

Regiospecific, Enantiospecific Total Synthesis of C-19 Methyl Substituted Sarpagine Alkaloids Dihydroperaksine-17-al and Dihydroperaksine

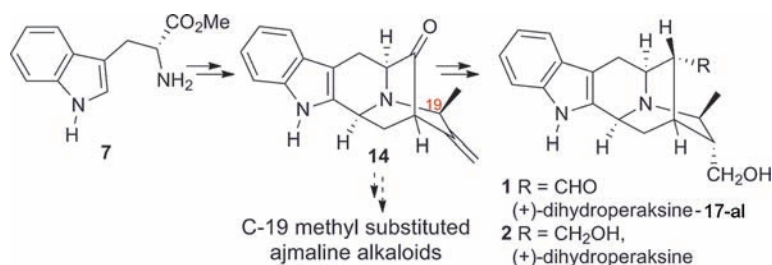
Rahul V. Edwankar,[†] Chitra R. Edwankar,[†] Jeffrey Deschamps,[‡] and James M. Cook^{*,†}

Department of Chemistry & Biochemistry, University of Wisconsin–Milwaukee, Milwaukee, Wisconsin 53201, United States, and Center for Biomolecular Science and Engineering, Naval Research Laboratory, Code 6930, Washington, D.C. 20375, United States

capncook@uwm.edu

Received August 2, 2011

ABSTRACT



The optically active tetracyclic ketone **8** was converted into the pentacyclic core **14** of the C-19 methyl substituted *N*_a-H sarpagine and ajmaline alkaloids via a critical haloboration reaction. The ketone **14** was then employed in the total synthesis of 19(*S*),20(*R*)-dihydroperaksine-17-al (**1**) and 19(*S*),20(*R*)-dihydroperaksine (**2**). The key regioselective hydroboration and controlled oxidation–epimerization sequence developed in this approach should provide a general method to functionalize the C(20)–C(21) double bond in the ajmaline-related indole alkaloids.

The root of *Rauwolfia serpentina* Benth (N.O. Apocynaceae) has been in use in India for hundreds of years for a host of unrelated ailments.¹ The plant has gained universal acclamation as a useful therapeutic weapon in the treatment of high blood pressure.² The presence of high concentrations of alkaloids and other phytochemicals has provided a basis for the ethnomedical use of this plant in treating various medical conditions.³ The monoterpene sarpagine indole alkaloids 19(*S*),20(*R*)-dihydroperaksine-17-al (**1**) and 19(*S*),20(*R*)-dihydroperaksine (**2**) (Figure 1) were isolated from the hairy root culture of *Rauwolfia*

serpentina by Stöckigt et al.⁴ along with 16 known alkaloids. The structures of these novel C-19 methyl substituted alkaloids were elucidated via analysis of 1D and 2D NMR spectroscopy. In addition to the asymmetric centers at C-3(*S*), C-5(*S*), C-15(*R*), and C-16(*R*) of the sarpagine framework,^{5a} the existence of a β-methyl group at C-19 and the α-primary hydroxyl group at C-20 attracted our attention. A number of alkaloids are known which belong to the sarpagine-ajmaline series, and share this unique feature.^{5b} These include the sarpagine alkaloids 10-hydroxy dihydroperaksine (**3**),⁴ *O*-acetyl preperakine (**4**),^{5,6} and

[†] University of Wisconsin–Milwaukee.

[‡] Naval Research Laboratory.

(1) Ebadi, M. *Pharmacodynamic Basis of Herbal Medicine*, 2nd ed.; CRC Press: Boca Raton, FL, 2006; Chapter 56, pp 515–519.

(2) (a) Vakil, R. J. *Brit. Heart J.* **1949**, *11*, 350. (b) Vakil, R. J. *Circulation* **1955**, *12*, 220.

(3) Harisaranraj, R.; Suresh, K.; Saravanababu, S. *Advan. Biol. Res.* **2009**, *3*, 174.

(4) Sheludko, Y.; Gerasimenko, I.; Kolshorn, H.; Stöckigt, J. *J. Nat. Prod.* **2002**, *65*, 1006.

