ORGANIC LETTERS

2011
Vol. 13, No. 1
138−141

Total Synthesis of (+)-Condylocarpine, (+)-Isocondylocarpine, and (+)-Tubotaiwine

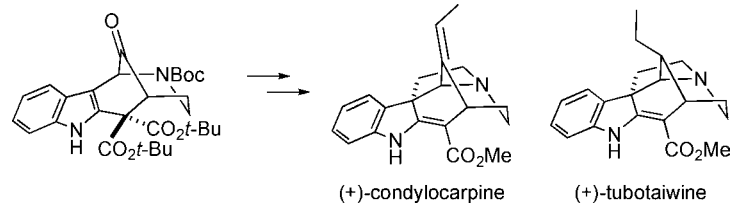
Connor L. Martin, Seiichi Nakamura,[†] Ralf Otte,[‡] and Larry E. Overman*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025

leoverma@uci.edu

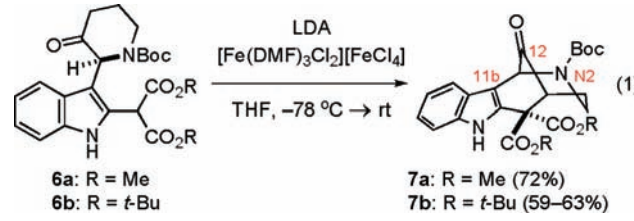
Received November 9, 2010

ABSTRACT



The first enantioselective total syntheses of indole alkaloids of the condylocarpine type are reported. (+)-Condylocarpine, (+)-isocondylocarpine, and (+)-tubotaiwine were prepared in high enantiomeric purity (er > 99:1) from (1*S*,5*R*)-hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole-12-one 7b by way of five or six isolated intermediates.

The hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system **1** is a major fragment of *Strychnos* alkaloids of the strychnan and aspidopermatan types (e.g., **2**−**4**, Figure 1) and the ring system of indole alkaloids of the uleine group (e.g., **5**, Figure 1).[1] During our recent total synthesis of the structurally unique indole alkaloid (−)-actinophyllic acid, we developed a concise synthesis of the hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system.[2,3] A central step in this synthesis is an iron(III)-promoted intramolecular oxidative coupling of malonate and ketone enolates generated from indole piperidones **6** to deliver hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole-12-ones **7** (eq 1). Ketone (1*S*,5*R*)-**7b** was prepared in enantioenriched form (er = 95:5) in 26% overall yield from 4-(*tert*-butoxycarbonylamino)butyric acid by way of six isolated intermediates.[2,4] Herein we report the use of tetracyclic intermediate (1*S*,5*R*)-**7b** for the enantioselective synthesis of three representative members of the condylocarpine subtype of the aspidospermatan group of alkaloids.[5,6]



Transformation of hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole-12-ones **7** to the condylocarpine skeleton requires introduction of a two-carbon unit at C12, installation of a two-carbon bridge between C11b and N2, and dealkoxycarbonylation of the malonate unit. Our early exploratory investigations were carried out in the racemic series and focused on elaboration of C12 and N2. Several observations made during these studies provided essential insight into the chemical reactivity of the hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system (Scheme 1). Wittig reaction

[†] Current address: Graduate School of Pharmaceutical Sciences, Nagoya City University, 3-1 Tanabe-dori, Mizuho-ku, Nagoya, Aichi 467-8603, Japan.

[‡] Current address: The Boston Consulting Group GmbH, Chilehaus A, Fischertwiete 2, 20095 Hamburg, Germany.

(1) (a) *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1996; Vol. 48, Chapter 4. (b) Alvarez, M.; Joule, J. A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 57, Chapter 4.

