JOC*Article*

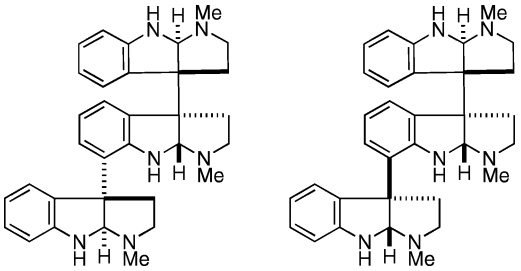
Synthesis of All Low-Energy Stereoisomers of the Tris(pyrrolidinoindoline) Alkaloid Hodgkinsine and Preliminary Assessment of Their Antinociceptive Activity

Jeremy J. Kodanko,[†] Sheldon Hiebert,[†] Emily A. Peterson,[†] Leonard Sung,[†] Larry E. Overman,*[,†] Viviane de Moura Linck,[‡] Greice Catrine Goerck,[‡] Tânia Alves Amador,[§] Mirna Bainy Leal,[‡] and Elaine Elisabetsky*[,‡]

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025, Laboratório de Etnofarmacologia, ICBS, Universidade Federal do Rio Grande do Sul, Rua Sarmento Leite 500/202, 90050-170, Porto Alegre, Brazil, and Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul, Av. Ipiranga 2752, 90610-000, Porto Alegre, Brazil

leoverma@uci.edu; elaine.elisabetsky@gmail.com

Received June 24, 2007



The previously unknown stereoisomers **3**, **4**, *ent*-**1**, and *ent*-**4** of the tris(pyrrolidinoindoline) alkaloids hodgkinsine (**1**) and hodgkinsine B (**2**) were prepared by stereocontrolled total synthesis. In each synthesis, a catalyst-controlled intramolecular Heck reaction was the key step in appending a third *cis*-pyrrolidinoindoline ring to a hexacyclic chimonanthine precursor. Results of the preliminary evaluation of these hodgkinsine stereoisomers in the tail flick and capsaicin pain models are reported.

Introduction

Despite the intensive research effort in the area of analgesics over the past decades, the therapeutic outcome for a number painful conditions, like those associated with chronic and neuropathic pain, still remain unsatisfactory.[1] Consequently, new approaches in pain treatment are needed.[1,2] The *N*-methyl-D-aspartate (NMDA) glutamate receptor is an excitatory amino acid receptor that has been implicated in the modulation of prolonged pain states in animal models.[3,4] NMDA antagonists, such as ketamine and dextromethorphan, have been shown to be useful in the reduction of acute postoperative pain and/or analgesic consumption when added to opioids and nonsteroidal anti-inflammatory drugs in the perioperative period.[5,6] The combination of NMDA antagonists with opioids has been proposed as an alternative in the treatment of neuropathic pain, in part for the analgesic properties of NMDA antagonists, but especially because NMDA antagonists decrease opioid tolerance.[7,8] It is not surprising that there is much interest in further understanding the cross talk between these systems, as a potential direction in the development of newer analgesics.

[†] University of California.

[‡] Laboratório de Etnofarmacologia, Universidade Federal do Rio Grande do Sul.

[§] Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul.

(1) Parsons, C. G. *Eur. J. Pharmacol.* **2001**, *429*, 71−78.

(2) LoGrasso, P.; McKelvy, J. *Curr. Opin. Chem. Biol.* **2003**, *7*, 452−456

(3) Chizh, B. A.; Headley, P. M.; Tzschentke, T. M. *Trends Pharmacol. Sci.* **2001**, *22*, 636−642.

(4) Wilson, A. W.; Medhurst, S. J.; Dixon, C. I.; Bontoft, N. C.; Winyard, L. A.; Brackenborough, K. T.; De Alba, J.; Clarke, C. J.; Gunthorpe, M. J.; Hicks, G. A.; Bountra, C.; McQueen, D. S.; Chessell, I. P. *Eur. J. Pain* **2006**, *10*, 537−549.

(5) Bell, R. F.; Dahl, J. B.; Moore, R. A.; Kalso, E. *Acta Anaesthesiol. Scand.* **2005**, *49*, 1405−1428.

(6) Duedahl, T. H.; Roemsing, J.; Moeiniche, S.; Dahl, J. B. *Acta Anaesthesiol. Scand.* **2006**, *50*, 1−13.

(7) Gilron, I.; Watson, C. P. N.; Cahill Catherine, M.; Moulin Dwight, E. *Can. Med. Assn. J.* **2006**, *175*, 265−275.

(8) Kalso, E. *Eur. J. Pain* **2005**, *9*, 131−135.

