulting solution was slowly allowed to warm to room temperature and stirred overnight. H_2O (300 mL) was added, and the resulting suspension was washed with Et_2O (2 × 400 mL). The aqueous layer was cooled to 0 °C, and the pH was adjusted (pH <1, pH paper) with concentrated HCl. The resulting aqueous layer was extracted with ethyl acetate (4 × 300 mL), dried (Na_2SO_4), and concentrated in vacuo. Crystallization from boiling CH_2Cl_2 yielded 28.05 g (82%) of white solid **12**: mp = 140−142 °C (lit. 138 °C);[9] ^{1}H NMR (300 MHz, D_2O) δ 7.82 (d, J = 6.6 Hz, 2H), 7.67 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 4.69 (dd, J = 5.3, 9.2 Hz, 1H), 2.60 (t, J = 7.0 Hz, 2H), 2.37 (m, 1H), 2.18 (m, 1H); ^{13}C (75 MHz, D_2O) δ 172.6, 170.6, 166.4, 128.3, 127.9, 124.2, 122.7, 48.1, 25.7, 21.1; IR (KBr) 3303, 3264, 3080, 1721, 1642 cm^{-1}; MS (DCI/IC4) m/z 252 (MH^+, 31), 235 (13), 234 (100), 206 (16), 122 (13), 105 (42); HRMS calcd for $C_{12}H_{14}NO_5$ (MH^+) 252.0872, found 252.0875; $[\alpha]^{23}_D$ = −11.6 (c 3.72, MeOH).

(4*S*,5*S*)-4-(Benzylamino)hept-6-ene-1,5-diol (15). DIBAL-H (neat, 3.3 mL, 17.8 mmol) was added dropwise to a stirred solution of lactone **11** (2.60 g, 11.9 mmol) in CH_2Cl_2 (120 mL) at −78 °C. After stirring for 30 min, a solution of vinylmagnesium chloride (19 mL of 1.87 M solution in THF, 35.6 mmol) was added in one portion. The resulting solution was allowed to warm to rt then refluxed for 14 h. The reaction mixture was cooled to 0 °C, and 1 N HCl (100 mL) was added. After stirring for 6 h, the aqueous layer was extracted with $CHCl_3$ (5 × 150 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford crude amide (3.45 g) as a pale yellow oil. The crude product was dissolved in THF (140 mL), the resulting solution was cooled to 0 °C, and 95% $LiAlH_4$ (1.66 g, 41.5 mmol) was added. The reaction mixture was refluxed for 6 h, cooled to 0 °C, and H_2O (1.7 mL), 15% NaOH (1.7 mL), H_2O (5.1 mL) were sequentially added. After stirring overnight, the resulting mixture was filtered and concentrated to afford a pale yellow oil (2.59 g, 8:1 dr **15**/**16** by ^{1}NMR). Flash chromatography (55:35:10 hexanes/ethyl acetate/*iso*-propanol) afforded **15** (2.10 g, 75% overall) as a clear colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 5.84 (ddd, J = 17.1, 10.5, 7.0 Hz, 1H), 5.36 (d, J = 17.6 Hz, 1H), 5.23 (d, J = 10.5 Hz, 1H), 4.10 (t, J = 7.0 Hz, 1H), 3.84 (ABq, J = 12.3 Hz, $\Delta\nu$ = 43.1 Hz, 2H), 3.63 (m, 2H), 3.06 (br s, 3H), 2.65 (ddd, J = 6.8, 6.8, 3.9 Hz, 1H), 1.82−1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.6, 128.4, 127.4, 117.3, 73.5, 62.7, 61.0, 51.2, 28.8, 27.4; IR (CH_2Cl_2) 3612, 3448, 3032, 1599 cm^{-1}; MS (DCI/NH_3) m/z 236 (MH^+, 100), 178 (3), 91 (3); HRMS calcd for $C_{14}H_{22}NO_2$ (MH^+) 236.1650, found 236.1659; $[\alpha]^{23}_D$ = +7.65 (c 7.89, CH_2Cl_2).

