Direct Stereo- and Enantiocontrolled Synthesis of Vicinal Stereogenic Quaternary Carbon Centers. Total Syntheses of *meso*- and (−)-Chimonanthine and (+)-Calycanthine

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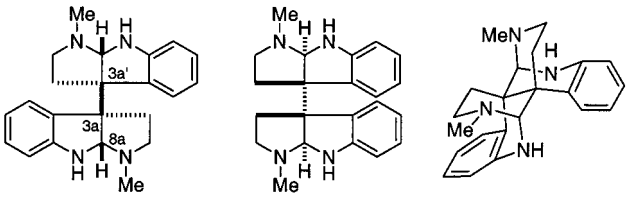
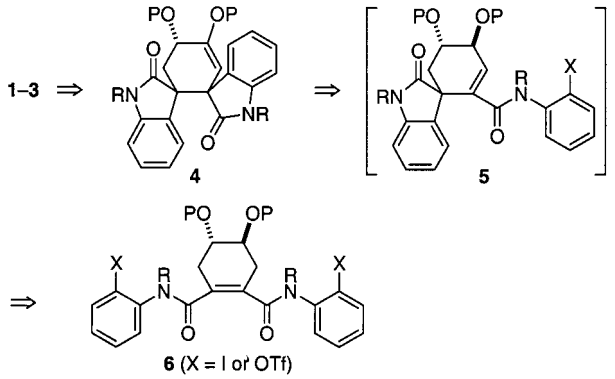
Among the most demanding challenges encountered in the synthesis of complex molecules is enantioselective formation of vicinal stereogenic quaternary carbon centers.[1,2] This problem typically has been addressed by constructing the quaternary centers sequentially,[3] often using a sigmatropic rearrangement to form the second center.[4] In this disclosure, we report that vicinal stereogenic carbon centers can be constructed in a single step and with excellent control of relative and absolute stereochemistry using an intramolecular Heck reaction cascade. We have addressed this problem in the context of the total synthesis of polypyrroloindoline alkaloids whose signature structural motif is the hexacyclic 3a,3a′-bispyrrolo[2,3-*b*]indoline ring system.[5] All possible stereoisomers of the simplest members of this indole alkaloid family, the chimonanthines, are found in Nature: (−)-chimonanthine (**1**)[6,7] and *meso*-chimonanthine (**2**)[8] in plants, (+)-chimonanthine in a dendrobatid frog[9] and in plants.[10] Absolute configuration assignments for the chiral chimonanthine enantiomers derive from circular dichroism studies[11] of (+)-calycanthine (**3**),[12] which under acidic conditions is in equilibrium with **1**.[12c] Chiral C_2-symmetric chimonanthines and their analogues have previously been prepared only as racemates through nonstereocontrolled routes.[5,12c−14] Herein we describe the first stereo- and enantiocontrolled total synthesis of (−)-chimonanthine (**1**) and (+)-calycanthine (**3**), and a second stereocontrolled route to *meso*-chimonanthine (**2**).[14]



Scheme 1



We envisaged pentacyclic bisoxindole **4** as a precursor of the chimonanthines and conjectured that this intermediate could be accessed by palladium-catalyzed cyclization of **6** (Scheme 1). Although we have previously utilized intramolecular Heck reactions to fashion various sterically congested quaternary carbon centers,[15] the projected conversion of **6** → **4** was expected to be particularly challenging since insertion of a tetrasubstituted double bond would be required in the first Heck reaction, while the second insertion would form adjacent quaternary centers. At the outset, we entertained the possibility that the stereochemistry of the trans oxygen substituents of **6** might regulate stereoselection in the generation of **4**.

