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Enantioselective Total Synthesis of Aspidophytine

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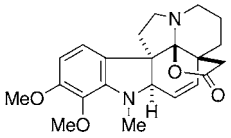
ABSTRACT



Aspidophytine

An enantioselective total synthesis of aspidophytine is described. The indole fragment bearing a *cis*-alkene substituent was efficiently prepared through radical cyclization of a 2-alkenylphenylisocyanide followed by Sonogashira coupling of the generated 2-iodoindole derivative with a functionalized acetylene unit. After formation of the 11-membered cyclic amine, the aspidosperma skeleton and lactone ring were constructed to complete the total synthesis.

In 1973, the groups of M. P. Cava and P. Yates reported the structural determination of haplophytine (**1**),[1] a dimeric indole alkaloid isolated from the dried leaves of the plant *Haplophyton cimicidum*.[2,3] In addition to the X-ray crystallographic study of haplophytine dihydrobromide,[4a] the structure was also supported by extensive chemical investigations, in which the right-half constituent aspidophytine (**2**), a lactonic aspidospermine type of alkaloid, was obtained as the product of acid cleavage of **1**.[1,5] Aspidophytine (**2**) should be not only a precursor of biosynthesis but also a possible synthetic intermediate to **1**. Recently, Corey and co-workers reported a concise and elegant protocol for the construction of **2**.[6] In the course of our project on the development and applications of the indole synthesis, the intriguing structure of this compound prompted us to begin synthetic studies toward the total synthesis of haplophytine (**1**).[7−9] We describe herein our stereoselective protocol for an efficient construction of **2**.

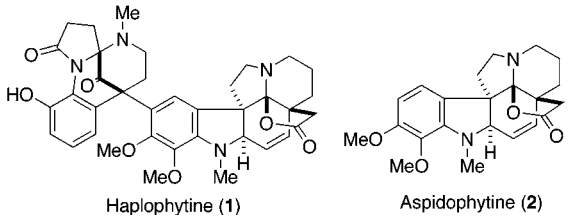


Figure 1.

The requisite terminal acetylene unit **8**, which was to be installed at the indole 2-position, was prepared using

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(1) 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.

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(6) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.

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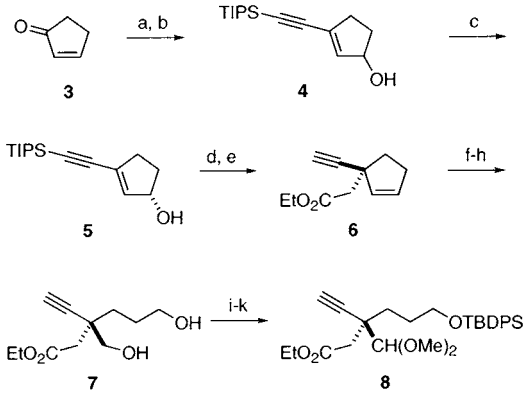
resolution of the allylic alcohol followed by Claisen−Johnson rearrangement (Scheme 1). 1,2-Addition of lithium TIPS-

Scheme 1[a]

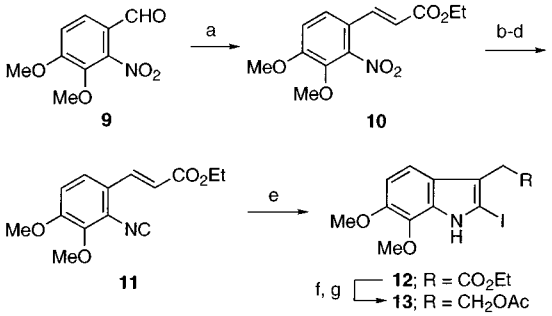


[a] (a) triisopropylsilylacetylene, *n*-BuLi, $CeCl_3$, THF, −78 °C; (b) 3% H_2SO_4, THF, rt, 6.5 h, 94% (2 steps); (c) vinyl acetate, Lipase PS, *t*-BuOMe, 45−50 °C, 48% (99% ee); (d) $CH_3C(OEt)_3$, *t*-$BuCO_2H$, xylene, reflux, 10 h; (e) TBAF, THF, 50 °C, 45 min; (f) OsO_4, NMO, acetone−H_2O, 0 °C to rt, 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, rt, 30 min, 74% (2 steps).

