Natural Products Synthesis

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Total Synthesis of the Monoterpenoid Indole Alkaloid (±)-Aspidophylline A**

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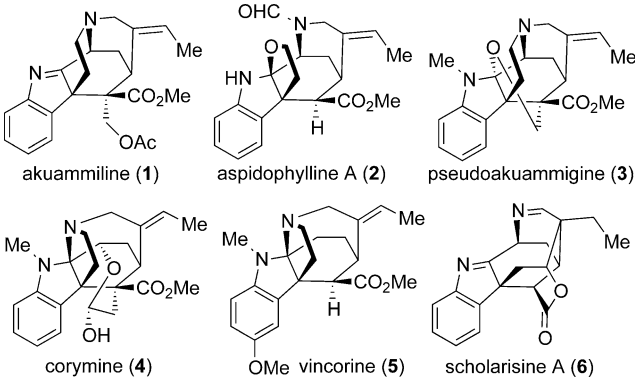
Abstract: *Aspidophylline A belongs to the akuammiline alkaloid family, the members of which possess intriguing cagelike structures and diverse biological activities. Herein we report a 15-step synthesis of this alkaloid from conveniently available starting materials. The key elements of the synthesis include an intramolecular oxidative coupling to create the tetracyclic furoindoline motif of the natural product and a [Ni(cod)$_2$]-mediated cyclization to install its piperidine ring.*

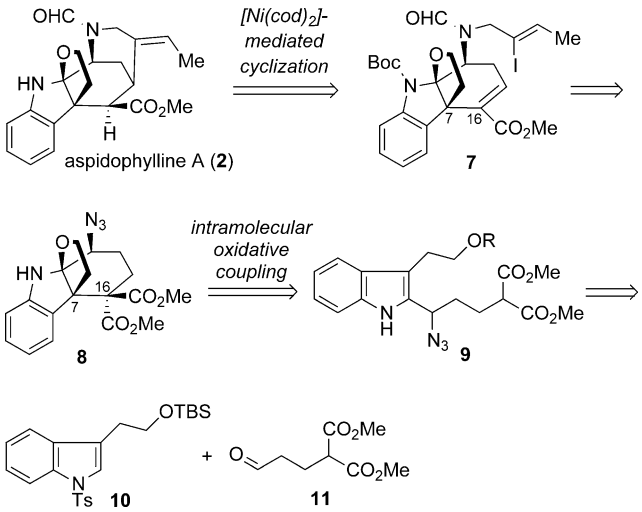
Since akuammiline (**1**, Scheme 1) was characterized in 1932,[1] more than 100 akuammiline monoterpenoid indole alkaloids have been discovered from different medicinal plants.[2–5] Preliminary studies have indicated that these



Scheme 1. Structures of some akuammiline alkaloids.

natural products possess a wide range of biological activity, such as the reversal of drug resistance in drug-resistant KB cells by aspidophylline A (**2**),[3] the in vivo antiinflammatory and analgesic activity exhibited by pseudoakuammigine (**3**),[6] and the mixed type of competitive and noncompetitive antagonism displayed by corymine (**4**) at the glycine receptor.[7] In the past decades, considerable efforts have been directed toward synthetic studies of these alkaloids.[8–11] These studies have resulted in three total syntheses of vincorine (**5**),[9] two total syntheses of scholarisine A (**6**),[10] and a total synthesis of aspidophylline A in 2011 by the Garg research group.[11]

In pursuit of a general strategy for assembling akuammiline alkaloids, we recently completed the enantioselective total synthesis of vincorine[9b] by using an intramolecular oxidative coupling[8i,k 12,13] between indole and malonate moieties as the key step. This success prompted us to explore whether a similar strategy could be applied to the total synthesis of other akuammiline alkaloids. Herein, we report the development of a 15-step synthesis of aspidophylline A from known 3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-tosyl-1*H*-indole (**10**)[14] and dimethyl 2-(3-oxopropyl)malonate (**11**)[15] (Scheme 2) in which a [Ni(cod)$_2$]-mediated cyclization



Scheme 2. Retrosynthetic analysis of aspidophylline A (**2**). Ts = *p*-toluenesulfonyl.

of vinyl iodide **7** was employed to install the bridged piperidine ring, and an intramolecular oxidative coupling of azide **9** was used to construct the required tetracyclic intermediate **8**.

