Desymmetrization of Benzoic Acid in the Context of the Asymmetric Birch Reduction−Alkylation Protocol. Asymmetric Total Syntheses of (−)-Eburnamonine and (−)-Aspidospermidine

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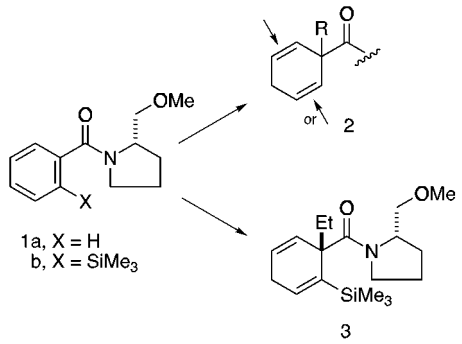
Received April 28, 1997[⊗]

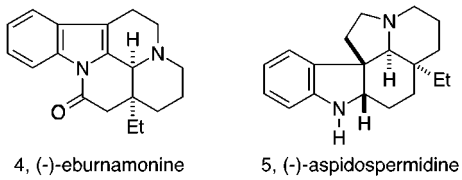
The highly diastereoselective potassium in ammonia reduction−ethylation (EtI) of the chiral 2-(trimethylsilyl)benzamide **1b** to give 1,4-cyclohexadiene **3** is the key step in asymmetric syntheses of (−)-eburnamonine (**4**) and (−)-aspidospermidine (**5**). Cyclohexadiene **3** was converted to cyclohexanone **7**, which provided the trimethylsilyl-substituted butyrolactone **9** utilized for the synthesis of **4** and butyrolactone **13** required for the synthesis of **5**. The preparation of **9** depended upon the completely regioselective silicon-directed Baeyer−Villiger oxidation **7** → **8**; Baeyer−Villiger oxidation of the cyclohexenone **10** also was regioselective to give the desired enol lactone **11** in 92% yield. Remarkable diastereoselectivity was observed for the kinetically controlled cyclization of the acyl imminium ion derived from the vinyl-substituted carboxaldehyde **16b**; treatment of **16b** with 5 equiv of CF_3CO_2H in CH_2Cl_2 at −55 °C gave an 18:1 mixture of **17** and its C(3) β-epimer in 93% yield. The oxidation of alcohol **18** containing sensitive indole and piperidine rings was best carried out with tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide to give (−)-eburnamonine (**4**) in 97% yield. The asymmetric synthesis of (−)-aspidospermidine **5** involved the conversion of butyrolactone **13** to the hydroxylactam **22**, the Harley-Mason cyclization of **22** to **23**, and reduction of **23** with $LiAlH_4$.

A structural requirement for the asymmetric Birch reduction−alkylation of chiral benzamides is that a substituent must be present at C(2) of the benzoyl moiety to provide for desymmetrization of the six-membered ring. Synthetically useful methodology has been developed for substituted benzamides of type **1**, wherein X = alkyl, aryl, and alkoxy.[1] However, for certain synthetic applications, it would be desirable to utilize benzoic acid itself. Conversion of benzoic acid or a derivative such as **1a** to **2** would set the stage for desymmetrization of the prochiral 1,4-cyclohexadiene ring system by regioselective olefin addition reactions.[2,3] We have selected for study an alternative solution wherein the 2-trimethylsilyl substituent in benzamide **1b** represents a proton equivalence and stereochemical control element during Birch reduction−alkylation.

We can now report that 2-(trimethylsilyl)benzamide **1b** undergoes efficient and highly diastereoselective Birch reduction−alkylation (*e.g.*, **1b** → **3**) and that subsequent synthetic conversions modulated by the trimethylsilyl substituent effectively provides the desired desymmetrization of benzoic acid. Furthermore, the conversion of **1b** to **3** represents the key step in asymmetric syntheses



of the eburnamine-vincamine alkaloid[4] (−)-eburnamonine (**4**)[5] and the *Aspidosperma* alkaloid[6] (−)-aspidospermidine (**5**).[7]



Results and Discussion

The 2-(trimethylsilyl)benzamide **1b** was prepared from 2-(trimethylsilyl)benzoic acid[8] and (*S*)-prolinol in 88% yield. Birch reduction−ethylation of **1b** gave the desired 1,4-cyclohexadiene **3**, and bis-allylic oxidation of **3** deliv-

[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1997.

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(2) For the asymmetric synthesis of decalin and hydrindan derivatives by palladium-catalyzed cyclization of prochiral 3,3-disubstituted-1,4-cyclohexadienes derived from benzoic acid, see: (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738−4739. (b) Sato, Y.; Watanabe, S.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2589−2592. (c) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593−2596. (d) Takemoto, T.; Nishikimi, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 3527−3530. (e) Takemoto, T.; Nishikimi, Y.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 3531−3532. (f) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 757−766.

(3) For the asymmetric halolactonizations (30−42% ee) of 1,4-cyclohexadienes related to **2** but with the (*S*)-2,5-dimethylpyrrolidine derived amide, see: Hart, D. J.; Huang, H.-C.; Krishnamurthy, R.; Schwartz, T. *J. Am. Chem. Soc.* **1989**, *111*, 7507−7519.

(4) Lounasmaa, M.; Toluanen, A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1992; Vol. 42, pp 1−116.

(5) For syntheses of eburnamonine, see: Kaufman, M. D.; Grieco, P. A. *J. Org. Chem.* **1994**, *59*, 7197−7198 and references cited therein.

(6) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1979; Vol. 17, pp 199−384.

(7) For syntheses of aspidospermidine, see: Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517−521 and references cited therein.

(8) Schultz, A. G.; Antoulinakis, E. G. *J. Org. Chem.* **1996**, *61*, 4555−4559.

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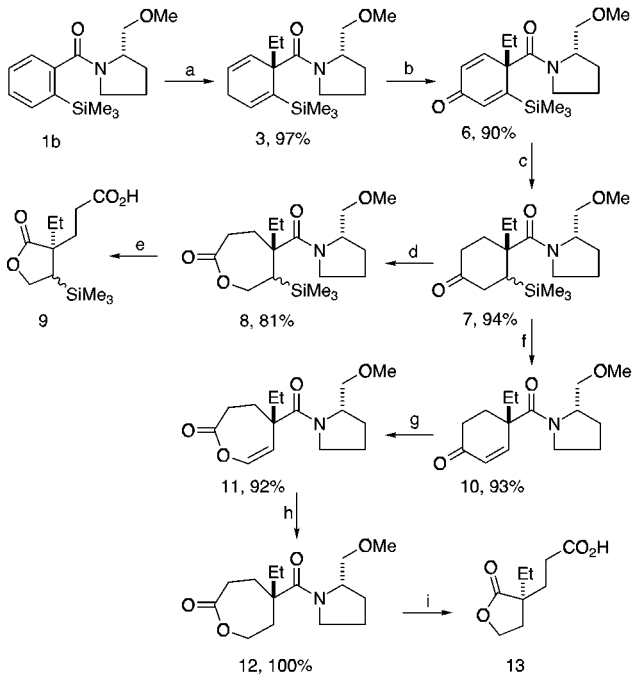
Scheme 1[a]



[a] Reaction conditions: (a) K, NH_3, *tert*-BuOH, THF, −78 °C; LiBr; piperylene; EtI, −78 °C; (b) PDC (cat.), Celite, *tert*-BuOOH, PhH; (c) H_2, 10% Pd/C, EtOAc (63 psi); (d) *m*-CPBA, CH_2Cl_2; (e) TsOH, PhH/H_2O, reflux; (f) $CuCl_2$, DMF, 60 °C; (g) TFAA, UHP, Na_2HPO_4, CH_2Cl_2; (h) H_2, 5% Rh/C, THF; (i) TsOH, PhH/H_2O, reflux.

ered the 3-(trimethylsilyl)-2,5-cyclohexadien-1-one **6** in 87% overall yield from **1b** (Scheme 1). Diastereomeric purity of **6** was determined to be >100:1 by GC comparison to a ∼1:1 mixture of diastereomers prepared as described in the Experimental Section.

Hydrogenation of **6** with 10% Pd/C in EtOAc gave cyclohexanone **7** as a 2:1 mixture of diastereomers at C(3). At this juncture, **7** was converted to the trimethylsilyl-substituted butyrolactone **9**, utilized for the synthesis of (−)-eburnamonine (**4**), and butyrolactone **13**, required for the synthesis of (−)-aspidospermidine (**5**); both transformations depended upon regioselective Baeyer−Villiger oxidations.