acetylide to cyclopentenone (**3**) in the presence of $CeCl_3$ and subsequent acid treatment gave the conjugated allylic alcohol **4**.[10] Resolution of **4** using Amano lipase PS gave the corresponding *S*-enantiomer **5** (48%, 99% ee).[11] The quaternary carbon center was constructed by Claisen−Johnson rearrangement, followed by desilylation, to give the desired chiral ester **6**. The cyclopentene ring was then cleaved by osmylation and oxidation with $NaIO_4$, and the resulting dialdehyde was reduced to give diol **7**. After regioselective silylation, the remaining primary alcohol was converted to the dimethyl acetal by Swern oxidation and subsequent acetal formation to furnish the desired acetylene unit **8**.

Preparation of the indole unit **13** commenced with Wittig olefination of the known benzaldehyde **9**[12] leading to the ethyl cinnamate derivative **10** (Scheme 2). Conversion of the nitro group to isonitrile was executed by a three-step

Scheme 2[a]



[a] (a) $(EtO)_2POCH_2CO_2Et$, *n*-Bu_4NI, CH_2Cl_2−aq NaOH, 5 °C, 25 min, 81%; (b) Zn, AcOH, CH_2Cl_2, 5 °C to rt, 1.5 h; (c) HCO_2H, Ac_2O, 5 °C, 20 min; (d) $POCl_3$, Py, CH_2Cl_2, 5 °C, 70 min, 63% (3 steps); (e) *n*-Bu_3SnH, AIBN, MeCN, reflux, 1.5 h; I_2, rt, 85%; (f) DIBAL, toluene, 10 °C, 50 min; (g) Ac_2O, Py, rt, 30 min, 85% (2 steps).

sequence including reduction, formylation of aniline, and dehydration. Tin-mediated indole formation and treatment of the 2-stannyl indole intermediate with iodine gave the 2-iodoindole derivative **12**.[7b] Finally, the ester function was reduced to the primary alcohol, which was protected as its acetate to give the desired indole unit **13**.

We then joined the two synthesized fragments **8** and **13** to form the 11-membered secondary amine, a precursor for the construction of the aspidosperma skeleton (Scheme 3). Sonogashira coupling[13] of **8** and **13** gave the 2-alkynyl indole derivative **14**.[7b] It was found that Boc protection of the indole nitrogen was key for the selective partial reduction of the alkyne, and the *cis*-olefin was obtained as the exclusive product. Formation of 11-membered ring was therefore effectively accomplished using *o*-nitrobenzenesulfonyl (Ns) group chemistry.[14,15] Thus, after hydrolysis of the acetate, the nitrogen function was introduced by the Mitsunobu reaction[16] of Ns-amide, followed by desilylation to give the cyclization precursor **16**. The crucial intramolecular Mitsunobu reaction took place smoothly to furnish the 11-membered ring compound **17** in 92% yield.

The synthesis was completed by construction of the aspidosperma skeleton and lactone ring. First, the protective groups of the aldehyde and secondary amine were sequentially removed with TMSBr and a combination of thiophenol and Cs_2CO_3, respectively. Upon treatment with TFA and buffer, initial loss of the Boc group was followed by an intramolecular Mannich-type reaction[17] to furnish the pen-

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(11) The corresponding acetate could be converted to the desired allylic alcohol **5** possessing the *S*-configuration by Mitsunobu inversion as follows: K_2CO_3, MeOH; $PhCO_2H$, DEAD, PPh_3, THF/toluene; K_2CO_3, MeOH, quant, 89% ee (3 steps). For the determination of absolute configuration, see Supporting Information.

