Total Synthesis

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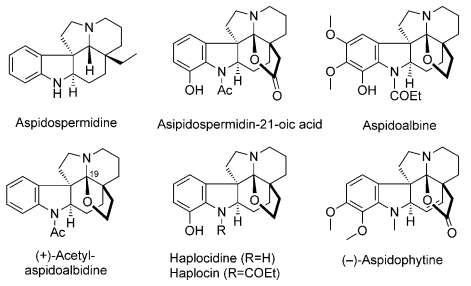
General Entry to Aspidosperma Alkaloids: Enantioselective Total Synthesis of (−)-Aspidophytine**

*Rongwen Yang and Fayang G. Qiu**

Dedicated to Professor Gideon Fraenkel on the occasion of his 81st birthday

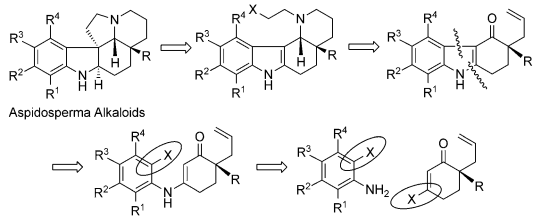
There are more than 250 compounds in the aspidosperma alkaloid family sharing a common pentacyclic skeleton imbedded in an indoline substructure (Scheme 1), many of



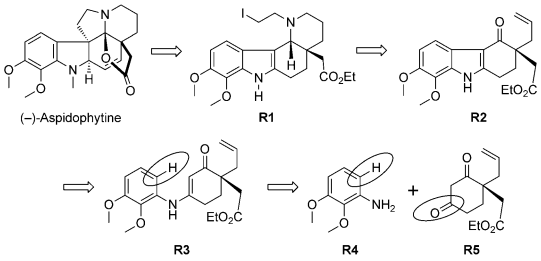
Scheme 1. Typical structures of aspidosperma alkaloids.

which have important biological activities.[1] Haplophytine, a dimeric alkaloid, was isolated from the dry leaves of the Mexican *Haplophyton Cimicidum* (Apocynaceae) in the early 1950s,[2] and its structural investigation was pioneered by Snyder and co-workers.[2b,c] Until 1973, Cava and Yates fully elucidated, by using chemical degradation techniques, the structure of haplophytine,[3] which was unambiguously established in 1975 by means of X-ray crystallographic analysis.[4] Aspidophytine, a member of the aspidosperma alkaloid family, was obtained[3] through treatment of haplophytine with acids. Since Corey's remarkable biomimetic synthesis of aspidophytine,[5] several elegant synthetic strategies have been developed for the construction of this alkaloid.[6] In view of the common structural features of the aspidosperma alkaloid family, it is highly desirable to develop a general synthetic strategy that may be applied to the synthesis of a large number of the alkaloid family members.[7] Owing to the common structural features, we thought it might be feasible to devise a general strategy to assemble the entire carbon framework of the aspidosperma alkaloids. To demonstrate the feasibility, we began the study of the enantioselective total synthesis of aspidophytine,[8] and the results are described herein.

The pyrrolidine and piperidine skeletons may be constructed through the alkylation of the C3 carbon atom of the indole fragment with a side chain bearing an alkylating carbon atom. The common pentacyclic framework may be derived from the tricyclic scaffold, which may be assembled through the pivotal formation of the carbon–carbon bond between the C3 of the indole moiety and the substituted aryl ring through a Heck-type reaction. Based on this consideration, a general retrosynthetic analysis of the aspidosperma alkaloids and the retrosynthetic analysis of aspidophytine are shown in Scheme 2 and Scheme 3, respectively.



Scheme 2. A general retrosynthetic analysis of the aspidosperma alkaloids.



Scheme 3. The retrosynthetic analysis of aspidophytine.

