## Enantioselective Total Synthesis of Aspidophytine

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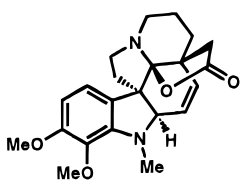
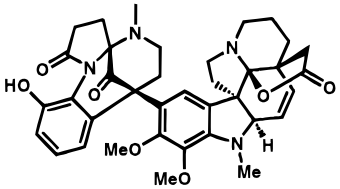
"La hierba de la cucaracha" is an anticockroach/insecticidal powder prepared from the dried leaves of the plant *Haplophyton cimicidum* which has been used at least since the Aztec era in parts of Mexico and Central America.[1,2] The pioneering studies of H. R. Snyder and co-workers at the University of Illinois (Urbana-Champaign) led to the isolation and chemical characterization of the active principles, including various dimeric and monomeric indole alkaloids which are chemical relatives of aspidospermine types. However, it remained for the groups of M. P. Cava, P. Yates, and D. E. Zacharias[3,4] to determine the complex structures of the individual alkaloids including aspidophytine (**1**) and haplophytine (**2**).[3,4] The synthesis of **1** and **2** has



Aspidophytine (1)

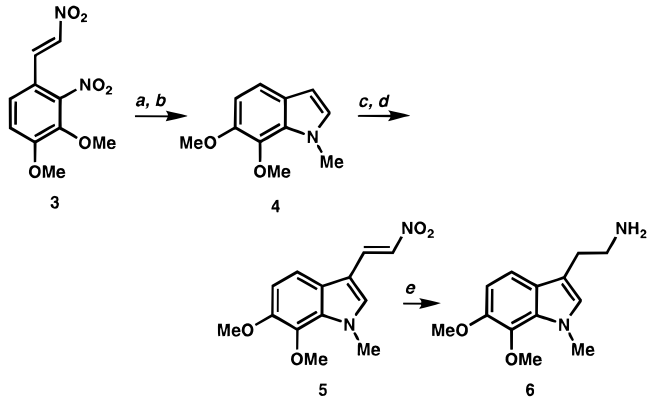


Haplophytine (2)

remained an unanswered challenge for more than a quarter century, despite remarkable achievements in the area of aspidospermine alkaloid synthesis.[5] We describe herein a short and convergent enantioselective synthesis of aspidophytine[4] (**1**), the logical first target on the path to the synthesis of haplophytine itself,[6] and an obvious biosynthetic precursor.

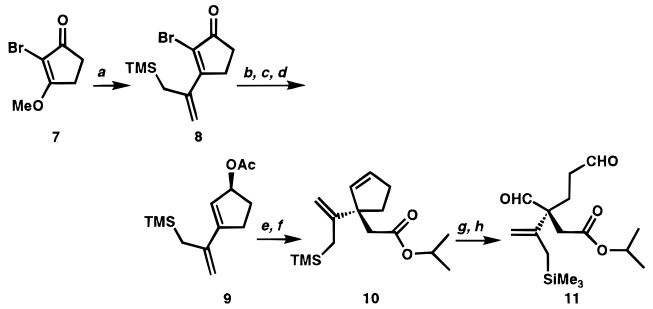
The construction of **1** entailed the synthesis of two building blocks, the substituted tryptamine **6** and the chiral dialdehyde **11**. The synthesis of tryptamine **6** is outlined in Scheme 1. Dinitro

**Scheme 1**[a]



[a] Reagents: (a) Fe, HOAc, silica gel, toluene, Δ, 71%. (b) $CH_3I$, KOH, $Bu_4NI$, THF, 23 °C, 94%. (c) $POCl_3$, DMF, 35 °C, 1 h, then aqueous NaOH, Δ, 99%. (d) $CH_3NO_2$, $NH_4OAc$, Δ, 1 h, 92%. (e) $LiAlH_4$, THF, Δ, 1 h, 88%.

