Asymmetric Total Synthesis of (+)-Apovincamine and a Formal Synthesis of (+)-Vincamine. Demonstration of a Practical "Asymmetric Linkage" between Aromatic Carboxylic Acids and Chiral Acyclic Substrates

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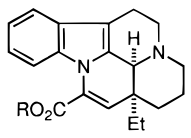
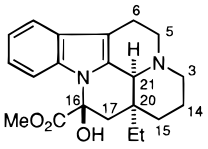
Asymmetric syntheses of (+)-apovincamine (**1a**) and (+)-vincamine (**2**) are described. Construction of the pentacyclic diene lactam **14**, a pivotal intermediate for synthesis of the cis-fused vincane-type alkaloids, began by Birch reduction−alkylation of the chiral benzamide **3** to give the 6-ethyl-1-methoxy-4-methyl-1,4-cyclohexadiene **4**. Conversion of **4** to 2,5-cyclohexadienone **5** (92% overall yield from **3**) and HPLC analysis of **5** demonstrated the diastereomeric purity resulting from the Birch reduction−alkylation to be >100:1. Dienone **5** was converted to butyrolactone **9** (47% overall yield from **3**), and **9** was coupled with tryptamine (**10**) to give the amide **11a**. Amido keto aldehyde **13** was obtained from **11a**, and acid-catalyzed tricyclization and subsequent base-induced elimination of MeOH provided the desired cis-fused pentacyclic diene lactam **14**. Examination of the two-step process **13** → **14** revealed a novel base-induced epimerization at C(21) which served to interconvert **14** and **17**, possibly by the involvement of a homoenolate. Diene lactam **14** was converted to (+)-apovincaminal **20a**, an intermediate in the synthesis of (+)-apovincamine (**1a**) reported by Winterfeldt and co-workers. A new procedure for conversion of **20a** to **1a** involves conversion of **20a** to the acetal **20b** and treatment of **20b** with NBS/AIBN in CCl_4. The conversion of **1a** to vincamine (**2**) has been reported by Oppolzer and co-workers.

The eburnamine−vincamine alkaloids are found in plants of the dogbane family (Apocynaceae).[1] Herein, we report asymmetric total syntheses of two of the most important vincane-type alkaloids, (+)-apovincamine (**1a**)



1a, R = Me (+)-apovincamine
b, R = Et

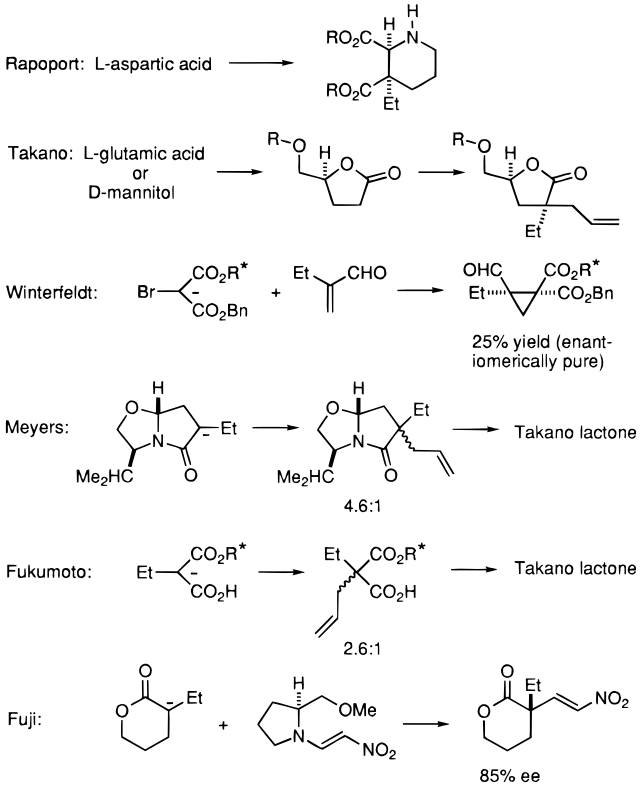


2, (+)-vincamine

and (+)-vincamine (**2**). Ethyl apovincaminate (**1b**) has been used for the treatment of cognitive and behavioral symptoms associated with vascular and degenerative disorders of the central nervous system[2] and has been reported to have beneficial effects in the treatment of cerebral ischemia.[3] Vincamine (**2**) is a vasodilator; it is noteworthy that Sankyo introduced brovincamine fumarate (trade name: Sabromin) in 1986 as a drug to selectively increase cranial and coronary blood flow for the treatment of multiinfarct dementia.[4]

Several strategies for asymmetric syntheses of the eburnamine-vincamine alkaloids (excluding resolutions) are highlighted in Scheme 1. The Rapoport[5] and Takano[6] groups have made direct use of the chiral pool; other research groups have utilized the chiral auxiliary approach with modest to good absolute stereocontrol.[7] Absolute stereocontrol in our synthesis of **1a** has been accomplished by the Birch reduction−alkylation of the chiral benzamide **3** to give **4** with a diastereomer distribution of >100:1.[8]

Scheme 1. The Preparation of Key Intermediates in Several Asymmetric Syntheses of the Eburnamine−Vincamine Alkaloids



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

(1) Lounasmaa, M.; Toluanen, A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1992; Vol. 42, pp 1−116.
(2) Neuss, N. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; p 294.
(3) King, G. A.; Narcavage, D. *Drug Dev. Res.* **1986**, *9*, 225.
(4) Hagstadius, S. *Psychopharmacology (Berlin)* **1984**, *83*, 321.
(5) Gmeiner, P.; Feldman, P. L.; Chu-Moyer, M. Y.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 3068.
(6) Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 305.

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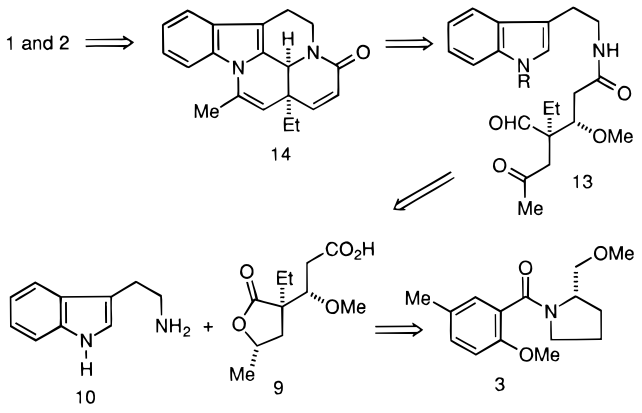
Results and Discussion

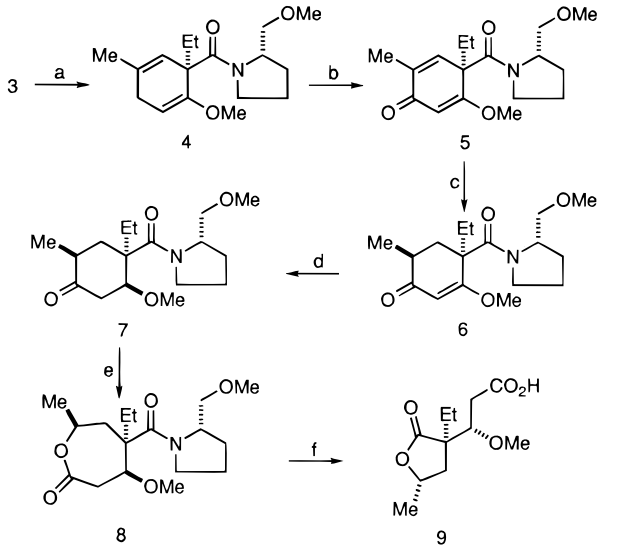
It was expected that a wide range of vincane-type alkaloids would be accessible by chemical modification of the pentacyclic diene lactam **14**. The strategy for construction of **14** involved coupling of tryptamine (**10**) with the chiral enantiomerically pure butyrolactone **9**, followed by acid-catalyzed tricyclization and elimination of MeOH from the amido keto aldehyde **13**. Butyrolactone **9** was obtained from the chiral benzamide **3** by a new process[9a] that provides a practical "asymmetric linkage" between aromatic carboxylic acids and chiral acyclic substrates.[9b]



Construction of Butyrolactone 9. A concise and efficient preparation of butyrolactone **9** from chiral benzamide **3**[10] is shown in Scheme 2. Birch reduction−ethylation of **3** (32.5 g scale) provided the 1,4-cyclohexadiene **4**, which was converted to the 2,5-cyclohexadienone **5** on oxidation with catalytic PDC and *t*-BuOOH in benzene in the presence of Celite.[11] The overall yield for this two-step conversion was 92%. Diastereomeric purity of **5** was determined to be >100:1 by direct HPLC comparison to a 1:1 mixture of diastereomers prepared by reductive alkylation of methyl 2-methoxy-5-methylbenzoate with ethyl iodide, saponification, coupling of the resulting cyclohexadienecarboxylic acid to L-prolinol (methyl ether),[12] and oxidation to the dienone.

