JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Total Synthesis of *Akuammiline* Alkaloid (−)-Vincorine via Intramolecular Oxidative Coupling

Weiwei Zi, Weiqing Xie, and Dawei Ma*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Supporting Information

ABSTRACT: An asymmetric total synthesis of the *Akuammiline* alkaloid (−)-vincorine (18 steps from 5-methoxytryptamine, 5% overall yield) is described. The key steps include Pd-catalyzed direct C−H functionalization of indole derivatives, organocatalyzed asymmetric Michael addition of aldehydes to alkylidene malonates, and intramolecular oxidative coupling between indole and malonate moieties.

3,4a-Disubstituted-2,3,4,4a-tetrahydro-1*H*-carbazole-4-carboxylic acid methyl ester (**1**) and its heteroatom-captured form **2** are highly congested polycyclic ring systems[1] that are common skeletons for *Akuammiline*-type alkaloids such as strictamine (**3**),[2] scholarisine A (**4**),[3] vincorine (**5**),[4] and aspidophylline A (**6**)[5] (Figure 1). Because of their interesting biological activity

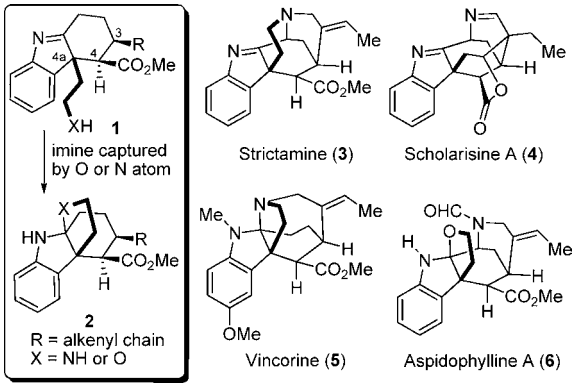


Figure 1. Representative *Akuammiline* alkaloids and their common carbazole carboxylate skeleton.

and inspiring architecture, these alkaloids have garnered considerable interest in the synthetic community.[6−9] In 2009, the Qin group completed the first total synthesis of (±)-vincorine,[7] in which they employed an intramolecular cyclopropanation and subsequent ring-opening strategy to elaborate a key tricyclic intermediate. Quite recently, Garg and co-workers reported a total synthesis of (±)-aspidophylline A utilizing the interrupted Fischer indolization reaction as a key step,[8] and the Smith group disclosed an elegant synthesis of (+)-scholarisine A featuring a reductive cyclization cascade to form the cage-shaped tricyclic intermediate.[9]

In our previous work, we achieved the first asymmetric total synthesis of (−)-communesin F via the formation of spiroindoline intermediate **8** through an intramolecular oxidative coupling of 3-substituted indole **7** (Figure 2).[10] As an extension

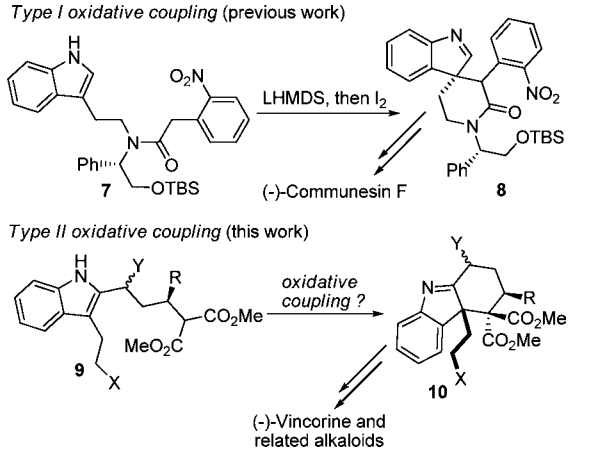


Figure 2. Two types of intramolecular oxidative coupling pathways.

of this work, we designed another type of intramolecular oxidative coupling[11] that uses compounds **9** as the substrates, in which the coupling might occur between indole and malonate moieties. If this reaction were to succeed, we would be able to obtain tricyclic intermediates **10**, which could be used to synthesize vincorine and related alkaloids.

