Alkaloid Total Synthesis

Enantioselective Total Syntheses of the Cyclotryptamine Alkaloids Hodgkinsine and Hodgkinsine B**

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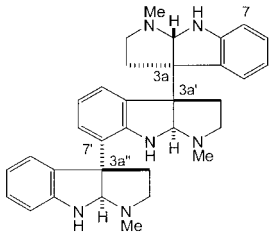
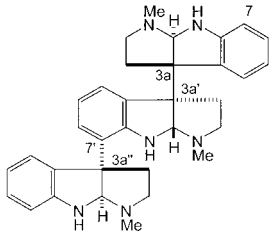
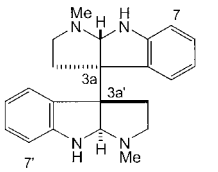
Hodgkinsine (**1**), first isolated in 1961 from the leaves of a shrub (*Hodgkinsonia frutescens*) growing in the coastal and tableland region of tropical Queensland, Australia,[1] was later identified in the alkaloid extracts of numerous members of



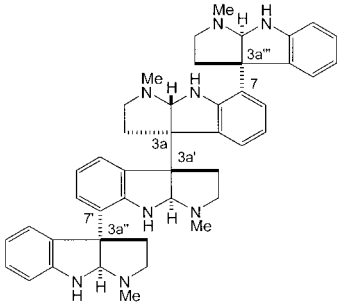
hodgkinsine (**1**)



hodgkinsine B (**2**)



meso-chimonanthine (**3**)



quadrigemine C (**4**)

the *Psychotria* genus,[2] including *P. colorata*, a plant traditionally used in the Brazilian Amazon as a remedy for pain.[3] Early chemical[1,4] and mass spectrometric evidence,[5] the latter complicated by the facile fragmentation of the C3a–C3a′ bond connecting the contiguous benzylic quaternary carbons, suggested that hodgkinsine was a N_b-methyltryptamine-derived dimer akin to chimonanthine and calycanthine. Single-crystal X-ray analysis of the trimethiodide

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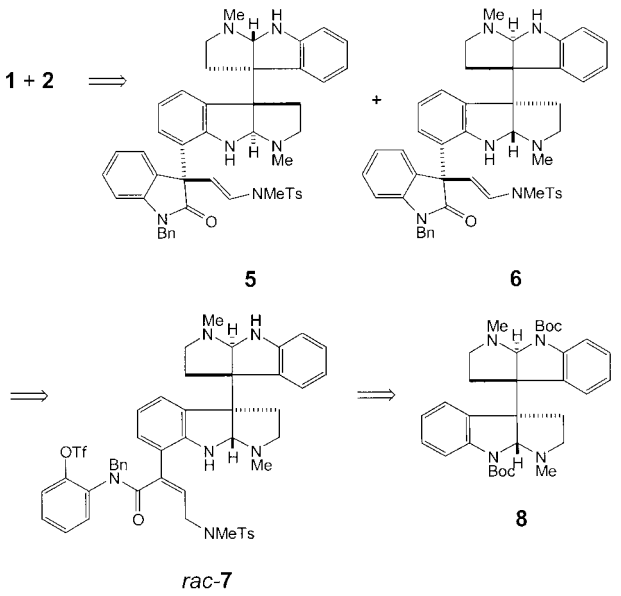
derivative subsequently established that hodgkinsine (**1**) is composed of three pyrrolidinoindoline units,[6] and it is thus the first member of the higher order polypyrrolidinoindoline alkaloids to be fully characterized.[7]