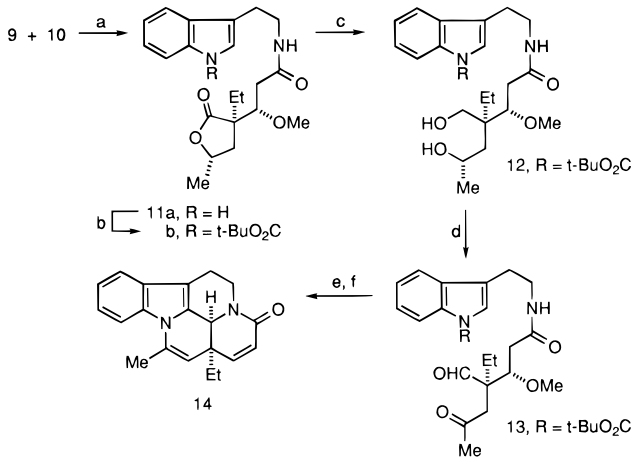
Hydrogenation of the C(5)−C(6) double bond in **5** with 5% Pd/C gave the crystalline vinylogous ester **6** in 90% yield as a single diastereomer. The C(2)−C(3) double bond in **6** was resistant to further hydrogenation;[13] efficient conversion of **6** to the 3-methoxycyclohexanone **7** required reduction with Li in NH_3 in the presence of *tert*-BuOH. Baeyer−Villiger oxidation of **7** gave the caprolactone derivative **8**, for which an X-ray structure

Scheme 2[a]



[a] Reaction conditions: (a) K, NH_3, *tert*-BuOH (1 equiv) −78 °C; piperylene; EtI (1.1 equiv), −78 °C to 25 °C; (b) PDC (cat.), *tert*-BuOOH, Celite, PhH; (c) H_2, 5% Pd/C, EtOAc (60 psi); (d) Li, NH_3, *tert*-BuOH, −78 °C; NH_4Cl, −78 °C; (e) TFAA, UHP, CH_2Cl_2, Na_2HPO_4; (f) TsOH, H_2O, PhH, reflux.

Scheme 3[a]



[a] Reaction conditions: (a) $(PhO)_2P(O)N_3$, DMF, Et_3N, 0 °C to 25 °C; (b) $(tert\text{-}BuO_2C)_2O$, CH_2Cl_2; (c) $LiBH_4$, THF; (d) ClCOCOCl, DMSO, CH_2Cl_2, −78 °C; Et_3N, −78 °C to 25 °C; (e) CF_3CO_2H, CH_2Cl_2, 25 °C; (f) *tert*-BuOK, *tert*-BuOH, reflux

determination provided the absolute configurational assignments at C(4), C(5), and C(7).[14] Treatment of **8** with *p*-toluenesulfonic acid in a refluxing mixture of PhH−H_2O gave the butyrolactone carboxylic acid **9** and released the chiral auxiliary for reutilization. It is noteworthy that **9** was prepared from **3** in six steps with an overall yield of 47%.

Conversion of 9 to the Pentacyclic Diene Lactam 14. Butyrolactone **9** was coupled to tryptamine (**10**) as shown in Scheme 3 to give the chiral amide **11a** (83%). It was necessary to protect the indole NH group as the *tert*-butoxycarbonyl derivative **11b** because an unprotected intermediate (not shown) underwent oxidative cyclization at C(2) of the indole ring and the neighboring

(7) (a) Meyers, A. I.; Romine, J.; Robichaud, A. J. *Heterocycles* **1990**, *30*, 339. (b) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *Heterocycles* **1990**, *31*, 1017. (c) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035. (d) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517.

(8) For a complete review of previous syntheses of the eburnamine−vincamine alkaloids, see: ref 1.

(9) (a) Schultz, A. G.; Hoglen, D. K.; Holoboski, M. A. *Tetrahedron Lett.* **1992**, *33*, 6611. (b) The first synthesis of racemic eburnamine involved the "abnormal Reimer−Tiemann reaction" of *p*-ethylphenol to give 4-(dichloromethyl)-4-ethyl-2,5-cyclohexadien-1-one in 4% yield; see: Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941.

(10) For the preparation and Birch reduction−methylation of benzamide **3**, see: Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828.

(11) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907.

(12) See ref 10 for details.

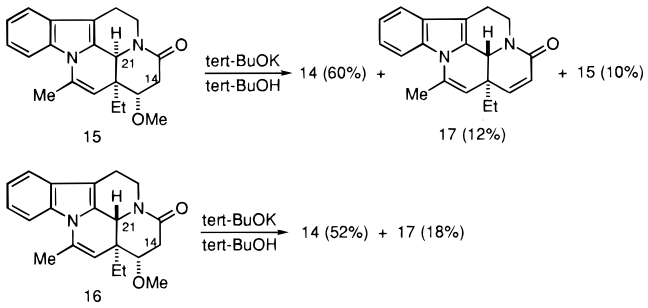
(13) Herndon, J. W.; Matasi, J. J. *Tetrahedron Lett.* **1992**, *33*, 5725 and references cited therein.

(14) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

secondary amide during a subsequent Swern oxidation. Reduction of the lactone ring in **11b** with $LiBH_4$ in THF provided the diol **12**, which was converted to the amido keto aldehyde **13** on Swern oxidation (68% overall yield from **11a**). Treatment of **13** with CF_3CO_2H in CH_2Cl_2 effected the desired tricyclization, and subsequent base-induced elimination of MeOH provided the cis-fused diene lactam **14** as the major reaction product (see Experimental Section).

Careful examination of the two-step process **13** → **14** revealed several remarkable features that make this solution to the stereocontrolled construction of the cis-fused vincane-type alkaloids unique. Separation of reaction products from the acid-catalyzed cyclization of **13** provided cis-fused **15** (47%) and trans-fused **16** (30%).

Treatment of **15** with *tert*-BuOK in *tert*-BuOH at reflux gave the crystalline cis-fused diene lactam **14** in 60% isolated yield and 12% of the trans-fused diene lactam **17**. To our initial surprise, trans-fused **16** also provided the cis-fused diene lactam **14** (52% isolated yield) under conditions identical to those utilized for the conversion of **15** to **14**. It was demonstrated in a separate experiment with **17** and *tert*-BuOK in *tert*-BuOH at reflux that epimerization at C(21) occurred to give a 4:1 mixture of **14** and **17**.



Deuterium labeling experiments were carried out to help elucidate the mechanism of isomerization at C(21). In both the cis- and trans-fused pentacyclic lactams **15** and **16** the protons at C(14) readily exchanged (see Experimental Section for details). With **15**, this resulted in the elimination of MeOH and formation of **14** without any deuterium incorporation at C(21). With **16**, elimination of MeOH to generate **17** was accompanied by exchange of the proton at C(21) and epimerization. Interconversion of **15** and **16** did not occur under the strongly basic conditions leading to elimination of MeOH from **15** and **16**. Therefore, the α,β-unsaturated lactam is a structural unit that is required for conversion of trans-fused **17** into cis-fused **14**. It is possible that interconversion of **14** and **17** is facilitated by the involvement of a homoenolate[15] as shown in Figure 1.

Completion of the Synthesis of (+)-Apovincamine (1a) and a Formal Total Synthesis of (+)-Vincamine (2). Reduction of the diene lactam **14** by the method of Shamma and Rosenstock[16] gave the piperidine **18** (Scheme 4). Electrophilic bromination of the enamine-like double bond in **18** with 2 equiv of *N*-bromoacetamide provided the dibromide **19** in 67% overall yield from **14**. Treatment of **19** with $AgBF_4$, DMSO, and Et_3N followed by an aqueous workup procedure gave (+)-apovincaminal **20a** in 83% yield.

(15) Nickon, A.; Lambert, J. L. *J. Am. Chem. Soc.* **1966**, *88*, 1905.
(16) Shamma, M.; Rosenstock, P. O. *J. Org. Chem.* **1961**, *26*, 718.

