(2 H, $^1/_2$ AB q, J = 8.9 Hz), 7.34 (5 H, br s).

Compound **27** (140 mg, 0.30 mmol) was mesylated under the standard conditions stated above, giving the title compound **28** [140 mg (86%)] as a colorless oil: $[\alpha]^{20}_D$ -42.0° (c 3.3, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.45 (3 H, d, J = 6.3 Hz), 2.97 (3 H, s), 3.03 (3 H, s), 3.44 (3 H, s), 3.79 (3 H, s), 3.86 (2 H, br s), 4.37 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.62 (1 H, $^1/_2$ AB q, J = 6.7 Hz), 4.65-5.19 (4 H, m), 5.92 (1 H, br d, J = 8.6 Hz), 6.87 (2 H, $^1/_2$ AB q, J = 8.6 Hz), 7.21 (2 H, $^1/_2$ AB q, J = 8.6 Hz), 7.34 (5 H, br s); mass spectrum, m/e (relative intensity) 464 (0.8), 374 (1.0), 324 (4.2), 283 (6.0), 278 (4.2), 266 (4.0), 234 (4.8), 204 (3.0), 148 (40), 121 (20), 91 (100).

(2*R*,3*S*,4*S*,5*R*)-*N*-[(Benzyloxy)carbonyl]-3,4-bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-5-methylpyrrolidine (29). The compound **28** (35 mg, 0.065 mmol) was treated in the same manner as described for the preparation of **14** to give **29** [16 mg (56%)] as a colorless oil: $[\alpha]^{20}_D$ +68.0° (c 0.41, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ ($CHCl_3$) 1.33 (3 H, d, J = 6.1 Hz), 3.28 (3 H, s), 3.38 (3 H, s), 3.81 (3 H, s), 4.20-5.20 (10 H, m), 6.65-7.40 (9 H, m); mass spectrum, m/e (relative intensity) 445 (M^+, 2.7), 414 (2.1), 400 (1.4), 383 (22), 324 (16), 323 (74), 322 (38), 310 (40), 278 (28), 234 (26), 162 (100).

(2*R*,3*S*,4*S*,5*R*)-3,4-Bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (31). A. From 29. In the same manner for the preparation of **15** from **14**, **29** (8 mg, 0.018 mmol) was subjected to $LiAlH_4$ reduction to give **31** [4.9 mg (84%)] as a colorless oil: $[\alpha]^{20}_D$ -18.7° (c 1.1, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ $CHCl_3$) 1.01 (3 H, d, J = 6.6 Hz), 2.13 (3 H, s), 3.06 (3 H, s), 3.41 (3 H, s), 3.50 (1 H, quint, J = 6.5 Hz), 3.80 (3 H, s), 3.84 (1 H, br s), 4.04-4.38 (4 H, m), 4.69 (1 H, $^1/_2$ AB q, J = 6.3 Hz), 4.78 (1 H, $^1/_2$ AB q, J = 6.3 Hz), 6.85 (2 H, $^1/_2$ AB q, J = 8.8 Hz), 7.24 (2 H, $^1/_2$ AB q, J = 8.8 Hz); mass spectrum, m/e (relative intensity) 325 (M^+, 12), 310 (12), 294 (10), 280 (38), 264 (22), 207 (14), 194 (32), 178 (12), 177 (94), 176 (100), 162 (32); exact mass calcd for $C_{17}H_{27}NO_5$ (M^+) 325.1887, found 325.1877.

B. From 28 via 30. Compound **28** (47 mg, 0.087 mmol) was hydrogenolyzed in the same manner as described for the preparation of **23**. As in the preparation of **24** from **23**, the crude product [20 mg (74%)] of (2*R*,3*S*,4*S*,5*R*)-3,4-bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-5-methylpyrrolidine (**30**) obtained was subsequently alkylated to afford **31** [14 mg (67%)], in all respects identical with the sample obtained from **29**.

(2*R*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (Codonopsinine Stereoisomer 1c). In the same manner as for the preparation of **1a** from **15**, **31** (10 mg, 0.031 mmol) was treated under the acidic condition to provide **1c** [7.2 mg (99%)] as white needles: mp 110-111 °C; $[\alpha]^{20}_D$ -40.4° (c 3.4, MeOH); ^{1}H NMR, Table I; mass spectrum, m/e (relative intensity) 237 (M^+, 22), 222 (8), 178 (6), 177 (65), 176 (100), 162 (40), 150 (10), 121 (23); exact mass calcd for $C_{13}H_{19}NO_3$ (M^+) 237.1364, found 237.1376.

(1*S*,2*S*,3*R*,4*S*)-1-[[(Benzyloxy)carbonyl]amino]-2,3-bis[(methoxymethyl)oxy]-1-(*p*-methoxyphenyl)-4-[(methylsulfonyl)oxy]pentane (32). By the same procedure as used for the formation of **13** from **10**, **20** (11 mg, 0.024 mmol) was subjected so sequential treatment involving dephthaloylation, benzyloxycarbonylation, and mesylation to give **32** [11 mg (85% overall yield)] as a colorless oil.

(2*S*,3*S*,4*S*,5*R*)-3,4-Bis[(methoxymethyl)oxy]-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (33). As in the preparation of **24** from **22** via **23**, **32** (2 mg, 0.0037 mmol) was subjected to hydrogenolysis followed by N-methylation to give **33** [1 mg (83% overall yield from **32**)] as a colorless oil.

(2*S*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2-(*p*-methoxyphenyl)-1,5-dimethylpyrrolidine (Codonopsinine Stereoisomer 1d). Acid treatement of **33** (1 mg, 0.0031 mmol), as described for the formation of **1a**, afforded **1d** [0.5 mg (69%)] as a colorless oil: ^{1}H NMR, Table I.

Total Syntheses of the Amaryllidaceae Alkaloids (±)-Haemanthidine and (±)-Pretazettine†[1]

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The concise total synthesis of the Amaryllidaceae alkaloid (±)-haemanthidine (**2**) has been completed in 3.1% overall yield from piperonal (**11**) by a linear sequence of 12 chemical operations. Thus, piperonal (**11**) was converted via Grignard addition followed by oxidation into the monoprotected 1,4-dione **12**. Elaboration of **12** into the key intermediate 4,4-disubstituted cyclohexenone **18d** was conveniently achieved by exploiting a general method developed in these laboratories for the efficient construction of quaternary carbon atoms at a carbonyl center by the net replacement of the two carbon-oxygen bonds with carbon-carbon bonds. Bromination of **18d** followed by dehydrobromination then furnished the cyclohexadienone **26**, which was transformed into a mixture of the hydroindolenones **27** and **28** upon the palladium(0)-catalyzed removal of the nitrogen protecting group. Treatment of this mixture of **27** and **28** with DIBAL followed by methanolysis of the mesylates that were derived from the mixture of allylic alcohols thus produced afforded a mixture of the hydroindoles **36** and **37**. After conversion of **37** into the *N*-formylindole **46**, Bischler-Napieralski cyclization and subsequent saponification of the ester protecting group from the hydroxyl function at C(11) delivered (±)-haemanthidine (**2**). Methylation of **2** followed by basic workup according to the Wildman protocol gave (±)-pretazettine (**3**).

Introduction

The alkaloids of the Amaryllidaceae family[3,4] comprise a group of over 100 architecturally interesting natural bases that may be classified into seven principal, skeletally homogeneous subgroups. Of these, the alkaloids possessing the 5,10-ethanophenanthridine and the [2]benzopyrano[3,4-*c*]hydroindole ring systems as structural subunits have captured a significant degree of attention, and crinine (**1**),[5] haemanthidine (**2**),[6] and pretazettine (**3**)[7] have emerged as attractive objects for the development of new synthetic

† Dedicated to Professor George H. Büchi on the occasion of his 65th birthday.

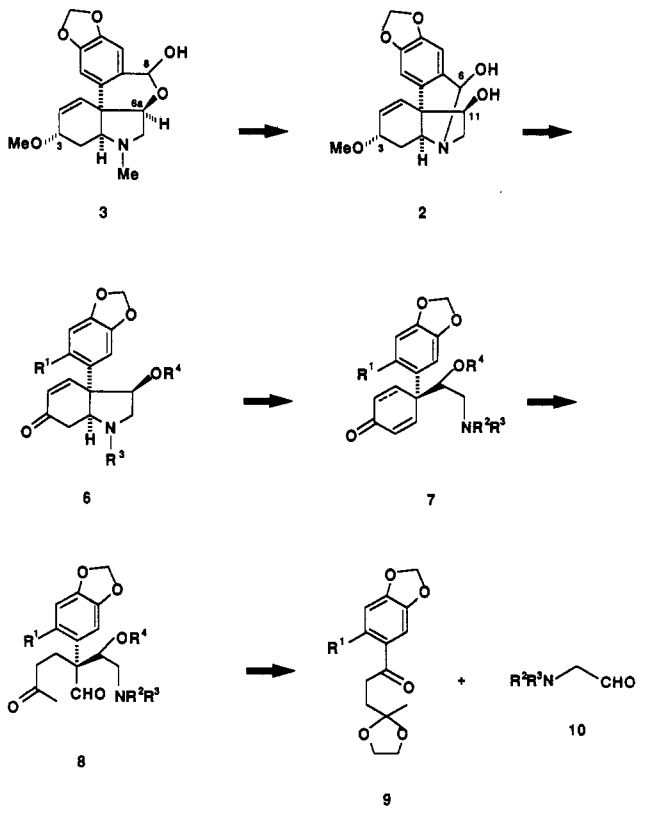
(1) For a preliminary account of a portion of this work, see: Martin, S. F.; Davidsen, S. K. *J. Am. Chem. Soc.* **1984**, *106*, 6431.

(2) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980-1985.

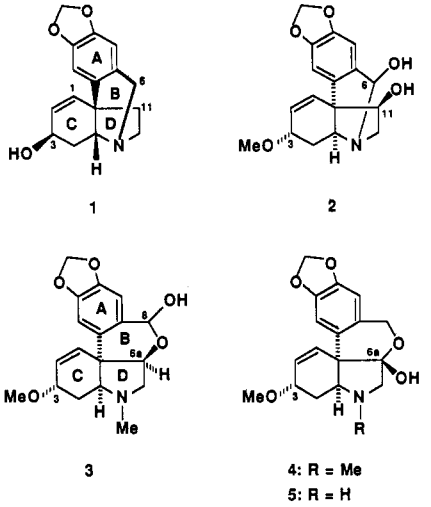
(3) For a review of the chemistry of the Amaryllidaceae alkaloids, see: (a) Fuganti, C. "The Amaryllidaceae Alkaloids" In *The Alkaloids, Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, pp 83-164. (b) Grundon, M. F. In *Specialist Periodical Reports, The Alkaloids*; The Chemical Society: London, 1983; Vol. 13, p 187. See also Vol. 1-12. (c) Grundon, M. F. *Nat. Prod. Rep.* **1985**, *2*, 249; **1984**, *1*, 247.