10.1021/jo7013643 CCC: $37.00
Published on Web 09/21/2007

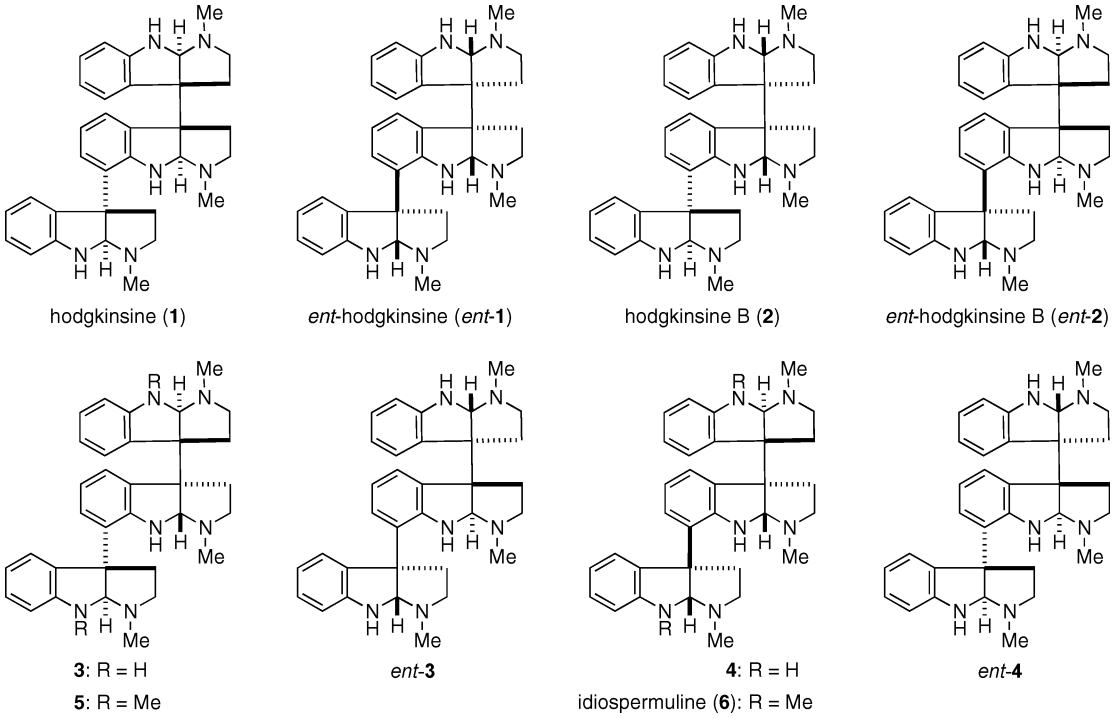


FIGURE 1. Structure of hodgkinsine, seven stereoisomers, and methyl derivatives **5** and **6**.

The discovery that alkaloids isolated from *Psychotria colorata* Muell Arg (RUBIACEAE), a medicinal species traditionally used as an analgesic in the Brazilian Amazon,[9] have a distinctive analgesic profile generated substantial interest.[10−12] The mechanisms of action by which these alkaloids exert antinociceptive action were investigated by in vivo and in vitro techniques, particularly regarding their involvement with opioid and glutamatergic pathways.[10,13−15] We reported that the natural alkaloid hodgkinsine (**1**) acts dose-dependently as a potent analgesic in mice.[13] Hodgkinsine's effects in thermal models of nociception were naloxone reversible, suggesting that activation of opioid receptors is involved in its mode of action.[13] Indeed, binding data revealed that hodgkinsine binds specifically to μ opioid receptors.[15] Hodgkinsine also showed a potent dose-dependent analgesic effect in capsaicin-induced pain,[13] suggesting the participation of NMDA receptors in its mode of action.[16]

Because hodgkinsine has such a unique analgesic mechanism, it is a potential scaffold for developing new analgesics with better profiles than available agents. Hodgkinsine, which was recently prepared for the first time by total synthesis,[17] is a chiral molecule having six centers of chirality. The chemistry developed to prepare hodgkinsine, as well as in cognate synthetic studies,[18,19] would allow the selective chemical synthesis of a family of hodgkinsine stereoisomers. The aim of the study reported herein was to prepare the hodgkinsine stereoisomers **1**−**4** and *ent*-**1**−*ent*-**4** depicted in Figure 1 and analyze their antinociceptive profile in mice. For the first time, this study would explore what aspects of the relative and absolute configuration of hodgkinsine are important for its analgesic activity.

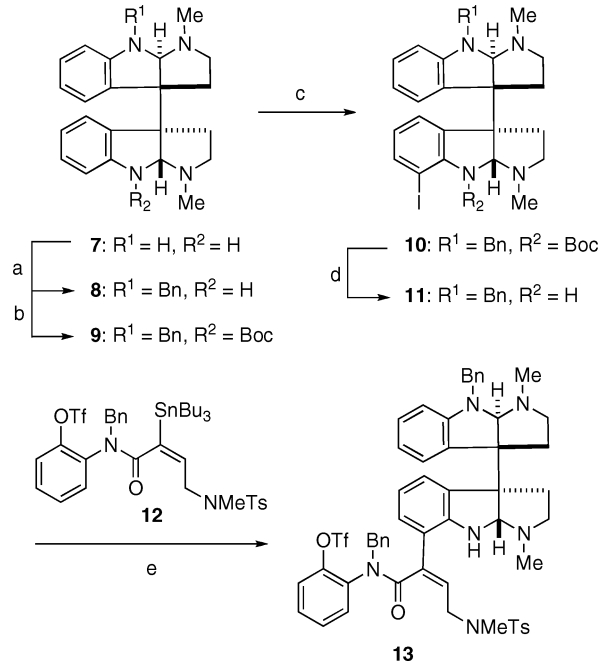
Results and Discussion

Synthesis. There are seven low-energy stereoisomers of hodgkinsine (**1**), **2**−**4**, and *ent*-**1**−*ent*-**4**, wherein the tricyclic 1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (pyrrolidinoindoline) rings are cis-fused (Figure 1). This library of eight stereoisomers was obtained as follows. The synthesis of hodgkinsine (**1**) and hodgkinsine B (**2**) has been described.[17] In these syntheses, a late-stage intramolecular Heck reaction employing a palladium catalyst derived from (*R*)-tol-BINAP was utilized to resolve a racemic precursor, to provide **1** and **2** in 79% ee and 83% ee, respectively. In the present study, enantiomers, *ent*-**1** and *ent*-**2**, were prepared in identical fashion and enantiopurity using the catalyst derived from (*S*)-tol-BINAP.