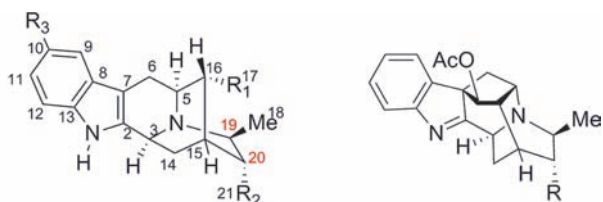
(5) (a) Lounasmaa, M.; Hanhinen, P.; Westersund, M. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1999; Vol. 52, pp 103–195 and references cited therein. (b) Lounasmaa, M.; Hanhinen, P. *J. Nat. Prod.* **2000**, *63*, 1456.

(6) (a) Akinloye, B. A.; Court, W. E. *Planta Med.* **1979**, *37*, 361. (b) Stereochemistry at C-20 depicted as per ref 5b.

(7) Lounasmaa, M.; Hanhinen, P. *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2001; Vol. 55, pp 1–89.

(8) Ulshafer, P. R.; Bartlett, M. F.; Dorfman, L.; Gillen, M. A.; Schlittler, E.; Wenkert, E. *Tetrahedron Lett.* **1961**, 363.

the ajmaline-related alkaloids perakine (**5**)^{5b,7,8} and raucaffrinoline (**6**)^{5b,7,9} illustrated in Figure 1, as well as macrosalpine chloride,⁵ peraksine,⁵ verticillatine,⁵ 10-methoxyperakine,^{5b,7} and vincawajine.^{5b,7} No enantiospecific total synthesis of this class of sarpagine-ajmaline alkaloids has appeared to date.



- 1 R₁ = CHO, R₂ = CH₂OH, R₃ = H,
(+)-dihydroperaksine-17-al,
2 R₁ = CH₂OH, R₂ = CH₂OH, R₃ = H,
(+)-dihydroperaksine,
3 R₁ = CH₂OH, R₂ = CH₂OH, R₃ = OH,
(+)-10-hydroxy dihydroperaksine
4 R₁ = CH₂OAc, R₂ = CHO, R₃ = H,
(+)-O-acetyl preperakine^{6b}
5 R = CHO,
(+)-perakine
6 R = CH₂OH,
(+)-raucaffrinoline

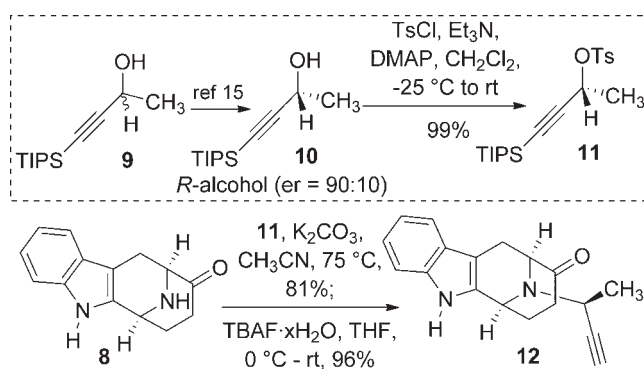
Figure 1. Sarpagine-ajmaline alkaloids containing additional chiral centers at C-19(*S*) and C-20(*R*).

An objective of this research effort was to gain entry into the C-19 methyl substituted sarpagine series which would permit a study of the potential synthesis of the northern hemisphere of the bisindole alkaloid macrospegatrine,¹⁰ and the basic pentacyclic framework **14** would also serve as the template for the synthesis of the biogenetically important ajmaline alkaloids, perakine (**5**) and raucaffrinoline (**6**).¹¹ The fact that a biogenetic link exists between the sarpagine and ajmaline alkaloids proposed by Stöckigt et al.¹² can be employed to achieve this interconversion. Herein we report the first enantiospecific total synthesis of the C-19 substituted sarpagine indole alkaloids (+)-dihydroperaksine-17-al (**1**) and (+)-dihydroperaksine (**2**).