10.1021/ol102709s
Published on Web 12/06/2010

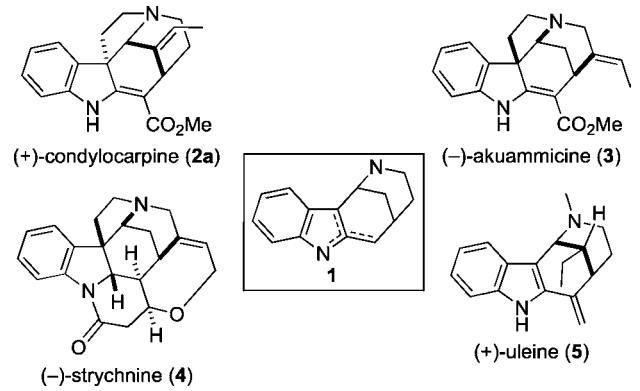
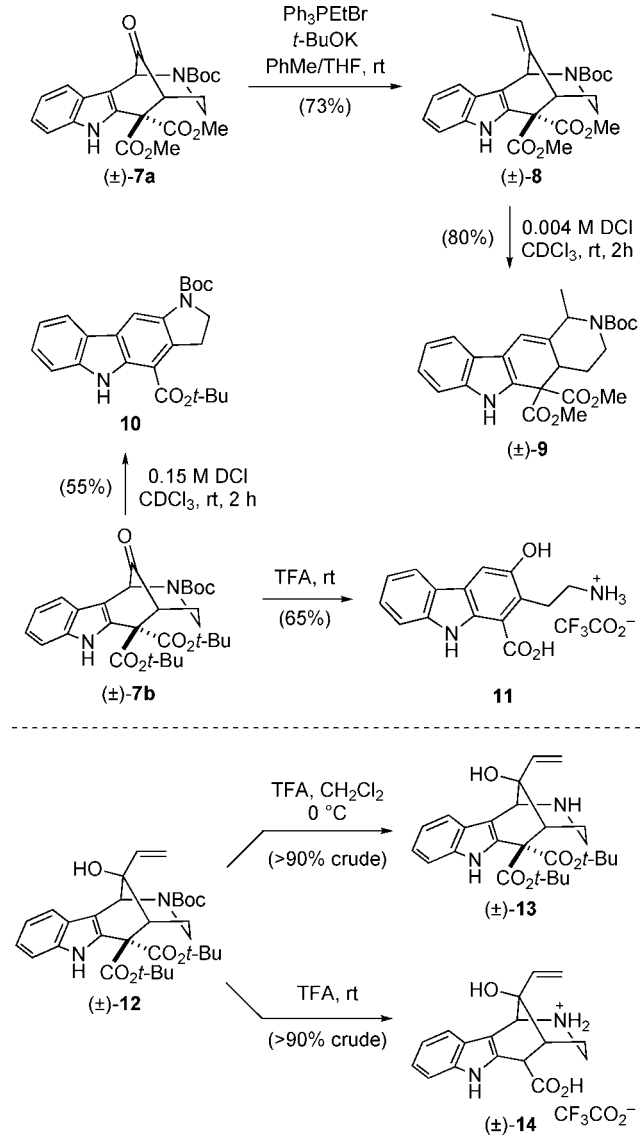


Figure 1. 1,5-Methanoazocino[4,3-*b*]indole ring system and some representative alkaloids that possess this fragment.

of ketone (±)-**7a** with ethylidenetriphenylphosphorane delivered ethylidene derivative (±)-**8** as a single stereoisomer in 73% yield, with the *Z* configuration of the double bond being readily secured by ^{1}H NMR NOE analysis. To our surprise, this product was extremely acid sensitive. For example, (±)-**8** rearranged to hexahydro-6*H*-pyrido[4,3-*b*]carbazole isomer (±)-**9** when stored in $CDCl_3$ for several days, or within 2 h at room temperature in the presence of 10 mol % of DCl (0.004 M). Related instability was observed with hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole-12-one (±)-**7b**, which when exposed in $CDCl_3$ to 0.15 M DCl for 2 h gave dihydropyrrolo[3,2-*b*]carbazole **10** in 55% yield.[7] Under stronger acidic conditions (neat TFA), ketone (±)-**7b** yielded 3-hydroxycarbazole-1-carboxylic acid **11** as the major product within 4 h at room temperature. In marked contrast, structurally related hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole diester (±)-**12** does not undergo skeletal rearrangement when exposed to TFA at 0 or 23 °C (Scheme 1).[2,8]

Scheme 1. Facile Gramine-Type Fragmentation of 12-Ethylidene and 12-Oxo Hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indoles and Contrasting Acid Stability of Structurally Related Indole Derivative **12**



(2) (a) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7568–7569. (b) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894–4906.