The silicon-directed Baeyer−Villiger oxidation, introduced by Hudrlik and co-workers,[9] provides an outstanding solution to regiocontrol for scission of the C(1)−C(2) bond in **7** to give the caprolactone derivative **8** in 81% isolated yield. A single crystal X-ray structure determination for the major C(6)-diastereomer of **8** established the absolute configuration at C(5); details of this characterization study along with other examples of the Birch reduction−alkylation of **1b** will be published elsewhere. It should be noted that the remote control of the Baeyer−Villiger oxidation exerted by the trimethylsilyl substituent offers a strategic complement to the more traditional regiocontrol by electron-releasing substituents positioned α to the cyclohexanone carbonyl group.[10]

Treatment of **8** with *p*-toluenesulfonic acid in a refluxing mixture of benzene/H_2O gave the butyrolactone carboxylic acid **9** in a total of five steps from the chiral benzamide **1b**. In contrast to other butyrolactone carboxylic acids that we have prepared,[10] **9** was difficult to purify by chromatographic techniques; however, it was of sufficient purity to be used directly in a subsequent condensation with tryptamine.

A modification[11] of the procedure for oxidative elimination of β-trimethylsilyl ketones described by Fleming and co-workers[12] enabled the conversion of **7** to the 4,4-disubstituted-2-cyclohexen-1-one **10** in 93% yield. This efficient preparation of chiral 2-cyclohexen-1-ones is expected to have substantial value in asymmetric synthesis. We will report additional applications of this chemistry in due course.

The vinyl group of an α,β-unsaturated primary alkyl ketone shows preferential migration in the Baeyer−Villiger oxidation.[13] The most efficient method for oxidation of cyclohexenone **10** involved treatment of **10** with trifluoroperacetic acid generated from the reaction of trifluoroacetic anhydride and the urea hydrogen peroxide complex[14] to give the desired enol lactone **11** in 92% yield. Hydrogenation of **11** provided the caprolactone **12**, and the usual hydrolytic removal of the chiral auxiliary gave the butyrolactone carboxylic acid **13**.

Asymmetric Synthesis of (−)-Eburnamonine (4). Butyrolactone carboxylic acid **9** was coupled to tryptamine to give the secondary amide **14** in 71% overall yield from **8** (Scheme 2). In an earlier synthesis of (+)-apovincamine by way of an intermediate with structure similar to **14**, we found it necessary to protect the indole NH group because of difficulties associated with a subsequent Swern oxidation. In this work, we were able to avoid protection by utilization of a more chemoselective method of oxidation. Thus, **14** was reduced to diol **15** after which **15** was subjected to KH-induced elimination of Me_3SiOH to give alkene **16a**; oxidation of **16a** with a catalytic quantity of tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide in CH_2Cl_2[15] gave carboxaldehyde **16b** in 50% overall yield from **14**.

The acid-catalyzed cyclization of carboxaldehyde **16b** carried out with 5 equiv of CF_3CO_2H in CH_2Cl_2 at −55 °C gave an 18:1 mixture of **17** and its C(3) β-epimer in 93% yield. Chromatography on silica gel afforded the pure α-epimer **17** in 88% yield. Cyclization of **16b** at higher reaction temperatures resulted in somewhat less selectivity for formation of the α-epimer **17** (*e.g.*, 10:1 at 0 °C and 7:1 at 20 °C). Control experiments with **17** and the β-epimer demonstrated that they do not interconvert at 20 °C; thus, the synthetically desirable product ratios for cyclization of **16b** in CF_3CO_2H are the result of kinetic control.[16]

The high diastereoselectivity for the cyclization of **16b** is remarkable considering the similarity in size of the ethyl and vinyl substituents; the conformational free energies ($-\Delta G°$) for these groups are as follows: ethyl, 1.8 kcal/mol[17a] and vinyl, 1.7 kcal/mol.[17b] To evaluate this

(9) The silicon-directed Baeyer−Villiger oxidation of 3-(trimethylsilyl)cyclohexanone with MCPBA in CH_2Cl_2/Na_2HPO_4 buffer has been reported to give 5-(trimethylsilyl)caprolactone in 99% yield, see: Hudrlik, P. F.; Hudrlik, A. M.; Nagendrappa, G.; Yimenu, T.; Zellers, E. T.; Chin, E. *J. Am. Chem. Soc.* **1980**, *102*, 6894−6896.

(10) (a) Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611−6614. (b) Schultz, A. G.; Malachowski, W. P.; Pan, Y. *J. Org. Chem.* **1997**, *62*, 1223−1229.

(11) Asaoka, M.; Shima, K.; Takei, H. *J. Chem. Soc., Chem. Commun.* **1988**, 430−431.

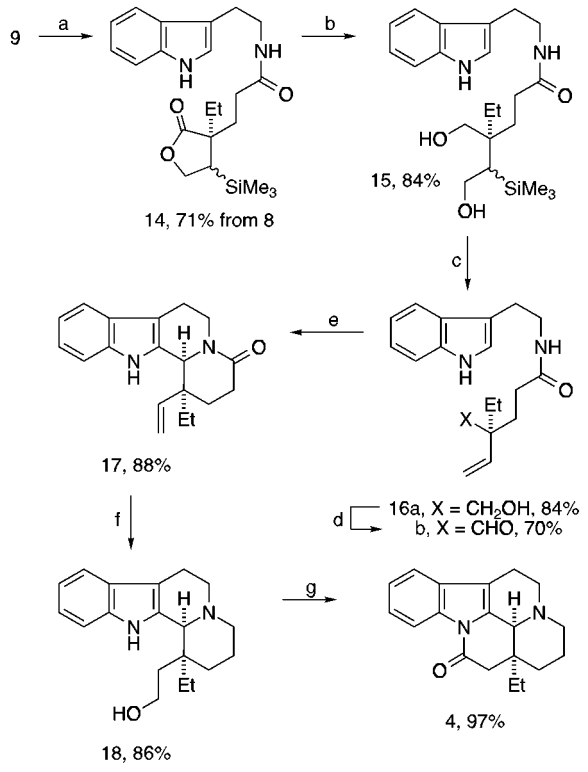
(12) (a) Fleming, I.; Goldhill, J. *J. Chem. Soc., Chem. Commun.* **1978**, 176−177. (b) Ager, D. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1978**, 177−178. (c) Fleming, I.; Percival, A. *J. Chem. Soc., Chem. Commun.* **1978**, 178−180. (d) Fleming, I.; Perry, D. A. *Tetrahedron* **1981**, *37*, 4027−4034.

(13) (a) Bocecken, M.; Jacobs, R. *Recl. Trav. Chim.* **1936**, *55*, 804−814. (b) Krafft, G.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459−5466.

(14) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett.* **1990**, 533−535.

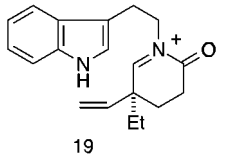
(15) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

Scheme 2[a]



[a] Reaction conditions: (a) tryptamine, $(PhO)_2P(O)N_3$, Et_3N, THF; (b) $LiBH_4$, MeOH, THF; (c) KH, THF; (d) TPAP (cat.), NMO, CH_2Cl_2; (e) CF_3CO_2H, CH_2Cl_2, −55 °C; (f) BH_3·THF, 0 °C → rt; H_2O_2/NaOH; (g) TPAP (cat.), NMO, CH_2Cl_2.

result in the context of extensive prior investigation by several research groups, it should be noted that product distributions for cyclizations analogous to that described for **16b** have been reported to be near 1:1[18] with one important exception. In pioneering work, Barton and Harley-Mason described the formation of a single diastereomer from cyclization of an analogue of **16b** in which the vinyl group is replaced with $CH_2CH{=}CH_2$.[19] Although the literature result was reported with little experimental detail, it does provide some support for the suggestion that electronic effects are responsible for the diastereoselectivity of cyclization of **16b**. Interactions between π-bonds of the vinyl substituent, the indole ring, and the acyl iminium ion in the presumed intermediate for cyclization, **19**, may contribute to a selection for the α-epimer **17**.[20]