0022-3263/87/1952-1962$01.50/0

Scheme I



methodology and as targets for total synthesis. One of the factors that has stimulated interest in the chemically labile base pretazettine has been the reports of its antiviral[8] and anticancer activity,[9] particularly in Rauscher leukemia, Lewis lung carcinoma, and spontaneous AKR lymphocytic leukemia. Unfortunately, this effective level of anticancer activity does not appear to carry over into other experimental tumor models.[10] Pretazettine has also been found to inhibit protein synthesis in eukaryotic cells by inhibiting peptide bond formation.[11]



In a seminal series of chemical and structural studies, Wildman unraveled a number of important interconversions[12,13] of haemanthidine and pretazettine that have had considerable impact upon the direction of subsequent synthetic efforts in the area. Of particular significance was the observation that treatment of haemanthidine (**2**) with methyl iodide followed by a workup under mildly basic (pH 10) conditions led to the production of pretazettine (**3**). Under the influence of stronger base, **3** suffered an irreversible, intramolecular crossed-Cannizzaro reaction of the hemiacetal array via the open-chain form of the B ring to deliver the unnatural base tazettine (**4**). Presumably, the driving force for this facile and unusual reorganization was the relief of strain in the trans-fused BD ring system that is present in pretazettine but absent in tazettine.

Two general strategies have evolved for the total synthesis of pretazettine. The first approach, which has been more successful thus far, has taken advantage of the earlier findings of Wildman and has focused upon the use of haemanthidine as the initial target and as the pivotal relay to pretazettine via haemanthidine methiodide. In this context, the previous contributions of Tsuda[6a-c] and Hendrickson[6d] are noteworthy. Subsequent attempts in the laboratories of Danishefsky[7a] and White[7b] to achieve a direct entry to pretazettine without proceeding via the

(4) For a summary of some of the developments in the syntheses of the Amaryllidaceae alkaloids, see: (a) Stevens, R. V. "Alkaloid Synthesis" In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons; New York, 1977; Vol. 3, pp 439–553. (b) Tsuda, Y. *Heterocycles* **1978**, *10*, 555.

(5) For approaches to and syntheses of crinine and related alkaloids, see: (a) Muxfeldt, H.; Schneider, S. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670. (b) Whitlock, H. W.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600. (c) Irie, H.; Uyeo, S.; Yoshitake, A. *J. Chem. Soc. C* **1968**, 1802. (d) Kametani, T.; Kohno, T.; Shibuya, S.; Fukumoto, K. *Tetrahedron* **1971**, *27*, 5441. (e) Schwartz, M. A.; Rose, B. F.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1973**, *95*, 612. (f) Kotani, E.; Takeuchi, N.; Tobinaga, S. *J. Chem. Soc. D* **1973**, 551. (g) Kotani, E.; Takeuchi, N.; Tobinaga, S. *Tetrahedron Lett.* **1973**, 2735. (h) Ninomiya, I.; Naito, T.; Kiguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2261. (i) Tomioka, K.; Koga, K.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 2681. (j) Fushimi, T.; Ikuta, H.; Irie, H.; Nakadachi, K.; Uyeo, S. *Heterocycles* **1979**, *12*, 1311. (k) Sanchez, I. H.; Mendoza, M. T. *Tetrahedron Lett.* **1980**, *21*, 3651. (l) Keck, G. E.; Webb, R. R., II. *J. Am. Chem. Soc.* **1981**, *103*, 3173. (m) Keck, G. E.; Webb, R. R., II. *J. Org. Chem.* **1982**, *47*, 1302. (n) Sanchez, I. H.; Lopez, F. J.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 7640. (o) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (p) Sanchez, I. H.; Lopez, F. J.; Flores, H. J.; Larraza, M. I. *Heterocycles* **1983**, *20*, 247. (q) Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 5739. (r) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. (s) Martin, S. F.; Campbell, C. L. *Tetrahedron Lett.* **1987**, *28*, 503.

(6) For previous syntheses of haemanthidine and related compounds, see: (a) Tsuda, Y.; Isobe, K. *J. Chem. Soc. D* **1971**, 1555. (b) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153. (c) Isobe, K.; Taga, J.; Tsuda, Y. *Tetrahedron Lett.* **1976**, 2331. (d) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781.

(7) For previous syntheses of pretazettine, tazettine, and related compounds, see: (a) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591. (b) White, J. D.; Chong, W. K. M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2300. (c) References 6b–d. (d) For an approach to pretazettine, see also: Baldwin, S. W.; Wilson, J. D.; Aube, J. *J. Org. Chem.* **1985**, *50*, 4432.

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(9) (a) Suzuki, N.; Tani, S.; Furusawa, S.; Furusawa, E. *Proc. Soc. Expl. Biol. Med.* **1974**, *145*, 771. (b) Furusawa, E.; Suzuki, N.; Furusawa, S.; Lee, J. Y. B. *Ibid.* **1975**, *149*, 771. (c) Furusawa, E.; Furusawa, S.; Lee, J. Y. B.; Patanavanich, S. *Ibid.* **1976**, *152*, 186. (d) Furusawa, E.; Furusawa, S.; Lee, J. Y. B.; Patanavanich, S. *Chemotherapy (Basel)* **1978**, *24*, 259. (e) Furusawa, E.; Lockwood, R. H.; Furusawa, S.; Lum, M. K. M.; Lee, J. Y. B. *Ibid.* **1979**, *25*, 308. (f) Furusawa, E.; Irie, H.; Combs, D.; Wildman, W. C. *Ibid.* **1980**, *26*, 36. (g) Furusawa, E.; Lockwood, R. H. *Proc. West. Pharmacol. Soc.* **1981**, *24*, 45. (h) Furusawa, E.; Lum, M. K. M.; Furusawa, S. *Ibid.* **1981**, *27*, 277. (i) Furusawa, E.; Furusawa, E.; Sokugawa, L. *Ibid.* **1983**, *29*, 294.

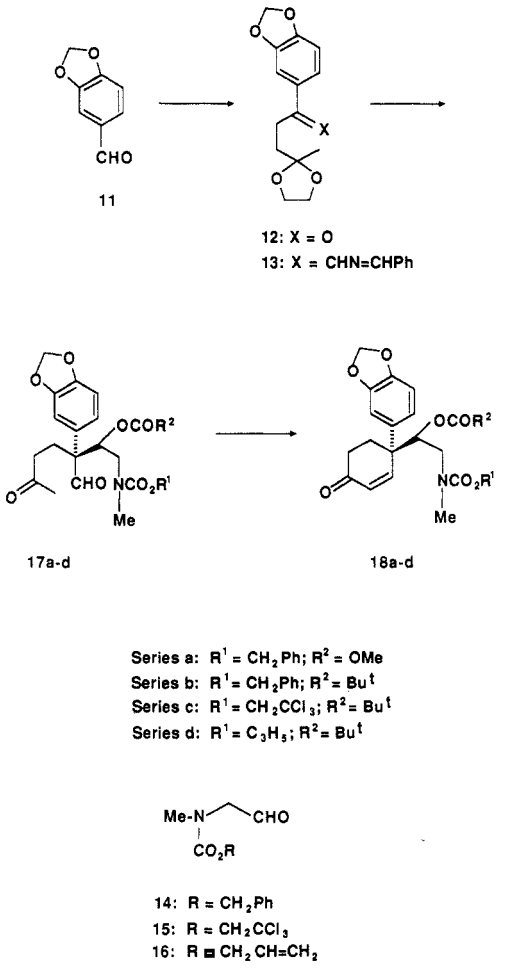
(10) We thank Dr. Matthew Suffness in the National Products Branch of the Developmental Therapeutics Program at the National Cancer Institute for this information.

(11) (a) Jimenez, A.; Santos, A.; Alonso, G.; Vazquez, D. *Biochim. Biophys. Acta* **1976**, *425*, 342. (b) Jimenez, A.; Sanchez, L.; Vazquez, D. *FEBS Lett.* **1975**, *60*, 66.

(12) Wildman, W. C.; Bailey, D. T. *J. Am. Chem. Soc.* **1969**, *91*, 150.

(13) Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1968**, *33*, 3749.

Scheme II



intermediacy of haemanthidine have led instead to syntheses of the more stable 6a-epipretazettine. Of some historical interest is the observation that, with the exception of the biomimetic approach of White, all previous work in this area has featured the use of a Diels–Alder reaction for the construction of the C ring of these alkaloids. Since the transformation of tazettine (**4**) into pretazettine (**3**) has been accomplished, albeit in low yield,[14] the preparation of **4** would now also constitute a synthesis of pretazettine in a formal sense.

Our own strategy for the synthesis of pretazettine (**3**), which is adumbrated in the retrosynthetic format depicted in Scheme I, was designed to be inherently flexible so that it might allow direct access to this primary target while also being suitable for the initial preparation of haemanthidine (**2**) as the crucial relay to pretazettine. The basic approach featured a general methodology for the efficient elaboration of a quaternary carbon atom bearing dissimilar alkyl appendages at a carbonyl center[15,16] as a key step for the construction of the requisite 4,4-disubstituted cyclohexenone **7** from the ketone **9** and the protected aminoacetaldehyde **10** via the highly functionalized intermediate **8**. The critical formyl moiety that ultimately becomes C(8) of **3** or C(6) of **2** could then be present in protected form at the outset of the synthesis on the aromatic ring of the ketone **9** [e.g., $R^1 = CH(OR)_2$, CH_2OR, etc.] or introduced at an advanced stage onto **7** or **6** via either an intra- or intermolecular process. The conversion of **7** into **6** would then require, in no particular order, the introduction of a new carbon–carbon double bond into the C ring and formation of the D ring via the intramolecular Michael cyclization of an unprotected secondary amine. Although the specific tactics would depend upon the precise nature of R^3, it was tacitly assumed that the *cis*-3a-arylhydroindole **6** could then be transformed into either **2** or **3**. For example, direct access to **3** would involve intermediates related to **6** in which R^3 = Me, whereas **6** (R^3 = CHO) could be subjected to a Bischler–Napieralski cyclization for the construction of the B ring of **2**. Provision would also have to be made for establishing the correct stereochemistry at C(11) of **2** or at C(6a) of **3** during the events, which would entail refunctionalization of the C ring and formation of the B ring, leading from **6** to either **2** or **3**.

With the general synthetic plan now established, the only remaining consideration lay in the selection of suitable nitrogen and hydroxyl protecting groups. Mindful of the ease with which pretazettine (**3**) and haemanthidine (**2**) would undergo rearrangement to tazettine (**4**)[12,13] and nortazettine (**5**),[17] respectively, it was necessary to select a hydroxyl protecting group R^4 to be employed on intermediates related to **6–8** that could be removed under mildly basic conditions but that would also be relatively stable to acid and remain intact until the final step in the synthesis. At the outset either a carbonate or an ester group appeared to be a suitable choice.

The specific choice of a group for protecting the nitrogen atom would depend upon whether pretazettine (**3**) or haemanthidine (**2**) was the initial synthetic objective. However, in either case it should be recognized that the protecting group(s) would have to be stable to the reactions involved in the preparation of the aminoacetaldehyde derivative **10**, and conditions for its removal at a later stage would have to be compatible with the then existing functionality. Thus, a direct approach to **3** would require only a monoprotected nitrogen atom with one of the substituents being methyl and the other being any one of a number of carbamates such as (benzyloxy)carbonyl, [(2,2,2-trichloroethyl)oxy]carbonyl, and (allyloxy)carbonyl. On the other hand, if **2** was the initial target, then two different protecting groups, each of which could be selectively removed at the appropriate stage, would be required. If one of the groups was formyl, it was conceivable that it might also serve as the eventual aryl formyl group corresponding to C(6) in **2** or C(8) in **3**. Thus, the possibilities included various combinations of the nitrogen substituents R^2 and R^3 being methyl, allyl, formyl, and the above-mentioned carbamates. However, after several preliminary experiments, it was discovered that the formyl and allyl protecting groups were not suited to the task, and other potentialities for a diprotected nitrogen atom were rejected. Consequently, the strategy that was ultimately adopted for the syntheses of haemanthidine (**2**) and pretazettine (**3**) featured a common, advanced intermediate that would be derived from protected aminoacetaldehyde **10** in which R^2 was a carbamate moiety and R^3 was methyl. Removal or oxidation of the methyl group as required for the synthesis of **2** would then be achieved by one of several standard procedures.[18]

(14) Kobayashi, S.; Kihara, M.; Shingu, T.; Shingu, K. *Chem. Pharm. Bull. Jpn.* **1980**, *28*, 2924.
(15) Martin, S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866.
(16) For other synthetic applications of this methodology, see: (a) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391. (b) Martin, S. F.; Garrison, P. J. *Ibid.* **1982**, *47*, 1513. (c) Reference 5s.
(17) Irie, H.; Tsuda, Y.; Uyeo, S. *J. Chem. Soc.* **1959**, 1446.