The synthesis of hodgkinsine stereoisomers **3** and **4** commenced with synthetic (−)-chimonanthine (**7**) (Scheme 1).[20−22]

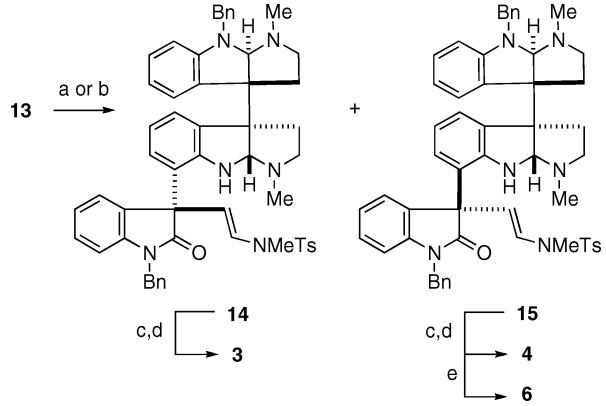
(9) Elisabetsky, E.; Castilhos, Z.C. *Int. Crude Drug Res.* **1990**, *28*, 309−320.
(10) Amador, T. A.; Elisabetsky, E.; Souza, D. O. *Neurochem. Res.* **1996**, *21*, 97−102.
(11) Elisabetsky, E.; Amador, T. A.; Albuquerque, R. R.; Nunes, D. S.; Carvalho, A. d. C. T. *J. Ethnopharmacol.* **1995**, *48*, 77−83.
(12) Verotta, L.; Peterlongo, F.; Elisabetsky, E.; Amador, T. A.; Nunes, D. S. *J. Chromatogr. A* **1999**, *841*, 165−176.
(13) Amador, T. A.; Verotta, L.; Nunes, D. S.; Elisabetsky, E. *Planta Med.* **2000**, *66*, 770−772.
(14) Amador, T. A.; Verotta, L.; Nunes, D. S.; Elisabetsky, E. *Phytomedicine* **2001**, *8*, 202−6.
(15) Verotta, L.; Orsini, F.; Sbacchi, M.; Scheildler, M. A.; Amador, T. A.; Elisabetsky, E. *Bioorg. Med. Chem.* **2002**, *10*, 2133−2142.
(16) Sakurada, T.; Wako, K.; Sugiyama, A.; Sakurada, C.; Tan-No, K.; Kisara, K. *Pharmacol. Biochem. Ber.* **1998**, *59*, 339−345.
(17) Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2528−2531.
(18) (a) Overman, L. E.; Peterson, E. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2525−2528. (b) Overman, L. E.; Peterson, E. A. *Tetrahedron* **2003**, *59*, 6905−6919.
(19) For a review of synthetic work in this area from UC Irvine, see: Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488−5508.
(20) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213−215.
(21) Prepared from (*R*)-tartaric acid using the sequence reported in ref 20.[22]

SCHEME 1. Synthesis of Butenanilide Triflate 13



Reaction conditions: [a]BnBr, NaHMDS, THF, −78 °C (75%); [b]Boc_2O, NaHMDS, THF, −78 °C (97%); [c]1. *s*-BuLi, TMEDA, Et_2O, −78 °C, 2. 1,2-diiodoethane (93%); [d]TMSOTf, CH_2Cl_2 (95%); [e]$Pd_2(dba)_3$, P(2-furyl)$_3$, CuI, NMP (91%).

SCHEME 2. Synthesis of Tris(pyrrolidinoindolines) 3 and 4



Reaction conditions: [a](*S*)-tol-BINAP, $Pd(OAc)_2$, PMP, MeCN, 80 °C, (86%, ratio of **14**/**15** = 1:20); [b](*R*)-tol-BINAP, $Pd(OAc)_2$, PMP, MeCN, 80 °C, (90%, ratio of **14**/**15** = 8:1); [c]H_2 (80 psi), $Pd(OH)_2$/C, K_2CO_3, EtOH, 80 °C; [d]Na/NH_3, THF, NH_4Cl, −78 °C (31% for **3**, 28% for **4**); [e]NaHMDS, MeI, THF, −78 °C (95%).

Because monoiodination of the di-*tert*-butoxycarbonyl derivative of **7** ($R^1 = R^2$ = Boc) occurred in poor yield and with low reproducibility,[22] the required differentiation of the indoline nitrogens of (−)-chimonanthine was accomplished by selective monobenzylation. This conversion was best accomplished by reaction of (−)-chimonanthine with 1.5 equiv of NaHMDS and 1.05 equiv of BnBr at −78 °C in THF to give largely monobenzylated product **8** (isolated in 75% yield). Treatment of benzyl derivative **8** with NaHMDS and Boc_2O at −78 °C delivered Boc derivative **9** in 97% yield. Selective introduction of an iodide substituent at the aromatic 7-position of the Boc-protected *cis*-pyrrolidinoindoline fragment was accomplished by reaction of an ether−TMEDA solution of carbamate **9** at −78 °C with excess *s*-BuLi, followed by quenching with 1,2-diodoethane to furnish iodide **10** in 93% yield. Removal of the *tert*-butoxycarbonyl group of **10** by reaction with TMSOTf, followed by chemoselective Stille cross-coupling of product **11** with stannane **12**[23] using stoichiometric CuI and catalytic amounts of $Pd_2(dba)_3$ and P(2-furyl)$_3$ provided the butenanilide triflate **13** in 86% yield for the two steps.

