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Natural Products Synthesis

Total Synthesis of (±)-Aspidophylline A**

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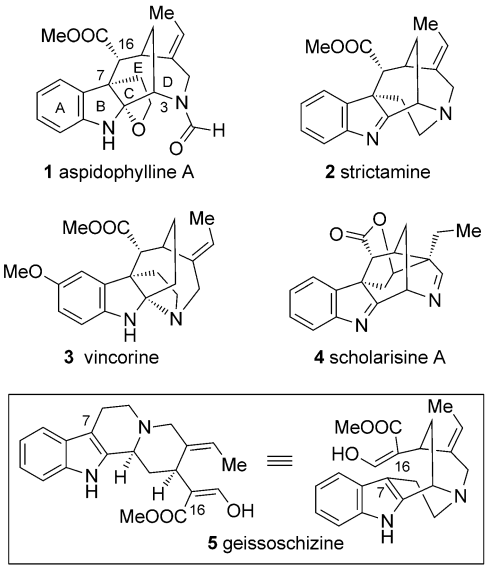
Abstract: *A total synthesis of aspidophylline A, a pentacyclic akuammiline-type monoterpene indole alkaloid, is described. The synthesis features: 1) rapid access to a fully functionalized dihydrocarbazole through the desymmetrization of readily available 2-allyl-2-(o-nitrophenyl)cyclohexane-1,3-dione; 2) an intramolecular azidoalkoxylation of an enecarbamate to install both the furoindoline ring and the azido functionality; and 3) an intramolecular Michael addition for the construction of the 2-azabicyclo[3.3.1]nonane ring system.*

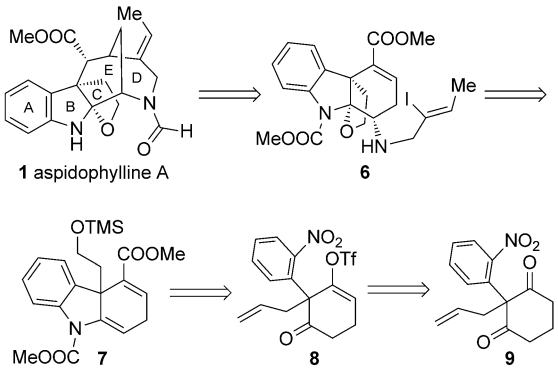
Aspidophylline A (**1**) was isolated from Malayan *Kopsia singapurensis* by Kam and co-workers in 2007 and was found to reverse drug resistance in drug-resistant KB cells (Scheme 1).[1] Structurally, it is a cagelike pentacyclic compound that includes a highly substituted cyclohexane (ring E) with five contiguous stereocenters, an embedded fused furoindoline ring, and a bridged [3.3.1] azabicycle.[2] It belongs to the family of akuammiline monoterpene indole alkaloids,[3] which includes strictamine (**2**),[4] vincorine (**3**),[5] and scholarisine A (**4**),[6] among others. Biogenetically, these compounds are all derived from geissoschizine (**5**) through formation of the characteristic C7–C16 bond with concurrent dearomatization of the indole unit.[7]



Scheme 1. Aspidophylline A and other representative akuammiline alkaloids.

The fascinating molecular architecture in conjunction with its interesting biological activity made aspidophylline A (**1**) a privileged synthetic target. Garg and co-workers reported in 2011 the first 18-step total synthesis of **1** featuring an elegant late-stage interrupted Fischer indole cyclization as the key step.[8] Shi and co-workers reported in 2013 their synthesis of a model pentacyclic core of aspidophylline A[9] by the use of a key ruthenium-catalyzed atom-transfer radical cyclization for the construction of the [3.3.1] azabicyclic ring system. In connection with our continued interest in the total synthesis of indole alkaloids,[4a,10] we report herein our successful approach to the total synthesis of aspidophylline A (**1**).

Our retrosynthetic analysis of aspidophylline A (**1**) is outlined in Scheme 2. We planned to build the pentacyclic skeleton of **1** from vinyl iodide **6** by way of an intramolecular Michael addition or an equivalent reaction. Compound **6** could be obtained by intramolecular azidoalkoxylation of tricycle **7** by taking advantage of its enecarbamate functionality. The tricycle **7** would be elaborated from **8**, which could in turn be prepared by desymmetrization of the known cyclohexane-1,3-dione **9**.