With this idea in mind, we proposed the retrosynthetic analysis for (−)-vincorine shown in Figure 3. Disconnection of the N4−C21 bond of (−)-vincorine would give rise to aminal intermediate **11**, which could be derived from carbazole carboxylate **12**. The latter could be accessed from **13** via the type-II oxidative coupling pathway (Figure 2), while olefin **13** could be constructed via an organocatalyzed Michael addition[12] of aldehyde **15** to alkylidene malonate **14** and subsequent transformations.

Our synthesis started with the preparation of the oxidative coupling precursor **13** (Scheme 1). After protection of commercially available 5-methoxytryptamine (**16**) with $(Boc)_2O$, the resultant 1,3,5-trisubstituted indole was subjected to direct C−H functionalization via a palladium-catalyzed alkenylation[13] to afford 1,2,3,5-tetrasubstituted indole **17** in 71% overall yield. Hydrogenation of the C−C double bond of **17** and subsequent reduction of the ester group with

Received: April 21, 2012
Published: May 22, 2012

dx.doi.org/10.1021/ja303602f | J. Am. Chem. Soc. 2012, 134, 9126−9129

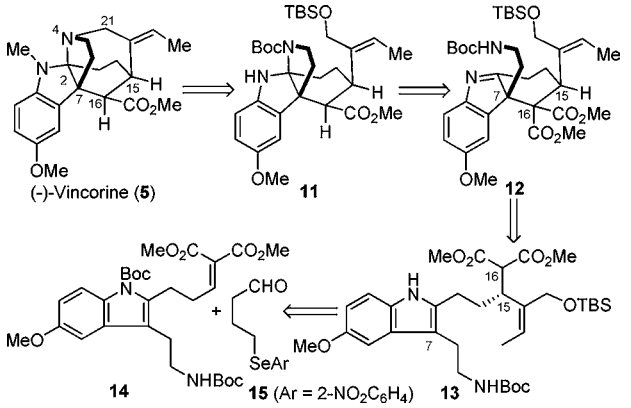
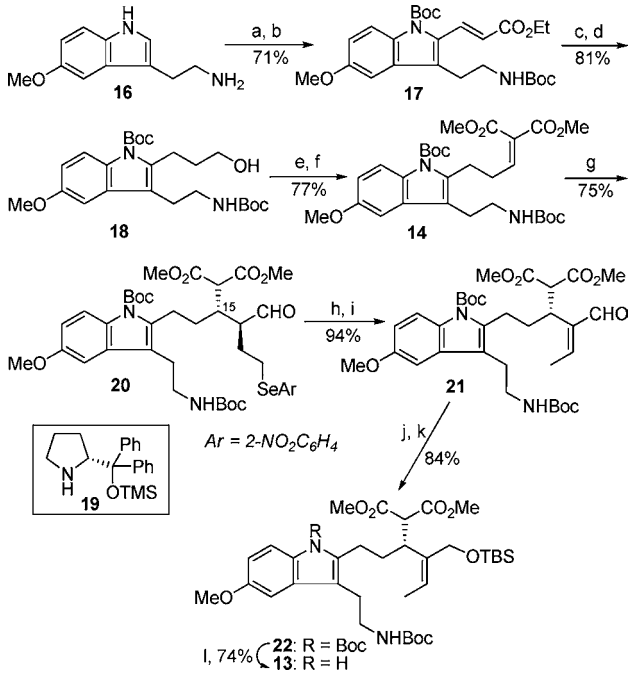


Figure 3. Retrosynthetic analysis for (−)-vincorine (**5**).