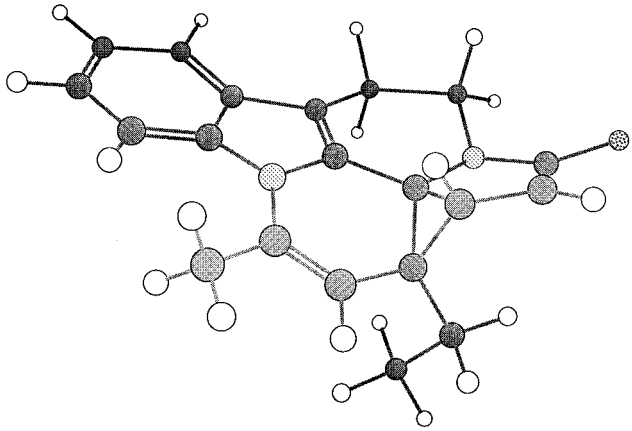
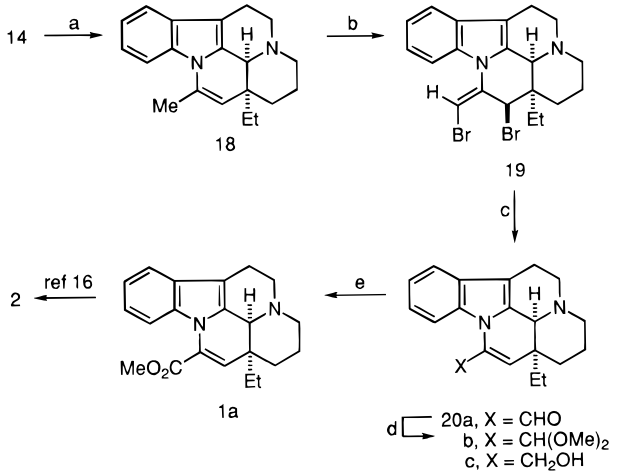


Figure 1. Energy-minimized (MM2 via MacroModel Version 3.0) of a homoenolate possibly involved with the interconversion of **14** and **17**.

Scheme 4[a]



[a] Reaction conditions: (a) $LiAlH_4$, Et_2O, reflux; (b) $CH_3CONHBr$ (2 equiv), THF; (c) $AgBF_4$, Et_3N, DMSO; (d) MeOH, $(MeO)_3CH$, TsOH, reflux; (e) AIBN, NBS, CCl_4, reflux.

The conversion of **20a** to (+)-apovincamine (**1a**) has been reported by Winterfeldt and co-workers.[7c] Aldehyde **20a** was reduced to apovincaminol **20c**, and a sample of this material sent to Hannover was found to be identical to apovincaminol in two TLC systems and by direct ^1H NMR comparison. Although the preparation of **20a** constitutes a formal total synthesis[17] of **1a**, we opted to develop a procedure for conversion of **20a** to (+)-apovincamine (**1a**) which avoids the use of metallic oxidants. Treatment of **20a** with MeOH, $(MeO)_3CH$, and *p*-toluenesulfonic acid gave the acetal **20b** and free radical bromination[18] of **20b** provided (+)-**1a**. This substance was found to be identical (^1H and ^{13}C NMR, TLC, IR) to (+)-apovincamine that had been prepared from natural vincamine by literature procedures.[19] The conversion of apovincamine to vincamine (**2**) has been reported by Oppolzer and co-workers.[20]

To confirm that the high diastereoselectivity obtained by Birch reduction−alkylation of **3** to give **4** was main-

(17) Najer, H.; Pascal, Y. German Patent P 236568.3,9 1973; also, see ref 7c.
(18) Markó, E.; Mekhalfia, A.; Ollis, D. *Synlett* **1990**, 347.
(19) (a) Trojánek, J.; Strouf, O.; Holubek, J.; Cekan, Z. *Tetrahedron Lett.* **1961**, 702. (b) Mokry, J.; Kompis, I. *Tetrahedron Lett.* **1963**, 1917. (c) Pfäfli, P.; Hauth, H. *Helv. Chim. Acta* **1978**, *61*, 1682.
(20) Pfäffli, P.; Oppolzer, W.; Wenger, R.; Hauth, H. *Helv. Chim. Acta* **1975**, *58*, 1131.

tained during subsequent synthetic conversions, (+)-apovincaminol (**20c**) was converted to the Mosher ester. This derivative was compared to a diastereomeric mixture of the corresponding Mosher ester of racemic apovincaminol obtained by Birch reduction−alkylation of the achiral pyrrolidine amide analogue of **3**. ^{1}H NMR spectroscopy indicated that the Mosher ester of (+)-**20c** was a single diastereomer; however, ^{19}F NMR spectroscopy revealed a small but reproducible resonance at the chemical shift corresponding to the second diastereomer, establishing the minimum enantiomeric composition to be >20:1. It can be concluded, therefore, that the process resulting in epimerization at C(21) during the conversion of **16** to **14** does not compromise the absolute configuration at C(20) to any significant degree.

Conclusion

This highly stereoselective synthesis of (+)-apovincamine (**1a**) was carried out in 17 steps from chiral benzamide **3**. Important general features of this synthesis are excellent control of absolute configuration at three stereogenic centers during the conversion of **3** to cyclohexanone **7**; complete regioselectivity for the Baeyer−Villiger oxidation of **7**; the efficient release of the chiral auxiliary by an acid-catalyzed transesterification to give butyrolactone **9**; effective stereocontrol for the sequence of reactions to convert **13** to the diene lactam **14**. It is expected that the pentacyclic diene lactam **14** also will serve as an intermediate for synthesis of the 14,15-dehydrovincane type alkaloids[1] and related analogues.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectroscopies were performed at 500 and 125 MHz, respectively, with chloroform used as the internal standard. ^{19}F NMR spectroscopy was performed at 470 MHz and trifluoroacetic acid (δ = 0.0) was used as an external reference. 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 Quantitative Technologies Inc., Whitehouse, N.J. HPLC analyses were performed on a Waters (6000A) chromatograph fitted with a Chiracel OJ (Daicel) column and a refractometer detection system (R40). Peak areas were measured with a Hewlett−Packard integrator (HP 3394). Methyl alcohol, *tert*-butyl alcohol, dimethyl sulfoxide, and triethylamine were dried over CaH_2 and distilled. Tetrahydrofuran and diethyl ether were dried over sodium/benzophenone ketyl and distilled. Methylene chloride and carbon tetrachloride were dried over P_2O_5 and distilled. Dimethylformamide and trimethyl orthoformate were dried over 4 Å molecular sieves and distilled.

N-Bromoacetamide was recrystallized from methylene chloride. Tryptamine was recrystallized from toluene. *N*-Bromosuccinimide was recrystallized from H_2O. All other reagents were used as purchased. Reactions requiring anhydrous conditions were performed under a nitrogen atmosphere.

(2′*S*,6*R*)-6-Ethyl-1-methoxy-4-methyl-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (4). To a solution of benzamide **3**[10] (32.5 g, 123 mmol) and *tert*-butyl alcohol (11.6 mL, 123 mmol) in THF (300 mL) and NH_3 (1200 mL) at −78 °C was added potassium in small pieces until a blue coloration was maintained for 30 min. Piperylene was added to consume the excess metal, and then EtI (11.1 mL, 136 mmol) was added over 10 min. The solution was stirred at −78 °C for 1.5 h and then slowly warmed to room temperature to allow the NH_3 to evaporate. Water was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give **4**, 36.8 g, (100%) as a light yellow oil which was used in the next reaction. Chromatography (silica gel, 30% EtOAc in hexane) gave **4** as a white solid (mp 34−39 °C). R_f = 0.54 (EtOAc:hexane 1:1) UV inactive. ^{1}H NMR ($CDCl_3$) δ 5.0 (1 H, s), 4.75 (1 H, t, J = 3 Hz), 4.30 (1 H, m), 3.62 (1 H, dd, J = 10 Hz, 4 Hz), 3.50 (1 H, m), 3.49 (3 H, s), 3.33 (3 H, s), 3.29−3.26 (2 H, m), 2.77 (1 H, d, J = 20 Hz), 2.66 (1 H, d, J = 19 Hz), 2.05 (2 H, m), 1.84−1.75 (2 H, m), 1.74 (3 H, s), 1.73−1.66 (2 H, m), 0.66 (3 H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.0, 152.6, 133.4, 121.2, 92.8, 71.8, 58.6, 57.8, 54.0, 53.0, 45.6, 31.4, 28.6, 26.1, 24.7, 22.0, 13.9, 7.7. CI-MS, *m*/*z* (relative intensity) 294 (M^+ + 1, 100%).

(2′*S*,4*R*)-4-Ethyl-3-methoxy-6-methyl-4-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-2,5-cyclohexadien-1-one (5). To a solution of **4** (19.9 g, 67.9 mmol) in benzene (600 mL) were added PDC (2.5 g, 6.8 mmol), Celite (2.5 g), and *t*-BuOOH (10 mL, 102 mmol). The mixture was stirred for 7 h at room temperature, and then another portion of PDC (2.5 g), Celite (2.5 g), and *t*-BuOOH (10 mL) was added. After stirring overnight, the mixture was filtered and the solution was evaporated under reduced pressure. Column chromatography (silica gel, 60% EtOAc in hexane) gave **5**, 19.28 g (92%), as a light yellow solid (mp 90−96 °C). R_f = 0.25 (EtOAc:hexane 1:1) UV active. HPLC analysis of diastereomers (9:1 hexanes:*i*-PrOH): retention times = 8.20 (major diastereomer) and 9.76 min (minor); ratio of integrated peak areas exceeded 100:1. An analysis of a mixture of the diastereomers prepared as described in the text had an integration ratio of 1:1. ^{1}H NMR ($CDCl_3$) δ 6.13 (1 H, s), 5.66 (1 H, s), 4.14 (1 H, br s), 3.62 (3 H, s), 3.40 (1 H, m), 3.27 (1 H, m), 3.20 (3 H, s), 3.07 (1 H, m), 2.90 (1 H, m), 2.14−2.10 (1 H, m), 1.97−1.92 (1 H, m), 1.83 (3 H, s), 1.74−1.71 (3 H, m), 1.59 (1 H, m), 0.45 (3 H, t, J = 9 Hz). ^{13}C NMR ($CDCl_3$) δ 187.7, 173.6, 166.1, 138.2, 136.8, 104.4, 71.5, 58.6, 58.3, 56.3, 55.7, 45.1, 29.5, 26.1, 24.4, 15.2, 7.1. IR ($CHCl_3$) 1622, 1603 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 308 (M^+ + 1, 40%), 142 (M^+ − 166, 100%). Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.28; H, 8.32; N, 4.49.