As outlined in Scheme 3, we started our total synthesis with the condensation of the protected indole **10** and aldehyde **11**. This reaction proceeded smoothly at −78 °C to afford the desired alcohol **12** in 55% yield. After removal of the tosyl protecting group in **12**, a Mitsunobu reaction of the resultant alcohol with diphenyl phosphorazidate and DBU led to the formation of azide **9a**,[16] which was treated with pyridine hydrofluoride in THF to provide alcohol **9b**. The protection of **9b** with MOMCl then gave rise to **9c**.

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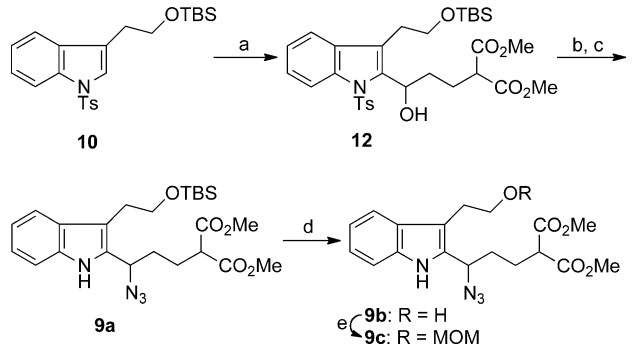
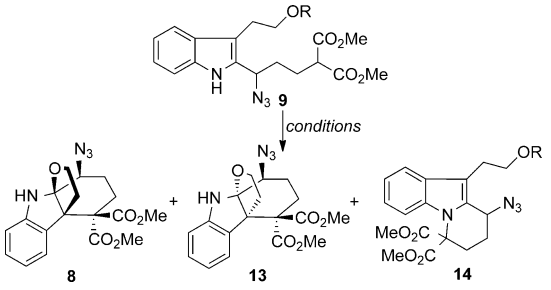


Scheme 3. Reagents and conditions: a) *n*BuLi, THF, −78 °C, then aldehyde **11**, 55 %; b) sodium naphthalenide, DME, −80 °C, 83 %; c) DPPA, DBU, toluene, 0 °C→RT, 60 %; d) pyridine hydrofluoride, THF, 0 °C→RT, 84 %; e) *i*PrNEt$_2$, MOMCl, CH_2Cl_2, 0 °C→RT, 63 %. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DME = dimethoxyethane, DPPA = diphenyl phosphorazidate, MOM = methoxymethyl.

With the 2,3-disubstituted indoles **9** in hand, we attempted the crucial intramolecular oxidative-coupling reaction. Surprisingly, under our previously described typical conditions for oxidative coupling,[9b] the reaction of the silyl ether **9a** afforded the tricyclic compound **14a** as the major product (Table 1, entry 1). The formation of **14a** might result from the oxidative coupling of a nitrogen anion and a carbanion. Zhu and co-workers observed similar C–N bond formation in their recent attempt to synthesize strictamine through an oxidative-coupling approach.[8k] They assumed that the preference for C–N bond formation over the desired C–C bond formation was caused by unfavorable geometric constraints in their tricyclic substrate. Since it was not apparent that there should be a similar problem with our substrates, we attempted to obtain the desired tetracyclic product **8** by changing the oxidation conditions and the substrates. When HMPA was added, the yield of **14a** increased to 73 %, but still no product of C–C bond formation was detected (Table 1, entry 2). A similar result was observed when the MOM-protected substrate **9c** was employed (Table 1, entry 3). However, when substrate **9b** with a free hydroxy group was subjected to oxidative coupling, the desired tetracycle **8** was isolated together with its diastereomer **13** in a 2:1 ratio under the same reaction conditions (Table 1, entry 4). Interestingly, in the presence of HMPA, the formation of **8** and **13** was inhibited, and the tricyclic product **14b** was isolated as the major product (Table 1, entry 5).