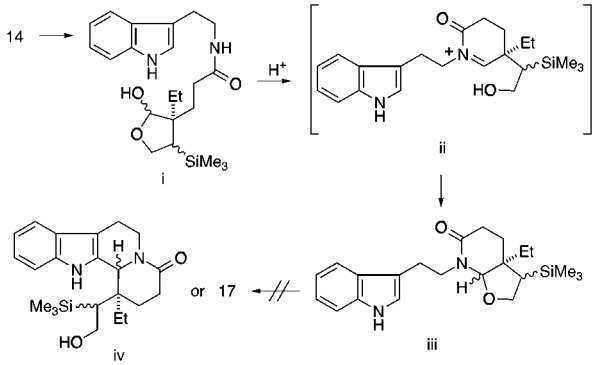


Reaction of **17** with BH_3·THF followed by H_2O_2/NaOH provided the previously reported[7] amino alcohol **18** in 86% yield. Although we were not able to convert **18** to (−)-eburnamonine (**4**) by the published procedure (BF_3·Et_2O/PCC),[7] oxidation of **18** with a catalytic amount of tetrapropylammonium perruthenate and *N*-methylmorpholine *N*-oxide gave crystalline **4** in 97% yield (mp 173−175 °C). The ^1H NMR, ^{13}C NMR, and IR spectra of the synthetic material were identical to those of a sample of commercial (−)-eburnamonine (mp 174−176 °C; mixed mp 173−176 °C). The synthesis of **4** required 12 steps from the chiral benzamide **1b** and was carried out with an overall yield of 17%.

Asymmetric Synthesis of (−)-Aspidospermidine (5). In 1967, Harley-Mason and Kaplan reported the first synthesis of (+)-aspidospermidine by the acid-catalyzed cyclization-rearrangement of racemic hydroxy lactam **22**.[21] An asymmetric synthesis of **5** involving this same cyclization−rearrangement was developed by Fuji and co-workers.[7] We attempted but were not able to convert the vinyl lactam **17** to **22**, and application of the Harley-Mason type of cyclization−rearrangement to the hydroxy amine **18** was not successful. For these reasons, we developed an asymmetric synthesis of (−)-aspidospermidine (**5**) from the butyrolactone carboxylic acid **13** (Scheme 3).

Butyrolactone carboxylic acid **13** was converted to amide **20** and reduction of **20** with diisobutylaluminum hydride (DIBAH) in CH_2Cl_2 gave the lactol **21**. Cyclization of **21** in refluxing acetic acid[22] followed by a basic hydrolysis of the intermediate acetate derivative provided the hydroxy lactam **22** as a 1:1 mixture of the C(3) α- and β-epimers in 65% yield. The epimers of **22** were separated by repeated chromatography on silica gel and were fully characterized; however, separation was not required for completion of the synthesis of **5**.

(16) We found it necessary to utilize the olefinic carboxaldehyde **16b** rather than the lactol **i**, obtained by reduction of **14** with diisobutylaluminum hydride (CH_2Cl_2, −78 °C, 86% yield) because **i** underwent cyclization to the bicyclic lactam **iii** in refluxing acetic acid (95% yield) presumably by way of the intermediate acyl iminium ion **ii**. The conversion of **iii** to **iv** or **17** was attempted but failed even in refluxing CF_3CO_2H.



(17) (a) Allinger, N. L.; Freiberg, L. A. *J. Org. Chem.* **1966**, *31*, 894−897. (b) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959−1962.

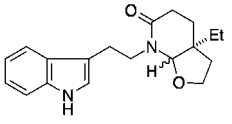
(18) For example, cyclization in refluxing acetic acid of an analogue of **16b** in which the vinyl group is replaced with CH_2CH_2OH has been reported to give a 1:1 mixture of the C(3) α- and β-epimers; see refs 7 and 22.

(19) Barton, J. E. D.; Harley-Mason, J. *J. Chem. Soc., Chem. Commun.* **1965**, 298−299.

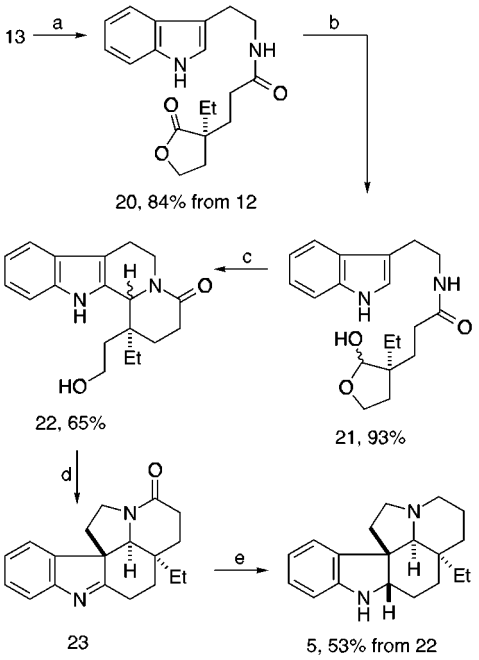
(20) For discussions of mechanisms for cyclization and isomerization in Pictet−Spengler type condensations, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842. (b) Cox, E. D.; Li, J.; Hamaker, L. K.; Yu, P.; Cook, J. M. *J. Chem. Soc., Chem. Commun.* **1996**, 2477−2478.

(21) (a) Harley-Mason, J.; Kaplan, M. *J. Chem. Soc., Chem. Commun.* **1967**, 915−916. (b) For a discussion of the mechanism of the Harley-Mason cyclization−rearrangement, see: Heathcock, C. H.; Norman, M. H.; Dickman, D. A. *J. Org. Chem.* **1990**, *55*, 798−811.

(22) Under these reaction conditions, a 20% yield of the bicyclic lactam **v** also was obtained. It was found that **v** underwent decomposition during prolonged exposure to refluxing acetic acid rather than conversion to the acetate derivative of hydroxy lactam **22**.



Scheme 3[a]



[a] Reaction conditions: (a) tryptamine, $(PhO)_2P(O)N_3$, Et_3N, THF; (b) DIBAH, CH_2Cl_2, −78 °C; (c) HOAC, reflux; 20% NaOH/MeOH; (d) 40% H_2SO_4, reflux; (e) $LiAlH_4$, THF, reflux.

The conversion of **22** to (−)-aspidospermidine (**5**) was best carried out as described by Harley-Mason[21] in 40% H_2SO_4 at 100−110 °C for 1.5 h to give **23**; immediate reduction of **23** with $LiAlH_4$ and chromatography on silica gel gave crystalline **5** in 53% yield from **22** (mp 114−116 °C). It should be noted that this procedure for cyclization−rearrangement of **22** gave lactam imine **23** free of the eburnamonine-type lactams that have been reported by Fuji and co-workers[7] for cyclization of **22** with $BF_3{\cdot}Et_2O$ at 100−110 °C. Synthetic **5** compared favorably (see Experimental Section) with a sample of **5** prepared from (−)-vincadifformine by literature procedures.[23,24] The synthesis of **5** required 12 steps from the chiral benzamide **1b** and was carried out with an overall yield of 19%.

Conclusion

Important features of the asymmetric syntheses of **4** and **5** include excellent control of absolute configuration at the key quaternary center at C(16) in **4** and C(5) in **5** by way of Birch reduction−alkylation of the 2-(trimethylsilyl)benzamide **1b** to give **3** (97% as a >100:1 mixture of diastereomers); complete regioselectivity for the silicon-directed Baeyer−Villiger oxidation of **7** to give **8** and the Baeyer−Villiger oxidation of the 4,4-disubstituted-2-cyclohexen-1-one **10**; remarkable diastereoselectivity for cyclization of the acyl imminium ion derived from the vinyl-substituted carboxaldehyde **16b**; the efficient oxidation of alcohol **18** containing sensitive indole and piperidine rings with tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide. The 2-trimethylsilyl group has been demonstrated to be an effective substituent for desymmetrization of benzoic acid in the asymmetric Birch reduction−alkylation protocol.

(23) (a) Smith, G. F.; Wahid, M. A. *J. Chem. Soc.* **1963**, 4002−4004. (b) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750−4757.