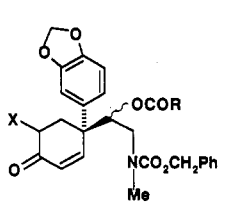
Results

The first stage of the synthesis of either pretazettine (3) or haemanthidine (2) required the preparation of a 4,4-disubstituted cyclohexenone related to 7. In our view, one particularly attractive entry to this initial subgoal involved the exploitation of a general methodology for the construction of a quaternary carbon atom by a protocol that resulted in the net geminal acylation–hydroxyalkylation at a carbonyl center that had been previously developed in these laboratories[15] (Scheme II). Accordingly, the monoprotected 1,4-dione **12** was conveniently prepared in 82% yield commencing with the reaction of piperonal (**11**) with the Grignard reagent derived from 2-methyl-2-(2-bromoethyl)-1,3-dioxolane[19] followed by oxidation of the intermediate benzylic alcohol with pyridinium dichromate.[20] The electrophilic partners that were selected to serve in the directed aldol reaction of the impending sequence were the protected aminoacetaldehydes **14–16**, and these substances were readily accessible by the reaction of commercially available *N*-methylaminoacetaldehyde diethyl acetal with benzyl, 2,2,2-trichloroethyl, or allyl chloroformate, respectively, in pyridine followed by the acid-catalyzed hydrolysis of the intermediate acetals.

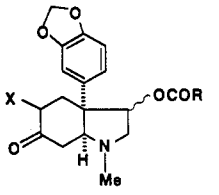
With the necessary starting materials on hand, the syntheses of **2** and **3** were then initiated by the reaction of **12** with diethyl [(benzylideneamino)lithiomethyl]-phosphonate[15] to furnish the 2-aza diene **13** as a mixture of geometric isomers. Regioselective addition of *n*-butyllithium to **13** afforded an intermediate lithiated imine that was then treated sequentially with zinc chloride, the aminoacetaldehyde **14**, excess methyl chloroformate, and finally aqueous hydrochloric acid to give the δ-keto aldehyde **17a**. Upon reaction with pyrrolidine in methanol containing 33% aqueous acetic acid, the keto aldehyde **17a** underwent facile cycloaldolization and dehydration to deliver **18a** as a mixture (1.5:1) of diastereoisomers in 51% overall yield from **12**. Although the above sequence of reactions could be executed without adding zinc chloride to generate the corresponding zinc imine anion prior to the directed aldol reaction, the overall yield for the process was found to be somewhat lower. The related cyclohexenones **18b–d** were prepared in overall yields of 58%, 21% (unoptimized), and 78%, respectively, in a similar fashion by using the corresponding aminoacetaldehydes **14–16** in the directed aldol reaction and employing excess pivaloyl chloride instead of methyl chloroformate as the trapping agent for the protection of the hydroxyl function. Although the diastereoisomeric mixtures of **18a–d** could be separated by conventional HPLC, this operation was unnecessary since they were eventually to be transformed into enantiomeric cyclohexadienones (vide infra).

The principal issue at this juncture was whether the double bond at C(1) should be installed prior to the formation of the D ring or subsequent thereto. Since cyclohexadienones derived from **18a,b** might be prone to undergo a dienone–phenol rearrangement[21] under the acidic conditions required for the removal of the *N*-carbobenzyloxy protecting group (e.g., 33% HBr/AcOH, room temperature, 15 min; or trifluoroacetic acid/anisole, reflux, 45 min), the tactic that was originally formulated involved postponing the incorporation of the double bond until after the elaboration of the D ring. The implementation of this plan then required the introduction of a suitable leaving group α′ to the carbonyl function of the enones **18a–d** prior to removal of the *N*-carbamate function.

Although the α′-(phenylselenyl)- and α′-(phenylsulfenyl)cyclohexenones **19** (X = SePh or SPh; R = OMe) could be accessed from **18a** and **18b** in modest yields according to standard methods, all efforts to cleave the *N*-carbobenzyloxy protecting group employing a variety of acidic conditions furnished the corresponding *cis*-3a-arylhydroindolones **20** (X = SePh or SPh; R = OMe) in only meager yields. During the course of these studies,

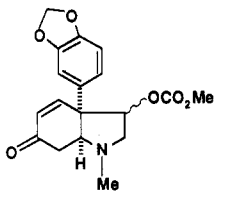


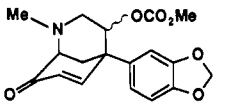
19



20

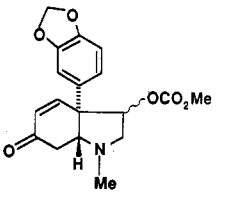
X = SePh, SPh, Br
R = OMe, Bu^t





21a: α-OCO_2Me
21b: β-OCO_2Me

22a: α-OCO_2Me
22b: β-OCO_2Me



23a: α-OCO_2Me
23b: β-OCO_2Me

it became apparent that the methyl carbonate protecting group was too labile, but attempts to effect the related transformation on the more robust pivaloates **19** (X = SePh or SPh; R = *t*-Bu) fared little better. On another front, the α′-bromo ketones **19** (X = Br; R = OMe, *t*-Bu) were readily prepared by the reaction of **18a** and **18b** with phenyltrimethylammonium perbromide (PTAB)[22] in either THF or ethyl acetate. Somewhat surprisingly, however, when the diastereomeric enones **19** (X = Br, R = OMe) were dissolved in refluxing trifluoroacetic acid in the presence of anisole followed by treatment of the residue with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene,

(18) For leading references on methodology for effecting *N*-demethylation, see: (a) Pelletier, S. W.; Desai, H. K.; Finer-Moore, J.; Mody, N. V. *Tetrahedron Lett.* **1982**, *23*, 4229. (b) Hunter, D. H.; Barton, D. H. R.; Motherwell, W. J. *Tetrahedron Lett.* **1984**, *25*, 603. (c) Cave, A.; Kan-Fan, C.; Potier, P.; Le Men, J. *Tetrahedron* **1967**, *23*, 4691. (d) Henbest, H. B.; Stratford, M. J. W. *J. Chem. Soc.* **1966**, 995. (e) Thomas, R. C. *J. Antibiot.* **1982**, *35*, 1202. (f) Cava, M. R.; Venkateswarlu, A.; Srinivasan, M.; Edie, D. L. *Tetrahedron* **1972**, *28*, 4299. (g) Rapoport, H.; Lovell, C. H.; Reist, H. R.; Warren, M. E., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1942. (h) Kraiss, G.; Nador, K. *Tetrahedron Lett.* **1971**, 57. (i) Rice, K. C. *J. Org. Chem.* **1975**, *40*, 1850. (j) Olofson, R. A.; Martz, J. T.; Senet, J.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081. (k) Tokitoh, N.; Okazaki, R.; Inamoto, N. *Heterocycles* **1984**, *21*, 646.
(19) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105.
(20) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(21) Perkin, M.; Ward, P. *Mech. Mol. Migr.* **1971**, *4*, 55.
(22) Marquet, A.; Jacques, J. *Bull. Chim. Soc. Fr.* **1962**, 90.

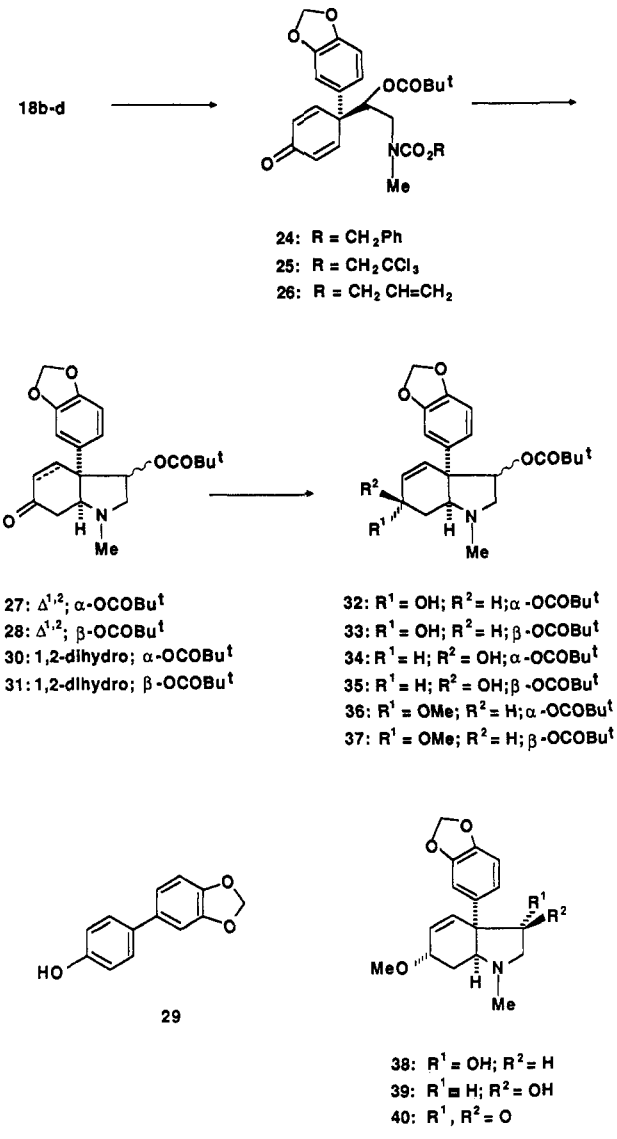
a mixture of the two 2-azabicyclo[3.3.1]nonenones **22a** and **22b** was obtained rather than the anticipated enones **21a,b**.[23] Thus, the intermediate α'-bromo amino cyclohexenones that were produced upon removal of the carbobenzyloxy protecting group suffered irreversible displacement of the α'-bromide moiety by the methylamino group rather than the expected cyclization via Michael addition. In retrospect, the formation of **22a** and **22b** was not totally without precedent as related reactions have been previously recorded.[23,24]

The structural assignments for **22a** and **22b** were deduced from a combination of spectral and chemical techniques. That these substances were not the desired hydroindolenones **21a,b** was readily established by spectral comparisons with the hydroindolenones **27** and **28**, which were prepared at a later stage, coupled with the observation that it was not possible to effect their conversion by a straightforward sequence of reactions into the known[7a] hydroindoles **38** and **39**. The unlikely possibility that the *trans*-hydroindolenones **23a,b** had been formed was excluded by a combination of ^1H and ^{13}C NMR spectroscopy. Of particular significance was the observation of a long-range W coupling (J = 2.3 Hz) between the β-vinyl proton of the enone moiety and the equatorial proton on the methylene bridge of the cyclohexenone ring, which is consistent with structures **22a,b** but not with **23a,b**. Furthermore, there were no large couplings ($w_{1/2}$ = ca. 6 Hz) observed for the bridgehead proton α to nitrogen as would be anticipated for structures **23a,b**. The observed differences between the ^{13}C NMR spectra of the two diastereomers were in accord with the γ-effects expected upon the changes in configuration at the epimeric center in **22a** and **22b** but not in **23a** and **23b**. Thus, the chemical shift for the β-vinyl carbon in **22b** appeared 2.3 δ units upfield from the corresponding carbon in **22a**, whereas the bridging methylene carbon of the cyclohexenone ring was shifted upfield by 9.7 δ in **22a** relative to **22b**.

