

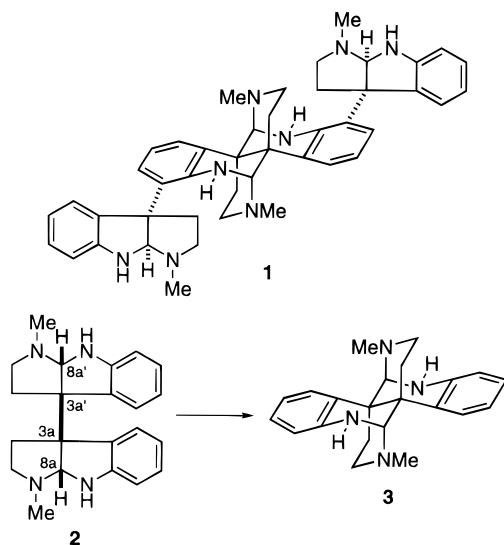
Stereocontrolled Total Syntheses of *meso*-Chimonanthine and *meso*-Calycanthine via a Novel Samarium Mediated Reductive Dialkylation

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The dodecacyclic polyindoline alkaloid psycholeine (**1**) was isolated from the New Caledonian plant *Psychotria oleoides* in 1992 by Sévenet and co-workers using a bioactivity-guided fractionation approach.¹ This novel natural product is reported to be the first non-peptide antagonist of the somatostatin family of receptors, and therefore is of potential therapeutic interest.² Psycholeine (**1**), $[\alpha]_D^{20} -150$, is structurally remarkable having a central achiral hexacyclic core that is adorned with two pyrroloindolines of the same absolute chirality. The achiral hexacyclic unit also is found in *meso*-calycanthine (**3**), which is obtained by acid-catalyzed rearrangement of the bis(pyrroloindoline) alkaloid *meso*-chimonanthine (**2**).³ In this communication, we report the first stereocontrolled total syntheses of *meso*-chimonanthine (**2**) and *meso*-calycanthine (**3**) as the initial step in the development of a strategy for the total synthesis of psycholeine (**1**).⁴



Past synthetic efforts directed toward bis(pyrroloindoline) alkaloids have produced predominantly the racemic isomers either by oxidative dimerization of oxindoles (or tryptamines)^{3,5} or from dialkylation of 3,3'-bis(oxindoles).⁶ We anticipated that *meso*-chimonanthine (**2**) could be constructed from cyclohexene **7**, an intermediate that contains the two key quaternary carbon centers present in **2** and **3** (Scheme 1). Cyclohexene **7** was

(1) Guéritte-Voegelein, F.; Sévenet, T.; Puset, J.; Adeline, M. T.; Gillet, B.; Beloeil, J. C.; Guénard, D.; Potier, P.; Rasolonjanahary, R.; Kordon, C. *J. Nat. Prod.* **1992**, *55*, 923.

(2) Rasolonjanahary, R.; Sévenet, T.; Voegelien, F. G.; Kordon, C. *Eur. J. Pharm.* **1995**, *285*, 19.

(3) (a) Hendrickson, J. B.; Göschke, R.; Rees, R. *Tetrahedron* **1964**, *20*, 565. (b) Hall, E. S.; McCapra, F.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4131.

(4) For reviews of previous synthetic efforts in this area, see: (a) Hino, T.; Nakagawa, M. *Alkaloids* **1989**, *34*, 1. (b) Kutney, J. P. In *Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1977; Vol. 3, pp 273–438. (c) Manske, R. H. F. *Alkaloids* **1965**, *8*, 581.

(5) (a) Hino, T.; Kodato, S.; Takahashi, K.; Yamaguchi, H.; Nakagawa, M. *Tetrahedron Lett.* **1978**, *19*, 4913. (b) Fang, C. L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480.

(6) (a) Hino, T. *Chem. Pharm. Bull.* **1961**, *9*, 979. (b) Hino, T.; Yamada, S. *Tetrahedron Lett.* **1963**, *4*, 1757.

envisaged as arising from isoindigo (**4**), which is available in one simple high-yielding step from commercially available oxindole and isatin.⁷ We conjectured that the pivotal conversion of **4** to **7** could be accomplished by a reductive dialkylation, whose stereochemical outcome would derive from chelate assembly **6**.⁸