(24) For the racemization of (−)-vincadifformine, see: Takano, S.; Kijima, A.; Sugihara, T.; Satoh, S.; Ogasawara, K. *Chem. Lett.* **1989**, 87−88.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were obtained at 500 and 125 MHz, respectively, and chloroform was used as the internal standard. Chemical ionization mass spectra were obtained on a Hewlett-Packard 5987A GC-MS system (isobutane). High resolution mass spectra were obtained from the University of Illinois facilities at Urbana−Champaign. Thin-layer chromatography was performed with Merck Kieselgel 60 F-254 and Whatman Linear-K silica gel precoated glass plates. Melting points are reported without correction. Elemental analyses were obtained from Atlantic Microlab, Inc., Norcross, GA. Analytical GC analyses were performed on a Hewlett-Packard 5710A gas chromatograph with a flame ionization detector (300 °C) fitted with a 6 ft × 1/8 in. stainless steel column filled with 3% OV-17 on chromosorb whp 80/100 mesh (gas pressures: N_2, 40 psi; air, 24 psi; H_2, 24 psi). Peak areas were measured with a HP-3394 integrator. Methylene chloride, methyl alcohol, *tert*-butyl alcohol, and triethylamine were dried over CaH_2 and distilled. Tetrahydrofuran was dried over sodium/benzophenone ketyl and distilled. All other reagents were used as purchased. Reactions requiring anhydrous conditions were performed under a nitrogen atmosphere. Baker silica gel (40 μm) was used for flash column chromatographies.

2-(Trimethylsilyl)benzamide (1b). To a solution of 2-(trimethylsilyl)benzoic acid[8] (9.90 g, 51.0 mmol) in CH_2Cl_2 (300 mL) at 0 °C was added $(COCl)_2$ (4.77 mL, 53.6 mmol) followed by DMF (0.20 mL, 2.5 mmol). The mixture was allowed to stir at room temperature for 5 h and then cooled to −40 °C; a solution of (*S*)-prolinol (5.67 g, 56.1 mmol) in CH_2Cl_2 (20 mL) was added followed by Et_3N (14.3 mL, 102 mmol). The mixture was slowly warmed to room temperature and then stirred overnight. The mixture was washed with water and brine, and then the organic layer was dried and concentrated. The residue was dissolved in 100 mL of THF and then cooled to 0 °C and treated with NaH (3.06 g, 76.5 mmol). After 30 min at room temperature, the mixture was cooled with an ice bath, and MeI (9.53 mL, 153 mmol) was added. The mixture was stirred at 0 °C for 30 min and room temperature for 30 min and then refluxed for 5 h. After cooling to 0 °C, the reaction was quenched with saturated NH_4Cl. The solution was extracted with EtOAc and then the organic layer was dried and concentrated. The residue was chromatographed to afford **1b** (13.07 g, 88%) as a pale yellow solid (mp 67.0−68.5 °C). $[\alpha]^{20}_D$ −118.5° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3006, 1622, 1434, 1413 cm^{-1}. R_f = 0.61 (1:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 7.58 (1 H, m), 7.33 (2 H, m), 7.24 (2 H, m), 4.36 (1 H, m), 3.66 (2 H, m), 3.39 (3 H, s), 3.28 (1 H, m), 3.18 (1 H, m), 2.08−1.88 (3 H, m), 1.70 (1 H, m), 0.27 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 171.5, 143.4, 137.4, 134.8, 128.4, 128.0, 126.0, 72.3, 59.0, 56.3, 50.2, 27.6, 24.5, −0.5. CI-MS, *m/z* (relative intensity) 292 ($M^+ + 1$, 100%). Anal. Calcd for $C_{16}H_{25}NO_2Si$: C, 65.93; H, 8.65. Found: C, 66.03; H, 8.60.

(2′*S*,6*R*)-6-Ethyl-1-(trimethylsilyl)-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (3). To a stirred solution of **1b** (12.93 g, 44.4 mmol) in dry THF (50 mL), *tert*-BuOH (4.25 mL, 44.4 mmol), and NH_3 (1800 mL) at −78 °C was added potassium (5.72 g, 146 mmol) in small pieces. The resulting dark blue solution was stirred for 10 min, and then LiBr (5.85 g, 66.6 mmol) was added in one portion. After 10 min, piperylene was added dropwise until the blue color disappeared. EtI (17.8 mL, 222 mmol) was added, and the resulting solution was stirred for 2 h at −78 °C. After the addition of NH_4Cl (10 g), the mixture was slowly warmed to room temperature while the NH_3 was removed with a stream of N_2. The mixture was extracted with CH_2Cl_2 (200 mL) and washed with water (20 mL) followed by saturated sodium thiosulfate (10 mL). The organic layer was dried and concentrated to give **3** (13.84 g, 97%) as a clear oil. $[\alpha]^{20}_D$ −41.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3017, 2969, 1616. R_f = 0.46 (hex/EtOAc = 4/1). ^1H NMR ($CDCl_3$) δ 6.29−6.18 (1 H, m), 5.88−5.85 (1 H, m), 5.34−5.28 (1 H, m), 4.25 (1 H, m), 3.60 (1 H, m), 3.41 (2 H, m), 3.33 (3 H, s), 3.32 (1 H, m), 2.65 (2 H, m), 1.96−1.65 (5 H, m), 1.48 (1 H, m), 0.96−0.65 (3 H, m), 0.05 (9 H, m). ^{13}C NMR ($CDCl_3$) δ 172.4, 141.6, 137.0, 128.4, 124.1, 72.0, 58.8, 57.9, 51.7, 46.7, 38.0, 30.1, 26.5, 24.6, 7.7, −0.2.

CI-MS, *m/z* (relative intensity) 322 ($M^+ + 1$, 100%). CI-HRMS Calcd for $C_{18}H_{31}NO_2Si$: ($M^+ + 1$) 322.2214. Found: 322.2213.

(2′*S*,4*R*)-4-Ethyl-3-(trimethylsilyl)-4-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-2,5-cyclohexadien-1-one (6). To a solution of **3** (13.84 g, 43.11 mmol) in benzene (300 mL) were added PDC (4.97 g, 12.9 mmol), Celite (14 g), and *tert*-BuOOH (9.58 mL, 86.2 mmol). The mixture was stirred for 12 h and then filtered through a small pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was chromatographed to provide **6** (13.00 g, 90%) as a yellow oil. $[\alpha]^{20}_D$ +4.0° (*c* 1.1, $CHCl_3$). IR ($CHCl_3$) 3011, 1630, 1528 cm^{-1}. R_f = 0.24 (2:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 6.79 (2 H, m), 6.50 (1 H, dd, J = 10.0, 1.7 Hz), 4.21 (1 H, m), 3.51 (1 H, m), 3.43 (1 H, m) 3.32 (3 H, s), 3.12 (2 H, m), 2.23 (1 H, m), 2.09 (1 H, m), 1.85−1.65 (4 H, m), 0.56 (3 H, t, J = 7.6 Hz), 0.17 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 183.9, 167.4, 163.7, 152.2, 140.2, 130.3, 71.7, 59.0, 58.7, 57.9, 46.0, 29.0, 26.6, 24.5, 7.3, −1.0. CI-MS, *m/z* (relative intensity) 336 ($M^+ + 1$, 5%). Anal. Calcd for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71. Found: C, 64.22; H, 8.66. The diastereomeric purity of **6** was determined by direct GC comparison to a 1:1 mixture of diastereomers prepared by Birch reductive alkylation of methyl 2-(trimethylsilyl)benzoate with ethyl iodide, saponification, coupling of the resulting cyclohexadienecarboxylic acid to L-prolinol (methyl ether),[25] and oxidation to the dienone. GC (200 → 250 °C, programming rate 1 °C/min): diastereomer ratio > 100:1, t_R (major isomer) = 16.55 min, t_R (minor isomer) = 19.93 min.

(2′*S*,4*R*)-4-Ethyl-3-(trimethylsilyl)-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1-cyclohexanone (7). A mixture of **6** (5.66 g, 16.9 mmol) and 10% Pd/C (3.58 g, 1.69 mmol) in EtOAc (200 mL) was shaken under H_2 (63 psi) for 5 h. The mixture was then filtered through a small pad of Celite. Concentration of the filtrate under reduced pressure afforded an approximately 2:1 mixture of diasteromers **7** as a colorless oil (5.38 g, 94%). IR ($CHCl_3$) 2972, 1703, 1610 cm^{-1}. R_f = 0.25 (2:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 4.38 (1 H, m), 3.67−3.38 (4 H, m), 3.25 (3 H, s), 2.88−1.42 (11 H, m), 1.50 (2 H, m), 0.86 (3 H, m), 0.07 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 174.1, 173.3, 72.2, 58.7, 58.2, 50.8, 48.3, 40.6, 38.9, 33.4, 31.3, 30.3, 26.0, 9.6, 8.4, 0.6. CI-MS, *m/z* (relative intensity) 340 ($M^+ + 1$, 100%). Anal. Calcd for $C_{18}H_{33}NO_3Si$: C, 63.67; H, 9.80. Found: C, 63.48; H, 9.76.

