J|A|C|S
COMMUNICATIONS

Published on Web 07/10/2002

Enantioselective Total Synthesis of Quadrigemine C and Psycholeine

Alec D. Lebsack, J. T. Link,[1a] Larry E. Overman,* and Brian A. Stearns[1b]

Department of Chemistry, 516 Rowland Hall, University of California Irvine, California 92697-2025

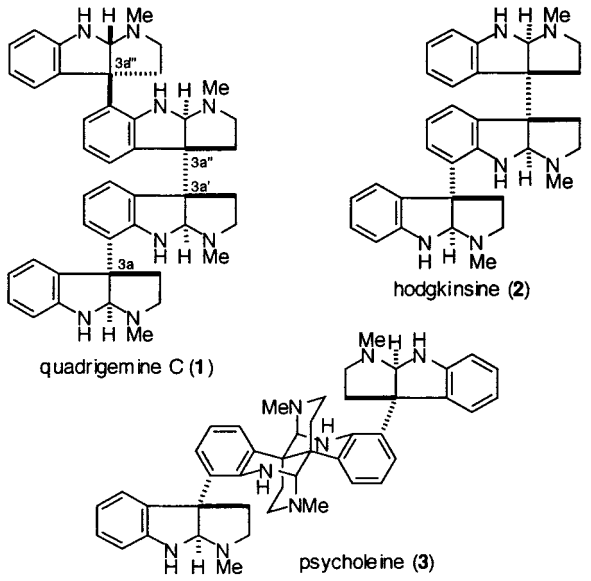
Received April 30, 2002

Quadrigemine C (**1**) is representative of the higher-order members of a remarkable series of N_b-methyltryptamine-derived plant alkaloids that link together two to eight pyrrolidinoindoline units.[2] First described in 1987 from an extract of *Psychotria oleoides* found in New Caledonia,[3] quadrigemine C (**1**) subsequently was isolated from *Psychotria colorata*, a plant used by indigenous peoples of the Amazon for treating pain.[4] The relative and absolute configuration of quadrigemine C (**1**) was proposed in 1992 by Sévenet and co-workers, who also identified an isomeric alkaloid, psycholeine (**3**), from the same extract.[5] The *R* absolute configuration of the two outer quaternary carbons of **1** is firmly established,[6] whereas the configuration of the central hexacyclic unit is less secure, being formulated on the basis of the similarities of NMR and circular dichroism measurements of quadrigemine C (**1**) with those of the simpler alkaloid hodgkinsine (**2**).[5,6] Quadrigemine C (**1**) is reported to exhibit significant antibacterial[7] and analgesic activity[4] and, like psycholeine (**3**), to be a weak antagonist of the SRIF (somatostatin) receptor.[8]

Stimulated by the unusual structures and varied biological activities of higher-order polypyrrolidinoindoline alkaloids,[2] we initiated a program to develop chemistry that would allow various members of this polycyclic alkaloid family and their congeners to be prepared by chemical synthesis.[9] Quadrigemine C (**1**) exemplifies the two formidable synthetic challenges posed by higher-order polypyrrolidinoindoline alkaloids: the contiguous stereogenic quaternary carbons 3a′ and 3a″ and the stereogenic diaryl quaternary carbons 3a and 3a‴. We report herein implementation of the methods we have developed for dealing with these issues[9,10] to concisely prepare quadrigemine C (**1**) and psycholeine (**3**).

As quaternary carbons 3a and 3a‴ of **1** have the same absolute configuration, our strategy was to use catalytic asymmetric Heck cyclizations[10] to desymmetrize an advanced *meso* intermediate and simultaneously install the two peripheral quaternary stereocenters.[11−13] The synthesis began with *meso*-chimonanthine (**4**), which was synthesized from commercially available oxindole and isatin in 13 steps and 35% overall yield (Scheme 1).[9c] The aniline nitrogens of **4** were protected by premixing **4** with 2.2 equiv of di-*tert*-butyl dicarbonate (Boc_2O), followed by adding excess sodium bis(trimethylsilyl)amide. Using these optimized conditions, dicarbamate **5** was produced in 77% yield. Double ortho-lithiation of **5** with 5 equiv of *s*-BuLi at −78 °C and subsequent quenching with 10 equiv of 1,2-diiodoethane delivered crystalline diiodide **6** in 88% yield.[14] Exposure of this intermediate to TMSOTf in CH_2Cl_2 cleaved the *tert*-butoxycarbonyl groups to afford diiodide **7** in 97% yield. Chemoselective double Stille cross coupling of diiodide **7** with stannane **8**[15] was realized using a catalyst system derived from $Pd_2(dba)_3{\cdot}CHCl_3$, tri-2-furylphosphine[16] and CuI[17] to give *meso* dibutenanilide **9** in 71% yield.