Scheme 1[a]

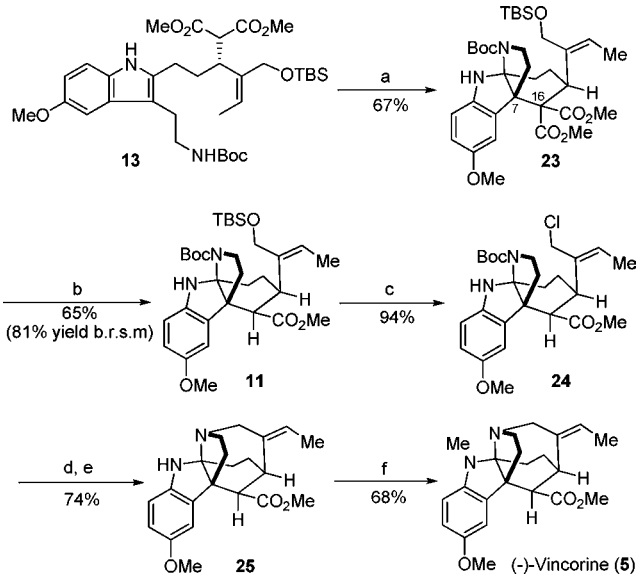


[a]Reagents and conditions: (a) $(Boc)_2O$, cat. DMAP, CH_2Cl_2; (b) $Pd(OAc)_2$, ethyl acrylate, *t*-BuO_2Bz, 1,4-dioxane/AcOH, 70 °C; (c) Pd/C, H_2 (1 atm), THF/MeOH; (d) DIBAL-H, THF, −78 to −40 °C; (e) IBX, ethyl acetate, reflux; (f) dimethyl malonate, cat. proline, DMSO, r.t.; (g) cat. **19**, **15**, CH_3CN, 0 °C, 3 days; (h) *m*-CPBA, THF, −78 °C to r.t., Et_3N workup; (i) UV light (360 nm); (j) $NaBH_4$, MeOH, −78 to 0 °C; (k) TBSCl, imidazole, DMF; (l) silica gel, 70 °C, 0.2−0.3 mmHg.

diisobutylaluminum hydride (DIBAL-H) provided alcohol **18**. Oxidation of **18** with 2-iodoxybenzoic acid (IBX) gave an aldehyde that was condensed with dimethyl malonate[14] to produce alkylidene malonate **14**. According to our proposed retrosynthetic analysis, we planned to introduce a side chain via organocatalyzed Michael addition of aldehyde **15** to **14**.[12] This seemed to be challenging because both the aldehyde and the Michael acceptor are much more complicated than those reported by Córdova and co-workers.[12a] After some experimentation, we were pleased to find that the best results were obtained by treating **14** and **15** under the catalysis of *O*-trimethylsilyl (TMS)-protected diphenylprolinol (**19**) in MeCN at 0 °C for 3 days. In this case, the desired Michael adduct **20** was isolated in 75% yield as a 5:1 diastereomeric mixture. After failing to increase the diastereoselectivity by changing the solvent, reaction temperature, and catalyst, we decided to use this mixture for further conversion. Accordingly, oxidation of the aryl selenide moiety in **20** followed by Et_3N-mediated elimination produced olefin **21** as a mixture of *E* and *Z* isomers. The ratio was ∼1.7:1, which could be enhanced to 30:1 by exposure to UV light (360 nm) for 16 h. It is noteworthy that using both bases and acids as catalysts for this isomerization failed to give any satisfactory results. Unfortunately, the ee value for **21** was only 64% (corresponding to an enantiomer ratio of ∼82:18) as determined by chiral HPLC. This probably originates from moderate diastereoselectivity at the C15 position during the formation of **20**. Next, reduction of aldehyde **21** and *tert*-butyldimethylsilyl (TBS) protection of the resultant alcohol delivered **22** in 84% yield. Finally, selective removal of the *tert*-butoxycarbonyl (Boc) protecting group in the indole moiety[15] was achieved by treatment with silica gel at low pressure to furnish **13** in 74% yield.