In view of the above results, an alternative plan was devised (Scheme III), in which the order of reactions was inverted so that the double bond at C(1) would be introduced prior to the construction of the D ring. In the event, **19** (X = Br, R = *t*-Bu) was dehydrobrominated to give the cyclohexadienone **24** in modest yield either by treatment with DBU in refluxing benzene or by heating with lithium carbonate and lithium bromide in DMF. Unfortunately, side reactions competed with simple removal of the *N*-carbobenzyloxy protecting group from such intermediates, and only low yields of the 3a-arylhydroindolenones **27** and **28** were produced upon treatment of **24** with acid under a variety of conditions. Although there was no firm evidence of a dienone–phenol rearrangement during these processes, a sequence that commenced with the loss of the aliphatic side chain at C(4) of **24** by retroaldolization followed by aromatization of the C ring did clearly intervene as evidenced by the formation of the substituted biphenyl **29**.

At this juncture, it was deemed necessary to select a different carbamate-derived protecting group for nitrogen. Although a variety of different possibilities were considered and examined, only those sequences involving intermediates possessing the *N*-[(2,2,2-trichloroethoxy)carbonyl] and the *N*-[(allyloxy)carbonyl] groups warrant mention. Namely, the requisite double bond at C(1) was introduced into the cyclohexenones **18c** and **18d** by the straightforward application of the two-step procedure for bromination and dehydrobromination previously described to give the corresponding dienones **25** and **26** in 73% and 77% overall yields, respectively. Subsequent treatment of **25** with zinc dust in buffered aqueous THF did induce cleavage of the (trichloroethoxy)carbonyl protecting group to furnish the desired 3a-arylhydroindolenones **27** and **28** as anticipated;[7b,25] however, the saturated hydroindoles **30** and **31** were also produced in approximately equal amounts. Neither modification of the experimental conditions or the use of other reductants[26] were to any avail. This observation stands in contrast to a recent report in which the enone moiety of a closely related substance was stable to the conditions required for the removal of a *N*-(trichloroethoxy)carbonyl protecting group.[7b] On the other hand, the scission of the *N*-(allyloxy)carbonyl array of **26** upon treatment with a catalytic amount of tetrakis(triphenylphosphine)palladium(0) in the presence of 2-ethylhexanoic acid followed by Michael cyclization of the intermediate amino cyclohexadienones led smoothly to an inseparable

Scheme III



(23) Furstoss, R.; Tadayoni, R.; Esposito, G.; Lacrampe, J.; Heumann, A.; Waegell, B. *Can. J. Chem.* **1976**, *54*, 3569.
(24) Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Diaz, E.; Jankowski, K. *Heterocycles* **1985**, *23*, 593.
(25) Just, G.; Grozinger, K. *Synthesis* **1976**, 457. See also: Semmelhack, M. F.; Heinson, G. E. *J. Am. Chem. Soc.* **1972**, *94*, 5139. Le Goff, E. *J. Org. Chem.* **1964**, *29*, 2048.
(26) For example, see: (a) Eckert, H.; Ugi, I. *Liebigs Ann. Chem.* **1979**, 278. (b) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* **1981**, *37*, 175.
(27) Jeffrey, P. D.; McCombie, S. W. *J. Org. Chem.* **1982**, *47*, 587.

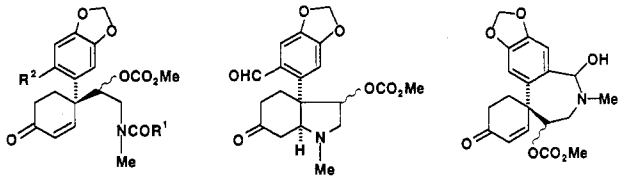
mixture (1.5:1) of **27** and **28** in 90% yield. The ratio of the epimers **27** and **28** that was obtained from this cyclization coincided with the apparent thermodynamic ratio, since there was no detectable change upon heating this mixture in the presence of pyridinium *p*-toluenesulfonate. Moreover, mixtures enriched by HPLC in either **27** or **28** reverted to an approximately 1.5:1 mixture upon subjection to these conditions.

Reduction of the mixture of **27** and **28** with diisobutylaluminum hydride gave a separable mixture of the four diastereomeric allylic alcohols **32–35** in an approximate ratio of 3:2:5:3. In preliminary experiments it was demonstrated that individual treatment of either **32** or **34** with methanesulfonic anhydride in THF in the presence of triethylamine, followed by solvolysis of the resulting mesylates in methanol,[7a] afforded the allylic ether **36** as the only isolable product. Similarly, methanolysis of each of the mesylates derived from the pure epimers **33** and **35** furnished solely **37**. In view of these results, it proved both more expeditious and efficient in practice to subject the crude mixture of **32–35** to sequential mesylation and methanolysis to provide, after separation by conventional HPLC, the ethers **36** and **37** in 33% and 22% overall yields, respectively, from the mixture of **27** and **28**.

The stereo- and regiochemical outcome of these solvolyses may be rationalized on the basis of the preferential attack of methanol on the intermediate cyclohexenyl cation in a pseudoaxial sense[5b,28] from the convex (exo) face of the 3a-arylhydroindole at the less hindered terminus. The correctness of the structural assignments for **36** and **37** was verified by cleavage of the pivaloate esters from the hydroxyl groups at C(3) (hydroindole numbering) by saponification using lithium hydroxide in methanol to deliver the corresponding alcohols **38** and **39**, the ^{1}H NMR spectra of which were identical with those of the same alcohols previously prepared independently by Danishefsky.[7a,29]

Since the hydroxyl group at C(3) of **38** has the opposite configuration required for the eventual synthesis of either pretazettine (**3**) or haemanthidine (**2**), efforts to effect its inversion to give the epimer **39** were undertaken. However, attempted inversion of the alcohol function in **38** according to the Mitsunobu[30] protocol returned only unreacted starting material. Although the corresponding mesylate could be easily prepared, it proved resistant in preliminary experiments to displacement with oxygen nucleophiles such as acetate and superoxide. Danishefsky had demonstrated that the carbonyl function in **40** underwent stereoselective reduction with sodium borohydride to afford a 1:3 mixture of the epimeric alcohols **38** and **39**, and we thus reasoned that oxidation of **38** followed by a similar hydride reduction might provide an acceptable solution to the problem at hand. However, since Swern oxidation of **38** furnished **40** in only modest yields, this approach too was abandoned. It presently seems that effective control of the hydroxyl stereochemistry at C(11) of the alkaloids related to haemanthidine (**2**) or at C(6a) of pretazettine (**3**) lingers as yet as an unsolved problem in this synthetic arena.

The remaining challenge in the synthesis of pretazettine (**3**) involved the introduction of the formyl group, which corresponds to C(8) in pretazettine, onto the aromatic ring of **39**. Several strategic devices that would allow the incorporation of this functional unit at different stages of the synthesis were examined. For example, the aryl-substituted monoprotected diones **9** (R^1 = Br and CH_2OCH_2OMe) were evaluated as potential substrates in the geminal acylation–hydroxyalkylation sequence, but the overall yields of 4,4-disubstituted cyclohexenones **7** (R^1 = Br and CH_2OCH_2OMe) were unsatisfactory. Although there existed as prior art several moderately compelling examples of electrophilic substitution reactions occurring at hindered positions on aromatic rings,[31] several preliminary attempts to formylate the cyclohexenone **18a** by bimolecular processes under a variety of conditions failed to produce **41** in useful quantities. Alternatively, the attempted delivery of the formyl group in an intramolecular sense via a Bischler–Napieralski cyclization of **42**, which was readily available from **18a** [(a) 25% HBr/AcOH; room temperature; 15 min, (b) AcOCHO/Py; CH_2Cl_2; room temperature; 24 h], to give either **43** or **44** in close analogy with a related step in our recent synthesis of lycoramine[16b] was also unmeritorious.



41: R^1 = OCH_2Ph; R^2 = CHO
42: R^1 = R^2 = H

43

44

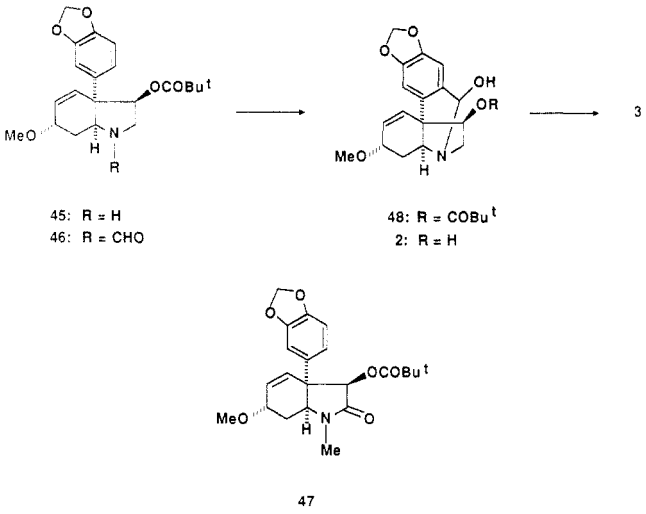
Having thus been forcibly diverted from the direct entry to pretazettine, efforts were refocused upon the development of tactics for the conversion of **37** into haemanthidine (**2**). This new approach would require the transformation of the *N*-methyl group of **37** into a formyl function followed by a Bischler–Napieralski cyclization and hydrolysis of the pivaloate ester. However, attempts to induce the *N*-demethylation of **37** with vinyl, 2,2,2-trichloroethyl, 2-bromoethyl, and benzyl chloroformate returned only unreacted starting material, and although **37** could be demethylated upon treatment with methyl and allyl chloroformate, the resulting carbamates could not be converted into the secondary amine **45** according to standard procedures. Heating **37** with iodine and sodium acetate in dioxane[18f] was also to no avail.

Consequently, the direct oxidation of the *N*-methyl group present in **37** to give the *N*-formyl derivative **46** was then examined. Indeed, treatment of **37** with manganese dioxide in benzene[18d] afforded **46**, albeit in low yield, and although reaction of **37** with chromium trioxide in pyridine[18c] did produce **46** in improved yield, the lactam **47** was also formed in significant amounts. Finally, it was discovered that when **37** was allowed to react with oxygen in the presence of platinum black in aqueous dioxane[18e] and the resulting mixture (1:3) of **45** and **46** was treated directly with acetic formic anhydride, the desired formamide **46** was obtained in 57% overall yield.