The pivotal, catalyst-controlled double Heck cyclization of **9** was accomplished at 80 °C in acetonitrile using $Pd(OAc)_2$ as precatalyst,



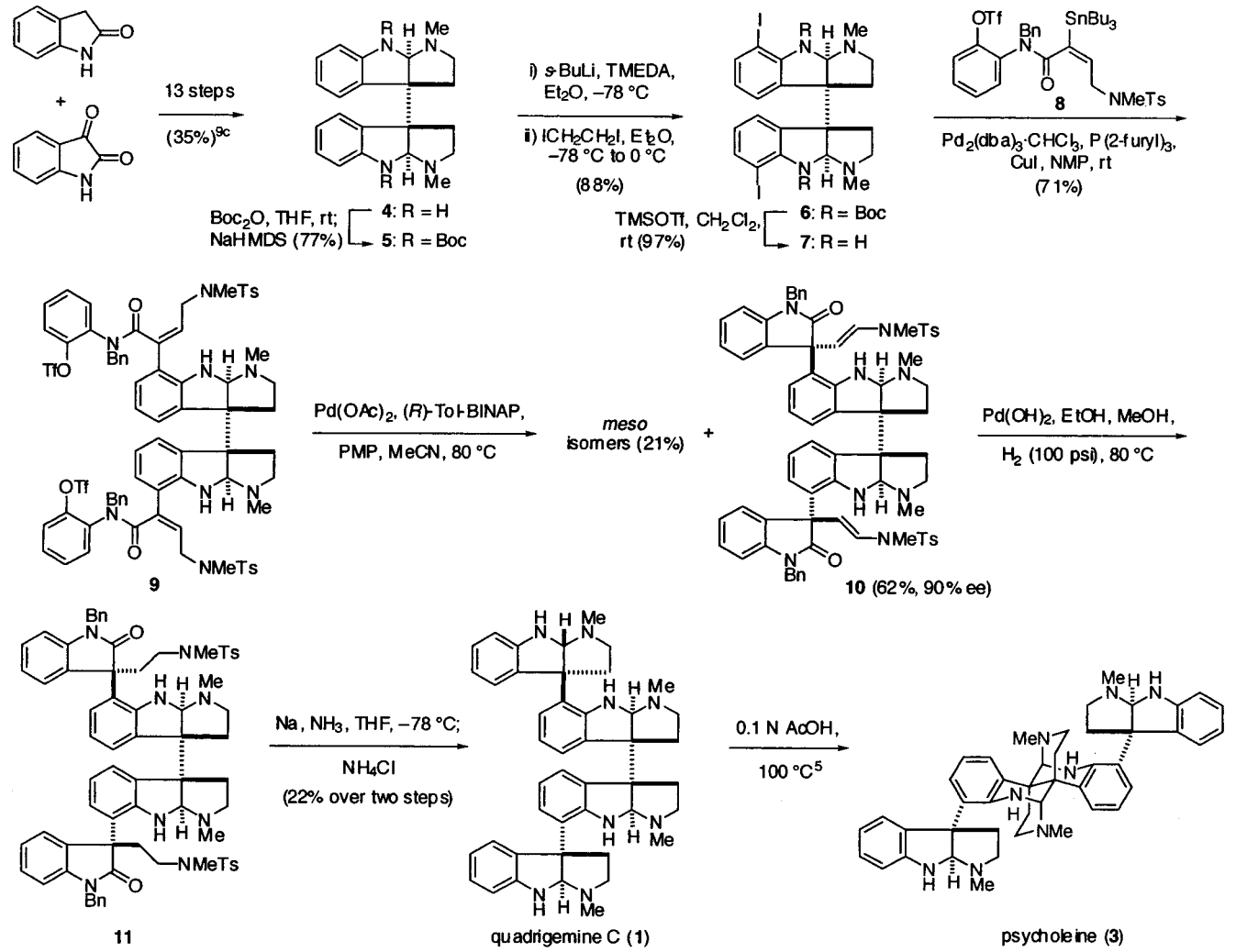
(*R*)-Tol-BINAP as ligand, and 1,2,2,6,6-pentamethylpiperidine (PMP) as base.[18] The major product formed under these conditions was the C_1-symmetric dioxindole **10**, which could be isolated in 62% yield (90% ee) after chromatographic purification. Also formed in this reaction were minor amounts (14 and 7% yields) of two *meso* dioxindole products of unknown relative configuration.[19] As separation of these stereoisomers was difficult, the isomer mixture was hydrogenated under 100 psi of H_2 in 10:1 EtOH−MeOH at 80 °C in the presence of $Pd(OH)_2$ to provide **11** contaminated with corresponding amounts of two *meso* stereoisomers. Exposure of this product to a large excess of sodium in THF−NH_3 at −78 °C for 20 min, followed by addition of solid NH_4Cl provided quadrigemine C (**1**) in 22% overall yield from **10** after purification by HPLC. In this final synthetic step, the four protecting groups of **11** are removed, the two oxindole carbonyl groups are reduced, and the final two rings are formed.[20] The optical rotation of synthetic **1**, $[\alpha]^{27}_D$ −66.5, compares well with that reported for the natural isolate,[5] $[\alpha]^{27}_D$ −69.0, as do other spectral (^1H and ^{13}C NMR, HRMS, and CD) and chromatographic (HPLC and TLC) properties. Synthetic psycholeine (**3**), $[\alpha]^{27}_D$ −150 (lit.[5] $[\alpha]^{27}_D$ −150) was obtained in 38% yield from synthetic **1** by acid-catalyzed isomerization.[5]