(2′*S*,4*R*,6*S*)-4-Ethyl-3-methoxy-6-methyl-4-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-5-cyclohexen-1-one (6). A mixture of **5** (3.07 g, 10.0 mmol) and Pd/C (5%, 2.00 g, 0.940 mmol) in EtOAc (225 mL) was shaken under H_2 (60 psi) for 4 h. Filtration and column chromatography (silica gel, 70% EtOAc in hexane) gave **6**, 2.80 g (90%), as colorless crystals (mp 82−84 °C). R_f = 0.29 (EtOAc:hexane 7:3) UV active. ^{1}H NMR ($CDCl_3$) δ 5.38 (1 H, s), 4.27 (1 H, br s), 3.69 (3 H, s), 3.60 (1 H, m), 3.54 (1 H, br s), 3.43 (1 H, m), 3.34 (3 H, s), 3.02 (1 H, m), 2.56 (1 H, m), 2.10 (1 H, m), 2.07 (2 H, m), 1.89 (3 H, m), 1.15 (3 H, d, J = 7 Hz), 0.97 (3 H, t, J = 8 Hz). ^{13}C NMR ($CDCl_3$) δ 199.7, 178.6, 169.7, 102.0, 72.1, 58.9, 58.0, 55.7, 51.8, 46.7, 38.5, 36.4, 30.4, 26.2, 24.9, 15.1, 10.7. IR ($CHCl_3$) 1632, 1601 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 310 (M^+ + 1, 100%). Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.72; H, 8.77; N, 4.42.

(2′*S*,3*S*,4*R*,6*S*)-4-Ethyl-3-methoxy-6-methyl-4-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1-cyclohexanone (7). To a solution of **6** (9.95 g, 32.2 mmol) and *t*-BuOH (9.6 mL, 96.6 mmol) in THF (200 mL) and NH_3 (1500 mL) at −78 °C was added Li until the blue coloration was maintained for 15−20 min at −78 °C. The enolate was quenched with NH_4Cl (~5 g), and the mixture was warmed to room temperature while NH_3 evaporated. Water was added, and the mixture was extracted with CH_2Cl_2; the organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography (silica gel, 50%, 70% EtOAc in hexane) provided **7**, 8.83 g (88%), as a white solid (mp 90−91 °C). R_f = 0.30 (EtOAc:hexane 7:3) UV inactive. ^{1}H NMR ($CDCl_3$) δ 4.42 (1 H, m), 4.15 (1 H, m), 3.61 (1 H, m), 3.57 (1 H, m), 3.49 (1 H, m), 3.42 (1 H, m), 3.31 (3 H, s), 3.27 (3 H, s), 2.69 (1 H, dd, J = 15 Hz, 3 Hz), 2.48 (1 H, dd, J = 15 Hz, 3 Hz), 2.40 (1 H, m), 2.22 (2 H, d, J = 10 Hz), 2.04 (1 H, m), 1.92−1.82 (5 H, m), 1.05 (3 H, d, J = 6 Hz), 0.95 (3 H, t, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 210.4, 172.1, 83.0, 72.1, 58.6, 58.5, 56.3, 52.4, 47.5, 40.0, 39.8, 35.7, 26.0, 25.3, 24.0, 14.2, 8.4. IR ($CHCl_3$) 1713, 1606 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 312 (M^+ + 1, 100%). Anal. Calcd for $C_{17}H_{29}NO_4$: C, 65.56; H, 9.39; N, 4.50. Found: C, 65.71; H, 9.56; N, 4.48.

(2′*S*,4*S*,5*R*,7*S*)-5-Ethyl-4-methoxy-7-methyl-5-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]oxacycloheptan-2-one (8). Na_2HPO_4 (7.39 g, 52.0 mmol) and urea hydrogen peroxide (UHP, 5.44 g, 57.8 mmol) were added to a solution of **7** (1.80 g, 5.78 mmol) in CH_2Cl_2 (40 mL). The mixture was cooled to 0 °C, treated with trifluoroacetic anhydride (2.05 mL, 14.5 mmol), and then allowed to warm to room temperature with stirring. After 2.5 h, another portion of trifluoroacetic anhydride (1.00 mL, 7.08 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 16 h and then 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 washed with H_2O, dried (Na_2SO_4), and concentrated at reduced pressure. Chromatography (silica gel, hexanes, 70% EtOAc/hexanes, and EtOAc) provided **8**, 1.56 g (83%), as a white solid (mp 182.5−185 °C). R_f = 0.18 (EtOAc:hexane 7:3) UV inactive. ^{1}H NMR ($CDCl_3$) δ 4.43 (1 H, m), 4.33 (1 H, m), 3.92 (1 H, d, J = 7 Hz), 3.55 (1 H, m), 3.48 (1 H, m), 3.40−3.34 (2 H, m), 3.34 (3 H, s), 3.22 (3 H, s), 3.04−2.99 (1 H, dd, J = 15 Hz, 8 Hz), 2.84 (1 H, d, J = 15 Hz), 2.39 (1 H, dd, J = 16 Hz, 10 Hz), 1.98 (2 H, d, J = 16 Hz), 1.86−1.60 (5 H, m), 1.33 (3 H, d, J = 6 Hz), 0.77 (3 H, t, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 171.4, 171.1, 71.9, 70.6, 58.8, 58.5, 56.9, 56.0, 53.5, 47.4, 36.0, 33.4, 25.8, 25.2, 23.6, 22.8, 7.8. IR ($CHCl_3$) 1717, 1606, 1203 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 328 (M^+ + 1, 100%). Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.03; H, 8.77; N, 4.24.

(1′*S*,3*R*,5*S*)-3-Ethyl-3-(1′-2′-carboxyethyl)-5-methyloxacyclopentan-1-one (9). A solution of **8** (2.27 g, 6.94 mmol) and 1.0 g (5.3 mmol) of TsOH·H_2O in benzene (100 mL) and water (14 mL) was heated at reflux for 7 h. Another 1 g of TsOH·H_2O was added, and the solution was heated overnight. After a third addition of TsOH·H_2O (1 g), the mixture was refluxed for 7 h. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the residue (silica gel, 60% EtOAc in hexane) gave **9**, 1.24 g (78%), as a colorless oil. R_f = streak from baseline (EtOAc:hexane 7:3) UV inactive. ^{1}H NMR ($CDCl_3$) δ 10.0 (1 H, br s), 4.60 (1 H, m), 4.00 (1 H, m), 3.40 (3 H, s), 2.58 (1 H, dd, J = 16 Hz, 4 Hz), 2.49−2.43 (2 H, m), 1.65−1.60 (2 H, m), 1.38 (3 H, d, J = 6 Hz), 1.32 (1 H, m), 0.93 (3 H, t, J = 7 Hz). ^{13}C ($CDCl_3$) δ 180.0, 176.5, 81.9, 74.8, 59.3, 54.6, 36.1, 34.1, 26.5, 21.5, 8.3. IR ($CDCl_3$) 3400−2500, 1765, 1713 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 231 (M^+ + 1, 100%). Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.49; H, 7.64.