At this juncture, we stood ready to complete the total syntheses of both haemanthidine (**2**) and pretazettine (**3**). In the event, when **46** was heated with freshly distilled phosphorus oxychloride at 90 °C, the pivaloate ester of haemanthidine **48** was produced. Careful saponification of **48** with methanolic lithium hydroxide then afforded **2** in 55% overall yield from **46**. The haemanthidine (**2**) thus obtained, which was identical with an authentic sample,[32]

(28) Goering, H. L. *Rec. Chem. Prog.* **1960**, *21*, 109.
(29) We thank Professor S. Danishefsky (Yale University) for providing spectra of compounds **38** and **39**.
(30) Mitsunobu, O. *Synthesis* **1981**, 1.

(31) Cf. (a) Buu-Hoi, N.; Xuong, N.; Sy, M.; Lejenne, G.; Tien, N. *Bull. Chim. Soc. Fr.* **1955**, 1594. (b) Edwards, J.; Cashaw, J. *J. Am. Chem. Soc.* **1956**, *78*, 3821. (c) Uyeo, S.; Irie, H.; Kitayama, U.; Hirose, T.; Yoshitake, A. *Chem. Pharm. Bull. Jpn.* **1964**, *12*, 489. (d) Royer, R.; Demerseman, P.; Laval-Jeantet, A.; Rossignol, J.; Cheutin, A.; Desvoye, M. *Bull. Chim. Soc. Fr.* **1968**, 1026.



was converted by slight modification of the Wildman protocol[12] involving N-methylation followed by mild basic workup, into pretazettine (3), also identical in all respects with an authentic sample.[32]

Thus, the concise total synthesis of the Amaryllidaceae alkaloid (±)-haemanthidine (2), which was then converted into the unstable natural base (±)-pretazettine (3), has been completed in 3.1% overall yield from commercially available piperonal (11) by a linear sequence of 12 chemical operations. The key tactical element of the synthetic strategy involved the application of a general procedure for the creation of a quaternary carbon atom at a carbonyl center by the net replacement of each of the carbon–oxygen bonds with carbon–carbon bonds. Further extensions of this methodology will be reported in due course.

Experimental Section

General. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. All boiling points are uncorrected. Diethyl ether (ether), tetrahydrofuran (THF), and dimethoxyethane (DME) were distilled from potassium/benzophenone ketyl immediately prior to use. Methanol was distilled from magnesium methoxide. Triethylamine, diisopropylamine, acetonitrile, chloroform ($CHCl_3$), and methylene chloride (CH_2Cl_2) were distilled from calcium hydride and stored under nitrogen. Benzene, xylene, and *p*-dioxane were distilled from potassium, while pyridine and dimethylformamide (DMF) were distilled from barium oxide and stored under nitrogen. All chloroformates and acyl halides were freshly distilled from calcium hydride immediately prior to use. IR spectra were recorded on a Beckman Acculab 8 spectrometer. The ^1H NMR spectra were determined on either a Varian EM-390 (90 MHz), a Nicolet NT-200 (200 MHz), or a GN-500 (500 MHz) spectrometer as indicated, and the chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad. Coupling constants are given in hertz (Hz). The ^{13}C NMR spectra were determined on a Varian FT-80A (20 MHz), a Bruker WH-90 FT (22.6 MHz), or a GN-500 (125.76 MHz) spectrometer as indicated, and the chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. Low-resolution mass spectra were obtained on a DuPont (CEC) 21-491 instrument at an ionization voltage of 70 eV, and the exact mass determinations were obtained on a DuPont (CEC) 21-110 instrument. Preparative high performance chromatography (HPLC) was performed on either a Waters Prep LC 500 instrument (sample size >500 mg) with two silica gel PrepPak columns or on a Waters 6000A solvent delivery system equipped with a Model U6K injector and two Porasil A columns (0.6 m × 7.8 mm) (sample size <500 mg). All reactions involving organometallic reagents or other moisture- or oxygen-sensitive intermediates were executed under an atmosphere of dry nitrogen or argon using oven-dried glassware. Combustion analyses were performed by Dr. Franz Scheidl, Hoffmann-LaRoche, Inc., Nutley, NJ.

2-Methyl-2-[3-[3,4-(methylenedioxy)phenyl]-3-oxopropyl]-1,3-dioxolane (12). To a stirred suspension of magnesium turnings (7.60 g, 317.0 mmol) in THF (50 mL) was added 1,2-dibromoethane (3.70 g, 19.5 mmol). After the initial exothermic reaction had subsided, a solution containing 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[19] (20.64 g, 105.8 mmol) and 1,2-dibromoethane (3.70 g, 19.5 mmol) in THF (100 mL) was added dropwise over 1 h while maintaining the reaction temperature at 25 °C with a water bath. Upon completion of the addition, the reaction mixture was stirred at room temperature for 1 h and then transferred via cannula to a solution of piperonal (11) (6.15 g, 30.8 mmol) in THF (150 mL) at 0 °C. The reaction mixture was then stirred at room temperature for 16 h, whereupon saturated NH_4Cl solution (150 mL) was added. Sufficient water was then added to dissolve the salts (ca. 150 mL), and the aqueous mixture was extracted with ether (3 × 100 mL). The combined organic layers were washed with water (1 × 100 mL) and saturated aqueous NaCl (1 × 100 mL) and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude alcohol was immediately dissolved in DMF (60 mL) at room temperature. Pyridinium dichromate[20] (25.80 g, 68.8 mmol) was added in a single portion with vigorous stirring. After being stirred for 4 h at room temperature, the reaction was quenched by being poured into water (200 mL), and the aqueous solution was extracted with ether (4 × 75 mL). The combined ether extract was washed with water (6 × 50 mL) and saturated aqueous NaCl (1 × 100 mL) and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude ketone **12** was purified by HPLC on silica gel with hexane–ethyl acetate (2.5:1) as the eluent. Subsequent Kugelrohr distillation, bp 160–162 °C (oven temperature, 0.05 mm), afforded 8.97 g (82%) of **12** which solidified upon standing: mp 36–38 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 1.33 (s, 3 H), 2.08 (t, J = 7 Hz, 2 H), 2.95 (t, J = 7 Hz, 2 H), 3.91 (s, 4 H), 5.98 (s, 2 H), 6.79 (d, J = 8 Hz, 1 H), 7.38 (d, J = 2 Hz, 1 H), 7.54 (dd, J = 2, 8 Hz, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 23.8, 32.8, 33.3, 64.6, 101.7, 107.7, 109.4, 124.0, 131.8, 148.0, 151.4, 197.7; IR ($CHCl_3$) 1672, 1422 cm^{-1}; mass spectrum, m/e 149, 87 (base). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.82; H, 6.31.

***N*-[(Allyloxy)carbonyl]-*N*-methylaminoacetaldehyde Diethyl Acetal.** To a solution of *N*-methylaminoacetaldehyde diethyl acetal (5.63 g, 38.3 mmol) in CH_2Cl_2 (100 mL) containing pyridine (9.07 g, 9.28 mL, 114.9 mmol) at 0 °C was added dropwise (5 min) allyl chloroformate (5.51 g, 4.85 mL, 46.0 mmol), and the cloudy, yellow mixture was warmed to room temperature over 1 h. The solvent was then removed under reduced pressure and the resulting solid partitioned between CH_2Cl_2 (50 mL) and 1 N HCl (50 mL). The layers were then separated, and the organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 25 mL), saturated aqueous NaCl (1 × 25 mL), and water (1 × 25 mL). The final aqueous wash was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organic solution dried ($MgSO_4$). The solvent was then removed under reduced pressure, and the crude product was purified by Kugelrohr distillation to give 8.68 g (90%) of the diethyl acetal as a clear liquid: bp 105–110 °C (oven temperature, 0.10 mm); ^1H NMR (90 MHz, $CDCl_3$) δ 1.19 (t, J = 6 Hz, 6 H), 2.97 (s, 3 H), 3.35 (d, J = 6 Hz, 2 H), 3.56 (comp, 5 H), 4.60 (dd, J = 1, 6 Hz, 2 H), 5.15 (m, 1 H), 5.28 (dd, J = 2, 12 Hz, 1 H), 5.90 (m, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 15.1, 36.0, 52.0, 62.8, 65.7, 101.5, 116.9, 133.0, 155.3; IR ($CHCl_3$) ν 2920, 1697, 1401, 1060 cm^{-1}; mass spectrum, m/e 186, 103 (base); exact mass calcd for $C_{11}H_{21}NO_4$ 231.1470, found 231.1464. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.33; H, 9.25; N, 6.04.

***N*-[(Allyloxy)carbonyl]-*N*-methylaminoacetaldehyde (16).** To a solution of the above acetal (20.00 g, 86.6 mmol) in THF (220 mL) was added concentrated HCl (4.4 mL) followed by formic acid (44.0 mL), and the reaction mixture was stirred at room temperature for 4 h. Methylene chloride (220 mL) and benzene

(32) We thank Professor J. B. Hendrickson (Brandeis University), Dr. P. Jeffs (Smith-Kline-Beckman), and Dr. H. Fales (National Institutes of Health) for providing authentic samples of haemanthidine, tazettine, and related alkaloids and Professor E. Furusawa (University of Hawaii) for an authentic sample of pretazettine hydrochloride.

(44 mL) were then added, and the excess solvent was removed under reduced pressure. The resulting yellow oil was dissolved in ether (150 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 100 mL) and saturated aqueous NaCl (1 × 100 mL), and the final aqueous wash was extracted with ether (1 × 100 mL). The combined organic phase was then dried ($MgSO_4$), and the solvent was removed under reduced pressure to give the crude aldehyde **16**. This oil was immediately purified by Kugelrohr distillation to give 10.05 g (72%) of **16** as a clear liquid: bp 110–112 °C (oven temperature, 0.30 mm); ^1H NMR (90 MHz, $CDCl_3$) δ 2.97 (s, 3 H), 4.02 (s, 2 H), 4.48 (d, J = 6 Hz, 2 H), 5.20 (m, 1 H), 5.90 (m, 1 H), 9.52 (s, 1 H); IR ($CHCl_3$) ν 2970, 1700, 1405, 1170 cm^{-1}; mass spectrum, m/e 157, 128, 84, 41 (base); exact mass calcd for $C_7H_{11}NO_3$ 157.0739, found 157.0736.

***N*-[(Benzyloxy)carbonyl]-*N*-methylaminoacetaldehyde (14)** was prepared in 87% yield according to the procedure described above for the preparation of **16** but using benzyl chloroformate instead of allyl chloroformate: bp 133–136 °C (0.15 mm); ^1H NMR (90 MHz, $CDCl_3$) δ 2.88 (s, 3 H), 3.90 (s, 2 H), 5.05 (s, 2 H), 7.23 (br s, 5 H), 9.40 (s, 1 H); IR ($CHCl_3$) ν 1724, 1689, 1160 cm^{-1}; mass spectrum, m/e 178, 134, 91 (base); exact mass calcd for $C_{11}H_{13}NO_3$ 207.0895, found 207.0888.