The synthesis began with the enantiospecific, stereospecific preparation of the (–)-*N*_a-H, *N*_b-H tetracyclic ketone **8** from *D*-tryptophan methyl ester **7** on a multihundred gram scale following the procedure developed in Milwaukee.¹³ In order to introduce the desired stereocenter at C-19 into the sarpagan skeleton, the synthesis of the optically active *R*-acetylenic tosylate **11** was carried out as illustrated in Scheme 1. The racemic TIPS propargylic alcohol **9** was synthesized according to the procedure of Jones et al.¹⁴ from commercially available triisopropylsilyl

acetylene in 95% yield. The optically active *R*-propargylic alcohol **10** [enantiomeric ratio (er) = 90:10] was synthesized from **9** via a two step oxidation/asymmetric hydrogenation sequence under the conditions developed by Marshall et al.¹⁵ for the *S*-propargylic alcohol. The asymmetric hydrogenation was performed on a 25 g scale with little erosion of the er. Treatment of the optically active *R*-alcohol **10** with 2.2 equiv of tosyl chloride in the presence of 4 equiv of triethylamine at –25 °C in dichloromethane for 3.5 h provided the *R*-tosylate **11**. An S_N2 alkylation of the *N*_b-nitrogen function in **8** with the tosylate **11** took place smoothly in dry acetonitrile/K₂CO₃ to provide the alkylated ketone which was then treated with tetrabutylammonium fluoride (TBAF·xH₂O) at 0 °C in THF to provide the acetylenic ketone **12** in 96% yield (Scheme 1).

Scheme 1. Synthesis of the Acetylenic Ketone **12**



The simplest method for converting terminal alkynes to vinyl iodides in a single step is by the use of HI¹⁶ which is not useful especially for sensitive substrates. Although other methods are reported¹⁷ to achieve this important conversion, there are very few reports on the direct synthesis of α-vinyl iodides from terminal alkynes.¹⁸ In 1983 Suzuki et al.¹⁹ reported the regioselective haloboration of terminal alkynes with B-bromo- or B-iodo-9-BBN [BBN: borabicyclo(3.3.1)nonane] to furnish the respective α-vinyl halides in excellent yields and very high regioselectivities. Initial attempts at haloboration of **12**, under these

(15) Marshall, J. A.; Eidam, P.; Eidam, H. S. *Org. Synth.* **2007**, *84*, 120.

(16) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 6th ed.; Wiley-Interscience: Hoboken, NJ, 2007; Chapter 15, pp 999–1250.

(17) (a) Katagiri, T.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2008**, *49*, 3242. (b) Va, P.; Roush, W. R. *Tetrahedron* **2007**, *63*, 5768. (c) Nielsen, T. E.; Le Quement, S.; Tanner, D. *Synthesis* **2004**, 1381. (d) Kazmaier, U.; Pohlman, M.; Schauss, D. *Eur. J. Org. Chem.* **2000**, 2761. (e) Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.* **1988**, 881.

(18) (a) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961. (b) Kawaguchi, S.; Ogawa, A. *Org. Lett.* **2010**, *12*, 1893. (c) Campos, P. J.; García, B.; Rodríguez, M. A. *Tetrahedron Lett.* **2002**, *43*, 6111. (d) Reddy, C. K.; Periasamy, M. *Tetrahedron Lett.* **1990**, *31*, 1919. (e) Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675. (f) Gras, J.-L.; Kong Win Chang, Y. Y.; Bertrand, M. *Tetrahedron Lett.* **1982**, *23*, 3571.

(19) (a) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731. (b) Suzuki, A. *Rev. Heteroatom. Chem.* **1997**, *17*, 271.

(9) Libot, F.; Kunesch, N.; Poisson, J. *Phytochemistry* **1980**, *19*, 989.

(10) Lin, X.; Zheng, Q.; Zhang, Y. *J. Struct. Chem.* **1987**, *6*, 89.

(11) Takayama, H.; Phisalaphong, C.; Kitajima, M.; Aimi, N.; Sakai, S.; Stöckigt, J. *Chem. Pharm. Bull.* **1991**, *39*, 266.

(12) (a) Pfitzner, A.; Stöckigt, J. *Tetrahedron Lett.* **1983**, *24*, 5197.