(4*S*,5*R*)-4-Benzylaminohept-6-ene-1,5-diol (16). Vinylmagnesium chloride (2.2 mL of a 1.27 M solution in THF) was added to a stirred 0 °C solution of **11** (0.200 g, 0.912 mmol) in CH_2CH_2 (10 mL). After stirring for 1 h, $LiAlH_4$ (0.182 g, 4.56 mmol) was added and the reaction mixture was warmed to rt, then refluxed for 6 h. After cooling the suspension to 0 °C, H_2O (0.18 mL), 15% NaOH (0.18 mL), and H_2O (0.55 mL) were sequentially added. After stirring overnight, the resulting mixture was filtered through Celite and concentrated to afford a pale yellow oil (0.194 g, 8.6:1 **16**/**15**). The diastereomer ratio was determined by ^{1}H NMR integration of C*H*OH signals at δ 4.34 (**16**) and δ 4.10 (**15**). Flash chromatography

(9) Nandi, M. M.; Ray, R. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1986**, *25*, 222−224.

(55:35:10 hexanes/ethyl acetate/*iso*-propanol) afforded **16** (0.150 g, 70%) as a white solid: mp = 118−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 5.83 (ddd, J = 17.1, 10.5, 5.7 Hz, 1H), 5.33 (apparent dt, J = 17.6, 1.3 Hz, 1H), 5.14 (apparent dt, J = 10.5, 1.3 Hz, 1H), 4.34 (m, 1H), 3.82 (ABq, J = 12.7 Hz, $\Delta\nu$ = 20.6 Hz, 2H), 3.58 (m, 2H), 3.03 (br s, 3H), 2.62 (dt, J = 7.9, 3.9 Hz, 1H), 1.73−1.44 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 137.9, 128.5, 128.3, 127.2, 116.2, 71.7, 62.7, 61.1, 51.3, 29.9, 26.9; IR (neat) (br) 3304, 2937, 1641 cm^{-1}; MS (DCI/NH_3) *m*/*z* 236 (MH^+, 100), 218 (10), 178 (17); HRMS calcd for $C_{14}H_{22}NO_2$ (MH^+) 236.1650, found 236.1642; $[\alpha]^{25}_D$ = + 5.3 (*c* 0.898, CH_2Cl_2).

(2*S*,6*S*)-*N*-Phenylmethyl-6-[[(2-triisopropylsilyl)oxy]carbonyl]-2-[[(3-triisopropylsilyl)oxy]propyl]-1-2,5,6-tetrahydropyridine (17). Triisopropylsilyltriflate (0.56 mL, 1.14 mmol) was added to a stirring solution of morpholinone **10** (0.273 mg, 0.993 mmol) and triethylamine (0.692 mL, 4.96 mmol) in benzene (10 mL) at rt. The resulting suspension was stirred for 6 h at rt then concentrated to approximately 2 mL. Filtration (silica gel, 9:1 hexanes/ethyl acetate/2% triethylamine) afforded crude pipecolic ester **17** (0.562 mg, 96%) as a pale yellow oil that was used in the next step without further purification. Flash chromatography (9:1 hexanes/ethyl acetate) of a similar sample afforded an analytical sample of **17** as a colorless oil: ^{1}H (300 MHz, $CDCl_3$) δ 7.40 (d, J = 6.6 Hz, 2H), 7.25 (m, 3H), 5.77 (m, 1H), 5.65 (dm, J = 10.1 Hz, 1H), 3.97 (ABq, J = 14.5 Hz, $\Delta\nu$ = 25.0 Hz, 2H), 3.54 (m, 3H), 3.20 (br m, 1H), 2.45 (dm, J = 16.7 Hz, 1H), 2.29 (dm, J = 15.8 Hz, 1H) 1.71−1.44 (m, 4H), 1.30 (m, 3H), 1.09−1.03 (m, 39H); ^{13}C (75 MHz, $CDCl_3$) δ 174.3, 138.9, 129.7, 129.0 128.1, 126.9, 122.7, 63.5, 59.7, 57.8, 57.1, 29.2, 29.0, 27.4, 18.0, 17.9, 12.0; IR (CH_2Cl_2) 3074, 3039, 2946, 1707 cm^{-1}; MS (FAB$^+$, ether, NBA, PEG) *m*/*z* 588 (MH^+, 59), 587 (15), 586 (30), 386 (100), 372 (36), 370 (13), 170 (28); HRMS calcd for $C_{34}H_{62}NO_3Si_2$ (MH^+) 588.4268, found 588.4237; $[\alpha]^{23}_D$ = −1.1 (*c* 0.73, CH_2Cl_2).

