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Natural Products

Concise Total Synthesis of (−)-Calycanthine, (+)-Chimonanthine, and (+)-Folicanthine**

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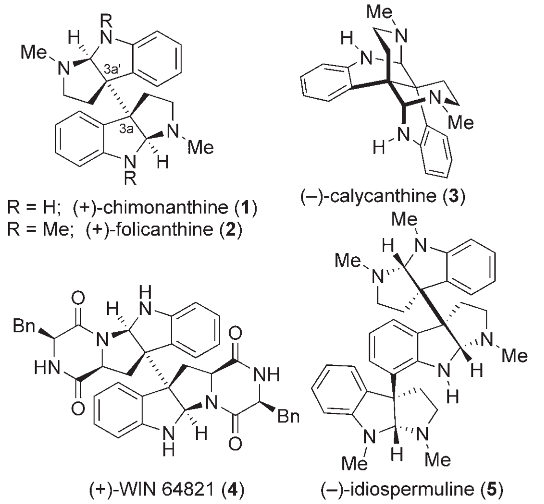
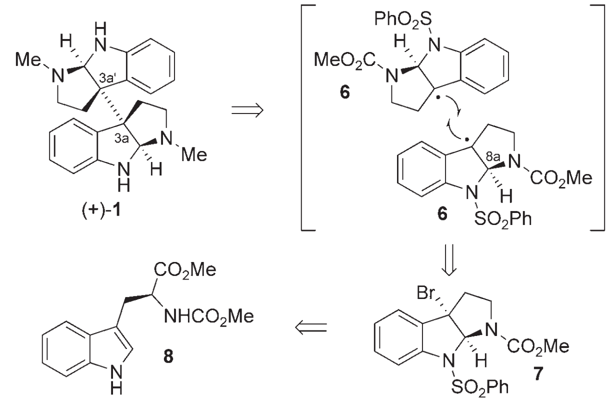
Hexahydropyrroloindole alkaloids constitute a large class of natural compounds that are formally derived from tryptophan.[1] A fascinating array of dimeric and oligomeric derivatives exist, a large subset of which contain vicinal quaternary stereocenters at C3a and C3a′ of the hexahydropyrroloindole substructure (Scheme 1). The alluring structure of these alkaloids combined with their biological activity has led to significant interest in their total syntheses. Important contributions in this area have established a biosynthetically inspired oxidative dimerization[2] of oxindoles and tryptamines for accessing derivatives in racemic and meso form.[3] Overman and co-workers have reported elegant enantioselective syntheses that take advantage of dialkylation or double Heck cyclizations to establish the quaternary stereocenters in these targets.[4] Herein we describe a concise enantioselective synthesis of (+)-chimonanthine (**1**), (+)-folicanthine (**2**), and (−)-calycanthine (**3**) by a convergent reductive dimerization strategy to simultaneously secure the vicinal quaternary stereocenters.



Scheme 1. Representative alkaloids derived from hexahydropyrroloindoles. Bn = benzyl.

Our retrosynthetic analysis of (+)-chimonanthine (**1**) is illustrated in Scheme 2. As part of a program directed toward the synthesis of dimeric hexahydropyrroloindole alkaloids we sought an efficient and convergent strategy for the introduction of the two quaternary stereocenters with complete stereoselectivity. A powerful disconnection that has heretofore been unexplored in the synthesis of these alkaloids would involve the homocoupling of the enantiomerically enriched tricyclic free radical **6**, or a related derivative, to provide the crucial C3a–C3a′ bond (Scheme 2).[5] We expected the stereochemistry at the C8a-position of the tricycle **6** to impose a high level of diastereoselectivity in the bond-forming event and secure the vicinal quaternary stereocenters in (+)-**1**. Tricyclic bromide **7** was predicted to serve as a versatile precursor to **6**, and was envisioned to be prepared based on the elegant reports on the synthesis of hexahydropyrroloindole alkaloids functionalized at the C3a-position by the research groups of Hino, Crich, and Danishefsky.[1d,6]



Scheme 2. Retrosynthetic analysis of (+)-**1**.