The preparation of hodgkinsine congeners **3** and **4** was completed using the sequence of reactions shown in Scheme 2. In the pivotal step, asymmetric intramolecular Heck cyclization of alkenyl aryl triflate **13**, using the catalyst generated from 10 mol % of $Pd(OAc)_2$ and 20 mol % of (*S*)-tol-BINAP at 80 °C, provided oxindole products **14** and **15** in a ratio of 1:20 and 90% yield. Cyclization of triflate **13** using the catalyst generated from (*R*)-tol-BINAP gave **14** and **15** in an 8:1 ratio and 86% yield. These results show that the catalyst derived from (*S*)-tol-BINAP was matched with the chirality of 3a,3a′-bispyrrolidindoline triflate **13**, whereas the catalyst formed from (*R*)-tol-BINAP was mismatched. Reduction of the enesulfonamide fragment of Heck products **14** and **15** was accomplished using 80 psi H_2, $Pd(OH)_2$/C, K_2CO_3, and EtOH at 80 °C. The inclusion of K_2CO_3 prevented acid-catalyzed decomposition of the acyclic enesulfonamide functionality, leading to higher reproducibility for this transformation. Further reduction of these dihydro products with Na/NH_3 using an NH_4Cl quench furnished hodgkinsine stereoisomers **3** and **4** in 31% and 28% yield, respectively. The relative configuration of tris(pyrrolidinoindoline) product **4** was confirmed by its conversion to (−)-idiospermuline (**6**)[24] upon reaction with MeI and NaHMDS. Stereoisomers *ent*-**3** and *ent*-**4** were prepared by an identical sequence starting from synthetic (+)-chimonanthine (*ent*-**7**).[20] Finally, tris(pyrrolidinoindolines) **5** and **6** were prepared using a previously disclosed sequence.[18]

Antinociceptive Activity. In agreement with previous results with hodgkinsine isolated from *Psychotria colorata*,[12] synthetic hodgkinsine **(1)** displayed significant analgesic activity in both the tail flick and capsaicin pain models, with analgesia in tail flick being reversed by pre-administration with the opioid antagonist naloxone. At 10 mg/kg, all analogues except **4**, **5**, *ent*-**4**, and *ent*-**3 (**which was not tested) showed activity in the tail flick pain model. E*nt*-**2** and **3 (**at 5 mg/kg), and *ent*-hodgkinsine (at 10 mg/kg), showed activity roughly comparable to that of hodgkinsine (**1**). In contrast to hodgkinsine (**1**), the analgesic effect in the tail-flick model of analogues *ent*-**2**, **3** and **6** was not reversed by naloxone, indicating that the involvement of opioid receptors in the analgesic activity of these analogues is unlikely.[25] In the capsaicin pain model, various analogs (except *ent*-**1**, *ent*-**3**, and *ent*-**4**) showed activity over the dosing range 0.5−5.0 mg/kg. Only analogue **5** at 2.5 mg/kg was more active than hodgkinsine.

Conclusion

The methods developed recently at UC Irvine for asymmetric synthesis of 3,3′-bispyrrolidinoindolines and for appending *cis*-

(22) Kodanko, J. J., Ph. D. Dissertation, University of California, Irvine, 2003.

(23) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008−9009.

(24) Duke, R. K.; Allan, R. D.; Johnston, G. A. R.; Mewett, K. N.; Mitrovic, A. D.; Duke, C. C.; Hambley, T. W. *J. Nat. Prod.* **1995**, *58*, 1200−1208.

(25) Naloxone reversibility was not studied for *ent*-**1**.

pyrrolidinoindoline fragments of either absolute configuration selectively at the 7 or 7′ carbons of these hexacyclic structures[19] allow any stereoisomer of tris(pyrrolidinoindolines) to be prepared by stereocontrolled total synthesis. This study establishes that the analgesic activity seen for the natural product hodgkinsine (**1**)[15] is not limited to this specific stereoisomer, but is seen to some extent in nearly all tris(pyrrolidinoindolines) of the hodgkinsine structural type. Nevertheless, additional pharmacological studies with enantiomerically pure samples of the tris(pyrrolidinoindolines) depicted in Figure 1 will be required to relate three-dimensional structure to activity in various pain models.

Experimental Section[26]