(b) Ruppert, M.; Ma, X.; Stöckigt, J. *Curr. Org. Chem.* **2005**, *9*, 1431.

(13) Yu, P.; Wang, T.; Li, J.; Cook, J. M. *J. Org. Chem.* **2000**, *65*, 3173.

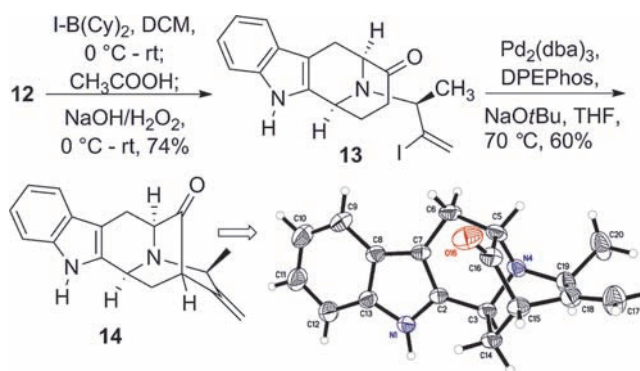
(14) Jones, G. B.; Wright, J. M.; Plourde, G. W., II; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937.

conditions, were accompanied by inconsistent reproducibility, purification problems, and very low yields. At best, up to 30% yield of the vinyl iodide **13** could be achieved by this method after varying many parameters. It was felt that the first few equivalents of the borane reagent resulted in complexation of the boron reagent to the ketone in **12** and created a steric cloud, which prevented/slowed further reaction of B-I-9-BBN from approaching the acetylenic function. With such low yields obtained in this critical step, attention turned to the use of other reagents that could be employed to achieve this conversion. The order of reactivity²⁰ of the haloborating reagents commonly used is: B-I-9-BBN, BBr₃ > BCl₃ > B-Br-9-BBN ≫ B-Cl-9-BBN. Although BBr₃ is equivalent in reactivity to B-I-9-BBN the propensity of the N_b-nitrogen in **12**, to form stable borane complexes with smaller boranes as observed earlier in a similar sarpagine framework²¹ and possibly altering the course of the reaction at the terminal alkyne, rendered it unsuitable.

The haloboranes, B-I-9-BBN, and dicyclohexylidoborane [I-B(Cy)₂] have been employed for the synthesis of (*Z*)-enolborinates exclusively from various ethyl ketones.²² I-B(Cy)₂ is also a highly stereoselective reagent for the enolboration of esters²³ and tertiary amides.²⁴ If all other parameters are kept the same, the inability of B-I-9-BBN to drive the haloboration reaction to completion was felt to be due to the rigid skeleton of the bicyclo ring of B-I-9-BBN as a major factor. In contrast, the two cyclohexyl rings of I-B(Cy)₂ are conformationally more flexible and should be able to adjust to the neighboring environment. As anticipated, the alkyne **12** on stirring with 2.5 equiv of I-B(Cy)₂ (added in two portions) furnished the desired boron adduct with complete consumption of the starting material **12** (Scheme 2). Subsequent protonolysis with acetic acid generated the vinyl iodide **13**. A modified workup was employed to ensure complete decomposition of excess borane, excess iodine, baseline impurities, and other boron impurities which were previously observed in the aliphatic region of the NMR spectrum with B-I-9BBN. With this improved procedure 74% of pure iodo-olefin **13** was achieved. To our knowledge, this is the first example of I-B(Cy)₂ as the haloboration reagent for terminal alkynes. The iodo-olefin **13** was then subjected to the conditions of the recently developed palladium catalyzed α -vinylation²⁵ to generate the key pentacyclic system **14** in 60% isolated yield (Scheme 2). The *S*-configuration at C-19 was confirmed by X-ray analysis of **14**.