Synthesis of the C_2-symmetric cyclization substrate began with double alkylation[16] of the lithium dienolate of dimethyl succinate (**7**) and tartrate-derived diiodide **8**,[17] followed by oxidation[18] of the resulting diastereomeric mixture of saturated diesters with LDA and I_2 to form **9** in 33% overall yield (Scheme 2). Although the efficiency of the initial dialkylation was low, this sequence could be performed conveniently on large scale to provide multigram quantities of enantiomerically pure **9**. Aminolysis of **9** with the dimethylaluminum amide of 2-iodoaniline[19] and conventional *N*-benzylation of the product generated **11**. Removal of the benzyl ethers with BCl_3, followed by silylation with *tert*-butyldimethylsilyl chloride (TBDMSCl) gave cyclization substrate **13**. Heck cyclization of **13** at 100 °C in *N*,*N*-dimethylacetamide (DMA) in the presence of 10% $(Ph_3P)_2PdCl_2$ and excess Et_3N provided bisoxindole **14** in 71% yield.[20] Only a single pentacyclic bisoxindole, which ultimately proved to have the meso relationship of the two oxindole groups, was isolated. Cleavage of the

(1) That no general methods exist is apparent in the lack of examples in recent reviews of asymmetric synthesis of quaternary carbon centers.[2]

(2) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066.

(3) Examples can be found, *inter alia*, in asymmetric syntheses of diterpenes. For recent reviews, see: (a) Hanson, J. R. *Nat. Prod. Rep.* **1999**, 209−219, and earlier reviews in this series.

(4) For a recent example of forming both quaternary centers by a sigmatropic rearrangement, see: Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453−5457.

(5) For recent reviews that briefly discuss this indole alkaloid family, see: (a) Hino, T.; Nakagawa, M. In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, 1989; Vol. 34, pp 1−75. (b) Wrobel, J. T. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1985; Vol. 26, pp 53−87.

(6) Hodson, H. F.; Robinson, B.; Smith, G. F. *Proc. Chem. Soc.* **1961**, 465−466.

(7) 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.

(8) Adjibade, Y.; Weniger, B.; Quirion, J. C.; Kuballa, B.; Cabalion, P.; Anton, R. *Phytochemistry* **1992**, *31*, 317−319.

(9) Tokuyama, T.; Daly, J. W. *Tetrahedron* **1983**, *39*, 41−47.

(10) (a) Lajis, N. H.; Mahmud, Z.; Toia, R. F. *Planta Med.* **1993**, *59*, 383−384. (b) Verotta, L.; Pilati, T.; Tatò, M.; Elisabetsky, E.; Amador, T. A.; Nunes, D. S. *J. Nat. Prod.* **1998**, *61*, 392−396.

(11) Mason, S. F.; Vane, G. W. *J. Chem. Soc. (B)* **1966**, 370−374.

(12) (a) Woodward, R. B.; Yang, N. C.; Katz, T. J.; Clark, V. M.; Harley-Mason, J.; Ingleby, R. F. J.; Sheppard, N. *Proc. Chem. Soc.* **1960**, 76−78. (b) Hamor, T. A.; Robertson, J. M.; Shrivastava, H. N.; Silverton, J. V. *Proc. Chem. Soc.* **1960**, 78−80. (c) Hendrickson, J. B.; Göschke, R.; Rees, R. *Tetrahedron* **1964**, *20*, 565−579.

(13) (a) Hino, T.; Yamada, S. *Tetrahedron Lett.* **1963**, *4*, 1757−1760. (b) Hall, E. S.; McCapra, F.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4131−4141. (c) Hino, T.; Kodata, S.; Takahashi, K.; Yamaguchi, H.; Nakagawa, M. *Tetrahedron Lett.* **1978**, 4913−4916. (d) Nakagawa, M.; Sugumi, H.; Kodato, S.; Hino, T. *Tetrahedron Lett.* **1981**, *22*, 5323−5326. (e) Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480−9486.

(14) For the first stereocontrolled total synthesis of a 3a,3a′-bispyrro[2,3-*b*]indoline alkaloid, see: Link, J. T.; Overman, L. E. *J. Am. Chem. Soc.* **1996**, *118*, 8166−8167.

(15) For a recent review of the use of intramolecular Heck reactions in natural products total synthesis, see: Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Stang, P. J., Diederich, F., Eds.; Wiley-VCH: Weinheim; 1998, Chapter 6.

(16) Misumi, A.; Iwanaga, K.; Furata, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343−3345.

(17) Raeppel, S.; Toussaint, D.; Suffert, J. *Synlett* **1997**, 1061−1062.

(18) Wilkening, D.; Mundy, B. P. *Synth. Commun.* **1984**, *14*, 227−238.

(19) Basha, A.; Lipton, M. F.; Weinreb, S. M. *Org. Synth.* **1979**, *59*, 49−53.

