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Stereocontrolled total synthesis of (−)-aspidophytine

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Dedicated to Professor K. C. Nicolaou in recognition of his receipt of the Tetrahedron Prize

Abstract—The enantioselective stereocontrolled total synthesis of aspidophytine is described. The key indole intermediate was prepared by radical cyclization of 2-alkenylphenylisocyanide, followed by Sonogashira-coupling with a highly functionalized terminal acetylene. The 11-membered cyclic amine, a precursor for the formation of the aspidosperma skeleton, was synthesized using nitrobenzenesulfonamide chemistry. After construction of the pentacyclic skeleton, the lactone ring was formed to complete the total synthesis.

1. Introduction

Haplophytine (**1**) is the major alkaloid isolated from the leaves of the Mexican 'cockroach plant', *Haplophyton cimicidum* (Apocynaceae).[1] After the pioneering work of Snyder and co-workers,[2] the structure of haplophytine (**1**) was reported by Cava and Yates in 1973,[3] and was unambiguously confirmed by X-ray crystallographic study in 1975.[4] During the study of the chemical degradation of **1**, the right-half constituent, a lactonic aspidospermine type of alkaloid, aspidophytine (**2**), was obtained as the acid-cleavage product.[3,5] Although no total synthesis of aspidophytine (**2**) has been reported, Corey recently published a concise and elegant synthetic route for the construction of **2**.[6] In the course of our project on the development of a novel indole synthesis[7,8] and its application to the synthesis of indole alkaloids,[9] we began studies towards the total synthesis of haplophytine (**1**).[10] We describe herein full details of our investigation of the enantioselective total synthesis of aspidophytine (**2**) (Fig. 1).[11]

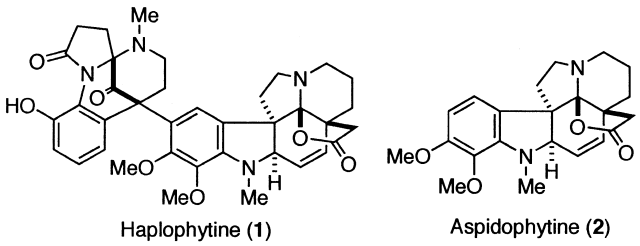

Figure 1.

Keywords: total synthesis; aspidophytine; indole; aspidosperma alkaloid; macrocycles.

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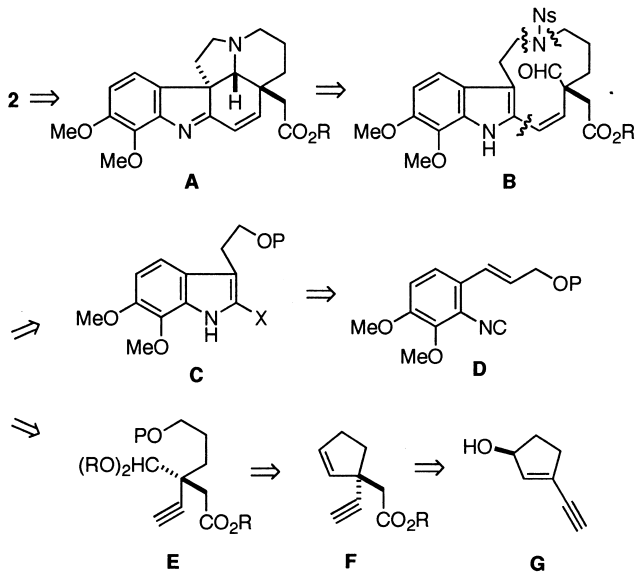
2. Results and discussion

2.1. Retrosynthetic analysis

Our retrosynthetic analysis is depicted in Scheme 1. The lactone ring would be formed in the final stage of the synthesis. For the formation of the pentacyclic aspidosperma skeleton A, we planned to employ an intramolecular Mannich-type reaction resulting in the formation of a new C–C bond at the 3-position of the indole.[12] The 11-membered ring precursor B would be constructed by our secondary amine synthesis using an *o*-nitrobenzenesulfonyl (Ns) group.[13] This method has proved to be quite effective



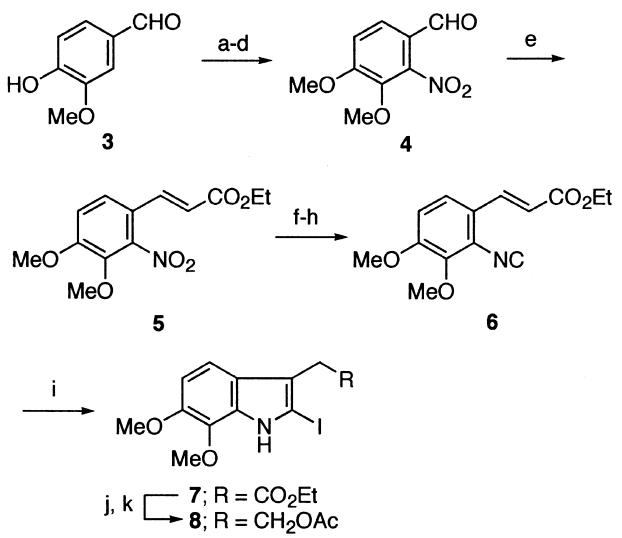
Scheme 1. Retrosynthetic analysis.

for formation of medium-sized cyclic secondary amines.[14] The key indole intermediate bearing a chiral side chain could be assembled by tin-mediated radical cyclization of the *o*-alkenylphenylisocyanide D[7a] and subsequent palladium-mediated coupling. Thus, the 2-stannylindole intermediate (C; X=Bu_3Sn) formed after the radical cyclization could be readily transformed into the 2-iodoindole derivative (C; X=I), which serves as a suitable substrate for coupling reactions.[7b] Using this reaction, the fully elaborated chiral side chain segment E would be installed at the indole 2-position. The side chain segment E, on the other hand, would be prepared by a Claisen–Johnson rearrangement[15] of a chiral allylic alcohol G and ring cleavage of the cyclopentene ring F.

2.2. First generation total synthesis

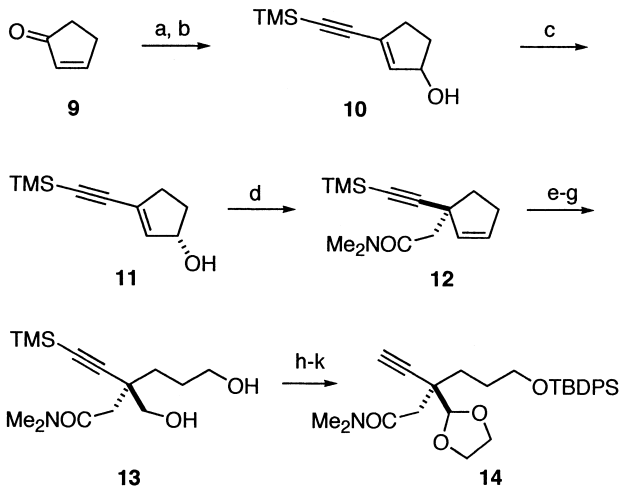
Preparation of the 2-iodoindole segment **8** is summarized in Scheme 2. Based on the reported protocol, 2-nitroveratraldehyde (**4**) was prepared from vanillin (**3**) by a four-step sequence.[16] Vanillin was converted to its acetate, which was exposed to fuming nitric acid to give the desired *o*-nitrobenzaldehyde derivative as a single isomer after precipitation.[17] The acetoxy group was then converted to the methoxy group by hydrolysis and methylation. Horner–Emmons olefination of the 2-nitroveratraldehyde (**4**) led to the ethyl cinnamate derivative **6**, whose nitro group was transformed into the isonitrile by a three-step sequence including reduction, formylation of aniline, and dehydration. The tin-mediated indole formation and treatment of the resultant 2-stannylindole intermediate with iodine gave the 2-iodoindole **7**.[7b] Finally, the ester function was reduced to the primary alcohol, which was protected as its acetate to give the 2-iodoindole derivative **8**.

Preparation of the requisite chiral acetylene segment began with the 1,2-addition of lithium trimethylsilylacetylide to



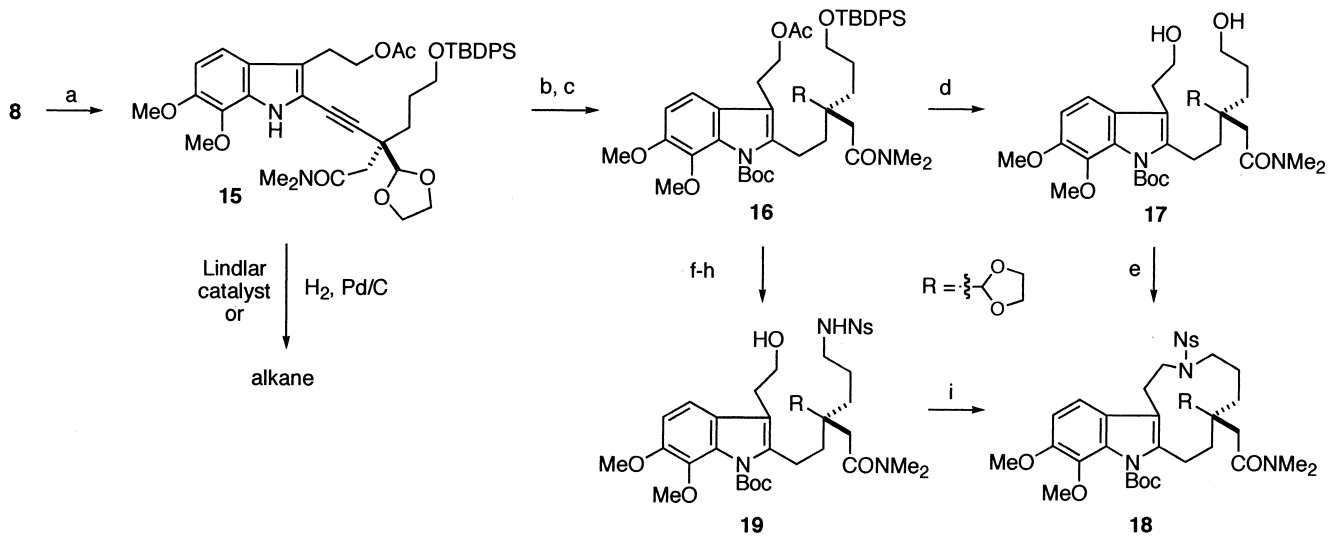
Scheme 2. *Reagents and conditions*: (a) Ac_2O, NaOH, Et_2O; (b) fuming HNO_3; (c) NaOH; (d) MeI, K_2CO_3, DMF, 69% (4 steps); (e) $(EtO)_2POCH_2CO_2Et$, *n*-Bu_4NI, CH_2Cl_2–H_2O, 5°C, 25 min, 81%; (f) Zn, AcOH, CH_2Cl_2, 10°C to room temperature, 1.5 h; (g) HCO_2H, Ac_2O, 5°C, 10 min; (h) $POCl_3$, Py, CH_2Cl_2, 5°C, 70 min, 63% (3 steps); (i) *n*-Bu_3SnH, AIBN, MeCN, reflux, 1.5 h; I_2, room temperature, 85% (2 steps); (j) DIBAL, toluene, 5°C, 50 min; (k) Ac_2O, Py, room temperature, 30 min, 85% (2 steps).

cyclopentenone (**9**) and subsequent treatment of the product with acid to furnish the conjugated allylic alcohol **10**[18] (Scheme 3). Resolution of **10** using Amano lipase PS gave the *S*-enantiomer **11** (45%, 99% ee). Since attempts to construct a quaternary carbon center by the Claisen–Johnson rearrangement[19] provided unsatisfactory results, we turned to the Claisen–Eschenmoser rearrangement[20] to obtain the desired dimethylamide **12** in 84% yield. The cyclopentene ring of **12** was next cleaved by osmylation and oxidation with $NaIO_4$, and the resultant dialdehyde was reduced to give the diol **13**. After regioselective silylation, the remaining primary alcohol was transformed to the 1,3-dioxolane by Swern oxidation[21] and acetalization. Finally, the TMS group was removed, leading to the desired acetylene **14**.



Scheme 3. *Reagents and conditions*: (a) trimethylsilylacetylene, *n*-BuLi, THF, −78°C, 1 h, 65%; (b) 3% H_2SO_4, Et_2O, room temperature, 10 h, 98%; (c) vinyl acetate, lipase PS, *t*-BuOMe, 45–50°C, 9 h, 45% (99% ee); (d) $MeC(OMe)_2NMe_2$, xylene, reflux, 2 h, 84%; (e) OsO_4, NMO, acetone–H_2O, 0°C to room temperature, 1.5 h; (f) $NaIO_4$, THF–H_2O, 0°C, 1 h; (g) $NaBH_4$, EtOH, room temperature, 20 min, 85% (3 steps); (h) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, −5°C, 2.5 h, 75%; (i) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; Et_3N, 95%; (j) p-TsOH, ethylene glycol-PhH, 2.5 h; (k) K_2CO_3, MeOH, room temperature, 2 h, 83% (2 steps).

With the two key segments **8** and **14** in hand, the union of these fragments and the formation of the 11-membered secondary amine were investigated (Scheme 4). Sonogashira-coupling[22] of **8** with **14** took place smoothly to furnish the 2-alkynyl indole **15** in 92% yield. At this stage, it was difficult to perform the selective partial reduction of the alkyne. Thus, under reduction conditions both with Lindlar catalyst or palladium on carbon, over-reduction to the alkane occurred. We therefore decided to reduce the alkyne to the alkane and regenerate the olefin at a later stage of the synthesis. After reduction of the alkyne **15** to the corresponding alkane, the indole nitrogen was protected with the Boc group and formation of the 11-membered ring using Ns-chemistry was examined. First, the diol **17** was subjected to the ring-closing double Mitsunobu reaction[23] with the Ns-amide. Although the expected ring formation took place, the yield of the 11-membered ring compound **18** was 48% at best. A stepwise protocol, on the other hand, provided better results. After desilylation, the nitrogen function was introduced by the Mitsunobu reaction



Scheme 4. *Reagents and conditions*: (a) acetylene **14**, $Pd(PPh_3)_4$, CuI, Et_3N, 65°C, 1 h, 92%; (b) Pd/C, H_2, EtOH, room temperature, 5.5 h; (c) Boc_2O, DMAP, MeCN, room temperature, 6 h, 93% (2 steps); (d) TBAF, THF, 45°C, 2 h; K_2CO_3, MeOH, room temperature, 30 min, 85% (2 steps); (e) $NsNH_2$, PPh_3, DEAD, PhH, room temperature, 10 min, 48%; (f) TBAF, THF, 45°C, 2 h, 85%; (g) $NsNH_2$, PPh_3, DEAD, PhH, room temperature, 5 min; (h) K_2CO_3, MeOH, room temperature, 1.5 h; (i) PPh_3, DEAD, PhH, room temperature, 5 min, 73% (3 steps).

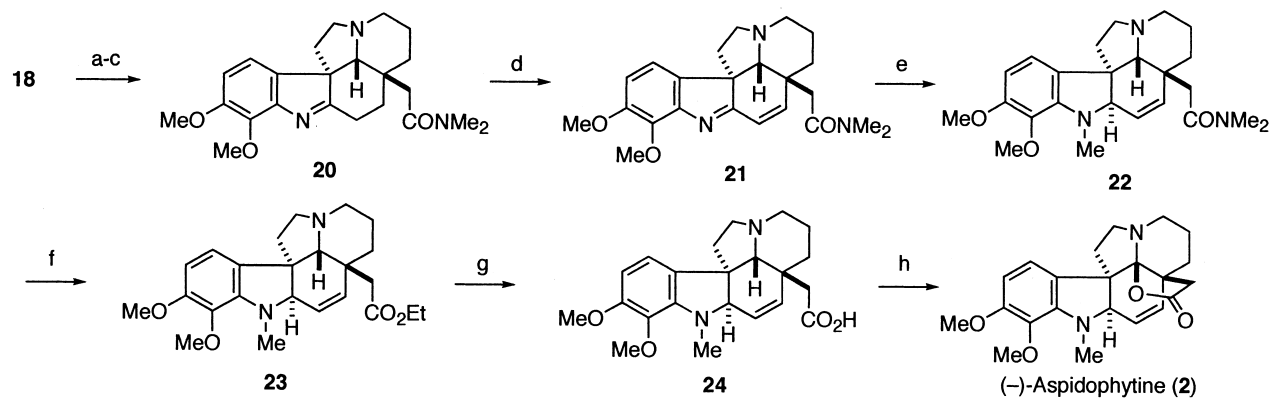
of the Ns-amide, followed by methanolysis of the acetate to give the cyclization precursor **19**. The crucial intramolecular Mitsunobu reaction furnished the desired 11-membered ring compound **18** in good yield.

