ORGANIC LETTERS

2000
Vol. 2, No. 2
99−102

Total Syntheses of (−)-Haemanthidine, (+)-Pretazettine, and (+)-Tazettine

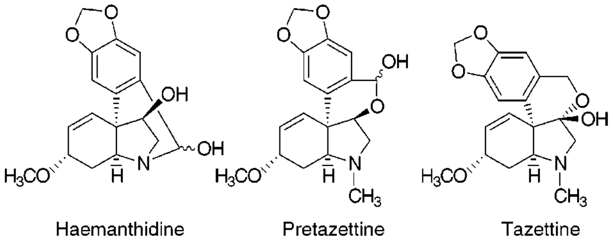
Steven W. Baldwin* and John S. Debenham[†]

Paul M. Gross Chemical Laboratory, Department of Chemistry, Duke University, Durham, North Carolina 27708

baldwin@chem.duke.edu

Received October 14, 1999

ABSTRACT



The total syntheses of the *amaryllidaceae* alkaloids haemanthidine, pretazettine, and tazettine as optically pure enantiomers are reported. Using D-mannose as the starting material, the critical relative stereochemical relationships are established with an intramolecular nitrone–alkene cycloaddition reaction. The synthetic route leads successively to (−)-haemanthidine and then to (+)-pretazettine and (+)-tazettine, taking advantage of the well-established complex relationships among these three alkaloids.

The crinine class of *amaryllidaceae* alkaloids is composed of approximately 50 members that are relatively widely distributed in nature.[1] These alkaloids possess the *cis*-3a-arylhydroindole ring system, the more pharmacologically active members also bearing an hydroxyl group at the 6a-position (pretazettine numbering) that can be either *cis* or *trans* to the adjacent aryl ring. Despite significant accomplishments in the synthesis of the crinine-related alkaloids lacking the 6a-hydroxyl, reliable methods for controlling the relative disposition of the aryl and hydroxyl groups in these important alkaloids have been problematic, as has control of absolute stereochemistry.

Some time ago we began a synthetic program to provide general access to these alkaloids. The initially selected target, pretazettine (**1**), first characterized in the 1960s,[2] has received considerable attention as a synthetic target, although adequate control of the stereochemical issues mentioned above has proved difficult.[3] Reported here are stereocontrolled syntheses of pretazettine and the related alkaloids tazettine (**2**) and haemanthidine (**3**), which afford optically pure materials and which verify that the absolute configurations of the natural

---

[†] Present Address: Eastman Chemical Company, Research Laboratories, P. O. Box 1972, B-150B, Kingsport, TN 37662-5150.

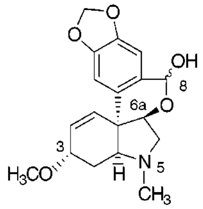
(1) (a) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 107. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed., Academic Press: New York, 1998; Vol. 51, p 323. (c) Martin, S. F. In *The Alkaloids*; Cordell, G. A., Ed., Academic Press: New York, 1987; Vol. 30, p 251.

(2) (a) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749. (b) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150. (c) Furusawa, E.; Furusawa, S.; Tani, S.; Irie, H.; Kitamura, K.; Wildman, W. C. *Chem. Pharm. Bull.* **1976**, *24*, 336. (d) Kobayashi, S.; Takeda, S.; Ishikawa, H.; Matsumoto, H.; Kihara, M.; Shingu, T.; Numata, A.; Uyeo, S. *Chem. Pharm. Bull.* **1976**, *24*, 1537.

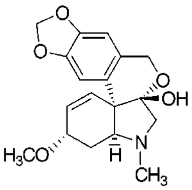
(3) (a) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 5538. (b) Tsuda, Y.; Isobe, K. *J. Chem. Soc., Chem. Commun.* **1971**, 1555. (c) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153. (d) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781. (e) Kobayashi, S.; Kihara, M.; Shingu, T.; Shingu, K. *Chem. Pharm. Bull.* **1980**, *28*, 2924. (f) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591. (g) White, J. D.; Chong, W. K. M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2300. (h) Martin, S. F.; Davidsen, S. K. *J. Am. Chem. Soc.* **1984**, *106*, 6431. (i) Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.*, **1987**, *52*, 1962. (j) Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*. 647. (k) Ishibashi, H.; Nakatani, H.; Iwami, S.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1767. (l) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959. (m) Ishibashi, H.; Uemura, N.; Nakatani, H.; Okazaki, M.; Sato, T.; Nakamumra, N., Ikeda, M. *J. Org. Chem.* **1993**, *58*, 2360. (n) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662. (o) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664. (p) Nishimata, T.; Mori, M. *J. Org. Chem.* **1998**, *63*, 7586.