(5*S*,6*R*)-4-Benzyl-5-[(3-hydroxy)propyl]-6-vinylmorpholin-2-one (18). A solution of phenyl bromoacetate (60.0 mg, 0.279 mmol) in CH_3CN (1 mL) was added dropwise to a stirred 0 °C solution of amino alcohol **16** (54.7 mg, 0.232 mmol), CH_3CN (3 mL), and *N*,*N*-diisopropylethylamine (0.121 mL, 0.698 mmol). The resulting solution was warmed to rt then stirred for 5 days. The solution was concentrated to dryness, ethyl acetate (10 mL) was added, and the mixture was stirred for 1 h at rt. Filtration followed by concentration afforded crude product (140.8 mg) as yellow oil. Flash chromatography (1:1 hexanes/ethyl acetate, 2% triethylamine) afforded lactone **18** (20.3 mg, 32%) as clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.85 (ddd, J = 16.7, 10.5, 5.7 Hz, 1H), 5.43 (apparent dt, J = 17.6, 1.3 Hz, 1H), 5.32 (apparent dt, J = 10.5, 1.3 Hz, 1H), 5.16 (ddt, J = 5.7, 3.1, 1.3 Hz, 1H), 3.79 (ABq, J = 13.2 Hz, $\Delta\nu$ = 35.6 Hz, 2H), 3.62 (dt, J = 3.1, 2.6 Hz, 2H), 3.41 (ABq, J = 18.4 Hz, $\Delta\nu$ = 37.3 Hz, 2H), 2.86 (m, 1H), 1.99 (br s, 1H), 1.70−1.54 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 136.9, 132.6, 128.7, 128.6, 127.7, 118.2, 80.1, 62.5, 58.8, 58.4, 49.8, 29.9, 21.2; IR (neat) 3350, 2931, 2870, 1736 cm^{-1}; MS (DCI/IC4) *m*/*z* 276 (MH^+, 100), 275 (3), 91 (3); HRMS calcd for $C_{16}H_{22}NO_3$ (MH^+) 276.1600, found 276.1598; $[\alpha]^{21}_D$ = +2.1 (*c* 0.34, CH_2Cl_2).

(2*S*,6*R*)-*N*-Phenylmethyl-6-[[(2-triisopropylsilyl)oxy]carbonyl]-2-[[(3-triisopropylsilyl)oxy]propyl]-1-2,5,6-tetrahydropyridine (20). Triisopropylsilyltriflate (0.0295 mL, 0.110 mmol) was added to a benzene (1 mL) solution of morpholinone **18** (15.1 mg, 0.0548 mmol) and triethylamine (0.0382 mL, 0.274 mmol) in a pressure vessel (Schlenk). The resulting mixture was cooled to −78 °C. The vessel was then evacuated and sealed. It was then slowly warmed to rt under vacuum. The process was repeated two more times. After the pressure vessel was sealed, the reaction mixture was heated to 200 °C for 18 h. After cooling to rt, the resulting suspension was filtered through basic Al_2O_3 (activity 1, 9:1 hexanes/ethyl acetate) and concentrated to give crude product (18.4 mg) as a pale yellow oil. Flash chromatography (3:1 hexanes/ethyl acetate, 2% Et_3N) afforded **20** (15.2 mg, 47%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.19 (m, 5H), 5.74 (m, 1H), 5.63 (dm, J = 10.1 Hz, 1H), 3.87 (ABq, J = 14.0 Hz, $\Delta\nu$ = 30.0 Hz, 2H), 3.71−3.50 (m, 4H), 2.39 (br m, 2H), 1.70−1.56 (m, 4H), 1.29 (m, 3H), 1.69−0.99 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 140.2, 130.9, 128.6, 128.1, 126.7, 122.7, 63.6, 56.8. 56.3, 54.3, 29.7, 29.6, 28.0, 18.0, 17.8, 12.0; IR (neat) 2943, 2808, 1717, 1654, 1260 cm^{-1}; MS (FAB/DCM/NBA) *m*/*z* 588 (MH^+, 54), 548 (33), 547 (52), 433 (32), 387 (37), 386 (100), 154 (84), 137 (41), 136 (45); HRMS calcd for $C_{34}H_{62}NO_3Si_2$ (MH^+) 588.4268, found 588.4294; $[\alpha]^{23}_D$ = +18.8 (*c* 0.52, CH_2Cl_2).