Having synthesized the 11-membered secondary amine intermediate, we were in a position to examine the construction of the aspidosperma skeleton. First, the protective groups of the aldehyde and secondary amine were sequentially removed with PPTS-water and a combination of thiophenol and Cs_2CO_3, respectively. Upon treatment with TFA and then aq $NaHCO_3$, the initial loss of the Boc group was followed by an intramolecular Mannich-type reaction to furnish the pentacyclic compound **20** as single isomer. Oxidative treatment of the imine with benzeneseleninic anhydride successfully provided the desired conjugated imine **21**.[24] Stereoselective 1,2-reduction of the imine and subsequent reductive methylation were effected in one pot to give **22** (Scheme 5).

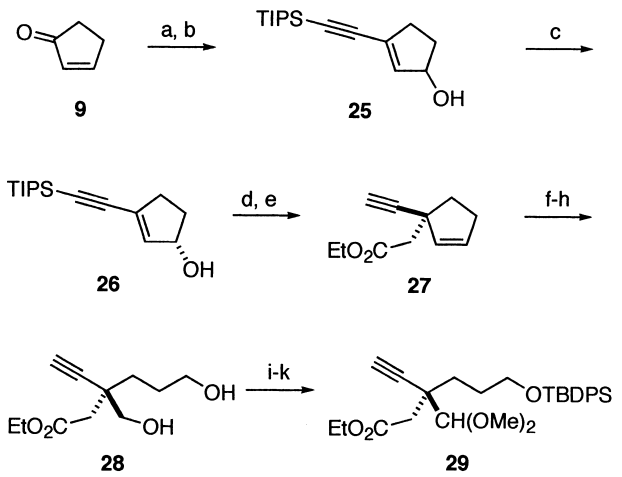
Direct lactonization using the *N*,*N*-dimethylamide **22** under Corey's oxidative conditions[6] resulted in recovery of the starting material, making it necessary to manipulate the *N*,*N*-dimethylamide functionality. Since this amide was rather robust, basic hydrolysis conditions, such as the use of KOH in hot ethylene glycol, were not effective. However, it was found that treatment with the Meerwein reagent[25] (Et_3OBF_4) gave the corresponding ethyl ester, albeit in low yield, while other reagents, such as FSO_3Me[26] or Me_2ISbF_6,[27] did not afford the desired ester. Finally, the ethyl ester was saponified and the resultant carboxylic acid was subjected to Corey's oxidative conditions to furnish aspidophytine (**2**) in 29% yield over 2 steps.

2.3. A second generation total synthesis by improved route

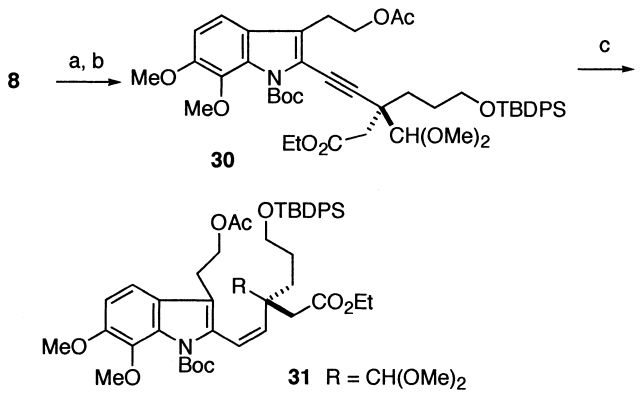
Due to the difficulty involved in manipulating the amide group in the end game of the aforementioned synthesis, we



Scheme 5. *Reagents and conditions*: (a) PPTS, acetone–H_2O, 70°C, 18 h, quant.; (b) PhSH, Cs_2CO_3, MeCN, room temperature, 3 h; (c) TFA, Me_2S, CH_2Cl_2, room temperature, 5 min; aq $NaHCO_3$, 84% (2 steps); (d) $(PhSe(O))_2O$, PhH, 65°C, 1.5 h, 65%; (e) HCHO, $NaBH_3CN$, MeOH-pH 7.0 buffer, room temperature, 1 h, 57%; (f) Et_3OBF_4, CH_2Cl_2, 40°C, 3.5 h, 12%; (g) NaOH, EtOH, 70°C, 2.5 h, 52%; (h) $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH–H_2O, 5°C to room temperature, 10 min, 56%.



Scheme 6. *Reagents and conditions*: (a) triisopropylsilylacetylene, *n*-BuLi, $CeCl_3$, THF, −78°C, 10 min; (b) 3% H_2SO_4, THF, room temperature, 6.5 h, 94% (2 steps); (c) vinyl acetate, Lipase PS, *t*-BuOMe, 45–50°C, 20 h, 48% (99% ee); (d) $CH_3C(OEt)_3$, *t*-$BuCO_2H$, xylene, reflux, 10 h; (e) TBAF, THF, 50°C, 45 min; (f) OsO_4, NMO, acetone–H_2O, 0°C to room temperature, 80 min; (g) $NaIO_4$, THF–H_2O, 0°C, 25 min; (h) $NaBH_4$, EtOH, −20°C, 15 min, 38% (5 steps); (i) TBDPSCl, DMAP, Et_3N, CH_2Cl_2, −20 to −10°C, 45 min, 95%; (j) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; Et_3N; (k) CSA, $HC(OMe)_3$, MeOH, room temperature, 30 min, 74% (2 steps).



Scheme 7. *Reagents and conditions*: (a) acetylene **29**, $Pd(PPh_3)_4$, CuI, Et_3N, 70°C, 2 h, 78%; (b) Boc_2O, DMAP, MeCN, room temperature, 15 min, 94%; (c) Pd/C, H_2, EtOH, room temperature, 3.5 h, 97%.

reasoned that it would be better to set up the ester functionality at an earlier stage of the synthesis. Thus, we reinvestigated the preparation of the acetylene segment to obtain a compound bearing an ester functionality. After extensive experimentation using the Claisen–Johnson rearrangement, it was found that switching from the TMS to the TIPS group of the substrate improved both product yield and reproducibility (Scheme 6). 1,2-Addition of lithium TIPS-acetylide to cyclopentenone (**9**) in the presence of $CeCl_3$,[28] and subsequent acid treatment gave the conjugated allylic alcohol **25** in 94% yield in 2 steps. Amano lipase PS was also effective in the resolution of the TIPS substrate **25**, and the *S*-enantiomer **26** was obtained in 48% yield (99% ee).[29] After the Claisen–Johnson rearrangement, desilylation gave the desired chiral ester **27**. A similar protocol used in the first generation synthesis including cleavage of the cyclopentene ring, reduction to the diol, regioselective silylation, and finally conversion of the remaining hydroxyl group to the dimethyl acetal, furnished the desired acetylene segment **29**.

The terminal acetylene segment **29** thus obtained was coupled with the 2-iodoindole **8** using the Sonogashira reaction, and the partial reduction of the alkyne to *cis*-alkene was thoroughly investigated. It was found that Boc protection of the indole nitrogen enabled the selective partial reduction to the *cis*-olefin. Thus, the desired *cis*-olefin product **31** was exclusively obtained in 97% yield under conventional hydrogenation conditions with palladium on carbon (Scheme 7).

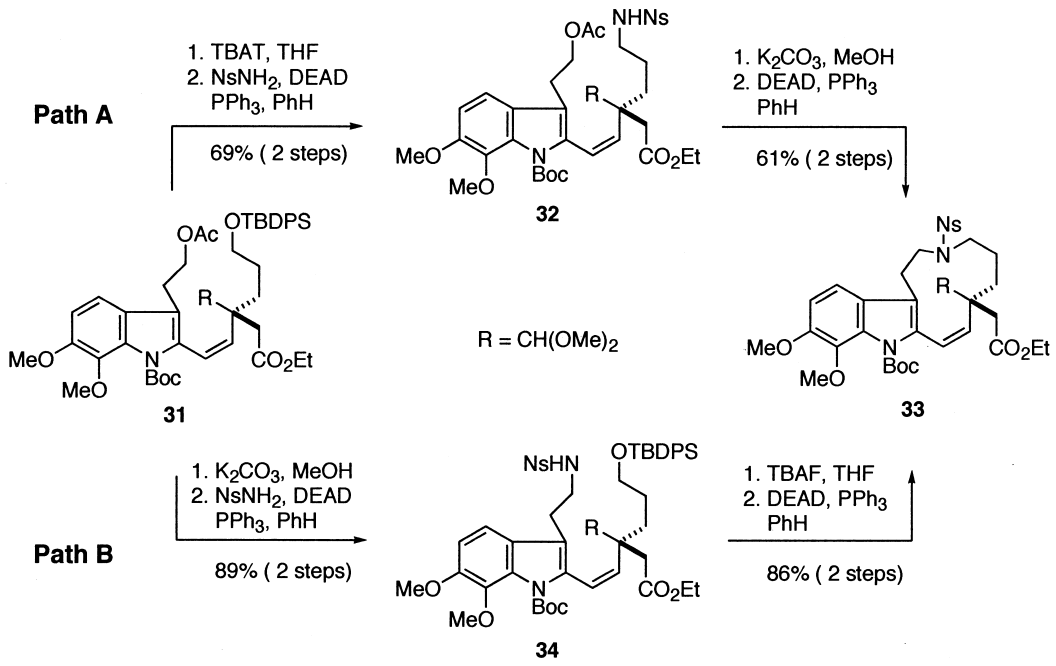
Next, formation of the 11-membered ring, based on the protocol established in the first generation synthesis, was carried out. However, the protocol (path A in Scheme 8) was ineffective, and the 11-membered ring product **33** was obtained in only 42% yield in 4 steps. It was found that the sequence starting from the introduction of the nitrogen function at the hydroxyethyl substituent (path B) proved to be more efficient than path A. The nitrogen function was introduced by methanolysis of the acetate **31** and a Mitsunobu reaction with $NsNH_2$ to give **34**. After desilylation, the 11-membered ring formation took place smoothly to furnish **33** in 77% overall yield in 4 steps.

Having synthesized the 11-membered ring, we then moved to the construction of the pentacyclic aspidosperma skeleton. After transformation of the acetal to the aldehyde **35** with TMSBr, the Ns group was removed by treatment with a mixture of thiophenol and cesium carbonate (Scheme 9). The resulting mixture was treated with TFA, and then buffer (pH 7.8) to furnish the desired pentacyclic product **36** in 56% yield as a single isomer associated with its thiophenol adduct **37** (29%). Compound **37** could be converted to the desired conjugated imine **36** by treatment with $Hg(OAc)_2$ in ethanol.

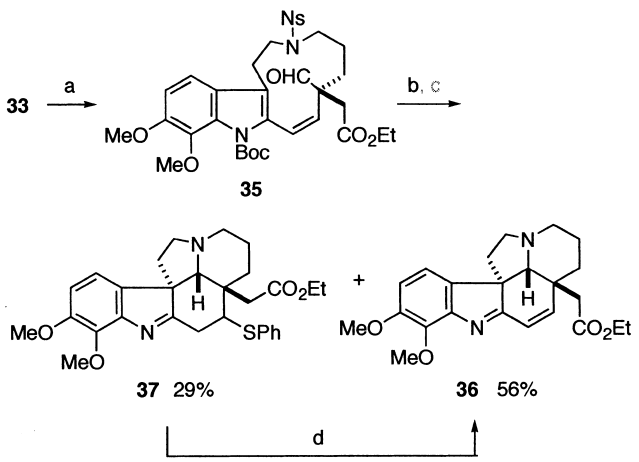
The total synthesis was completed by conversion to the *N*-methylindoline derivative and lactone formation. Stereoselective 1,2-reduction of the conjugated imine **36** and reductive methylation were executed in one pot to obtain **23** (Scheme 10). Finally, saponification of the ester **23** and oxidative lactone ring formation of the resultant carboxylic acid **24** under Corey's conditions[6] provided (−)-aspidophytine **2**. All the spectral data of the synthetic material were identical with those published.[6]

3. Summary

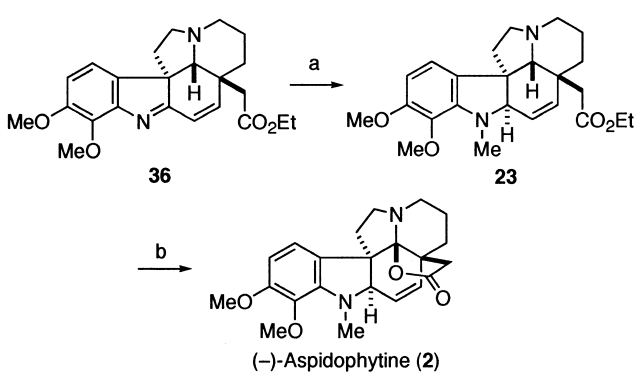
We have accomplished an enantioselective total synthesis of aspidophytine (**2**). Notable features of this synthesis include the facile assembly of the fully functionalized 2,3-disubstituted indole intermediate by radical-mediated indole formation, followed by a palladium mediated coupling, and an 11-membered ring formation utilizing Ns technology. Synthetic studies on haplophytine (**1**) based on this efficient synthetic method are currently under investigation in our laboratories.



Scheme 8. Formation of 11-membered secondary amine.



Scheme 9. *Reagents and conditions*: (a) TMSBr, CH_2Cl_2, −78°C, 15 min, 92%; (b) PhSH, Cs_2CO_3, MeCN, 55°C, 20 min; (c) TFA, Me_2S, CH_2Cl_2, room temperature, 5 min; pH 7.8 buffer, 5°C, 30 min, 56% (2 steps); (d) $Hg(OAc)_2$, EtOH, 79%.



Scheme 10. *Reagents and conditions*: (a) HCHO, $NaBH_3CN$, pH 7.0 buffer, −70°C to room temperature, 2.5 h, 67%; (b) NaOH, EtOH, 70°C, 2.5 h; $K_3Fe(CN)_6$, $NaHCO_3$, 5°C to room temperature, 10 min, 39%.

4. Experimental

4.1. General

All reactions sensitive to oxygen and moisture were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Melting points (mp), determined on a Yanako MP-500V melting point apparatus, are uncorrected. ^{1}H NMR (400 Hz), and ^{13}C NMR (100 Hz) spectra were determined on a JEOL JNM-AL400 or JEOL JNM-LA400 instrument. Chemical shifts for ^{1}H NMR were reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are in Hertz (Hz). Chemical shifts for ^{13}C NMR were reported in ppm relative to the central line of a triplet at 77.0 ppm for deuteriochloroform. Infrared (IR) spectra were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer and are reported in wave numbers (cm^{-1}). Mass spectra (MS) were obtained on a JEOL JMS-700 or a JEOL JMS-GCmate at 70 eV, using direct probe insertion at temperatures of 70–350°C. High resolution mass spectra were obtained under similar conditions. Optical rotations were measured on a JASCO DIP-1000 Digital Polarimeter at room temperature, using the sodium D line. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel 60 F_{245}. Flash column chromatography was performed on Merck Kieselgel 60 (230–400 mesh) or KANTO CHEMICAL Silica Gel (spherical 40–100 μm). Reagents and solvents were commercial grades and were used as supplied. Dichloromethane, dimethyl sulfoxide, benzene, and toluene were distilled from calcium hydride and stored over molecular sieves 4 Å. THF, *N*,*N*-dimethylformamide, methanol, ethanol, diethyl ether, and acetonitrile were purchased anhydrous and stored over molecular sieves 4 Å under argon. Methanol was purchased anhydrous and stored over molecular sieves 3 Å.

Triethylamine was distilled from calcium hydride and stored over potassium hydroxide pellets.

4.1.1. 3-(3,4-Dimethoxy-2-nitro-phenyl)-acrylic acid ethyl ester (5). To a two-phase mixture of *n*-Bu_4NI (1.75 g, 4.7 mmol) in NaOH (50% in water, 105 mL) and CH_2Cl_2 (105 mL) were added CH_2Cl_2 solution (70 mL) of 2-nitroveratraldehyde (**4**) (37.0 g, 175 mmol) and triethyl phosphonoacetate (43.2 g, 193 mmol) dropwise at 5°C over 25 min. The organic phase was separated and evaporated under reduced pressure to give a yellow solid (44.5 g). This solid was purified by crystallization from EtOAc to afford **5** (36.4 g, 74.1%) as yellow needles. The second crop was recovered from the mother to obtain additional **5** (3.2 g, 6.4%); mp: (EtOAc–hexane, 2:1) 136.3–139.7°C; IR (film, cm^{-1}) 3020, 2985, 2956, 1704, 1638, 1604, 1536, 1510, 1374, 1230; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 1H, J=15.6 Hz), 7.38 (d, 1H, J=8.8 Hz), 7.04 (d, 1H, J=8.8 Hz), 6.34 (dd, 1H, J=15.9, 1.7 Hz), 4.25 (q, 2H, J=7.0 Hz), 3.96 (s, 3H), 3.94 (s, 3H), 1.32 (t, 3H, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 154.4, 145.8, 140.7, 135.9, 122.6, 121.0, 119.2, 113.7, 62.1, 60.7, 56.4, 19.7; HR-MS (FAB) calcd for $C_{13}H_{16}NO_6$ [$(M+H)^+$] 282.0977, found 282.0977.