**Scheme 2**[a]



[a] Reagents: (a) $TMSCH_2C(=CH_2)MgBr$, $CeCl_3$, THF, then $H_3O^+$, 82%. (b) *R*-CBS B-methyloxazaborolidine catalyst, catecholborane, $CH_2Cl_2$, −78 °C, 97.4% ee, 94%. (c) 5% Na(Hg), MeOH, 23 °C, 82%. (d) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, 97%. (e) LDA, TBSCI, THF, −78 °C, then Δ. (f) EDCI, *i*-PrOH, DMAP, 57% for two steps. (g) $OsO_4$ (cat), NMO (1.2 equiv), acetone−$H_2O$, 23 °C, 6 h, 57%. (h) $NaIO_4$, THF−$H_2O$ 4:1, 23 °C, 35 min, 98%.

compound **3**[7,8] was converted to the corresponding indole, mp 98−100 °C, by reductive cyclization[9] which occurred upon heating with iron powder, acetic acid, and silica gel in toluene at reflux for 15 min (71% yield). Methylation of this product (MeI, KOH, $Bu_4NI$, THF, 23 °C, 3 h) afforded the *N*-methyl derivative (**4**) in 94% yield. Villsmeier formylation of **4**[10] furnished the C-3 aldehyde (99%) which was condensed with nitromethane to form the vinyl nitro compound **5** (92%), reduction of which by $LiAlH_4$ at reflux in THF gave tryptamine **6** (88% yield).

An enantioselective synthesis of dialdehyde **11** is summarized in Scheme 2. Reaction of 2-bromo-3-methoxycyclopent-2-enone (**7**)[11] in THF with 1-(trimethylsilylmethyl) vinylmagnesium bromide[12,13] in the presence of anhydrous $CeCl_3$ at 0 °C for 0.3 h followed by treatment with aqueous acid gave the α,β-enone **8** (82%). Enantioselective CBS reduction[14] of **8** using as catalyst the oxazaborolidine derived from (*R*)-diphenylprolinol and meth-

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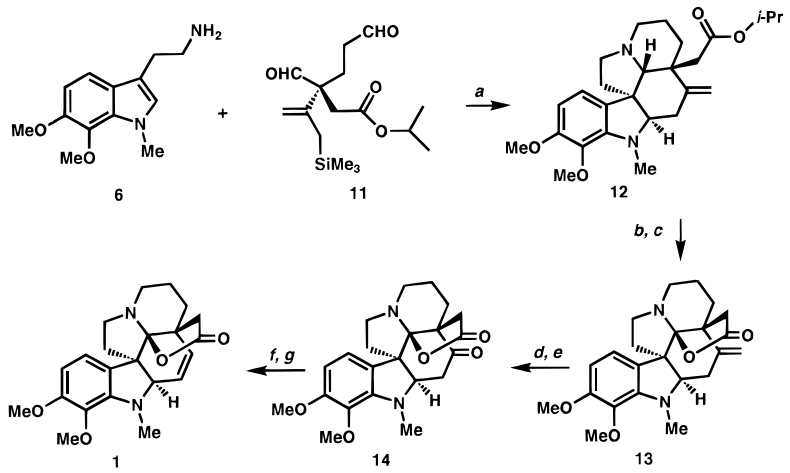
**Scheme 3**[a]

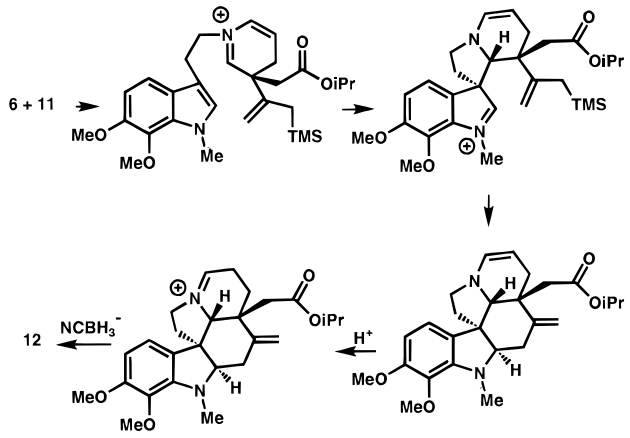



[a] Reagents: (a) $CH_3CN$, 23 °C, then TFAA, 0 °C, then $NaBH_3CN$, 23 °C, 66%. (b) NaOH, EtOH, 75 °C, 24 h, 88%. (c) $K_3Fe(CN)_6$, $NaHCO_3$, *t*-BuOH−$H_2O$ 1:2, 92%. (d) $OsO_4$ (1 equiv), DMAP (2 equiv), *t*-BuOH/$H_2O$ (1:1), then $NaSO_3$. (e) $Pb(OAc)_4$, AcOH, $CH_2Cl_2$, −20 °C, 71% for two steps. (f) KHMDS, THF, −78 °C, then $PhNTf_2$, −78 °C, 54%. (g) $Pd(PPh_3)_4$ (0.2 equiv), $Bu_3SnH$ (8 equiv), THF, 23 °C, 1 h, 86%.