10.1021/ol9911472 CCC: $19.00

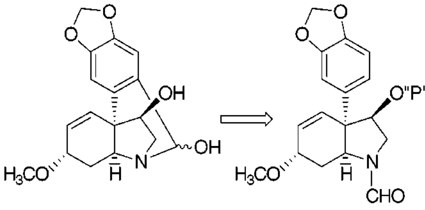
products are as reported. Since this work was completed, another synthesis of optically active (−)-haemanthidine and (+)-pretazettine, as well as (+)-crinamine, has been reported.[3p]



1



2

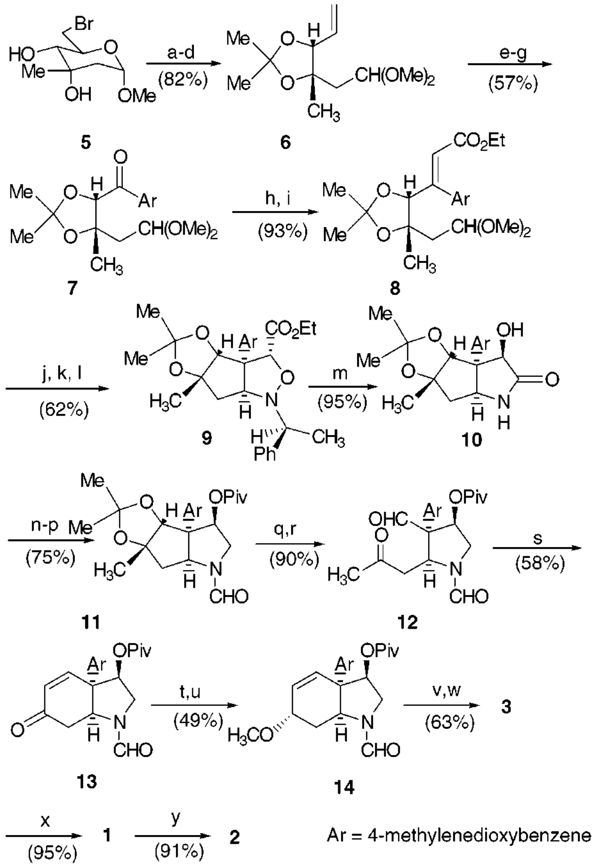


3 **4**

Consistent with the findings of previous workers, our approach to pretazettine takes advantage of the complex relationships that exist among haemanthidine, pretazettine, and tazettine, which have been elegantly detailed by Wildman.[2] In particular, Wildman showed that haemanthidine methiodide is converted to pretazettine under mild conditions and that pretazettine is chemically labile, being further converted to tazettine under basic conditions. It has also been shown that tazettine can be converted back to pretazettine, although with very low efficiency.[3e] Finally, others have demonstrated that haemanthidine can be formed by Bischler−Napieralski cyclization of a suitably substituted aryl hydroindole such as **4**, and this is the route adopted in our studies.[3b,c]

The plan for assembling the requisite aryl hydroindole (e.g., **14**) was to take advantage of an intramolecular nitrone−alkene cycloaddition reaction,[4] as has been outlined in earlier reports from these laboratories.[5] Optically pure products were expected to be the result of employing either an optically active cycloaddition substrate or a chiral auxiliary on the nitrone nitrogen, or both. In practice the requisite nitrone has been prepared from D-mannose, which allows for the unambiguous assignment of the absolute stereochemistry of the final product (Scheme 1).

Scheme 1[a]



[a] Reagents and conditions: (a) $(CH_3)_2C(OCH_3)_2$, TsOH, 80 °C; (b) 2-butanone, NaI, $NaHCO_3$, 80 °C; (c) Zn, EtOH, H_2O, 80 °C; (d) $CH(OCH_3)_3$, Amberlyst 15 resin, 25 °C; (e) O_3, $NaHCO_3$, 2:1 CH_2Cl_2/CH_3OH, −78 °C, then $(CH_3)_2S$, −78 to 25 °C; (f) ArMgBr, THF, 0 to 25 °C; (g) PDC, CH_2Cl_2, 4 Å molecular seives, Ac_2O; (h) LDA, ethyl (trimethylsilyl)acetate, THF, −78 to −50 °C; (i) AIBN, PhSH, benzene, 80 °C; (j) acetone (containing ~0.5% H_2O), Amberlyst 15 resin, 42 °C, 90%; (k) (*S*)-α-methylbenzyl hydroxylamine oxylate, K_2CO_3, benzene, 25 °C; (l) benzene, 55 to 80 °C, 75%; (m) Pd/C, 1:1 THF/CH_3OH, 25 °C; (n) $LiAlH_4$, THF, 60 °C; (o) acetic formic anhydride, THF, −60 to −20 °C; (p) pivaloyl chloride, pyridine, DMAP, 80 °C; (q) TFA, H_2O, 25 °C; (r) $NaIO_4$, 2:1 THF/H_2O, 25 °C; (s) pyrrolidine, acetic acid, benzene, 25 °C; (t) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, CH_3OH, −78 °C; (u) methanesulfonic anhydride, NEt_3, THF, 0 °C, then CH_3OH, −78 to 0 °C; (v) $POCl_3$, 80 °C; (w) LiOH, CH_3OH, 25 °C; (x) CH_3I, CH_3OH, then aq HCl, then $NaHCO_3$ to pH 8, 25 °C; (y) NaOH, CH_3OH, 25 °C.