4.1.2. 3-(2-Formylamino-3,4-dimethoxy-phenyl)-acrylic acid ethyl ester. To a suspension of **5** (40.5 g, 144 mmol) and Zn powder in CH_2Cl_2 (200 mL) was added AcOH (70 mL) dropwise at 10°C over an hour, and the resulting mixture was stirred for an additional 30 min at room temperature. The reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2 (400 mL). To the combined filtrates was added water (200 mL) and solid $NaHCO_3$ until pH reached to 8.0 (67 g). The resulting mixture was separated, and aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give yellow oil. A mixture of HCO_2H (16.3 mL, 432 mmol) and Ac_2O (40.8 mL, 432 mmol) was stirred at 55°C for 30 min and cooled to 5°C, to which was added a CH_2Cl_2 (80 mL) solution of the above crude product at 5°C. After stirring for 10 min, the reaction mixture was poured into a mixture of CH_2Cl_2 (300 mL) and water (200 mL), and solid $NaHCO_3$ was added until pH reached to 7 (100 g). The resulting two-phase mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (40 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to dryness to afford the titled formanilide as white needles (40.6 g, quantitative in 2 steps), which was pure enough for next step. This material was obtained as a mixture of rotational isomers; mp: (EtOAc–hexane, 1:4) 147.6–149.5°C; IR (film, cm^{-1}) 3259, 2982, 1703, 1634, 1596, 1490, 1300, 1267, 1182; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 0.4H), 8.33 (s, 0.3H), 8.30 (s, 0.3H), 7.76 (d, 0.4H, J=15.9 Hz), 7.68 (d, 0.3H, J=15.9 Hz), 7.66 (d, 0.3H, J=15.9 Hz), 7.42 (d, 0.4H, J=8.7 Hz), 7.36 (d, 0.6H, J=8.7 Hz), 6.89 (d, 0.4H, J=8.7 Hz), 6.34 (d, 1H, J=15.9 Hz), 4.24 (q, 2H, J=7.1 Hz), 3.93 (s, 1.8H), 3.90 (s, 1.2H), 3.83 (s, 1.2H), 3.82 (s, 1.8H), 1.32 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 166.4, 164.8, 160.3, 154.3, 154.1, 143.5, 142.5, 140.1, 138.9, 129.4, 128.7, 124.5, 123.1, 122.2, 119.1, 117.4, 111.1, 110.4, 60.8, 60.6, 60.5, 60.4, 56.0, 55.9, 14.3; HR-MS (FAB) calcd for $C_{14}H_{18}NO_5$ [$(M+H)+$] 280.1185, found 280.1188.

4.1.3. 3-(3,4-Dimethoxy-2-isocyano-phenyl)-acrylic acid ethyl ester (6). To a solution of the formanilide (39.3 g, 141 mmol) and pyridine (87 mL) in CH_2Cl_2 (160 mL) was added phosphorus oxychloride (22 mL, 233 mmol) dropwise over 20 min at 5°C. After stirring for 50 min, the reaction mixture was slowly poured into a mixture of CH_2Cl_2 (80 mL) and saturated $NaHCO_3$ (80 mL), and separated. The organic phase was washed with saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (CH_2Cl_2) afforded **6** (23.3 g, 63.3% in 3 steps) as white needles; mp: (EtOAc–hexane, 1:4) 96.6–97.4°C; IR (film, cm^{-1}) 2988, 2122, 1714, 1638, 1593, 1499, 1259, 1184, 1075; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, 1H, J=15.9 Hz), 7.36 (d, 1H, J=8.8 Hz), 6.97 (d, 1H, J=8.8 Hz), 6.43 (d, 1H, J=15.9 Hz), 4.28 (q, 2H, J=7.1 Hz), 3.97 (s, 3H), 3.93 (s, 3H), 1.35 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 166.1, 154.2, 145.6, 137.6, 123.7, 122.1, 120.0, 113.0, 61.1, 60.7, 56.2, 14.3; HR-MS (FAB) calcd for $C_{14}H_{15}NO_4$ [M^+] 261.1001, found 261.0994.

4.1.4. (2-Iodo-6,7-dimethoxy-1*H*-indol-3-yl)-acetic acid ethyl ester (7). A mixture of **6** (20.1 g, 77 mmol), AIBN (0.63 g, 3.9 mmol), and Bu_3SnH (24 mL, 85 mmol) in CH_3CN (400 mL) was heated at reflux for 1.5 h and then cooled to room temperature. To this solution was added I_2 (19.5 g, 77.0 mmol). After stirring for an hour, the reaction mixture was washed with hexane (100 mL×3), and the combined hexane layer was extracted with CH_3CN (20 mL). The combined CH_3CN layers were evaporated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc–hexane, 1:4) afforded **7** (29.1 g, 84.6%) as pale yellow oil; IR (film, cm^{-1}) 3325, 2980, 2934, 1728, 1512, 1426, 1346, 1288, 1250; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (br s, 1H), 7.19 (d, 1H, J=8.8 Hz), 6.84 (d, 1H, J=8.8 Hz), 4.16 (q, 2H, J=7.1 Hz), 3.98 (s, 3H), 3.91 (s, 3H), 3.67 (d, 1H, J=8.8 Hz), 3.65 (d, 1H, J=8.8 Hz), 1.26 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 147.1, 133.4, 133.0, 123.9, 115.4, 113.1, 108.4, 77.9, 60.8, 57.2, 33.2, 14.2. Anal. calcd for $C_{14}H_{16}INO_4$. C, 43.21; H, 4.14. Found. C, 43.02; H, 4.32.

4.1.5. Acetic acid 2-(2-iodo-6,7-dimethoxy-1*H*-indol-3-yl)-ethyl ester (8). To a solution of **7** (14.3 g, 37.7 mmol) in toluene (225 mL) was added DIBAL (1.0 M in toluene, 84 mL, 84 mmol) slowly at 5°C. After stirring for 50 min at this temperature, the reaction was quenched by addition of MeOH (59 mL). The mixture was diluted with EtOAc (155 mL) and washed with potassium sodium tartrate (30% solution in water, 100 mL×1, 45 mL×2), and aqueous phase was back-extracted with EtOAc (25 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to yield crystalline solid (12.5 g). This solid was dissolved in pyridine (56 mL), to which was added Ac_2O (27 mL) slowly. After stirring for 30 min, the reaction mixture was diluted with EtOAc (150 mL) and water

(100 mL), and solid $NaHCO_3$ was added until pH reached to 7 (ca. 38 g). The resulting mixture was separated and the organic phase was washed with 4N HCl (80 mL), saturated $NaHCO_3$ (80 mL), and brine (80 mL), and dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification by flash column chromatography on silica gel (EtOAc–hexane, 1:4) afforded **8** (12.2 g, 85.3%) as pale brown plates; mp: (EtOAc–hexane, 1:4) 85.2–86.8°C; IR (film, cm^{-1}) 3322, 2955, 2934, 2834, 1732, 1510, 1425, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 7.20 (d, 1H, J=8.5 Hz), 6.82 (d, 1H, J=8.5 Hz), 4.19 (t, 2H, J=7.1 Hz), 3.98 (s, 3H), 3.91 (s, 3H), 2.99 (t, 2H, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 147.0, 133.5, 133.1, 124.1, 118.1, 112.7, 108.2, 76.9, 63.8, 60.8, 57.2, 26.5, 21.1; HR-MS (FAB) calcd for $C_{14}H_{16}INO_4$ [M^+] 389.0124, found 389.0128.

4.1.6. 3-[(Trimethyl-silanyl)-ethynyl]-cyclopent-2-enol (10). To a solution of (trimethylsilyl)acetylene (2.92 mL, 20.7 mmol) in THF (28 mL) was added *n*-BuLi (1.50 M solution in hexane, 13.7 mL, 20.7 mmol) dropwise at −70°C over 10 min, and 2-cyclopentene-1-one (1.68 mL, 20.0 mmol) dropwise over 5 min. After being stirred at −70°C for an hour, the reaction was quenched by addition of 10% NH_4Cl (50 mL), and the layers were separated. The aqueous layer was back-extracted with Et_2O (20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 1:7–1:5 gradient) afforded 1,2-adduct (2.33 g, 64.7%) as a colorless oil; IR (film, cm^{-1}) 3333, 3057, 2959, 2854, 2164, 1251, 1181, 1079, 1047; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 1H), 5.99 (dd, 1H, J=5.2, 2.2 Hz), 5.80 (d, 1H, J=5.2 Hz), 2.53 (m, 1H), 2.41 (m, 2H), 2.15 (m, 1H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 134.5, 107.9, 88.4, 77.9, 41.0, 31.0, 0.0; EI-MS m/z 180 [M^+].

To a solution of the 1,2-adduct (2.28 g, 12.7 mmol) in Et_2O (23 mL) was added 3% H_2SO_4 at room temperature. The mixture was stirred vigorously for 10 h, and separated. The aqueous layer was back-extracted with Et_2O (10 mL). The combined organic extracts were washed with brine (15 mL×2), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford **10** (2.24 g, 98.2%) as a colorless oil, which was pure enough for the next step. This oil was solidified under storage at −30°C; IR (film, cm^{-1}) 3315, 2960, 2898, 2858, 2150, 1609, 1319, 1250, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (d, 1H, J=2.2 Hz), 4.89 (br s, 1H), 2.67–2.59 (m, 1H), 2.43–2.26 (m, 2H), 1.73 (ddd, 1H, J=17.6, 8.4, 3.8 Hz), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 128.4, 101.1, 98.0, 77.0, 34.4, 33.1, 0.0; EI-MS m/z 180 [M^+].

4.1.7. (2*S*)-3-[(Trimethyl-silanyl)-ethynyl]-cyclopent-2-enol (11). A suspension of **10** (10.5 g, 58.0 mmol), vinyl acetate (10.7 mL, 116 mmol), and lipase PS (2.0 g, Amano enzyme) in *t*-BuOMe (200 mL) was stirred at 45–50°C for 9 h. The suspension was filtered through a pad of Celite and evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 1:10–1:5 gradient) afforded (*S*)-alcohol **11** (4.66 g, 44.6%, 99.0% ee) as a colorless oil and (*R*)-acetate (5.64 g, 43.7%, 97.2% ee) as a colorless oil. These oil was solidified under storage at −30°C. The optical purity of alcohol and acetate was determined by HPLC analysis (Daicel, Chiralpack AS, 1% *i*-PrOH in hexane); $[\alpha]_D^{25}$=−39.4 (*c* 0.32, $CHCl_3$); IR (film, cm^{-1}) 3315, 2960, 2898, 2858, 2150, 1609, 1319, 1250, 1038; ^1H NMR (400 MHz, $CDCl_3$) δ 6.10 (d, 1H, J=2.2 Hz), 4.89 (br s, 1H), 2.67–2.59 (m, 1H), 2.43–2.26 (m, 2H), 1.73 (ddd, 1H, J=17.6, 8.4, 3.8 Hz), 0.20 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 139.1, 128.4, 101.1, 98.0, 77.0, 34.4, 33.1, 0.0; EI-MS m/z 180 [M^+].

The absolute configuration of the recovered alcohol was determined according to Kusumi–Kakisawa method[30] after conversion to both (*R*)-MTPA and (*S*)-MTPA ester.

To a solution of alcohol **11** (1.4 mg, 7.8 μmol) was added DMAP (3.60 mg, 29.5 μmol), Et_3N (2.0 μL, 14 μmol), and (*R*)-α-methyl-α-(trifluoromethyl) phenylacetic acid chloride ((*R*)-MTPACl) (4.0 μL, 29.5 μmol) sequentially at room temperature. After being stirred for 10 min, the reaction mixture was diluted with CH_2Cl_2, washed with 0.1N HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to dryness to give (*S*)-MTPA ester (2.7 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, 2H, J=3.2 Hz), 7.40 (m, 3H), 6.12 (t, 1H, J=2.0 Hz), 5.93 (d, 1H, J=4.8 Hz), 3.54 (s, 3H), 2.63 (m, 1H), 2.47–2.32 (m, 2H), 1.92–1.84 (m, 1H), 0.20 (s, 9H).

The above procedure was repeated with use of (*S*)-MTPACl to afford (*R*)-MTPA ester (2.5 mg from 1.1 mg of **11**); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.40 (m, 3H), 6.07 (t, 1H, J=2.0 Hz), 5.93 (m, 1H), 3.53 (s, 3H), 2.65 (m, 1H), 2.50–2.36 (m, 2H), 2.02–1.90 (m, 1H), 0.19 (s, 9H).

4.1.8. (2*R*)-Acetic acid 3-[(trimethyl-silanyl)-ethynyl]-cyclopent-2-enyl ester. $[\alpha]_D^{25}$=+161.9 (*c* 1.05, $CHCl_3$); IR (film, cm^{-1}) 2960, 2900, 2152, 1737, 1372, 1238, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ 6.08 (d, 1H, J=2.0 Hz), 5.69 (dd, 1H, J=5.1, 2.0 Hz), 2.65 (m, 1H), 2.40 (m, 1H), 2.31 (m, 1H), 2.02 (s, 3H), 1.86 (m, 1H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 135.0, 130.8, 100.6, 79.9, 34.9, 30.0, 21.1, 0.0.

4.1.9. (2*R*)-*N*,*N*-Dimethyl-2-[(trimethyl-silanyl)-ethynyl]-cyclopent-2-enyl]-acetamide (12). A mixture of (2*S*)-alcohol **11** (5.06 g, 28.1 mmol) and *N*,*N*-dimethyl-acetamide dimethyl acetal (23 mL, 0.14 mol) was heated at reflux. Additional amount of *N*,*N*-dimethylacetamide dimethyl acetal (9.00 mL, 54.8 mmol) was in two portions over 2 h. The reaction mixture was diluted with AcOEt (100 mL) and washed with 10% NH_4Cl (100 mL×1, 50 mL×1). The aqueous phase was backextracted with AcOEt (25 mL×2). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, decolorized by activated charcoal (0.5 g), filtered through a pad of Celite, and evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 1:3) afforded **12** (5.88 g, 84.0%) as brown oil, which was solidified under storage at −30°C; $[\alpha]_D^{25}$=−124.1 (*c* 0.67, $CHCl_3$); IR (film, cm^{-1}) 2957, 2852, 2158, 1646, 1495, 1454, 1394, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (t, 2H, J=6.0 Hz), 3.11 (s, 3H), 2.97 (s, 3H), 2.59 (d, 1H, J=3.5 Hz), 2.53 (d, 1H, J=3.5 Hz), 2.43 (m, 1H), 2.33 (m,

1H), 2.19 (m, 1H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 135.4, 131.1, 110.6, 84.8, 46.5, 41.8, 39.5, 38.6, 35.4, 31.1, 0.0; HR-MS (FAB) calcd for $C_{14}H_{24}NOSi$ [(M+H)$^+$] 250.1627, found 250.1629.

4.1.10. (3*R*)-3-(3-Hydroxy-propyl)-3-hydroxymethyl-5-trimethylsilanyl-pent-4-ynoic acid dimethylamide (13). To a solution of **12** (5.60 g, 22.5 mmol) in acetone (57 mL) was added *N*-methylmorphorine *N*-oxide (5.07 g, 43.3 mmol), water (14 mL), and OsO_4 (1% solution in *t*-BuOH, 5.5 mL, 0.21 mmol) at 0°C. The reaction mixture was warmed to room temperature and stirred for 1.5 h, and 10% $NaHSO_3$ (30 mL) was added. After being stirred for 20 min, the mixture was filtered through a pad of Celite, concentrated under reduced pressure, and diluted with AcOEt (100 mL). The layers were separated and the aqueous layer was back-extracted with AcOEt (20 mL×2). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give a diastereomeric mixture of 1,2-diol (6.20 g), which was used for the next step without purification. To a solution of crude 1,2-diol (6.20 g) in THF (100 mL) was added water (25 mL) and $NaIO_4$ (6.82 g, 31.9 mmol) at 0°C. After being stirred for an hour, the reaction mixture was filtered through a pad of Celite, and AcOEt (80 mL) and water (40 mL) were added. The layers were separated and aqueous layer was back-extracted with AcOEt (15 mL×3). The combined organic extracts were washed with saturated $NaHCO_3$ (15 mL), brine (30 mL), dried over $MgSO_4$, filtered, evaporated under reduced pressure to give gelatinous solid, which was used for the next step without purification. To an EtOH (80 mL) solution of the crude product was added $NaBH_4$ (0.88 g, 23.37 mmol) at room temperature. After stirring for 20 min, the reaction was quenched by addition of 10% NH_4Cl (10 mL). The reaction mixture was evaporated under reduced pressure, and $CHCl_3$ (50 mL) and water were added. The layers were separated, and the organic extracts were washed with brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure. Flash column chromatography on silica gel ($CHCl_3$–MeOH, 30:1) afforded **13** (5.47 g, 85.4% in 3 steps) as a colorless oil; $[\alpha]_D^{25}=-1.2$ (*c* 0.49, $CHCl_3$); IR (film, cm^{-1}) 3394, 2955, 2163, 1620, 1500, 1402, 1250, 1057; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (br s, 1H), 3.68 (m, 3H), 3.54 (t, 1H, *J*=10.0 Hz), 3.17 (s, 3H), 2.99 (s, 3H), 2.81 (d, 1H, *J*=13.6 Hz), 2.47 (d, 1H, *J*=13.6 Hz), 1.75–1.63 (m, 4H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 108.8, 88.4, 67.0, 62.6, 40.8, 39.0, 38.8, 35.7, 33.1, 27.8, 0.0; HR-MS (FAB) calcd for $C_{14}H_{28}NO_3Si$ [(M+H)$^+$] 286.1838, found 286.1833.

