Asymmetric Total Synthesis of the *Stemona* Alkaloid (−)-Stenine

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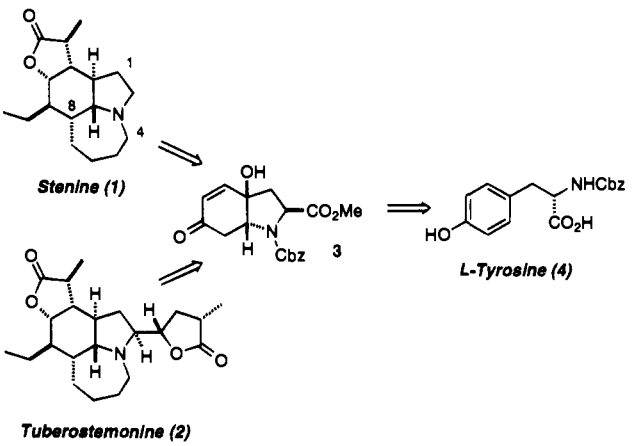
Abstract: Stenine can be extracted from the roots of the Chinese medicinal plant *Stemona tuberosa* (Stemonaceae), and its structure and absolute configuration were derived by comparison to the major *Stemona* alkaloid tuberostemonine. We report the first enantioselective total synthesis of (−)-stenine by a strategy that takes advantage of a diastereoselective end-group-differentiating cyclization in the oxidation of L-tyrosine. The resulting *cis*-fused indolone is converted to the *trans*-fused core of stenine upon reduction of a π-allylpalladium complex, and by stereoselective introduction of four additional stereocenters, a butyrolactone and an azepine ring are attached to this alkaloid building block.

Extracts of *Stemona* and *Croomia* species have been used in Chinese and Japanese folk medicine as insecticides, as drugs for the treatment of respiratory diseases such as bronchitis, pertussis, and tuberculosis, and as antihelmintics.[1] A large number of polycyclic alkaloids are found in the roots and rhizomes of *Stemonaceae*, and to date, the diverse structures of more than 20 polycyclic members of this class have been elucidated by a combination of crystallographic, spectroscopic, and degradative techniques.[2] However, synthetic work has been quite limited, with total syntheses of *racemic* stenine reported by Hart and Chen[3] and (+)-croomine and (−)-stemoamide by Williams[4] and co-workers.[5]

The efficient preparation of the novel and highly functionalized azepinoindole core of the major *Stemona* alkaloids stenine (**1**)[6] and tuberostemonine (**2**)[7] offers an interesting synthetic problem. We envisioned a concise entry toward the perhydroindole ring system by means of bicycle **3**, which is obtained enantio- and diastereomerically pure *in a single step* from L-tyrosine (**4**).[8] In this article, we document the potential for a general use of **3** in pyrrolidine alkaloid synthesis with a specific application for the first asymmetric synthesis of (−)-stenine. A major challenge of this strategy, the conversion of the *cis*-hydroxyindole ring system in **3** to the *trans*-fused perhydroindole present in **1** and **2**, was effectively solved by π-allylpalladium chemistry.



Results and Discussion

The yield of the transformation of tyrosines **4** and **5** to bicycles **3** and **8** depends on the nature of the protective group R and the scale of the reaction (Scheme 1).[8] With R = OBn, typical yields are 40−55% on a 1 g scale, whereas with R = OBu^t, yields as high as 60% can be obtained.[9] The high selectivity of this diastereotopic end-group-differentiating[10] cyclization is due to destabilizing steric interactions in conformers **7**, especially $A^{1,3}$-strain[11] between the amide oxygen and the methyl ester (E) substituent. Additionally, face-to-face interaction of the *trans*-amide and enone π-systems in the transition state for the cyclization positions the ester function in conformers **7** underneath the dienone in a sterically crowded environment. Traces of isomers **9** are only observed if the cyclization is performed at $T > 100$ °C in DMSO, and attempted further thermodynamic equilibrations of **8** (R = OBu^t) to **9** (R

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(2) See, for example: (a) Dao, C. N.; Luger, P.; Ky, P. T.; Kim, V. N.; Dung, N. X. *Acta Crystallogr. C* **1994**, *C50*, 1612. (b) Ye, Y.; Qin, G. W.; Xu, R. S. *Phytochemistry* **1994**, *37*, 1205, 1201. (c) Ye, Y.; Qin, G. W.; Xu, R. S. *J. Nat. Prod.* **1994**, *57*, 665. (d) Lin, W.; Ye, Y.; Xu, R. *J. Nat. Prod.* **1992**, *55*, 571. (e) Lin, W.; Xu, R.; Zhong, Q. *Huaxue Xuebao* **1991**, *49*, 927. (f) Lin, W.; Ye, Y.; Xu, R. *Chin. Chem. Lett.* **1991**, *2*, 369.

(3) (a) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840. (b) Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1990**, *55*, 6236.

(4) (a) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (b) Williams, D. R.; Reddy, J. P.; Amato, G. S. *Tetrahedron Lett.* **1994**, *35*, 6417.

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(6) (a) Uyeo, S.; Irie, H.; Harada, H. *Chem. Pharm. Bull.* **1967**, *15*, 768. (b) Harada, H.; Irie, H.; Masaki, N.; Osaki, K.; Uyeo, S. *J. Chem. Soc., Chem. Commun.* **1967**, 460.

(7) (a) Schild, H. *Ber. Dtsch. Chem. Ges.* **1936**, *69*, 74. (b) Goetz, M.; Boegri, T.; Gray, A. H.; Strunz, G. M. *Tetrahedron* **1968**, *24*, 2631.

(8) Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477.

(9) The structural assignments of bicycles **3** and **8** are based on NOE and coupling constant analyses.[8]

(10) (a) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (b) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738.

(11) Hoffman, R. W. *Chem Rev.* **1989**, *89*, 1841.

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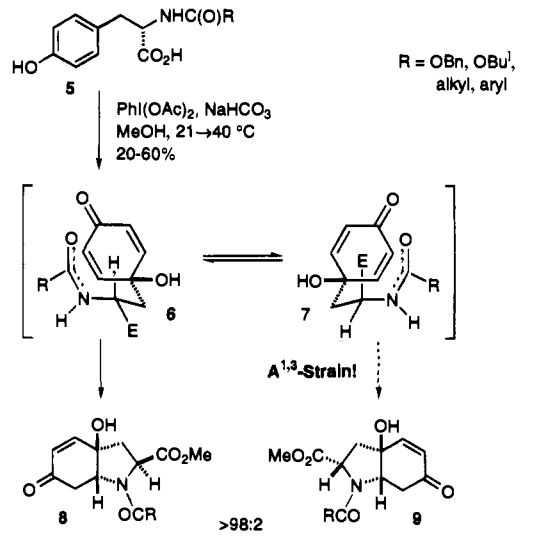
Scheme 1



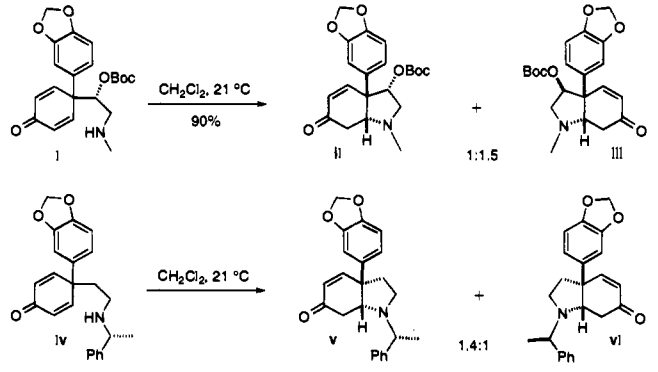
= OBu^t) failed under acidic and basic, as well as thermal, reaction conditions.[12,13]

Benzoylation of the tertiary allylic alcohol in the Cbz-protected bicycle **3** and reduction of the enone with $NaBH_4$ in the presence of $CeCl_3$[14] gave the equatorial alcohol **10** in 89% yield as a single diastereomer (Scheme 2). Reduction of the π-allylpalladium complex derived from **10** at the more hindered tertiary carbon required considerable optimization of the reaction conditions. The use of catalytic tris(dibenzylideneacetone)-dipalladium(0) chloroform complex (2.5 mol %), tributylphosphine (10 mol %), and triethylammonium formate[15] at 60 °C under strictly anaerobic conditions maximized the yield of the desired *trans*-hexahydroindole **11**.

Variations in the nature of the reducing agent and palladium ligands had a major impact on the product distribution in this reaction. In the presence of catalytic tricyclohexylphosphine, homoallylic alcohol **12** was formed in 65% as the major product, and in the absence of amines, the more acidic reaction conditions provided diene **13** as the sole product even in the presence of tributylphosphine. The use of sodium borohydride as the reducing agent resulted in a mixture of allylic alcohol **11** and

(12) The ^1H NMR spectrum of a mixture of bicyclic products obtained by the cyclization to **8** (R = OBu^t) in DMSO-d_6 at 100 °C is shown in the supporting information.

(13) The importance of the proposed allylic strain interactions in the highly diastereoselective formation of bicycles **3** and **8** is clearly illustrated by comparison to the results of Martin et al. in the cyclization of dienone amines **i** and **iv**, which lack the conformational rigidity of tyrosine carbamates and provide mixtures of hydroindoles: (a) Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962. (b) Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184.