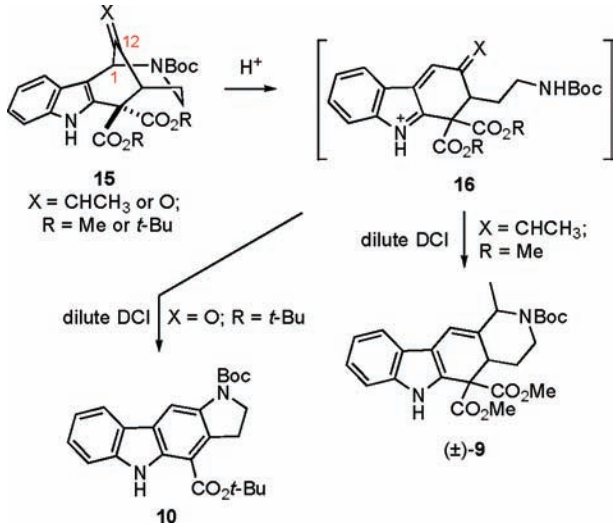
(3) For representative examples of syntheses of the hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole ring system, see: (a) Jackson, A.; Joule, J. A. *Chem. Commun.* **1967**, 459–460. Full paper: Jackson, A.; Wilson, N. D. V.; Gaskell, A. J.; Joule, J. A. *J. Chem. Soc. C* **1969**, *19*, 2738–2747. (b) Büchi, G.; Gould, S. J.; Näf, F. *J. Am. Chem. Soc.* **1971**, *93*, 2492–2501. (c) Grierson, D. S.; Harris, M.; Husson, H.-P. *Tetrahedron* **1983**, *39*, 3683–3694. (d) Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70–78. (e) Gràcia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939–3951. (f) Micouin, L.; Diez, A.; Castells, J.; López, D.; Rubiralta, M.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 1693–1696. (g) Blechert, S.; Knier, R.; Schroers, H.; Wirth, T. *Synthesis* **1995**, 592–604. (h) Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1997**, 765–766. (i) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158–3175. (j) Ergün, Y.; Patir, S.; Okay, G. *J. Heterocycl. Chem.* **2002**, *39*, 315–317. (k) Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534–3538. (l) Ishikura, M.; Takahashi, N.; Takahashi, H.; Yanada, K. *Heterocycles* **2005**, *66*, 45–50. (m) Uludag, N.; Hökelek, T.; Patir, S. *J. Heterocycl. Chem.* **2006**, *43*, 585–591. (n) Bennasar, M.-L.; Roca, T.; García-Díaz, D. *J. Org. Chem.* **2008**, *73*, 9033–9039.

(4) Ketones **7a** and **7b** are available in racemic form in four steps from dimethyl or di-*tert*-butyl malonate in 24% and 33% overall yield, respectively.[2]

(5) For review of this group of alkaloids, see: (a) Lounasmaa, M.; Somersalo, P. The Condylocarpine Group of Indole Alkaloids. In *Progress in the Chemistry of Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer-Verlag/Wien: New York, 1986; Vol. 50, pp 27−56. For the recent isolation of isocondylocarpine, see: (b) Wu, Y.; Kitajima, M.; Kogure, N.; Wang, Y.; Zhang, R.; Takayama, H. *J. Nat. Med.* **2009**, *63*, 283–289.