Benzyl Derivative 8. Benzyl bromide (450 μL, 3.80 mmol) was added to a solution of (−)-chimonanthine (**7**)[21,22] (1.25 g, 3.61 mmol) in THF (50 mL) at −78 °C under nitrogen. A THF solution of NaHMDS (5.4 mL, 1.0 M, 5.40 mmol) was then added slowly (over 5 min) down the side of the flask to prevent excessive warming of the reaction mixture. The reaction was allowed to stir at −78 °C for 5 min, and the cold bath was removed to allow the reaction to warm to room temperature. After 30 min, the reaction was quenched by careful addition of a solution of $NaHCO_3$ (20 mL, saturated aqueous) and EtOAc (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic phases were dried (Na_2SO_4) and concentrated, and the crude residue was purified by silica gel chromatography (90:10:0 to 90:10:1 CH_2Cl_2/MeOH/NH_4OH) to give **8** as a colorless foam (1.17 g, 75%): $[\alpha]^{27}_D$ −254, $[\alpha]^{27}_{577}$ −267, $[\alpha]^{27}_{546}$ −312, $[\alpha]^{27}_{435}$ −664 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 4H), 7.26 (m, 1H), 7.14 (d, J = 7.1 Hz, 1H), 7.06 (br s, 1H), 6.95 (t, J = 7.1 Hz, 2H), 6.60 (m, 2H), 6.47 (d, J = 7.8 Hz, 1H), 6.27 (d, J = 7.3 Hz, 1H), 4.55 (d, J = 16.2 Hz, 1H), 4.42 (d, J = 16.2 Hz, 1H), 4.31 (br s, 1H), 4.22 (br s, 1H), 4.02 (br s, 1H), 2.61−2.45 (m, 6H), 2.27 (s, 3H), 2.19 (s, 3H), 2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 150.6, 139.2, 133.4, 132.8, 128.3, 128.0, 127.8, 127.4, 126.8, 124.5, 123.9, 118.3, 117.1, 109.0, 106.5, 91.8, 85.3, 63.1, 62.8, 52.7, 52.5, 52.4, 39.1, 37.3, 35.5, 35.3; IR (film) 3392, 3031, 2933, 2863, 2792, 1602, 1488, 1353, 1250, 1158, 1027, 735 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{33}N_4$ $(M + H)^+$: 437.2705, found: 437.2709.

Boc Derivative 9. A solution of Boc_2O (3.2 mL, 3.2 mmol, 1.0 M in THF) was added to a solution of **8** (1.17 g, 2.68 mmol) and THF (50 mL) at −78 °C under nitrogen. A THF solution of NaHMDS (9.65 mL, 1.0 M, 9.65 mmol) was then added dropwise over 5 min, and the reaction was stirred at −78 °C for 30 min. The reaction was then opened to air and quenched by the addition of a solution of $NaHCO_3$ (5 mL, saturated aqueous) at −78 °C. The reaction mixture was warmed to room temperature, and additional $NaHCO_3$ (15 mL, saturated aqueous) and EtOAc (20 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the crude residue was purified by silica gel chromatography (95:5:0 to 95:5:1 CH_2Cl_2/MeOH/NH_4OH) to give **9** as a colorless foam (1.40 g, 97%): $[\alpha]^{27}_D$ −186, $[\alpha]^{27}_{577}$ −195, $[\alpha]^{27}_{546}$ −226, $[\alpha]^{27}_{435}$ −457 (*c* 2.10, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 323K) δ 7.38−7.26 (m, 5H), 7.23 (m, 1H), 7.05 (m, 2H), 6.95 (d, J = 7.4 Hz, 1H), 6.85 (t, J = 7.6 Hz, 2H), 6.48 (t, J = 7.3 Hz, 1H), 6.10 (d, J = 7.8 Hz, 1H), 5.27 (br s, 1H), 4.47 (br s, 1H), 4.45 (s, 2H), 2.66−2.59 (m, 3H), 2.52−2.32 (m, 3H), 2.47 (s, 3H), 2.29 (s, 3H), 2.09−1.98 (m, 2H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 323K) δ 152.1, 139.4, 132.2, 128.4, 128.3, 128.2, 128.0, 127.3, 126.8, 124.1, 123.3, 122.4, 117.3, 115.9, 106.8, 93.1, 85.9, 81.1, 63.0, 53.1, 53.0, 52.7, 39.3, 37.5, 35.5, 34.4, 28.5; IR (film) 2975, 2943, 2796, 1696, 1602, 1484, 1366, 1160, 745 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{41}N_4O_2$ $(M + H)^+$: 537.3229, found: 537.3220.

Iodide 10. A cyclohexane solution of *s*-BuLi (760 mL, 1.1 M, 0.84 mmol) was added dropwise to a solution of **9** (150 mg, 0.28 mmol), TMEDA (127 mL, 0.84 mmol), and Et_2O (3 mL) at −78 °C under nitrogen. After 45 min at −78 °C, a solution of diiodoethane (393 mg, 1.40 mmol) and Et_2O (2 mL) was added dropwise over 5 min. The reaction mixture was then warmed to 0 °C, maintained at this temperature for 20 min, and then allowed to warm to room temperature, whereupon it turned a dark violet color. The reaction was then quenched by addition of $Na_2S_2O_3$ (10 mL, saturated aqueous) and CH_2Cl_2 (10 mL), which caused the dark color to dissipate. The aqueous layer was then extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried ($MgSO_4$) and concentrated, and the crude residue was purified by silica gel chromatography (95:5 CH_2Cl_2/MeOH) to give **10** as a colorless foam (172 mg, 93%): $[\alpha]^{27}_D$ −198, $[\alpha]^{27}_{577}$ −207, $[\alpha]^{27}_{546}$ −237, $[\alpha]^{27}_{435}$ −250 (*c* 3.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 323K) δ 7.59 (d, J = 7.8 Hz, 1H), 7.38−7.28 (m, 4H), 7.26−7.21 (m, 1H), 7.08 (d, J = 7.0 Hz, 1H), 7.00−6.93 (m, 2H), 6.67 (t, J = 7.8 Hz, 1H), 6.58 (t, J = 7.0 Hz, 1H), 6.27 (d, J = 7.8 Hz, 1H), 5.35 (s, 1H), 4.61 (s, 1H), 4.55 (d, J = 16.3 Hz, 1H), 4.50 (d, J = 16.3 Hz, 1H), 2.66−2.54 (m, 3H), 2.52 (s, 3H), 2.40 (s, 3H), 2.23−2.09 (m, 3H), 1.93−1.88 (m, 1H), 1.70−1.64 (m, 1H), 1.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 323K) δ 152.6, 152.4, 146.8, 139.7, 139.1, 139.0, 131.9, 128.4, 127.4, 126.9, 125.5, 125.0, 124.3, 117.4, 107.0, 92.7, 88.5, 84.9, 81.8, 63.0, 62.3, 52.6, 52.2, 39.0, 36.3, 35.8, 35.7, 28.4; IR (film) 2973, 2939, 2796, 1702, 1602, 1490, 1453, 1351, 1158, 750 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{40}N_4O_2I$ $(M + H)^+$: 663.2196, found: 663.2206.