The synthesis of pretazettine begins with bromo diol **5**, prepared on a 50 g scale from α-methyl-D-mannopyranoside (55% yield for five steps) using modified literature procedures.[6] Protection of the diol as its acetonide followed by reductive fragmentation and acetal formation then afforded **6**. Assembling the necessary trisubstituted alkene of **8** was accomplished by Peterson olefination of ketone **7**, prepared in three steps from **6**. Obtaining the required *trans* relationship between the aryl and hydroxyl groups of pretazettine requires that the aryl and ester groups of **8** have the *cis* relationship found in the indicated E alkene. Treatment of **7** with the lithium enolate of ethyl (trimethylsilyl)acetate according to the usual protocol[7] afforded alkene **8** in 96% yield as a 1.5:1 mixture of double bond isomers enriched in

---

(4) For pertinent reviews of nitrone−alkene cycloaddition reactions. see: (a) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 4, pp 1111−1168. (b) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, pp 83−168. (c) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, pp 277−406.

(5) (a) Baldwin, S. W.; Wilson, J. D.; Aubé, J. A. *J. Org. Chem.* **1985**, *50*, 4432. (b) Baldwin, S. W.; Gedon, S. C. *Synth. Commun.* **1991**, *21*, 587. (c) Baldwin, S. W.; McFadyen, R. B.; Aubé, J. A.; Wilson, J. D. *Tetrahedron Lett.* **1991**, *32*, 4431. (d) Baldwin, S. W.; Aubé, J.; McPhail, A. T. *J. Org. Chem.* **1991**, *56*, 6546.

(6) (a) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1975**, *44*, 227. (b) Thiem, J.; Elvers, J. *Chem. Ber.* **1981**, *114*, 1442. (c) Krohn, K.; Broser, E.; Heins, H. *Carbohydr. Res.* **1987**, *164*, 59.

the unwanted Z isomer. Although adjusting the reaction conditions had little impact on this ratio, it was possible to equilibrate the mixture. Exposure of **8** to thiophenol and AIBN in refluxing benzene[8] led to a 9:91 mixture of Z and E alkenes from which pure **8E** could be isolated by flash chromatography. In practice, pure **8E** could be isolated from **7** in 93% yield from a process involving two olefination reactions and three isomerization cycles. The stereochemical assignment of alkenes **8E** and **8Z** was based on ^{1}H NMR data, specifically the chemical shift of the vinyl protons in the two isomers. This proton was observed at δ 6.29 for the desired isomer **8E** and at δ 5.97 for isomer **8Z**, a trend that has been consistent for several pairs of related compounds in this series. Further justification for this assignment was the significant NOE enhancement observed between the vinyl proton of **8Z** and the isolated ortho proton in the aryl ring; a similar enhancement was not seen for isomer **8E**.

The necessary stereochemical outcome of the cycloaddition step at C-4a and C-6b (*cis* ring fusion, pretazettine numbering) was anticipated on the basis of earlier work. For instance, one set of model studies suggested that the acetonide ring would lead to a slight preference (~3:1) for a *cis/anti/cis* cycloadduct.[5b] Furthermore, other studies had indicated that the (*R*)-α-methylbenzyl substituent on the nitrone nitrogen would favor the creation of the C-4a stereogenic center with the desired S configuration, creating the opportunity for an exercise in double diastereoselection.[5c,d] Hydrolysis of the dimethyl acetal followed by treatment with (*R*)-α-methylbenzyl hydroxylamine[9] then afforded the nitrone, which without purification was heated at 80 °C in benzene for 17 h to yield cycloadduct **9** in 65% yield after purification by flash chromatography. The room temperature 400 MHz ^{1}H NMR spectrum of **9** was difficult to interpret because of significant broadening of the signals associated with the isoxazolidine ring. At 90 °C, however, the spectrum was well resolved.