4-[1-(Pivaloyloxy)-2-[[(allyloxy)carbonyl]methylamino]-ethyl]-4-[3,4-(methylenedioxy)phenyl]-2-cyclohexenone (18d). To a well-stirred solution of *n*-butyllithium (2.75 N in hexane, 64.0 mmol) in THF (450 mL) at −78 °C was added dropwise a solution of diethyl [(benzylideneamino)methyl]-phosphonate[15] (16.32 g, 64.0 mmol) in THF (20 mL). After 1 h, a solution of the monoprotected 1,4-diketone **12** (14.08 g, 53.0 mmol) in THF (20 mL) was added dropwise, and the solution was allowed to warm to room temperature (ca. 1 h) and then heated at reflux for 2 h. The resulting solution of 2-aza diene **13** was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was then partitioned between ether (200 mL) and saturated NaCl solution (200 mL), and the layers were separated. The aqueous phase was then extracted with ether (3 × 100 mL), and the combined organic phase was washed with saturated aqueous NaCl (1 × 200 mL) and dried ($MgSO_4$). The solvent was completely removed under reduced pressure, the resulting yellow oil was dissolved in THF (450 mL), and this solution was then cooled to −78 °C. *n*-Butyllithium (2.75 N in hexane (64.0 mmol) was added dropwise and the stirring continued at −78 °C for 0.5 h. A solution of zinc chloride (10.90 g, 79.5 mmol) in THF (100 mL) was then added and the resulting mixture stirred for an additional 0.5 h, whereupon a solution of aldehyde **16** (10.05 g, 64.0 mmol) in THF (20 mL) was added dropwise. This mixture was then stirred at −78 °C for 0.5 h, after which freshly distilled pivaloyl chloride (25.20 g, 26.4 mL, 212.0 mmol) was added dropwise. The cooling bath was then removed and the solution warmed to room temperature (ca. 1 h) and stirred for 5 h. The yellow solution was then poured into 3 N HCl (500 mL) and stirred vigorously for 18 h. A saturated aqueous NaCl solution (450 mL) was added, and the layers were separated. The aqueous phase was then extracted with ether (2 × 200 mL) and ether/ethyl acetate (2:1, 3 × 200 mL), and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 400 mL) and 0.5 N aqueous NaOH (2 × 300 mL). The combined aqueous phase was back-washed with ether (200 mL) and the combined organic portion dried ($MgSO_4$). The excess solvent was removed under reduced pressure, and the resulting yellow oil was dissolved in ethyl acetate (20 mL) and passed through a column (2-cm diameter) of silica gel (100 g) using ethyl acetate (ca. 500 mL) as the eluent. The solvent was removed under reduced pressure, the residue of crude keto aldehyde **17d** was dissolved in methanol (173 mL) and 33% aqueous acetic acid (17.3 mL), and then freshly distilled pyrrolidine (4.93 g, 5.78 mL, 68.9 mmol) was added. After stirring at room temperature for 42 h, 1 N HCl (100 mL) was added and the mixture stirred at room temperature for 0.5 h, whereupon saturated aqueous NaCl (100 mL) and ether (100 mL) were added. The layers were separated, and the aqueous phase was extracted with ether/ethyl acetate (2:1, 3 × 200 mL). The combined organic extract was washed with water (1 × 200 mL), saturated aqueous $NaHCO_3$ (1 × 200 mL), and saturated aqueous NaCl (1 × 200 mL). The aqueous washes were back-extracted with ether/ethyl acetate (2:1, 2 × 100 mL), and the combined organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting viscous yellow oil was purified by preparative HPLC using hexane/ethyl acetate (2:1) to afford 11.47 g (47%) of the major diastereoisomer and 7.49 g (31%) of the minor diastereoisomer as viscous yellow oils.

Major Diastereoisomer: ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (s, 9 H), 2.25 (comp, 4 H), 2.78 (s, 2 H), 2.82 (s, 1 H), 2.91 (dd, J = 3.0, 13.5 Hz, 0.66 H), 3.08 (dd, J = 3.0, 13.5 Hz, 0.33 H), 3.50 (dd, J = 10.5, 13.5 Hz, 0.33 H), 3.77 (dd, J = 10.5, 13.5 Hz, 0.66 H), 4.51 (d, J = 6.5 Hz, 0.66 H), 4.56 (d, J = 6.5 Hz, 0.33 H), 5.25 (comp, 2 H), 5.49 (dd, J = 3.0, 10.5 Hz, 0.66 H), 5.58 (dd, J = 3.0, 10.5 Hz, 0.33 H), 5.90 (m, 1 H), 5.98 (s, 2 H), 6.03 (d, J = 10.5 Hz, 0.33 H), 6.25 (d, J = 10.5 Hz, 0.66 H), 6.78 (br s, 2 H), 6.84 (br s, 1 H), 7.18 (d, J = 10.5 Hz, 0.33 H), 7.32 (d, J = 10.5 Hz, 0.66 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 27.0, 33.0, 34.0, 38.9, 47.4, 48.8, 66.1, 74.5, 101.3, 107.8, 108.3, 117.3, 120.8, 131.0, 132.8, 133.0, 146.5, 148.3, 150.2, 155.5, 177.5, 198.3; IR ($CHCl_3$) ν 1725, 1685, 1485, 1245, 1150 cm^{-1}; mass spectrum, m/e 457, 411 (base), 368, 216, 149, 57; exact mass calcd for $C_{25}H_{31}NO_7$ 457.2100, found 457.2114.

Minor Diastereoisomer: ^1H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 2.30 (comp, 4 H), 2.32 (s, 3 H), 3.35 (m, 1 H), 3.55 (m, 1 H), 4.54 (d, J = 5.0 Hz, 2 H), 5.23 (comp, 2 H), 5.52 (m, 1 H), 5.90 (m, 1 H), 5.95 (s, 2 H), 6.18 (d, J = 10.5 Hz, 0.33 H), 6.19 (d, J = 10.5 Hz, 0.66 H), 6.78 (br s, 2 H), 6.86 (br s, 1 H), 7.12 (d, J = 10.5 Hz, 0.33 H), 7.19 (d, J = 10.5 Hz, 0.66 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 26.9, 30.3, 33.9, 38.7, 47.3, 49.3, 66.1, 75.0, 101.2, 107.7, 108.1, 117.3, 120.8, 130.5, 132.8, 133.3, 146.8, 148.1, 151.4, 155.0, 177.2, 198.1; IR ($CHCl_3$) ν 1725, 1690, 1490, 1250, 1150 cm^{-1}; mass spectrum, m/e 457, 411 (base), 368, 300, 242, 216, 158, 57; exact mass calcd for $C_{25}H_{31}NO_7$ 457.2100, found 457.2114.

Conversion of 18a into 22a and 22b. To a solution of a mixture of the diastereoisomeric cyclohexenones **18a** (840 mg, 1.75 mmol) in THF (200 mL) at room temperature was added in one portion phenyltrimethylammonium perbromide[22] (PTAB) (723 mg, 1.92 mmol), and the reaction was stirred in the dark for 20 h. The reaction mixture was then poured into saturated $NaHCO_3$ (200 mL), and ether (200 mL) was added. The layers were separated, and the aqueous phase was washed with ether (2 × 100 mL). The combined organic layers were washed with saturated NaCl (1 × 100 mL) and dried ($MgSO_4$), and the excess solvents were removed under reduced pressure to provide ca. 1.0 g of the crude α′-bromo enone **19** (X = Br, R = OMe), which was then heated at reflux in trifluoroacetic acid (10 mL) containing anisole (943 mg, 8.73 mmol) for 45 min. The reaction mixture was cooled, the trifluoroacetic acid was removed under reduced pressure, and the thick black residue was partitioned between ether (20 mL) and 0.5 N HCl (20 mL). The layers were separated, and the aqueous phase was washed with ether (1 × 20 mL). The aqueous layer was saturated with NaCl, made basic with saturated Na_2CO_3, and then extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried ($MgSO_4$), and the excess solvent was evaporated under reduced pressure to give a residue, which was then dissolved in benzene (20 mL) containing 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) (532 mg, 3.49 mmol), and the solution was stirred at room temperature for 2 h. The solvents were removed under reduced pressure, and the crude product mixture was separated by HPLC using hexane/ethyl acetate (1.4:1) containing 1% triethylamine to give **22a** (125 mg, 21%) and **22b** (153 mg, 26%).

(1*S,4*R**,5*R**)-*N*-Methyl-4-[(methoxycarbonyl)oxy]-5-[3,4-(methylenedioxy)phenyl]-2-azabicyclo[3.3.1]non-6-en-8-one (22a)**: mp 168–170 °C; ^{1}NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.42 (ddd, J = 2.0, 3.0, 12.4 Hz, 1 H), 2.80 (ddd, J = 2.4, 3.0, 12.4 Hz, 1 H), 2.89 (dd, J = 2.5, 13.8, 1 H), 3.07 (dd, J = 2.0, 13.8, 1 H), 3.30 (br dd, J = 2.0, 3.0 Hz, 1 H), 3.61 (s, 3 H), 5.04 (br dd, J = 2.0, 2.5 Hz, 1 H), 5.94 (s, 2 H), 6.19 (dd, J = 1.2, 10.2, 1 H), 6.79 (m, 2 H), 6.83 (br s, 1 H), 6.98 (dd, J = 2.4, 10.2, 1 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 32.7, 42.6, 42.7, 51.1, 54.8, 62.7, 75.7, 101.2, 106.3, 108.4, 119.1, 133.2, 135.5, 146.6, 148.2, 154.1, 155.1, 194.4; mass spectrum, m/e 345, 269 (base), 214; exact mass calcd for $C_{18}H_{19}NO_6$ 345.1212, found 345.1217.

(1*S,4*S**,5*R**)-*N*-Methyl-4-[(methoxycarbonyl)oxy]-5-[3,4-(methylenedioxy)phenyl]-2-azabicyclo[3.3.1]non-6-en-8-one (22b)**: mp 128–130 °C; ^{1}NMR (360 MHz, $CDCl_3$) δ 2.19 (ddd, J = 2.3, 2.9, 13.9 Hz, 1 H), 2.26 (dd, J = 2.6, 13.9 Hz, 1 H), 2.33 (s, 3 H), 2.40 (dd, J = 10.1, 11.1 Hz, 1 H), 3.02 (dd, J = 2.6,

2.9 Hz, 1 H), 3.19 (dd, J = 5.6, 11.1 Hz, 1 H), 3.70 (s, 3 H), 5.36 (dd, J = 5.6, 10.1 Hz, 1 H), 5.96 (s, 2 H), 6.41 (dd, J = 1.1, 10.3 Hz, 1 H), 6.78 (m, 2 H), 7.08 (dd, J = 2.3, 10.3 Hz, 1 H); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 42.4 (2 C), 43.5, 51.0, 55.0, 62.3, 75.4, 101.2, 106.4, 108.6, 118.9, 133.5, 136.4, 146.7, 148.3, 151.8, 154.8, 194.6; mass spectrum, m/e 345, 269, 214 (base); exact mass calcd for $C_{18}H_{19}NO_6$ 345.1212, found 345.1219.