With diester **13** in hand, we attempted the crucial intramolecular oxidative coupling (Scheme 2). Deprotonation

Scheme 2[a]



[a]Reagents and conditions: (a) LiHMDS, I_2, THF, −40 °C to r.t.; (b) KCN, H_2O, DMF, 100 °C; (c) Ph_3PCl_2, CH_2Cl_2; (d) TMSOTf, 2,6-lutidine, CH_2Cl_2, r.t.; (e) K_2CO_3, KI, CH_3CN, 60 °C; (f) 37% aq. HCHO, $NaBH_3CN$, CH_3CN, AcOH.

of **13** with 2 equiv of lithium hexamethyldisilazide (LiHMDS) followed by addition of an iodine solution at −78 °C gave the desired coupling product **23** in only a low yield (<10%).[10a] Since most of the starting material was recovered in this case, we decided to improve the yield by increasing the reaction temperature in the oxidative coupling step. Fortunately, when the coupling reaction was carried out at −40 °C, **23** was isolated in 67% yield as a single isomer. At higher temperatures, the reaction yield dropped dramatically. Other oxidants such as *N*-iodosuccinimide, Cu(II) salts, and Fe(III) salts[11a,d] were found to be less effective for this transformation.

The stereochemical outcome during the formation of **23** could be explained through two chairlike transition states, as depicted in Figure 4. The strong repulsion between the axial

dx.doi.org/10.1021/ja303602f | J. Am. Chem. Soc. 2012, 134, 9126−9129

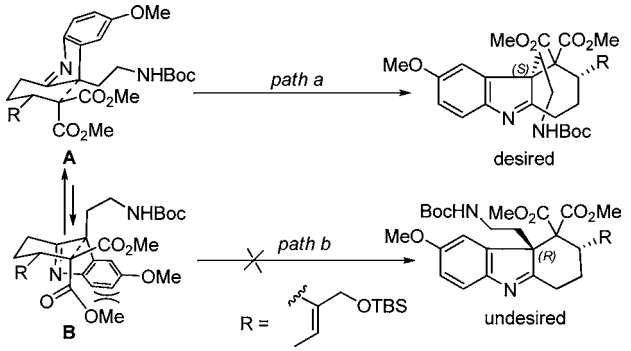


Figure 4. Favored and unfavored conformations during the oxidative coupling.

ester group and the indole moiety in transition state **B** prevents path b. Thus, the coupling reaction proceeds through transition state **A** to create the quaternary carbon center and set the desired stereochemistry.

After elaboration of carbazole carboxylate intermediate **23**, the stage would be set for introduction of the last seven-membered E ring. Accordingly, removal of one methyl ester at the C16 position of **23** using Krapcho's reaction conditions[16] gave **11** in 65% yield as a single isomer, together with some recovered starting material. Next, the TBS-protected hydroxyl group in **11** was directly chlorinated with Ph_3PCl_2 in methylene chloride at room temperature,[17] affording allyl chloride **24** in 94% yield. After removal of the Boc protecting group in **24** with TMSOTf, a subsequent alkylative cyclization was carried out with the assistance of KI to provide **25**, whose structure was confirmed by X-ray analysis.[18] Finally, reductive amination of **25** with HCHO and $NaBH_3CN$ furnished (−)-vincorine (**5**) in 68% yield. The synthetic **5** had ^1H and ^{13}C NMR data identical to those of natural vincorine. However, because of unsatisfactory diastereoselectivity in the organocatalyzed Michael addition, the optical rotation of our synthetic vincorine ($[\alpha]_D^{23.6}$ = −93.1, *c* = 0.65, EtOH) was somewhat lower than that reported for the natural product ($[\alpha]_D^{20.0}$ = −139, *c* = 1.0, EtOH).[4b]