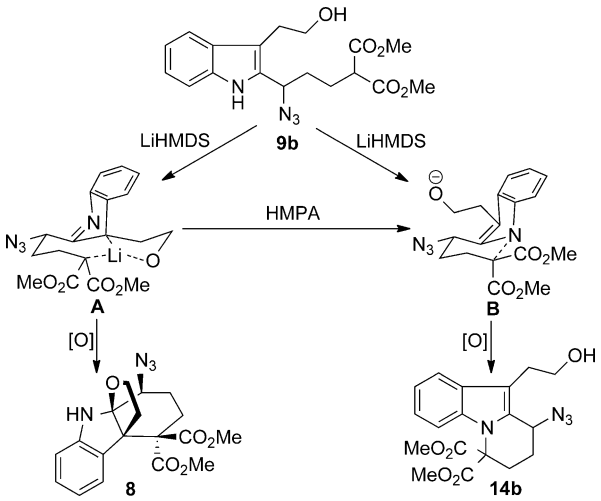
Table 1: Intramolecular oxidative coupling of **9**.[a]



Entry	R	Conditions	Product (yield [%])[b]
1	TBS	LiHMDS, THF, −40 °C, then I_2, −40→0 °C	**14a** (38)
2	TBS	LiHMDS, THF, HMPA, −40 °C, then I_2, −40→0 °C	**14a** (73)
3	MOM	LiHMDS, THF, −40 °C, then I_2, −40→0 °C	**14c** (40)
4	H	LiHMDS, THF, −40 °C, then I_2, −40→0 °C	**8**/**13** (2:1, 54)
5	H	LiHMDS, THF, HMPA, −40 °C, then I_2, −40→0 °C	**14b** (36)

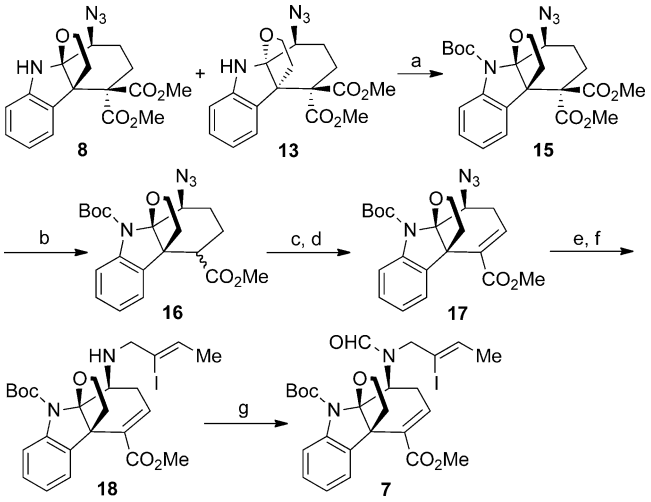
[a] General reaction conditions: azide **9** (0.043 mmol), base (0.11 mmol), iodine (0.043 mmol), THF (1.7 mL), HMPA (0 or 0.17 mL). [b] Yield of the isolated product. HMDS = hexamethyldisilazide, HMPA = hexamethylphosphoramide.

We propose the following mechanism to rationalize the above oxidative-coupling results (Scheme 4). We believe that for substrate **9b**, deprotonation of the free hydroxy group occurs rapidly to form a chelated intermediate **A**. This chelation might stabilize the intermediate anion and thus favor C–C bond formation to produce **8**. The addition of HMPA would suppress chelation and potentially enable the reaction proceed via the more favorable conformer **B** to deliver the product of C–N bond formation, **14b**. The present analysis suggests that the similar binding provided through deprotonation of a secondary carbamate moiety might be essential for the corresponding C–C bond formation in our total synthesis of vincorine,[9b] and the lack of an acidic hydrogen atom in the side chain of **14a** and **14c** might be responsible for exclusive C–N bond formation.



