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Nine-Step Enantioselective Total Synthesis of (−)-Vincorine

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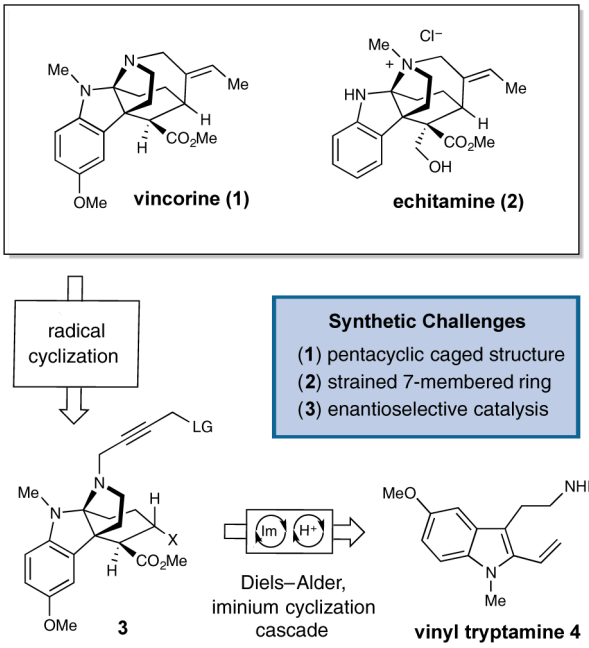
Supporting Information

ABSTRACT: A concise and highly enantioselective total synthesis of the akuammiline alkaloid (−)-vincorine has been accomplished. A key element of the synthesis is a stereoselective organocatalytic Diels−Alder, iminium cyclization cascade sequence, which serves to construct the tetracyclic alkaloid core architecture in one step from simple achiral precursors. The challenging seven-membered azepanyl ring system is installed by way of a single electron-mediated cyclization event initiated from an acyl telluride precursor. The total synthesis of (−)-vincorine is achieved in nine steps and 9% overall yield from commercially available starting materials.

The *Vinca* alkaloid natural products have historically served as valuable lead candidates in the development of anticancer agents (vinblastine),[1a,b] vasodilators (vincamine),[1c] antipsychotics, and anti-hypertensives (reserpine).[1d] Recently, members of the biologically active akuammiline family of *Vinca* alkaloids have emerged as high-profile targets for chemical synthesis and medicinal chemistry studies.[2] Vincorine (**1**) is the parent compound of an akuammiline alkaloid subclass characterized by a synthetically challenging tetracyclic core that incorporates a strained seven-membered azepanyl ring and a pyrroloindoline motif. In preliminary assays, the related alkaloids echitamine (**2**) and corymine (not shown) were found to exhibit anti-cancer activity[3] and glycine receptor antagonism,[4] respectively. With the goal of devising a concise synthesis of this common core structure for further biological investigation, a number of research laboratories have undertaken the synthesis of vincorine.[5] Indeed, recent total syntheses by the Qin group[6a] (35 steps, racemic) and the Ma group[6b] (18 steps, 64% ee) have served to highlight the significant structural challenges posed by this cage-like system. In this Communication, we disclose a highly enantioselective nine-step total synthesis of (−)-vincorine, which employs organocascade catalysis[7] as a central enabling feature. We anticipate that the general synthetic strategy described herein will prove readily adaptable to other bioactive akuammiline alkaloid natural products and analogues thereof.

Design Plan. From a retrosynthetic standpoint, we envisioned the disconnection of vincorine via two key steps (Scheme 1). While previous syntheses of vincorine have relied on C−N bond formation to forge the strained seven-membered azepanyl system, we reasoned that an intramolecular single electron-mediated C−C bond formation (initiated from compound **3**) might offer additional strategic advantages in that the requisite allylic methine stereochemistry would be produced along with the embedded heterocycle. The remaining

Scheme 1. Akuammiline Alkaloids—Retrosynthesis of Vincorine



structural and stereochemical elements of the akuammiline core would arise from a single organocatalytic Diels−Alder[8] iminium cyclization cascade event beginning from simple, achiral starting materials (**4** and **5**). We have previously demonstrated the complexity-generating capacity of other organocatalytic[9,10] cascade mechanisms in the recent total syntheses of strychnine, minfiensine,[11a] and additional selected alkaloids of the *Strychnos*, *Aspidosperma*, and *Kopsia* families.[11b]

