Natural Products

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Total Syntheses of (±)-Aspidophylline A**

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In memory of Sir Derek H. R. Barton

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Aspidophylline A (**1**) is an indole alkaloid which has been isolated in 2007 from the stem bark of *Kopsia singapurensis*, a plant of the *Apocynaceae* family.[1] Aspidophylline A exhibits a complex pentacyclic structure featuring a tricyclic furoindoline motif, five contiguous stereogenic centers incorporated in a highly substituted cyclohexyl ring, and a bridged aza-bicycle (Figure 1). There are three reported total syntheses of the title compound (in its racemic form).

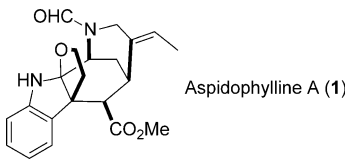
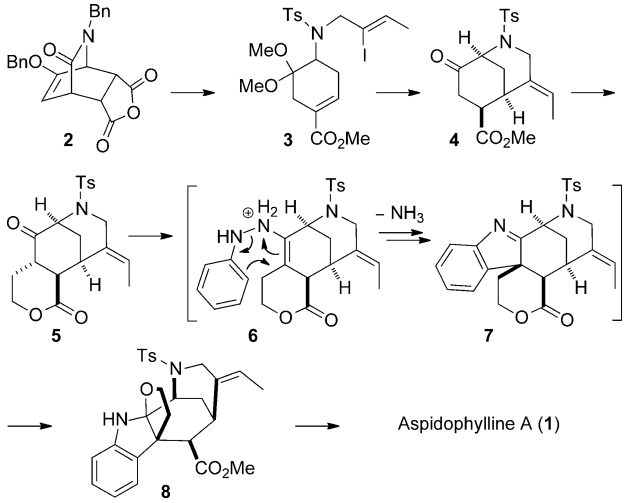


Figure 1. Structure of aspidophylline A.

The first total synthesis of aspidophylline A was achieved by Garg and co-workers in 2011.[2] Their approach started from a Diels–Alder reaction between pyridinone and maleic anhydride to give the known bicyclic lactam **2** which was further converted by a multistep process into the amino ester **3** (Scheme 1). An intramolecular Heck-type cyclization of **3** and subsequent deprotection of the ketone and reduction of the doubly conjugated olefin provided access to the bicyclic ketoester **4**. The lactone unit of **5** was subsequently introduced by allylation α to the ketone of **4**, oxidative cleavage/reduction, and lactonization. The most remarkable transformation in the synthetic route developed by Garg and co-workers is the so-called interrupted Fisher indolization which had been previously investigated by the same group for the construction of fused indolenine systems. Thus, treatment of **5** with phenylhydrazine under acidic conditions led to the formation of the intermediate **6**, which spontaneously evolved to the imine **7** with concomitant loss of ammonia. The oxygenated ring of aspidophylline A was introduced at a later stage of the synthesis by methanolysis of **7** and cyclization of the released alcohol onto the aromatic imine. Removal of the *N*-tosyl group of **8** and *N*-formylation finally afforded aspidophylline A in 18 linear steps and approximately 7% overall yield.



Scheme 1. Synthetic pathway reported by Garg and co-workers. Ts = 4-toluenesulfonyl.

The total synthesis of aspidophylline A was recently reinvestigated simultaneously by the groups of Ma and Zhu. The scheme developed by Ma and co-workers started from the known indole **9** and aldehyde **10** which were coupled under basic conditions to afford the alcohol **11** (Scheme 2).[3] The secondary alcohol group was substituted by an azide, and the indole and primary alcohol were deprotected (**12**) before the key cyclization step was attempted. The strategy used for construction of the tetracyclic unit was guided by the long-standing interest of the group of Ma in intramolecular oxidative couplings, which they successfully applied, for example, to the total synthesis of (−)-vincorine. The iodine-mediated oxidative coupling between the indole and malonate moieties of **12** likely led to the formation of the transient imine **13** which was trapped in situ by the adjacent alcoholate. This step permitted the efficient and simultaneous assembly of the cyclohexyl and oxygenated rings of aspidophylline A, although the compound **14** was obtained as a 2:1 mixture of diastereomers. The indoline group of **14** was protected and the malonate decarboxylated prior to the introduction of an ester-conjugated double bond by selenoxide elimination. This double bond played a pivotal role in the later construction of