Scheme 4. Possible reaction course for the intramolecular oxidative coupling of **9b**.

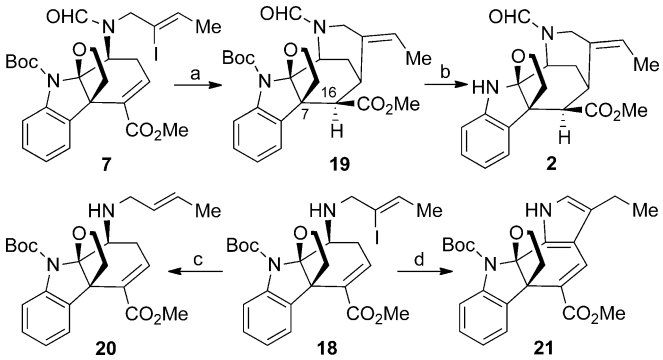
Treatment of the mixture of **8** and **13** with $(Boc)_2O$ in the presence of DMAP produced a separable mixture of diastereomers, and the pure carbamate **15** was isolated in 60 % yield (Scheme 5). Decarboalkoxylation by the heating of **15** in a solution of lithium chloride in DMF provided monoester **16** as a diastereomeric mixture, which was treated sequentially with LDA/PhSeBr and peroxide to deliver the α,β-unsatu-



Scheme 5. Reagents and conditions: a) $(Boc)_2O$, DMAP, DMF, 60%; b) LiCl, DMF, 120°C, then $(Boc)_2O$, DMAP, 68% (82% yield b.r.s.m.); c) LDA, then PhSeBr, THF, −78°C; d) H_2O_2, pyridine, CH_2Cl_2, 0°C, 53% for 2 steps; e) PPh_3, H_2O, THF, 50°C; f) (*Z*)-1-bromo-2-iodobut-2-ene, Cs_2CO_3, 4 Å molecular sieves, THF/DMF, room temperature, 62% for 2 steps; g) formic acid, DIC, DMAP, CH_2Cl_2, 0°C→RT, 82%. Boc = *tert*-butoxycarbonyl, b.r.s.m. = based on recovered starting material, DIC = *N*,*N*′-diisopropylcarbodiimide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, LDA = lithium diisopropylamide.

rated ester **17**.[17] After reduction of the azide moiety in **17** to give an amine, allylation with (*Z*)-1-bromo-2-iodobut-2-ene afforded the secondary amine **18**. Next, formylation of the amine **18** with formic acid/DIC furnished amide **7**.

The formation of the piperidine ring of aspidophylline A through metal-mediated cyclization of the vinyl iodide **7** proved to be another challenging step in our total synthesis (Scheme 6). Initially, we attempted the $[Ni(cod)_2]$-mediated cyclization under the typical reaction conditions ($[Ni(cod)_2]$, Et_3N, MeCN, BHT, RT)[18] and found that the desired cyclization product **19** could be obtained, but the yield was only 19%. After some experimentation, we were pleased to discover that the use of a mixture of MeCN and DMF as the



Scheme 6. Reagents and conditions: a) $[Ni(cod)_2]$, Et_3N, MeCN, DMF, BHT, room temperature, 58%; b) TMSOTf, CH_2Cl_2, 0°C, 95%; c) $[Ni(cod)_2]$, Et_3N, MeCN, BHT, room temperature, 27%; d) $Pd(OAc)_2$, K_2CO_3, $nBu_4NCl{\cdot}H_2O$, HCO_2Na, DMF, 80°C, 48%. BHT = 2,6-bis(1,1-dimethylethyl)-4-methylphenol, cod = 1,5-cyclooctadiene, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

reaction medium dramatically improved the cyclization reaction and led to the formation of the pentacyclic product **19** in 58% yield, together with its C16 epimer in 23% yield. Finally, deprotection of **19** with TMSOTf delivered aspidophylline A (**2**) in 95% yield, the structure of which was confirmed by X-ray crystallographic analysis.[17] Notably, the $[Ni(cod)_2]$-mediated cyclization of secondary amine **18** gave the deiodination product **20** as the major product, thus indicating that amine protection was essential for $[Ni(cod)_2]$-mediated cyclization. Additionally, a palladium-catalyzed reductive Heck reaction[19] of **18** produced pyrrole **21** in 48% yield. Although the detailed mechanism for the formation of **21** awaits investigation, we assume that this transformation might involve a direct C–H bond functionalization/isomerization/oxidation process.