In the specific context of this vincorine synthesis program, we envisioned employing a catalytic cascade sequence to effect the overall conversion of tryptamine **4** to the tetracyclic adduct **7** in one step. As outlined in Scheme 2, the sequence would begin with condensation of secondary amine catalyst **6** onto enal **5** to form an activated iminium ion. In the proposed transition state (**TS-A**), orientation of the reactive π-system away from the catalyst *gem*-dimethyl group would facilitate effective shielding of one π-face by the benzyl group, thereby enabling a highly stereoselective *endo* Diels−Alder reaction with diene **4**, to deliver enamine cycloadduct **8**. Brønsted acid-catalyzed interconversion of enamine **8** and iminium ion **9** by the ammonium salt of **6** would precipitate intramolecular 5-*exo*

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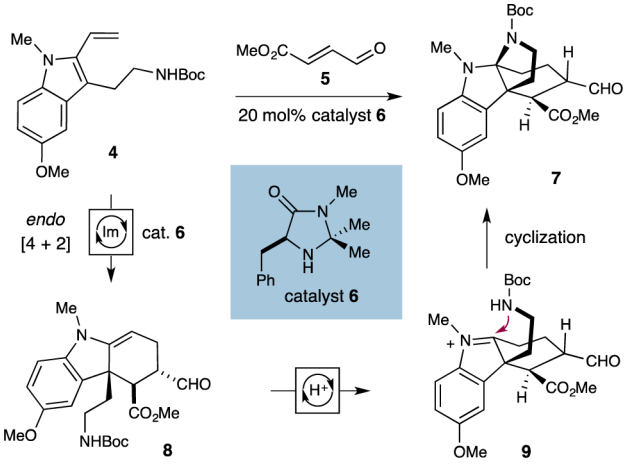
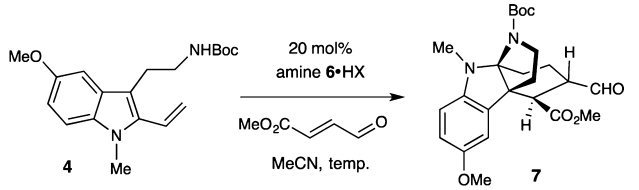
Scheme 2. Enantioselective Organocatalytic Cascade Sequence



amine cyclization via the pendant carbamate group to generate the tetracyclic product **7**.[12] Notably, the core structure **7** would emerge from this transformation bearing three of the four vincorine stereocenters—including the all-carbon quaternary center C(8)—with the correct relative and absolute configuration.

The total synthesis of vincorine was initiated with the preparation of diene **4** in two steps from commercially available 5-methoxy-*N*′-Boc tryptamine (**10**), via methylation and then directed metalation/Negishi coupling[13] (Scheme 3). For the key Diels–Alder/cyclization cascade, a survey of chiral secondary amines revealed that the first-generation Diels–Alder imidazolidinone catalyst **6** was both highly efficient and stereoselective. Using optimized reaction conditions (**6**·HBF_4, MeCN, −20 °C), the tetracyclic vincorine core system **7** was generated in 70% yield and 95% ee (Table 1, entry 6).