(2′*S*,5*R*)-5-Ethyl-6-(trimethylsilyl)-5-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]oxacycloheptan-2-one (8). To a stirred solution of **7** (3.42 g, 10.1 mmol) in CH_2Cl_2 (80 mL) was added *m*-chloroperbenzoic acid (*m*-CPBA) (4.35 g, 56−87%). The mixture was stirred for 24 h, and then an additional portion of *m*-CPBA (0.87 g) was added; 12 h later the mixture was diluted with CH_2Cl_2 (120 mL) and washed with saturated $NaHCO_3$ followed by saturated sodium thiosulfate. The organic layer was separated, dried, and concentrated. The residue was chromatographed to afford **8** (2.90 g, 81%) as a colorless solid. IR ($CHCl_3$) 2976, 1727, 1612 cm^{-1}. R_f = 0.22 (2:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 4.47−4.30 (2 H, m), 3.60−3.40 (5 H, m), 3.32 (3 H, s), 2.58 (2 H, m), 2.21 (1 H, m), 2.05−1.68 (8 H, m), 0.85 (3 H, t, J = 7.3 Hz), 0.12 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 175.9, 173.8, 76.3, 72.0, 68.3, 59.3, 58.6, 51.5, 47.6, 36.3, 29.6, 27.3, 25.9, 25.0, 8.2, 0.4. CI-MS, *m/z* (relative intensity) 356 ($M^+ + 1$, 100%). Anal. Calcd for $C_{18}H_{33}NO_4Si$: C, 60.81; H, 9.36. Found: C, 60.73; H, 9.31.

(2′*S*,4*S*)-4-Ethyl-4-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-2-cyclohexen-1-one (10). A mixture of **7** (0.62 g, 1.8 mmol) and anhydrous $CuCl_2$ (0.74 g, 5.5 mmol) in DMF (1.8 mL) was heated at 60 °C for 1 h, and then the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (100 mL), washed with brine (10 mL), dried, and evaporated. Chromatography afforded **10** as a pale yellow oil (0.45 g, 93%). $[\alpha]^{20}_D$ −104.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3019, 1672, 1623 cm^{-1}. R_f = 0.24 (1:1 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 7.04 (1 H, d, J = 10.2 Hz), 5.96 (1 H, d, J = 10.3 Hz), 4.32 (1 H, m), 3.56−3.38 (4 H, m), 3.28 (3 H, s), 2.61 (1 H, m), 2.48 (2 H, m), 1.98 (1 H, m), 1.92−1.75 (6 H, m), 0.96 (3 H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 188.6, 170.6, 152.8, 128.4, 71.9, 58.8, 58.4, 49.3, 48.1, 35.0, 33.0, 30.5, 26.3, 25.0, 8.8. CI-MS, *m/z* (relative intensity) 266 ($M^+ + 1$, 100%). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74. Found: C, 67.87; H, 8.71.

(2′*S*,5*S*)-5-Ethyl-5-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]oxa-6-cyclohepten-2-one (11). To a three-neck 250 mL round bottom flask equipped with mechanical stirrer and containing **10** (2.61 g, 9.84 mmol), urea hydrogen peroxide (9.27 g, 98.5 mmol), and Na_2HPO_4 (12.59 g, 88.64 mmol) in 100 mL CH_2Cl_2 at 0 °C was added trifluoroacetic anhydride (3.48 mL, 24.6 mmol). After stirring at room temperature for 4 h, another aliquot of trifluoroacetic anhydride (1.74 mL, 12.3 mmol) was added at 0 °C, and the reaction was allowed to continue at room temperature overnight. The mixture was cooled to 0 °C and quenched with saturated $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried and evaporated. Chromatography gave **11** as a colorless solid (2.54 g, 92%). Mp 70−71 °C. $[\alpha]^{23}_D$ −152.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3024, 2976, 1768, 1623 cm^{-1}. R_f = 0.20 (1:1 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 6.34 (1 H, d, J = 6.4 Hz), 5.42 (1 H, d, J = 6.5 Hz), 4.32 (1 H, m), 3.58 (1 H, m), 3.40 (2 H, m), 3.35 (3 H, s), 3.19 (1 H, m), 2.72 (1 H, m), 2.56 (1 H, m), 1.88 (3 H, m), 1.76 (4 H, m), 1.60 (1 H, m), 0.87 (3 H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 170.1, 167.7, 139.1, 119.0, 71.1, 58.4, 57.9, 48.5, 35.0, 34.7, 31.1, 30.9, 26.3, 25.2, 8.6. CI-MS, *m/z* (relative intensity) 282 ($M^+ + 1$, 100%). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 64.04; H, 8.24. Found: C, 64.22; H, 8.20.

(2′*S*,5*R*)-5-Ethyl-5-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]oxacycloheptan-2-one (12). A flask containing **11** (2.06 g, 7.33 mmol) and 5% Rh on carbon (0.75 g, 0.36 mmol) in 50 mL of anhydrous THF was thoroughly purged with hydrogen and was then fitted with a hydrogen-containing balloon. After the mixture was stirred for 2 h, it was filtered through a small pad of Celite. Concentration of the filtrate under reduced pressure afforded **12** as a colorless oil (2.07 g, 100%). $[\alpha]^{23}_D$ −38.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 1727, 1609 cm^{-1}. R_f = 0.18 (1:1 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 4.42 (2 H, m), 4.36 (1 H, m), 3.58 (2 H, m), 3.44 (2 H, m), 3.32 (3 H, s), 2.77 (1 H, m), 2.62 (2 H, m), 2.51 (1 H, m), 2.12 (1 H, m), 1.85 (3 H, m), 1.68−1.48(4 H, m), 0.86 (3 H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 176.1, 172.1, 76.3, 71.9, 66.3, 58.8, 58.6, 50.2, 47.9, 37.8, 31.4, 30.9, 26.0, 25.5, 8.4. CI-MS, *m/z* (relative intensity) 284 ($M^+ + 1$, 100%). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 63.58; H, 8.89. Found: C, 63.34; H, 8.95.

Amide 14. A mixture of **8** (4.13 g, 11.63 mmol) and *p*-toluenesulfonic acid monohydrate (3.68 g, 17.4 mmol) in benzene (100 mL) and H_2O (14 mL) was refluxed for 12 h. Another portion of PTSA·H_2O (0.73 g, 3.5 mmol) was added, and the mixture was refluxed for 12 h. The aqueous layer was separated and extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried and concentrated to afford acid **9** as a colorless oil which was not purified. To a solution of crude **9** in dry THF (50 mL) at 0 °C were added tryptamine (2.05 g, 12.79 mmol) and Et_3N (3.25 mL, 23.3 mmol). Ten minutes later, diphenylphosphoryl azide (2.84 mL, 12.8 mmol) was added. The mixture was allowed to stir at room temperature overnight, and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with 1 N NaOH (10 mL), water (10 mL), 1 N HCl (10 mL), and brine (10 mL). The organic layer was dried and concentrated. Chromatography gave **14** (3.30 g, 71%) as a white glass. IR ($CHCl_3$) 3478, 3026, 1752, 1665, 1517 cm^{-1}. R_f = 0.35 (1:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 8.05 (1 H, br), 7.61 (1 H, m), 7.38 (1 H, m), 7.21 (1 H, m), 7.13 (1 H, m), 7.05 (1 H, s), 5.52 (1 H, br), 4.46 (1 H, m), 4.36 (1 H, m), 3.52 (2 H, m), 2.96 (2 H, m), 2.25 (1 H, m), 2.17 (1 H, m), 2.01−1.76 (3 H, m), 1.52−1.32 (2 H, m), 0.96−0.82 (3 H, m), 0.14 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 180.5, 172.0, 136.3, 128.2, 127.1, 122.0, 119.3, 118.5, 112.7, 111.2, 67.7, 59.4, 39.5, 31.5, 30.7, 29.7, 27.7, 25.1, 9.2, −1.3. CI-MS, *m/z* (relative intensity) 401 ($M^+ + 1$, 76%). HRMS (CI) Calcd for $C_{22}H_{32}N_2O_3Si$: ($M^+ + H$) 401.2260, Found: 401.2256.