Amide 11a. A solution of **9** (3.09 g, 13.4 mmol) in DMF (75 mL) was treated with Et_3N (4.67 mL, 33.5 mmol). The solution was cooled to 0 °C, and diphenylphosphoryl azide (3.47 mL, 16.1 mmol) and tryptamine (2.58 g, 16.1 mmol) were added. The mixture was warmed to room temperature and stirred overnight. Quenching with H_2O was followed by extraction with Et_2O and drying with Na_2SO_4. Concentration *in vacuo* and chromatography (silica gel, 70% EtOAc/hexanes) afforded **11a** as a white crystalline solid (mp 42−45 °C), 4.13 g (83%). R_f = 0.21 (EtOAc:hexane 3:1) UV active. ^{1}H NMR ($CDCl_3$) δ 8.29 (1 H, br s), 7.60 (1 H, d, J = 8 Hz), 7.37 (1 H, d, J = 8 Hz), 7.20 (1 H, t, J = 8 Hz), 7.12 (1 H, t, J = 7 Hz), 7.05 (1 H, s), 5.83 (1 H, br s), 4.46 (1 H, m), 3.92 (1 H, m), 3.63 (2 H, m), 3.29 (3 H, s), 2.99 (2 H, m), 2.37 (1 H, dd, J = 15 Hz, 3 Hz), 2.35−2.30 (1 H, m), 2.11 (1 H, dd, J = 15 Hz, 8 Hz), 1.61−1.51 (2 H, m), 1.37 (3 H, d, J = 6 Hz), 1.26 (1 H, m), 0.88 (3 H, t, J = 8 Hz). ^{13}C NMR ($CDCl_3$) δ 180.1, 170.4, 136.4, 127.2, 122.1, 122.0, 119.2, 118.5, 112.4, 111.4, 82.6, 74.6, 59.7, 54.6, 39.9, 38.1, 34.4, 26.7, 25.1, 21.7, 8.6. IR ($CHCl_3$) 1754, 1662, 1522 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 373 (M^+ + 1, 100%). HRMS (CI) calcd for $C_{21}H_{29}N_2O_4$ (M^+ + 1) 373.2127, found 373.2122.

N-Boc-Indole 11b. To a solution of **11a** (1.10 g, 2.96 mmol) and (t-BuO_2C)$_2$O (0.77 g, 3.6 mmol) in CH_2Cl_2 (60 mL) was added DMAP (36 mg, 0.30 mmol). The mixture was stirred at room temperature for 30 min, washed with water, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvent was removed *in vacuo* to give a white crystalline solid (mp 44−46 °C). Flash chromatography of the residue (silica gel, 70% EtOAc in hexane) afforded **11b**, 1.30 g (93%). R_f = 0.39 (EtOAc:hexane 7:3) UV active. ^{1}H NMR ($CDCl_3$) δ 8.03 (1 H, br s), 7.47 (1 H, d, J = 8 Hz), 7.35 (1 H, s), 7.22 (1 H, t, J = 8 Hz), 7.14 (1 H, t, J = 8 Hz), 6.48 (1 H, m), 4.42 (1 H, m), 3.91 (1 H, dd, J = 8 Hz, 3 Hz), 3.51 (2 H, m), 3.25 (3 H, s), 2.84 (2 H, m), 2.31−2.28 (2 H, m), 2.13 (1 H, dd, J = 14 Hz, 8 Hz), 1.57 (9 H, s), 1.54−1.43 (2 H, m), 1.25 (3 H, d, J = 6 Hz), 1.25 (1 H, m), 0.81 (3 H, t, J = 8 Hz). ^{13}C NMR ($CDCl_3$) δ 179.9, 170.4, 149.4, 135.3, 130.1, 124.2, 122.8, 122.3, 118.7, 117.4, 115.0, 83.3, 82.4, 74.4, 59.3, 54.4, 39.0, 37.8, 34.2, 27.9, 26.5, 24.8, 21.4, 8.3. IR ($CHCl_3$) 1747, 1730, 1667, 1514 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 473 (M^+ + 1, 100%). HRMS (CI) calcd for $C_{26}H_{36}N_2O_6$ (M^+ + 1) 472.2573, found 472.2569.

Diol 12. To a solution of **11b** (5.15 g, 10.9 mmol) in THF (130 mL) at room temperature was added $LiBH_4$ (0.712 g, 32.7 mmol) which was followed by stirring for 12 h. Additional portions of $LiBH_4$ (0.30 g, 14 mmol) were added each 8−12 h until the reaction was complete. Water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the solvent was removed *in vacuo* to give a white foam. Flash chromatography of the residue (silica gel, 85% EtOAc in hexane) provided **12**, 4.07 g (78%), as a white crystalline solid (mp 41.5−45 °C). R_f = 0.24 (EtOAc:hexane 7:3) UV active. ^{1}H NMR ($CDCl_3$) δ 8.10 (1 H, br s), 7.55 (1 H, d, J = 8 Hz), 7.42 (1 H, s), 7.33 (1 H, t, J = 7 Hz), 7.25 (1 H, t, J = 7 Hz), 6.41 (1 H, br s), 3.91 (1 H, m), 3.85 (1 H, m), 3.74 (2 H, m), 3.52 (2 H, d, J = 12 Hz), 3.38 (1 H, d, J = 12 Hz), 3.27 (3 H, s), 2.93 (2 H, m), 2.63 (1 H, dd, J = 16 Hz, 4 Hz), 2.19 (1 H, dd, J = 16 Hz, 6 Hz), 1.85 (1 H, m), 1.67 (9 H, s), 1.62 (1 H, m), 1.37−1.25 (3 H, m), 1.19 (3 H, d, J = 6 Hz), 0.79 (3 H, t, J = 8 Hz). ^{13}C NMR ($CDCl_3$) δ 173.6, 149.9, 135.4, 130.4, 124.6, 123.1, 122.6, 118.9, 117.8, 115.3, 83.9, 81.3, 67.1, 63.5, 58.4, 44.3, 43.2, 39.0, 37.8, 28.2, 27.8, 25.4, 25.1, 24.8, 7.6. IR ($CHCl_3$) 3500−3100, 1724, 1650, 1518 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 477 (M^+ + 1, 4%), 377 (M^+ + 1 − 100, 100%). HRMS (CI) Calcd for $C_{26}H_{41}N_2O_6$ (M^+ + 1) 477.2965, found 477.2975.

Amido Keto Aldehyde 13. A solution of oxalyl chloride (81 mg, 0.63 mmol) in CH_2Cl_2 (5.8 mL) at −78 °C was treated with DMSO (98 mg, 1.3 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at −78 °C for 5 min, and then diol **12** (60 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) was added. The reaction mixture was stirred at −78 °C for 25 min and was then treated with Et_3N. After stirring at −78 °C for 5 min, the solution was warmed to room temperature. The reaction mixture was washed with water and extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure to give a colorless oil. Flash chromatography of the residue (silica gel, 70% EtOAc in hexane) afforded **13**, 56 mg (94%), as a colorless oil. The product was used immediately in the next reaction because of decomposition. R_f = 0.39 (EtOAc:hexane 7:3) UV active. ^{1}H NMR ($CDCl_3$) δ 9.58 (1 H, s), 8.16 (1 H, br s), 7.59 (1 H, d, J = 8 Hz), 7.47 (1 H, s), 7.36 (1 H, t, J = 7 Hz), 7.30 (1 H, t, J = 7 Hz), 5.95 (1 H, br s), 4.16 (1 H, m), 3.64 (2 H, m), 3.33 (3 H, s), 2.95 (2 H, m), 2.81−2.70 (2 H, q, J = 17 Hz), 2.46 (1 H, dd, J = 15 Hz, 4 Hz), 2.20 (1 H, m), 2.16 (3 H, s), 1.86 (1 H, m), 1.76 (1 H, m), 1.70 (9 H, s), 0.83 (3 H, t, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 206.9, 203.9, 170.8, 149.5, 135.4, 130.1, 124.3, 123.0, 122.4, 118.7, 117.4, 115.1, 83.4, 79.8, 59.3, 55.9, 42.6, 39.0, 37.7, 30.6, 28.0, 24.9, 22.9, 8.03. IR ($CHCl_3$) 1723, 1664, 1518 cm^{-1}. CI-MS, *m*/*z* (relative intensity) 473 (M^+ + 1, 6%), 455 (M^+ + 1 − H_2O, 100%).

Pentacyclic Lactams 15 and 16. A solution of **13** (960 mg, 2.03 mmol) and CF_3CO_2H (10 mL) in CH_2Cl_2 (100 mL) was stirred at room temperature for 15 h, after which saturated $NaHCO_3$ was added and then solid $NaHCO_3$ until the aqueous solution was a neutral pH. The aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to give a mixture of **15** and **16** (^{1}H NMR analysis). Chromatography (silica gel, 30% EtOAc in hexane) provided **15**, 319 mg (47%), and **16**, 208 mg (30%). **15**: yellow solid, mp 144.5−146.5 °C. R_f = 0.65 (EtOAc:hexane 3:1) UV active. ^{1}H NMR ($CDCl_3$) δ 7.66 (1 H, d, J = 8 Hz), 7.44 (1 H, d, J = 8 Hz), 7.18 (1 H, t, J = 7 Hz), 7.12 (1 H, t, J