(14) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.

(15) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1992**, *57*, 1326.

Scheme 2

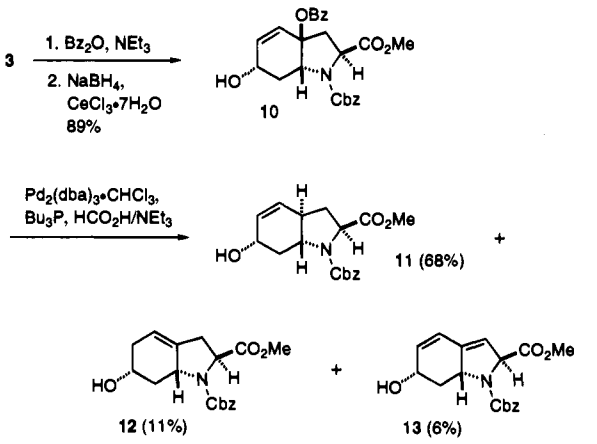


Table 1. Regioselective Reduction of Allylic Benzoate **10**

		isolated yields (%)		
entry	reaction conditions (solvent = THF)	**11**	**12**	**13**
1	$Pd_2(dba)_3$•$CHCl_3$, Bu_3P, HCO_2H/NEt_3, 60 °C	68	11	6
2	$Pd_2(dba)_3$•$CHCl_3$, Bu_3P, HCO_2NH_4, 60 °C	69	12	11
3	$Pd_2(dba)_3$•$CHCl_3$, $(C_6H_{11})_3P$, HCO_2NH_4, 60 °C	7	65	6
4	$Pd_2(dba)_3$•$CHCl_3$, Bu_3P, HCO_2H, 60 °C			82
5	$Pd_2(dba)_3$•$CHCl_3$, Bu_3P, $NaBH_4$, 22 °C	7	65	
6	$Pd(Ph_3P)_4$, Ph_3P, $NaBH_4$, 22 °C	37	52	

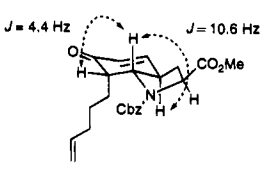
homoallylic alcohol **12** (Table 1). In contrast, attempted reduction of *O*-protected derivatives of **10** was unsuccessful and starting material was recovered unchanged. The allylic alcohol probably assists in the complexation of Pd(0) from the sterically very hindered concave face of the bicycle (Figure 1). Subsequently, hydride transfer is proposed to occur from complexed formate to the more hindered terminus of the alkene in **15**.

Oxidation of the allylic alcohol **11** with tetrapropylammonium perruthenate (TPAP)[16] regenerated the enone which was deprotonated with KHMDSA (Scheme 3). Due to the low reactivity of the resulting cross-conjugated dienolate and its instability at temperatures > -10 °C (probably due to β-elimination of the carbamate), the subsequent alkylation had to be performed with pentenyl triflate. In contrast to the previously observed preferential equatorial alkylation from the β-face of the *cis*-bicycle **3**,[8] the *trans*-fused dienolate derived from **11** underwent exclusive axial attack from the α-face to give the desired enone **16** in 34% yield (51% based on recovered starting material).[17] The moderate yield in this transformation is due to competitive *O*-alkylation by the alkyl triflate, which we have yet been unable to suppress by variation of the dienolate counterion.

1,2-Reduction of enone **16** to the equatorial alcohol with $NaBH_4/CeCl_3$[14] set the stage for the introduction of the butyrolactone moiety (Scheme 3). Before the planned iodolactonization of the γ,δ-unsaturated amide **17**, obtained in 77% yield from enone **16** by an Eschenmoser−Claisen rearrangement,[18,3] functional group manipulations at the terminal alkene and the pyrrolidine ring were performed. Selective cleavage

(16) Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13.

(17) The stereochemistry of **16** was assigned on the basis of the vicinal coupling constants:



(18) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425.

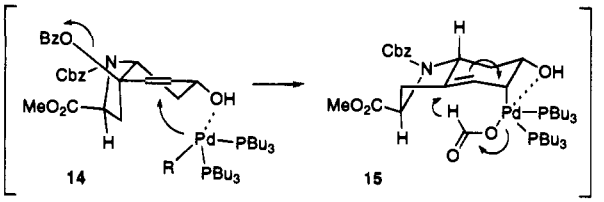
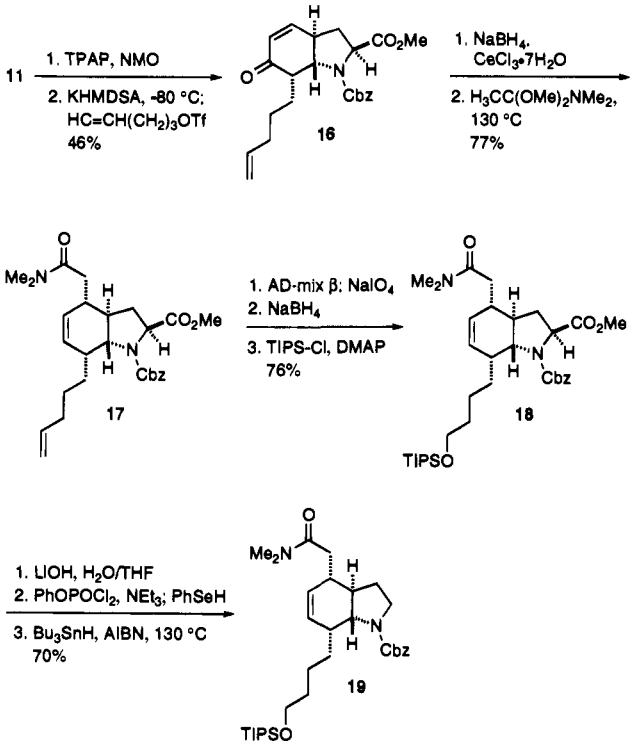


Figure 1.

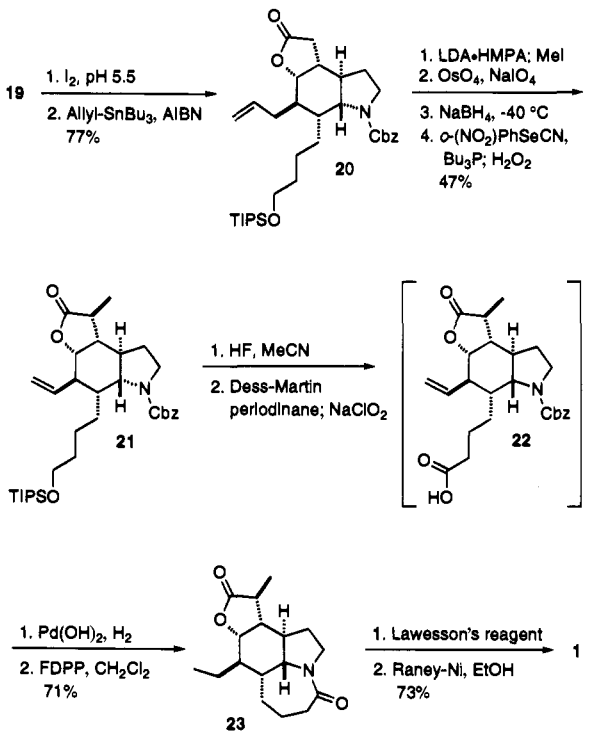
Scheme 3



of the monosubstituted alkene over the cyclohexene ring was best performed with AD-mix-β[19] followed by sodium periodate cleavage of the resulting diol. These conditions provided a considerably improved selectivity over the standard Johnson–Lemieux[20] protocol. Reduction of the aldehyde and silylation of the primary alcohol gave the triisopropylsilyl ether **18** in 76% overall yield from alkene **17**. The tyrosine-derived methyl ester at C(2) of bicycle **18** provides a convenient handle for the introduction of the butyrolactone ring in tuberostemonine (**2**), but since this moiety is not present in stenine, the ester was reductively decarbonylated with the method of Ireland et al.[21] to give **19** in 70% yield.

During the iodolactonization[3] of the γ,δ-unsaturated amide **19**, the pH of the reaction medium had to be adjusted to 5.5 to minimize silyl ether hydrolysis (Scheme 4). Subsequent Keck allylation[22] in neat allyltributylstannane gave **20** in 77% yield. Methylation of the lactone occurred selectively in 87% yield from the sterically more accessible face, and subsequent conversion of the allyl to a vinyl group by a Johnson–Lemieux oxidation,[20] reduction, and Grieco-elimination[23] sequence provided tricycle **21** in 54% yield.