4-[1-(Pivaloyloxy)-2-[[(allyloxy)carbonyl]methylamino]-ethyl]-4-[3,4-(methylenedioxy)phenyl]cyclohexadienone (26). To a solution of a mixture of the diastereomers **18d** (7.39 g, 16.0 mmol) in ethyl acetate (540 mL) at room temperature was added dropwise a solution of concentrated H_2SO_4 (0.4 mL) in ethyl acetate (5 mL) followed by PTAB (7.30 g, 20.8 mmol) in one portion, and the orange solution was stirred at room temperature in the dark for 20 h. Saturated aqueous $NaHCO_3$ (540 mL) and ethyl acetate (250 mL) were then added and the layers separated, and the aqueous phase was extracted with ethyl acetate (2 × 250 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (1 × 300 mL) and saturated aqueous NaCl (1 × 300 mL), and the aqueous washes were back-extracted with ethyl acetate (1 × 200 mL). The combined organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the crude bromo cyclohexenone, which was immediately dissolved in benzene (550 mL), and the solution was placed under nitrogen. To this solution was added DBU (12.10 g, 12.09 mL, 80.0 mmol), and the dark mixture was heated at reflux under nitrogen for 18 h. The mixture was cooled to room temperature and the solvent removed under reduced pressure. The resulting residue was then partitioned between 1 N HCl (250 mL) and ethyl acetate (250 mL), and the layers were separated. The aqueous phase was then extracted with ethyl acetate (3 × 150 mL), and the combined organic extract was washed with saturated aqueous $NaHCO_3$ (2 × 150 mL) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a dark oil that was purified by preparative HPLC using hexane/ethyl acetate (2:1) to afford 5.73 g (77%) of **26** as a viscous yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (s, 9 H), 2.88 (s, 3 H), 3.42 (comp, 2 H), 4.60 (comp, 2 H), 5.27 (comp, 2 H), 5.87 (comp, 2 H), 5.95 (br s, 2 H), 6.36 (br d, J = 10.5 Hz, 0.6 H), 6.49 (br d, J = 10.5 Hz, 0.4 H), 6.78 (br s, 2 H), 6.82 (br s, 1 H), 7.08 (dd, J = 3.0, 10.5 Hz, 0.4 H), 7.20 (dd, J = 3.0, 10.5 Hz, 0.6 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 26.8, 38.6, 49.8, 51.3, 66.1, 72.4, 101.3, 107.0, 108.5, 117.2, 119.9, 129.6, 130.4, 131.2, 132.8, 147.2, 148.6, 149.5, 155.2, 177.2, 184.8; IR ($CHCl_3$) ν 1780, 1700, 1675, 1485, 1250, 1150 cm^{-1}; mass spectrum, m/e 411 (base), 214, 57; exact mass calcd for $C_{25}H_{29}NO_7$ 455.1944, found 455.1932.

(3aS*,7aS*)-N-Methyl-3(R*/S*)-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-2,3,3a,6,7,7a-hexahydroindol-6-ones (27 and 28). To a solution of **26** (3.77 g, 8.3 mmol) in CH_2Cl_2 (166 mL) at room temperature was added 2-ethylhexanoic acid (2.86 g, 3.17 mL, 19.8 mmol) followed by tetrakis(triphenylphosphine)palladium(0)[27] (191 mg, 0.165 mmol) and triphenylphosphine (191 mg, 0.745 mmol), and the solution was stirred for 18 h. The solvent was then removed under reduced pressure and the residue partitioned between 1 N HCl (75 mL) and ether (75 mL). The layers were separated, and the organic phase was extracted with 1 N HCl (2 × 50 mL). The combined aqueous phase was then made basic with Na_2CO_3 (pH 8) and extracted with ethyl acetate (3 × 100 mL), and the combined organic extract was dried ($MgSO_4$). The solvent was then removed and the crude product purified by semipreparative HPLC using hexane/ethyl acetate (1:1) containing 1% triethylamine to afford 2.78 g (90%) of an inseparable mixture of **27** and **28** in a 1.5:1 ratio (by ^{1}H NMR) as a viscous yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (s, 6 H), 1.12 (s, 3 H), 2.27 (s, 1 H), 2.31 (s, 2 H), 2.44 (comp, 2 H), 2.58 (d, J = 3.0 Hz, 0.67 H), 2.66 (d, J = 3.0 Hz, 0.33 H), 2.90 (comp, 0.67 H), 3.20 (m, 0.67 H), 3.49 (dd, J = 6.5, 11.5 Hz, 0.67 H), 5.10 (t, J = 6.5 Hz, 0.67 H), 5.44 (dd, J = 4.0, 8.5 Hz, 0.33 H), 5.85 (s, 0.67 H), 5.88 (s, 0.33 H), 5.98 (d, J = 10.5 Hz, 0.67 H), 6.13 (d, J = 10.5 Hz, 0.33 H), 6.70 (m, 2 H), 6.76 (m, 1 H), 6.83 (dd, J = 2.0, 10.5 Hz, 0.33 H), 7.02 (dd, J = 2.0, 10.5 Hz, 0.67 H); IR (CCl_4) ν 1735, 1695, 1490, 1240, 1150, 1050 cm^{-1}; mass spectrum, m/e 370, 356, 269 (base), 214, 134, 57; exact mass calcd for $C_{21}H_{25}NO_5$ 371.1733, found 371.1724.

Diisobutylaluminum Hydride Reduction of 27 and 28. To a solution of **27** and **28** (629 mg, 1.70 mmol) in THF (35 mL) at −78 °C was added diisobutylaluminum hydride (1.0 M in toluene, 8.47 mmol) dropwise over 15 min. The mixture was then stirred for 30 min at which time the cooling bath was removed, and saturated aqueous $NaHCO_3$ (25 mL) was added dropwise over 10 min. The heterogeneous solution was allowed to warm to room temperature over 15 min, and ethyl acetate (25 mL) was added. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 75 mL). The organic phase was dried ($MgSO_4$), and the excess solvent was removed under reduced pressure to give 587 mg of a mixture of the four diastereomeric alcohols **32–35** (ca. 3:2:5:3).

In one such experiment, the mixture of diastereomeric alcohols **32–35** was partially separated by semipreparative HPLC using hexane/ethyl acetate (1:2.5) containing 1% triethylamine to afford **32**, **33**, and a mixture of **34** and **35**. The allylic alcohols **34** and **35** were subsquently separated by semipreparative HPLC using hexane/ethyl acetate (3:1) containing 1% triethylamine.

(3S*,3aS*,6S*,7aS*)-N-Methyl-3-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-6-hydroxy-2,3,3a,6,7,7a-hexahydroindole (32) (as a gummy solid): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 9 H), 1.41 (ddd, J = 2.0, 10.5, 12.5 Hz, 1 H), 2.20 (m, 1 H), 2.40 (s, 3 H) 2.41 (dd, J = 7.0, 10.5 Hz, 1 H), 2.89 (br s, 1 H), 3.53 (dd, J = 7.0, 10.5 Hz, 1 H), 4.36 (m, 1 H), 5.00 (t, J = 7.0 Hz, 1 H), 5.38 (br d, J = 10.5 Hz, 1 H), 5.90 (s, 2 H), 6.10 (br d, J = 10.5 Hz, 1 H), 6.71 (d, J = 7.0 Hz, 1 H), 6.78 (dd, J = 2.0, 7.0 Hz, 1 H), 6.81 (d, J = 2.0 Hz, 1 H); mass spectrum, m/e 277, 253, 214, 121 (base), 57; exact mass calcd for $C_{21}H_{27}NO_5$ 373.1889, found 373.1876.

(3R*,3aS*,6S*,7aS*)-N-Methyl-3-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-6-hydroxy-2,3,3a,6,7,7a-hexahydroindole (33) (as a viscous yellow oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 9 H), 1.40, (ddd, J = 2.0, 10.5, 13.5 Hz, 1 H), 2.18 (m, 1 H), 2.34 (s, 3 H), 2.52 (br s, 1 H), 2.75 (dd, J = 7.0, 10.5 Hz, 1 H), 3.08 (dd, J = 2.0, 10.5 Hz, 1 H), 4.42 (m, 1 H), 5.42 (dd, J = 2.0, 7.0 Hz, 1 H), 5.62 (br d, J = 11.5 Hz, 1 H), 5.95 (s, 2 H), 5.98 (br d, J = 11.5 Hz, 1 H), 6.73 (d, J = 7.0 Hz, 1 H), 6.81 (dd, J = 2.0, 7.0 Hz, 1 H), 6.85 (d, J = 2.0 Hz, 1 H); mass spectrum, m/e 373, 303, 271, 253, 214, 202, 198, 121 (base), 57; exact mass calcd for $C_{21}H_{27}NO_5$ 373.1889, found 373.1879.

(3S*,3aS*,6R*,7aS*)-N-Methyl-3-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-6-hydroxy-2,3,3a,6,7,7a-hexahydroindole (34) (as a gummy solid): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (s, 9 H), 1.81 (ddd, J = 2.0, 4.0, 15.0 Hz, 1 H), 2.31 (br d, J = 15.0 Hz, 1 H), 2.49 (dd, J = 3.0, 12.5 Hz, 1 H), 2.56 (s, 3 H), 3.40 (br s, 1 H), 3.55 (dd, J = 4.0, 12.5 Hz, 1 H), 3.98 (m, 1 H), 5.17 (dd, J = 3.0, 4.0 Hz, 1 H), 5.90 (s, 2 H), 6.00 (dd, J = 1.0, 10.5 Hz, 1 H), 6.11 (ddd, J = 1.0, 5.0, 10.5 Hz, 1 H), 6.71 (br s, 2 H), 6.77 (br s, 1 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 26.8, 27.9, 38.5, 42.3, 53.7, 60.7, 63.2, 68.4, 79.3, 101.1, 107.9, 108.7, 121.0, 130.1, 130.6, 134.0, 146.1, 147.6, 177.3; IR ($CHCl_3$) ν 3150, 1720, 1490, 1240, 1150, 1045 cm^{-1}; mass spectrum, m/e 372, 303, 271 (base), 253, 214, 198, 57; exact mass calcd for $C_{21}H_{27}NO_5$ 373.1889, found 373.1879.

(3R*,3aS*,6R*,7aS*)-N-Methyl-3-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-6-hydroxy-2,3,3a,6,7,7a-hexahydroindole (35) (as a viscous yellow oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 9 H), 1.63 (ddd, J = 2.0, 3.0, 15.0 Hz, 1 H), 2.28 (br d, J = 15.0 Hz, 1 H), 2.47 (s, 3 H), 2.82 (br s, 1 H), 2.87 (dd, J = 7.0, 10.5 Hz, 1 H), 3.12 (dd, J = 4.0, 10.5 Hz, 1 H), 4.05 (m, 1 H), 5.49 (dd, J = 4.0, 7.0 Hz, 1 H), 5.81 (br d, J = 10.5 Hz, 1 H), 5.95 (s, 2 H), 6.30 (dd, J = 4.0, 10.5 Hz, 1 H), 6.77 (br s, 2 H), 6.80 (br s, 1 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 27.2, 38.8, 41.4, 53.3, 60.7, 63.2, 71.7, 79.0, 101.2, 107.4, 108.2, 120.0, 128.1, 130.9, 136.9, 146.5, 148.1, 178.2; IR ($CHCl_3$) ν 3150, 1720, 1490, 1250, 1165, 1050 cm^{-1}; mass spectrum, m/e 372, 303, 271, 253, 214, 198, 57 (base); exact mass calcd for $C_{21}H_{27}NO_5$ 373.1889, found 373.1879.

Conversion of 32–35 into 36 and 37. To a solution of **32–35** (587 mg, 1.57 mmol) prepared as described above in THF (39 mL) at 0 °C was added dropwise triethylamine (1.53 mL, 11.0 mmol) followed by a solution of freshly prepared methanesulfonic anhydride (1.91 g, 11.0 mmol) in THF (7 mL). The cloudy solution was then stirred vigorously at 0 °C for 0.5 h. Methanol (40 mL) was then added dropwise, and the mixture was stirred at 0 °C for 0.5 h and then at room temperature for 48 h. This solution was then poured into a mixture of ether (50 mL) and 1 N HCl

(50 mL), and the layers were separated. The organic phase was extracted with 1 N HCl (2 × 25 mL), and the combined aqueous phase was made basic (pH 8) with Na_2CO_3 and extracted with ethyl acetate (3 × 50 mL). This combined organic portion was dried ($MgSO_4$) and concentrated under reduced pressure. Separation of the crude products by semipreparative HPLC using hexane/ethyl acetate (5:1) containing 1% triethylamine afforded the two diastereomeric allyl ethers **36** and **37**; yields, physical properties, and spectral data are given.