ylboronic acid[15] (10 mol %) with 1.2 equiv of catecholborane as reductant in $CH_2Cl_2$ at −78 °C gave the corresponding allylic alcohol of 97% ee (measured by HPLC analysis with a Chiracel OD column) in 94% yield, which by debromination (Na·Hg-MeOH at 23 °C, 82%) and acetylation provided the allylic acetate **9** (97%). Ireland-Claisen rearrangement of **9** afforded a chiral carboxylic acid, which after esterification with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 4-(dimethylamino)pyridine in isopropyl alcohol provided the corresponding isopropyl ester **10** in 57% overall yield. The endocyclic olefinic linkage of **10** was selectively dihydroxylated (1.2 equiv of *N*-methylmorpholine-*N*-oxide and 0.05 equiv of $OsO_4$ in aqueous acetone at 23 °C for 6 h) to give a diol (57%) which upon oxidation with $NaIO_4$ in THF−$H_2O$ at 23 °C for 35 min furnished the required dialdehyde **11** in 98% yield.

The completion of the synthesis of aspidophytine (**1**) from **6** and **11** is outlined in Scheme 3. A solution of amine **6** in dry $CH_3CN$ was added to a solution of dialdehyde **11** (1 equiv) in $CH_3CN$ at 23 °C and after 5 min, the resulting solution was cooled to 0 °C and then added dropwise to a vigorously stirred solution of 2 equiv of $(CF_3CO)_2O$ in $CH_3CN$ at 0 °C. After a further 2 h at 0° the resulting yellow solution was treated with 5 equiv of $NaBH_3CN$. Extractive isolation of the resulting product and flash chromatography on silica gel provided pentacyclic ester **12** in 66% yield. Base-catalyzed hydrolysis of ester **12** followed by oxidative lactonization using potassium ferricyanide gave the pentacyclic lactone **13** (81% overall from **12**), in a process consisting of tertiary amine → iminium ion oxidation and subsequent nucleophilic attack of carboxylate on the cationic carbon. The next step, oxidative cleavage of the exocyclic double bond, initially proved difficult because the olefinic group was resistant to attack by various $OsO_4$-based reagents, e.g., $OsO_4$−pyridine and $OsO_4$−quinuclidine, presumably due to strong steric shielding at each $\pi$-face. However, under guidance by recent developments on the mechanistic details of amine-accelerated dihydroxylation by $OsO_4$,[16] it was surmised that the 2:1 complex of 4-(dimethylamino)pyridine and $OsO_4$ could be an especially effective reagent for the dihydroxylation of sterically hindered substrates such as **13**.[17] In fact, this reagent effected smooth and selective dihydroxylation of the exomethylene double bond of

**Scheme 4**




**13** to form a diol which upon cleavage with lead tetraacetate in $CH_2Cl_2$ and acetic acid produced the required nor-ketolactone **14** in 71% overall yield. The carbonyl function of **14** was transformed to the corresponding enol triflate (54%, not optimized) which upon treatment with 0.2 equiv of $Pd(Ph_3P)_4$ and tri-*n*-butylstannane gave aspidophytine **1** (86%). The totally synthetic **1** was shown to be identical with a sample of naturally produced aspidophytine[4,18] by comparison of $^1H$ and $^{13}C$ NMR spectra, IR and mass spectra, optical rotation, mp and mixed mp, and thin layer chromatographic comparison in three different solvent systems.

At the heart of the synthesis of aspidophytine described herein is the conversion of the components **6** and **11** to pentacyclic intermediate **12**. The likely pathway for this key operation is outline in Scheme 4.

The transformation of **1** to haplophytine **2** is currently under investigation.

**Acknowledgment.** We are very grateful to Professor Michael P. Cava for an authentic sample of haplophytine, to the Schering-Plough Co. for a graduate fellowship, and to the National Science Foundation and the National Institutes of Health for financial support. This article is dedicated to the memory of Jason D. Altom (October 6, 1971−August 15, 1998).

**Supporting Information Available:** Experimental procedures and spectroscopic data for all steps for the synthesis of **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The combination of strong basicity of 4-(dimethylamino)pyridine, modest steric size (e.g., compared to quinuclidine), and the use of the 2:1 stoichiometry with $OsO_4$ was expected[16] to result in an especially potent dihydroxylation catalyst.

(18) An authentic sample of aspidophytine was prepared in high yield from haplophytine by the literature[4] procedure involving proteolytic cleavage with aqueous hydrochloric acid at reflux.