Scheme 2. Retrosynthetic analysis of aspidophylline A. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

Our synthesis commenced with the elaboration of 2-allyl-2-(*o*-nitrophenyl)cyclohexane-1,3-dione (**9**), which was readily accessible on a multigram scale by the procedure developed by Bonjoch, Bosch, and co-workers.[11,12] The treatment of **9** with TMSCl in the presence of Et_3N and DMAP afforded the silyl enol ether **10**, which was subsequently converted into the corresponding enol triflate **8**

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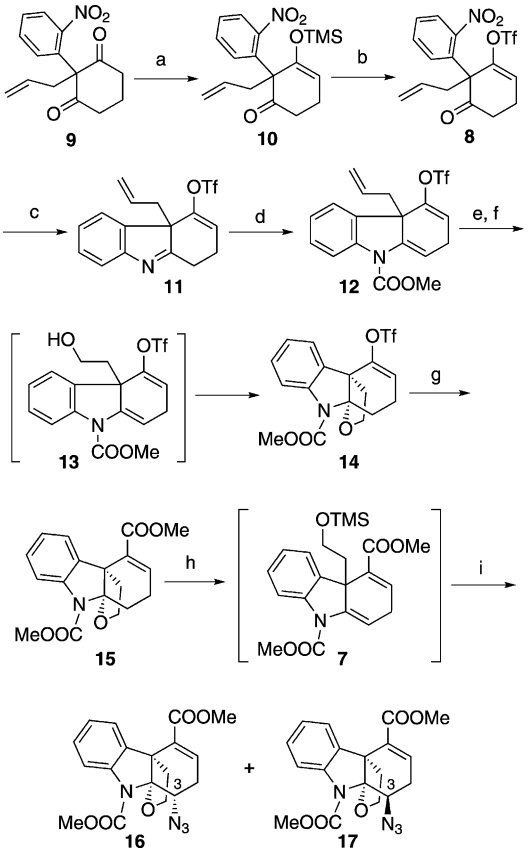
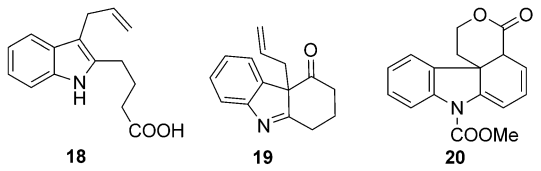


Scheme 3. a) TMSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C→RT, 48 h; b) CsF, $PhNTf_2$, DME, room temperature, 1 h, 55 % over 2 steps (84 % based on conversion); c) $TiCl_3$, NH_4OAc, acetone/H_2O (1:1), room temperature, 10 min, 80 %; d) NaH, ClCOOMe, THF, 0 °C→RT, 24 h, 84 %; e) OsO_4 (4 mol %), NMO, THF/H_2O, 0 °C→RT, 12 h; $NaIO_4$, room temperature, 1 h; f) $NaBH_4$, MeOH, 0 °C→RT, 1 h, then 1.0 M HCl (aqueous), room temperature, 2 h, 71 % over 2 steps; g) $[Pd(PPh_3)_4]$, Et_3N, CO (1 atm), MeOH/DMF (2:1), 50 °C, 1 h, 92 %; h) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C→RT, 24 h; i) NaN_3, CAN, acetone, 0 °C, 5 min; −40 °C, 8 h, 53 % of **16**. CAN = ceric ammonium nitrate, DMAP = 4-dimethylaminopyridine, DME = dimethoxyethane, DMF = *N*,*N*-dimethylformamide, NMO = 4-methylmorpholine *N*-oxide.

(Scheme 3).[13] We stress that direct monotriflation under a variety of conditions with different triflating agents (Tf_2O, $PhNTf_2$) and bases (LDA, LHMDS, KHMDS, Et_3N, 2,6-di-*tert*-butyl-4-methylpyridine) resulted only in decomposition.[14] The nitro group in **8** was then reduced with $TiCl_3$,[15] whereupon spontaneous intramolecular condensation of the resulting aniline with the carbonyl group yielded indolenine **11**. The methyl carbamate **12** was formed by treating **11** with NaH and methyl chloroformate. Selective cleavage of the terminal double bond within the triene system of **12** (OsO_4/NMO then $NaIO_4$) then afforded an aldehyde.[16] Without purification, the crude aldehyde was reduced with $NaBH_4$ to provide **13**, which was partially cyclized to aminal **14** upon column-chromatographic purification. In practice, acidic workup of the reduction step afforded **14** directly in 71 % yield from **12**. The formation of an aminal, a protected enecarbamate moiety, played a pivotal role in the subsequent transformation, as it effectively avoided the double-bond migration encountered in the palladium-catalyzed functionalization of **13** (see Scheme 4, compound **20**). Methoxycarbonylation of **14** afforded the α,β-unsaturated ester **15** in high yield, which then underwent furan-ring opening in the presence of TMSOTf and lutidine to afford enecarbamate **7**, ready for the installation of the missing C–N bond. To our delight, submission of the crude enecarbamate **7** to the azidoalkoxylation conditions (CAN and NaN_3 at 0 °C) provided the desired product **16** (44 % yield over 2 steps) and its C3 epimer **17** (44 % yield) in a 1:1 ratio.[9,17] Further optimization of the reaction conditions showed that the desired diastereomer **16** could be obtained in 53 % yield (**16**/**17** 1.9:1) by lowering the reaction temperature to −40 °C.[18] That compound **16** possessed the right relative configuration was proven by X-ray diffraction analysis of an advanced intermediate (see below).