In summary, the first total synthesis of a higher-order member of the polypyrrolidinoindoline alkaloid family has been accomplished. The synthesis of quadrigemine C (**1**), which rigorously confirms its relative and absolute configuration, was executed in 19 linear steps from commercially available starting materials. At this stage of refinement, the overall yield is 2%. When properly orchestrated, the chemistry introduced here and in our earlier total syntheses of *meso*-, (+)-, and (−)-chimonanthine[9] should allow

* To whom correspondence should be addressed. E-mail: leoverma@uci.edu.

10.1021/ja0267425 CCC: $22.00

Scheme 1



many complex polypyrrolidinoindoline alkaloids and their analogues to be obtained by sterocontrolled chemical synthesis.

Acknowledgment. We thank NIH (HL-25854) for financial support, Professor Françoise Guéritte-Voegelein for a sample of quadrigemine C, and Mr. Jeremy Kodanko for advice and developing the synthesis of **8**. Fellowship support to J.T.L. (American Cancer Society), B.A.S. (Bristol-Myers Squibb), and A.D.L. (Pharmacia) is gratefully acknowledged.

Supporting Information Available: Experimental procedures for the preparation of **1**, **3**, **5**, **6**, **7**, **8**, **9**, **10**, and **11**; copies of ^{1}H and ^{13}C NMR spectra of these compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Current addresses: (a) Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-6098. (b) Merck Research Laboratories, 3535 General Atomics Court, San Diego, CA 92121.
(2) Anthoni, U.; Christophersen, C.; Nielsen, P. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1999; Vol. 14, pp 163−236.
(3) Libot, F.; Miet, C.; Kunesch, N.; Poisson, J. E.; Pusset, J.; Sévenet, T. *J. Nat. Prod.* **1987**, *50*, 468−473.
(4) Verotta, L.; Pilati, T.; Tatø, M.; Eilsabetsky, E.; Amador, T. A.; Nunes, D. S. *J. Nat. Prod.* **1998**, *61*, 392−396.
(5) Guéritte-Voegelein, F.; Sévenet, T.; Pusset, J.; Adeline, M. T.; Gillet, B.; Beloeil, J. C.; Guenard, D.; Potier, P. *J. Nat. Prod.* **1992**, *55*, 923−930.
(6) Jannic, V.; Guéritte, F.; Laprévote, O.; Serani, L.; Martin, M.-T.; Sévenet, T.; Potier, P. *J. Nat. Prod.* **1999**, *62*, 838−843.
(7) Saad, H.-E. A.; El-Sharkawy, S. H.; Shier, W. T. *Planta Med.* **1995**, *61*, 313−316.
(8) Rasolonjanahary, R.; Sévenet, T.; Voegelein, F. G.; Kordon, C. *Eur. J. Pharmacol.* **1995**, *285*, 19−23.
(9) (a) Link, J. T.; Overman, L. E. *J. Am. Chem. Soc.* **1996**, *118*, 8166−8167. (b) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702−7703. (c) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213-215.
(10) (a) Ashimori, A. Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (c) Oestreich, M.; Dennison, P. R.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1439−1442.
(11) This approach represents an uncommon variant of two-directional synthesis.[12] In the present case, reagent control is employed to simultaneously functionalize both termini.[13]
(12) For reviews, see: (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563−566. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. (c) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213.
(13) For the first report of this strategy, see: Wang, Z.; Deschênes *J. Am. Chem. Soc.* **1992**, *114*, 1090−1091.
(14) Iwao, M.; Kuraishi, T. *Org Synth.* **1996**, *73*, 85−93.
(15) Stannane **8** was synthesized in four steps from commercially available 3*H*-benzooxazol-2-one (see Supporting Information).
(16) Farina, V.; Krishnan, B. J. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.
(17) (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364. (b) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600−7605.
(18) The catalyst generated from $Pd(OAc)_2$ and (*R*)-BINAP was less selective and provided **10** in lower yield and 65% ee.
(19) Four dioxindole products are possible, two *meso* isomers and a pair of C_1-symmetric enantiomers.
(20) Sodium (in ethanol) was the reductant employed in the first reported conversion of a 3-(2-aminoethyl)oxindole to a pyrrolidinoindoline: Julian, P. L.; Pikl, J. *J. Am. Chem. Soc.* **1935**, *57*, 539−544.

JA0267425