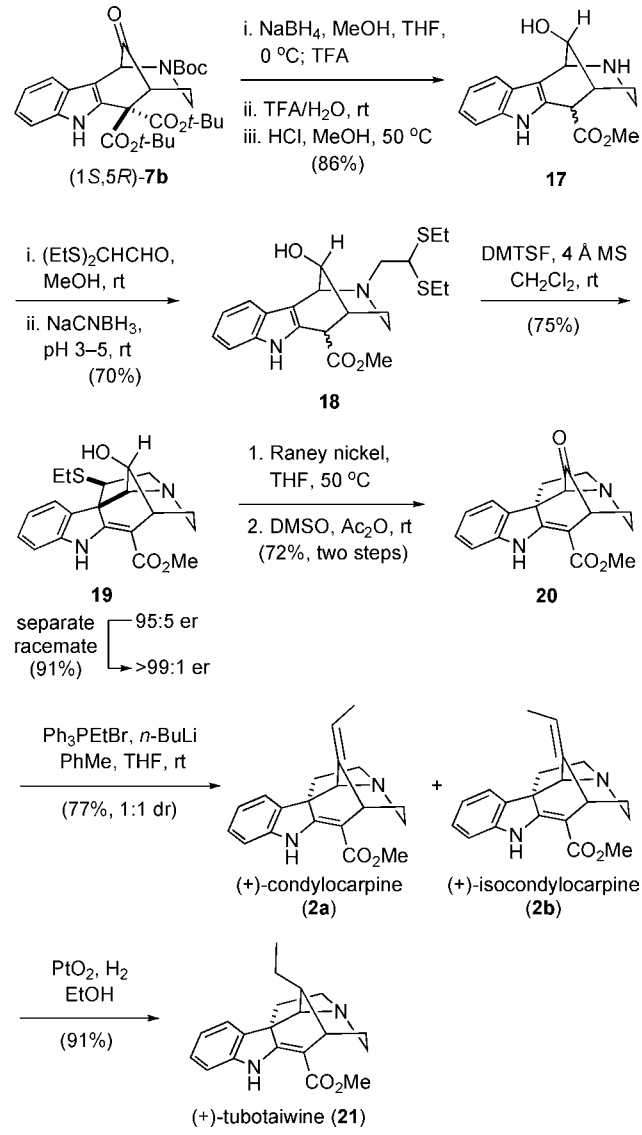
(6) For total syntheses of (±)-condylocarpine, see: (a) Harley-Mason, J. *Pure Appl. Chem.* **1975**, *41*, 167–174. (b) Kuehne, M. E.; Brook, C. S.; Frasier, D. A.; Xu, F. *J. Org. Chem.* **1995**, *60*, 1864–1867. For studies on the synthesis of condylocarpine, see: (c) Lounasmaa, M.; Somersalo, P. *Tetrahedron* **1986**, *42*, 1501–1509. For total syntheses of (±)-tubotaiwine, see: (d) Dadson, B. A.; Harley-Mason, J. *J. Chem. Soc. D* **1969**, 665b. (e) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696–2700. (f) Gracia, J.; Bonjoch, J.; Casamitjana, N.; Amat, M.; Bosch, J. *J. Chem. Soc., Chem. Commun.* **1991**, 614–615. (g) Gracia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.* **1994**, *59*, 3939–3951. (h) Amat, M.; Hadida, S.; Pshenichnyi, G.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3158–3175. For studies on the synthesis of tubotaiwine, see: (i) Legseir, B.; Henin, J.; Massiot, G.; Vercauteren, J. *Tetrahedron Lett.* **1987**, *28*, 3573–3576. (j) Lavilla, R.; Gotsens, T.; Rodriguez, S.; Bosch, J. *Tetrahedron* **1992**, *48*, 6445–6454.

Scheme 2. Fragmentation of Ethylidene- and Keto-Bridged Hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole Intermediates



Gramine-type fragmentations of hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indoles to carbazoles and pyridinocarbazoles are well-known.[9] However, not previously recognized is the notable accelerating effect of a keto or alkylidene substituent at C12 on this fragmentation. The formation of products (±)-**9** and **10** from respectively ethylidene and keto precursors (±)-**8** and (±)-**7b** suggests that the initial step is cleavage of the C1−N bond to generate delocalized iminium ion intermediate **16** (Scheme 2). In the ethylidene series, cyclization of the pendant side chain of **16** delivers (±)-**9** as a single stereoisomer.[10] In the oxo series, dehydrative cyclization of the *β*-(*tert*-butoxycarbonylamino)ethyl side chain of **16** and loss of isobutylene and CO_2 leads to dihydropyrrolocarbazole ester **10**.[11] The facile fragmentations in the keto and ethylidene series to generate intermediate **16** undoubtedly reflect activation of the C1−NBoc bond as a result of its excellent overlap with the exocyclic *π*-bond.[12]

Scheme 3. Total Syntheses of (+)-Condylocarpine, (+)-Isocondylocarpine, and (+)-Tubotaiwine



With a better understanding of the potential gramine-type fragmentation of hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole-12-ones and their alkylidene derivatives, a successful synthetic sequence was developed in which the pyrrolidine ring of the condylocarpine skeleton was constructed using intermediates in which C12 is an sp^3 carbon (Scheme 3). The syntheses began with stereoselective reduction of (1*S*,5*R*)-ketone **7b** (er = 95:5)[2] with sodium borohydride.[13] After quenching the reduction with TFA, the reaction mixture

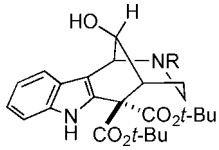
(7) Precursor (±)-**7b** was recovered in 25% yield.