In conclusion, we have developed a 15-step total synthesis of aspidophylline A from conveniently available starting materials. The key elements in the synthesis include an intramolecular oxidative coupling to create the tetracyclic furoindoline motif and a $[Ni(cod)_2]$-mediated cyclization to install the bridged piperidine ring. This study further demonstrates that intramolecular oxidative coupling is a reliable strategy for assembling akuammiline alkaloids. The present results for oxidative coupling between indole and malonate moieties should shed light on further synthetic applications of this method and related mechanistic studies. The extension of this strategy to the total synthesis of other members of the akuammiline family of alkaloids and their analogues for structure–activity-relationship studies is being actively pursued in our laboratory.

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[1] T. A. Henry, *J. Chem. Soc.* **1932**, 2759.
[2] For a review, see: A. Ramírez, S. García-Rubio, *Curr. Med. Chem.* **2003**, *10*, 1891.
[3] G. Subramaniam, O. Hiraku, M. Hayashi, T. Koyano, K. Komiyama, T.-S. Kam, *J. Nat. Prod.* **2007**, *70*, 1783.
[4] X.-H. Cai, Q.-G. Tan, Y.-P. Liu, T. Feng, Z.-Z. Du, W.-Q. Li, X.-D. Luo, *Org. Lett.* **2008**, *10*, 577.
[5] L.-M. Li, T. Yang, Y. Liu, J. Liu, M.-H. Li, Y.-T. Wang, S.-X. Yang, Q. Zou, G.-Y. Li, *Org. Lett.* **2012**, *14*, 3450.
[6] M. Duwiejua, E. Woode, D. D. Obiri, *J. Ethnopharmacol.* **2002**, *81*, 73.
[7] P. Leewanich, M. Tohda, K. Matsumoto, S. Subhadhirasakul, H. Takayama, N. Aimi, H. Watanabe, *Eur. J. Pharmacol.* **1997**, *332*, 321.
[8] For selected examples, see: a) L. J. Dolby, Z. Esfandiari, *J. Org. Chem.* **1972**, *37*, 43; b) L. J. Dolby, S. J. Nelson, *J. Org. Chem.* **1973**, *38*, 2882; c) E. Wenkert, M. Guo, M. J. Pestchanker, Y.-J. Shi, Y. D. Vankar, *J. Org. Chem.* **1989**, *54*, 1166; d) T. Hoike, H. Takayama, S. Sakai, *Chem. Pharm. Bull.* **1991**, *39*, 1677; e) J. Lévy, J. Sapi, J.-Y. Laronze, D. Royer, L. Toupet, *Synlett* **1992**, 601; f) M.-L. Bennasar, E. Zulaica, A. Ramírez, J. Bosch, *J. Org. Chem.* **1996**, *61*, 1239; g) M. Amat, S. Hadida, G. Pshenichnyi, J. Bosch, *J. Org. Chem.* **1997**, *62*, 3158; h) Y. Yasui, T. Kinugawab, Y. Takemoto, *Chem. Commun.* **2009**, 4275; i) T. Watanabe, N. Kato, N. Umezawa, T. Higuchi, *Chem. Eur. J.* **2013**, *19*, 4255;

j) Q. Li, G. Li, S. Ma, P. Feng, Y. Shi, *Org. Lett.* **2013**, *15*, 2601; k) W. Ren, N. Tappin, Q. Wang, J. Zhu, *Synlett* **2013**, 1941.