With the critical formation of the E ring in place, the pentacyclic ketone **14** was subjected to a one carbon atom homologation process at C-16 to provide the

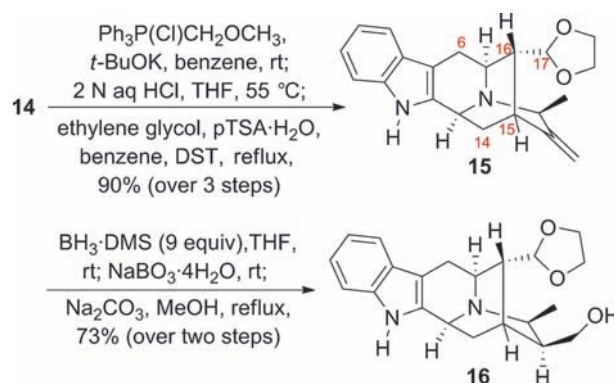
Scheme 2. Synthesis of the Pentacyclic Ketone **14**^a



^a Sarpagine numbering not followed.

thermodynamically stable C-17 α -aldehyde even with the presence of the C-19 methyl group in the β -position, via a Wittig–hydrolysis–epimerization sequence (Scheme 3). The aldehydic group was then protected as the cyclic acetal **15** with ethylene glycol in the presence of *p*-toluene sulfonic acid monohydrate (pTSA·H₂O) in refluxing benzene. With the acetal olefin **15** readily available, the hydroboration–oxidation sequence was employed to functionalize C-20. As illustrated in Scheme 3, the desired primary alcohol **16**, accompanied by the tertiary alcohol, was obtained in the ratio 25:1 (both obtained as N_b-borane complexes as observed in other sarpagine systems).²⁶ Clearly hydroboration of the C(20)–C(21) terminal olefinic bond had taken place from the α -face and supported its hindered nature from the β -face. The mixture of N_b-borane complexes of the primary alcohol **16** and tertiary alcohol was stirred in the presence of 5 equiv of sodium carbonate in refluxing methanol for 5 h, after which the desired β -primary alcohol **16** along with tertiary alcohol was obtained with the free N_b nitrogen function in 88% yield.

Scheme 3. Regioselective Hydroboration^a



^a DST = Dean–Stark trap.

(20) Suzuki, A.; Brown, H. C. *Organic Synthesis Via Boranes*; Aldrich Chemical Company, Inc.: Milwaukee, WI, 2003; Vol. 3, Chapter 2, pp 5–36.

(21) Liu, X.; Cook, J. M. *Org. Lett.* **2002**, 3, 4023.

(22) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1993**, 58, 147.

(23) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, 59, 2336.

(24) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, 59, 7346.

(25) Liao, X.; Zhou, H.; Yu, J.; Cook, J. M. *J. Org. Chem.* **2006**, 71, 8884.