Isoindigo (**4**) was first converted to *N*-benzyl derivative **5**.⁹ Treatment of **5** with 2 equiv of SmI₂ apparently generates the samarium diolate, since (*N*-benzyl)dihydroisoindigo was obtained upon protolytic quenching.^{10,11} However, this dianion did not react to an appreciable extent with *cis*-1,4-dichloro-2-butene even in the presence of HMPA at room temperature.¹² The presumed lithium diolate obtained upon treatment of (*N*-benzyl)dihydroisoindigo with 2.1 equiv of *n*-BuLi did react at room temperature with *cis*-1,4-dichloro-2-butene to deliver a mixture of the desired *meso* product **7** and an isomeric cyclobutane resulting from S_N2' closure. Related experiments with the potassium diolate (formed from reaction of (*N*-benzyl)dihydroisoindigo with 2.2 equiv of KHMDS) gave a similar product distribution. After some experimentation, a remarkable procedure for converting **5** into **7** was discovered. Isoindigo **5** was reduced at room temperature with 2 equiv of SmI₂ in the presence of 10 equiv of LiCl and then alkylated at this temperature with *cis*-1,4-dichloro-2-butene. After 8 h, cyclohexene **7** was isolated in 82% yield. None of the corresponding *dl* isomer was observed by ¹H-NMR analysis of the crude reaction mixture or of any chromatographic fraction, suggesting that diastereoselectivity for this process was at least 20:1. Although it is tempting to invoke transmetalation (Sm → Li) to explain this reaction, subtle changes in the samarium coordination sphere or degree of aggregation brought about by the added halide salt could be responsible for the reaction outcome.¹³ It should be noted that these reaction conditions provide a room temperature alternative to lithium in liquid ammonia, which in the present case would not have been compatible with the benzyl protecting groups in **5**.

The conversion of cyclohexene **7** to *meso*-chimonanthine (**2**) proved challenging due to the facile cleavage of the doubly benzylic C_{3a},C_{3a'} bond.¹⁴ However, a satisfactory means of attaining the desired oxidation state at C_{8a},C_{8a'} was found when **7** was treated with sodium bis(2-methoxyethoxy)aluminum

(7) (a) Stolle, R. *J. Prakt. Chem.* **1930**, *128*, 1. (b) Papageorgiou, C.; Borer, X. *Helv. Chim. Acta* **1988**, *71*, 1079.

(8) Although not proposed by previous workers, a related chelate is presumably responsible for the selectivity observed by Hino in his synthesis of *d,l*-chimonanthine.^{6a}

(9) New compounds were fully characterized by ¹H and ¹³C NMR, IR, and MS analysis, while elemental composition was confirmed by combustion analysis or high-resolution mass spectrometry. Yields refer to isolated products purified on silica gel unless noted otherwise. Standard abbreviations employed are defined in: *J. Org. Chem.* **1996**, *61*, 22A.

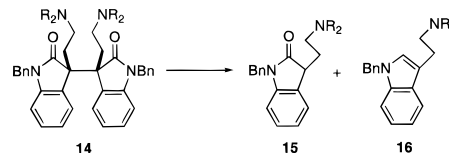
(10) Addition of 2 equiv of SmI₂ to **5** at room temperature yields a blue solution that rapidly turns light yellow indicating complete consumption of SmI₂. Quenching with saturated aqueous NH₄Cl provided both isomers of (*N*-benzyl)dihydroisoindigo (in 1.5:1 ratio) in 97% yield.

(11) For a recent review of the chemistry mediated by samarium diiodide, see: Molander, G. A. *Org. React.* **1994**, *46*, 2111.

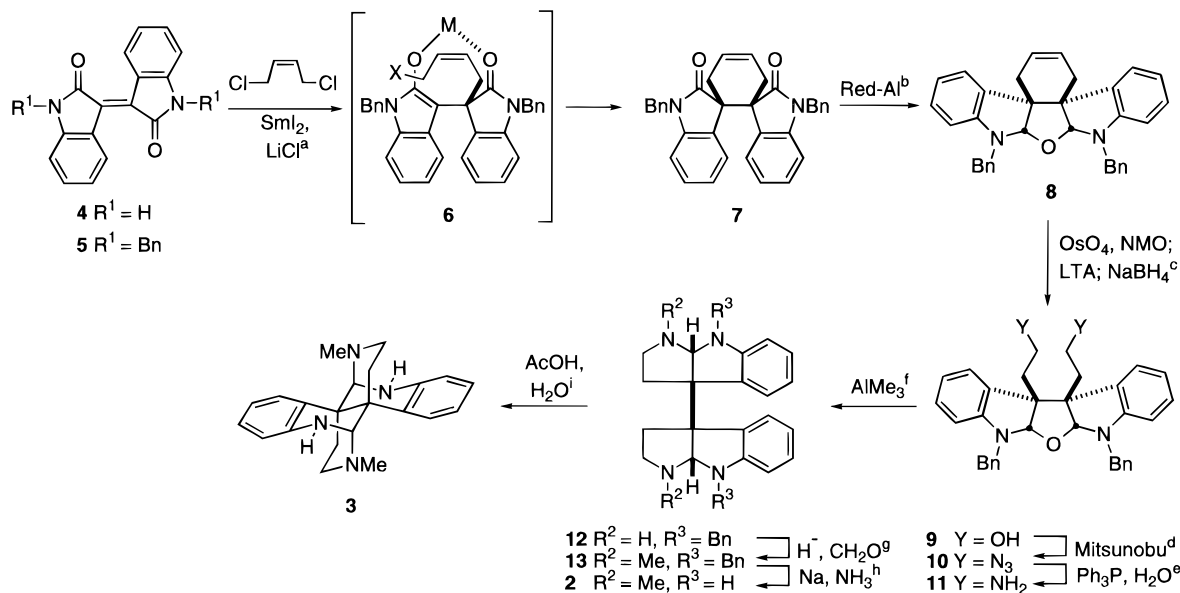
(12) Enholm, E. J.; Schreier, J. A. *J. Org. Chem.* **1995**, *60*, 1110.