Aspidophytine may be constructed from intermediate **R1** through a reaction sequence that involves an intramolecular alkylation, introduction of the carbon–carbon double bond, reduction of the imine, and methylation of the indolyl nitrogen atom, while intermediate **R1** may be synthesized from intermediate **R2** through conversion of the terminal carbon–carbon double bond into the tosylate of the corresponding primary alcohol, followed by reduction of the carbonyl functional group and subsequent reaction with 2-

[*] R. Yang, Prof. Dr. F. G. Qiu
Laboratory of Molecular Engineering and Laboratory of Natural Product Synthesis, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences
190 Kaiyuan Boulevard, The Science Park of Guangzhou
Guangdong 510530 (China)
E-mail: qiu_fayang@gibh.ac.cn

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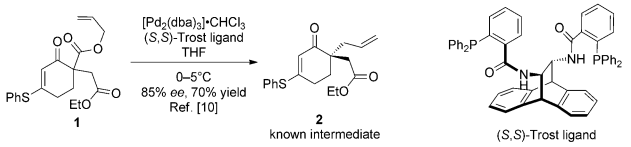
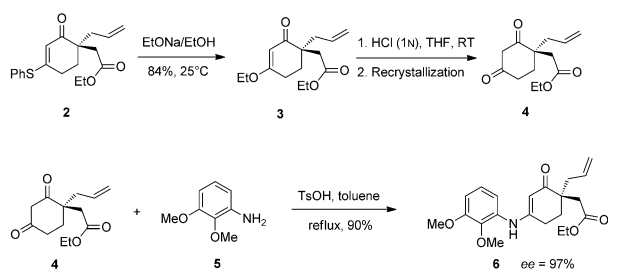
bromo-ethylamine. Intermediate **R2** may be formed through condensation of **R4** and **R5** followed by the formation of the indole ring.

Most of the substituted anilines are either commercially available or readily accessible, and the 4,4-disubstituted 1,3-cyclohexanedione **4** may be efficiently prepared in its asymmetric form based on a protocol developed by Trost et al.[9] a few years ago (Scheme 4). Since the enantiomeric

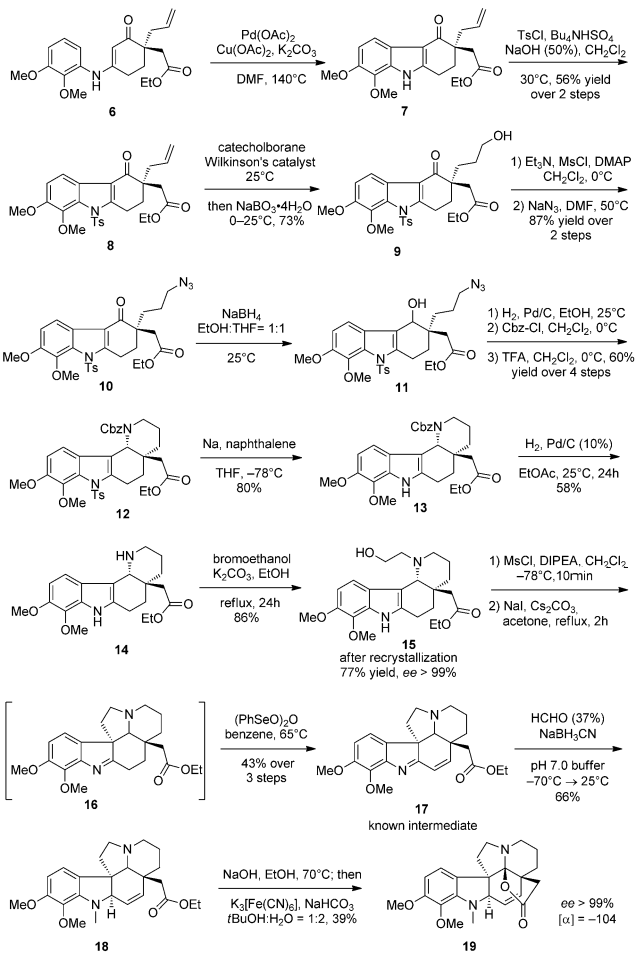


Scheme 4. The synthesis of 4,4-disubstituted 1,3-cyclohexanedione derivatives developed by Trost. dba = *trans*,*trans*-Dibenzylideneacetone.

excess of the phenylthioether intermediate **2** was not high enough, it was treated with sodium ethoxide to afford ethyl ether **3** (Scheme 5). After acid hydrolysis, the resulting crude



Scheme 5. Condensation of the 4,4-disubstituted cyclohexane-1,3-dione with 2,3-dimethoxyaniline for measurement of the enantiomeric excess. Ts = 4-Toluenesulfonyl.



Scheme 6. Synthetic route to aspidophytine. Cbz = benzyloxycarbonyl, DIPEA = diisopropylethylamine, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, Ms = methanesulfonyl, TFA = trifluoroacetic acid, Wilkinson's catalyst = $[Ru(PPh_3)_3Cl]$.