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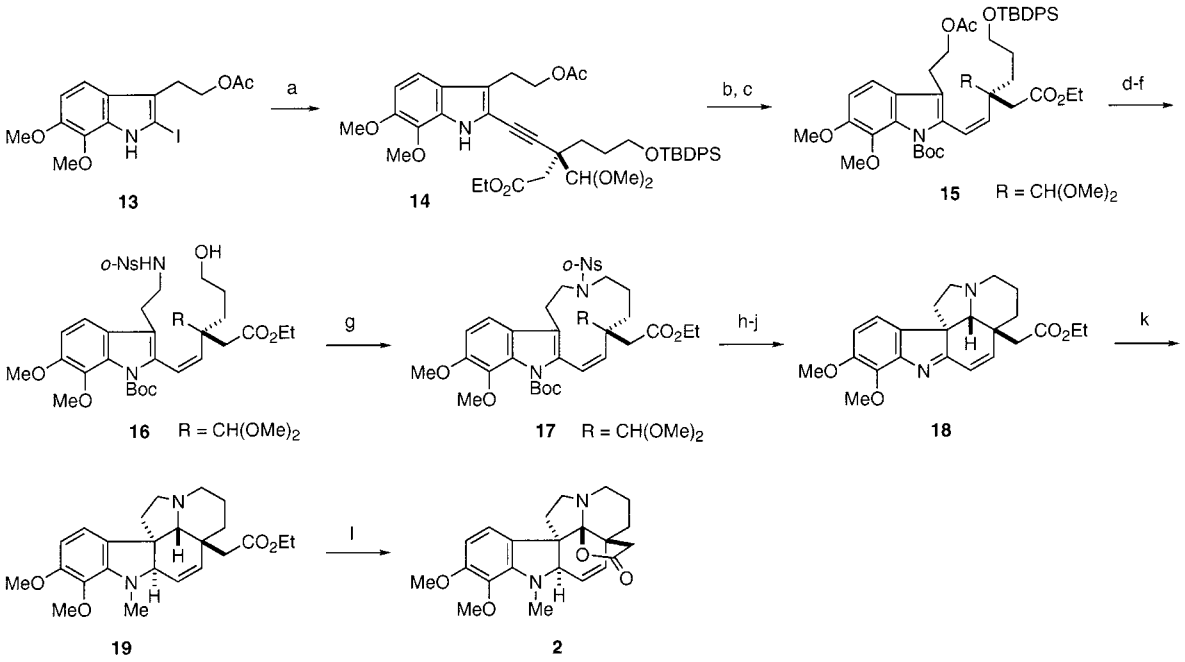
(15) For the cyclization of medium-size cyclic amines, see: (a) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 697. (b) Kan, T.; Fujiwara, A.; Kobayashi, H.; Fukuyama, T. *Tetrahedron* **2002**, *58*, 6267.

(16) Mitsunobu, O. *Synthesis* **1981**, 1.

(17) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T. *J. Am. Chem. Soc.* **1981**, *103*, 6990.

Scheme 3[a]



[a] (a) acetylene **8**, $Pd(PPh_3)_4$, CuI, Et_3N, 70 °C, 2 h, 78%; (b) Boc_2O, DMAP, MeCN, rt, 15 min, 94%; (c) Pd/C, H_2, EtOH, rt, 3.5 h, 97%; (d) K_2CO_3, MeOH, rt, 1 h, 96%; (e) $NsNH_2$, PPh_3, DEAD, PhH, rt, 5 min, 93%; (f) TBAF, THF, rt, 1 h, 93%; (g) PPh_3, DEAD, PhH, rt, 5 min, 92%; (h) TMSBr, CH_2Cl_2, −78 °C, 15 min, 92%; (i) PhSH, Cs_2CO_3, MeCN, 55 °C, 20 min; (j) TFA, Me_2S, CH_2Cl_2, rt, 5 min; pH 7.8 buffer, 56% (2 steps); (k) HCHO, $NaBH_3CN$, pH 7.0 buffer, −70 °C to rt, 2.5 h, 67%; (l) NaOH, EtOH, 70 °C; $K_3Fe(CN)_6$, $NaHCO_3$, 5 °C to rt, 40 min, 39%.

tacyclic compound **18** as a single isomer. Stereoselective 1,2-reduction of the conjugated imine and reductive methylation were effected in one pot to give **19**. Finally, saponification of the ester **19** and subsequent subjection of the resulting carboxylic acid to oxidative lactone formation conditions[6] provided aspidophytine **2**. All spectral data of the synthetic material were identical with those published.[1,6]

In summary, we have accomplished an enantioselective total synthesis of aspidophytine (**2**) featuring a facile preparation of the fully functionalized indole derivative and 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.

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Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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