(13) A simple salt effect is not involved, since addition of KCl (instead of LiCl) yielded (*N*-benzyl)dihydroisoindigo after protonolysis, rather than cyclohexene **7**.

(14) Cyclohexene **7** could be converted into **14** (R = alkyl or R = H and CO₂R'), which upon treatment with reducing agents typically lead to a ~1:1 mixture of oxindole **15** and indole **16**.



(15) For previous reports of the preparation of similar ring systems, see: (a) Hodson, H. F.; Smith, G. F.; Wróbel, J. T. *Chem. Ind.* **1958**, 1551. (b) Hino, T. *Chem. Pharm. Bull.* **1961**, *9*, 988.

Scheme 1^a

^a Key: (a) SmI_2 , $LiCl$, THF, rt; *cis*-1,4-dichloro-2-butene, rt, 82%; (b) RedAl, PhH, rt→reflux, 78%; (c) OsO_4 , NMO, acetone, H_2O , 96%; $Pb(OAc)_4$, EtOH, PhH, 0 °C; $NaBH_4$, 94%; (d) HN_3 , Ph_3P , $MeO_2CNCNCO_2Me$, THF, 0 °C, 87%; (e) Ph_3P , H_2O , THF; (f) Me_3Al , PhH, 68%; (g) CH_2O , $NaCNBH_3$, MeCN, H_2O , 87%; (h) Na , NH_3 , THF, -78 °C, 92%; (i) AcOH, H_2O , 100 °C, 25%.

hydride (Red-Al[®]) in refluxing benzene to provide hexacycle **8** in high yield. The unusual structure of this intermediate was verified by X-ray crystallography.^{15,16} The cyclohexene ring then was cleaved to provide diol **9** through sequential reaction of **8** with OsO_4 -*N*-methylmorpholine *N*-oxide (NMO), lead tetraacetate (LTA), and $NaBH_4$. This unstable diol was immediately converted into diazide **10**, which was obtained in 78% overall yield from **8**. Reduction of **10** to the corresponding diamine **11** followed by exposure of **11** to excess Me_3Al at room temperature provided the desired bis(pyroloindoline) **12** in 68% yield. Reductive methylation of **12** yielded **13**, which upon treatment with Na/NH_3 delivered *meso*-chimonanthine (**2**), mp 199–201 °C (lit.^{5a,3b} mp 198–203 and 199–202 °C),¹⁷ in 92% yield. Since a comparison sample of *meso*-chimonanthine (**2**) was unavailable, the structure of synthetic **2** was confirmed by single crystal X-ray analysis.¹⁶ Finally, exposure of **2** to hot dilute acetic acid provided *meso*-calycanthine (**3**), mp 264–267 °C (lit.^{3b} mp 265–268 °C).^{3,18}

(16) Crystallographic data for this intermediate have been deposited 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, UK.

(17) A slightly lower melting point (176 °C) was recently reported for **2** isolated from *Psychotria forsbriana*, see: Adjibade, Y.; Weniger, B.; Quirion, J. C.; Kuballa, B.; Cabalion, P.; Anton, R. *Phytochemistry* **1992**, *31*, 317.

In summary, a concise, stereocontrolled route to *meso*-chimonanthine (**2**) and *meso*-calycanthine (**3**) has been developed. The sequence features an unusual samarium-mediated reductive dialkylation to control the relative stereochemistry of the two critical quaternary centers. Application of this chemistry to the total synthesis of psycholeine (**1**) will be described in due course.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for new compounds reported in Scheme 1 (6 pages). See any current masthead page for ordering and Internet access instructions.

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(18) This product showed a diagnostic signal at 71.1 ppm for $C_{8a}, C_{8a'}$.¹⁹

(19) (a) Libot, F.; Kunesch, N.; Poisson, J.; Kaiser, M.; Duddeck, H. *Heterocycles* **1988**, *27*, 2381. (b) Libot, F.; Miet, C.; Kunesch, N.; Poisson, J. E.; Puset, J.; Sévenet, T. *J. Nat. Prod.* **1987**, *50*, 468.