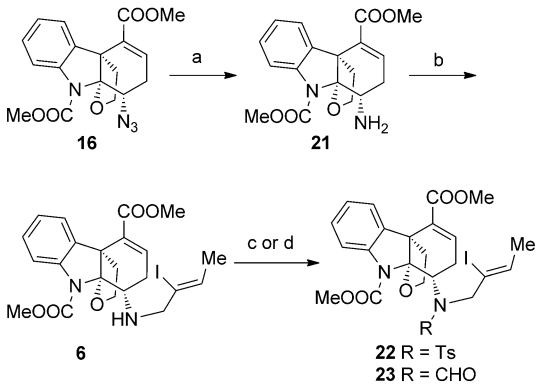
In other attempts to synthesize the key intermediate **16**, the direct reductive cyclization of **9** afforded the 2,3-disubstituted indole **18**, which presumably results from the ring opening of the desired indolenine **19** (Scheme 4).[19] On



Scheme 4. Interesting products observed during the elaboration of compound **9**.

the other hand, the treatment of **13** under palladium-catalyzed methoxycarbonylation conditions afforded lactone **20**, in which the double bond had migrated to give this conjugated diene as the major product. All attempts to advance the synthesis from **20** met with failure.

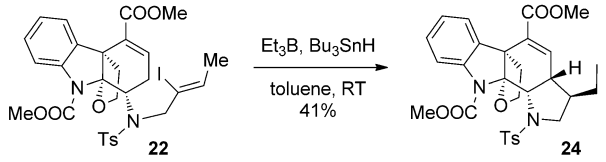
The reduction of azide **16** under Staudinger conditions (PPh_3, THF–H_2O, 50 °C) afforded the primary amine **21** in 81 % yield (Scheme 5). N-Monoallylation with (*Z*)-1-bromo-



Scheme 5. a) PPh_3, H_2O, THF, 50 °C, 3 h, 81 %; b) (*Z*)-1-bromo-2-iodobut-2-ene, Cs_2CO_3, 4 Å molecular sieves, THF/DMF (1:1), room temperature, 24 h, 79 %; c) TsCl, Et_3N, CH_2Cl_2, room temperature, 12 h, 55 % (**22**); d) Ac_2O, HCOOH, THF, 0 °C, 2 h, 94 % (**23**). Ts = *p*-toluenesulfonyl.

2-iodobut-2-ene then provided **6** in 79% yield.[20] The N-tosylation and N-formylation of **6** under standard conditions proceeded uneventfully to furnish *N*-tosyl (compound **22**) and *N*-formyl derivatives (compound **23**), respectively. A crystal of **22** suitable for X-ray crystal-structure analysis enabled the unambiguous determination of its relative configuration, and hence that of **16**.[21]

The cyclization of *N*-Ts and *N*-formyl derivatives **22** and **23** was investigated. Although neither of these compounds afforded the desired product under a variety of conditions, the radical cyclization of **22** provided an interesting pentacyclic compound **24** as a single stereoisomer (41% yield), whose structure was fully determined by X-ray crystallographic analysis (Scheme 6).[21] A sequence involving vinyl radical

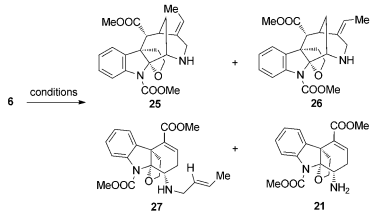


Scheme 6. Radical cyclization of *N*-Ts derivative **22** to pentacycle **24**.

formation/1,5-H abstraction/5-*exo*-trig cyclization of the resulting allylic radical could account for the formation of **24**.