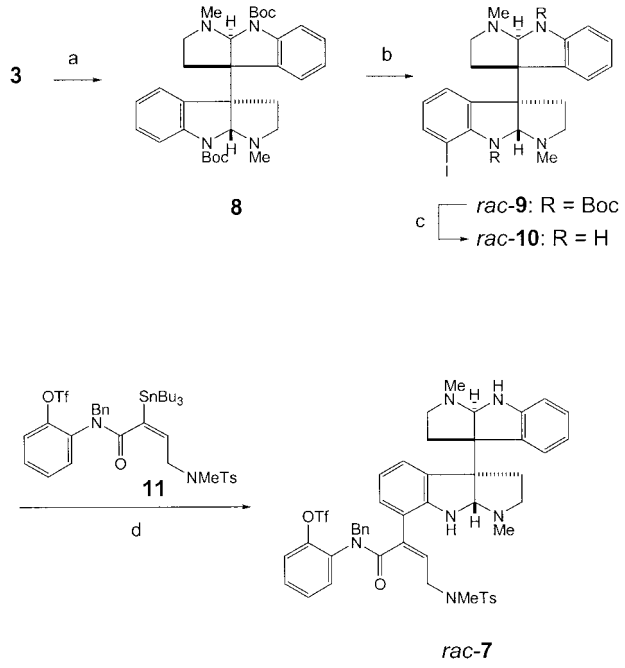
Recent pharmacological studies have shown hodgkinsine (**1**) to be a micromolar agonist of the μ-opiod receptor and to show potent dose-dependent analgesic activity against capsaicin-induced pain, the latter of which also implies the involvement of NMDA receptors.[8] In this communication we report the first total synthesis of hodgkinsine (**1**) as well as its stereoisomer **2**, a previously undisclosed alkaloid isolated from Amazon *Psychotria* species for which the name hodgkinsine B has been suggested.[9]

The approach we pursued (Scheme 1) to synthesize hodgkinsine (**1**) and hodgkinsine B (**2**) was based on a number of considerations. The vicinal quaternary stereocenters of **1** and **2** (3a and 3a′) have opposite relative configurations, making the hexacyclic 3a,3a′-bispyrrolidinoindoline moieties of these alkaloids similar to those of *meso*-chimonanthine (**3**) and quadrigemine C (**4**).[2b,7] In both alkaloids the third all-carbon-substituted quaternary stereocenter C3a″ has the *R* absolute configuration. What differentiates hodgkinsine and hodgkinsine B is the opposite absolute configurations of their contiguous quaternary stereocenters. Thus, the synthetic problem in preparing **1** and **2** reduces to selectively joining a pyrrolidinoindoline having the *R* absolute configuration at C3a″ to either the enantiotopic C7 or C7′ *peri* position of *meso*-chimonanthine (**3**). We envisioned accomplishing this stereochemical differentiation by catalyst-controlled asymmetric Heck cyclization of the racemic triflate *rac*-**7** to generate the octacyclic oxindoles **5** and **6**.[10,11] This late-stage catalytic asymmetric transformation would resolve the *meso*-3a,3a′-bispyrrolidinoindoline unit of *rac*-**7** while appending the diaryl-substituted quaternary stereocenter C3a″. The heptacyclic triflate *rac*-**7** in turn would be accessed from the known di-*tert*-butoxycarbonyl derivative **8** of *meso*-chimonanthine in a fashion similar to that employed in our recent total synthesis of quadrigemine C (**4**).[12]



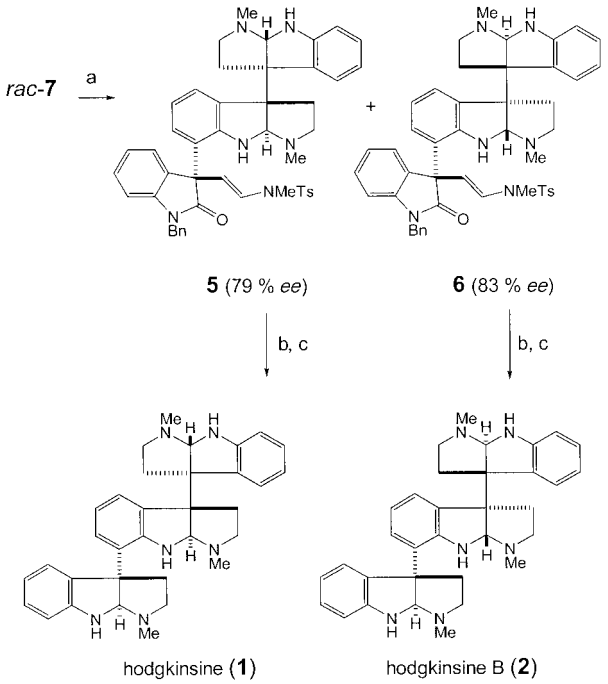
Scheme 1. Retrosynthesis for hodgkinsine (**1**) and hodgkinsine B (**2**).