(20) (a) The stereochemistry of the siloxy substituent of **14** has not yet been established. (b) Due to slow conformational equilibration on the NMR time scale, NMR spectra of this intermediate are highly complex.

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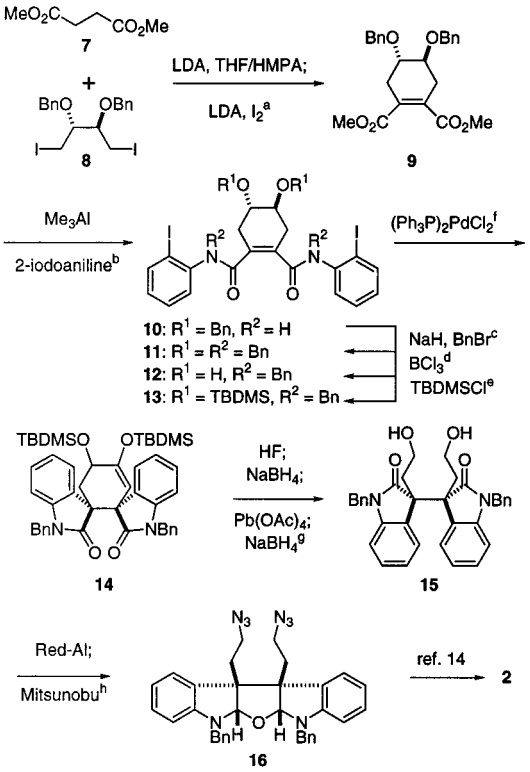
Scheme 2[a]

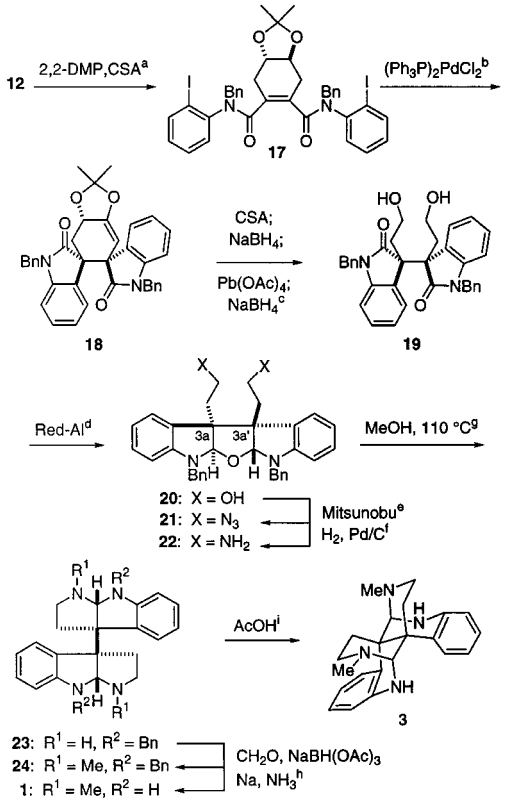


[a] Reaction conditions: (a) LDA, THF/HMPA, −78 °C, 46%; LDA, THF, I_2, −78 °C, 72%; (b) 2-iodoaniline, Me_3Al, toluene, rt, 92%; (c) NaH, BnBr, DMF, 87%; d) BCl_3, −78 °C, 70%; (e) TBDMSCl, imidazole, CH_2Cl_2, 86%; (f) 10% $(Ph_3P)_2PdCl_2$, Et_3N, DMA, 100 °C, 71%; (g) HF, MeCN; $NaBH_4$, MeOH; $Pb(OAc)_4$, PhH, then $NaBH_4$, MeOH, 88% overall; (h) Red-Al, THF, rt → reflux; HN_3, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 78%.

silyl ethers of **14** with HF in acetonitrile and reduction of the α-hydroxy ketone product with $NaBH_4$ provided the corresponding cyclohexanediol. This diol was cleaved with $Pb(OAc)_4$, and the resulting labile dialdehyde was immediately reduced to furnish diol **15** in 88% overall yield from **14**. Reduction of **15** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in refluxing THF provided a delicate pentacyclic diol which was immediately converted to its diazide derivative **16**, an intermediate in our earlier synthesis of *meso*-chimonanthine.[14]