Scheme 4



Closure of the azepine, the last remaining ring of the tetracyclic stenine, was initiated by desilylation of **21** and oxidation of the primary alcohol to the acid by sequential treatment with Dess–Martin periodinane[24] and sodium chlorite.[25] Without purification, the resulting acid **22** was directly hydrogenated and cyclized with pentafluorophenyl diphenylphosphinate (FDPP)[26] for 30 h at room temperature to give lactam **23** in 71% yield from **21**. Conversion of the amide to the thioamide with Lawesson's reagent[27,3] and desulfurization with Raney nickel provided (−)-stenine with an $[\alpha]^{21}_D$ −29.4° (*c* 0.4, CH_3OH)[28] and an overall yield of 2% for the 25-step sequence starting with bicycle **3**. Spectroscopic data (^1H NMR, ^{13}C NMR, MS (EI)) for synthetic (−)-**1** were in complete agreement with the reported[3,6] values. The asymmetric synthesis of (−)-stenine confirms the absolute configuration of the natural product that was previously tentatively assigned[6] on the basis of chemical and X-ray analyses of the related alkaloid tuberostemonine.

Whereas the formation of the azepine ring via lactam **23** was successful, cyclization of the amino alcohol **24** under a variety of Mitsunobu conditions[29] failed (Scheme 5). In contrast, a similar cyclization of the closely related amino alcohol **25**[30] provided azepine **26** in 59% yield. Since the success of medium ring formation under Mitsunobu conditions depends on the rate of cyclization vs side reactions of the activated alcohol,[29] the conformation of *cis*-hydroindole **25** is probably considerably more preorganized toward seven-membered ring formation than that of *trans*-hydroindole **24**.

(19) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(20) Pappo, R.; Allen, D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478. Under these conditions, yields of <30% of the desired aldehyde were obtained.

(21) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285.

(22) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.

(23) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(24) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(25) Pinnick, H. W.; Balakrishna, S. B.; Childers, W. E. *Tetrahedron* **1981**, *37*, 2091.

(26) (a) Chen, S.; Xu, J. *Tetrahedron Lett.* **1991**, *32*, 6711. (b) Dudash, J.; Jiang, J.; Mayer, S. C.; Joullié, M. M. *Synth. Commun.* **1993**, *23*, 349.

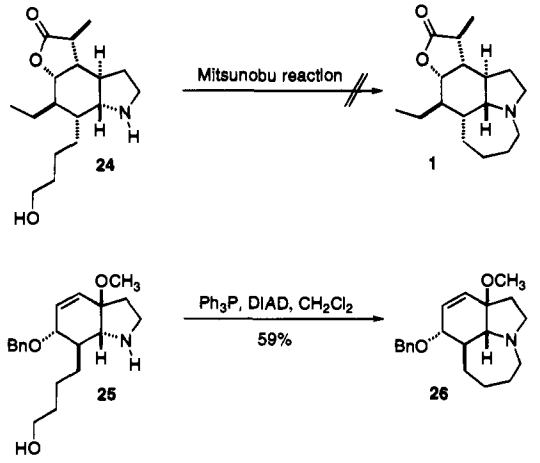
(27) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

(28) Natural (−)-**1** was reported with an $[\alpha]^{21}_D$ of −30.2° (CH_3OH).[6]

(29) (a) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (b) Bernotas, R. C.; Cube, R. V. *Tetrahedron Lett.* **1991**, *32*, 161.

(30) This compound was prepared as part of a model study toward racemic stenine: Wipf, P.; Goldstein, D. M. Unpublished results.

Scheme 5



In conclusion, the first asymmetric total synthesis of (−)-stenine highlights the potential for pyrrolidine alkaloid synthesis offered by the ready availability of bicycle **3**. All six stereocenters at the perhydroindole core of the *Stemona* alkaloid can be derived directly and with high stereoselectivity from the functionality present in this versatile building block. It is worthwhile pointing out that a dienone intermediate in the formation of bicycle **3** has also been used as a starting material for the total synthesis of a structurally very different natural product, the antifungal antibiotic (−)-aranorosin.[31] Further applications of **3** and related oxidative rearrangement products of tyrosine for the synthesis of tuberostemonine and other *Stemona* and *Amaryllidaceae* alkaloids are currently in progress.

Experimental Section

General Methods. NMR spectra were recorded on a 500 or 300 MHz spectrometer in $CDCl_3$ unless otherwise noted. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. Analytical TLC used Merck silica gel 60 F-254 plates, and flash chromatography was used to separate and purify the crude reaction mixtures.

(2*S*,3a*R*,7a*R*)-3a-Hydroxy-6-oxo-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Methyl Ester (3).[8] To a vigorously stirred mixture of 500 mg (1.59 mmol) of Cbz-tyrosine (**4**) and 534 mg (6.36 mmol) of $NaHCO_3$ in 20 mL of MeOH was added 783 mg (2.39 mmol) of iodobenzenediacetate in three portions in 10 min intervals. The reaction mixture was stirred at 23 °C for 14 h, poured into 50 mL of H_2O, and extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine and dried (Na_2SO_4). Chromatography on SiO_2 (hexanes/EtOAc, 1:1) of the residue gave 296 mg (54%) of bicycle **3** as an oil: $[\alpha]_D$ −65.3° (*c* 0.3, $CHCl_3$, 21 °C); IR (neat) 3420, 2960, 1750, 1730, 1700, 1420, 1360 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.34 (s, 5 H), 6.74 (d, 2 H, J = 10.3 Hz), 5.88 (d, 2 H, J = 10.3 Hz), 5.09 (s, 2 H), 4.48 (dd, 2 H, J = 9.0, 2.5 Hz), 4.21 (dd, 2 H, J = 9.4, 5.9 Hz), 3.60 (s, 3 H), 2.90 (dd, 1 H, J = 16.1, 5.7 Hz), 2.65−2.53 (m, 2 H), 2.27 (ddd, 1 H, J = 13.2, 2.5, 0.8 Hz); ^{13}C NMR δ 196.0, 174.0, 173.6, 154.1, 153.5, 148.2, 148.0, 135.6, 128.6, 128.4, 128.3, 128.1, 128.0, 127.9, 76.2, 75.1, 67.6, 67.3, 65.3, 65.1, 58.7, 58.4, 52.9, 52.5, 42.4, 41.5, 40.2, 39.2; MS (EI) *m/z* (relative intensity) 286 ([M − CO_2CH_3]$^+$, 4), 242 (19), 211 (8), 107 (8), 91 (100); HRMS (EI) calcd for $C_{16}H_{16}NO_4$ [M − CO_2CH_3] 286.1079, found 286.1084.

(2*S*,3a*R*,6*S*,7a*R*)-3a-(Benzoyloxy)-6-hydroxy-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Methyl Ester (10). To a solution of 10.7 g (31.0 mmol) of **3** in 20 mL of dry CH_2Cl_2 was added 11.4 g (50.0 mmol) of benzoic anhydride, 0.50 g (4.1 mmol) of DMAP, and 12.5 g (158 mmol) of pyridine. The solution was heated at reflux for 24 h before 10 mL of 10% HCl was added. The reaction mixture was extracted into $CHCl_3$, dried ($MgSO_4$), and concentrated in vacuo to give a brown oil. Chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 2:1) yielded 12.5 g (90%) of (2*S*,3a*R*,7a*R*)-3a-(benzoyloxy)-6-oxo-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**27**) as a pale yellow foam: $[\alpha]_D$ −172.0° (*c* 0.37, $CHCl_3$, 21 °C); IR (neat) 3025, 2951, 1757, 1713 (br), 1412, 1348, 1279, 1252, 1178, 1109, 1039, 951, 756, 713 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.88 (d, 2 H, J = 8.2 Hz), 7.65 (t, 1 H, J = 7.4 Hz), 7.51 (t, 2 H, J = 7.6 Hz), 7.32 (s, 5 H), 7.10 (d, 1 H, J = 10.4 Hz), 6.07 (d, 2 H, J = 10.4 Hz), 5.11, 5.09 (AB, 2 H, J = 12.5 Hz), 4.94 (dd, 1 H, J = 9.9, 6.7 Hz), 4.70 (dd, 1 H, J = 8.2, 3.2 Hz), 3.50 (s, 3 H), 2.88−3.10 (m, 3 H), 2.76 (dd, 1 H, J = 16.5, 10.0 Hz); ^{13}C NMR δ 194.6, 194.5, 170.9, 170.4, 165.0, 164.8, 153.7, 153.4, 144.6, 143.9, 135.7, 135.6, 133.4, 129.6, 129.4, 129.1, 129.0, 128.3, 128.1, 128.0, 127.8, 127.7, 83.6, 82.5, 67.4, 67.0, 61.6, 60.9, 60.0, 58.1, 57.9, 52.1, 52.0, 42.4, 41.2, 39.1, 38.2, 20.7, 13.9; MS (EI) *m/z* (relative intensity) 327 ([M − $C_7H_6O_2$]$^+$, 4), 283 (10), 224 (16), 91 (100); HRMS *m/z* calcd for $C_{18}H_{17}NO_5$ [M − $C_7H_6O_2$] 327.1107, found 327.1089.