Table 1. Organocatalytic Diels–Alder/Cyclization Cascade

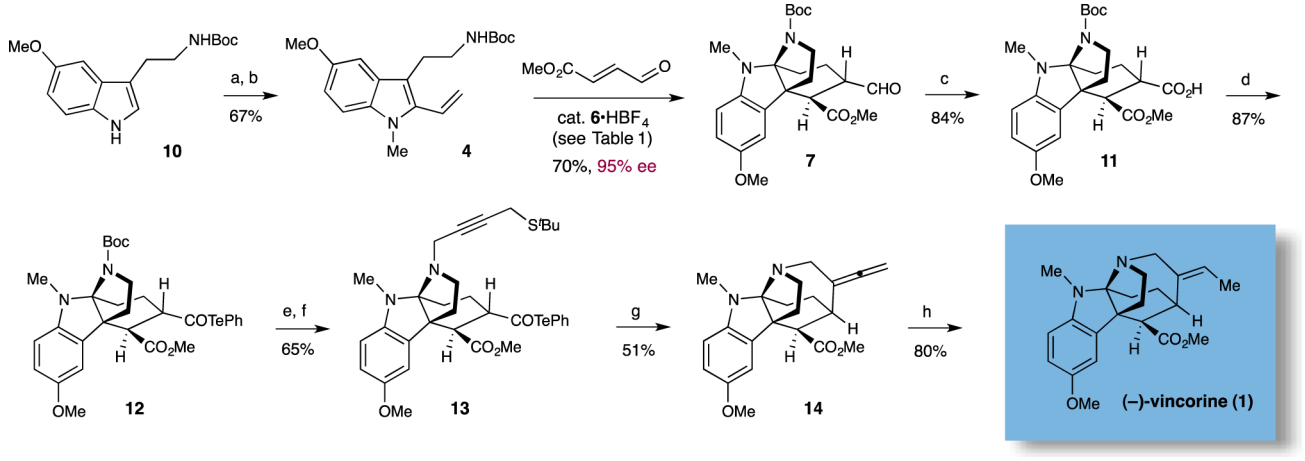


entry	HX	temp (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	$HClO_4$	0	4	38	88
2	HCl	0	4	25	73
3	HBF_4	0	4	71	93
4	HBF_4	−10	6	75	94
5[c]	HBF_4	−10	6	62	94
6	HBF_4	−20	6	73 (70)[d]	95

[a]Yield based on SFC analysis relative to an internal standard. [b]Determined by SFC analysis. [c]Reaction run with 5% v/v water. [d]Isolated yield.

With the majority of the requisite vincorine architecture in hand, we next sought to rapidly install the final seven-membered azepanyl ring by way of a 7-*exo*-dig radical cyclization. As shown in Scheme 3, Pinnick oxidation[14] served to convert aldehyde **7** to carboxylic acid **11**, prior to the formation of an alkyl radical precursor in the form of an acyl telluride. Specifically, the telluride **12** was generated in a sequence involving formation of a mixed anhydride followed by displacement with sodium phenyl telluride in good yield for the overall transformation. Installation of a suitable π-system to

Scheme 3. Nine-Step Enantioselective Catalytic Total Synthesis of Vincorine[a]



[a]Reagents and conditions: (a) NaH, DMF, 0 °C; MeI. (b) *n*-BuLi, DME, −40 °C; $ZnCl_2$, −78 °C to rt; XPhos precatalyst, vinyl iodide. (c) $NaClO_2$, 2-methyl-2-butene, THF, *tert*-butanol, H_2O, 0 °C. (d) Isobutyl chloroformate, *N*-methylmorpholine, THF; diphenyl ditelluride, $NaBH_4$, THF/MeOH, rt. (e) TFA, rt. (f) 4-(*tert*-Butylthio)but-2-ynal, $NaBH(OAc)_3$, CH_2Cl_2, rt. (g) 1,2-Dichlorobenzene, 200 °C. (h) Pd/C, H_2, THF, −15 °C.

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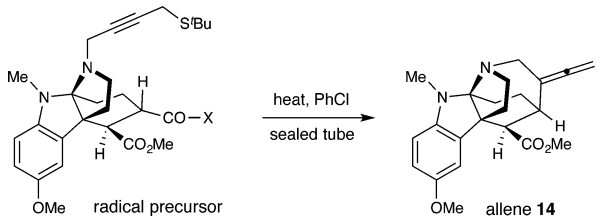
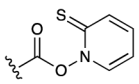
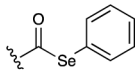
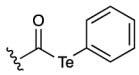
enable radical-mediated C−C bond cyclization was accomplished via Boc-deprotection and subsequent nitrogen alkylation using 2-butynal-4-*tert*-butyl sulfide in a reductive amination step. Notably, the acyl telluride moiety was successfully maintained through multiple transformations, readily withstanding exposure to neat trifluoroacetic acid and sodium triacetoxyborohydride.

The suitability of the acyl telluride unit as the preferred alkyl radical precursor was determined by comparison to a range of alternative acyl-X fragmentation partners in the key cyclization event (**13**→**14**, see Table 2).[15] Attempts to achieve useful

Table 2. Evaluation of Radical Cyclization Substrates



entry	CO–X	conditions	conc (mM)	conversion (%)	yield[a] (%)
1		120 °C, 1 h	1	100	18
2		120 °C, 3 h Bu_6Sn_6, $h\nu$	5	38	17
3		120 °C, 5 h Bu_6Sn_6, $h\nu$	5	85	17
4		120 °C, 12 h	5	100	8
5		160 °C, 12 h	5	100	31
6[b]		200 °C, 10 h	0.5	100	51[c]

[a]Yield based on ^{1}H NMR analysis. [b]1,2-Dichlorobenzene used as solvent. [c]Isolated yield.