Diol 15. To a solution of **14** (1.97 g, 4.92 mmol) in THF (5 mL) and MeOH (0.1 mL) at 0 °C was added $LiBH_4$ (12.3 mL of 2 M solution in THF, 24.6 mmol). The mixture was stirred at room temperature for 48 h and then cooled to 0 °C and

(25) For details, see: Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828−7841.

quenched with saturated NH_4Cl. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried and concentrated. Flash chromatography of the residue gave **15** (1.67 g, 84%) as a white foam. IR ($CHCl_3$) 3479, 3017, 2969, 1653, 1520 cm^{-1}. R_f = 0.13 (1:2 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 8.08 (1 H, br), 7.60 (1 H, d, J = 7.2 Hz), 7.40−7.05 (3 H, m), 5.60 (3 H, br), 3.84 (2 H, m), 3.61 (2 H, m), 3.46 (1 H, d, J = 12.2 Hz), 3.36 (1 H, d, J = 12.0 Hz), 2.98 (2 H, t, J = 6.9 Hz), 2.09 (2 H, t, J = 7.3 Hz), 1.95 (1 H, m), 1.43 (1 H, m), 1.33 (2 H, m), 1.13 (1 H, m), 0.77 (3 H, m), 0.13 (9 H, s). ^{13}C NMR ($CDCl_3$) δ 173.8, 136.3, 127.2, 122.1, 122.0, 119.4, 118.5, 112.7, 111.2, 67.3, 60.5, 42.8, 39.7, 37.3, 29.6, 26.3, 25.1, 14.1, 7.6, 1.3. CI-MS, *m/z* (relative intensity) 405 (M^+ +1, 7%). CI-HRMS Calcd for $C_{22}H_{36}N_2O_3Si$: (M^+ + 1) 405.2573, Found: 405.2558.

Alkene 16a. A solution of **15** (92 mg, 2.3 mmol) in THF (5 mL) was added to a mixture of KH (2.61 g, 35%, 22.8 mmol) suspended in THF (5 mL) at 0 °C. After the resulting mixture was stirred at room temperature for 3 h, it was poured into saturated NH_4Cl (20 mL) cooled with ice. The solution was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layers were combined, dried, and concentrated. Flash chromatography of the residue provided **16a** (60 mg, 84%) as a colorless oil. $[\alpha]^{23}_D$ −4.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3480, 3019, 1657, 1520 cm^{-1}. R_f = 0.26 (5% CH_2Cl_2 in MeOH). ^1H NMR ($CDCl_3$) δ 8.09 (1 H, br), 7.60 (1 H, d, J = 8.0 Hz), 7.37 (1 H, d, J = 8.1 Hz), 7.21 (1 H, m), 7.13 (1 H, m), 7.04 (1 H, s), 5.53 (1 H, m), 5.51 (2 H, br), 5.14 (1 H, d, J = 10.9 Hz), 4.91 (1 H, d, J = 17.8 Hz), 3.60 (2 H, m), 3.35 (2 H, m), 2.96 (2 H, m), 2.75 (1 H, t, J = 6.4 Hz), 2.08 (2 H, t, J = 7.1 Hz), 1.77 (1 H, m), 1.60 (1 H, m), 1.41 (1 H, m), 1.35 (1 H, m), 0.79 (3 H, t, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$) δ 174.2, 142.7, 136.3, 127.1, 122.1, 121.8, 119.1, 118.4, 114.5, 112.3, 111.3, 64.4, 44.3, 39.8, 30.5, 28.0, 26.9, 25.0, 7.6. CI-MS, *m/z* (relative intensity) 315 (M^+ + 1, 39%). HRMS (CI) Calcd for $C_{19}H_{26}N_2O_2$: (M^+ + 1) 315.2072, Found: 315.2066.

Lactam 17. To a mixture of **16a** (130 mg, 0.41 mmol) and small amount of ground molecular sieves in CH_2Cl_2 (10 mL) at 0 °C was added *N*-methylmorpholine *N*-oxide (54 mg, 0.45 mmol) followed by tetrapropylammonium perruthenate (7 mg, 0.02 mmol) 10 min later. The mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (30 mL), and filtered through a small pad of Celite. The filtrate was washed with saturated Na_2SO_3 (5 mL), brine (5 mL) and saturated $CuSO_4$ (5 mL). The organic layer was dried, concentrated, and chromatographed to afford **16b** (90 mg, 70%) as a colorless oil. IR ($CHCl_3$) 3479, 3015, 1723, 1662, 1519 cm^{-1}; R_f = 0.36 (1:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 9.37 (1 H, s), 8.04 (1 H, br), 7.60 (1 H, d, J = 8.1 Hz), 7.38 (1 H, d, J = 7.3 Hz), 7.21 (1 H, d, J = 7.1 Hz), 7.13 (1 H, m), 7.05 (1 H, s), 5.71 (1 H, m), 5.49 (1 H, br), 5.33 (1 H, dd, J = 11.0, 0.7 Hz), 5.11 (1 H, dd, J = 17.8, 0.7 Hz), 3.59 (2 H, m), 2.97 (2 H, t, J = 6.6 Hz), 2.04 (2 H, m), 1.98 (2 H, m), 1.64 (2 H, m), 0.82 (3 H, t, J = 7.7 Hz). ^{13}C NMR ($CDCl_3$) δ 172.2, 171.1, 136.7, 136.3, 127.2, 122.1, 122.0, 119.4, 118.6, 117.9, 112.8, 111.2, 55.6, 39.6, 31.0, 27.4, 25.8, 25.1, 7.9. CI-MS, *m/z* (relative intensity) 313 (M^+ + 1, 100%). HRMS (CI) Calcd for $C_{19}H_{26}N_2O_2$: (M^+ + 1) 313.1916, Found: 313.1919. Aldehyde **11** readily decomposed at room temperature and, therefore, was used immediately in the next step.

A solution of **16b** (90 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) at −55 °C was treated with CF_3CO_2H (0.11 mL, 1.4 mmol) and then stirred for 10 h and quenched with saturated $NaHCO_3$. The aqueous layer was separated and extracted with CH_2Cl_2 (30 mL). The organic layers were combined, dried, and concentrated. An NMR spectrum of the reaction mixture showed an approximately 18/1 mixture of α/β epimers. The residue was chromatographed to give the major diastereomer **17** (75 mg, 88% yield) as a colorless solid (mp 265.0−267.0 °C). $[\alpha]^{23}_D$ −98.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3453, 3018, 2969, 1632, 1426 cm^{-1}. R_f = 0.34 (1:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 8.36 (1 H, br), 7.48 (1 H, d, J = 7.8 Hz), 7.30 (1 H, dd, J = 8.1, 1.0 Hz), 7.17 (1 H, dt, J = 7.5, 1.0 Hz), 7.10 (1 H, dt, J = 7.5, 1.0 Hz), 6.03 (1 H, dd, J = 17.8, 10.95 Hz), 5.49 (1 H, dd, J = 10.85, 0.80 Hz), 5.26 (1 H, dd, J = 17.95, 0.8 Hz), 4.97 (1 H, m), 4.68 (1 H, s), 3.05 (1 H, m), 2.84 (1 H, dt, J = 12.5, 4.4 Hz), 2.69 (1 H, m), 2.42 (2 H, m), 2.03 (1 H, m), 1.84 (2 H, m), 1.61 (1 H, m), 0.92 (3 H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 170.5, 141.4, 135.2, 132.3, 128.2, 126.5, 122.1, 119.6, 118.1, 116.9, 112.4, 110.9, 110.1, 62.8, 43.2, 43.0, 23.4, 20.6, 7.2. CI-MS, *m/z* (relative intensity) 295 (M^+ + 1, 100%). CI-HRMS Calcd for $C_{19}H_{22}N_2O$: (M^+ + 1) 295.1810, Found: 295.1805.