Iodide 11. Trimethylsilyl triflate (140 mL, 0.73 mmol) was added dropwise to a solution of **10** (160 mg, 0.24 mmol) and CH_2Cl_2 (3 mL) at room temperature. The reaction flask was left open to air so that adventitious H_2O would create a small amount of triflic acid. The reaction progress was monitored by TLC; upon completion after 3.5 h, the reaction was quenched with $NaHCO_3$ (5 mL, saturated aqueous). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic layers were dried (Na_2SO_4) and concentrated, and the crude residue was purified by silica gel chromatography (95:5:0 to 95:5:0.1 CH_2Cl_2/MeOH/NH_4OH) to give **11** as a colorless foam (129 mg, 95%): $[\alpha]^{27}_D$ −242, $[\alpha]^{27}_{577}$ −254, $[\alpha]^{27}_{546}$ −297, $[\alpha]^{27}_{435}$ −632 (1.65, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 7.29−7.24 (m, 2H), 7.11 (d, J = 7.3 Hz, 1H), 7.00−6.93 (m, 2H), 6.57 (t, J = 7.4 Hz, 1H), 6.33 (t, J = 7.6 Hz, 1H), 6.30 (d, J = 8.0 Hz, 1H), 4.53 (d, J = 16.0 Hz, 1H), 4.40 (d, J = 16.0 Hz, 1H), 4.33 (br s, 1H), 4.25 (s, 1H), 2.61−2.55 (m, 2H), 2.52−2.45 (m, 4H), 2.29 (s, 3H), 2.19 (s, 3H), 2.03−1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.33, 152.29, 139.2, 136.3, 133.5, 132.5, 128.5, 128.3, 127.7, 127.0, 124.4, 124.0, 119.7, 117.3, 106.7, 91.7, 84.0, 77.2, 74.6, 65.3, 63.2, 52.7, 52.4, 39.2, 36.9, 36.0, 35.4, 31.8; IR (film) 3409, 2933, 2863, 2792, 1600, 1490, 1465, 1453, 1353, 1158, 737 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{32}N_4I$ $(M + H)^+$: 563.1672, found: 563.1686.

Triflate 13. A solution of $Pd_2(dba)_3$ (85 mg, 0.080 mmol), P(2-furyl)$_3$ (77 mg, 0.32 mmol), and NMP (4 mL) was sparged with nitrogen for 1 h in a base-washed, sealable reaction vessel. At the same time, a solution of iodide **11** (450 mg, 0.80 mmol), stannane **12** (1.05 g, 1.21 mmol), and NMP (4 mL) was sparged with nitrogen for 1 h and then transferred to the catalyst solution via cannula. This mixture was subjected to three cycles of freeze−pump−thaw (−78 °C cooling bath, 0.5 mm) to completely degas the solution. CuI (156 mg, 0.80 mmol) was then added under nitrogen, and the reaction vessel was sealed. The reaction was stirred at room temperature for 48 h, at which point the reaction was opened to

(26) General experimental procedures can be found in the Supporting Information.

the air and partitioned between 5% aqueous NH_4OH (25 mL) and EtOAc (25 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with brine (2 × 10 mL), dried (Na_2SO_4), concentrated, and the crude residue was purified by silica gel chromatography (95:5:0 to 95:5:1 CH_2Cl_2/MeOH/NH_4OH) to give **13** as a colorless foam (740 mg, 91%): ^1H and ^{13}C NMR spectra of this compound are complicated because of the presence of rotamers; see Supporting Information for copies of the spectra. IR (film) 3421, 2933, 2875, 2794, 1673, 1422, 1218, 1162, 906, 727 cm^{-1}; HRMS (ESI) calcd for $C_{55}H_{56}F_3N_6O_6S_2$ $(M + H)^+$: 1017.3655, found: 1017.3660.

Oxindoles 14 and 15. In a sealable reaction vessel, alkenyl triflate **13** (275 mg, 0.27 mmol), $Pd(OAc)_2$ (6.0 mg, 0.027 mmol), (*S*)-tol-BINAP (36 mg, 0.054 mmol), and PMP (195 mL, 1.08 mmol) were dissolved in MeCN (4 mL) that had been sparged with nitrogen for 3 h. This solution was sparged for another 15 min with nitrogen until the color became dark red. The reaction was then sealed, and the tube was heated at 80 °C with stirring for 18 h. After allowing the reaction to cool to room temperature, it was quenched by the addition of 0.5 mL of aqueous NaCN solution. After stirring for 20 min, the reaction mixture was partitioned between $NaHCO_3$ (5 mL saturated aqueous) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (10 mL) and CH_2Cl_2 (3 × 5 mL), and the combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 95:5:0 to 95:5:1) to give a mixture of oxindole epimers **14** and **15** (the ratio of **14**/**15** was 1:20 according to ^1H NMR and HPLC analysis). The diastereomers were separated by HPLC on a Zorbax Extend C-18 column (5 mm, 150 × 21.2 mm, 16.0 mL/min, 4:1 acetonitrile/water containing 1% NH_4OH) to give **15** (189 mg, 81%, T_R = 15.6 min) and **14** (12 mg, 5%, T_R = 18.7 min).