4.1.11. (3*R*)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3-hydroxymethyl-5-trimethylsilanyl-pent-4-ynoic acid dimethylamide. To a solution of diol **13** (5.25 g, 18.4 mmol) in CH_2Cl_2 (107 mL) was added Et_3N (7.20 mL, 52.6 mmol), *t*-butylchlorodiphenylsilane (TBDPSCl) (8.30 mL, 31.6 mmol), and 4-dimethylaminopyridine (DMAP) (0.22 g, 1.80 mmol) sequentially at −5°C. After being stirred for 2.5 h, 0.5N HCl was added to the reaction mixture until pH was reached 7 (35 mL). The layers were separated and aqueous layer was back-extracted with CH_2Cl_2 twice. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 1:4–1:2 gradient) afforded the titled compound (7.25 g, 75.3%) as a colorless oil; $[\alpha]_D^{25}=-6.9$ (*c* 0.28, $CHCl_3$); IR (film, cm^{-1}) 3396, 3071, 2956, 2858, 2162, 1623, 1472, 1428, 1397, 1250, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 4H, *J*=6.8 Hz), 7.44–7.26 (m, 6H), 4.31 (dd, 1H, *J*=10.0, 5.0 Hz), 3.68 (m, 3H), 3.52 (t, 1H, *J*=10.0 Hz), 3.16 (s, 3H), 2.99 (s, 3H), 2.80 (d, 1H, *J*=13.6 Hz), 2.42 (d, 1H, *J*=13.6 Hz), 1.74 (m, 2H), 1.66 (m, 2H), 1.05 (s, 9H), 0.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 135.4, 133.8, 129.4, 127.4, 108.3, 88.2, 67.6, 63.9, 41.0, 39.1, 38.8, 35.7, 33.7, 28.0, 26.8, 19.2, 0.0; HR-MS (FAB) calcd for $C_{30}H_{46}NO_3Si_2$ [(M+H)$^+$] 524.3016, found 524.3018.

4.1.12. (3*R*)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3-formyl-5-trimethylsilanyl-pent-4-ynoic acid dimethylamide. To a solution of $(COCl)_2$ (2.30 mL, 26.4 mmol) in CH_2Cl_2 (50 mL) was added DMSO (3.70 mL, 52.8 mmol) slowly at −65°C, and the solution of the above monosilylated diol (7.10 g, 13.2 mmol) in CH_2Cl_2 (40 mL) at this temperature. The mixture was warmed to −22°C over 15 min and cooled −65°C again, and Et_3N (9.20 mL, 66.0 mmol) was added. The reaction mixture was warmed to 5°C over 30 min. To this suspension was added CH_2Cl_2 (30 mL) and water (40 mL), and separated. The aqueous phase was back-extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 1:4–1:2 gradient) afforded aldehyde (6.69 g, 94.6%) as a colorless oil; $[\alpha]_D^{25}=-16.5$ (*c* 0.30, $CHCl_3$); IR (film, cm^{-1}) 3071, 2957, 2858, 2166, 1731, 1646, 1472, 1428, 1250, 1111; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.65 (dd, 4H, *J*=7.6, 1.7 Hz), 7.44–7.35 (m, 6H) 3.68 (dd, 2H, *J*=10.0, 5.4 Hz), 3.01 (s, 3H), 2.91 (s, 3H), 2.90 (d, 1H, *J*=15.6 Hz), 2.85 (d, 1H, *J*=15.6 Hz), 1.91 (m, 1H), 1.73 (m, 3H), 1.05 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 168.9, 135.3, 133.6, 129.4, 127.4, 104.8, 90.2, 63.5, 48.9, 41.9, 37.5, 35.4, 32.2, 28.0, 26.8, 19.1, 0.0; HR-MS (FAB) calcd for $C_{30}H_{44}NO_3Si_2$ [(M+H)$^+$] 522.2859, found 522.2852.

4.1.13. (3*R*)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3[1,3]dioxolan-2-yl-5-trimethylsilanyl-pent-4-ynoic acid dimethylamide. The mixture of the above aldehyde (6.54 g, 12.5 mmol), ethylene glycol (6.8 mL), and *p*-toluenesulfonic acid monohydrate ($TsOH\cdot H_2O$) (0.23 g, 1.2 mmol) in benzene (300 mL) was heated at reflux. Water was removed gradually as the benzene azeotrope. Additional ethylene glycol (3.4 mL, 61 mmol), $TsOH\cdot H_2O$ (0.10 g, 0.53 mmol), and benzene (250 mL) were added over 2.5 h. The reaction mixture was concentrated to about 40 mL under reduced pressure and centrifuged to separate ethylene glycol. The benzene phase was evaporated under reduced pressure to dryness to afford 1,3-dioxolane derivative (8.63 g), which was used for the next step without purification; $[\alpha]_D^{25}=+8.9$ (*c* 0.53, $CHCl_3$); IR (film, cm^{-1}) 3070, 2957, 2859, 2166, 1650, 1472, 1428, 1394, 1250, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, 4H, *J*=6.4, 1.4 Hz), 7.41–7.35 (m, 6H), 5.17 (s, 1H), 4.03 (dd,

2H, J=7.2, 4.0 Hz), 3.94–3.87 (m, 2H), 3.68 (t, 2H, J=5.8 Hz), 3.08 (s, 3H), 2.92 (s, 3H), 2.73 (d, 1H, J=14.6 Hz), 2.51 (d, 1H, J=14.6 Hz), 1.92–1.76 (m, 4H), 1.05 (s, 9H), 0.14 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.0, 135.4, 134.0, 129.2, 127.4, 107.3, 106.0, 87.9, 65.6, 65.5, 64.3, 43.7, 38.5, 36.1, 35.5, 30.5, 28.0, 26.8, 19.2, 0.0; HR-MS (FAB) calcd for $C_{32}H_{48}NO_4Si_2$ [(M+H)$^+$] 566.3122, found 566.3128.

4.1.14. (3*R*)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3-[1,3]dioxolan-2-yl-pent-4-ynoic acid dimethylamide (14). The above crude material (8.28 g) was stirred in saturated K_2CO_3 in MeOH (260 mL) at 50°C for 2 h. The reaction mixture was concentrated under reduced pressure, diluted AcOEt (80 mL), washed with 10% NH_4Cl (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 2:3–1:1 gradient) afforded **14** (5.14 g, 83.1% in 2 steps); $[\alpha]_D^{25}$=+3.6 (*c* 0.31, $CHCl_3$); IR (film, cm^{-1}) 3286, 3071, 2931, 2858, 1647, 1472, 1428, 1395, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, 4H, J=6.4, 1.5 Hz), 7.42–7.34 (m, 6H), 5.21 (s, 1H), 4.02 (m, 2H), 3.91 (m, 2H), 3.69 (t, 2H, J=6.2 Hz), 3.04 (s, 3H), 2.93 (s, 3H), 2.71 (d, 1H, J=15.1 Hz), 2.59 (d, 1H, J=15.1 Hz), 2.21 (s, 1H), 1.96–1.78 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 136.1, 134.6, 129.9, 128.0, 105.8, 85.6, 72.0, 65.9, 65.8, 64.5, 61.4, 42.6, 38.3, 36.2, 35.6, 30.2, 28.0, 27.0, 19.3; HR-MS (FAB) calcd for $C_{29}H_{40}NO_4Si$ [(M+H)$^+$] 494.2726, found 494.2720.

4.1.15. (3*R*)-(5-[3-(2-Acetoxy-ethyl)-6,7-dimethoxy-1*H*indol-2-yl]-3-[3-(*tert*-butyl-diphenyl-silanyloxy)-propyl]-3-[1,3]dioxolan-2-yl-pent-4-ynoic acid dimethylamide (15). To a solution of indole **8** (3.55 g, 9.11 mmol) and acetylene **14** (4.95 g, 10.02 mmol) in Et_3N (100 mL) was added $Pd(PPh_3)_4$ (211 mg, 0.18 mmol) and CuI (104 mg, 0.55 mmol) at room temperature under Ar. The mixture was stirred at 65°C for an hour, cooled to room temperature, and evaporated under reduced pressure. The residue was dissolved in AcOEt (100 mL), washed with 10% NH_4Cl (70 mL). The aqueous phase was back-extracted with AcOEt (20 mL×2). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure. Flash chromatography on silica gel (AcOEt–hexane, 3:2–2:1 gradient) afforded **15** (6.31 g, 91.7%) as a yellow oil; $[\alpha]_D^{25}$=+10.8 (*c* 0.37, $CHCl_3$); IR (film, cm^{-1}) 3297, 2932, 2224, 1739, 1645, 1516, 1456, 1429, 1362, 1243, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.66 (d, 4H, J=6.4 Hz), 7.36 (m, 6H), 7.22 (d, 1H, J=8.6 Hz), 6.84 (d, 1H, J=8.6 Hz), 5.31 (s, 1H), 4.28 (t, 2H, J=7.2 Hz), 4.04 (m, 2H), 3.96 (s, 3H), 3.93 (m, 2H), 3.92 (s, 3H) 3.72 (t, 2H, J=6.2 Hz), 3.07 (s, 3H), 3.07 (t, 2H, J=6.2 Hz), 2.94 (s, 3H), 2.81 (d, 1H, J=15.3 Hz), 2.71 (d, 1H, J=15.3 Hz), 2.09–1.89 (m, 4H), 1.99 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.7, 147.8, 135.4, 133.8, 133.7, 130.0, 129.3, 127.4, 123.7, 117.3, 117.0, 113.9, 108.3, 105.7, 96.8, 75.3, 65.6, 65.5, 64.2, 64.1, 60.8, 57.1, 43.6, 38.0, 36.3, 35.5, 30.3, 28.1, 26.8, 24.8, 21.0, 19.2; HR-MS (FAB) calcd for $C_{43}H_{55}N_2O_8Si$ [(M+H)$^+$] 755.3707, found 755.3721.

4.1.16. (3*R*)-(5-[3-(2-Acetoxy-ethyl)-6,7-dimethoxy-1*H*indol-2-yl]-3-[3-(*tert*-butyl-diphenyl-silanyloxy)-propyl]-3-[1,3]dioxolan-2-yl-pentanoic acid dimethylamide. A mixture of **15** (6.20 g, 8.21 mmol) and 10% Pd on carbon (50.9% H_2O, 2.0 g) in EtOH (100 mL) was stirred at room temperature for 5.5 h. The resulting suspension was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to dryness to afford the corresponding alkane (6.20 g), which was pure enough for the next step; $[\alpha]_D^{25}$=−0.3 (*c* 0.29, $CHCl_3$); IR (film, cm^{-1}) 3339, 2932, 1738, 1621, 1512, 1463, 1428, 1392, 1362, 1242, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (s, 1H), 6.65 (d, 4H, J=6.8 Hz), 7.37 (m, 6H), 7.15 (d, 1H, J=8.6 Hz), 6.78 (d, 1H, J=8.6 Hz), 4.77 (s, 1H), 4.22 (t, 2H, J=7.3 Hz), 4.02 (s, 3H), 3.92 (m, 2H), 3.90 (s, 3H), 3.84 (dd, 2H, J=7.6, 3.0 Hz), 3.65 (t, 2H, J=5.6 Hz), 3.04 (s, 3H), 2.98 (t, 2H, J=8.6 Hz), 2.95 (s, 3H), 2.80 (m, 2H), 2.56 (d, 1H, J=14.9 Hz), 2.42 (d, 1H, J=14.9 Hz), 2.02 (m, 2H), 2.01 (s, 3H), 1.64 (m, 4H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 170.9, 146.3, 137.3, 135.4, 134.3, 133.8, 129.5, 129.4, 127.4, 125.3, 112.5, 107.9, 107.4, 106.0, 64.82, 64.80, 64.6, 64.5, 60.6, 57.6, 42.6, 38.1, 35.5, 33.8, 33.3, 30.9, 30.8, 26.9, 26.8, 23.9, 21.1, 20.5, 19.2; HR-MS (FAB) calcd for $C_{43}H_{58}N_2O_8Si$ [M$^+$] 758.3962, found 758.3963.

4.1.17. (3′*R*)-3-(2-Acetoxy-ethyl)-2-[6-(*tert*-butyldiphenyl-silanyloxy)-3-dimethylcarbamoylmethyl-3-[1,3]dioxolan-2-yl-hexyl]-6,7-dimethyl-indole-1-carcoxylic acid *tert*-butyl ester (16). To a solution of the above indole derivative (6.20 g) in CH_3CN (100 mL) were added Boc_2O (5.38 g, 24.6 mmol) and 4-dimethylaminopyridine (DMAP) (1.50 g, 12.3 mmol) at room temperature. After stirred for 2 h, additional amount of Boc_2O (3.58 g, 16.4 mmol) and DMAP (0.95 g, 7.8 mmol) was added in two portions over 6 h. The reaction mixture was evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 1:1) afforded **16** (6.54 g, 92.7% in 2 steps) as a pale yellow oil; $[\alpha]_D^{25}$=−0.3 (*c*=0.25, $CHCl_3$); IR (film, cm^{-1}) 2932, 1738, 1651, 1501, 1428, 1393, 1363, 1347, 1243, 1153, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, 4H, J=7.3, 1.6 Hz), 7.35 (m, 6H), 7.16 (d, 1H, J=8.5 Hz), 6.88 (d, 1H, J=8.5 Hz), 5.05 (s, 1H), 4.24 (t, 2H, J=7.4 Hz), 3.94 (dd, 2H, J=14.4, 6.6 Hz), 3.90 (s, 3H), 3.86 (m, 2H), 3.84 (s, 3H), 3.69 (m, 2H), 3.04 (s, 3H), 2.97 (dd, 4H, J=14.4, 7.6 Hz), 2.91 (s, 3H), 2.57 (d, 1H, J=15.4 Hz), 2.48 (d, 1H, J=15.4 Hz), 2.01 (s, 3H), 1.87–1.73 (m, 6H), 1.61 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.7, 151.2, 148.6, 138.6, 136.7, 135.4, 133.9, 129.3, 129.0, 127.4, 126.0, 112.7, 110.6, 109.4, 107.9, 83.5, 77.3, 77.2, 77.0, 76.7, 64.8, 64.7, 64.4, 64.1, 60.4, 57.3, 42.0, 37.8, 35.4, 35.0, 34.8, 29.6, 27.6, 27.0, 26.8, 23.8, 21.0, 20.2, 19.2; HR-MS (FAB) calcd for $C_{48}H_{67}N_2O_{10}Si$ [(M+H)$^+$] 859.4565, found 859.4568.