The transformation of cycloadduct **9** to the target alkaloids **1**−**3** was accomplished as outlined. Thus, hydrogenolysis of **9** afforded hydroxy lactam **10** in 95% yield after cleavage of the N−O and benzylic nitrogen bonds followed by intramolecular transamination. That the structure of **10** is as indicated was verified by single-crystal X-ray analysis, proving that the important *trans* relative stereochemical relationship between the aryl and C6a-hydroxyl group had been established. Moreover, by relating these stereocenters to C-4 of the mannose starting material (* in **10**), the absolute configuration of **10**, and of pretazettine (**1**), haemanthidine (**2**), and tazettine (**3**), have been verified.[10]

Conversion of **10** to formamide **14** was accomplished as indicated, the critical transformation being the construction of the cyclohexenone A ring in **13** by aldol cyclization. Several sets of reaction conditions were tried, the best proving to be treatment with pyrrolidine and acetic acid in benzene at ambient temperature. The C-3 α-methoxyl group was installed by Luche reduction[11] of the enone followed by mesylation and methanolysis. It is significant that methanolysis at room temperature produced a 4:1 mixture of the α- and β-methoxyl isomers. In contrast, extended methanolysis at lower temperatures (−25 °C) afforded a 10:1 mixture of the same compounds. It should be noted that ^{1}H NMR analyses of all intermediate compounds between **11** and **14** were complicated by the presence of formamide rotational isomers (~3:2 ratio). Compound **14** (racemic) has been previously prepared and carried on to racemic haemanthidine, pretazettine, and tazettine, and spectral data for the optically active **14** described here were in complete accord.[3h,i]

Transformation of **14** to the title alkaloids pretazettine (**1**), haemanthidine (**2**), and tazettine (**3**) was accomplished efficiently following the original Wildman protocol,[2] as practiced by Martin.[3h,i] Thus, Bischler−Napieralski[12] cyclization of **14** followed by pivalate hydrolysis afforded optically pure haemanthidine (**2**) in 63% yield. Spectroscopic data for this material, including specific rotation, were consistent with those reported for the natural alkaloid. Treatment of haemanthidine (**2**) with methyl iodide followed by stirring with 0.01 M aqueous HCl afforded, after workup and flash chromatography, optically pure pretazettine (**1**) in 95% yield. Finally, exposure of pretazettine to 0.1 M aqueous NaOH led to rapid (<30 min) conversion to tazettine (**3**) in 91% purified yield. All spectroscopic data were in complete accord with those reported for this material. Moreover, the specific rotations of these materials verify that the absolute stereochemistry of (+)-pretazettine, (+)-tazettine, and (−)-haemanthidine are as indicated in structures **1**, **2**, and **3**, respectively.

The considerable length of the synthetic scheme reported here is largely the result of our interest in confirming the absolute stereochemistry of the target alkaloids. Thus, of the total synthetic manipulations required to produce alkaloids **1**−**3** from α-methyl-D-mannopyranoside, nearly half (12) were needed to obtain aryl ketone **7**. We are currently developing alternative efficient routes to **7** and related compounds that take advantage of asymmetric alkene oxidation protocols.

Acknowledgment. We gratefully acknowledge NSF (CHE 95 22580) for financial assistance in the purchase of the 400 MHz NMR instrument used in support of this work. We also thank Dr. Peter White of the Department of Chemistry at the University of North Carolina − Chapel Hill

---

(7) (a) Shimoji, K.; Taguchi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 1620. (b) For a review of Peterson-type olefination reactions, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Elmsford, NY, 1991; Vol. 1, pp 729−817.

(8) Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem.* **1986**, *51*, 260. This equilibration method, originally applied to disubstituted alkenes, has been applied to the trisubstituted analogues for the current work. Details will be provided in due course.

(9) Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron* **1985**, *41*, 3455. An improved preparation of this material will be reported in the full paper.

(10) The original assignment of absolute configuration to these alkaloids was based on tenuous circular dichroism studies, eventually confirmed by the conversion of tazettine to (+)-3-methoxyadipic acid (known configuration). Highet, R. J.; Highet, P. F *Tetrahedron Lett.* **1966**, 4099.

(11) (a) Luche, J. L.; Rodrigues, H. L.; Cragge, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (b) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(12) Fodor, G.; Gal, J.; Phillips, B. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 919.

for the single crystal X-ray analysis of intermediate **11**. The Drug Synthesis and Chemistry Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute is acknowledged with appreciation for the samples of authentic (+)-pretazettine and (+)-tazettine used for obtaining comparison spectra. Finally, we are indebted to Professor James Rigby for providing a 500 MHz ^{1}H NMR comparison spectrum of authentic (+)-tazettine.

Supporting Information Available: Experimental procedures for the preparation of compounds **6**−**14** (including intermediate compounds) and **1**−**3**, with selected analytical data; pertinent crystallographic information for intermediate **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9911472