(2*R*,6*S*)-1-Benzyl-2-methyl-6-[(3-triisopropylsilyloxy)propyl]-1,2,3,6-tetrahydropyridine (21). Methylsulfonyl chloride (0.0206 mL, 0.266 mmol) was added dropwise to a stirred 0 °C solution of **9** (74.0 mg, 0.177 mmol) and triethylamine (0.0543 mL, 0.390 mmol) in ether (2 mL). The reaction mixture was allowed to warm to rt, stirred for 2 h, then filtered through Celite. The residue was washed with dry ether, then the combined organic layers were cooled to 0 °C and $LiAlH_4$ (70.7 mg, 1.77 mmol) was added. The suspension was allowed to warm to rt and stirred for 1 h. The reaction mixture was cooled to 0 °C, then H_2O (0.071 mL), 15% NaOH (0.071 mL), and H_2O (0.21 mL) were added sequentially and the resulting suspension was stirred at rt for 1 h. Filtration through Celite followed by concentration afforded crude product (63.7 mg) as light yellow oil. Flash chromatography (9:1 hexanes/ethyl acetate, 2% triethylamine) afforded methyl piperidine **21** (54.2 mg, 76%) as clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 2H), 7.28 (t, J = 7.2 Hz, 2H), 7.19 (t, J = 7.2 Hz, 1H), 5.75 (m, 1H), 5.62 (dm, J = 10.2 Hz, 1H), 3.78 (ABq, J = 15.6 Hz, $\Delta\nu$ = 23.1 Hz, 2H), 3.59 (m, 2H), 3.12 (br m, 1H), 2.88 (m, 1H), 2.09 (br dm, J = 15.9 Hz, 1H), 1.90 (br dm, J = 15.6 Hz, 1H), 1.66−1.47 (m, 4H), 1.09−1.00 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 129.6, 128.0, 126.2, 124.0, 63.5, 60.3, 56.0, 52.9, 32.1, 30.7, 29.3, 21.5, 18.0, 12.0; IR (CH_2Cl_2) 2989, 2942, 2865, 1280 cm^{-1}; MS (DCI/NH_3) *m*/*z* 402 (MH^+, 100), 186 (7); HRMS calcd for $C_{25}H_{44}NOSi$ (MH^+) 402.3192, found 402.3203; $[\alpha]^{23}_D$ = +34.06 (*c* 2.63, CH_2Cl_2).

(2*S*,6*R*)-3-(1-Benzyl-6-methyl-1,2,5,6-tetrahydropyridin-2-yl)-propan-1-ol (22). A solution of tetrabutylamonium fluoride (1.34 mL of a 1.0 M solution in THF, 1.34 mmol) was added to a stirring solution of **21** (0.540 g, 1.34 mmol) in THF (15 mL). After stirring for 5 h at rt, $NaHCO_3$ (saturated aqueous 20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), dried (Na_2SO_4), and concentrated to afford crude product (0.906 g) as yellow oil. Flash chromatography (1:1 hexanes/ethyl acetate, 2% triethylamine) gave alcohol **22** (0.325 g, 98%) as clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H), 5.76 (dm, J = 10.1 Hz, 1H), 5.45 (br dm, J = 10.1 Hz, 1H), 3.92 (ABq, J = 15.4 Hz, $\Delta\nu$ = 42.2 Hz, 2H), 3.52 (m, 2H), 3.24 (br m, 1H), 2.94 (m, 1H), 2.10 (dm, J = 17.1 Hz, 1H), 1.94 (dm, J = 17.6 Hz, 1H), 1.83−1.49 (m, 4H), 1.25 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 129.3, 128.8, 128.2, 127.1 124.5, 62.7, 58.0, 54.1, 50.9, 31.8, 31.5, 28.5, 21.2; IR (CH_2Cl_2) 3613, 3058, 2985 cm^{-1}; MS (DCI/NH_3) *m*/*z* 246 (MH^+, 100), 244 (3), 191 (7), 186 (11), 174 (17); HRMS calcd for $C_{16}H_{24}NO$ (MH^+) 246.1858, found 246.1867; $[\alpha]^{22}_D$ = −21.1 (*c* 1.51, CH_2Cl_2).