A solution of 19.1 g (42.6 mmol) of enone **27** in 90 mL of THF was treated with a solution of 15.9 g (42.6 mmol) of cerium(III) chloride heptahydrate in 70 mL of MeOH. After being stirred for 5 min at room temperature, the solution was cooled to 0 °C and 2.74 g (21.9 mmol) of $NaBH_4$ was added over a 30 min. After the addition was complete, the reaction mixture was stirred at 0 °C for 2 h, warmed to room temperature, and stirred for 5 h. Brine (100 mL) was added, followed by 1 mL of 10% HCl, and the product was extracted into EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to give 18.95 g (99%) of foamy **10**: $[\alpha]_D$ −101.0° (*c* 2.7, $CHCl_3$, 21 °C); IR (neat) 3447, 3065, 3033, 2953, 1757, 1712 (br), 1414, 1354, 1278, 1211, 1110, 1069, 757, 712, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.84 (d, 2 H, J = 7.9 Hz), 7.61 (t, 1 H, J = 7.5 Hz), 7.48 (t, 2 H, J = 7.6 Hz), 7.32 (bs, 5 H), 5.96−5.85 (m, 2 H), 5.10 (bs, 2 H), 4.7−4.6 (m, 2 H), 4.4−4.3 (m, 1 H), 3.38 (s, 3 H), 2.9−2.7 (m, 1 H), 2.66 (dd, 2 H, J = 14.5, 9.7 Hz), 1.47 (q, 1 H, J = 11.2 Hz); ^{13}C NMR δ 171.7, 171.2, 165.4, 165.2, 154.6, 154.2, 137.4, 136.7, 136.2, 136.1, 133.2, 130.1, 129.6, 128.6, 128.4, 128.3, 128.0, 124.9, 124.5, 86.2, 85.2, 67.5, 67.2, 65.7, 65.5, 61.0, 60.3, 58.5, 52.3, 52.1, 39.7, 39.0, 38.8, 37.9; MS (CI) *m/z* (relative intensity) 452 ([M + 1]$^+$, 1), 434 ([M − H_2O + 1]$^+$, 25), 344 (30), 330 (100), 286 (65), 268 (50), 194 (20), 91 (50).

(2*S*,3a*R*,6*S*,7a*R*)-6-Hydroxy-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Methyl Ester (11). A base washed (10% NaOH) and silylated (TMS-Cl) Schlenk tube attached to a Firestone adapter was charged with 0.114 g (0.11 mmol) of tris(dibenzylideneacetone)dipalladium(0) chloroform complex, 2.0 g (4.43 mmol) of benzoate **10**, 20 mL of freshly distilled anhydrous THF, and 108 μL (0.443 mmol) of tri-*n*-butylphosphine. After being stirred for 1 min, 2.0 mL (14.3 mmol) of triethylamine and 0.5 mL (14.3 mmol) of distilled formic acid were added. The reaction mixture was immediately degassed by repetitive freezing, evacuating (0.2 Torr), and thawing under an argon atmosphere. Once degassed, the solution was stirred at 60 °C for 7 h and cooled to room temperature, and the solvent was removed in vacuo. The remaining oil was purified by chromatography on SiO_2 (hexanes/EtOAc, 3:1 to 2:1) to give 87 mg (6%) of diene **13** and 1.160 mg (79%) of a 1:6.2 mixture of homoallylic alcohols **12** and **11**: IR (neat) 3409, 3029, 2953, 2942, 2880, 1747, 1713 (br), 1699, 1423, 1347, 1261, 1201, 1131, 1040, 1027, 753, 712, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.4−7.3 (m, 5 H), 5.71 (d, 1 H, J = 9.8 Hz), 5.65−5.55 (m, 1 H), 5.07, 5.04 (AB, 2 H, J = 12.6 Hz), 4.56 (t, 1 H, J = 5.0 Hz), 4.4−4.35 (m, 2 H), 3.55 (s, 3 H), 3.22−3.12 (m, 1 H), 2.5−2.35 (m, 1 H), 1.7−1.3 (m, 2 H), 0.95−0.85 (m, 1 H); ^{13}C NMR δ 173.2, 155.3, 154.2, 136.2, 136.1, 132.3, 131.9, 128.4, 128.2, 128.1, 127.2, 126.8, 120.0, 84.0, 68.5, 67.3, 66.7, 60.7, 60.2, 52.0, 44.2, 43.7, 38.2, 37.6, 34.3, 33.2, 32.6; MS (EI) *m/z* (relative intensity) 331 (M$^+$, 4), 286 (1), 272 (45), 245 (20), 228 (65),196 (65), 91 (100); HRMS *m/z* calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1400.

(2*S*,3a*R*,7*S*,7a*S*)-6-Oxo-7-pent-4-enyl-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Methyl Ester (16). A solution of 4.96 g (14.98 mmol) of a 6.2:1 mixture of alcohols **11** and **12** and 2.23 g (16.5 mmol) of *N*-methylmorpholine *N*-oxide monohydrate in 100 mL of anhydrous CH_2Cl_2 was cooled to 0 °C, and 5.0 g of powdered 4 Å molecular sieves was added followed by 0.526 g

(31) Wipf, P.; Kim, Y.; Fritch, P. C. *J. Org. Chem.* **1993**, *58*, 7195.

(1.5 mmol) of tetrapropylammonium perruthenate. The reaction mixture was stirred at 0 °C for 2 h and at room temperature for 2 h. The solution was concentrated to 40 mL, filtered through a plug of SiO_2 (hexanes/EtOAc, 1:1), concentrated, and purified by chromatography on SiO_2 (hexanes/EtOAc, 3:1) to yield 3.81 g (90%) of (2*S*,3a,-7a*R*)-6-oxo-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**28**): $[\alpha]_D$ −103.1° (*c* 0.65, $CHCl_3$, 21 °C); IR (neat) 3034, 2992, 2984, 2953, 2884, 1747, 1714 (br), 1680 (br), 1454, 1423, 1344, 1262, 1226, 1197, 1169, 1132, 767, 753 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.0−6.9 (m, 5 H), 6.70 (dd, 1 H, J = 9.8, 2.0 Hz), 5.54 (dd, 1 H, J = 9.8, 2.7 Hz), 4.67, 4.64 (AB, 2 H, J = 12.5 Hz), 4.07 (dd, 1 H, J = 8.8, 8.0 Hz), 3.18 (s, 3 H), 3.2−3.12 (m, 1 H), 2.98 (dd, 1 H, J = 16.6, 3.8 Hz), 2.25 (ddd, 1 H, J = 12.4, 7.6, 6.8 Hz), 2.15−2.05 (m, 2 H), 1.3−1.18 (m, 1 H); ^{13}C NMR δ 197.7, 172.7, 154.9, 153.9, 146.5, 145.9, 136.0, 131.9, 131.6, 128.6, 128.5, 128.3, 67.6, 67.0, 60.9, 60.6, 60.3, 52.5, 52.2, 45.8, 45.0, 43.8, 43.2, 32.2, 31.6; MS (CI) *m/z* (relative intensity) 330 ($[M + 1]^+$, 25), 285 (1), 270 (2), 226 (10), 194 (20), 91 (100); MS (EI) *m/z* (relative intensity) 329 (M^+, 1), 283 (10), 224 (16), 91 (100).

A solution of 52 mg (0.158 mmol) of enone **28** in 0.5 mL of toluene was added at −80 °C to 0.175 mL (0.175 mmol) of 1 M potassium hexamethyldisilazane. The resulting dark red solution was stirred for 2 min, 100 mg (0.458 mmol) of 4-pentenyl-1-triflate was added, and the reaction mixture was warmed to −60 °C. After addition of 0.20 mL of THF, the solution was stirred at −60 °C for an additional 3 h, quenched by the addition of saturated $NaHCO_3$, and warmed to room temperature. The product was extracted into EtOAc, washed with brine, and dried ($MgSO_4$). Purification by chromatography on SiO_2 (hexanes/EtOAc, 9:1 to 4:1) yielded 17.8 mg (33%) of **28** and 21.3 mg (34%) of **16**: $[\alpha]_D$ −92.5° (*c* 1.0, $CHCl_3$, 21 °C); IR (neat) 3069, 3034, 2947, 2858, 1750, 1711, 1674, 1420, 1341, 1263, 1200, 1171, 1132 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.4−7.3 (m, 5 H), 7.03 (dd, 1 H, J = 10.7, 1.4 Hz), 5.87 (dd, 1 H, J = 9.8, 2.9 Hz), 5.85−5.65 (m, 1 H), 5.06 (s, 2 H), 5.1−4.85 (m, 2 H), 4.46 (t, 1 H, J = 7.2 Hz), 3.69 (dd, 1 H, J = 10.6, 4.4 Hz), 3.58 (s, 3 H), 3.5−3.2 (m, 3 H), 2.65−2.55 (m, 1 H), 2.1−1.8 (m, 2 H), 1.65−1.25 (m, 4 H); ^{13}C NMR δ 200.4, 172.7, 154.9, 153.6, 145.7, 145.2, 138.5, 138.2, 136.0, 135.8, 135.4, 130.6, 130.3, 128.7, 128.6, 128.4, 128.2, 128.2, 117.7, 114.6, 114.5, 70.6, 67.6, 66.9, 64.0, 63.5, 60.6, 60.1, 52.4, 52.1, 50.5, 49.5, 38.1, 37.4, 33.8, 33.7, 32.1, 31.4, 25.6, 25.5, 22.6, 22.5; MS (EI) *m/z* (relative intensity) 397 (M^+, 10), 328 (10), 311(10), 294 (50), 262 (100), 243 (50), 175 (50), 107 (70); HRMS *m/z* calcd for $C_{15}H_{20}NO_3$ ($M - CO_2CH_2Ph$) 262.1143, found 262.1460.