4.1.18. Ring-closing double Mitsunobu reaction. Preparation of (11*R*)-11-dimethylcarbamoylmethyl-11-[1,3]dioxolan-2-yl-1,2-dimethoxy-7-(2-nitrobenzene-sulfonyl)-6,7,8,9,10,11,12,13-octahydro-5*H*-7,14-diaza-cycloundeca[*a*]indene-14-carboxylic acid *tert*butyl ester (18). To a solution of diol **17** (504 mg, 0.870 mmol) in benzene (7.5 mL) was added PPh_3 (685 mg, 2.61 mmol), $NsNH_2$ (193 mg, 0.960 mmol), and DEAD (40% solution in toluene, 1.2 mL, 2.61 mmol) at room temperature. After being stirred for 10 min, the reaction mixture was evaporated under reduced pressure. The residue was

purified twice with flash chromatography on silica gel (AcOEt–hexane, 3:1 and benzene–acetone, 4:1) to afford **18** (309 mg, 47.7%) as pale yellow foam; $[\alpha]_D^{25}=-11.2$ (*c* 0.44, $CHCl_3$); IR (film, cm^{-1}) 2940, 1740, 1637, 1545, 1500, 1347, 1258, 1161; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 1H), 7.69 (m, 2H), 7.60 (m, 1H), 6.94 (d, 1H, *J*=8.3 Hz), 6.86 (d, 1H, *J*=8.3 Hz), 5.02 (s, 1H), 3.90 (s, 3H), 3.89 (m, 2H), 3.88 (s, 3H), 3.83 (m, 2H), 3.55–3.35 (m, 2H), 3.27–2.96 (m, 5H), 3.08 (s, 3H), 2.93 (s, 3H), 2.75 (dt, 1H, *J*=15.6, 5.6 Hz), 2.45 (d, 1H, *J*=14.9 Hz), 2.36 (d, 1H, *J*=14.9 Hz), 2.05–1.97 (m, 2H), 1.94–1.80 (m, 2H), 1.64 (s, 9H), 1.690–1.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 151.0, 149.3, 148.3, 138.5, 136.8, 133.2, 132.2, 131.3, 130.5, 129.4, 125.5, 123.8, 113.8, 112.8, 109.6, 83.7, 64.8, 64.7, 60.3, 57.3, 50.7, 48.7, 44.0, 38.1, 37.1, 35.5, 27.6, 27.3, 22.8, 18.3; HRMS (FAB) calcd for $C_{36}H_{49}N_4O_{11}S$ $[(M+H)^+]$ 745.3118, found 745.3115.

4.1.19. (3′*R*)-3-(2-Acetoxy-ethyl)-2-[3-dimethylcarbamoylmethyl-3-[1,3]dioxolan-2-yl-6-hydroxy-hexyl]-6,7-dimethyl-indole-1-carboxylic acid *tert*-butyl ester. To a solution of **16** (6.36 g, 7.40 mmol) in THF (100 mL) was added TBAF (1 M solution in THF, 37.0 mL) at 45°C. After being stirred for 2 h, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (75 mL) and washed with water (25 mL×3). The aqueous phase was back-extracted with CH_2Cl_2 (10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel ($CHCl_3$–MeOH, 100:1–30:1 gradient) afforded to the titled diol monoacetate (3.91 g, 85.2%) as a colorless oil; $[\alpha]_D^{25}=-1.7$ (*c* 0.51, $CHCl_3$); IR (film, cm^{-1}) 3447, 2940, 1738, 1634, 1502, 1448, 1394, 1368, 1348, 1246, 1153; ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, 1H, *J*=8.5 Hz), 6.89 (d, 1H, *J*=8.5 Hz), 4.96 (s, 1H), 4.23 (t, 2H, *J*=7.6 Hz), 3.96 (m, 2H), 3.91 (s, 3H), 3.86 (m, 2H), 3.83 (s, 3H), 3.67 (m, 2H), 3.07 (m, 2H), 2.94 (dd, 4H, *J*=15.6, 7.8 Hz), 2.92 (s, 3H), 2.58 (d, 1H, *J*=15.4 Hz), 2.43 (d, 1H, *J*=15.4 Hz), 2.06 (s, 3H), 1.84 (m, 3H), 1.75 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 171.0, 151.2, 148.7, 138.5, 136.9, 129.1, 126.0, 112.6, 110.6, 109.6, 107.8, 83.7, 64.6, 64.5, 64.0, 63.3, 60.4, 57.3, 42.3, 37.9, 35.5, 34.81, 34.77, 28.8, 27.6, 27.1, 23.8, 21.1, 20.2; HR-MS (FAB) calcd for $C_{32}H_{49}N_2O_{10}$ $[(M+H)^+]$ 621.3387, found 621.3379.

4.1.20. (3′*R*)-3-(2-Acetoxy-ethyl)-2-[3-dimethylcarbamoylmeth-yl-3-[1,3]dioxolan-2-yl-6-(2-nitro-benzenesulfonylamino)-hexyl]-6,7-dimethylindole-1-carboxylic acid *tert*-butyl ester. To a solution of the above diol monoacetate (3.57 g, 5.75 mmol) in benzene (70 mL) were added PPh_3 (1.80 g, 6.90 mmol), 2-nitrobenzenesulfonamide ($NsNH_2$) (1.51 g, 7.47 mmol), and diethyl azodicarboxylate (DEAD) (40% solution in toluene, 3.10 mL, 6.90 mmol) at room temperature under Ar. After being stirred 5 min, the reaction mixture was evaporated under reduced pressure.

The residue was slurried in AcOEt–hexane (3:1) to precipitate triphenylphosphine oxide, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 3:1–4:1 gradient) afforded the Ns-amide (5.63 g), which was contained triphenylphosphine oxide. The product was used for the next step without purification. For the characterization, a portion of the product was purified by preparative thin layer chromatography ($CHCl_3$–MeOH, 20:1); $[\alpha]_D^{25}=-4.2$ (*c* 0.48, $CHCl_3$); IR (film, cm^{-1}) 2391, 1737, 1636, 1543, 1502, 1438, 1368, 1345, 1246, 1166, 1119; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, 1H, *J*=7.6, 1.7 Hz), 7.80 (dd, 1H, *J*=7.6, 1.5 Hz), 7.70 (m, 2H), 7.14 (d, 1H, *J*=7.5 Hz), 6.89 (d, 1H, *J*=7.5 Hz), 5.90 (t, 1H, *J*=5.8 Hz), 4.88 (s, 1H), 4.21 (t, 2H, *J*=7.6 Hz), 3.93 (m, 2H), 3.92 (s, 1H), 3.84 (s, 3H), 3.84 (m, 2H), 3.12 (m, 2H), 3.05 (s, 3H), 2.93 (m, 2H), 2.92 (s, 3H), 2.84 (br t, 2H, *J*=5.8 Hz), 2.53 (d, 1H, *J*=15.6 Hz), 2.38 (d, 1H, *J*=15.6 Hz), 2.07 (s, 3H), 1.73–1.56 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 171.0, 151.2, 148.7, 147.9, 138.2, 136.8, 133.8, 133.0, 132.3, 131.0, 129.1, 125.9, 125.0, 112.6, 110.6, 109.7, 107.7, 83.7, 64.7, 64.5, 64.0, 60.4, 57.3, 44.5, 42.1, 37.9, 35.5, 34.6, 30.1, 27.6, 23.9, 21.1, 20.1; HR-MS (FAB) calcd for $C_{38}H_{53}N_4O_{13}S$ $[(M+H)^+]$ 805.3330, found 805.3338.

4.1.21. (3′*R*)-2-[3-Dimethylcarbamoylmethyl-3-[1,3]dioxolan-2-yl-6-(2-nitro-benzenesulfonylamino)-hexyl]-3-(2-hydroxy-ethyl)-6,7-dimethyl-indole-1-carboxylic acid *tert*-butyl ester (19). To a solution of the above Ns-amide (5.58 g) in MeOH (120 mL) was added aqueous K_2CO_3 (0.5 M, 20 mL) at room temperature, which was stirred for 1.5 h. The reaction mixture was concentrated under reduced pressure, diluted with AcOEt (80 mL), and separated. The aqueous layer was back-extracted with AcOEt (10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (AcOEt–hexane, 3:1) afforded **19** (5.55 g), which contained triphenyphosphine oxide. The product was used for the next step without purification. For the characterization, a portion of **19** was purified by preparative thin layer chromatography ($CHCl_3$–MeOH, 20:1); $[\alpha]_D^{25}=-5.3$ (*c* 0.26, $CHCl_3$); IR (film, cm^{-1}) 2939, 1735, 1618, 1541, 1500, 1448, 1345, 1255, 1165; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, *J*=7.6 Hz), 7.80 (d, 1H, *J*=7.6 Hz), 7.65 (m, 2H), 7.10 (d, 1H, *J*=8.5 Hz), 6.88 (d, 1H, *J*=8.5 Hz), 5.69 (t, 1H, *J*=5.8 Hz), 4.78 (s, 1H), 3.93 (m, 2H), 3.91 (s, 3H), 3.83 (s, 3H), 3.83 (m, 4H), 3.09 (m, 2H), 3.07 (s, 3H), 2.93 (s, 3H), 2.93–2.83 (m, 4H), 2.46 (s, 2H), 1.81–1.59 (m, 6H), 1.59 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 151.3, 148.6, 147.9, 138.1, 136.8, 133.6, 133.2, 132.4, 130.9, 129.1, 126.1, 125.1, 112.7, 111.9, 109.5, 107.7, 83.5, 64.8, 64.5, 62.5, 60.4, 57.3, 44.5, 42.4, 38.1, 35.6, 34.2, 33.8, 31.0, 28.2, 27.6, 23.8, 20.2; HR-MS (FAB) calcd for $C_{36}H_{51}N_4O_{12}S$ $[(M+H)^+]$ 763.3224, found 763.3220.

4.1.22. Intramolecular Mitsunobu reaction. Preparation of (11*R*)-11-dimethylcarbamoylmethyl-11-[1,3]dioxolan-2-yl-1,2-dimethoxy-7-(2-nitrobenzenesulfonyl)-6,7,8,9,10,11,12,13-octahydro-5*H*-7,14-diaza-cycloundeca[*a*]indene-14-carboxylic acid *tert*-butyl ester (18). To a solution of **19** (5.50 g) in benzene (70 mL) was added PPh_3 (1.80 g, 6.90 mmol), and DEAD (40% solution in toluene, 3.10 mL, 6.90 mmol) at room temperature. After being stirred for 5 min, the reaction mixture was evaporated under reduced pressure. The residue was purified twice with flash chromatography on silica gel (benzene–acetone, 5:1

and AcOEt–hexane, 3:1) to afford **18** (3.12 g, 72.9% in 3 steps) as a pale yellow foam.

4.1.23. (11*R*)-11-Dimethylcarbamoylmethyl-11-folmyl-1,2-dimethoxy-7-(2-nitro-benzenesulfonyl)-6,7,8,9,10,11,12,13-octahydro-5*H*-7,14-diazacycloundeca[*a*]indene-14-carboxylic acid *tert*-butyl ester. A mixture of **18** (3.05 g, 4.09 mmol) and pyridinium ptoluenesulfonate (PPTS) (206 mg, 0.82 mmol) in acetone (90 mL) and water (10 mL) was stirred at 70°C for 18 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in AcOEt (50 mL), washed with saturated $NaHCO_3$ and brine. The organic Phase was dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the titled aldehyde (2.88 g, quant.) as a pale yellow foam, which was pure enough for the next step; $[\alpha]_D^{25}=-37.3$ (*c* 0.63, $CHCl_3$); IR (film, cm^{-1}) 2939, 1735, 1637, 1546, 1501, 1347, 1257, 1153; ^1H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.94 (m, 1H), 7.71 (m, 2H), 7.63 (dd, 1H, *J*=7.1, 2.2 Hz), 6.92 (d, 1H, *J*=8.5 Hz), 6.86 (d, 1H, *J*=8.5 Hz), 3.90 (s, 3H), 3.88 (s, 3H), 3.43 (br t, 1H, *J*=10.0 Hz), 3.20 (m, 1H), 3.06 (s, 3H), 2.99 (br s, 2H), 2.94 (br s, 2H), 2.89 (m, 1H), 2.76 (d, 1H, *J*=16.4 Hz), 2.65 (d, 1H, *J*=16.4 Hz), 2.17 (m, 1H), 2.00 (m, 2H), 1.85 (m, 1H), 1.63 (s, 9H), 1.60 (m, 1H), 1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 169.5, 150.9, 149.5, 148.3, 137.2, 137.0, 133.4, 132.0, 131.9, 131.4, 130.3, 129.5, 125.2, 124.0, 114.1, 112.8, 109.8, 84.1, 60.3, 57.3, 50.8, 50.4, 49.0, 37.6, 35.5, 27.7, 27.6, 22.6, 17.7; HR-MS (FAB) calcd for $C_{34}H_{45}N_4O_{10}S$ $[(M+H)^+]$ 701.2856, found 701.2853.

4.1.24. Pentacyclic compound (20). To a suspension of the above aldehyde (2.86 g, 4.08 mmol) and Cs_2CO_3 (4.32 g, 12.2 mmol) in CH_3CN (60 mL) was added PhSH (0.83 mL, 8.2 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was concentrated under reduced pressure. The residue was slurried in CH_2Cl_2, filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. To remove 2-nitrophenyl phenyl sulfide, the residue was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 100:1, and then 10% MeOH in CH_2Cl_2–*i*-$PrNH_2$, 20:1). The product (2.05 g) obtained as yellow foam was used for the next step without purification. The product (2.00 g) was dissolved in CH_2Cl_2 (20 mL), to which were added Me2S (15 mL) and TFA (15 mL) at room temperature. After being stirred for 5 min, the reaction mixture was evaporated under reduced pressure to dryness. The residue was dissolved in AcOEt (60 mL), and saturated $NaHCO_3$ (90 mL) was added. After being stirred for 10 min, the organic layer was separated. The aqueous layer was back-extracted with AcOEt (30 mL×2). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to afford the pentacyclic compound **20** (1.32 g, 83.5%) as a brown oil, which was used for the next step without purification; $[\alpha]_D^{25}=+208.1$ (*c*=0.68, $CHCl_3$); IR (film, cm^{-1}) 3480, 2935, 2783, 1639, 1493, 1257, 1080; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, 1H, *J*=7.6 Hz), 6.71(d, 1H, *J*=7.6 Hz), 4.16 (s, 3H), 3.88 (s, 3H), 3.15 (m, 2H), 2.79 (ddd, 1H, *J*=13.6, 10.8, 2.8 Hz), 2.68 (s, 3H), 2.64 (s, 1H), 2.61 (s, 3H), 2.55 (m, 1H), 2.19 (m, 2H), 1.88 (t, 1H, *J*=13.6 Hz), 1.78 (m, 2H), 1.66 (d, 1H, *J*=15.6 Hz), 1.66–1.46 (m, 5H), 1.57 (d, 1H, *J*=15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 170.2, 168.7, 162.5, 151.5, 145.5, 140.9, 128.9, 115.0, 109.0, 78.6, 61.7, 60.8, 56.4, 52.1, 38.7, 37.3, 36.7, 35.1, 34.1, 28.8, 23.8, 21.9; HR-MS (FAB) calcd for $C_{23}H_{31}N_3O_3$ $[(M+H)^+]$ 398.2433, found 398.2483.

4.1.25. Conjugated imine derivative (21). A suspension of **20** (1.30 g, 3.27 mmol) and benzeneseleninic anhydride (70% content, 2.00 g, 3.89 mmol) in benzene (60 mL) was stirred at 65°C for 1.5 h. The reaction mixture was diluted with AcOEt (50 mL), and washed with aqueous 1 M K_2CO_3 (30 mL×1, 20 mL×1). The aqueous phase was back-extracted with AcOEt (10 mL×2). The combined organic extracts were washed with brine twice, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel ($CHCl_3$–MeOH, 30:1) afforded **21** (0.84 g, 65%) as a yellow oil; $[\alpha]_D^{25}=+273.6$ (*c* 0.46, $CHCl_3$); IR (film, cm^{-1}) 3480, 2934, 2776, 2242, 1644, 1593, 1495, 1332, 1256, 1137, 1081; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, 1H, *J*=8.1 Hz), 6.79 (d, 1H, *J*=10.0 Hz), 6.73 (d, 1H, *J*=8.1 Hz), 6.62 (dd, 1H, *J*=10.0, 1.8 Hz), 4.17 (s, 3H), 3.89 (s, 3H), 3.15 (d, 1H, *J*=11.0 Hz), 3.09 (t, 1H, *J*=7.0 Hz), 2.77 (s, 3H), 2.72–2.60 (m, 2H), 2.68 (s, 1H), 2.43 (td, 1H, *J*=11.0, 4.0 Hz), 2.21 (dt, 1H, *J*=11.8, 7.0 Hz), 1.76 (d, 1H, *J*=15.4 Hz), 1.73–1.60 (m, 3H), 1.70 (d, 1H, *J*=15.4 Hz), 1.40 (td, 1H, *J*=12.4, 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 169.4, 151.6, 150.2, 145.2, 141.4, 139.4, 123.3, 114.0, 109.1, 96.0, 69.5, 62.5, 61.7, 56.3, 52.7, 50.8, 43.4, 40.6, 37.9, 37.4, 35.3, 34.8, 30.9, 29.6, 23.0; HR-MS (FAB) calcd for $C_{23}H_{30}N_3O_3$ $[(M+H)^+]$ 396.2287, found 396.2279.