Treatment of the commercially available N_α-methoxycarbonyl-L-tryptophan methyl ester (**8**, Scheme 2) with neat phosphoric acid followed by N sulfonylation provided the desired tricyclic hexahydropyrroloindole (+)-**9** (> 99% de, > 99% *ee*) on multigram scale (Scheme 3).[1d,7] Hydrolysis of the methyl ester followed by decarboxylation at the C2-position[8] of tricycle (+)-**9** afforded the desired hexahydro-

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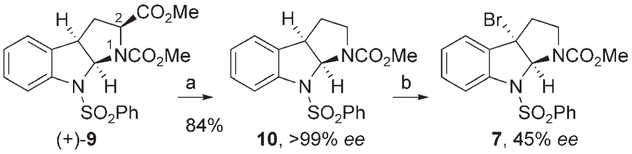


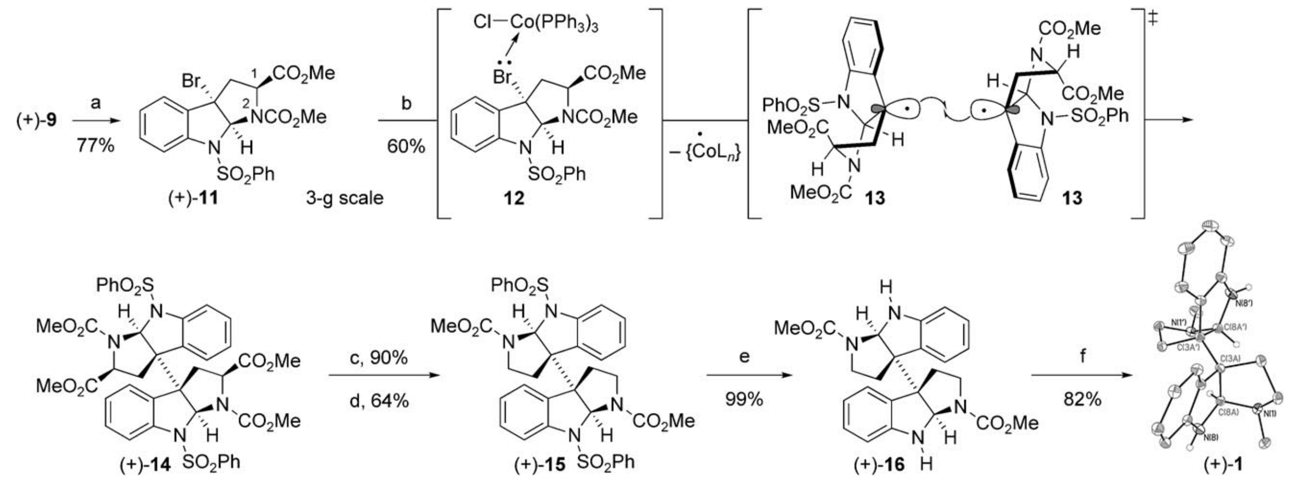
Scheme 3. Synthesis of the tricyclic bromide **7**: a) 1. aq KOH/MeOH (1:1), 23 °C, 30 min; 2. oxalyl chloride, DMF, CH_2Cl_2, 23 °C, 1 h; 3. $(Me_3Si)_3SiH$, AIBN, toluene, 80 °C, 4 h, 84% from **9**. b) 1,3-dibromo-5,5-dimethylhydantoin, CCl_4, 23 °C, 5 h, see text. AIBN = 2,2′-azobisisobutyronitrile, DMF = dimethylformamide.

pyrroloindole (+)-**10** in 84% yield and > 99% *ee*. Unfortunately, the benzylic bromination of **10** was found to be capricious, and afforded bromide **7** in variable yields and with significant loss of optical activity (45% *ee*, Scheme 3). We speculated that **10** had been converted into **7** in part via the corresponding achiral *N*-benzenesulfonyl tryptamine tautomer.[6] The sensitivity of **10** to trace amounts of acid was confirmed independently. Examination of a wide range of reaction conditions, which included bromination attempts in the presence of scavengers of Brønsted acids, failed to completely suppress loss in optical activity or increase the overall efficiency of the process. Importantly, the marked stability of the derivative **11** with the *endo*-methoxycarbonyl group at C2[1d] (Scheme 4) prompted us to explore a postdimerization decarboxylation at that position.[9]