(2*S*,3a*R*,4*S*,7*R*,7a*S*)-4-((Dimethylcarbamoyl)methyl)-7-pent-4-enyl-2,3,3a,4,7,7a-hexahydroindole-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Methyl Ester (17). A solution of 1.09 g (2.74 mmol) of enone **16** in 15 mL of THF and 15 mL of MeOH was treated with 1.02 g (2.74 mmol) of cerium trichloride heptahydrate and warmed to 40 °C, and 0.165 g (4.38 mmol) of $NaBH_4$ was added over a 5 min period. Subsequently, the reaction mixture was stirred at 40 °C for 1.5 h, added to 10 mL of distilled H_2O and 2 mL of 10% HCl solution, and extracted into $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated in vacuo to a foam which was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1 to 3:1) to give 0.992 g (91%) of (2*S*,3a*R*,6*R*,7*S*,7a*S*)-6-hydroxy-7-pent-4-enyl-2,3,3a,6,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**29**): $[\alpha]_D$ −169.8° (*c* 1.1, $CHCl_3$, 21 °C); IR (neat) 3465, 3065, 3031, 2949, 2929, 2859, 1746, 1712, 1699, 1435, 1425, 1347, 1263, 1197, 1166, 1133, 699 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.35−7.25 (m, 5 H), 5.8−5.7 (m, 1 H), 5.64 (d, 1 H, J = 9.9 Hz), 5.50 (bd, 1 H, J = 10 Hz), 5.06, 4.98 (AB, 2 H, J = 12.8 Hz), 4.95−4.85 (m, 2 H), 4.5−4.3 (m, 2 H), 3.55 (s, 3 H), 3.28 (dd, 1 H, J = 10.3, 2.8 Hz), 3.15−3.05 (m, 1 H), 2.46 (m, 1 H), 2.55−2.4 (m, 2 H), 2.0−1.9 (m, 2 H), 1.6−1.5 (m, 1 H), 1.45−1.3 (m, 3 H) 1.15−1.05 (m, 1 H); ^{13}C NMR δ 173.2, 155.3, 153.9, 139.0, 138.7, 136.3, 132.4, 131.6, 129.4, 128.5, 128.4, 128.3, 128.1, 127.4, 125.5, 114.3, 114.2, 71.2, 71.0, 67.3, 66.6, 64.0, 63.7, 60.1, 51.9, 40.6, 39.8, 37.8, 37.2, 34.4, 33.0, 32.3, 28.8, 28.4, 23.1; MS (EI) *m/z* (relative intensity) 399 (M^+, 2), 381 (5), 354 (3), 340 (9), 320 (3), 311(3), 296 (15), 264 (35), 246 (30), 186 (15), 91 (100); HRMS *m/z* calcd for $C_{21}H_{26}NO_3$ ($M - CO_2CH_3$) 340.1913, found 340.1920.

A solution of 650 mg (1.63 mmol) of allylic alcohol **29** and 1.73 g (13.0 mmol) of *N,N*-dimethylacetamide dimethyl acetal in 10 mL of freshly distilled xylenes was heated at reflux for 8 h, cooled to room temperature, concentrated in vacuo to an oil, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:2) to give 650 mg (85%) of **17** as an oil: $[\alpha]_D$ −107.4° (*c* 1.9, $CHCl_3$, 21 °C); IR (neat) 3028, 3025, 2933, 2905, 2858, 1750, 1713 (br), 1699 (br), 1651, 1421, 1425, 1414, 1337, 1200, 1176, 1131, 772, 748, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.4−7.3 (m, 5 H), 5.85−5.7 (m, 2 H), 5.53 (d, 1 H, J = 10.5 Hz), 5.1−4.9 (m, 4 H), 4.25 (bt, 1 H, J = 8.4 Hz), 3.56 (s, 3 H), 3.46 (dd, 1 H, J = 11.1, 5.1 Hz), 2.89 (bs, 6 H), 2.55 −2.4 (m, 2 H), 2.3−2.2 (dd, 1 H, J = 15.3, 7.6 Hz), 2.0−1.9 (m, 2 H), 1.9−1.75 (m, 1 H), 1.5−1.0 (m, 7 H); ^{13}C NMR δ 173.4, 173.1, 171.1, 155.2, 154.1, 138.9, 138.7, 136.4, 136.2, 130.8, 130.4, 130.2, 130.0, 128.6, 128.5, 128.4, 128.3, 128.0, 114.4, 114.3, 67.3, 66.7, 63.5, 63.0, 61.1, 60.6, 52.2, 51.9, 41.8, 41.1, 39.0, 38.9, 38.3, 37.7, 37.6, 37.4, 35.6, 34.2, 34.0, 33.3, 29.2, 29.0, 26.6, 26.4; MS (EI) *m/z* (relative intensity) 468 (M^+, 10), 409 (4), 365 (12), 333 (18), 278 (6), 246 (10), 186 (10), 158 (12), 130 (10), 118 (10), 91 (100), 72 (30); HRMS *m/z* calcd for $C_{27}H_{36}N_2O_5$ 468.2624, found 468.2608.

(2*S*,3a*R*,4*S*,7*R*,7a*S*)-4-((Dimethylcarbamoyl)methyl)-7-(4-((triisopropylsilyl)oxy)butyl)-2,3,3a,4,7,7a-hexahydroindole-1,2-dicarboxylic Acid 1-Benzyl Ester 2-Methyl Ester (18). A solution of 0.180 g (0.385 mmol) of amide **17** in 2.0 mL of *tert*-BuOH was treated with a solution of 0.600 g of AD-mix-β[19] in 2.0 mL of distilled H_2O. After 1 min, the solution was cooled to 5 °C and was stirred for 36 h. Saturated NaCl (3.0 mL) was added, the reaction was extracted with EtOAc (5× 5 mL), and the combined organic layers were concentrated in vacuo to an oil which was redissolved in a mixture of 2 mL of *t*-BuOH and 2 mL of distilled H_2O. To this solution was added 0.300 g (1.40 mmol) of $NaIO_4$. After the mixture was stirred at room temperature for 45 min, the product was extracted into EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The oily residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:2) to afford 0.148 g (82%) of (2*S*,3a*R*,4*S*,7*R*,7a*S*)-4-((dimethylcarbamoyl)methyl)-7-(4-oxobutyl)-2,3,3a,4,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**30**): $[\alpha]_D$ −100.1° (*c* 1.2, $CHCl_3$, 21 °C); IR (neat) 3024, 2936, 1748, 1711 (br), 1645, 1499, 1414, 1337, 1263, 1200, 1177, 1132, 1028, 771, 748, 700 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 9.68 (s, 1 H), 7.35−7.3 (m, 5 H), 5.8−5.7 (m, 1 H), 5.55 (d, 1 H, J = 9.6 Hz), 5.04 (s, 2 H), 4.25 (dd, 1 H, J = 9.3, 7.5 Hz), 3.56 (s, 3 H), 3.49 (dd, 1 H, J = 11.1, 5.1 Hz), 2.90 (bs, 6 H), 2.5−2.4 (m, 2 H), 2.3−2.2 (m, 3 H),1.9−1.1 (m, 8 H); ^{13}C NMR δ 202.6, 202.1, 173.2, 172.9, 171.0, 155.0, 154.0, 136.2, 130.7, 130.4, 130.0, 139.6, 128.8, 128.5, 128.3, 128.1, 128.0, 67.1, 66.7, 63.2, 62.7, 60.9, 60.4, 52.1, 51.8, 43.9, 41.7, 40.9, 38.9, 38.1, 37.5, 37.3, 37.0, 35.4, 33.9, 33.1, 28.9, 19.5, 19.4; MS (EI) *m/z* (relative intensity) 470 (M^+, 5), 442 (7), 411 (5), 399 (7), 367 (40), 335 (35), 248 (20), 230 (20), 158 (20), 118 (12), 91 (100), 72 (70); HRMS *m/z* calcd for $C_{24}H_{31}N_2O_4$ ($M - CO_2CH_3$) 411.2284, found 411.2266.