meso-Chimonanthine (**3**), the starting point for preparing hodgkinsine (**1**) and hodgkinsine B (**2**), is available by stereocontrolled total synthesis,[13] or more conveniently in 30% overall yield from tryptamine by a recently reported three-step, stereorandom sequence.[14] After conversion of **3** to dicarbamate **8** (Scheme 2),[12] this latter intermediate was *ortho*-lithiated by reaction with 2 equiv *sec*-butyllithium at −78 °C in THF containing 2 equiv TMEDA.[15] Quenching of the resulting lithium species with an excess of 1,2-diiodoethane delivered the monoiodide *rac*-**9** in 64% yield. Cleavage of the Boc groups followed by Stille cross-coupling of *rac*-**10** with stannane **11**[10b,12] furnished the racemic intramolecular Heck precursor *rac*-**7** in 39% overall yield from *meso*-chimonanthine (**3**).



Scheme 2. Reaction conditions: a) Boc_2O, THF, RT; NaHMDS (77%, ref. [13]); b) 1) sBuLi, TMEDA, THF, −78 °C; 2) diiodoethane, −78 °C to 0 °C (64%); c) TMSOTf, CH_2Cl_2 (97%); d) **10**, $Pd_2(dba_3)\cdot CHCl_3$, P(2-furyl)$_3$, CuI, DMA, RT (81%). Boc = *tert*-butoxycarbonyl, dba = dibenzylideneacetone, DMA = *N*,*N*-dimethylacetamide, NaHMDS = sodium bis(trimethylsilyl)amide, RT = room temperature, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, TMSOTf = trimethylsilyl trifluoromethanesulfonate.

The critical catalyst-controlled Heck cyclization of *rac*-**7** was investigated in some detail (Scheme 3 and Table 1). First we established that there was little substrate-controlled diastereoselection in the cyclization of *rac*-**7** with palladium catalysts containing achiral diphosphane ligands such as dppb (**5**:**6** = 2:1). Of the chiral, enantiopure diphosphanes screened, Tol-BINAP[16] provided the highest degree of catalyst control.[17] With this ligand, stereoselectivity was



Scheme 3. Reaction conditions: a) 10% $Pd(OAc)_2$, 20% (*R*)-Tol-BINAP, PMP, MeCN, 80°C, (93%,1:1 ratio of **5**:**6**); b) $Pd(OH)_2$, 80 psi H_2, EtOH, 80°C; c) Na/NH_3 −78°C, NH_4Cl quench (29%, 2 steps).

Table 1: Intramolecular Heck reactions of *rac*-**7**.[a]

Ligand	Solvent	Base	Yield of % **5** [%] (% *ee*)[b]	Yield of **6** [%] (% *ee*)[b]
dppb[c]	MeCN	PS[d]	50 (–)	24 (–)
(*R*)-BINAP	MeCN	PS[d]	40 (68)	38 (69)
(*R*)-Tol-BINAP[e]	MeCN	PS[d]	37 (78)	37 (82)
(*S*)-Cy-BINAP[f]	MeCN	PS[d]	7[g] (11)[h]	6[g] (6)
(*R*)-Tol-BINAP	DMA	PS[d]	31 (71)	28 (82)
(*R*)-Tol-BINAP	toluene	PS[d]	24 (55)	24 (48)
(*R*)-Tol-BINAP	MeCN	PMP[i]	48 (79)	45 (83)