4,4-disubstituted cyclohexanedione was recrystallized from a mixture of dichloromethane and petroleum ether, which provided the enantiomerically pure 4,4-disubstituted 1,3-cyclohexanedione **4** in 80% yield. The enantiomeric purity of **4** was determined after its condensation with 2,3-dimethoxyaniline in refluxing toluene to form intermediate **6** in 90% yield after chromatographic separation. The *ee* value of **6** was 97%, indicating that the enantiomeric purity of the recrystallized **4** was about 97% *ee*.

Initially, we planned to form the requisite indole skeleton through a Heck-type coupling. However, we soon realized that C–H bond activation[10] might be more efficient for the construction of the indole moiety (Scheme 6). Thus, treatment of **6** with a mixture of $Pd(OAc)_2/Cu(OAc)_2/K_2CO_3$ in DMF at 140°C afforded the desired indole intermediate **7**, which was tosylated using tosyl chloride under phase-transfer conditions to protect the indolyl nitrogen atom (56% over two steps). The terminal alkene of intermediate **8** was converted into the primary alcohol functionality of intermediate **9** in 73% yield through hydroboration of the alkene with catecholborane and Wilkinson's catalyst, followed by oxidation with sodium perborate.[11] Upon mesylation with methanesulfonyl chloride, the hydroxy group was converted into the azido group of intermediate **10** through treatment with sodium azide in DMF; the yield for the combined two-step sequence was 87%. Selective reduction of the ketone carbonyl moiety in the presence of the ester functionality was realized using sodium borohydride in a 1:1 mixture of THF and ethanol, accompanied by the formation of a small amount of diol, which was generated through reduction of both the ketone and the ester functionalities. The azido group of intermediate **11** was hydrogenated using Pd/C catalyst, and the resulting amino group was protected with CbzCl. Without isolation, the mixture was treated with trifluoroacetic acid to provide the cyclization product **12** (60% over four steps), possibly through the acidic dehydration of the indolyl alcohol to form a Michael acceptor, followed by Michael addition of the CBz-protected nitrogen atom from the same side of the substituted cyclohexane ring.[7p,12] Removal of the tosyl group was realized through the treatment of intermediate **12** with Na/naphthalene in THF at −78°C (80%) while the Cbz protective group and the ester functionality remained intact.[13] The Cbz group of intermediate **13** was removed through hydrogenolysis using Pd/C in ethyl acetate (58%),

and the product of this deprotection was reacted with bromoethanol/potassium carbonate in refluxing ethanol to afford the desired product **15** in 86% yield after chromatographic separation, and the enantiomeric excess was over 99% after recrystallization (77% yield). Intermediate **15** was converted into the iodide through treatment at −78°C with methanesulfonyl chloride and then sodium iodide and cesium carbonate in refluxing acetone. However, cyclization of the iodo intermediate through alkylation at the C_3 position of the indole occurred simultaneously under the reaction conditions to give the desired intermediate **16**, which is unstable upon isolation.[7k] Thus, after removal of the solvent, the crude mixture was treated with phenylselenoic anhydride in benzene at 65°C and elimination occurred under the reaction conditions to afford intermediate **17**, which is stable in the pure state, in 43% yield over the three steps. Reduction of the imine and subsequent methylation with aqueous formaldehyde was achieved in a one-pot fashion when intermediate **17** was treated with sodium cyanoborohydride in a neutral pH buffer (66%).[6d,e] Finally, after saponification of the ester functionality, the resulting acid was treated with potassium ferrocyanide, a procedure initially developed by Corey,[5] to afford the final product aspidophytine (39% yield over two steps), which showed identical patterns of characteristic signals in both the ^1H and ^{13}C NMR spectra, with an enantiomeric excess of over 99%.

In summary, an enantioselective total synthesis of aspidophytine was achieved in 18 steps starting from 4,4-disubstituted cyclohexane-1,3-dione and the commercially available 2,3-dimethoxyaniline. The key elements of the synthesis include the enantioselective formation of the 4,4-disubstituted cyclohexane-1,3-dione using the protocol previously developed by Trost, the application of a pivotal indole synthesis through the combination of a C–H bond activation with a Heck-type coupling, and the stereo-controlled formation of the piperidine and the pyrrolidine rings. Because the 4,4-disubstituted cyclohexane-1,3-dione contains either the right substituents or the functional groups that may be converted into the desired ones in a later stage, most of the aspidosperma alkaloids may be constructed by adapting this synthetic strategy with properly substituted anilines.

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