Benzylic bromination of **9** was optimally achieved using 1,3-dibromo-5,5-dimethylhydantoin on a greater than 4-g scale to afford the bromide (+)-**11** as a single diastereomer in 77% yield and greater than 99% *ee*.[1d,7] We next focused our attention on the development of the reaction conditions for the vital homodimerization step. Photochemical or thermal activation of hexaalkyldistannanes in the presence of tricyclic bromide (+)-**11** did not afford the desired dimeric hexacycle **14** and predominantly returned the bromide. A variety of reducing conditions were either ineffective in providing the desired dimeric product **14** and led to slow decomposition of bromide **11**, or promoted an anionic fragmentation as evidenced by predominant isolation of the corresponding tryptophan derivatives. We reasoned that photolytic cleavage of the weak Mn–Mn bond in dimanganese decacarbonyl complex $[Mn_2(CO)_{10}]$ could lead to bromide abstraction by $\{Mn(CO)_5\}$ under mild reaction conditions that could afford the desired dimer **14**.[10] In the event, irradiation of a mixture of bromide (+)-**11** and $[Mn_2(CO)_{10}]$ (0.5 equiv) by visible light (CH_2Cl_2, 16 h) provided the desired dimer (+)-**14**[11] in 18% yield and greater than 99% *ee* along with the corresponding product **9** with reduction at the C3a-position (ca. 5%) and several by-products. The yield of the isolated hexacycle (+)-**14** was increased to 32% by using an equimolar quantity of $[Mn_2(CO)_{10}]$; however, despite examination of a wide range of reaction conditions, none were found to be superior.

Given the expected second-order dependence of the dimerization rate on the concentration of the activated monomer, we reasoned that more rapid activation of the bromide might provide a solution. Gratifyingly, the use of the highly reactive tris(triphenylphosphine)cobalt(I) chloride $[CoCl(PPh_3)_3]$[12] as a stoichiometric reducing agent in benzene was found to provide rapidly the desired dimer (+)-**14** in 34% yield with a marked decrease in the number of by-products. A dramatic solvent and concentration dependence was also noted for this reductive dimerization with the best solvents being acetone and 2-butanone. Treatment of the tricyclic bromide (+)-**11** with $[CoCl(PPh_3)_3]$ under optimum reaction conditions (acetone, 23 °C, 0.1 M, 15 min) provided the desired dimer (+)-**14** in 60% yield and greater than 99% *ee* on a 3-g scale (Scheme 4).[13] This dimerization process may involve a bromide abstraction from (+)-**11**, thus allowing the union of two free radicals, which had escaped from the solvent cage, to give (+)-**14**.[12] Alternatively, the process may involve a net oxidative insertion of the cobalt(I) reagent to afford a tertiary benzylic cobalt(III) complex that could afford (+)-**14** by homodimerization followed by fragmentation of the C–Co bonds and formation of a C–C bond within a solvent cage.[14]

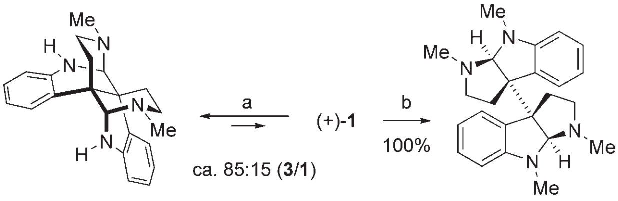
With an efficient strategy for the preparation of multigram quantities of enantiomerically enriched hexacycle



Scheme 4. Concise total synthesis of (+)-**1**: a) 1,3-dibromo-5,5-dimethylhydantoin, AIBN, CCl_4, 80 °C, 1 h, 77%. b) $[CoCl(PPh_3)_3]$, acetone, 23 °C, 15 min, 60%. c) aq KOH/MeOH, 23 °C, 30 min, 90%. d) oxalyl chloride, DMF, CH_2Cl_2, 23 °C, 1.5 h; $(Me_3Si)_3SiH$, AIBN, toluene, 80 °C, 3.5 h, 64%. e) Na(Hg), Na_2HPO_4, MeOH, 23 °C, 3.5 h, 99%. f) Sodium bis(2-methoxyethoxy)aluminum hydride, toluene, 110 °C, 1.5 h, 82%.