In conclusion, we have developed an efficient approach for the synthesis of (−)-vincorine. This protocol allows the assembly of the target molecule in 18 steps from commercially available 5-methoxytryptamine in an overall yield of 5%. The key elements in this synthesis include the use of two newly developed reactions, namely, a Pd-catalyzed direct C−H functionalization of indole derivatives and an organocatalyzed asymmetric Michael addition of aldehydes to alkylidene malonates, as well as an intramolecular oxidative coupling between indole and malonate moieties. The completion of the (−)-vincorine synthesis also demonstrates the versatility of these new methodologies in natural product synthesis. Obviously, such a synthetic strategy is also promising for assembling other *Akuammiline*-type alkaloids. Investigations to prove this hypothesis are being actively pursued, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, compound characterization, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

madw@mail.sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to the National Basic Research Program of China (973 Program, Grant 2010CB833200), the Chinese Academy of Sciences, and the National Natural Science Foundation of China (Grants 21132008 and 20921091) for their financial support.

■ REFERENCES

(1) For reviews, see: (a) Antonio, R.; Silvina, G. R. *Curr. Med. Chem.* **2003**, *10*, 1891. (b) Kam, T. S. *Alkaloids: Chem. Biol. Perspect.* **1999**, *14*, 285. (c) Arai, H.; Hirasawa, Y.; Rahman, A.; Kusumawati, I.; Zaini, N. C.; Sato, S.; Aoyama, C.; Takeo, J.; Morita, H. *Bioorg. Med. Chem.* **2010**, *18*, 2152. (d) Pearce, H. L. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. *37*, p 145.

(2) (a) Schnoes, H.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem.* **1966**, *31*, 1641. (b) Ahmad, Y.; Fatima, K.; Rahman, A.; Occolowitz, J.; Solheim, B.; Clardy, J.; Garnick, R.; Le Quesne, P. *J. Am. Chem. Soc.* **1977**, *99*, 1943.

(3) Cai, X.-H.; Tan, Q.-G.; Liu, Y.-P.; Feng, T.; Du, Z.-Z.; Li, W.-Q.; Luo, X.-D. *Org. Lett.* **2008**, *10*, 577.

(4) (a) Mokrý, J.; Dúbravková, L.; Šefčovič, P. *Experientia* **1962**, *18*, 564. (b) Kamatas, S. M.; Sevenet, T.; Thal, C.; Potier, P. *Phytochemistry* **1975**, *14*, 1637.

(5) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T. S. *J. Nat. Prod.* **2007**, *70*, 1783.

(6) (a) Dounay, D. B.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1990**, *112*, 5653. (b) Lévy, J.; Sapi, J.; Laronze, J. Y.; Royer, D.; Toupet, L. *Synlett* **1992**, 601. (c) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186. (d) Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3618. (e) Jones, S. B.; Simons, B.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (f) Yasui, Y.; Kinugawab, T.; Takemoto, Y. *Chem. Commun.* **2009**, 4275.

(7) (a) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013. (b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447.

(8) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.

(9) Adams, G. L.; Caroll, P. J.; Smith, A. B. *J. Am. Chem. Soc.* **2012**, *134*, 4037.

(10) (a) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226. (b) Zuo, Z.; Ma, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008.

(11) For studies of intermolecular oxidative coupling between carbonyl compounds and unfunctionalized indoles and pyrroles, see: (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. (b) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394. (c) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 606. (d) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (e) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938.

(12) For organocatalytic conjugate addition of aldehydes to alkylidene malonates, see: (a) Zhao, G.; Vesely, J.; Sun, J.; Christensen, E. E.; Bonneau, C.; Córdova, A. *Adv. Synth. Catal.* **2008**, *350*, 657. (b) Wen, L.; Shen, Q.; Lu, L. *Org. Lett.* **2010**, *12*, 4655. (c) Chowdhury, R.; Ghosh, S. K. *Tetrahedron: Asymmetry* **2010**, *21*, 2696.

(13) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125.

(14) Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Synth. Commun.* **2003**, *33*, 1587.

(15) Apelqvist, T.; Wensbo, D. *Tetrahedron Lett.* **1996**, *37*, 1472.

(16) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.
(17) Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941.
(18) CCDC 874147 contains the supplementary crystallographic data for the compound **25**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.