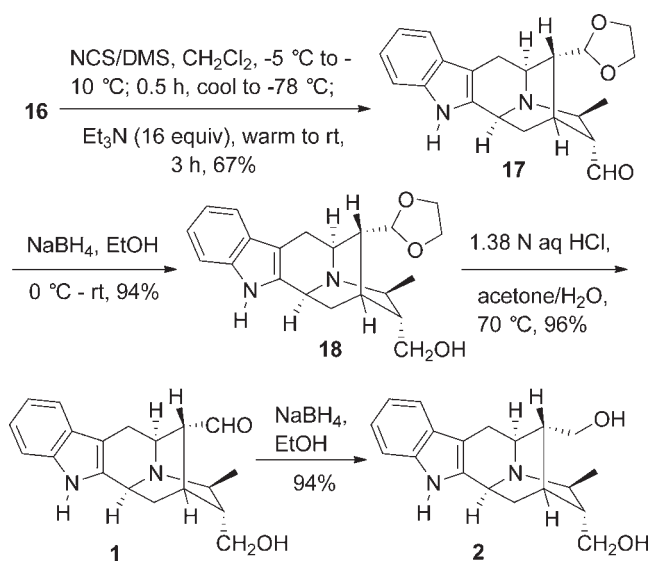
Because of the basicity of the N_b -nitrogen function in the sarpagine framework and the electron-rich character of the indole nucleus (especially with the indole N_a -H function), the oxidation of the primary alcohol **16** was a much bigger problem than earlier anticipated. Oxidation of **16** under various conditions²⁷ always led to the formation of trace amounts of the aldehyde accompanied by the aldehyde N_b -oxide and some overoxidized byproduct. A modified Corey–Kim oxidation (with lesser equivalents of the reagent and lower temperature) completely eliminated the formation of any overoxidized byproducts with sole formation of the epimeric α,β -aldehydes. Complete epimerization to the α -aldehyde **17** (67% yield) was achieved in the same reaction vessel by addition of a large excess of triethylamine (up to 16 equiv) and stirring the reaction mixture at room temperature (up to 3 h) (Scheme 4). The α -aldehyde **17** was then reduced with sodium borohydride in ethanol for 3 h at room temperature to furnish the α -alcohol **18** in 94% yield. The acetal group in **18** was cleaved under acidic conditions (1.38 N aqueous HCl) in refluxing acetone. Advantage was taken of the basicity of the N_b -nitrogen function to remove all the nonalkaloidal impurities by washing the aqueous layer containing the HCl salt of the alkaloid with ether, followed by regeneration of the free amine by treatment with 10% aqueous ammonium hydroxide. This completed the first regiospecific, enantiospecific total synthesis of (+)-dihydroperaksine-17-al (**1**) in 96% yield. Reduction of **1** with sodium borohydride completed the first total synthesis of (+)-dihydroperaksine (**2**) as well (Scheme 4). The synthetic alkaloids **1** and **2** were identical on TLC (including a mixed TLC sample) to the sample of natural (+)-dihydroperaksine-17-al (**1**) and natural (+)-dihydroperaksine (**2**) kindly supplied by Professor Joachim Stöckigt at Johannes Gutenberg-University (Germany).²⁸ The spectral data of **1** (¹H and ¹³C NMR) are in complete agreement with those of the natural product. For compound **2**, some ambiguity was observed in the ¹H NMR (difference in chemical shifts), and a ¹³C NMR comparison between it and the natural product indicated that C-15 and C-6 carbon atoms were interchanged. A detailed NMR analysis of the synthetic alkaloid **2** including ¹³C DEPT 135 as well as 2D COSY, HSQC, NOESY, and 1D NOE experiments (see Supporting Information) unequivocally support the structure as indicated in Scheme 4, in agreement with that of natural (+)-dihydroperaksine (**2**).

(26) Edwankar, C. R.; Edwankar, R. V.; Rallapalli, S. K.; Cook, J. M. *Nat. Prod. Commun.* **2008**, *3*, 1389.

(27) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (c) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

(28) Currently Dr. J. Stöckigt is Professor at the College of Pharmaceutical Sciences, Zhejiang University (Hangzhou, China) and retired from the Institute of Pharmacy, Johannes Gutenberg-University, Mainz, Germany.

Scheme 4. Completion of the Total Synthesis of Dihydroperaksine-17-al (**1**) and Dihydroperaksine (**2**)



In summary, the first enantiospecific, stereospecific total synthesis of 19(*S*),20(*R*)-dihydroperaksine-17-al (**1**) and 19(*S*),20(*R*)-dihydroperaksine (**2**) has been accomplished in overall yields of 10.2% (14 reaction vessels) and 9.6% (15 reaction vessels), respectively, from commercially available D-(+)-tryptophan methyl ester **7**. The critical haloboration of terminal alkyne **12** was achieved by employing dicyclohexylidoborane as the haloborating agent for the first time. The stereospecific synthesis of the core pentacyclic ketone **14** contained in the C-19 methyl substituted sarpagine alkaloids thus provides a potentially general entry into a whole series of biosynthetically important monoterpene C-19 substituted indole alkaloids.

Acknowledgment. We thank Professor J. Stöckigt (Johannes Gutenberg-University)²⁸ for providing samples of **1** and **2** for TLC comparison. We wish to acknowledge NIMH (in part) and the Lynde and Harry Bradley Foundation for support of this work. X-ray crystallographic studies were supported by NIDA-NRL Interagency Agreement Number Y1-DA1101.

Supporting Information Available. Experimental procedures and spectral data for all new compounds including X-ray data for **14** and ¹H and ¹³C comparison tables between natural and synthetic **1** and **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.