4.1.26. *N*-Methylindoline derivative (22). To a solution of **21** (0.74 g, 1.87 mmol) in MeOH (45 mL) were added aqueous 37% HCHO (2.80 mL, 37.4 mmol), phosphate buffer (0.2 M, pH 7.0, 9 mL), and $NaBH_3CN$ (0.72 g, 11.2 mmol) at room temperature. After being stirred for an hour, the reaction mixture was concentrated under reduced pressure. The residue was diluted with AcOEt (40 mL) and washed with brine (15 mL). The aqueous phase was back-extracted with AcOEt (10 mL×2). The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel ($CHCl_3$–MeOH, 100:1–50:1 gradient) afforded **22** (0.44 g, 57%) as a yellowish brown oil; $[\alpha]_D^{25}=+68.4$ (*c* 0.35, $CHCl_3$); IR (film, cm^{-1}) 2931, 2793, 1645, 1611, 1480, 1327, 1266, 1128, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, 1H, *J*=8.2 Hz), 6.24 (d, 1H, *J*=8.2 Hz), 6.07 (dd, 1H, *J*=10.0, 4.8 Hz), 5.97 (d, 1H, *J*=10.0 Hz), 3.81 (s, 3H), 3.73 (s, 3H), 3.67 (d, 1H, *J*=4.8 Hz), 3.15–3.05 (m, 2H), 3.10 (s, 3H), 2.78 (s, 3H), 2.57 (s, 3H), 2.50 (d, 1H, *J*=15.1 Hz), 2.33 (m, 2H), 2.21 (br d, 1H, *J*=12.0 Hz), 2.07 (m, 2H), 1.78 (d, 1H, *J*=15.1 Hz), 1.58–1.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 153.3, 137.5, 133.1, 130.9, 125.0, 118.1, 101.5, 75.3, 60.8, 55.9, 52.9, 51.6, 45.0, 43.5, 38.4, 37.4, 36.1, 35.20, 35.16, 22.9; HR-MS (FAB) calcd for $C_{24}H_{34}N_3O_3$ $[(M+H)^+]$ 412.2600, found 412.2595.

4.1.27. Ethyl ester derivative (23). To a suspension of **22** (245 mg, 0.594 mmol) and K_2CO_3 (dried on P_2O_5, 1.64 g,

11.9 mmol) was added $Et_3O^+ \cdot BF_4^-$ (2.26 g, 11.9 mmol) at 40°C, and the reaction mixture was stirred for 3.5 h. To the resulting suspension were added CH_2Cl_2 and phosphate buffer (pH 3.5), and aqueous 1 M K_2CO_3 was added until pH was reached to 9. The layers were separated and aqueous layer was back extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, evaporated under reduced pressure. Flash column chromatography on silica gel ($CHCl_3$–MeOH, 25:1–4:1 gradient) afforded **23** (30 mg, 12%) and ethyl ammonium salt **23′** (69 mg).

Ethyl ester derivative (**23**); $[\alpha]_D^{25}$=+65.3 (*c* 0.19, $CHCl_3$); IR (film, cm^{-1}) 2933, 2782, 1732, 1611, 1475, 1266, 1175, 1070; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, 1H, *J*=8.1 Hz), 6.24 (d, 1H, *J*=8.1 Hz), 6.12 (dd, 1H, *J*=9.3, 5.0 Hz), 5.97 (d, 1H, *J*=9.3 Hz), 4.03–3.92 (m, 2H), 3.81 (s, 3H), 3.71 (s, 3H), 3.63 (d, 1H, *J*=5.0 Hz), 3.12 (d, 1H, *J*=9.8 Hz), 3.08 (s, 3H), 3.05 (d, 1H, *J*=8.6 Hz), 2.39 (d, 1H, *J*=15.1 Hz), 2.32 (q, 1H, *J*=8.6 Hz), 2.22 (br s, 1H), 2.12 (d, 1H, *J*=13.2 Hz), 2.04 (m, 2H), 1.99 (d, 1H, *J*=15.1 Hz), 1.94 (d, 1H, *J*=13.2 Hz), 1.60 (br s, 2H), 1.41 (br t, 1H, *J*=13.2 Hz), 1.15 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 153.2, 143.2, 137.7, 133.4, 130.8, 125.2, 118.1, 101.6, 75.9, 72.8, 60.4, 59.7, 55.8, 53.1, 52.4, 51.6, 45.0, 37.7, 36.2, 34.8, 22.8, 14.1; HR-MS (FAB) calcd for $C_{24}H_{32}N_2O_4$ [M^+] 412.2362, found 412.2358.

4.1.28. Carboxylic acid derivative (24). To a solution of **23** (32 mg, 85 μmol) in EtOH (3 mL) was added 1N NaOH (1 mL) at 70°C under Ar. After being stirred for 2.5 h, the reaction mixture was cooled to 5°C and 1N HCl was added dropwise until pH was reached 6. The resulting mixture was evaporated under reduced pressure. Preparative thin layer chromatography (CH_2Cl_2–MeOH, 4:1) afforded **24** (17 mg, 52%) as white solid.

4.1.29. Aspidophytine (2). Compound **24** (13 mg, 34 μmol) was dissolved in *t*-BuOH–H_2O (1:2) at 5°C under Ar, and solid $NaHCO_3$ (31 mg, 0.36 mmol) was added followed by solid $K_3Fe(CN)_6$ (60 mg, 0.18 mmol). The mixture was warmed to room temperature immediately. After being stirred for 10 min, the reaction mixture was diluted with water and extracted with CH_2Cl_2 three times. The organic extracts were washed saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Preparative thin layer chromatography (10% MeOH in CH_2Cl_2–hexane, 3:1) afforded aspidophytine (7.2 mg, 56%) as white crystals; $[\alpha]_D^{25}$=−122.0 (*c* 0.16, $CHCl_3$) (lit.[6] −121.1); mp: (CH_2Cl_2–MeOH, 1:2) 198.6–201.9°C (lit.[6] 196–198°C); IR (film, cm^{-1}) 2944, 2851, 1750, 1608, 1493, 1466, 1446, 1417, 1267, 1222, 1133, 1069; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, 1H, *J*=8.3 Hz), 6.19 (d, 1H, *J*=8.3 Hz), 5.84 (dd, 1H, *J*=10.2, 2.2 Hz), 5.52 (dd, 1H, *J*=10.2, 1.3 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 3.67 (t, 1H, *J*=1.8 Hz), 3.19 (q, 1H, *J*=8.3 Hz), 3.15 (s, 3H), 3.07 (m, 1H), 2.90 (m, 1H), 2.73 (br d, 1H, *J*=11.5 Hz), 2.36 (d, 1H, *J*=16.4 Hz), 2.30 (ddd, *J*=12.9, 8.6, 3.5 Hz), 2.23 (d, 1H, *J*=16.4 Hz), 2.07 (ddd, 1H, *J*=12.9, 10.5, 6.8 Hz), 1.71 (br d, 1H, *J*=12.7 Hz), 1.64–1.51 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 153.6, 143.4, 133.4, 130.3, 128.9, 125.3, 125.2, 119.9, 107.0, 101.8, 96.0, 71.6, 61.1, 56.9, 55.6, 53.4, 47.7, 47.2, 43.2, 41.3, 35.2, 35.1, 34.4, 21.4; HR-MS (FAB) calcd for $C_{22}H_{26}N_2O_4$ [M^+] 382.1963, found 382.1963.

4.1.30. 3-[(Triisopropyl-silanyl)-ethynyl]-cyclopent-2-enol (25). To a THF (6 mL) solution of ethynyl-triisopropyl-silane (1.61 mL, 7.16 mmol) was added *n*-BuLi (4.36 mL, 5.97 mmol, 1.37 M in hexane) dropwise at −78°C over 5 min. After stirring for 30 min, anhydrous $CeCl_3$ (7.16 mmol, 0.24 M in THF) was added to the mixture over 5 min, and the resulting yellow suspension was stirred at −78°C for 30 min. To the mixture was added cyclopentenone (**9**) (0.500 mL, 5.97 mmol) dropwise, and the mixture was stirred for 10 min, at which time the reaction temperature was allowed to raise to room temperature. The reaction was quenched by addition of saturated NH_4Cl. The reaction mixture was diluted with Et_2O, filtered, and concentrated. The residue was dissolved in EtOAc and washed with saturated NH_4Cl. The aqueous layer was back-extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to obtain crude product. The crude material was passed through a silica gel short column (elution with 10 to 30% EtOAc in hexane) and used for the next step without further purification. To a THF (14 mL) solution of the crude material was added 3% H_2SO_4 (6 mL) and the solution was stirred at room temperature for 6.5 h. The reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was back-extracted with EtOAc twice. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a crude product. Purification by column chromatography on silica gel (elution with 10% EtOAc in hexane) gave the desired product **25** (1.48 g, 94% in 2 steps); IR (film, cm^{-1}) 3308, 2943, 2892, 2866, 2147, 1609, 1463, 1038, 883; ^1H NMR (400 MHz, $CDCl_3$) δ 6.09 (d, 1H, *J*=2.0 Hz), 4.90 (br s, 1H), 2.68–2.62 (m, 1H), 2.42–2.29 (m, 2H), 1.79–1.71 (m, 1H) 1.08 (s, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 129.0, 103.2, 94.7, 77.6, 35.1, 33.6, 18.6, 11.2; HR-MS (FAB) calcd for $C_{16}H_{28}OSi$ [M^+] 264.1909, found 264.1921.

4.1.31. (2*S*)-3-[(Triisopropyl-silanyl)-ethynyl]-cyclopent-2-enol (26). A white suspension of 3-[(triisopropyl-silanyl)-ethynyl]-cyclopent-2-enol (**25**) (10.7 g, 40.5 mmol), vinyl acetate (7.46 mL, 80.9 mmol) and lipase PS (2.14 g, Amano enzymes) in *t*-BuOMe (135 mL) was stirred at 48–50°C for 20 h. The suspension was filtered through a pad of Celite and concentrated. The residual material was purified by column chromatography on silica gel (elution with 5 to 20% EtOAc in hexane) to give the desired (*S*)-alcohol (**26**) (5.11 g, 48.0%) and (*R*)-acetate (6.00 g, 48.0%). The optical purity of the alcohol was determined by NMR analysis after conversion to MTPA ester to be >99% ee; $[\alpha]_D^{24}$=−27.7 (*c* 1.01, methanol).

The absolute configuration of the recovered alcohol was determined according to Kusumi–Kakisawa method[30] as used for the corresponding TMS-derivatives **11**.

(*S*)-MTPA ester of **26**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, 2H, *J*=3.9 Hz), 7.40 (dd, 3H, *J*=3.9, 5.8 Hz), 6.11 (d, 1H, *J*=2.0 Hz), 5.95 (dd, 1H, *J*=2.9, 6.8 Hz), 3.56 (s, 3H),

2.68–2.61 (m, 1H), 2.49–2.34 (m, 2H), 1.91–1.85 (m, 1H), 1.08 (s, 21H).

(*R*)-MTPA ester of **26**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, 2H, *J*=3.9 Hz), 7.41 (dd, 3H, *J*=3.9, 5.9 Hz), 6.05 (d, 1H, *J*=4.9 Hz), 5.94 (dd, 1H, *J*=2.0, 5.9 Hz), 3.55 (s, 3H), 2.69–2.61 (m, 1H), 2.50–2.39 (m, 2H), 2.03–1.95 (m, 1H), 1.08 (s, 21H).

4.1.32. (1*R*)-(1-Ethynyl-cyclopent-2-enyl)-acetic acid ethyl ester (27). A mixture of cyclopentenol **26** (5.00 g, 18.9 mmol), triethy orthoacetate (34.7 mL, 189 mmol), and pivalic acid (38.6 mg, 0.378 mmol) in xylene (190 mL) was heated at reflux. Ethanol was gradually removed through Dean–Stark trap. Additional amount of pivalic acid (231.6 mg, 2.27 mmol), and triethy orthoacetate (27.7 mL, 151 mmol) were added in several portions over 8 h and the solution was stirred at reflux for 2 h. To the reaction mixture was added 1N HCl, and the resulting reaction mixture was stirred for 20 min at room temperature. The organic phase was diluted with EtOAc, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was passed through a silica gel short pass to obtain a crude product. The crude material was used in the next step without further purification. To a THF (30 mL) of the oily crude material was added tetra-*n*-butylammonium fluoride (1.0 M in THF, 22.9 mL, 22.9 mmol), and the resulting mixture was stirred at 50°C for 45 min. The reaction mixture was partitioned between EtOAc and saturated ammonium chloride. The aqueous layer was back-extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was passed through a silica gel short-column to give a crude product as a mixture of the desired terminal acetylene **27** and inseparable compounds (5.3 g). Spectral data of **27** were determined after a careful purification of the small portion of the crude material; IR (film, cm^{-1}) 3291, 2980, 2938, 2109, 1737; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (dt, 1H, *J*=2.9, 5.9 Hz), 5.79 (dt, 1H, *J*=2.0, 5.9 Hz), 4.17 (q, 2H, *J*=6.8 Hz), 2.57 (dd, 2H, *J*=14.4, 15.6 Hz, 2H), 2.46–2.51 (m, 1H), 2.50 (s, 1H), 2.25–2.42 (m, 2H), 2.09–2.16 (m, 1H), 1.27 (t, 2H, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 134.8, 132.0, 88.1, 79.1, 69.5, 60.4, 44.9, 38.1, 31.2, 14.3; HR-MS (FAB) calcd for $C_{11}H_{14}O_2$ [M^+] 178.0994, found 178.0990.

4.1.33. (3*R*)-3-(3-Hydroxy-propyl)-3-hydroxymethyl-pent-4-ynoic acid ethyl ester (28). To a crude product containing ethynyl cyclopentene **27** (5.3 g) in acetone (40 mL) were added *N*-methylmorphorine *N*oxide (3.58 g, 30.4 mmol), water (10 mL), and OsO_4 (1% w/v solution in *t*-BuOH, 3.88 mL, 0.15 mmol) at 0°C. The reaction mixture was stirred at room temperature for 80 min. The mixture was partitioned between EtOAc and saturated $Na_2S_2O_3$. The aqueous layer was back-extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give a crude material. Purification by passing the oily material through a silica gel short pass (neutral silica gel, 20 to 100% EtOAc in hexane) afforded a diastereomeric mixture of 1,2-diol (2.10 g). A mixture of the 1,2-diol was oxidatively cleaved with $NaIO_4$. To a solution of 1,2-diol (2.10 g) in 5:1 mixture of THF and water (30 mL) was added $NaIO_4$ (3.17 g, 14.8 mmol) at 0°C, and the resulting mixture was stirred at 0°C for 25 min. The reaction mixture was diluted with EtOAc, and washed with water. The aqueous layer was back-extracted with EtOAc four times. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated to obtain a crude material (2.30 g), which was used for the next step without purification. To the crude product dissolved in ethanol (30 mL) was added $NaBH_4$ (0.749 g, 19.8 mmol) at −20°C and the mixture was stirred for 15 min at this temperature. The reaction mixture was then terminated by addition of saturated NH_4Cl and diluted with EtOAc. The aqueous layer was washed extracted with EtOAc four times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to a crude material. Purification by column chromatography on silica gel (elution with 50 to 80% EtOAc in hexane) gave the desired diol **28** (1.49 g, 38% in 5 steps); $[\alpha]_D^{25}=-1.7$ (*c* 0.57, methanol); IR (film, cm^{-1}) 3376, 3291, 2944, 2876, 2110, 1729, 1372, 1187, 1056; ^{1}HNMR δ 4.17 (q, 2H, *J*=6.8 Hz), 3.74–3.65 (m, 4H), 2.63 (d, 1H, *J*=14.6 Hz), 2.58 (d, 1H, *J*=14.6 Hz), 2.50 (t, 1H, *J*=6.8 Hz), 2.26 (s, 1H), 1.79–1.73 (m, 2H), 1.70–1.66 (m, 2H), 1.42 (br s, 1H), 1.28 (t, 3H, *J*=6.8 Hz); ^{13}C NMR δ 171.2, 85.4, 72.3, 67.0, 62.7, 60.8, 40.6, 39.8, 31.7, 27.5, 14.2; HR-MS (FAB) calcd for $C_{11}H_{19}O_4$ [$(M+H)^+$] 215.1283, found 215.1275.