To a solution of 0.492 g (1.04 mmol) of aldehyde **30** in a mixture of 2.0 mL of THF and 2.0 mL of MeOH was added 0.067 g (1.78 mmol) of $NaBH_4$. The reaction mixture was stirred for 12 h and treated with 5 mL of distilled H_2O and 1 mL of 10% HCl, and the product was extracted into EtOAc. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.460 g (93%) of (2*S*,3a*R*,4*S*,7*R*,7a*S*)-4-((dimethylcarbamoyl)methyl)-7-(4-hydroxybutyl)-2,3,3a,4,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (**31**) as a pale yellow foam. A solution of this alcohol in 3 mL of CH_2Cl_2 was treated with 77 mg (1.16 mmol) of imidazole, 14 mg (0.12 mmol) of (dimethylamino)pyridine, and 224 mg (1.16 mmol) of triisopropylsilyl chloride. The solution was stirred at room temperature for 5 h, concentrated in vacuo, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1 to 1:2) to yield 607 mg (quantitative) of silyl ether **18**: $[\alpha]_D$ −96.0° (*c* 1.1, $CHCl_3$, 21 °C); IR (neat) 3016, 2941, 2893, 2865, 1750, 1710 (br), 1649, 1458, 1437, 1413, 1337, 1294, 1263, 1200, 1176, 1128, 1108, 1066, 1032, 1013, 997, 883 cm^{-1}; ^1H NMR (DMSO-d_6, 373 K) δ 7.32 (bs, 5 H), 5.8−5.7 (m, 1 H), 5.53 (d, 1 H, J = 9.6 Hz), 5.1−4.95 (m, 2 H), 4.24 (bt, 1 H, J = 8.0 Hz), 3.7−3.4 (m, 7 H), 2.90 (bs, 6 H), 2.55−2.4 (m, 2 H), 2.22 (bdd, 1 H, J = 15.1, 7.4 Hz), 1.85−1.75 (m, 1 H), 1.5−1.2 (m, 7 H), 1.01 (bs, 22 H); ^{13}C NMR δ 173.3, 173.1, 171.1, 155.2, 154.1, 136.3, 130.8, 130.4, 130.1, 129.8,

128.4, 128.3, 128.2, 127.9, 67.2, 66.7, 63.3, 63.0, 61.0, 60.5, 52.1, 51.8, 41.8, 41.1, 39.0, 38.3, 37.7, 37.4, 35.5, 34.0, 33.3, 29.3, 23.4, 18.0, 11.9; MS (EI) *m/z* (relative intensity) 585 ($M^+ - C_3H_7$, 10), 541 (5), 525 (5), 493 (7), 449 (25), 435 (10), 408 (10), 391 (12), 261 (10), 220 (14), 91 (100), 72 (40); HRMS *m/z* calcd for $C_{32}H_{49}N_2O_6Si$ ($M - C_3H_7$) 585.3360, found 585.3437.

(3a*R*,4*S*,7*R*,7a*S*)-4-((Dimethylcarbamoyl)methyl)-7-(4-((triisopropylsilyl)oxy)butyl)-2,3,3a,4,7,7a-hexahydroindole-1-carboxylic Acid Benzyl Ester (19). To a solution of 0.350 g (0.557 mmol) of methyl ester **18** in a mixture of 0.25 mL of THF and 0.5 mL of MeOH were added 0.5 mL of H_2O and 40 mg (0.953 mmol) of LiOH monohydrate. The reaction mixture was warmed to 40 °C, stirred for 24 h, acidified by the dropwise addition of 10% HCl, and concentrated in vacuo. The residue was redissolved in a mixture of 5 mL of $CHCl_3$ and 0.5 mL of brine, and the solution was extracted with $CHCl_3$ (5×). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give 0.307 g (90%) of (2*S*,3a*R*,4*S*,7*R*,7a*S*)-4-((dimethylcarbamoyl)methyl)-7-(4-((triisopropylsilyl)oxy)butyl)-2,3,3a,4,7,7a-hexahydroindole-1,2-dicarboxylic acid 1-benzyl ester (**31**) as a white foam that was directly used for the next transformation.

To a solution of 0.307 g ((0.50 mmol) of carboxylic acid **31** in 5.1 mL of anhydrous THF was added at 0 °C 429 μL (3.1 mmol) of NEt_3, followed by 307 μL (2.06 mmol) of dichloro phenyl phosphate. The reaction mixture was stirred for 20 min at 0 °C and for 20 min at 22 °C and cooled to 0 °C, and 0.86 mL (6.15 mmol) of NEt_3 and 426 μL (4.01 mmol) of freshly distilled benzene selenol were added. The solution was stirred for 30 min, warmed to 22 °C for 30 min, and quenched with 2 mL of brine. The seleno ester was extracted into $CHCl_3$, dried ($MgSO_4$), and concentrated to give a yellow oil which was purified by chromatography on neutral Al_2O_3 (hexanes/EtOAc, 20:1 to 1:1) to give an unstable seleno ester that was immediately dissolved in 12 mL of thoroughly degassed xylenes, heated to 130 °C, and treated with 197 μL (9.74 mmol) of tri-*n*-butyltin hydride and 12 mg of AIBN. After 1 h, the solvent was removed in vacuo and the residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 1:1 to 1:2) to give 0.225 g (79%) of **19** as a colorless oil: $[\alpha]_D$ −87.1° (*c* 1.1, $CHCl_3$, 21 °C); IR (neat) 2941, 2890, 2865, 1703 (br), 1650, 1460, 1457, 1414, 1348, 1329, 1134, 1114, 1070, 1044, 882, 739, 679, 653 cm^{-1}; ^1H NMR (323 K) δ 7.4−7.3 (bs, 5 H), 5.85−5.75 (m, 1 H), 5.55 (d, 1 H, *J* = 10.0 Hz), 5.23, 5.10 (AB, 2 H, *J* = 12.4 Hz), 3.85−3.75 (m, 1 H), 3.7−3.6 (m, 2 H), 3.45 (dd, 1 H, *J* = 10.9, 5.1 Hz), 3.3−3.2 (m, 1 H), 3.02 (s, 3 H), 2.97 (s, 3 H), 2.7−2.6 (m, 1 H), 2.44 (dd, 1 H, *J* = 15.2, 5.6 Hz), 2.26 (dd, 1 H, *J* = 15.1, 8.4 Hz), 2.0−1.9 (m, 1 H), 1.8−1.7 (m, 1 H), 1.55−1.4 (m, 7 H), 1.07 (s, 21 H), 1.0−0.9 (m, 1 H); ^{13}C NMR (323 K) δ 171.2, 155.4, 137.0, 130.8, 130.4, 128.3, 127.8, 66.5, 63.3, 63.0, 47.9, 39.1, 37.6, 37.2, 35.4, 33.4, 29.1, 28.3, 23.6, 18.0, 12.1; MS (EI) *m/z* (relative intensity) 527 ($[M - C_3H_7]^+$, 40), 483 (10), 435 (15), 391 (25), 304 (20), 172 (6), 115 (6), 91 (100), 72 (20); HRMS *m/z* calcd for $C_{30}H_{47}N_2O_4Si$ ($M - C_3H_7$) 527.3305, found 527.3307.

(1a*R*,3a*S*,4*R*,5*R*,5a*R*,8a*R*)-4-Allyl-5-(4-((triisopropylsilyl)oxy)butyl)-2-oxodecahydro-3-oxa-6-aza-*as*-indacene-6-carboxylic Acid Benzyl Ester (20). To a solution of 0.245 g (0.430 mmol) of amide **19** in 2.1 mL of THF were added 2.1 mL of 1 M phosphate buffer (pH = 5.5) and 327 mg (1.29 mmol) of iodine. The reaction mixture was stirred at 21 °C in the dark for 2 h. Aqueous 10% $NaHSO_3$ was added dropwise until the iodine color dissipated, and the products were extracted into $CHCl_3$ (5 × 5mL) and EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and purified by chromatography on SiO_2 (hexanes/EtOAc, 2:1) to give 245 mg (85%) of (1a*R*,3a*R*,4*R*,5*S*,5a*S*,8a*R*)-5-(4-((triisopropylsilyl)oxy)-butyl)-4-iodo-2-oxodecahydro-3-oxa-6-aza-*as*-indacene-6-carboxylic acid benzyl ester (**32**): $[\alpha]_D$ −25.3° (*c* 0.95, $CHCl_3$, 21 °C); IR (neat) 2942, 2892, 2865, 1788, 1705, 1498, 1462, 1457, 1349, 1332, 1288,1258, 1248, 1211, 1153, 1127, 1119, 1070, 1016, 993, 977, 883, 734, 682, 657 cm^{-1}; ^1H NMR (323 K) δ 7.4−7.3 (m, 5 H), 5.13 (s, 2 H), 5.00 (bs, 1 H), 4.88 (bs, 1 H), 3.99 (dd, 1 H, *J* = 11.5, 4.0 Hz), 3.9−3.8 (m, 1 H), 3.6−3.5 (m, 2 H), 3.4−3.3 (m, 1 H), 3.06 (bs, 1 H), 2.85−2.65 (m, 2 H), 2.45 (d, 1 H, *J* = 16.8 Hz), 2.05−1.95 (m, 1 H), 1.85−1.75 (m, 1 H), 1.6−1.3 (m, 7 H), 1.08 (s, 21 H), 0.95−0.85 (m, 1 H); ^{13}C NMR (323 K) δ 174.3, 155.3, 136.6, 128.4, 128.0, 84.3, 66.9, 63.1, 60.3, 47.5, 44.8, 38.8, 38.0, 35.9, 32.9, 27.7, 27.5, 26.7, 24.2, 18.0, 12.1; MS (EI) *m/z* (relative intensity) 626 ($[M - C_3H_7]^+$, 5), 582 (4), 492 (3), 364 (5), 247 (3), 205 (3), 120 (4), 105 (4), 91 (100); HRMS *m/z* calcd for $C_{28}H_{41}INO_5Si$ ($M - C_3H_7$) 626.1799, found 626.1843.

