

Total Synthesis of (±)-Aspidophylline A**

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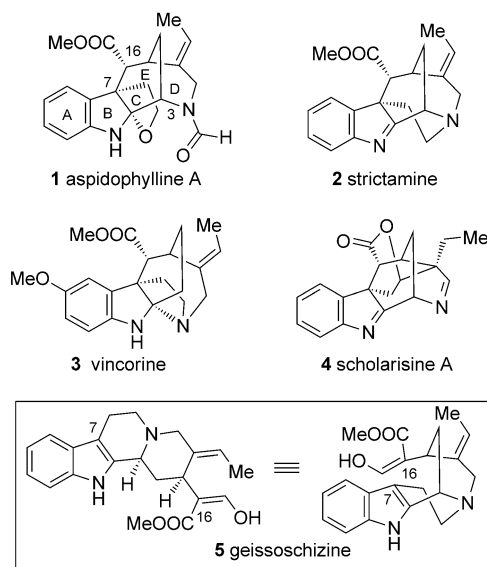
Abstract: A total synthesis of aspidophylline A, a pentacyclic akuammiline-type monoterpene indole alkaloid, is described. The synthesis features: 1) rapid access to a fully functionalized dihydrocarbazole through the desymmetrization of readily available 2-allyl-2-(*o*-nitrophenyl)cyclohexane-1,3-dione; 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 cage-like 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] azabicyclo system.^[2] It belongs to the family of akuammiline monoterpene indole alkaloids,^[3]

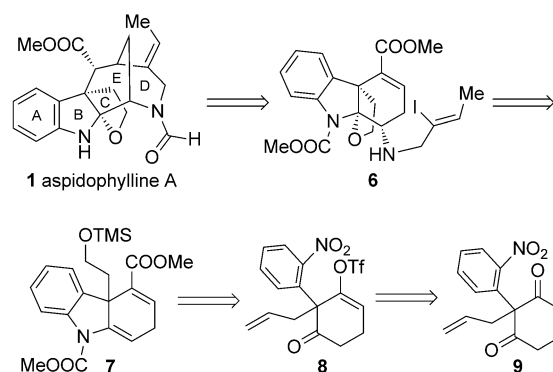
which includes strictamine (**2**),^[4] vincorine (**3**),^[5] and scholarisine A (**4**),^[6] among others. Biogenetically, these compounds are all derived from geissoschizine (**5**) through formation of the characteristic C7–C16 bond with concurrent dearomatization of the indole unit.^[7]

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



Scheme 1. Aspidophylline A and other representative akuammiline alkaloids.



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

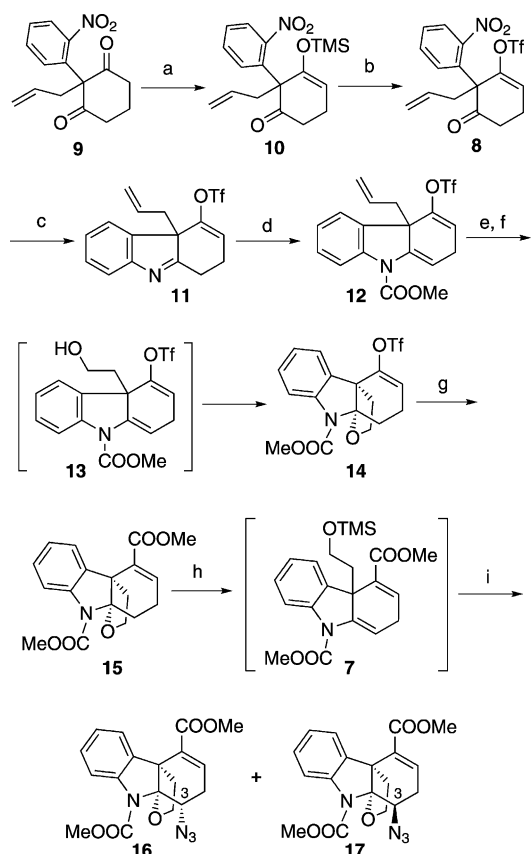
skeleton of **1** from vinyl iodide **6** by way of an intramolecular Michael addition or an equivalent reaction. Compound **6** could be obtained by intramolecular azidoalkoxylation of tricycle **7** by taking advantage of its enecarbamate functionality. The tricycle **7** would be elaborated from **8**, which could in turn be prepared by desymmetrization of the known cyclohexane-1,3-dione **9**.

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 Et₃N and DMAP afforded the silyl enol ether **10**, which was subsequently converted into the corresponding enol triflate **8**

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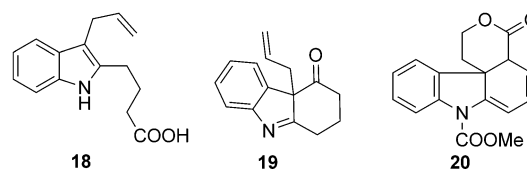