isolated yields with a thiohydroxamic acid derivative (Barton ester)[16] were largely unsuccessful, due to competitive formation of a thiopyridyl byproduct via radical recombination (Table 2, entry 1, 18%). Similarly disappointing results were obtained using a thermally stable acyl selenide[17] precursor with hexabutyl ditin radical initiator. Although the stannyl radical—formed from hexabutyl ditin via photolysis with a high-pressure mercury lamp—was able to successfully initiate the desired cyclization, extensive decomposition of the allene product under the reaction conditions led to low isolated yields of the desired adduct (entries 2 and 3). We ultimately achieved success with a thermally initiated alkyl radical precursor, namely acyl telluride **13**.[18] Under optimal conditions (200 °C, 0.5 mM), radical cyclization of the acyl telluride precursor provided the allene product **14** in 51% isolated yield (entry 6). We postulate that the transformation of telluride **13** to the desired azepanyl allene **14** proceeds through carbon−Te bond homolysis, followed by loss of carbon monoxide to generate an alkyl radical. This result is notable given the difficulty of building seven-membered azepanes in comparison with the corresponding six-membered alkaloid analogues. Moreover, to our knowledge, this example represents the first use of an acyl telluride as an effective alkyl radical precursor.

In the final step of the synthesis, the terminal unsaturation of the allene functionality underwent selective hydrogenation from the less hindered face to provide (−)-vincorine in 80% yield as a single olefin isomer in nine steps and 9% overall yield from the commercially available indole **10**. The product generated was identical in all spectroscopic respects to the natural isolate (see Supporting Information).

In conclusion, we have developed a nine-step synthetic route to (−)-vincorine from commercially available starting materials. Key features of the synthesis include an organocatalytic Diels−Alder/amine cyclization cascade and a 7-*exo*-dig radical cyclization initiated from an unusual acyl telluride precursor. The utility of this new cascade catalysis strategy is now being explored in the production of a large collection of natural and un-natural vincorine analogues including echitamine. Findings from these studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Neuss, N.; Neuss, M. N. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic: San Diego, 1990; Vol. *37*, p 229. (b) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253. (c) Cook, P.; James, I. *New Engl. J. Med.* **1981**, *305*, 1560. (d) Davies, D. L.; Shepherd, M. *Lancet* **1955**, *269*, 117.

(2) For a review on akuammiline alkaloids, see: (a) Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891. For recent syntheses of akuammiline alkaloids, see: (b) Adams, G. L.; Carroll, P. J.; Smith, A. B., III *J. Am. Chem. Soc.* **2013**, *135*, 519. (c) Zu, L.; Boal, B. W.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.

(3) (a) Kamarajan, P.; Sekar, N.; Mathuram, V.; Govindasamy, S. *Biochem. Int.* **1991**, *25*, 491. (b) Kamarajan, P.; Ramamoorthy, N.; Govindasamy, S. *J. Clin. Biochem. Nutr.* **1995**, *18*, 65. (c) Saraswathi, V.; Ramamoorthy, N.; Subramanian, S.; Gunasekaran, P.; Govindasamy, S. *Chemotherapy* **1998**, *44*, 198.

(4) Leewanich, P.; Tohda, M.; Matsumoto, K.; Subhadhirasukul, S.; Takayama, H.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **1997**, *332*, 321.

(5) (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.

(6) (a) Zhang, M.; Huang, X.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2009**, *131*, 6013. (b) Zi, W.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2012**, *134*, 9126.

(7) (a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (b) Simmons, B.; Walji, A. M.;

MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4349. (c) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, *10*, 1477.
(8) (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4243. (b) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. (c) Wilson, R. M.; Jen, W. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 11616.
(9) Lelais, G.; MacMillan, D. W. C. *Aldrichimica Acta* **2006**, *39*, 79.
(10) MacMillan, D. W. C. *Nature* **2008**, *455*, 304.
(11) (a) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (b) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2011**, *475*, 183.
(12) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482.
(13) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
(14) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(15) For a related radical addition/fragmentation utilizing a sulfide fragmenting group, see: Barton, D. H. R.; Crich, D. *J. Chem. Soc., Perkin Trans. 1* **1986**, *0*, 1613.
(16) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1983**, *0*, 939.
(17) For an excellent review on acyl radical chemistry, see: Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.
(18) Chen, C.; Crich, D.; Papadatos, A. *J. Am. Chem. Soc.* **1992**, *114*, 8313. It is noteworthy that in this report, acyl tellurides derived from aliphatic carboxylic acids are found to be unreactive under both thermal and photochemical conditions.