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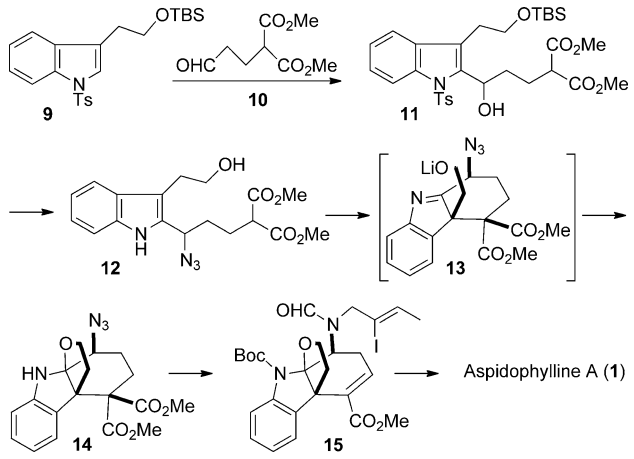
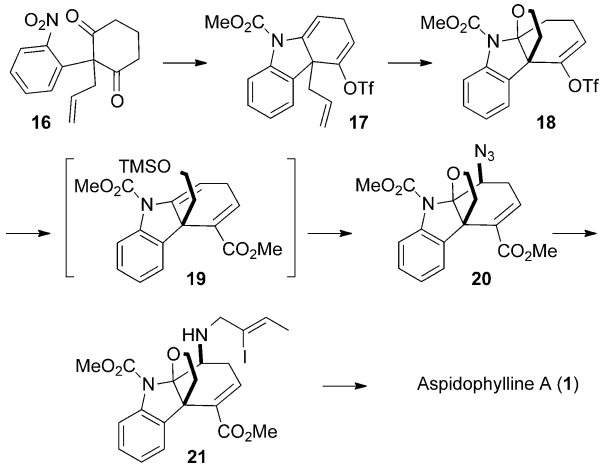


Scheme 2. Synthetic pathway reported by Ma and co-workers. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

the azacycle. The azido moiety was then reduced and the resulting amine allylated and formylated (**15**). Completion of the synthesis of aspidophylline A involved cyclization of the vinyl iodide on the conjugated ester using $[Ni(cod)_2]$ as a reagent, and removal of the indoline protecting group. Aspidophylline A was synthesized in 14 steps with an overall yield of approximately 1%.

The synthesis of aspidophylline A developed by Zhu and co-workers involved the known substituted cyclohexane dione **16** (Scheme 3).[4] One of the two ketone groups of **16** was converted into an enol triflate before the nitroaryl group was reduced into aniline and further condensed with the remaining ketone. The indolenine nitrogen atom was then protected as a methyl carbamate (**17**). The construction of the furan ring commenced with the oxidative cleavage/reduction of the olefinic side chain and subsequent condensation of the newly formed alcohol on the enecarbamate. The ester group of aspidophylline A was installed by methoxycarbonylation of the triflate **18** and the introduction of the masked amino group proceeded by the transient ring opening of the furan and azidoalkoxylation of the enecarbamate **19**. This remarkable synthetic sequence had also been exploited by Shi and co-workers in their approach to the skeleton of aspidophilline A.[5] It permitted access to an advanced intermediate, **20**, as a 1.9:1 mixture of diastereomers. The azacycle was then sequentially built by reduction of the azido group and allylation of the resulting amine, thus leading to the compound **21**. Piperidine ring closure was achieved by halogen–lithium exchange and nucleophilic 1,4-addition to the ester. Aspidophylline A was finally obtained after formylation of the secondary amine and indoline deprotection in 14 steps and approximately 2% overall yield.



Scheme 3. Synthetic pathway reported by Zhu and co-workers. Tf = trifluoromethanesulfonyl.

The pioneering synthesis of Garg and co-workers paved the way to the more recent total syntheses of aspidophylline A by the groups of Zhu and Ma. The above synthetic schemes are all original although they share some common features such as, for example, the use of the same blocks for the construction of the piperidine unit. The latter was assembled at different stages of the synthetic schemes by connecting a vinyl iodide with a conjugated ester under variable reaction conditions. The approaches which have been put in place are remarkably conceived and elegant. Nevertheless, the development of a synthetic route that would allow access to the title compound in its optically active form is a challenge that still needs to be tackled.

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