A reaction was carried out in identical fashion using **13** (200 mg, 0.20 mmol), $Pd(OAc)_2$ (4.4 mg, 0.020 mmol), (*R*)-tol-BINAP (27 mg, 0.040 mmol), PMP (142 mL, 0.79 mmol), and MeCN (4 mL) to give a mixture of oxindole epimers **14** and **15** (the ratio of **14**/**15** was 7.6:1 according to ^1H NMR and HPLC analysis). These epimers were separated by HPLC on a Zorbax Extend C-18 column (5 mm, 150 × 21.2 mm, 16.0 mL/min, 4:1 acetonitrile/water containing 1% NH_4OH), to give oxindoles **14** (141 mg, 83%, T_R = 18.7 min) and **15** (12 mg, 7%, T_R = 15.8 min).

Data for oxindole epimer **14**: $[\alpha]^{27}_D$ −143, $[\alpha]^{27}_{577}$ −151, $[\alpha]^{27}_{546}$ −176 (*c* 1.02, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, 323K) δ 7.51 (d, *J* = 8.3 Hz, 2H), 7.37−7.26 (m, 8H), 7.25−7.16 (m, 5H), 7.12 (d, *J* = 7.0 Hz, 1H), 7.08−7.02 (m, 2H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 14.3 Hz, 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 6.54 (t, *J* = 7.5 Hz, 1H), 6.52 (t, *J* = 7.8 Hz, 1H), 6.16 (d, *J* = 7.8 Hz, 1H), 5.32 (t, *J* = 14.3 Hz, 1H), 4.89 (d, *J* = 15.6 Hz, 1H), 4.84 (d, *J* = 15.6 Hz, 1H), 4.74 (s, 1H), 4.47 (d, *J* = 17.5 Hz, 1H), 4.43 (d, *J* = 17.7 Hz, 1H), 4.40 (br s, 1H), 4.11 (br s, 1H), 2.88 (s, 3H), 2.61−2.55 (m, 2H), 2.46−2.40 (m, 1H), 2.38 (s, 3H), 2.38−2.32 (m, 2H), 2.30−2.22 (m, 1H), 2.22 (s, 3H), 1.98−1.89 (m, 2H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, 323K) δ 177.4, 152.23, 149.7, 143.7, 142.2, 139.6, 135.8, 135.0, 134.7, 132.9, 130.81, 130.79, 129.7, 128.8, 128.4, 128.3, 128.0, 127.7, 127.5, 127.2, 127.0, 126.9, 126.6, 125.7, 124.4, 124.0, 122.9, 119.8, 117.9, 117.2, 110.3, 109.5, 106.8, 92.8, 85.2, 62.82, 62.79, 56.8, 53.2, 52.6, 52.5, 44.1, 38.9, 36.2, 35.7, 35.6, 32.4, 21.4; IR (film) 3064, 2929, 2856, 2794, 1708, 1600, 1488, 1453, 1355, 1160, 907, 727 cm^{-1}; HRMS (ESI) calcd for $C_{54}H_{55}N_6O_3S$ $(M + H)^+$: 867.4056, found: 867.4048.

Data for oxindole epimer **15**: $[\alpha]^{27}_D$ −66, $[\alpha]^{27}_{577}$ −69, $[\alpha]^{27}_{546}$ −81 (*c* 0.94, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, 323K) δ 7.50 (d, *J* = 8.2 Hz, 2H), 7.35−7.27 (m, 4H), 7.26−7.15 (m, 9H), 7.08 (t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 7.0 Hz, 1H), 6.86 (br s, 1H), 6.81 (br s, 1H), 6.77−6.74 (m, 3H), 6.55 (d, *J* = 7.3 Hz, 1H), 6.43−6.34 (m, 2H), 6.09 (d, *J* = 7.6 Hz, 1H), 5.53 (d, *J* = 14.4 Hz, 1H), 5.17 (d, *J* = 3.3 Hz, 1H), 4.94 (d, *J* = 15.7 Hz, 1H), 4.85 (d, *J* = 15.7 Hz, 1H), 4.67−4.52 (br m, 2H), 4.47 (d, *J* = 16.6 Hz, 1H), 4.42 (d, *J* = 16.5 Hz, 1H), 2.89 (s, 3H), 2.62−2.57 (m, 3H), 2.50−2.42 (m, 2H), 2.36 (s, 3H), 2.34−2.30 (m, 1H), 2.24 (s, 3H), 2.16 (s, 3H), 1.98−1.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 323K) δ 177.9, 152.4, 150.6, 143.7, 142.4, 139.6, 135.8, 135.7, 134.8, 133.4, 131.2, 130.7, 129.7, 128.8, 128.5, 128.3, 127.6, 127.5, 127.2, 127.1, 127.0, 126.6, 126.4, 126.0, 123.7, 123.0, 122.7, 119.8, 118.2, 117.5, 109.9, 109.6, 106.6, 92.9, 84.1, 63.3, 56.9, 53.8, 52.1, 51.7, 43.9, 38.5, 35.8, 35.6, 34.2, 32.3, 21.4; IR (film) 3371, 2925, 2856, 2794, 1700, 1648, 1602, 1490, 1353, 1160, 906, 727 cm^{-1}; HRMS (ESI) calcd for $C_{54}H_{55}N_6O_3S$ $(M + H)^+$: 867.4056, found: 867.4073.