(2*S*,6*R*)-3-(1-Benzyl-6-methyl-1,2,5,6-tetrahydropyridin-2-yl)-propionaldehyde (23). A solution of DMSO (0.116 mL, 1.63 mmol) in CH_2Cl_2 (2 mL) was added to a stirred solution of oxalyl chloride (0.0853 mL, 0.978 mmol) in CH_2Cl_2 (5 mL) at −78 °C over 5 min. A solution of alcohol **22** (80.0 mg, 0.326 mmol) in CH_2Cl_2 (4 mL) was added, and the resulting mixture was stirred for 30 min at −78 °C. Triethylamine (0.273 mL, 1.96 mmol) in CH_2Cl_2 (2 mL) was then added, and the resulting solution was allowed to warm to 0 °C over 20 min. Aqueous K_2CO_3 (0.3 M, 10 mL) was added, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with H_2O and brine, dried (K_2CO_3), and concentrated to give crude product (178 mg) as dark yellow oil. Flash chromatography (5:1

hexanes/ethyl acetate, 2% triethylamine) afforded aldehyde **23** (52.3 mg, 65%) as light yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (t, J = 1.8 Hz, 1H), 7.35−7.19 (m, 5H), 5.80 (dm, J = 10.1 Hz, 1H), 5.47 (dm, J = 10.1 Hz, 1H), 3.78 (s, 2H), 3.23 (m, 1H), 2.90 (dd, J = 11.0, 6.6 Hz, 1H), 2.44 (m, 2H), 2.10 (br dm, J = 16.7 Hz, 1H), 1.89 (m, 2H), 1.75 (m, 1H), 1.11 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 140.8, 128.7, 128.3, 128.1, 126.6, 125.4, 58.7, 56.1, 52.1, 39.6, 31.8, 26.5, 21.7; IR (CH_2Cl_2) 3026, 2962, 2920, 1699 cm^{-1}; MS (DEI) m/z 244 (MH^+, 6) 187 (17), 186 (100), 92 (10), 91 (98), 65 (9); HRMS calcd for $C_{16}H_{22}NO$ (MH^+) 244.1701, found 244.1691; $[\alpha]^{23}_D$ = +12.1 (c 0.41, CH_2Cl_2).

(2*R*,6*S*)-1-Benzyl-6-[(3,3-dimethoxy)propyl]-2-methyl-1,2,3,6-tetrahydropyridine (24). Trimethyl orthoformate (2.5 mL) and *p*-toluene sulfonic acid monohydrate (198 mg, 1.0 mmol) were added to a stirred solution of aldehyde **23** (170 mg, 0.693 mmol) in MeOH (12 mL). The resulting solution was stirred for 19 h at rt, and then triethylamine (0.28 mL, 2.0 mmol) was added. Concentration gave the crude product (473 mg) as dark brown oil. Flash chromatography (5:1 hexanes/ethyl acetate, 2% triethylamine) afforded acetal **24** (180 mg, 90%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, J = 7.0 Hz, 2H), 7.28 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 5.75 (dm, J = 10.5 Hz, 1H), 5.56 (dq, J = 10.1, 2.2, 1.8 Hz, 1H), 4.19 (t, J = 5.3 Hz, 1H), 3.78 (s, 2H), 3.24 (s, 3H), 3.23 (s, 3H), 3.13 (m, J = 2.6 Hz, 1H), 2.87 (m, 1H), 2.09 (dm, J = 17.1 Hz, 1H), 1.89 (dm, J = 17.1 Hz, 1H), 1.70−1.46 (m, 4H), 1.06 (d, J = 6.59 Hz, 3H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 141.9, 129.3, 128.0, 126.3, 124.5, 104.8, 60.0, 56.3, 52.7, 52.6, 52.5, 32.0, 29.1, 28.2, 21.7; IR (CH_2Cl_2) 2961, 2933, 1454, 1438, 1127 cm^{-1}; MS (DCI/NH_3) m/z 290 (MH^+, 100), 258 (15), 186 (7); HRMS calcd for $C_{18}H_{28}NO_2$ (MH^+) 290.2120, found 290.2126; $[\alpha]^{23}_D$ = +37.2 (c 0.4, CH_2Cl_2).

(2*R*,6*R*)-2-[(3,3-Dimethoxy)propyl]-6-methylpiperidine (25). A solution of tetrahydropyridine **24** (22 mg, 0.088 mmol) and 20% $Pd(OH)_2$ on carbon (6.2 mg, 0.0088 mmol) in MeOH (4 mL) was attached to a Parr hydrogenator and shaken for 15 h under an atmosphere of H_2 (35 psi) at 50 °C. The resulting suspension was filtered and concentrated to give crude product as pale yellow oil (18 mg). Flash chromatography (55:35:10 hexanes/ethyl acetate/MeOH, 2% triethylamine) afforded piperidine **25** (15 mg, 87%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (t, J = 5.3 Hz, 1H), 3.31 (s, 6H), 2.62 (m, 1H), 2.49 (m, 1H), 1.81−1.25 (m, 9H), 1.05 (d, J = 6.6 Hz, 3H), 0.99 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.6, 56.8, 52.7, 52.4, 34.3, 32.2, 32.1, 29.0, 24.8, 23.0; IR (CH_2Cl_2) 2929, 1464, 1377, 1057, 704 cm^{-1}; MS (DCI/NH_3) m/z 202 (MH^+, 26), 170 (44), 139 (10), 138 (100), 98 (27), 56 (5), 48 (6); HRMS calcd for $C_{11}H_{24}NO_2$ (MH^+) 202.1807, found 202.1807; $[\alpha]^{23}_D$ = +8.5 (c 6.7, CH_2Cl_2).