Amino Alcohol 18. To a solution of **17** (60 mg, 0.20 mmol) in THF (3 mL) at 0 °C was added BH_3·THF (0.92 mL of 1 M solution, 0.92 mmol). After stirring at room temperature for 2 h, the mixture was cooled to 0 °C, and then EtOH (0.36 mL), H_2O (0.14 mL), 6 N NaOH (0.36 mL), and H_2O_2 (0.84 mL of 30% wt) were added. The mixture was heated at an oil bath temperature of 55 °C for 1.5 h and then cooled to room temperature and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried, concentrated, and chromatographed to afford **18** (52 mg, 86% yield) as a white solid (mp 167.0−168.0 °C) (lit.[7] mp 166−168 °C). $[\alpha]^{23}_D$ −98.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3496, 3017, 2966 cm^{-1}. R_f = 0.38 (1:1 hexane/EtOAc). ^1H NMR ($CDCl_3$) δ 7.83 (1 H, br), 7.47 (1 H, d, J = 7.8 Hz), 7.30 (1 H, dd, J = 8.0, 0.7 Hz), 7.13 (1 H, dt, J = 7.1, 1.3 Hz), 7.09 (1 H, dt, J = 7.7, 1.2 Hz), 6.58 (1 H, br), 3.75 (1 H, dt, J = 11.7, 3 Hz), 3.42 (1 H, m), 3.35 (1 H, s), 3.17 (2 H, m), 3.03 (1 H, m), 2.66 (2 H, m), 2.43 (1 H, m), 2.12 (1 H, m), 1.78 (1 H, m), 1.71−1.61 (5 H, m), 1.33 (1 H, m), 1.12 (3 H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 135.9, 132.2, 126.6, 121.6, 119.3, 118.1, 111.8, 110.5, 67.0, 58.6, 56.2, 53.9, 40.7, 38.7, 35.5, 32.2, 22.9, 21.2, 8.4. CI-MS, *m/z* (relative intensity) 299 (M^+ + 1, 100%). HRMS (CI) calcd for $C_{19}H_{26}N_2O$: (M^+ + H) 299.2123, Found: 299.2115.

(−)-Eburnamonine (4). To a solution of **18** (51 mg, 0.17 mmol) and a small amount of ground molecular sieves in CH_2Cl_2 (5 mL) was added *N*-methylmorpholine *N*-oxide (41 mg, 0.34 mmol) followed by tetrapropylammonium perruthenate (7 mg, 0.02 mmol) 10 min later. After the resulting mixture was stirred for 1 h, it was filtered through a small pad of Celite. The Celite was washed with a large amount of CH_2Cl_2, and the filtrate was washed with saturated Na_2SO_3 (8 mL), brine (5 mL), and saturated $CuSO_4$ (5 mL). The organic layer was separated, dried, and concentrated. The residue was chromatographed to afford (−)-eburnamonine (**4**) (49 mg, 97% yield) as a white solid. Mp 173−175 °C. $[\alpha]^{23}_D$ = −93.0° (*c* 0.5, $CHCl_3$). ^1H NMR, ^{13}C NMR, and IR spectra and TLC behavior were identical to those of the authentic sample {mp 174−176 °C. $[\alpha]^{23}_D$ −94.0° (*c* = 0.5, $CHCl_3$)} purchased from Aldrich Chemical Co. Mixed mp of synthetic and authentic samples: 173−176 °C.

Amide 20. A solution of **12** (1.93 g, 6.82 mmol) and *p*-toluenesulfonic monohydrate (1.97 g, 10.2 mmol) in benzene (50 mL) and water (5.5 mL) was refluxed for 48 h. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated to give **13** as a pale yellow oil which was not purified. To a solution of **13** in THF (50 mL) at 0 °C were added tryptamine (1.45 g, 8.87 mmol) and Et_3N (1.91 mL, 13.6 mmol). After the mixture was stirred at 0 °C for 10 min, diphenylphosphoryl azide (1.97 mL, 8.87 mmol) was added. The reaction mixture was warmed to room tempererature and stirred overnight. After volatile material was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (200 mL). The resulting solution was washed with 15% NaOH, brine, 2 N HCl, and saturated $NaHCO_3$. The organic layer was separated, dried, and evaporated. Chromatography afforded **20** as a pale yellow amorphous solid (1.88 g, 84%). $[\alpha]^{23}_D$ −13.0° (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3479, 3027, 1760, 1663, 1519 cm^{-1}. R_f = 0.10 (1:3 hexane:EtOAc). ^1H NMR ($CDCl_3$) δ 8.50 (1 H, br s), 7.58 (1 H, d, J = 7.8 Hz), 7.35 (1 H, t, J = 1.0 Hz), 7.17 (1 H, td, J = 7.7, 1.2 Hz), 7.10 (1 H, td, J = 7.8, 1.0 Hz), 6.98 (1 H, d, J = 2.2 Hz), 5.81 (1 H, br s), 4.21 (2 H, t, J = 7.6 Hz), 3.58 (2 H, q, J = 6.6 Hz), 2.97 (2 H, t, J = 6.9 Hz), 2.38 (1 H, m), 2.15−2.04 (3 H, m), 1.82 (2 H, m), 1.58 (2 H, m), 0.92 (3 H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 180.9, 172.0, 136.3, 127.1, 122.0, 121.9, 119.2, 118.5, 112.5, 111.2, 65.1, 45.7, 39.6, 31.6, 31.1, 30.3, 28.0, 25.0, 8.4. CI-MS, *m/z* (relative intensity) 329 (M^+ + 1, 100%). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37, Found: C, 69.67; H 7.41.

Lactol 21. To a solution of **20** (90 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added diisobutylaluminum hydride (1.32

mL of 1 M solution in CH_2Cl_2, 1.32 mmol). After the reaction was allowed to proceed at −78 °C for 45 min, it was quenched by the addition of MeOH (0.1 mL) followed by saturated potassium sodium tartrate solution. The aqueous was separated and extracted with CH_2Cl_2, and the combined organic layers were dried and concentrated. Chromatography afforded **21** (85 mg, 93%) as a 2:1 mixture of diastereomers (^{1}H NMR). IR ($CHCl_3$) 3479, 3017, 1660, 1519. R_f = 0.14 (1:4 hexane: EtOAc). ^{1}H NMR ($CDCl_3$) δ 8.58 (1 H, br), 7.57 (1 H, m), 7.35 (1 H, m), 7.18 (1 H, m), 7.09 (1 H, m), 6.99 (1 H, m), 5.89 (1 H major, t, J = 5.6 Hz), 5.76 (1 H minor, t, J = 5.7 Hz), 4.93 (1 H minor, s), 4.86 (1 H major, s), 4.02 (1 H, m), 3.70 (1 H, m), 3.61 (1 H, br), 3.55 (2 H, m), 2.92 (2 H, m), 2.13−2.02 (2 H, m), 1.80−1.61 (4 H, m), 1.54−1.42 (1 H, m), 1.30 (1 H, m), 0.83 (3 H, m). ^{13}C NMR ($CDCl_3$) δ major: 173.7, 136.3, 127.2, 122.2, 121.9, 119.2, 118.5, 112.5, 111.2, 102.4, 65.8, 49.3, 39.7, 32.8, 32.1, 27.1, 25.4, 26.0, 10.0, 8.0; minor: 173.7, 136.3, 127.2, 122.1, 121.9, 119.2, 118.5, 112.6, 111.2, 101.9, 65.7, 49.0, 39.7, 33.7, 31.4, 28.9, 25.0, 25.0, 8.9. CI-MS, *m/z* (relative intensity) 331 (M^+ + 1.2%), 313 ($(M - H_2O)^+$ + 1, 100%). CI-HRMS calcd for $C_{21}H_{29}N_2O_2$: ($M^+ - H_2O + C_2H_5$) 341.2229, found 341.2224.

Hydroxylactam 22. A solution of **21** (73 mg, 0.22 mmol) in glacial acetic acid (4 mL) was heated at reflux for 48 h. After acetic acid was removed under reduced pressure, the residue was dissolved in CH_2Cl_2, and the resulting solution was washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. Chromatography afforded aminal **v** (14 mg, 20%) as a white glass and the acetate derivative of hydroxylactam **22** (55 mg, 70%) as a white glass. Aminal **v**: IR ($CHCl_3$) 3481, 3017, 1637. R_f = 0.26 (1:4 hexane: EtOAc). ^{1}H NMR ($CDCl_3$) δ 7.99 (1 H, br), 7.71 (1 H, d, J = 7.8 Hz), 7.34 (1 H, d, J = 8.0 Hz), 7.18 (1 H, td, J = 7.6, 1.0 Hz), 7.12 (1 H, td, J = 7.3, 1.2 Hz), 7.03 (1 H, d, J = 2.0 Hz), 4.45 (1 H, s), 3.91−3.76 (3 H, m), 3.57 (1 H, m), 3.12 (1 H, m), 3.03 (1 H, m), 2.42 (2 H, m), 1.88−1.71 (3 H, m), 1.57 (1 H, m), 1.35−1.20 (2 H, m), 0.78 (3 H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 171.1, 136.1, 127.6, 121.9, 119.3, 119.0, 113.7, 113.5, 110.9, 95.5, 64.8, 46.7, 43.4, 34.5, 30.2, 28.5, 26.5, 23.6, 8.5. CI-MS, *m/z* (relative intensity) 313 (M^+ + 1, 100%). CI-HRMS calcd for $C_{19}H_{24}N_2O_2$: (M^+ + 1) 313.1916, found: 313.1910.