4.1.34. (3*R*)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3-hydroxymethyl-pent-4-ynoic acid ethyl ester. To the diol **28** (1.44 g, 6.72 mmol) in CH_2Cl_2 (23 mL) was added *t*-butylchlorodiphenylsilane (2.10 mL. 8.06 mmol), Et_3N (1.87 mL, 13.4 mmol), and 4-dimethylaminopyridine (246 mg, 2.02 mmol) at −20°C. The reaction mixture was stirred for 45 min as the temperature was raised to −10°C. The reaction was terminated by addition of ammonium chloride, and diluted with EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (elution with 15 to 20% EtOAc in hexane) gave the desired mono-protected compound (2.88 g, 95%); $[\alpha]_D^{26}=-2.1$ (*c* 0.63, methanol); IR (film, cm^{-1}) 3461, 3304, 2956, 2932, 2858, 1732, 1428, 1188, 1112; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 4H, *J*=6.8 Hz), 7.44–7.35 (m, 6H), 4.15 (dq, 2H, *J*=2.0, 6.8 Hz), 3.70–3.62 (m, 4H), 2.60 (d, 1H, *J*=14.8 Hz), 2.55 (d, 1H, *J*=14.8 Hz), 2.41 (t, 1H, *J*=6.8 Hz), 2.23 (s, 1H), 1.76–1.69 (m, 2H), 1.67–1.62 (m, 2H), 1.26 (t, 3H, *J*=6.8 Hz), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 135.6, 133.9, 129.6, 127.6, 85.5, 72.2, 67.6, 63.9, 60.7, 40.6, 40.0, 32.2, 27.6, 26.8, 19.2, 14.2; HR-MS (FAB) calcd for $C_{27}H_{37}O_4Si$ [$(M+H)^+$] 453.2461, found 453.2456.

4.1.35. (3*R*)-3-[3-(*tert*-Butyl-diphenyl-silanyloxy)-propyl]-3-dimethoxymethyl-pent-4-ynoic acid ethyl ester (29). To a CH_2Cl_2 (5 mL) solution of DMSO (1.35 mL, 19.1 mmol) was added $(COCl)_2$ (1.11 mL, 12.7 mmol) at -78°C over 5 min. After stirring for 30 min at this temperature, CH_2Cl_2 solution of alcohol (2.88 g, 6.36 mmol) was added over 10 min. After the reaction mixture was stirred for 30 min, Et_3N (3.55 mL, 25.4 mmol) was added and the reaction temperature was allow to warm to room temperature. The reaction mixture was partitioned

between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a crude material, which was used for the next acetal formation without purification. To the crude product in a 1:1 mixture of MeOH and trimethy orthoformate (20 mL) was added camphorsulfonic acid (444 mg, 1.91 mmol). The reaction mixture was stirred at room temperature for 30 min. The reaction was terminated by addition of excess Et_3N, and the resulting mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with 5 to 10% EtOAc in hexane) afforded the desired dimethyl acetal **29** (2.35 g, 74% in 2 steps); $[\alpha]_D^{26}=+2.4$ (*c* 0.85, methanol); IR (film, cm^{-1}) 3286, 2956, 2932, 2858, 1735, 1428, 1189, 1111, 1082; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 4H, *J*=7.8 Hz), 7.43–7.35 (m, 6H), 4.49 (s, 1H), 4.13 (q, 2H, *J*=6.8 Hz), 3.67 (t, 2H, *J*=5.9 Hz), 3.55 (s, 3H), 3.54 (s, 3H), 2.61 (s, 2H), 2.23 (s, 1H), 1.79–1.70 (m, 4H), 1.25 (t, 3H, *J*=6.8 Hz), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 135.5, 133.9, 129.5, 127.5, 108.3, 84.9, 71.8, 64.1, 60.2, 58.5, 58.2, 43.3, 38.8, 30.1, 27.7, 26.8, 19.2, 14.2; HR-MS (FAB) calcd for $C_{29}H_{40}O_5Si$ [M^+] 496.2645, found 496.2636.

4.1.36. (3*R*)-(5-[3-(2-Acetoxy-ethyl)-6,7-dimethoxy-1*H*indol-2-yl]-3-[3-(*tert*-butyl-diphenyl-silanyloxy)-propyl]-3-dimethoxymethyl-pent-4-ynoic acid ethyl ester. To a solution of indole **8** (1.25 g, 3.20 mmol) and acetylene **29** (1.59 g, 3.20 mmol) in Et_3N (30 mL) were added $Pd(PPh_3)_4$ (74 mg, 0.06 mmol) and CuI (24 mg, 0.13 mmol) under Ar. This solution was stirred at 70°C for 2 h. The resulting mixture was cooled to room temperature, diluted with EtOAc (90 mL), and washed with 10% NH_4Cl (30 mL). The aqueous phase was extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (30 mL×2), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc–hexane, 1:5) afforded the titled coupling product (1.89 g, 78.0%) as pale yellow oil; $[\alpha]_D^{25}=+7.6$ (*c* 0.25, CH_3Cl); IR (film, cm^{-1}) 3338, 2934, 2858, 1737, 1515, 1459, 1365, 1242, 1111, 1094;; ^1HNMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.67 (d, 4H, *J*=7.3 Hz), 7.37 (m, 6H), 7.23 (d, 1H, *J*= 8.8 Hz), 6.84 (d, 1H, *J*=8.8 Hz), 4.28 (t, 2H, *J*=7.1 Hz), 4.14 (q, 2H, *J*=7.1 Hz), 3.96 (s, 3H), 3.92 (s, 3H), 3.70 (m, 2H), 3.58 (s, 3H), 3.57 (s, 3H), 3.08 (t, 2H, *J*=7.1 Hz), 2.73 (d, 1H, *J*=14.9 Hz), 2.67 (d, 1H, *J*=14.9 Hz), 1.90–1.78 (m, 4H), 1.25 (t, 3H, *J*=7.1 Hz), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 147.8, 135.4, 133.7, 133.6, 130.0, 129.4, 127.4, 123.7, 117.5, 116.9, 113.9, 108.2, 108.1, 96.5, 75.4, 64.1, 64.0, 60.8, 60.3, 58.4, 58.2, 57.1, 44.3, 39.0, 30.3, 28.0, 26.8, 24.7, 21.0, 19.2, 14.2; HR-MS (FAB) calcd for $C_{43}H_{55}NO_9Si$ [M^+] 757.3643, found 757.3646.

4.1.37. (3′*R*)-3-(2-Acetoxy-ethyl)-2-[6-(*tert*-butyldiphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-ynyl]-6,7-dimethoxyindole-1-carboxylic acid *tert*-butyl ester (30). To a solution of the above coupling product (4.40 g, 3.22 mmol) in CH_3CN (37 mL) were added Boc_2O (0.94 g, 4.31 mmol) and DMAP (40 mg, 0.33 mmol) at room temperature. After being stirred for 15 min, the reaction mixture was evaporated under reduced pressure to dryness. Flash column chromatography on silica gel (EtOAc–hexane, 1:6) afforded **30** (2.61 g, 94.3%) as a colorless oil; $[\alpha]_D^{25}=+5.4$ (*c* 0.33, $CHCl_3$); IR (film, cm^{-1}) 2934, 2857, 1741, 1505, 1428, 1368, 1348, 1242, 1152, 1112; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.41–7.33 (m, 6H), 7.21 (d, 1H, *J*=8.6 Hz), 6.92(d, 1H, *J*=8.6 Hz), 4.61(s, 1H), 4.26 (t, 2H, *J*=7.1 Hz), 4.13 (q, 2H, *J*=7.1 Hz), 3.92 (s, 3H), 3.85 (s, 3H), 3.69 (m, 2H), 3.57 (s, 3H), 3.56 (s, 3H), 3.07 (t, 2H, *J*=7.1 Hz), 2.73 (s, 2H), 1.99 (s, 3H), 1.86 (m, 4H), 1.61 (s, 9H), 1.23 (t, 3H, *J*=7.1 Hz), 1.04 (s, 9H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 170.8, 170.6, 150.2, 149.7, 136.2, 135.4, 133.8, 129.3, 129.0, 127.4, 124.9, 121.6, 119.1, 113.8, 109.7, 108.1, 99.7, 83.8, 74.1, 64.2, 63.7, 60.4, 60.2, 58.2, 57.9, 57.0, 44.4, 38.9, 30.4, 27.9, 27.6, 26.8, 24.6, 21.0, 19.2, 14.2; HR-MS (FAB) calcd for $C_{48}H_{63}NO_{11}Si$ [M^+] 857.4170, found 857.4174.

4.1.38. (1*Z*)-(3*R*)-3-(2-Acetoxy-ethyl)-2-[6-(*tert*-butyl-diphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-enyl]-6,7-dimethoxyindole-1-carboxylic acid *tert*-butyl ester (31). To a solution of **30** (2.57 g, 3.00 mmol) in EtOH (39 mL) was added 10% Pd on carbon (50.9% H_2O, 1.2 g). The reaction mixture was stirred at room temperature under H_2 (1 atm) for 3.5 h. The resulting suspension was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to dryness to afford **31** (2.56 g, 97.0%) as a colorless oil, which was pure enough for the next step; $[\alpha]_D^{25}=-12.5$ (*c* 0.35, $CHCl_3$); IR (film, cm^{-1}) 2935, 2902, 2858, 1739, 1502, 1429, 1369, 1344, 1241, 1152, 1111; ^1HNMR (400 MHz, C_6D_6, 60°C) δ 7.77 (br s, 4H), 7.27–7.18 (m, 7H), 6.73 (d, 1H, *J*=8.5 Hz), 6.48 (br d, 1H, *J*=12.7 Hz), 6.11(br d, 1H, *J*=12.7 Hz), 4.63 (br s, 1H), 4.41–3.80 (m, 2H), 3.88 (s, 3H), 3.78 (q, 2H, *J*=7.1 Hz), 3.71 (m, 2H), 3.53 (s, 3H), 3.38 (s, 3H), 3.32 (m, 1H), 3.26 (s, 3H), 3.16 (br s, 1H), 2.78 (br d, 1H, *J*=14.9 Hz), 2.65 (br d, 1H, *J*=14.9 Hz), 1.95 (m, 4H), 1.67 (s, 3H), 1.51(s, 9H), 1.17 (s, 9H), 0.83 (t, 3H, *J*=7.1 Hz); ^{13}C NMR (100 MHz, C_6D_6, 60°C) δ 171.6, 170.0, 150.9, 150.5, 140.8, 138.4, 136.1, 134.9, 133.6, 130.5, 129.9, 128.6, 128.5, 128.2, 127.7, 126.9, 119.9, 114.0, 111.4, 83.4, 65.5, 63.9, 60.5, 59.9, 58.4, 58.2, 57.6, 49.9, 31.8, 28.5, 27.5, 25.5, 20.8, 19.8, 14.3; HR-MS (FAB) calcd for $C_{48}H_{65}NO_{11}Si$ [M^+] 859.4327, found 859.4329.

4.1.39. (1*Z*)-(3*R*)-2-[6-(*tert*-Butyl-diphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-enyl]-3-(2-hydroxy-ethyl)-6,7-dimethoxy-indole-1-carboxylic acid *tert*-butyl ester. To a solution of **31** (2.47 g, 2.87 mmol) in MeOH (120 mL) was added aqueous K_2CO_3 (0.5 M, 27 mL) at room temperature, which was then stirred for an hour. The reaction mixture was concentrated under reduced pressure to remove MeOH, diluted with CH_2Cl_2 (50 mL), and separated. The aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc–hexane, 1:3–2:3) afforded an 3-indolylethanol derivative (2.28 g, 96.2%) as a pale yellow oil; $[\alpha]_D^{25}=-10.1$ (*c* 0.43, $CHCl_3$); IR (film, cm^{-1}) 3482, 2933, 2858, 1499, 1429, 1369, 1344, 1256, 1152, 1112; ^1H NMR (400 MHz, C_6D_6, 60°C) δ 7.78

(m, 4H), 7.24 (m, 6H), 7.11 (d, 1H, J=8.5 Hz), 6.74 (d, 1H, J=8.5 Hz), 6.50 (d, 1H, J=13.0 Hz), 6.10 (d, 1H, J=13.0 Hz), 4.64 (s, 1H), 3.90 (s, 3H), 3.80 (q, 2H, J=7.1 Hz), 3.76 (m, 4H), 3.55 (s, 3H), 3.34 (s, 3H), 3.26 (s, 3H), 2.95–3.10 (m, 1H), 2.80 (d, 1H, J=15.0 Hz), 2.67 (d, 1H, J=15.0 Hz), 1.95 (m, 4H), 1.52 (s, 9H), 1.17 (s, 9H), 0.83 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, C_6D_6, 60°C) δ 171.6, 150.4, 138.4, 136.0, 134.8, 133.5, 130.4, 129.7, 128.5, 128.1, 127.9, 127.0, 120.1, 114.1, 111.3, 111.2, 83.2, 65.4, 62.4, 60.4, 59.8, 58.3, 58.2, 57.5, 49.7, 31.6, 29.5, 28.4, 27.4, 19.7, 14.2; HR-MS (FAB) calcd for $C_{46}H_{63}NO_{10}Si$ [M^+] 817.4221, found 817.4218.

4.1.40. (1*Z*)-(3*R*)-2-[6-(*tert*-Butyl-diphenyl-silanyloxy)-3-dimethoxymethyl-3-ethoxycarbonylmethyl-hex-1-enyl]-6,7-dimethoxy-3-[2-(2-nitro-benzenesulfonylamino)-ethyl]-indole-1-carboxylic acid *tert*-butyl ester (34). To a solution of the 3-indolylethanol derivative (2.21 g, 2.71 mmol) in benzene (60 mL) were added PPh_3 (0.99 g, 3.79 mmol), 2-nitrobenzenesulfonamide (*o*-$NsNH_2$) (0.77 g, 3.79 mmol), and DEAD (40% solution in toluene, 1.71 mL, 3.79 mmol) at room temperature under Ar. After being stirred for 5 min, the reaction mixture was cooled in an ice bath to precipitate triphenylphosphine oxide, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (CH_2Cl_2–hexane, 3:1) afforded **34** (2.51 g, 92.7%) as yellow oil; $[\alpha]_D^{25}$=−1.9 (*c* 0.31, $CHCl_3$); IR (film, cm^{-1}) 3322, 2935, 2900, 2859, 1732, 1541, 1501, 1428, 1367, 1258, 1170, 1111; ^{1}H NMR (400 MHz, C_6D_6, 60°C) δ 7.77 (dt, 4H, J=7.3, 2.2, 2.2 Hz), 7.69 (d, 1H, J=8.5 Hz), 7.25 (m, 6H), 7.08 (d, 1H, J=8.5 Hz), 6.84 (d, 1H, J=8.5 Hz), 6.68 (td, 1H, J=7.6, 2.0 Hz), 6.63 (td, 1H, J=7.6, 2.0 Hz), 6.57 (d, 1H, J=8.5 Hz), 6.38 (d, 1H, J=12.9 Hz), 6.00 (d, 1H, J=12.9 Hz), 5.24 (br s, 1H), 4.53 (s, 1H), 3.86 (s, 3H), 3.78 (m, 2H), 3.65 (br s, 2H), 3.50 (s, 3H), 3.32 (m, 3H), 3.29 (s, 3H), 3.24 (s, 3H), 3.16 (br s, 1H), 2.63 (d, 1H, J=14.7 Hz), 2.52 (d, 1H, J=14.7 Hz), 1.85 (m, 4H), 1.54 (s, 9H), 1.16 (s, 9H), 0.82 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, C_6D_6, 60°C) δ 171.4, 150.3, 148.0, 141.0, 138.0, 136.0, 134.7, 134.3, 133.9, 132.4, 131.7, 130.5, 130.1, 129.8, 128.4, 128.1, 127.9, 125.8, 125.0, 119.5, 113.4, 111.2, 110.9, 83.6, 65.3, 60.3, 59.9, 58.5, 58.1, 57.3, 49.6, 43.7, 28.2, 28.0, 27.4, 25.8, 19.7, 14.2; HR-MS (FAB) calcd for $C_{52}H_{67}NO_{13}SSi$ [M^+] 1001.4164, found 1001.4169.

4.1.41. (1*Z*)-(3*R*)-2-(3-Dimethoxymethyl-3-ethoxycarbonylmethyl-6-hydroxy-hex-1-enyl)-6,7-dimethoxy-3-[2-(2-nitro-benzenesulfonylamino)-ethyl]-indole-1-carboxylic acid *tert*-butyl ester. To a solution of the Ns-amide **34** (2.48 g, 2.47 mmol) in THF (50 mL) was added TBAF (1 M solution in THF, 5.0 mL, 5.0 mmol) at room temperature. After being stirred for an hour, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed with brine (20 mL×2). The aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic extract were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc–hexane, 1:1–2:1 gradient) afforded the titled alcohol derivative (1.76 g, 93.0%) as a yellow oil; $[\alpha]_D^{25}$=−10.8 (*c* 0.30, $CHCl_3$); IR (film, cm^{-1}) 3568, 3316, 2980, 2938, 1732, 1542, 1501, 1444, 1368, 1344, 1258, 1164, 1089, 1072; ^{1}H NMR (400 MHz, C_6D_6, 60°C) δ 7.73 (d, 1H, J=7.8 Hz), 7.08 (d, 1H, J=7.8 Hz), 6.91 (d, 1H, J=7.8 Hz), 6.72 (t, 1H, J=7.8 Hz), 6.66 (t, 1H, J=7.8 Hz), 6.61 (d, 1H, J=7.8 Hz), 6.38 (d, 1H, J=12.7 Hz), 6.02 (d, 1H, J=12.7 Hz), 4.50 (s, 1H), 3.90 (s, 3H), 3.50 (s, 3H), 3.32 (m, 3H), 3.28 (s, 3H), 3.22 (s, 3H), 2.95 (m, 1H), 2.61 (d, 1H, J=15.6 Hz), 2.53 (d, 1H, J=15.6 Hz), 1.82–1.61 (m, 4H), 1.55 (s, 9H), 0.86 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 171.8, 150.9, 150.7, 148.4, 141.2, 138.2, 134.7, 134.0, 132.8, 132.0, 130.7, 130.4, 128.1, 126.1, 125.2, 119.7, 113.7, 111.5, 111.2, 83.9, 63.6, 60.5, 60.1, 58.42, 58.41, 57.4, 49.7, 43.7, 31.3, 28.5, 28.1, 26.1, 14.3; HR-MS (FAB) calcd for $C_{36}H_{49}NO_{13}S$ [M^+] 763.2986, found 763.2978.