(8) In our earlier total synthesis of actinophyllic acid, products (±)-**13** and (±)-**14** were not purified, but directly employed in aza-Cope-Mannich transformations.[2] ^{1}H NMR analysis of these crude intermediates showed no significant impurities, which we indicate in Scheme 1 as a crude yield of >90%.

(9) To our knowledge, the first unambiguous example of such fragmentation promoted by acid was described by Husson: Besselièvre, R.; Husson, H.-P. *Tetrahedron* **1983**, *37* (Supplement 1), 241–246.

(10) The stereoisomer having a cis relationship of the angular hydrogen and the methyl substituent would be both the expected kinetic product of cyclization of (*E*)-ethylidene intermediate **16** and the thermodynamic product of reversible gramine-type fragmentation of product (±)-**9**; an axial orientation of the Me substituent minimizes destabilizing $A^{1,3}$ interactions with the Boc substituent.

(11) (a) Gramine-type cleavage is likely the first step in the keto series also, because exposure of **i** to 0.15 M DCl in $CDCl_3$ at room temperature for 2 h yielded a mixture of **i** (48%) and **ii** (36%). (b) In neat TFA, decarboxylative aromatization of **16** (X = O, R = *t*-Bu) apparently occurs rapidly leading to the eventual formation of carbazole acid **11**.



i R = Boc
ii R = H

(12) For a concise discussion of the effect of adjacent C−C and C−O *π*-bonds on nucleophilic substitution reactions, see: Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science: Sausalito, CA, 2006; pp 653−655.

(13) The *β*-*tert*-butoxycarbonyl group sterically shields the *Si* face of the ketone carbonyl group,[2] resulting in hydride addition from the *Re* face.

was concentrated and the crude residue was dissolved in a 4:1 mixture of TFA and water to promote cleavage of the Boc and *tert*-butyl esters, and decarboxylation to yield the corresponding amino acid. Removal of TFA and water in vacuo, followed by dissolution of the residue in a 0.5 M solution of hydrochloric acid in methanol and heating at 50 °C delivered amino ester **17**, a 2:1 mixture of ester epimers, in 86% overall yield from **7b**. Reductive alkylation of this crude amine with 2,2-bis(ethylthio)acetaldehyde[14] furnished tertiary amine **18** in 70% yield. Exposure of **18** to a suspension of dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[15] and 4 Å molecular sieves in dichloromethane at room temperature delivered pentacyclic alcohol **19** as a single stereoisomer in 75% yield.[16−18] It was essential that this ring construction be carried out after dealkoxycarbonylation, as earlier extensive attempts to cyclize malonate precursors under various conditions were unsuccessful. Enantiomerically pure **19** (er >99:1) was obtained in 91% yield after separation of the highly crystalline racemate.

In three additional steps, pentacyclic intermediate **19** was converted to (+)-condylocarpine (**2a**) and (+)-isocondylocarpine (**2b**). The thioether group of **19** was cleaved with Raney nickel in THF at 50 °C to deliver the desulfurized product in 75% yield.[19] After extensively screening conditions for oxidation of the secondary alcohol of this product, Albright-Goldman oxidation[20] was identified as optimal for accomplishing this transformation, giving **20** in 72% yield for the 2 steps.[21] Reaction of pentacyclic ketone **20** with ethyltriphenylphosphonium ylide in a mixture of THF and toluene at room temperature delivered a 1:1 mixture of enantiopure (+)-condylocarpine (**2a**) and (+)-isocondylocarpine (**2b**) in 77% combined yield. Pure samples of these interconvertible stereoisomers[22] were obtained by preparative HPLC: (+)-condylocarpine (**2a**), $[\alpha]_D$ +854 (*c* 0.39, $CHCl_3$), and (+)-isocondylocarpine (**2b**), $[\alpha]_D$ +798 (*c* 0.15, $CHCl_3$). Catalytic hydrogenation[23] of the initially produced mixture of **2a** and **2b** delivered (+)-tubotaiwine (**21**), $[\alpha]_D$ +584 (*c* 0.91, $CHCl_3$), in 91% yield.[24−26]

In summary, the first enantioselective total syntheses of indole alkaloids of the condylocarpine type have been accomplished. One important outcome of this study was the discovery that hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indoles having a carbonyl or alkylidene group as the one carbon bridge undergo facile gramine-type fragmentation in the presence of even dilute acids. This lability necessitated that the C12 carbonyl group of precursor **7b** be masked by reduction during formation of the pyrrolidine ring. As a result, a synthetic sequence proceeding via five isolated intermediates was required for the elaboration of (1*S*,5*R*)-hexahydro-1,5-methano-1*H*-azocino[4,3-*b*]indole **7b** to enantiopure (+)-condylocarpine (**2a**) and (+)-isocondylocarpine (**2b**).