To a solution of the acetate derivative of hydroxylactam **22** (50 mg, 0.14 mmol) in MeOH (0.8 mL) was added 20% NaOH (0.5 mL). The mixture was stirred at room temperature for 30 min. After addition of water, the resulting solution was extracted with CH_2Cl_2. The extract was washed with brine, dried, and concentrated. Chromatography produced an approximately 1:1 mixture of **22*β*** and **22α** (41 mg, 93%); each epimer was obtained by repeated chromatography. **22*β***: mp 106−108 °C (lit.[7] mp 107−108.5 °C; lit.[26] mp 104−106 °C). $[\alpha]^{23}_D$ = +98.7° (*c* 0.2, MeOH) {lit.[7] $[\alpha]^{23}_D$ = +88.3° (*c* 0.13, MeOH); lit.[26] $[\alpha]^{23}_D$ = +87.2° (*c* 0.21, MeOH)}. IR ($CHCl_3$) 3369, 3006, 1621 cm^{-1}. R_f = 0.41 (5% MeOH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 9.88 (1 H, br), 7.47 (1 H, d, J = 7.8 Hz), 7.35 (1 H, d, J = 8.1 Hz), 7.14 (1 H, td, J = 8.2 Hz), 7.09 (1 H, td, J = 7.5 Hz), 5.19 (1 H, s), 5.10 (1 H, m), 4.08 (2 H, m), 3.80−3.60 (1 H, br), 2.76−2.68 (3 H, m), 2.58−2.52 (1 H, m), 2.49−2.42 (1 H, m), 2.21 (1 H, m), 1.92 (1 H, m), 1.81−1.76 (1 H, m), 1.55 (1 H, m), 1.44 (1 H, m), 0.88 (1 H, m), 0.68 (3 H, t, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 170.5, 136.0, 131.7, 126.4, 121.4, 119.0, 117.8, 112.1, 111.1, 57.6, 41.0, 39.1, 37.7, 29.0, 26.6, 23.9, 21.0, 6.9. CI-MS, *m/z* (relative intensity) 313 (M^+ + 1, 100%). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74. Found: C, 72.88; H, 7.73. **22α**: mp 261−263 °C dec (lit.[7] mp 263−265 °C dec; lit.[26] mp 262−263 °C). $[\alpha]^{23}_D$ = −214.8° (*c* 0.2, MeOH) {lit.[7] $[\alpha]^{23}_D$ = −195.5° (*c* 0.16, MeOH); lit.[26] $[\alpha]^{23}_D$ = −193.2° (*c* 0.51, MeOH)}. IR (KBr) 3374, 3011, 1601. R_f = 0.35 (5% MeOH in CH_2Cl_2). ^{1}H NMR (DMSO-d_6) δ 10.25 (1 H, br), 7.44−7.39 (2 H, m), 7.05 (1 H, t, J = 7.5 Hz), 6.96 (1 H, t, J = 7.6 Hz), 4.88 (1 H, m), 4.82 (1 H, br s), 4.17 (1 H, t, J = 4.8 Hz), 3.30−3.17 (3 H, m), 2.76−2.55 (3 H, m), 2.34 (2 H, m), 1.94 (1 H, m), 1.86 (1 H, m), 1.73 (1 H, m), 1.52 (1 H, m), 1.37 (1 H, m), 1.04 (3 H, t, J = 7.4 Hz). ^{13}C NMR (DMSO-d_6) δ 169.3, 136.7, 131.8, 126.1, 121.2, 118.8, 117.5, 111.8, 111.2, 77.4, 60.2, 56.5, 38.4, 35.2, 29.6, 29.0, 27.4, 21.0, 8.6. CI-MS, *m/z* (relative intensity) 313 (M^+ + 1, 100%). HRMS (CI) Calcd for $C_{19}H_{24}N_2O_2$: (M^+ + 1) 313.1916, Found 313.1917.

(−)-Aspidospermidine (5). A solution of **22** (α- and *β*-epimers 30 mg, 96 μmol) in 40% H_2SO_4 (0.8 mL) was heated at 100−110 °C for 1.5 h. After the reaction mixture was cooled to 0 °C, it was diluted with CH_2Cl_2 (30 mL) and made basic with 25% NaOH. The organic layer was separated, dried, and concentrated to afford **23** as a pale yellow amorphous solid that was used immediately. To **23** dissolved in anhydrous THF (4 mL) at 0 °C was added $LiAlH_4$ (32 mg, 0.78 mmol). After the mixture was refluxed for 1.5 h, it was cooled to 0 °C and treated with 25% KOH (3 mL). The resulting mixture was stirred at room temperature for 20 min before being filtered through a small pad of Celite. The Celite was washed with CH_2Cl_2 (50 mL), and the filtrate was washed with brine (5 mL). The organic layer was separated, dried, and concentrated. The residue was chromatographed to provide (−)-aspidospermidine (**5**) as a colorless solid (15 mg, 53%). Mp 114−116 °C (lit.[23a] (+)-aspidospermidine mp 120−121 °C, lit.[23b] (+)-aspidospermidine mp 116−118 °C, (±)-aspidospermidine mp 99−103 °C). $[\alpha]^{23}_D$ −16.0° (*c* 0.75, MeOH) {lit.[23a] (+)-aspidospermidine $[\alpha]^{23}_D$ +17.0° (EtOH)}. R_f = 0.28 (10% MeOH in EtOAc). IR ($CHCl_3$) 3357, 3014, 1606 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.07 (1 H, d, J = 7.4 Hz), 7.01 (1 H, t, J = 6.8 Hz), 6.72 (1 H, td, J = 7.3, 0.8 Hz), 6.64 (1 H, d, J = 7.8 Hz), 3.50 (1 H, dd, J = 10.9, 6.71 Hz), 3.11 (1 H, m), 3.06 (1 H, br d, J = 10.5 Hz), 2.28 (2 H, m), 2.20 (1 H, s), 1.95 (2 H, m), 1.75−1.71 (1 H, m), 1.67−1.61 (2 H, m), 1.56−1.46 (3 H, m), 1.43−1.38 (1 H, m), 1.16−1.02 (2 H, m), 0.87 (1 H, m), 0.63 (3 H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 149.3, 135.6, 127.0, 122.7, 118.9, 110.2, 71.2, 65.6, 53.8, 53.2, 52.9, 38.7, 35.5, 34.4, 29.9, 28.0, 22.9, 21.7, 6.7. CI-MS, *m/z* (relative intensity) 283 (M^+ + 1, 100%).

Aspidospermidine. Prepared from (−)-Vincadifformine. A solution of (−)-vincadifformine (28 mg, 83 μmol) in 2 N HCl (3 mL) in a sealed tube was heated at 100 °C for 6 h. The reaction was cooled with an ice bath, quenched with ammonium hydroxide (1 mL), and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (5 mL), separated, dried, and concentrated to give dehydroaspidospermidine (**23**). To the crude product in anhydrous ether (4 mL) at 0 °C was added powder $LiAlH_4$ (30 mg, 0.75 mmol). The mixture was heated at reflux for 15 min, cooled to 0 °C, and treated with 25% KOH (2.5 mL) to decompose the excess $LiAlH_4$. The mixture was treated as described above to give **5** as a colorless solid (19 mg, 81%). Mp 114−116 °C. $[\alpha]^{23}_D$ = −5.3° (*c* 0.75, MeOH). The ^{1}H NMR, ^{13}C NMR, IR spectra, and TLC behaviors were identical to those of synthetic (−)-aspidospermidine prepared from **1b**. The low value for the optical rotation of **5** prepared from (−)-vincadifformine revealed that partial racemization occurred during the conversion of (−)-vincadifformine to **23**.[24]

Acknowledgment. This work was supported by the National Institutes of Health (GM 26568). We thank Dr. You Pan for the development of some preliminary experimental procedures and Professor Martin Kuehne for a generous gift of (−)-vincadifformine.

Supporting Information Available: Copies of proton NMR spectra (9 pages). This material is contained in 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.

JO9707592

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