= 7 Hz), 4.98 (1 H, m), 4.82 (1 H, s), 4.78 (1 H, s), 3.33 (1 H, dd, J = 12 Hz, 5 Hz), 3.25 (3 H, s), 3.04 (2 H, m), 2.73 (1 H, dd, J = 17 Hz, 5 Hz), 2.65 (1 H, d, J = 12 Hz), 2.58 (3 H, s), 2.46 (1 H, dd, J = 17 Hz, 12 Hz), 1.86 (1 H, m), 1.70 (1 H, m), 1.03 (3 H, t, J = 7 Hz). (C_6D_6) δ 7.40 (1 H, m), 7.35 (1 H, m), 7.15−7.10 (2 H, m), 5.03 (1 H, dd, J = 13 Hz, 6 Hz), 4.60 (1 H, s), 4.28 (1 H, s), 3.07 (1 H, m), 3.03 (1 H, dd, J = 12 Hz, 5 Hz), 2.73 (1 H, dd, J = 16 Hz, 5 Hz), 2.70 (3 H, s), 2.47 (1 H, dt, J = 12 Hz, 5 Hz), 2.33 (1 H, dd, J = 16 Hz, 12 Hz), 2.22 (1 H, dd, J = 15 Hz, 3 Hz), 2.03 (3 H, s), 1.78 (1 H, m), 1.41 (1 H, m), 0.78 (3 H, t, J = 7 Hz). ^{13}C NMR (DEPT): δ 168.3 (s), 134.8 (s), 133.0 (s), 131.2 (s), 128.5 (s), 122.7 (d), 120.2 (d), 118.7 (d), 112.2 (d), 110.5 (d), 110.4 (s), 78.3 (d), 57.8 (q), 54.7 (d), 43.0 (t), 34.4 (t), 29.7(s), 21.1 (t), 20.7 (q), 20.3 (t), 8.7 (q). IR (KBr) 1648, 1406 cm^{-1}. CI-MS, m/z (relative intensity) 337 (M^+ + 1, 100%). HRMS (CI) calcd for $C_{21}H_{25}N_2O_2$ (M^+ + 1) 337.1916, found 337.1912. **16**: R_f = 0.53 (EtOAc:hexane 3:1) UV active. ^{1}H NMR ($CDCl_3$) δ 7.64 (1 H, d, J = 8 Hz), 7.48 (1 H, d, J = 8 Hz), 7.20 (1 H, t, J = 7 Hz), 7.15 (1 H, t, J = 7 Hz), 5.30 (1 H, s), 4.85 (1 H, dd, J = 13 Hz, 5 Hz), 4.40 (1 H, s), 3.64 (1 H, t, J = 7 Hz), 3.41 (3 H, s), 3.12 (1 H, m), 3.07 (1 H, dd, J = 18 Hz, 7 Hz), 2.85 (2 H, m), 2.57 (3 H, s), 2.52 (1 H, dd, J = 18 Hz, 10 Hz), 1.48 (1 H, m), 1.02 (1 H, m), 0.56 (3 H, t, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 169.9, 135.5, 134.4, 130.6, 128.3, 122.4, 120.2, 118.7, 112.0, 110.4, 108.7, 80.3, 57.2, 55.7, 42.4, 39.3, 36.2, 20.1, 19.7, 19.6, 9.1. CI-MS, m/z (relative intensity) 337 (M^+ + 1, 100%).

Pentacyclic Diene Lactams 14 and 17. A solution of **15** (275 mg, 0.817 mmol) and *t*-BuOK (208 mg, 1.85 mmol) in *t*-BuOH (25 mL) was refluxed for 2 days. Water was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Flash chromatography (silica gel, 30% EtOAc in hexane) afforded **14**, 150 mg (60%), as a light yellow foam, **17**, 29 mg (12%), and recovered **15**, 27 mg (10%). **14** was crystallized from Et_2O on standing, mp 157−160 °C.

From 16. Procedure identical to that from **15**: 14 mg (0.042 mmol) of **16**, 10 mg (0.092 mmol) of *t*-BuOK, and 3 mL of *t*-BuOH were used. The procedure afforded **14**, 6.8 mg (52%), and **17**, 2.3 mg (18%).

From a mixture of 15 and 16. Procedure identical to that from **15**: 1.19 g (3.54 mmol) of a mixture of **15** and **16**, 0.873 g (7.78 mmol) of *t*-BuOK, and 100 mL of *t*-BuOH were used. The procedure afforded **14**, 0.599 g (55%), **17**, 98 mg (9%), and recovered **15**, 78 mg (7%). **14**: R_f = 0.75 (EtOAc:hexane 3:1) UV active. ^{1}H NMR ($CDCl_3$) δ 7.61 (1 H, d, J = 8 Hz), 7.43 (1 H, d, J = 8 Hz), 7.15 (1 H, t, J = 7 Hz), 7.10 (1 H, t, J = 7 Hz), 6.02 (1 H, d, J = 10 Hz), 5.72 (1 H, d, J = 10 Hz), 4.89 (1 H, m), 4.87 (1 H, s), 4.62 (1 H, s), 3.20−3.12 (2 H, m), 2.62 (1 H, br d, J = 15 Hz), 2.55 (3 H, s), 1.81 (1 H, m), 1.72 (1 H, m), 1.06 (3 H, t, J = 7 Hz). (C_6D_6) δ 7.34−7.29 (2 H, m), 7.20−7.08 (2 H, m), 5.78 (1 H, d, J = 10 Hz), 5.49 (1 H, dd, J = 10 Hz, 1.5 Hz), 4.93 (1 H, dd, J = 13 Hz, 6 Hz), 4.32 (1 H, s), 4.05 (1 H, s), 3.22 (1 H, m), 2.60 (1 H, dddd, J = 11 Hz, 7 Hz, 5 Hz, 5 Hz), 2.18 (1 H, ddd, J = 15 Hz, 5 Hz, 2 Hz), 1.96 (3 H, s), 1.44−1.30 (2 H, m), 0.76 (3 H, t, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 165.5, 144.3, 134.6, 134.4, 131.3, 128.8, 122.6, 121.3, 120.3, 118.8, 112.3, 110.6, 108.3, 57.2, 44.2, 37.8, 33.5, 20.9, 19.4, 8.1. IR ($CHCl_3$) 1665, 1609 cm^{-1}. CI-MS, m/z (relative intensity) 305 (M^+ + 1, 100%). HRMS (CI) calcd for $C_{20}H_{21}N_2O$ (M^+ + 1) 305.1654, found 305.1657. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.21. Found: C, 78.81; H, 6.55; N, 9.13.

17: R_f = 0.71 (EtOAc:hexane 3:1) UV active. ^{1}H NMR ($CDCl_3$) δ 7.63 (1 H, d, J = 8 Hz), 7.52 (1 H, d, J = 8 Hz), 7.21 (1 H, t, J = 7 Hz), 7.17 (1 H, t, J = 7 Hz), 6.83 (1 H, d, J = 10 Hz), 6.02 (1 H, d, J = 10 Hz), 5.21 (1 H, s), 4.66 (1 H, dd, J = 13 Hz, 8 Hz), 4.62 (1 H, s), 3.29 (1 H, m), 2.93 (2 H, m), 2.54 (3 H, s), 1.46 (1 H, m), 0.78 (1 H, m), 0.74 (3 H, t, J = 7 Hz). (C_6D_6) δ 7.39 (1 H, d, J = 8 Hz), 7.34 (1 H, d, J = 8 Hz), 7.16−7.06 (2 H, m), 6.20 (1 H, d, J = 10 Hz), 6.04 (1 H, d, J = 10 Hz), 4.73 (1 H, ddd, J = 13 Hz, 6 Hz, 2 Hz), 4.59 (1 H, s), 4.24 (1 H, s), 2.96 (1 H, dddd, J = 11 Hz, 7 Hz, 5 Hz, 5 Hz), 2.60 (1 H, m), 2.35 (1 H, ddd, J = 16 Hz, 5 Hz, 2 Hz), 1.95 (3 H, s), 1.36−1.29 (2 H, m), 0.47 (3 H, t, J = 7 Hz). CI-MS, m/z (relative intensity) 305 (M^+ + 1, 100%).

Deuterium Exchange Experiments. A solution of **15** (5 mg, 0.02 mmol) and *t*-BuOK (4 mg, 0.03 mmol) in *t*-BuOD (2 mL) was heated at reflux for 2 days. Water was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give a yellow oil. Flash chromatography (silica gel, 30% EtOAc in hexane) afforded **14**-14-d (1 mg) and **15**-14-d_2 (4 mg). **14**-14-d: R_f = 0.57 (EtOAc:hexane = 7:3). ^{1}H NMR (C_6D_6) δ 7.34−7.29 (2 H, m), 7.20−7.08 (2 H, m), 5.49 (1 H, s), 4.93 (1 H, dd, J = 13 Hz, 6 Hz), 4.32 (0.7 H, s), 4.05 (1 H, s), 3.22 (1 H, m), 2.60 (1 H, dddd, J = 11 Hz, 7 Hz, 5 Hz, 5 Hz), 2.18 (1 H, ddd, J = 15 Hz, 5 Hz, 2 Hz), 1.96 (3 H, s), 1.44−1.30 (2 H, m), 0.76 (3 H, t, J = 7 Hz). **15**-14-d_2: R_f = 0.44 (EtOAc:hexane = 7:3). ^{1}H NMR ($CDCl_3$) δ 7.66 (1 H, d, J = 8 Hz), 7.44 (1 H, d, J = 8 Hz), 7.18 (1 H, t, J = 7 Hz), 7.12 (1 H, t, J = 7 Hz), 4.98 (1 H, m), 4.82 (1 H, s), 4.78 (1 H, s), 3.33 (1 H, s), 3.25 (3 H, s), 3.04 (2 H, m), 2.65 (1 H, d, J = 12 Hz), 2.58 (3 H, s), 1.86 (1 H, m), 1.70 (1 H, m), 1.03 (3 H, t, J = 7 Hz).