[a] Conditions: 10 mol% $Pd(OAc)_2$, 20 mol% ligand, 4.0 equiv base, substrate concentration (0.05 M), 12 h. [b] Determined by HPLC analysis with a Chiracel OD-R column. [c] dppb = 1,4-bis(diphenylphosphanyl)butane. [d] PS = 1,8-bis(dimethylamino)naphthalene (Proton-Sponge). [e] (*R*)-Tol-BINAP = (*R*)-2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl. [f] (*S*)-Cy-BINAP = (*S*)-2,2′-bis(dicyclohexylphosphanyl)-1,1′-binaphthyl. [g] Yields measured by HPLC with an internal standard (2-aminophenol). [h] The major enantiomer formed is *ent*-**5**. [i] PMP = 1,2,2,6,6-pentamethylpiperidine.

slightly enhanced in more polar solvents, whereas the yields of **5** and **6** were improved upon substitution of PMP (1,2,2,6,6-pentamethylpiperidene) for 1,8-bis(dimethylamino)naphthalene (Proton-Sponge). Temperature changes over the range 65–80°C had no discernable effect on enantioselectivity. Under optimized conditions Heck cyclization of *rac*-**7** in acetonitrile at 80°C using the catalyst generated from 10 mol% $Pd(OAc)_2$ and 20 mol% (*R*)-Tol-BINAP provided a separable 1:1 mixture of diastereomers **5** (48% yield) and **6** (45% yield). The enantiopurity of these products (**5** 79% *ee*, **6** 83% *ee*) shows that under these conditions (*R*)-Tol-BINAP regulated stereoselection at the newly formed quaternary center to the extent of 9:1.

Saturation of the alkene double bonds of **5** and **6**, followed by reductive deprotection–cyclization of the dihydro products with Na/NH_3 and NH_4Cl[12] furnished hodgkinsine (**1**) and hodgkinsine B (**2**), each in 29% overall yield (Scheme 3). NMR spectra (^1H and ^{13}C) for synthetic **1** at room temperature and at 243 K were identical to those reported for natural hodgkinsine.[2e] Synthetic **2** was identical to an authentic sample of hodgkinsine B (**2**) by comparison of ^1H and ^{13}C NMR spectroscopic and mass spectrometric data and by HPLC coinjection.[18a] Synthetic **1** (79% *ee*) showed an optical rotation $[\alpha]_D^{27} = -25$ ($c = 0.8$, $CHCl_3$); rotations at the D line in $CHCl_3$ ranging from −26 to −42 (typically at $c = 1$) have been reported for natural samples of hodgkinsine.[2a,e,19] Synthetic **2** (83% *ee*) showed an optical rotation $[\alpha]_D^{27} = -55$ ($c = 0.8$, $CHCl_3$), whereas $[\alpha]_D^{27} = -77$ ($c = 1$, $CHCl_3$) was reported for a natural sample.[18b]

In summary, the first total syntheses of hodgkinsine (**1**) and hodgkinsine B (**2**) were accomplished from tryptamine by highly concise sequences of ten total steps. The alkaloid products were produced in enantioenriched form (~80% *ee*) and in 1.5% overall yield. The stereorational total synthesis of **2** establishes the relative and absolute configuration of this *Psychotria* natural product. To the best of our knowledge, the conversion of *rac*-**7** to enantioenriched **5** and **6** represents the first successful use of an asymmetric intramolecular Heck reaction for resolution.[20] This work, together with our recent enantioselective total syntheses of idiospermuline[21] and quadrigemine C,[12] firmly establishes the utility of catalytic asymmetric Heck cyclizations for appending pyrrolidinoindoline units in stereocontrolled fashion to hindered *peri* positions of either chiral or *meso* 3a,3a′-bispyrrolidinoindoline (chimonanthine) fragments. This chemistry, and the diastereoselective dialkylation chemistry we developed contemporaneously for preparing either enantiomer of chiral 3a,3a′-bispyrrolidinoindolines,[13b,c,22] should allow a wide variety of polypyrrolidinoindoline alkaloids and their analogues to be prepared by stereocontrolled chemical synthesis. Use of these tools to prepare all eight hodgkinsine stereoisomers and preliminary pharmacological assessment of this series will be reported elsewhere.

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