Tris(pyrrolidinoindoline) 3. A mixture of **14** (60 mg, 0.069 mmol), $Pd(OH)_2$ (48 mg, 0.069 mmol, Degussa type, 20 wt %), K_2CO_3 (10 mg, 0.069 mmol), and EtOH (3 mL) was placed in a 16 × 125 mm test tube. The test tube was immersed in EtOH (50 mL) within a pressure reactor (Parr bottle 500 mL) and heated to 80 °C under a hydrogen atmosphere (80 psi). The reaction was stirred at 80 °C for 4 h and then removed from the Parr bottle and allowed to cool to room temperature. The suspension was filtered through a 0.45 mm nylon filter, and the filter cake was washed with EtOH. The organic layers were combined and evaporated, and the crude residue was dried (vacuum pump for 1 h). This crude product was dissolved in THF (3 mL) and added dropwise to a dark blue solution of Na (159 mg, 6.90 mmol) and NH_3 (16 mL) at −78 °C. The reaction was stirred at −78 °C for an additional 20 min, NH_4Cl (200 mg) was added, and the reaction was stirred until the blue color had dissipated. The reaction was then allowed to warm to room temperature while the NH_3 evaporated. The residue was partitioned between water and $CHCl_3$ (saturated with NH_3). The aqueous layer was extracted with $CHCl_3$ (saturated with NH_3) (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4) and evaporated. The crude residue was purified by silica gel chromatography (7:3:0 to 7:3:1 benzene/EtOAc/Et_2NH) to give a yellow solid, which was further purified by preparative HPLC on a Zorbax Extend C-18 column (5 mm, 150 × 21.2 mm, 16.0 mL/min, 70:30:1 MeOH/water/Et_3N) to give **3** as a colorless solid (14 mg, 31%, T_R = 9.9 min): $[\alpha]^{27}_D$ −272, $[\alpha]^{27}_{577}$ −298, $[\alpha]^{27}_{546}$ −342 (*c* 0.62, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 6.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 2H), 6.99 (br s, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.65 (br s, 1H), 6.61 (d, *J* = 7.8 Hz, 2H), 6.52 (br m, 2H), 4.95 (s, 1H), 4.50 (br s, 2H), 4.14 (s, 1H), 3.00−2.95 (m, 1H), 2.61−2.58 (m, 2H), 2.52−2.48 (m, 3H), 2.44 (s, 3H), 2.36 (s, 3H), 2.34−2.31 (m, 2H), 2.18 (s, 3H), 1.95 (br m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 133.1, 132.8, 132.1, 127.9, 127.8, 126.4, 125.3, 118.8, 118.3, 116.7, 109.1, 86.7, 84.8, 84.5, 63.4, 62.5, 60.8, 58.9, 52.2, 39.0, 36.2, 35.7, 35.6, 35.4; IR (film) 3392, 3240, 2962, 2933, 2860, 2792, 1605, 1488, 1248 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{39}N_6$ $(M + H)^+$: 519.3236, found: 519.3239.

Tris(pyrrolidinoindoline) 4. Prepared in the same manner as **3** starting with 75 mg (0.086) of **15**. The crude product was purified by silica gel chromatography (7:3:0 to 7:3:1 benzene/EtOAc/Et_2NH) to give a yellow solid, which was further purified by preparative HPLC on a Zorbax Extend C-18 column (5 mm, 150 × 21.2 mm, 16.0 mL/min, 70:30:1 MeOH/water/Et_3N) to give **4** as a colorless solid (14 mg, 31%, T_R = 8.0 min): $[\alpha]^{27}_D$ −242, $[\alpha]^{27}_{577}$ −254, $[\alpha]^{27}_{546}$ −286 (*c* 0.45, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (t, *J* = 7.6 Hz, 1H), 7.04−6.85 (br m, 5H), 6.77 (t, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.43 (br s, 2H), 5.96 (br m, 1H), 4.88 (br s, 1H), 4.12 (br s, 1H), 3.04−2.94 (m, 2H), 2.69−2.58 (m, 3H), 2.47 (br s, 5H), 2.40 (br s, 7H), 1.94−1.84 (br m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.7, 132.5, 127.9, 127.6, 126.1, 125.1, 118.8, 118.2, 116.4, 108.9, 108.7, 87.0, 84.6, 83.6, 60.7, 52.4, 38.5, 36.6, 35.9, 35.8, 34.3; IR (film) 3382, 3274, 2962, 2933, 2854, 2792, 1605, 1488, 1246 cm^{-1}; HRMS (ESI) calcd for $C_{33}H_{39}N_6$ $(M + H)^+$: 519.3236, found: 519.3240.

Acknowledgment. Research at UC Irvine was supported by the NIH National Institutes of General Medical Sciences (GM-30859) and by a predoctoral fellowship to J.J.K. from Dupont Pharmaceuticals. NMR and mass spectra were determined at UC Irvine using instruments acquired with the assistance of NSF and NIH shared instrumentation grants. Research at UFRGS was supported by CNPq grant (472973/2004-5) and fellowships to E.E., V.M.L., and G.C.G.

Supporting Information Available: General experimental details and procedure for the conversion of **4** to **6**; tables of the activity of hodgkinsine and its stereisomers in antinociceptive tests; copies of ^{1}H and ^{13}C NMR spectra of new compounds and copies of CD spectra of hodgkinsine and its stereoisomers (29 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

JO7013643