To a mixure of 55 mg (0.082 mmol) of iodolactone **32** and 3.0 mg of AIBN was added 0.5 mL of degassed allyltri-*n*-butyltin. The solution was warmed to 80 °C under an argon atmosphere, stirred for 12 h, and purified by chromatography on SiO_2 (hexanes/EtOAc, 10:1 to 4:1 to 2:1) to give 43.3 mg (90%) of **20** as a colorless oil: $[\alpha]_D$ −39.1° (*c* 0.52, $CHCl_3$, 21 °C); IR (neat) 2941, 2931, 2892, 2865, 1779, 1703, 1462, 1455, 1417, 1388, 1349, 1331, 1209, 1160, 1113, 1013, 986, 917, 883, 770, 697 cm^{-1}; ^1H NMR (323 K) δ 7.31 (s, 5 H), 5.8−5.7 (m, 1 H), 5.16 (s, 2 H), 5.1−5.0 (m, 2 H), 4.38 (brs, 1 H), 3.81 (t, 1 H, *J* = 10.0 Hz), 3.65 (t, 2 H, *J* = 6.0 Hz), 3.4−3.35 (m, 2 H), 2.67 (dd, 1 H, *J* = 17.1, 6.9 Hz), 2.45−2.35 (m, 2 H), 2.2−2.1 (m, 2 H), 2.0−1.9 (m, 1 H), 1.9−1.8 (m, 1 H), 1.7−1.6 (m, 1 H), 1.55−1.2 (m, 7 H), 1.08 (s, 21 H), 0.9 (t, 1 H, *J* = 12.0 Hz); ^{13}C NMR (323 K) δ 175.5, 155.6, 136.1, 128.6, 128.1, 117.4, 83.1, 67.0, 63.5, 60.8, 47.9, 39.4, 38.9, 38.4, 37.4, 35.8, 33.3, 29.2, 28.0, 26.8, 26.6, 24.4, 18.1, 12.3; MS (EI) *m/z* (relative intensity) 540 ($[M - C_3H_7]^+$, 15),496 (25), 406 (25), 362 (3), 205 (3), 120 (4), 91 (100); HRMS *m/z* calcd for $C_{31}H_{46}NO_5Si$ ($M - C_3H_7$) 540.3145, found 540.3191

(1a*R*,1*S*,3a*S*,4*R*,5*R*,5a*R*,8a*R*)-5-(4-((Trilsopropylsilyl)oxy)butyl)-1-methyl-2-oxo-4-vinyldecahydro-3-oxa-6-aza-*as*-indacene-6-carboxylic Acid Benzyl Ester (21). To a solution of 0.35 mL (2.5 mmol) of diisopropylamine in 3.2 mL of THF was added dropwise at 0 °C 1 mL (2.5 mmol) of a 2.5 M solution of *n*-BuLi in hexanes. The mixture was stirred for 10 min and cooled to −78 °C, and 0.450 mL (2.58 mmol) of HMPA was added. After 30 min, 0.221 mL of this solution was added to a cold (−78 °C) solution of 43 mg (0.074 mmol) of **20** in 0.7 mL of THF and 0.1 mL of HMPA. Stirring was continued for 30 min, and 0.46 mL (0.737 mmol) of methyl iodide was added. The reaction mixtured was stirred for 20 min, quenched by the addition of saturated $NaHCO_3$, extracted into $CHCl_3$, and dried ($MgSO_4$). The residue was purified by chromatography on SiO_2 (hexanes/EtOAc, 4:1) to yield 38 mg (87%) of (1a*R*,1*S*,3a*S*,4*R*,5*R*,5a*R*,8a*R*)-4-allyl-5-(4-((triisopropylsilyl)oxy)butyl)-1-methyl-2-oxodecahydro-3-oxa-6-aza-*as*-indacene-6-carboxylic acid benzyl ester (**33**): $[\alpha]_D$ −42.2° (*c* 1.3, $CHCl_3$, 21 °C); IR (neat) 2936, 2894, 2865, 1776, 1704, 1456, 1416, 1389, 1349, 1330, 1201, 1183, 1160, 1110, 1013, 993, 919, 883, 771 cm^{-1}; ^1H NMR (323 K) δ 7.32 (bs, 5 H), 5.9−5.7 (m,1 H), 5.17 (bs, 2 H), 5.1−5.0 (m, 2 H), 4.55−4.45 (m, 1 H), 3.84 (t, 1 H, *J* = 9.4 Hz), 3.65 (t, 2 H, *J* = 5.8 Hz), 3.4−3.25 (m, 2 H), 2.55−2.45 (m, 2 H), 2.25−2.25 (m, 3 H), 2.1−1.9 (m, 3 H), 1.6−1.2 (m, 6 H), 1.31 (d, 3 H, *J* = 7.6 Hz), 1.08 (s, 21 H), 1.0−0.85 (m, 1 H); ^{13}C NMR (323 K) δ 178.7, 155.5, 136.8, 135.6, 128.5, 128.1,126.2, 125.9, 117.6, 80.3, 67.0, 63.4, 60.8, 48.2, 46.5, 41.5, 40.5, 39.9, 37.9, 36.8, 33.4, 29.7, 28.5, 27.5, 24.4, 22.6, 18.1, 14.5, 12.2; MS (EI) *m/z* (relative intensity) 554 ($[M - C_3H_7]^+$, 16), 510 (16), 420 (10),187 (3), 105 (20), 91 (100); HRMS *m/z* calcd for $C_{32}H_{48}NO_5Si$ ($M - C_3H_7$) 544.3302, found 554.3273.

A solution of 72 mg (0.12 mmol) of **33** in 2 mL of THF and 2 mL of H_2O was treated at 0 °C with 2.4 g (0.24 mmol) of a 2.5% solution of OsO_4 in *t*-BuOH and 130 mg (0.6 mmol) of $NaIO_4$. The reaction mixture was warmed to 21 °C, stirred for 1 h, diluted with 10 mL of EtOAc, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The oily residue was passed through a short plug of SiO_2 (EtOAc/hexanes, 1:1) to give a crude aldehyde which was immediately diluted with 3 mL of THF and 3 mL of CH_3OH and cooled to −40 °C. The solution was treated with 5 mg (0.12 mmol) of $NaBH_4$ and, after 30 min, quenched by addition of 1 mL of acetone in 20 mL of EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to give 46 mg (63%) of (1a*R*,1*S*,3a*S*,4*R*,5*R*,5a*R*,8a*R*)-5-(4-((triisopropylsilyl)oxy)butyl)-4-(2-hydroxyethyl)-1-methyl-2-oxodecahydro-3-oxa-6-aza-*as*-indacene-6-carboxylic acid benzyl ester (**34**) as a colorless oil: $[\alpha]_D$ −56.4° (*c* 2.5, 21 °C, CH_2Cl_2); IR (neat) 3420, 2915, 1757, 1690, 1674, 1447, 1408, 1339, 1196, 1152, 1102, 980, 876, 677, 664 cm^{-1}; ^1H NMR (343 K) δ 7.35−7.32 (m, 5 H), 5.11 (bs, 2 H), 4.48 (t, 1 H, *J* = 4.8 Hz), 3.9−3.8 (m, 1 H), 3.8−3.6 (m, 4 H), 3.36 (dd, 1 H, *J* = 11.2, 4.8 Hz), 3.28 (q, 1 H, *J* = 5.6 Hz), 2.55−2.4 (m, 2 H), 2.3−2.2 (m, 1 H), 2.1−1.8 (m, 4 H), 1.7−1.6 (m, 3 H), 1.5−1.2 (m, 9 H), 1.30 (d, 3 H, *J* = 7.2 Hz), 1.08 (bs, 18 H); ^{13}C NMR (323 K) δ 178.7, 155.6, 136.8, 128.6, 128.1, 81.9, 67.0, 63.4, 60.8, 48.1, 46.6, 41.7, 40.1, 38.5, 37.0,

36.0, 33.4, 28.4, 27.4, 24.5, 18.1, 17.8, 14.5, 12.2; MS (EI) *m/z* (relative intensity) 558 ([M − C_3H_7]$^+$, 55), 542 (5), 514 (90), 496 (7), 466 (10), 450 (12), 424 (90), 406 (17), 378 (10), 310 (40), 292 (10), 199 (10), 187 (15), 173 (10), 146 (10), 131 (20), 120 (13), 109 (28), 91 (100), 69 (5); HRMS (EI) calcd for $C_{31}H_{48}NO_6Si$ (M − C_3H_7) 558.3251, found 558.3238.