Scheme 3. a) TMSCl, DMAP, Et₃N, CH₂Cl₂, 0°C→RT, 48 h; b) CsF, PhNTf₂, DME, room temperature, 1 h, 55% over 2 steps (84% based on conversion); c) TiCl₃, NH₄OAc, acetone/H₂O (1:1), room temperature, 10 min, 80%; d) NaH, ClCOOMe, THF, 0°C→RT, 24 h, 84%; e) OsO₄ (4 mol%), NMO, THF/H₂O, 0°C→RT, 12 h; NaIO₄, room temperature, 1 h; f) NaBH₄, MeOH, 0°C→RT, 1 h, then 1.0 M HCl (aqueous), room temperature, 2 h, 71% over 2 steps; g) [Pd(PPh₃)₄], Et₃N, CO (1 atm), MeOH/DMF (2:1), 50°C, 1 h, 92%; h) TMSOTf, 2,6-lutidine, CH₂Cl₂, 0°C→RT, 24 h; i) NaN₃, 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 (Tf₂O, PhNTf₂) and bases (LDA, LHMDs, KHMDs, Et₃N, 2,6-di-*tert*-butyl-4-methylpyridine) resulted only in decomposition.^[14] The nitro group in **8** was then reduced with TiCl₃,^[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** (OsO₄/NMO then NaIO₄) then afforded an aldehyde.^[16] Without purification, the crude aldehyde was reduced with NaBH₄ to provide **13**, which was partially cyclized to amina **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 amina, 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 NaN₃ 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).

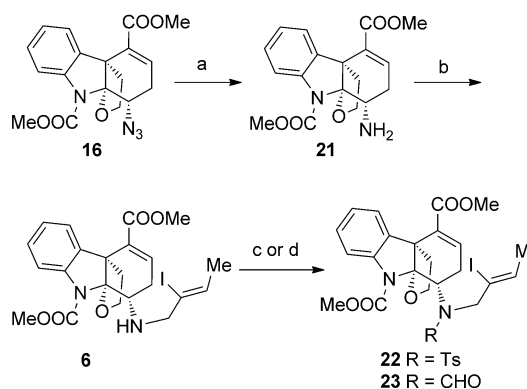
In other attempts to synthesize the key intermediate **16**, the direct reductive cyclization of **9** afforded the 2,3-disubstituted indole **18**, which presumably results from the ring opening of the desired indolenine **19** (Scheme 4).^[19] On



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.

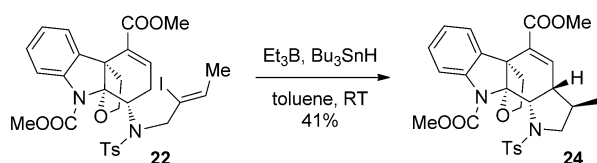
The reduction of azide **16** under Staudinger conditions (PPh₃, THF–H₂O, 50°C) afforded the primary amine **21** in 81% yield (Scheme 5). *N*-Monoallylation with (*Z*)-1-bromo-



Scheme 5. a) PPh₃, H₂O, THF, 50°C, 3 h, 81%; b) (*Z*)-1-bromo-2-iodobut-2-ene, Cs₂CO₃, 4 Å molecular sieves, THF/DMF (1:1), room temperature, 24 h, 79%; c) TsCl, Et₃N, CH₂Cl₂, room temperature, 12 h, 55% (**22**); d) Ac₂O, 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

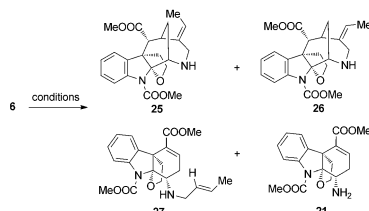


Scheme 6. Radical cyclization of *N*-Ts derivative **22** to pentacyclic **24**.

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

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

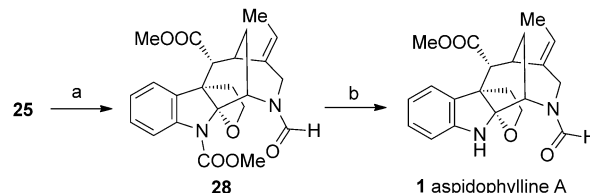


Entry	Conditions	Result
1	[Ni(cod) ₂], Et ₃ N, CH ₃ CN, RT, then Et ₃ SiH	decomposition
2	Pd(OAc) ₂ , PPh ₃ , Et ₃ N, 90 °C	27 + 21
3	Pd(OAc) ₂ , HCOONa, K ₂ CO ₃ , DMF, 60 °C ^[a]	27 ^[b]
4	Pd(OAc) ₂ , HCOOH, piperidine, DMF, 60 °C	27 + 21
5	<i>n</i> Bu ₃ SnH, Et ₃ B, toluene, RT	25 (40%) + 26 (44%)
6	<i>n</i> Bu ₃ SnH, AIBN, benzene, 80 °C	25 (40%) + 26 (44%)
7	<i>n</i> BuLi, THF, −78 °C → RT	27
8	<i>t</i> BuLi, THF, −78 °C → RT	25 ^[c] + 27 + 21
9	<i>t</i> BuLi, HMPA, TMSCl, THF, −78 → 0 °C	25 (51%) + 27 (5%)

[a] *n*Bu₄NCl was added. [b] Complex reaction mixture. [c] A trace amount of **25** was obtained. AIBN = azobisisobutyronitrile, cod = 1,5-cyclooctadiene, HMPA = hexamethylphosphoramide.

reductive Heck coupling with different combinations of catalysts, ligands, bases, and additives, such as Pd(OAc)₂/PPh₃/Et₃N,^[23] Pd(OAc)₂/HCOONa/K₂CO₃/*n*Bu₄NCl,^[24] and [Pd(PPh₃)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 *n*Bu₃SnH/Et₃B or *n*Bu₃SnH/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 vinyl lithium 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).

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) Ac₂O, 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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