[9] a) M. Zhang, X. Huang, L. Shen, Y. Qin, *J. Am. Chem. Soc.* **2009**, *131*, 6013; b) W. Zi, W. Xie, D. Ma, *J. Am. Chem. Soc.* **2012**, *134*, 9126; c) B. D. Horning, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, *135*, 6442.

[10] a) G. L. Adams, P. J. Carroll, A. B. Smith, *J. Am. Chem. Soc.* **2012**, *134*, 4037; b) G. L. Adams, P. J. Carroll, A. B. Smith, *J. Am. Chem. Soc.* **2013**, *135*, 519; c) M. W. Smith, S. A. Snyder, *J. Am. Chem. Soc.* **2013**, *135*, 12964.

[11] L. Zu, B. W. Boal, N. K. Garg, *J. Am. Chem. Soc.* **2011**, *133*, 8877.

[12] a) Z. Zuo, W. Xie, D. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 13226; b) Z. Zuo, D. Ma, *Angew. Chem.* **2011**, *123*, 12214; *Angew. Chem. Int. Ed.* **2011**, *50*, 12008; c) F. Fan, W. Xie, D. Ma, *Org. Lett.* **2012**, *14*, 1405; d) Y. Wei, D. Zhao, D. Ma, *Angew. Chem.* **2013**, *125*, 13226; *Angew. Chem. Int. Ed.* **2013**, *52*, 12988.

[13] For intermolecular oxidative coupling, see: a) P. S. Baran, J. M. Richter, *J. Am. Chem. Soc.* **2004**, *126*, 7450; b) P. S. Baran, J. M. Richter, D. W. Lin, *Angew. Chem.* **2005**, *117*, 612; *Angew. Chem. Int. Ed.* **2005**, *44*, 606; c) P. S. Baran, M. P. DeMartino, *Angew. Chem.* **2006**, *118*, 7241; *Angew. Chem. Int. Ed.* **2006**, *45*, 7083; d) J. M. Richter, B. W. Whitefield, T. J. Maimone, D. W. Lin, M. P. Castroviejo, P. S. Baran, *J. Am. Chem. Soc.* **2007**, *129*, 12875; e) J. M. Richter, Y. Ishihara, T. Masuda, B. W. Whitefield, T. Llamas, A. Pohjakallio, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 17938.

[14] R. Kuwano, M. Kashiwabara, K. Sato, T. Ito, K. Kaneda, Y. Ito, *Tetrahedron: Asymmetry* **2006**, *17*, 521.

[15] R. V. Stevens, A. W. M. Lee, *J. Am. Chem. Soc.* **1979**, *101*, 7032.

[16] A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, E. J. J. Crabowski, *J. Org. Chem.* **1993**, *58*, 5886.

[17] CCDC 976846 (**17**) and 976847 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] a) D. Solé, Y. Cancho, A. Llebaria, J. M. Moretó, A. Delgado, *J. Am. Chem. Soc.* **1994**, *116*, 12133; b) J. Bonjoch, D. Solé, J. Bosch, *J. Am. Chem. Soc.* **1995**, *117*, 11017; c) D. Solé, J. Bonjoch, J. Bosch, *J. Org. Chem.* **1996**, *61*, 4194; d) J. Bonjoch, D. Solé, S. García-Rubio, J. Bosch, *J. Am. Chem. Soc.* **1997**, *119*, 7230; e) J. Ma, W. Yin, H. Zhou, J. M. Cook, *Org. Lett.* **2007**, *9*, 3491; f) F. Yu, B. Cheng, H. Zhai, *Org. Lett.* **2011**, *13*, 5782.

[19] a) C. D. Cox, J. R. Malpass, *Tetrahedron* **1999**, *55*, 11879; b) D. Solé, J. Bonjoch, S. García-Rubio, E. Peidró, J. Bosch, *Chem. Eur. J.* **2000**, *6*, 655; c) A. B. Dounay, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2005**, *127*, 10186; d) A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc.* **2008**, *130*, 5368.