Acknowledgment. This research was supported by the NIH Neurological Disorders & Stroke Institute (NS-12389) and the National Institute of General Medical Sciences (GM-098601). Fellowship assistance for C.L.M. (UC Irvine Chancellor's Fellowship, Bristol-Myers Squibb Graduate Fellowship, and ACS Division of Organic Chemistry Fellowship sponsored by Amgen) and R.O. (Feodor Lynen Fellowship of the Alexander von Humboldt Foundation) is gratefully acknowledged. We thank Dr. Jason M. Rohde, Ironwood Pharmaceuticals, Inc., 301 Binney Street, Cambridge, MA 02142, for preliminary studies, and Dr. Joe Ziller, School of Physical Sciences, UC Irvine, for X-ray analyses. NMR, mass spectra, and X-ray analyses were obtained at UC Irvine using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation programs.

Supporting Information Available: Experimental details and copies of ^1H and ^{13}C NMR spectra of new compounds; CIF files for compounds (±)-**20** and (±)-**iii**. This material is available free of charge via the Internet at http://pubs.acs.org.

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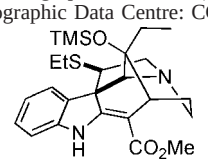
(14) Bates, G. S.; Ramaswamy, S. *Can. J. Chem.* **1983**, *61*, 2466–2475.

(15) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529–6530.

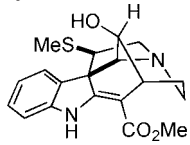
(16) The relative configuration of **19**, and that of the secondary alcohol in precursors **17** and **18**, was secured on the basis of X-ray crystallographic analysis of silyl ether derivative (±)-**iii**, which was prepared in an analogous fashion to **19**. Crystallographic data for (±)-**iii** were deposited at the Cambridge Crystallographic Data Centre: CCDC 799190.



(±)-**iii**

(17) The use of 5-exo thionium ion cyclizations to form this ring of indole alkaloids is a well-established tactic in indole alkaloid synthesis, see: (a) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750–4757. (b) Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.* **1990**, *55*, 6299–1312. (c) Amat, M.; Bosch, J. *J. Org. Chem.* **1992**, *57*, 5792–5796.

(18) Methyl thioether (±)-**iv** was isolated with **19** as an inseparable contaminant (diagnostic ^1H NMR singlet corresponding to the methyl thioether group at 1.81 ppm and LRMS analysis). This inconsequential side product likely arose by hydrolysis of DMTSF by adventitious water to give methanethiol, which underwent thiol exchange by way of the reactive thionium ion prior to cyclization.



(±)-**iv**

(19) It was advantageous to use THF as the solvent instead of methanol or ethanol, as byproducts arising from reduction of the vinylogous carbamate were suppressed in THF.

(20) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214–4216.

(21) Crystallographic data for a racemic sample of intermediate **20** were deposited at the Cambridge Crystallographic Data Centre: CCDC 799189.

(22) Condylocarpine (**2a**) and isocondylocarpine (**2b**) equilibrate to a 2:1 mixture of **2a**:**2b** when heated for 4 h at reflux in toluene or when exposed for 24 h at room temperature to acetic acid in chloroform.[6b]

(23) Schumann, D.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 1996–2003.

(24) A range of optical rotations at the sodium D line has been reported for natural samples of condylocarpine (+501 to +901[25] in $CHCl_3$) and tubotaiwine (+417 to +628[26] in $CHCl_3$); citation to the highest reported rotation is provided here, and a complete summary is provided in the Supporting Information. Natural isocondylocarpine is reported to show $[\alpha]_D$ +537 (*c* 0.1, $CHCl_3$).[5b]

(25) Stauffacher, D. *Helv. Chim. Acta* **1961**, *44*, 2006–2015.

(26) Pinar, M.; Renner, U.; Hesse, M.; Schmid, H. *Helv. Chim. Acta* **1972**, *55*, 2972–2974.