4.1.42. (11*R*)-(12*Z*)-11-Dimethoxymethyl-11-ethoxycarbonylmethyl-1,2-dimethoxy-7-(2-nitrobenzenesulfonyl)-6,7,8,9,10,11-hexahydro-5*H*-7,14-diaza-cycloundeca-[*a*]indene-14-carboxylic acid *tert*-butyl ester (33). To a solution of the above alcohol (1.72 g, 2.25 mmol) in benzene (60 mL) were added PPh_3 (0.76 g, 2.91 mmol), and DEAD (40% solution in toluene, 1.32 mL, 2.91 mmol) at room temperature under Ar. After being stirred for 5 min, the reaction mixture was evaporated under reduced pressure. The residue was slurried in EtOAc–hexane (1:1) to precipitate triphenylphosphine oxide, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel ($CHCl_3$–MeOH, 150:1) afforded **33** (0.55 g, 92.4%) as yellow foam; $[\alpha]_D^{25}$=+14.3 (*c* 0.33, $CHCl_3$); IR (film, cm^{-1}) 2981, 2939, 2834, 1732, 1544, 1503, 1371, 1348, 1257, 1153, 1073; ^{1}H NMR (400 MHz, C_6D_6, 60°C) δ 7.52 (d, 1H, J=8.5 Hz), 7.21 (d, 1H, J=8.5 Hz), 6.78 (m, 2H), 6.76 (d, 1H, J=8.5 Hz), 6.60 (br t, 1H, J=7.8 Hz), 6.29 (d, 1H, J=24.9 Hz), 6.26 (d, 1H, J=24.9 Hz), 4.63 (s, 1H), 3.96 (dd, 1H, J=7.1, 2.4 Hz), 3.94 (dd, J=7.1, 2.4 Hz), 3.91 (s, 3H), 3.78 (m, 2H), 3.51 (s, 3H), 3.28 (s, 3H), 3.11–3.24 (m, 2H), 2.95 (d, 1H, J=16.0 Hz), 2.86 (dd, J=12.0, 6.0 Hz), 2.60 (d, 1H, J=16.0 Hz), 2.02 (m, 1H), 1.94 (m, 1H), 1.84 (m, 2H), 1.48 (s, 9H), 0.98 (t, 3H, J=7.1 Hz); ^{13}C NMR (100 MHz, C_6D_6, 60°C) δ 171.7, 151.1, 150.4, 149.1, 141.9, 138.0, 133.7, 133.3, 132.7, 131.3, 130.7, 127.8, 126.5, 123.8, 120.8, 115.2, 111.6, 111.1, 83.5, 60.6, 60.0, 58.5, 58.0, 57.3, 50.4, 49.3, 41.2, 32.3, 28.1, 27.6, 26.1, 14.5; HR-MS (FAB) calcd for $C_{36}H_{47}N_3O_{12}S$ [M^+] 745.2880, found 745.2871.

4.1.43. (11*R*)-(12*Z*)-11-Ethoxycarbonylmethyl-11-formyl-1,2-dimethoxy-7-(2-nitro-benzenesulfonyl)-6,7,8,9,10,11-hexahydro-5*H*-7,14-diazacycloundeca-[*a*]indene-14-carboxylic acid *tert*-butyl ester (35). To a solution of **33** (1.46 g, 1.95 mmol) in CH_2Cl_2 (45 mL) was added TMSBr (0.34 mL, 2.54 mmol) at -70°C under Ar. After being stirred for 15 min, the reaction mixture was diluted with THF (15 mL), poured into the mixture of phosphate buffer (0.2 M, pH 7.0, 45 mL) and THF (9 mL) with vigorous stirring, and separated. The aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Since compound **35** was regenerated during post-treatment, the residue was dissolved in CH_2Cl_2 (45 mL), and TMSBr (0.15 mL, 1.17 mmol) was added at −70°C under Ar. After being stirred for 15 min, the same post-treatment was performed. The residue was purified by flash column chromatography on silica gel

(EtOAc–hexane, 1:3–1:2 gradient) to afford an aldehyde (1.26 g, 91.9%) as yellow foam; $[\alpha]_D^{25}=-18.6$ (*c* 0.31, $CHCl_3$); IR (film, cm^{-1}) 2981, 2938, 2837, 1732, 1543, 1504, 1372, 1348, 1257, 1152, 1070; ^1H NMR (400 MHz, DMSO, 100°C) δ 9.52 (s, 1H), 7.88–7.76 (m, 4H), 7.26 (d, 1H, *J*=8.8 Hz), 6.97 (d, 1H, *J*=7.8 Hz), 6.50 (d, 1H, *J*=11.7 Hz), 6.19 (d, 1H *J*=11.7 Hz), 4.05 (q, 2H, *J*=6.8 Hz), 3.88 (br s, 5H), 3.83 (s, 3H), 3.26 (m, 2H), 2.99 (br s, 2H), 2.87 (d, 1H, *J*=16.6 Hz), 2.70 (d, 1H, *J*=16.6 Hz), 1.93–1.63 (m, 4H), 1.52 (s, 9H), 1.18 (t, 3H, *J*=6.8 Hz); ^{13}CNMR (100 MHz, DMSO, 100°C) δ 200.3, 169.6, 149.6, 148.7, 147.6, 136.6, 133.7, 131.6, 131.1, 130.9, 129.4, 129.0, 124.8, 123.6, 122.5, 114.6, 114.0, 110.3, 83.6, 59.5, 59.4, 56.9, 52.4, 48.6, 48.3, 29.6, 26.8, 26.1, 23.4, 13.3; HR-MS (FAB) calcd for $C_{34}H_{41}N_3O_{11}S$ [M^+] 699.2462, found 699.2469.

4.1.44. Pentacyclic compound (36). To a solution of **35** (1.14 g, 1.62 mmol) in CH_3CN (20 mL) was added Cs_2CO_3 (1.72 g, 4.87 mmol) and thiophenol (0.39 mL, 3.73 mmol). After being stirred for 20 min at 55°C, resulting suspension was diluted with CH_2Cl_2, cooled in an ice-bath, filtered through a pad of Celite, and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), and Me_2S (6 mL) and TFA (6 mL) were added sequentially at room temperature. After being stirred for 5 min, the reaction mixture was evaporated under reduced pressure and dissolved in EtOAc (30 mL). Phosphate buffer (0.2 M, pH 7.8, 120 mL) was added to the solution, stirred for 30 min at 5°C, and separated. The aqueous phase was extracted with EtOAc (20 mL×1, 10 mL×1). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (EtOAc–hexane, 1:1–2:1) afforded **36** (0.36 g, 56.4%) and **37** (0.24 g, 29.4%) as yellowish brown oil.

Compound **36**; $[\alpha]_D^{25}=+417.7$ (*c* 0.15, $CHCl_3$); IR (film, cm^{-1}) 2937, 2776, 1731, 1429, 1256, 1174, 1080; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, 1H, *J*=7.8 Hz), 6.84 (d, 1H, *J*=10.0 Hz), 6.72 (d, 1H, *J*=7.8 Hz), 6.54 (dd, 1H, *J*=10.0, 2.0 Hz), 4.19 (s, 3H), 3.97 (q, 2H, *J*=7.1 Hz), 3.89 (s, 3H), 3.16 (br d, 1H, *J*=11.0 Hz), 3.09 (t, 1H, *J*=7.0 Hz), 2.67 (m, 2H), 2.42 (br t, 1H, *J*=10.5 Hz), 2.32 (br d, 1H, *J*=13.7 Hz), 2.21 (td, 1H, *J*=10.5, 7.0 Hz), 1.81 (d, 1H, *J*=15.5 Hz), 1.72 (d, 1H, *J*=15.5 Hz), 1.69 (br s, 2H), 1.36 (td, 1H, *J*=13.7, 5.3 Hz), 1.14 (t, 3H, *J*=7.1 Hz); ^{13}CNMR ($CDCl_3$) δ 182.9, 170.1, 151.7, 149.1, 145.2, 141.6, 139.1, 123.9, 113.9, 109.1, 68.9, 62.2, 61.8, 60.2, 56.3, 52.5, 50.6, 45.3, 39.7, 38.0, 33.9, 22.8, 14.0; HR-MS (FAB) calcd for $C_{23}H_{29}N_2O_4$ [$(M+H)^+$]+ 397.2127, found 397.2124.

Compound **37**; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J*=7.6 Hz), 7.32 (t, 1H, *J*=7.2 Hz), 7.26 (m, 1H), 6.93 (d, 1H, *J*=8.0 Hz), 6.72 (d, 1H, *J*=8.0 Hz), 4.21 (t, 1H, *J*=8.8 Hz), 4.10 (s, 3H), 3.96 (m, 2H), 3.88 (s, 3H), 3.56 (dd, 1H, *J*=8.8, 12.0 Hz), 3.33 (dd, 1H, *J*=7.6, 8.0 Hz), 3.30 (m, 1H), 3.13 (dd, *J*=8.8, 12.0 Hz), 2.47 (m, 1H), 2.41 (s, 1H), 2.40 (m, 1H), 2.30 (m, 1H), 2.13 (m, 1H), 1.72–1.57 (m, 2H), 1.65 (d, 1H, *J*=13.6 Hz), 1.56 (d, 1H, *J*=13.6 Hz), 1.24 (m, 1H), 1.11 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 170.4, 151.9, 146.1, 141.5, 139.9, 136.2, 132.0, 128.9, 127.1, 114.9, 109.4, 82.0, 61.9, 61.4, 60.3, 56.5, 55.5, 54.8, 53.0, 45.5, 40.5, 35.0, 34.4, 33.4, 24.2, 14.3; MS (FAB) 507 [M+1], 397.

4.1.45. *N*-Methylindoline derivative (23). To a solution of **35** (333 mg, 0.84 mmol) in MeOH (20 mL) was added HCHO (37% in water, 1.3 mL 16.8 mmol), phosphate buffer (0.2 M, pH 7.0, 5 mL), and then $NaBH_3CN$ (317 mg, 5.04 mmol) at −70°C. The reaction mixture was stirred at −70°C for additional 30 min and warmed to room temperature over a period of 2 h. To the reaction mixture were added EtOAc (20 mL) and brine (15 mL), and separated. The aqueous phase was extracted with EtOAc (15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (5% MeOH in $CHCl_3$–hexane 1:1) afforded **23** (231 mg, 66.7%) as a yellowish brown oil.

4.1.46. (−)-Aspidophytine (2). To a solution of **23** (181 mg) in EtOH (12 mL) was added NaOH (1 M, 4 mL) at 70°C under Ar. After being stirred for 2.5 h, the reaction mixture was cooled to 5°C, and concd HCl was added dropwise until pH reached to 8.0. The resulting mixture was evaporated under reduced pressure to dryness. The residue was dissolved *t*-BuOH–H_2O (1:2) at 5°C under Ar, and solid $NaHCO_3$ (0.55 g, 6.59 mmol) was added followed by solid $K_3Fe(CN)_6$ (1.08 g, 3.29 mmol) and warmed to room temperature immediately. The reaction mixture was diluted with water (10 mL), extracted with CH_2Cl_2 (15 mL×1, 5 mL×2). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Flash column chromatography on silica gel (5% MeOH in $CHCl_3$–hexane 1:1) afforded aspidophytine (66 mg, 39.4%) as white needles.

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References

1. For a review of earlier work on haplophytine, see: Saxton, J. E. *Alkaloids* **1965**, *8*, 673.
2. Rogers, E. F.; Snyder, H. R.; Fischer, R. F. *J. Am. Chem. Soc.* **1987**, *1952*, 74. Snyder, H. R.; Fischer, R. F.; Walker, J. F.; Els, H. E.; Nussberger, G. A. *J. Am. Chem. Soc.* **1954**, *2819*, 4601. Synder, H. R.; Strohmayer, H. F.; Mooney, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 3708.
3. Yates, P.; MacLachlan, F. N.; Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Cava, M. P.; Behforouz, M.; Lakshmikantham, M. V.; Zeigler, W. *J. Am. Chem. Soc.* **1973**, *95*, 7842.
4. Cheng, P.-T.; Nyburg, S. C.; MacLachlan, F. N.; Yates, P. *Can. J. Chem.* **1975**, *54*, 726.

5. Cava, M. P.; Talapatra, S. K.; Nomura, K.; Weisbach, J. A.; Douglas, B.; Shoop, E. C. *Chem. Ind. (London)* **1963**, 1242. Cava, M. P.; Talapatra, S. K.; Yates, P.; Rosenberger, M.; Szabo, A. G.; Douglas, B.; Raffauf, R. F.; Shoop, E. C.; Weisbach, J. A. *Chem. Ind. (London)* **1963**, 1875. Rae, I. D.; Rosenberger, M.; Szabo, A. G.; Willis, C. R.; Yates, P.; Zacharias, D. E.; Jeffrey, G. A.; Douglas, B.; Kirkpatrick, J. L.; Weisbach, J. A. *J. Am. Chem. Soc.* **1967**, *89*, 3061.
6. He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.
7. (a) Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, *116*, 3127. Tokuyama, H.; Kaburagi, Y.; Chen, X.; Fukuyama, T. *Synthesis* **2000**, 429. (a) Tokuyama, H.; Watanabe, M.; Hayashi, Y.; Kurokawa, T.; Peng, G.; Fukuyama, T. *Synlett* **2001**, 1403.
8. Tokuyama, H.; Fukuyama, T. *Chem. Rec.* **2002**, *2*, 37.
9. Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519. Kobayashi, S.; Ueda, T.; Fukuyama, T. *Synlett* **2000**, 883.
10. For the synthetic studies, see: Yates, P.; Schwarty, D. A. *Can. J. Chem.* **1983**, *61*, 509. Schwarty, D. A.; Yates, P. *Can. J. Chem.* **1983**, *61*, 1126.
11. For the preliminary communication on this work, see: Sumi, S.; Matsumoto, S.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891.
12. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990. Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657.
13. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831. For a review on nitrobenzenesulfonamide chemistry, see: Kan, T.; Fukuyama, T. *J. Synth. Org. Chem. Jpn* **2001**, *59*, 779.
14. Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 697. Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267.
15. An approach using Claisen-Ireland rearrangement, see Ref. 6.
16. Magnus, P.; Westlund, N. *Tetrahedron Lett.* **2000**, *41*, 9369.
17. Ross, S. T.; Frantz, R. G.; Wilson, J. W.; Hahn, R. A.; Sarau, H. M. *J. Heterocycl. Chem.* **1986**, *23*, 1805.
18. Bertrand, M.; Santelli-Rouvier, C. *Bull. Chem. Soc. Fr.* **1972**, 2775.
19. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
20. Felix, D.; Gschwendt-Steen, K.; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030. Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198.
21. Mancuso, A. J.; Huang, S. J.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
22. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
23. Mitsunobu, O. *Synthesis* **1981**, 1.
24. Danieli, B.; Lesma, G.; Palnisano, G.; Riva, R. *J. Chem. Soc., Chem. Commun.* **1984**, 909.
25. Meerwein, H. *Org. Synth.* **1966**, *46*, 113. *Coll. Vol. 5*, 1080.
26. For the review, see: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.
27. For the review, see: Olah, G. A. *Halonium Ions*; Wiley: New York, 1975; Chapter 3.
28. Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283.
29. The corresponding acetate could be converted to the desired allylic alcohol **26** possessing the *S*-configuration through a Mitsunobu inversion reaction as follows; K_2CO_3, MeOH; $PhCO_2H$, DEAD, PPh_3, THF/toluene; K_2CO_3, MeOH, quant, (89% ee) (3 steps).
30. Otani, I.; Kusumi, T.; Kashmar, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.