The cyclization of the N-unprotected secondary amine **6** was next investigated (Table 1). An attempted nickel-catalyzed cyclization of **6** led only to the decomposition of the starting material (Table 1, entry 1).[22] Palladium-catalyzed reductive Heck coupling with different combinations of catalysts, ligands, bases, and additives, such as $Pd(OAc)_2$/PPh_3/Et_3N,[23] $Pd(OAc)_2$/HCOONa/K_2CO_3/nBu_4NCl,[24] and $[Pd(PPh_3)_4]$/HCOOH/piperidine,[25] also failed to give the desired product but instead afforded mainly the deiodination compound **27** and deallylated product **21** (Table 1, entries 2–4). The radical cyclization turned out to be more productive.[26] In the presence of nBu_3SnH/Et_3B or nBu_3SnH/AIBN, the desired cyclization occurred to provide a pair of diastereomers (1:1.1 ratio; Table 1, entries 5 and 6). Apparently, the remote N-protecting group had a significant effect on the outcome of the radical cyclization. With the unprotected secondary amine **6**, the vinyl radical generated in situ cyclized in the 6-*exo*-trig mode to provide the desired compound, whereas the vinyl radical generated from *N*-Ts derivative **22** preferentially underwent the sequence initiated by 1,5-H transfer. The loss of stereochemical integrity in the ethylidene substituent was not unexpected.[26a,27] Unfortunately, all efforts to avoid this double-bond isomerization and attempts to reisomerize the *Z* double bond of **26** to give the *E* isomer **25** under different conditions failed. Finally, an intramolecular Michael addition of the corresponding vinyllithium moiety, generated in situ by lithium–halogen exchange, was more effective (Table 1, entries 7–9).[28] Under the optimum conditions, which involved the use of *t*BuLi in THF in the presence of HMPA and TMSCl, the expected pentacyclic product **25** was isolated in 51% yield (Table 1, entry 9).

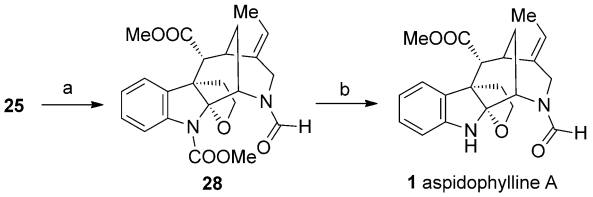
Table 1: Screening of conditions for the cyclization of **6**.



Entry	Conditions	Result
1	$[Ni(cod)_2]$, Et_3N, CH_3CN, RT, then Et_3SiH	decomposition
2	$Pd(OAc)_2$, PPh_3, Et_3N, 90 °C	**27** + **21**
3	$Pd(OAc)_2$, HCOONa, K_2CO_3, DMF, 60 °C[a]	**27**[b]
4	$Pd(OAc)_2$, HCOOH, piperidine, DMF, 60 °C	**27** + **21**
5	nBu_3SnH, Et_3B, toluene, RT	**25** (40%) + **26** (44%)
6	nBu_3SnH, AIBN, benzene, 80 °C	**25** (40%) + **26** (44%)
7	*n*BuLi, THF, −78 °C→RT	**27**
8	*t*BuLi, THF, −78 °C→RT	**25**[c] + **27** + **21**
9	*t*BuLi, HMPA, TMSCl, THF, −78→0 °C	**25** (51%) + **27** (5%)

[a] nBu_4NCl was added. [b] Complex reaction mixture. [c] A trace amount of **25** was obtained. AIBN = azobisisobutyronitrile, cod = 1,5-cyclooctadiene, HMPA = hexamethylphosphoramide.

The completion of the total synthesis of aspidophylline A (**1**) is depicted in Scheme 7. The treatment of **25** with acetic anhydride and formic acid in THF afforded *N*-formamide **28**.



Scheme 7. Completion of the total synthesis of aspidophylline A. a) Ac_2O, HCOOH, THF, 0 °C, 1 h, 88%; b) NaOMe, MeOH, 60 °C, 4 h, 60%.

Selective removal of the *N*-methoxycarbonyl group in the presence of the methyl ester and *N*-formamide was found to be nontrivial. After many unsuccessful trials, the heating of a solution of **28** in methanol in the presence of NaOMe at 60 °C finally delivered aspidophylline A (**1**) in 60% yield.[29] Synthetic **1** displayed physical and spectroscopic data identical in all respects to those reported for the natural product.

In summary, a total synthesis of aspidophylline A (**1**) from readily available 2-allyl-2-(*o*-nitrophenyl)cyclohexane-1,3-dione (**9**) has been completed. Key features of our synthesis include: 1) rapid access to the fully functionalized dihydrocarbazole **11** through the desymmetrization of **9**; 2) intramolecular azidoalkoxylation of enecarbamate **7** to install both the furoindoline ring and the azido group; and 3) an intramolecular Michael addition for the construction of the [3.3.1] azabicyclic ring system. The synthetic strategy could poten-

tially provide a feasible route to other congeners of the akuammiline family of alkaloids.

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