The outcome of the double Heck cyclization was dramatically altered when the cyclohexanediol was protected as an acetonide (Scheme 3).[21] Thus, Heck cyclization of acetonide **17**[20b] under identical conditions occurred efficiently to give bisoxindole **18** in 90% yield; the relative stereochemistry of **18** was secured by single-crystal X-ray analysis.[22] Processing of **18** to **19** and reduction of the latter with Red-Al in refluxing THF gave unstable pentacyclic diol **20**, which was immediately converted into diazide **21**. Stereoselection in the cascade Heck cyclization of **17** was extremely high, since no trace of the meso stereoisomer **15** was seen in the 500 MHz ^1H NMR spectrum of diol **19**. Transformation of diazide **21** to the corresponding C_2-symmetric bispyrroloindoline proved challenging due to facile fragmentation of the 3a-3a′ bond. We eventually discovered that heating a methanol solution of diamine **22** at 110 °C in a sealed tube generated bispyrroloindoline **23** in high yield. Reductive methylation of this product and discharge of the benzyl groups of **24** using Na/NH_3 gave (−)-chimonanthine (**1**), $[\alpha]^{23}_D$ −310° (*c* 0.5 EtOH), in 67% overall yield from diazide **21**.[23,24] Finally, exposure of **1** to hot

Scheme 3[a]



[a] Reaction conditions: (a) camphorsulfonic acid monohydrate (CSA), 2,2-dimethoxypropane, 80%; (b) 10% $(Ph_3P)_2PdCl_2$, Et_3N, DMA, 100 °C, 90%; (c) CSA, THF; $NaBH_4$, MeOH; $Pb(OAc)_4$, PhH, then $NaBH_4$, MeOH, 88% overall; (d) Red-Al, THF, rt → reflux; (e) $(PhO)_2P(O)N_3$, Ph_3P, $EtO_2CN{=}NCO_2Et$, THF, 92% over two steps; (f) H_2, 10% Pd/C, EtOH, 100%; (g) MeOH, 110 °C, sealed tube; (h) CH_2O, $NaBH(OAc)_3$, MeOH, 75% over two steps; Na, NH_3/THF, 98%; (i) AcOH, reflux, 60%.

acetic acid provided (+)-calycanthine (**3**)[12] in 60% yield.[25,26] Due to an error in drawing[11] the enantiomer of chimonanthine that would lead to (+)-calycanthine upon equilibration in acid, the absolute configuration of (−)-chimonanthine has been represented incorrectly in the literature and should be revised to be as depicted in this paper.[27]

In summary, the first stereo- and enantioselective route for preparing chiral 3a,3a′-bispyrrolo[2,3-*b*]indolines and their calycanthine isomers has been developed. The central step in this sequence is a double Heck cyclization that forges vicinal quaternary carbon centers in high yield (up to 90%) and with complete stereocontrol.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for compounds **9**, **14**, **18**, **21**, and **24** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The trans vicinal siloxy groups of **13** preferentially adopt diaxial orientations, while the oxygen substituents are locked diequatorial in **17**.

(22) The authors have deposited coordinates for this compound with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(23) (a) Synthetic **1**, mp 184−185 °C (lit.[6] mp 188−189 °C) exhibited ^1H and ^{13}C NMR spectra identical to those described.[10b,24] (b) Optical rotations at the sodium D line of varying magnitudes in alcohol solvents have been reported for the chiral chimonanthine enantiomers: (−)-chimonanthine: −329,[6] −328;[7] (+)-chimonanthine: +224,[10a] +280,[9] +264.[10b]

(24) Libot, F.; Kunesch, N.; Poisson, J.; Kaiser, M.; Duddeck, H. *Heterocycles* **1988**, *27*, 2381−2385.

(25) Synthetic (+)-calycanthine (**3**) was recrystallized from EtOH to give colorless crystals: mp 244−245 °C, $[\alpha]^{23}_D$ +664° (*c* 0.7, EtOH); comparison data for natural **3** are: mp 243−245 °C, $[\alpha]^{23}_D$ +684° (EtOH).[26]

(26) Späth, E.; Stroh, W. *Chem. Ber.* **1925**, *58*, 2131−2132.

(27) The total synthesis of (+)-calycanthine recorded herein confirms the absolute configuration of calycanthine originally assigned by Mason and Vane[11] using the coupled oscillator CD method.