(3*S*,5*R*,8a*R*)-5-Methyloctahydroindolizine-3-carbonitrile (26). KCN (38.8 mg, 0.596 mmol) was added to a stirred solution of acetal **25** (30.0 mg, 0.149 mmol) in 1 N HCl (5 mL) at rt. The resulting solution was stirred for 16 h, then the pH was adjusted to 14 (pH paper) with 30% KOH (w/v). The aqueous layer was extracted with $CHCl_3$ (3 × 5 mL) and CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (K_2CO_3) and concentrated to give crude product (27.3 mg) as yellow oil. Flash chromatography (5:1 hexanes/ethyl acetate, 2% triethylamine) afforded nitrile **26** (21.9 mg, 89%) as a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (d, J = 8.3 Hz, 1H), 2.47 (m, 1H), 2.35 (m, 1H), 2.16 (m, 1H), 1.99 (m, 2H), 1.87 (dm, J = 11.8 Hz, 1H), 1.72 (m, 2H), 1.50−1.17 (m, 4H), 1.12 (d, J = 6.1 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 117.7, 61.1, 54.6, 51.4, 33.7, 31.2, 29.1, 26.7, 24.0, 20.5; IR (CH_2Cl_2) 2935, 2801, 2221, 1460, cm^{-1}; MS (EI, 20 eV) m/z 164 (M^+, 11), 163 (9), 150 (13), 149 (100), 122 (15), 121 (9); HRMS calcd for $C_{10}H_{16}N_2$ (M^+) 164.1313, found 164.1315; $[\alpha]^{22}_D$ = −112.5 (c 1.54, CH_2Cl_2).

(3*R*,5*R*,8a*R*)-3-Butyl-5-methyloctahydroindolizine (1) [(−)-Indolizidine 195B]. *n*-BuMgBr (0.350 mL of 1.0 M solution in diethyl ether, 0.347 mmol) was added to a stirred 0 °C solution of nitrile **26** (19.0 mg, 0.116 mmol) in diethyl ether (5 mL). The reaction mixture was allowed to warm to rt. After stirring for 15 h, saturated NH_4Cl (5 mL) was added at 0 °C and the organic layer was separated. NaF (0.1 g in 1 mL of H_2O) was added to the aqueous layer, and Mg_2F was removed by filtration. The aqueous layer was then basified with 30% KOH (pH <14) and extracted with ethyl acetate to give crude product (34.3 mg) as yellow oil. Flash chromatography (55:35:10 hexanes/ethyl acetate/*i*-PrOH, 2% Et_3N) afforded a mixture of the C-3 epimer (14.1 mg, 62%) in 2:1 diastereomer ratio by ^{1}H NMR as pale yellow oil. Preparative TLC (Al_2O_3, 3:1 hexane/CH_2Cl_2) of the mixture afforded **1** [(−)-indolizidine 195B] (8.4 mg, 37%) as clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.37−3.25 (m, 1H), 2.61−2.36 (m, 2H), 1.94−1.02 [m, 16H, 1.12 (d, J = 5.7 Hz, 3H)], 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 60.2, 58.9, 51.9, 34.5, 32.4, 30.0, 29.4, 26.3, 24.9, 24.8, 23.0, 20.4, 14.2; IR (neat) 2924, 1456 cm^{-1}; MS (EI, 20 eV) m/z 195 (M^+, 5), 139 (25), 138 (100); HRMS calcd for $C_{13}H_{25}N$ (M^+) 195.1987, found 195.1981; $[\alpha]^{23}_D$ = −96 (c 0.19, MeOH).

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **9**, **10**, **11**, **12**, **15**, **16**, **17**, **18**, **20**, **21**, **22**, **23**, **24**, **25**, and **26**, determination of diastereomer ratio of **15**, **16**, and **1**, decoupling study of **18**, and natural product comparison of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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