A solution of 42 mg (0.069 mmol) of **34** in 3 mL of THF was treated at 0 °C with 47 mg (0.14 mmol) of *o*-(nitrophenyl)selenyl cyanide and 28 mg (0.14 mmol) of tri-*n*-butylphosphine. After 10 min, the reaction mixture was diluted with 20 mL of EtOAc, washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The yellow oily residue was chromatographed on SiO_2 (EtOAc/hexanes, 1:3 to 1:1) to give a seleno ether that was diluted at 21 °C with 5 mL of THF and 2 mL of 30% H_2O_2 and stirred for 6 h. The reaction mixture was quenched with cold (0 °C) saturated aqueous $NaHCO_3$ solution, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The oily residue was chromatographed on SiO_2 (EtOAc/hexanes, 1:1) to give 35 mg (87%) of **21** as a colorless oil: $[\alpha]_D$ −72.1° (*c* 1.2, 21 °C, CH_2Cl_2); IR (neat) 2917, 1759, 1690, 1443, 1401, 1339, 1102, 984, 909, 876, 764, 729 cm^{-1}; ^{1}H NMR (323 K) δ 7.35−7.29 (m, 5 H), 5.85−5.7 (m, 1 H), 5.2−5.05 (m, 4 H), 4.54 (t, 1 H, J = 5.8 Hz), 3.82 (t, 1 H, J = 8.9 Hz), 3.63 (t, 2 H, J = 5.7 Hz), 3.43 (dd, 1 H, J = 10.9, 4.8 Hz), 3.29 (dt, 1 H, J = 11.3, 5.7 Hz), 2.8−2.6 (m, 1 H), 2.48 (dq, 1 H, J = 7.4, 5.3 Hz), 2.12−1.90 (m, 3 H), 1.52−1.28 (m, 8 H), 1.31 (d, 3 H, J = 7.4 Hz), 1.11−0.86 (m, 21 H); ^{13}C NMR (323 K) δ 178.5, 155.6, 138.6, 136.9, 128.6, 128.1, 116.9, 80.3, 67.0, 63.4, 60.7, 48.4, 46.9, 44.8, 41.4, 33.5, 28.8, 27.4, 24.3, 18.2, 14.6, 12.2; MS (EI) *m/z* (relative intensity) 556 (15), 540 ([M − C_3H_7]$^+$, 10), 496 (15), 406 (70), 187 (13), 131 (10), 105 (7), 91 (100), 75 (10), 65 (12); HRMS (EI) calcd for $C_{31}H_{46}NO_5Si$ (M − C_3H_7) 540.3145, found 540.3141.

(−)-4-Oxostenine (23). A solution of 33.4 mg (0.057 mmol) of **21** in 2 mL of CH_3CN was treated at 0 °C with 0.5 mL of a 48% HF solution, stirred for 2 h, and quenched by addition of cold saturated aqueous $NaHCO_3$ under vigorous stirring. The resulting solution was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The oily residue was chromatographed on SiO_2 (EtOAc/hexanes, 3:1) to give 23 mg (0.053 mmol, 94%) of the primary alcohol as a colorless oil that was dissolved in 5 mL of CH_2Cl_2 and treated at 21 °C with 39 mg (0.09 mmol) of Dess−Martin periodinane. After 30 min, the reaction mixture was filtered through a short plug of SiO_2 to give a crude aldehyde that was diluted with 2 mL of THF and 0.3 mL of 2-methyl-2-butene. The reaction mixture was treated at 0 °C with a solution of 14.4 mg (0.16 mmol) of sodium chlorite and 14.7 mg (0.11 mmol) of sodium phosphate monobasic monohydrate in 1 mL of H_2O, stirred for 2.5 h, and partitioned between 20 mL of EtOAc and 20 mL of brine. The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The crude acid **22** was diluted with 5 mL of absolute MeOH and treated with 5 mg of $Pd(OH)_2/C$ at 21 °C. The reaction mixture was stirred for 20 min while H_2 was bubbled through it, filtered through a cotton filter, concentrated in vacuo, and immediately diluted with 10 mL of dry CH_2Cl_2. The resulting solution was treated at 21 °C with 31 mg (0.08 mmol) of FDPP. After 30 h, the reaction mixture was directly loaded onto a SiO_2 column and eluted (EtOAc) to give 11.8 mg (71% from **21**) of the amide **23** as a colorless solid: mp 179 °C (EtOAc); $[\alpha]_D$ −84.7° (*c* 0.37, 21 °C, CH_2Cl_2); IR (neat) 2911, 1740, 1698, 1678, 1647, 1615, 1561, 1555, 1539, 1520, 1503, 1468, 1451, 1437, 1304, 1177, 1028, 1003, 928, 706 cm^{-1}; ^{1}H NMR δ 4.44 (dd, 1 H, J = 12.1, 9.2 Hz), 3.72 (dd, 1 H, J = 12.2, 9.0 Hz), 3.51−3.40 (m, 2 H), 2.44−2.39 (m, 2 H), 2.29 (dd, 1 H, J = 11.7, 4.4 Hz), 2.21−2.11 (m, 2 H), 2.00−1.85 (m, 3 H), 1.70−1.56 (m, 4 H), 1.53−1.41 (m, 3 H), 1.33 (d, 3 H, J = 7.1 Hz), 0.96 (t, 3 H, J = 7.5 Hz); ^{13}C NMR δ 178.7, 171.1, 79.2, 60.6, 46.9, 45.7, 44.4, 42.3, 39.8, 35.8, 33.1, 27.9, 23.4, 22.9, 22.6, 15.5, 10.2; MS (EI) *m/z* (relative intensity) 291 (M$^+$, 45), 279 (20), 220 (7), 199 (8), 176 (9), 167 (17), 155 (7), 149 (65), 135 (10), 119 (10), 111 (15), 105 (22), 89 (15), 83 (15), 75 (20), 69 (25), 57 (50), 44 (100); HRMS (EI) calcd for $C_{17}H_{25}NO_3$ 291.1834, found 291.1823.

(−)-Stenine (1). To a solution of 9.1 mg (0.031 mmol) of **23** in 5 mL of CH_2Cl_2 was added at 21 °C 19 mg (0.047 mmol) of Lawesson's reagent. After 3 h, the reaction mixture was concentrated under reduced pressure and chromatographed on SiO_2 (EtOAc/hexanes, 3:1) to give 9 mg (93%) of (−)-4-thiostenine (**35**) as a colorless solid: mp 203 °C (EtOAc/hexanes); $[\alpha]_D$ −54.3° (*c* 0.4, 21 °C, CH_2Cl_2); IR (neat) 2905, 1745, 1472, 1462, 1439, 1300, 1156, 999, 722 cm^{-1}; ^{1}H NMR δ 4.42 (dd, 1 H, J = 12.0, 8.8 Hz), 4.12 (dd, 1 H, J = 13.9, 8.7 Hz), 3.78−3.63 (m, 2 H), 3.00 (ddd, 1 H, J = 12.4, 5.1, 1,6 Hz), 2.85 (dt, 1 H, J = 12.7, 5.6 Hz), 2.44 (dq, 1 H, J = 9.4, 7.1 Hz), 2.26−2.12 (m, 3 H), 2.01−1.91 (m, 2 H), 1.72−1.46 (m, 6 H), 1.4−1.2 (m, 1 H), 1.34 (d, 3 H, J = 7.1 Hz), 0.95 (t, 3 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 199.3, 178.5, 78.8, 65.8, 55.2, 45.6, 44.6, 42.7, 42.2, 39.7, 35.6, 27.9, 24.8, 23.2, 22.6, 15.6, 10.2; MS (EI) *m/z* (relative intensity) 307 (M$^+$, 85), 292 (10), 278 (100), 208 (15), 176 (10), 93 (10), 81 (10), 71 (12), 55 (15); HRMS (EI) calcd for $C_{17}H_{25}NO_3S$ 307.1658, found 307.1626.

A solution of 7.4 mg (0.024 mmol) of the thioamide **35** in 3 mL of EtOH was treated at 21 °C with 60 mg of Raney Ni (washed with H_2O prior to use). The reaction mixture was shaken for 30 min and filtered through a cotton filter. The solvent was removed under reduced pressure, and the solid residue was chromatographed on SiO_2 (EtOAc) to give 5.2 mg (78%) of **1** as a colorless solid: mp 59 °C (EtOAc); $[\alpha]_D$ −29.4° (*c* 0.44, 21 °C, CH_3OH); IR (neat) 2886, 1744, 1156, 994 cm^{-1}; ^{1}H NMR (C_6D_6) δ 4.00 (dd, 1 H, J = 12.1, 8.7 Hz), 2.93 (dt, 1 H, J = 8.8, 3.8 Hz), 2.63 (dt, 1 H, J = 12.6, 4.4 Hz), 2.22−2.04 (m, 2 H), 1.92−1.83 (m, 1 H), 1.73−1.66 (m, 2 H), 1.61−1.50 (m, 4 H), 1.44−1.35 (m, 3 H), 1.29−1.26 (m, 2 H), 1.09−1.02 (m, 3 H), 1.03 (d, 3 H, J = 7.1 Hz), 0.91 (t, 3 H, J = 7.6 Hz), 0.88−0.77 (m, 1 H); ^{13}C NMR (C_6D_6) δ 178.0, 79.6, 67.2, 54.9, 52.8, 47.2, 43.1, 42.6, 40.4, 40.0, 30.1 (2C), 27.8, 26.3, 23.0, 15.1, 10.2; MS (EI) *m/z* (relative intensity) 277 (M$^+$, 30), 276 ([M − H]$^+$, 100), 248 (10), 220 (3), 206 (5), 199 (4), 149 (3), 138 (3), 110 (4), 84 (6), 111 (15), 105 (22), 89 (15), 83 (15), 75 (20), 69 (25), 57 (50), 44 (100); HRMS (EI) calcd for $C_{17}H_{26}NO_2$ (M − H) 276.1964, found 276.1965.

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Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and HRMS spectra of **1** and ^{1}H NMR and ^{13}C NMR spectra of synthetic intermediates (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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