A mixture of **14**-14-d and **15**-14-d_2 (5 mg, 0.02 mmol) and *t*-BuOK (4 mg, 0.03 mmol) in *t*-BuOD (2 mL) was heated at reflux for 3 days. Water was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. Flash chromatography (silica gel, hexane followed by 30% EtOAc in hexane) afforded **14**-14-d (0.9 mg) as a light yellow oil and **15**-14-d_2 (0.4 mg).

A solution of **16** (6 mg, 0.02 mmol) and *t*-BuOK (5 mg, 0.05 mmol) in *t*-BuOD (2 mL) was heated at reflux for 3 days. Water was added to the reaction mixture, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. Flash chromatography (silica gel, hexane followed by 30% EtOAc in hexane) afforded **14**-21-d,14-d (0.7 mg), a mixture of **14**-21-d,14-d, **17**-21-d,14-d (2.9 mg), and a third fraction containing **16**-14-d_2 (0.8 mg). **14**-21-d,14-d: R_f = 0.57 (EtOAc:hexane = 7:3). ^{1}H NMR (C_6D_6) δ 7.34−7.29 (2 H, m), 7.20−7.08 (2 H, m), 5.49 (1 H, s), 4.93 (1 H, dd, J = 13 Hz, 6 Hz), 4.32 (0.1 H, s), 4.05 (1 H, s), 3.22 (1 H, m), 2.60 (1 H, dddd, J = 11 Hz, 7 Hz, 5 Hz, 5 Hz), 2.18 (1 H, ddd, J = 15 Hz, 5 Hz, 2 Hz), 1.96 (3 H, s), 1.44−1.30 (2 H, m), 0.76 (3 H, t, J = 7 Hz).

17-21-d,14-d: R_f = 0.44 (EtOAc:hexane = 7:3). ^{1}H NMR (C_6D_6) δ 7.39 (1 H, d, J = 8 Hz), 7.34 (1 H, d, J = 8 Hz), 7.16−7.06 (2 H, m), 6.20 (1 H, s), 4.73 (1 H, ddd, J = 13 Hz, 6 Hz, 2 Hz), 4.59 (1 H, s), 2.96 (1 H, dddd, J = 11 Hz, 7 Hz, 5 Hz, 5 Hz), 2.60 (1 H, m), 2.35 (1 H, ddd, J = 16 Hz, 5 Hz, 2 Hz), 1.95 (3 H, s), 1.36−1.29 (2 H, m), 0.47 (3 H, t, J = 7 Hz). **16**-14-d_2: R_f = 0.26 (EtOAc:hexane = 7:3). ^{1}H NMR ($CDCl_3$) δ 7.64 (1 H, d, J = 8 Hz), 7.48 (1 H, d, J = 8 Hz), 7.20 (1 H, t, J = 7 Hz), 7.15 (1 H, t, J = 7 Hz), 5.30 (1 H, s), 4.85 (1 H, dd, J = 13 Hz, 5 Hz), 3.64 (1 H, s), 3.41 (3 H, s), 3.12 (1 H, m), 2.85 (2 H, m), 2.57 (3 H, s), 1.48 (1 H, m), 1.02 (1 H, m), 0.56 (3 H, t, J = 7 Hz).

Pentacyclic Amine 18. To a solution of **14** (20 mg, 0.066 mmol) in Et_2O (10 mL) was added $LiAlH_4$ (10 mg, 0.26 mmol). The mixture was stirred and refluxed for 1 h. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a colorless oil. Flash chromatography (silica gel, EtOAc and 10% MeOH in CH_2Cl_2) afforded **18**, 14 mg (73%), as a colorless oil, which solidified after a few days. R_f = 0.17 (EtOAc:hexane 7:3) UV active. ^{1}H NMR ($CDCl_3$) δ 7.63 (1 H, d, J = 8 Hz), 7.46 (1 H, d, J = 8 Hz), 7.15−7.08 (2 H, m), 4.76 (1 H, s), 4.15 (1 H, s), 3.35 (1 H, dd, J = 14 Hz, 6 Hz), 3.25 (1 H, dt, J = 12 Hz, 5 Hz), 3.03 (1 H, m), 2.70 (1 H, dt, J = 12 Hz, 3 Hz), 2.65 (1 H, br d, J = 11 Hz), 2.51 (1 H, m), 2.49 (3 H, s), 1.89 (1 H, m), 1.71 (2 H, m), 1.40 (2 H, t, J = 13 Hz), 1.13 (1 H, dt, J = 14 Hz, 4 Hz), 0.98 (3 H, t, J = 7 Hz). ^{13}C NMR ($CDCl_3$) δ 134.4, 131.9, 129.0, 121.6, 119.5, 118.3, 115.2, 112.0, 107.2, 62.7, 56.3, 51.7, 45.2, 36.4, 30.1, 27.5, 20.7, 20.6, 16.3, 8.7. IR ($CHCl_3$) 1450 cm^{-1}. CI-MS, m/z (relative intensity) 293 (M^+ + 1, 100%). HRMS calcd for $C_{20}H_{25}N_2$ (M^+ + 1): 293.2018, found 293.2013.

Dibromide 19. Amine **18** (83 mg, 0.28 mmol) was dissolved in THF (20 mL) and treated with *N*-bromoacetamide (82 mg,

0.60 mmol) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature. After 45 min, saturated $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2, dried (Na_2SO_4), and concentrated *in vacuo* to afford a yellowish white foam. Chromatography (silica, 70% EtOAc/hexane) afforded **19** as a yellow oil, 114 mg (91%). $R_f = 0.33$ (EtOAc:hexane 7:3) UV active. ^{1}H NMR ($CDCl_3$) δ 7.66 (1 H, d, $J = 8$ Hz), 7.52 (1 H, d, $J = 8$ Hz), 7.27 (1 H, t, $J = 7$ Hz), 7.22 (1 H, t, $J = 7$ Hz), 6.66 (1 H, s), 5.47 (1 H, s), 4.20 (1 H, br s), 3.35 (2 H, m), 2.95 (1 H, m), 2.67−2.58 (2 H, m), 2.51 (1 H, dt, $J = 12$ Hz, 3 Hz), 2.42 (1 H, m), 1.85−1.77 (2 H, m), 1.57 (1 H, d, $J = 14$ Hz), 1.47 (1 H, d, $J = 14$ Hz), 0.99 (2 H, m), 0.94 (3 H, t, $J = 8$ Hz). ^{13}C NMR ($CDCl_3$) δ 138.1, 134.5, 130.8, 130.3, 122.7, 121.6, 118.9, 113.3, 108.5, 90.4, 58.0, 54.2, 50.8, 44.7, 40.5, 24.8, 22.7, 21.4, 16.7, 6.4. CI-MS, *m/z* (relative intensity) 453 ($M^+ + 3$, 50%), 451 ($M^+ + 1$, 100%), 449 ($M^+ - 1$, 50%). HRMS (EI) calcd for $C_{20}H_{22}Br_2N_2$ ($M^+ - 2$): 448.01497, found 448.01480.

(+)-Apovincaminal (20a). To a solution of **19** (115 mg, 0.254 mmol) in DMSO (15 mL) were added $AgBF_4$ (250 mg, 1.2 mmol) and Et_3N (0.20 mL, 1.4 mmol) under strictly anhydrous conditions. The reaction mixture was heated at 90 °C for 9 h. After cooling to room temperature, the mixture was partitioned between H_2O and CH_2Cl_2. The organic layer was separated, and the aqueous layer was neutralized with saturated $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to provide a brown foam. Column chromatography (silica, CH_2Cl_2, 70% EtOAc in hexane, and 5% MeOH in CH_2Cl_2) gave **20a**, 65 mg, 83%. $R_f = 0.26$ (CH_2Cl_2:MeOH 95:5). UV (CH_3OH) λ_{max} 310, 280, 221, 210 nm.[7c] ^{1}H NMR ($CDCl_3$) δ 9.53 (1 H, s), 7.61 (1 H, d, $J = 8$ Hz), 7.45 (1 H, d, $J = 8$ Hz), 7.21 (1 H, t, $J = 7$ Hz), 7.14 (1 H, t, $J = 7$ Hz), 6.20 (1 H, s), 4.16 (1 H, s), 3.37 (1 H, dd, $J = 14$ Hz, 6 Hz), 3.28 (1 H, dt, $J = 12$ Hz, 7 Hz), 3.03 (1 H, m), 2.67 (2 H, d, $J = 7$ Hz), 2.54 (1 H, br d, $J = 13$ Hz), 2.03 (1 H, m), 1.95 (1 H, m), 1.78 (1 H, m), 1.56 (1 H, d, $J = 8$ Hz), 1.46 (1 H, d, $J = 13$ Hz), 1.07 (1 H, m), 1.05 (3 H, t, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$) δ 186.1, 140.5, 137.6, 134.4, 129.1, 122.5, 120.6, 118.1, 114.3, 109.5, 55.5, 51.4, 44.8, 38.5, 28.5, 27.0, 20.2, 16.3, 8.8. IR ($CHCl_3$) 1697, 1600 cm^{-1}. CI-MS, *m/z* (relative intensity) 307 ($M^+ + 1$, 100%). HRMS calcd for $C_{20}H_{23}N_2O$ ($M^+ + 1$): 307.1810, found 307.1810.