(+)-**14** in four steps from the commercially available N_α-methoxycarbonyl-L-tryptophan methyl ester (**8**), we focused on the completion of the synthesis of (+)-chimonanthine (**1**, Scheme 4). Under optimal reaction conditions, treatment of the diester (+)-**14** with a mixture of methanol and aqueous potassium hydroxide provided the corresponding dicarboxylic acid in 90% yield. Decarboxylation at the C2- and C2′-position was achieved by sequential conversion into the dicarboxylic acid chloride followed by treatment with tris(trimethylsilyl)silane and AIBN in toluene at 80 °C,[8] to afford the hexacycle (+)-**15** in 64% yield. At this point photochemical[15] conditions for the removal of the benzenesulfonyl groups of **15** led to decomposition whereas strong reductive conditions resulted in cleavage of the benzenesulfonyl groups and fragmentation of the C3−C3′ bond, as supported by the isolation (61%) of *N*-methoxycarbonyltryptamine. Significantly, treatment of a methanolic solution of hexacycle (+)-**15** and sodium phosphate dibasic with freshly prepared sodium amalgam[16] afforded the desired diamine (+)-**16** in 99% yield and greater than 99% *ee*. Reduction of the two *N*-methoxycarbonyl groups of **16** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) gave (+)-chimonanthine (**1**) in 82% yield. The structure of synthetic (+)-**1** was confirmed by single-crystal X-ray analysis (Scheme 4).[7]

Dissolution of (+)-**1** in a mixture of [D$_4$]acetic acid and deuterium oxide followed by heating to 95 °C led to formation of the isomeric calycanthine (**3**, Scheme 5).[17] We monitored this transformation in situ by ^{1}H NMR spectroscopy, which revealed an equilibrium was established between **1** and **3** within 24 h in favor of calycanthine (ca. 85:15 **3**/**1**). Chromatographic separation of the mixture afforded a 54% yield of (−)-**3** along with recovered chimonanthine (5%). We obtained clear evidence for this equilibrium ratio when (−)-**3** was subject to identical conditions and the same ratio was reached between **1** and **3** within 24 h. N-Methylation of (+)-**1** using formalin and sodium triacetoxyborohydride provided the first synthetic sample of (+)-folicanthine (**2**) in quantitative yield (Scheme 5).[7,18]



(−)-calycanthine (**3**)   (+)-folicanthine (**2**)

Scheme 5. Synthesis of (−)-calycanthine and (+)-folicanthine: a) [D$_4$]acetic acid, D$_2$O, 95 °C, 24 h; 54% of (−)-**3** and 5% of (+)-**1** isolated; b) aq formaldehyde, NaBH(OAc)$_3$, MeCN, 23 °C, 30 min, 100%.

The concise and efficient total synthesis of (+)-chimonanthine, (+)-folicanthine, and (−)-calycanthine is described. The convergent assembly of these alkaloids used a reductive Co$^{\mathrm{I}}$-promoted dimerization of the readily available *endo* bromide (+)-**11**. The gram-scale synthesis of the enantiomerically enriched hexacycle (+)-**14** provided a ready access to the optically active alkaloids **1**–**3**. This chemistry simultaneously secures the vicinal quaternary stereocenters directed by the stereochemistry at the C8a-position, and offers the shortest enantioselective synthesis of these alkaloids from commercially available materials. The application of this chemistry to more complex hexahydropyrroloindole alkaloids will be reported in due course.

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