(+)-Apovincaminal Dimethyl Acetal (20b). 20a (120 mg, 0.39 mmol) was dissolved in anhydrous methanol (70 mL) and treated with $(MeO)_3CH$ (4.3 mL, 39 mmol) and $TsOH \cdot H_2O$ (0.35 g, 2.0 mmol). The solution was heated at reflux for 0.5 h and then cooled to room temperature. Saturated $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2; the organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to provide a light brown oil. Column chromatography (silica, 5% MeOH in CH_2Cl_2) afforded **20b**, 90 mg (66%). $R_f = 0.23$ (CH_2Cl_2:MeOH 95:5) UV active. ^{1}H NMR ($CDCl_3$) δ 7.74 (1 H, d, $J = 8$ Hz), 7.44 (1 H, d, $J = 8$ Hz), 7.17 (1 H, t, $J = 7$ Hz), 7.10 (1 H, t, $J = 7$ Hz), 5.54 (1 H, s), 5.44 (1 H, s), 4.19 (1 H, s), 3.48 (3 H, s), 3.36 (1 H, dt, $J = 14$ Hz, 6 Hz), 3.33 (3 H, s), 3.26 (1 H, dt, $J = 13$ Hz, 5 Hz), 3.03 (1 H, m), 2.71 (2 H, m), 2.52 (1 H, bd, $J = 4$ Hz), 1.97 (1 H, m), 1.79 (1 H, m), 1.76 (1 H, m), 1.49 (1 H, bd, $J = 14$ Hz), 1.42 (1 H, bd, $J = 11$ Hz), 1.14 (1 H, dt, $J = 14$ Hz, 3 Hz), 1.01 (3 H, t, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$) δ 133.9, 131.5, 129.0, 121.9, 119.8, 118.0, 117.9, 113.6, 108.0, 99.8, 56.1, 53.6, 52.2, 51.6, 45.1, 36.6, 29.8, 27.5, 20.5, 16.4, 8.9. IR ($CHCl_3$) 1455 cm^{-1}. CI-MS, *m/z* (relative intensity) 352 (M^+, 75%), 321 ($M^+ - CH_3O$, 100%). HRMS (CI) calcd for $C_{22}H_{29}N_2O_2^+$ (M^+): 352.2151, found 352.2156.

(+)-Apovincaminol (20c). 20a (12 mg, 0.039 mmol) was dissolved in MeOH (3 mL) and added to a cooled (0 °C) solution of $NaBH_4$ (6 mg, 0.12 mmol) in MeOH (4 mL). After 30 min, saturated sodium bicarbonate (1 mL) was added at 0 °C. The methanol was removed in vacuo, and the concentrated reaction material was partitioned between H_2O and CH_2Cl_2. The aqueous layer was washed with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and evaporated to provide a yellow-white foam. Purification by column chromatography (silica, 10% MeOH in CH_2Cl_2) afforded **20c**, 9 mg (75%).

$R_f = 0.33$ (CH_2Cl_2:MeOH 90:10). UV active. ^{1}H ($CDCl_3$) δ 7.70 (1 H, d, $J = 9$ Hz), 7.47 (1 H, d, $J = 7$ Hz), 7.22 (1 H, t, $J = 7$ Hz), 7.16 (1 H, t, $J = 7$ Hz), 5.14 (1 H, s), 4.88 (1 H, d, $J = 13$ Hz), 4.62 (1 H, d, $J = 13$ Hz), 4.28 (1 H, bs), 3.40 (1 H, dd, $J = 14$ Hz, 6 Hz), 3.29 (1 H, dt, $J = 12$ Hz, 7 Hz), 3.00 (1 H, m), 2.78 (2 H, bs), 2.49 (1 H, dd, $J = 14$ Hz, 6 Hz), 1.97 (1 H, m), 1.84 (2 H, m), 1.47 (2 H, t, $J = 12$ Hz), 1.17 (1 H, t, $J = 14$ Hz), 1.01 (3 H, t, $J = 7$ Hz). See text for additional characterization at Hannover.

Mosher Ester of (+)-Apovincaminol. To a CH_2Cl_2 (5 mL) solution of (S)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (21 mg, 0.088 mmol) wwew added DMAP (2 mg, 0.015 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (20 mg, 0.102 mmol), and **20c** (9 mg, 0.029 mmol) in CH_2Cl_2 (5 mL). The solution was stirred for 15 h and then concentrated under reduced pressure to afford a yellow film. Purification by column chromatography (silica, CH_2Cl_2, 2% MeOH/CH_2Cl_2, and 5% MeOH/CH_2Cl_2) provided 15 mg (quantitative yield) of the Mosher ester. $R_f = 0.22$ (CH_2Cl_2:MeOH 95:5). UV active. ^{1}H NMR ($CDCl_3$) δ 7.47 (2 H, d, $J = 8$ Hz), 7.43 (1 H, d, $J = 8$ Hz), 7.37−7.27 (4 H, m), 7.07 (1 H, t, $J = 7$ Hz), 7.01 (1 H, t, $J = 8$ Hz), 5.61 (1 H, d, $J = 13$ Hz), 5.27 (1 H, s), 5.17 (1 H, d, $J = 13$ Hz), 4.17 (1 H, s), 3.44 (3 H, s), 3.37 (1 H, dd, $J = 14$ Hz, 6 Hz), 3.27 (1 H, dt, $J = 13$ Hz, 5 Hz), 3.01 (1 H, m), 2.68 (2 H, bs), 2.53 (1 H, bd, $J = 17$ Hz), 1.94 (1 H, m), 1.75 (2 H, m), 1.42 (2 H, bs), 1.08 (1 H, dt, $J = 14$ Hz, 4 Hz), 0.97 (3 H, t, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$) δ 166.2, 133.5, 131.9, 129.8, 129.6, 128.9, 128.3, 127.1, 124.3, 122.6, 122.3, 122.0, 120.1, 118.4, 111.5, 108.3, 64.6, 55.8, 55.5, 51.6, 46.5, 45.0, 37.0, 29.4, 27.2, 20.4, 16.3, 8.7. ^{19}F NMR ($CDCl_3$) δ 4.12 (major diastereomer), 4.23 (minor). The ratio of integrated areas of the ^{19}F signals was 22:1. A mixture of the diastereomers also was prepared (see text). ^{19}F NMR ($CDCl_3$) δ 4.11, 4.21 (ratio of integrated areas = 1:1).

(+)-Apovincamine (1a). To a solution of **20b** (25 mg, 0.071 mmol) in CCl_4 (30 mL) were added AIBN (7 mg, 0.04 mmol) and NBS (15 mg, 0.085 mmol). The mixture was immediately immersed in an oil bath at 95 °C and heated for 0.5 h. After cooling to room temperature, the reaction was concentrated under reduced pressure. Column chromatography (silica, EtOAc, 5% MeOH/CH_2Cl_2) gave (+)-apovincamine (**1a**), 11 mg (47%). $R_f = 0.28$ (CH_2Cl_2/MeOH 95:5) UV active. ^{1}H NMR ($CDCl_3$) δ 7.48 (1 H, d, $J = 8$ Hz), 7.24−7.14 (3 H, m), 6.15 (1 H, s), 4.32 (1 H, bs), 3.96 (3 H, s), 3.51 (1 H, m), 3.37 (1 H, dt, $J = 13$ Hz, 5 Hz), 3.06 (1 H, m), 2.85 (1 H, bd, $J = 11$ Hz), 2.72 (1 H, m), 2.03 (2 H, m), 1.89 (1 H, m), 1.58 (1 H, d, $J = 14$ Hz), 1.49 (1 H, d, $J = 14$ Hz), 1.07 (1 H, m), 1.04 (3 H, t, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$) δ 163.5, 134.3, 128.5, 128.3, 127.4, 122.6, 120.7, 118.4, 112.6, 108.4, 56.1, 52.7, 51.5, 44.8, 37.9, 27.8, 27.2, 19.4, 16.1, 8.6. IR ($CHCl_3$) 1731, 1636, 1610, 1456, 1266 cm^{-1}. See text for additional discussion of product characterization.

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Supporting Information Available: Copies of proton and carbon NMR spectra (20 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.

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