(3*S,3a*S**,6*S**,7a*S**)-*N*-Methyl-3-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-6-methoxy-2,3,3a,6,7,7a-hexahydroindole (36)** (213 mg, 35%, white solid, mp 79–80 °C): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 9 H), 1.43 (ddd, *J* = 2.0, 10.5, 12.5 Hz, 1 H), 2.20 (m, 1 H), 2.41 (s, 3 H), 2.44 (dd, *J* = 7.0, 11.0 Hz, 1 H), 2.88 (m, 1 H), 3.48 (s, 3 H), 3.54 (dd, *J* = 7.0, 11.0 Hz, 1 H), 3.95 (m, 1 H), 5.00 (t, *J* = 7.0 Hz, 1 H), 5.90 (s, 2 H), 5.98 (br d, *J* = 9.5 Hz, 1 H) 6.13 (br d, *J* = 9.5 Hz, 1 H), 6.70 (d, *J* = 8.5 Hz, 1 H), 6.78 (dd, *J* = 2.0, 8.5 Hz, 1 H), 6.81 (d, *J* = 2.0 Hz, 1 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 26.3, 26.7, 38.3, 40.7, 53.1, 55.7, 61.2, 71.5, 72.2, 78.4, 100.8, 107.4, 109.7, 122.1, 127.8, 132.6, 134.2, 145.9, 147.0, 177.5; IR ($CHCl_3$) ν 1720, 1490, 1245, 1160, 1045 cm^{-1}; mass spectrum, *m/e* 387, 372, 303, 228, 202 (base), 70, 57. Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 68.13; H, 7.53; N, 3.63.

(3*R,3a*S**,6*S**,7a*S**)-*N*-Methyl-3-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-6-methoxy-2,3,3a,6,7,7a-hexahydroindole (37)** (146 mg, 24%, viscous yellow oil): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (s, 9 H), 1.42 (ddd, *J* = 2.0, 10.5, 12.5 Hz, 1 H), 2.12 (m, 1 H), 2.34 (s, 3 H), 2.52 (m, 1 H), 2.76 (dd, *J* = 7.0, 11.5 Hz, 1 H), 3.09 (dd, *J* = 3.0, 11.5 Hz, 1 H), 3.40 (s, 3 H), 4.00 (m, 1 H), 5.45 (dd, *J* = 3.0, 7.0 Hz, 1 H), 5.64 (br d, *J* = 10.5 Hz, 1 H), 5.92 (s, 2 H), 6.07 (br d, *J* = 10.5 Hz, 1 H), 6.73 (d, *J* = 7.0 Hz, 1 H), 6.81 (dd, *J* = 1.0, 7.0 Hz, 1 H), 6.85 (d, *J* = 1.0 Hz, 1 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) δ 26.1, 27.0, 38.7, 40.4, 53.6, 55.8, 62.0, 72.3, 80.0, 101.0, 107.6, 107.9, 120.2, 128.8, 129.0, 138.2, 146.2, 147.8, 178.3; IR ($CHCl_3$) ν 1720, 1485, 1250, 1165, 1050 cm^{-1}; mass spectrum, *m/e* 387, 372, 303, 228, 202, 70 (base), 57; exact mass calcd for $C_{22}H_{29}NO_5$ 387.2046, found 387.2058.

(3*R,3a*S**,6*S**,7a*S**)-*N*-Formyl-3-(pivaloyloxy)-3a-[3,4-(methylenedioxy)phenyl]-6-methoxy-2,3,3a,6,7,7a-hexahydroindole (46).** Hydrogen was bubbled through a solution of platinum(IV) oxide (106 mg, 0.467 mmol) in water (1.2 mL) for 1 h. To this heterogeneous mixture was then added a solution of **37** (45 mg, 0.116 mmol) in *p*-dioxane (1.2 mL) dropwise over 2 min. Oxygen was then bubbled through this black mixture with stirring at room temperature for 22 h. To the solution were then added ethyl acetate (3 mL) and water (3 mL), and this mixture was filtered through a Celite pad. The layers were separated, and the aqueous phase was extracted with ethyl acetate (2 × 3 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (1 × 2 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 44 mg of a 3:1 mixture (by ^{1}H NMR) of formamide **46** and the secondary amine **45** as a yellow oil. This mixture was dissolved in pyridine (2 mL), acetic formic anhydride (46 mg, 0.750 mmol) was added dropwise, and the solution was stirred under nitrogen at room temperature for 16 h. The solvent was removed under reduced pressure and the residue partitioned between 1 N HCl (2 mL) and ethyl acetate (2 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 3 mL). The combined organic portion was dried ($MgSO_4$), the solvent was then removed under reduced pressure, and the resulting oil was purified by semipreparative HPLC using hexane/ethyl acetate (1:1.75) to afford 27 mg (57%) of **46** as a viscous yellow oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (s, 9 H), 2.03 (t, *J* = 5.5 Hz, 0.33 H), 2.10 (t, *J* = 5.5 Hz, 0.67 H), 2.25 (m, 1 H), 3.30 (m, 1 H), 3.40 (s, 3 H), 3.86 (m, 1 H), 4.01 (m, 1 H), 4.31 (dd, *J* = 4.0, 10.5 Hz, 1 H), 5.48 (t, *J* = 6.0 Hz, 0.33 H), 5.66 (dd, *J* = 4.0, 7.0 Hz, 0.67 H), 5.86 (d, *J* = 10.5 Hz, 1 H, H-4), 5.95 (s, 2 H), 6.17 (dd, *J* = 4.0, 10.5 Hz, 0.67 H), 6.19 (dd, *J* = 3.0, 10.5 Hz, 0.33 H), 6.76 (d, *J* = 8.5 Hz, 1 H), 6.85 (comp, 2 H), 8.24 (s, 0.33 H), 8.30 (s, 0.67 H); IR ($CHCl_3$) ν 1740, 1670, 1495, 1255, 1160, 1060 cm^{-1}; mass spectrum, *m/e* 401, 317, 299, 241, 230, 198, 57 (base), 43; exact mass calcd for $C_{22}H_{27}NO_6$ 401.1838, found 401.1830.

11-*O*-Pivaloylhaemanthidine (48). To **46** (27 mg, 0.066 mmol) in a conical vial at room temperature was added dropwise freshly distilled (under nitrogen) phosphorous oxychloride (0.22 mL). The vial was closed and heated with stirring at 80 °C for 6 h. The mixture was then cooled to room temperature and the excess phosphorous oxychloride was removed under reduced pressure. A solution of water/THF (1:1, 1.0 mL) was added dropwise and the resulting solution stirred at room temperature for 24 h. The excess solvent was then removed under reduced pressure and the residue partitioned between 1 N HCl (2 mL) and ether (2 mL). The layers were separated, and the organic phase was extracted with 1 N HCl (3 × 3 mL). This acidic aqueous portion was made basic (pH 8) with Na_2CO_3 and extracted with $CHCl_3$ (4 × 3 mL). The resulting organic phase was dried ($MgSO_4$), and solvents were removed under reduced pressure to give a yellow oil, which was purified by column chromatography on silica gel using chloroform/methanol (98:2) to give 19 mg (71%) of **48** as a white solid: mp 184–189 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 9 H), 2.18 (comp, 2 H), 3.10 (dd, *J* = 3.0, 15.0 Hz, 0.45 H), 3.33 (s, 0.55 H), 3.37 (m, 1 H), 3.38 (s, 0.45 H), 3.70 (dd, *J* = 5.0, 13.5 Hz, 0.55 H), 3.84 (m, 1 H), 3.98 (dd, *J* = 5.0, 12.5 Hz, 0.45 H), 4.30 (dd, *J* = 7.0, 15.0 Hz, 0.55 H), 4.89 (m, 1 H), 5.19 (s, 0.55 H), 5.84 (s, 0.45 H), 5.92 (m, 2 H), 6.16 (dd, *J* = 5.0, 10.5 Hz, 1 H), 6.28 (dd, *J* = 5.0, 10.5 Hz, 1 H), 6.83 (s, 0.55 H), 6.88 (s, 0.45 H), 6.89 (s, 0.55 H), 6.98 (s, 0.45 H); IR ($CHCl_3$) ν 1725, 1490, 1160, 1055 cm^{-1}; mass spectrum, *m/e* 401, 299, 284, 266, 257 (base), 250, 238, 225, 57. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.53; H, 6.78; N, 3.55.

(±)-Haemanthidine (2). To **48** (13 mg, 0.032 mmol) was added a solution of lithium hydroxide in methanol (1.5 M, 1.65 mL), and the resulting mixture was stirred at room temperature for 23 h. The solvent was then removed under reduced pressure and the residue partitioned between 1 N HCl (2 mL) and ether (2 mL). The layers were separated, and the organic phase was extracted with 1 N HCl (3 × 3 mL). The combined aqueous phase was made basic (pH 8) and extracted with $CHCl_3$ (4 × 3 mL), and the combined extract was dried ($MgSO_4$) and concentrated under reduced pressure. The resulting yellow solid was purified by column chromatography on silica gel using chloroform/methanol (90:10) to afford 8 mg (78%) of **2** as a white solid that was identical (^{1}H NMR, IR, mass spectrum, TLC) with an authentic sample:[32] mp 217–218 °C dec (from acetone) [lit. mp 221–223 °C,[6b] 193–195 °C[6c]]; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00–2.45 (comp, 2 H), 3.01 (dd, *J* = 3.0, 15.0 Hz, 0.45 H), 3.31 (m, 1 H), 3.34 (s, 1.65 H), 3.37 (s, 1.35 H), 3.65 (dd, *J* = 4.0, 15.0 Hz, 0.55 H), 3.90 (comp, 2.45 H), 4.21 (dd, *J* = 7.5, 13.5 Hz, 0.55 H), 5.08 (s, 0.55 H), 5.77 (s, 0.45 H), 5.92 (m, 2 H), 6.38 (m, 2 H), 6.78 (s, 0.45 H), 6.80 (s, 0.55 H), 6.81 (s, 0.55 H), 6.97 (s, 0.45 H); IR ($CHCl_3$) 1490, 1250, 1210, 1045 cm^{-1}; mass spectrum, *m/e* 317, 284, 258, 225 (base), 199, 139, 115; exact mass calcd for $C_{17}H_{19}NO_5$ 317.1263, found 317.1256.

(±)-Pretazettine (3). To a solution of **2** (23 mg, 0.072 mmol) in methanol (1.8 mL) at room temperature was added iodomethane (0.47 mL) dropwise over 2 min, and the solution was stirred for 6 h at room temperature. The solvent was then removed under reduced pressure and the residue dissolved in dilute aqueous HCl (2.1 mL) at pH 5. The pH of the solution was then adjusted to pH 8 by the dropwise addition with stirring of saturated aqueous $NaHCO_3$ (ca. 3 drops). Chloroform (3 mL) was then added, and the layers were separated. The aqueous phase was extracted with chloroform (10 × 3 mL), and the combined organic portions were dried ($MgSO_4$). The solvent was then removed under reduced pressure to provide 16 mg (66%) of **3** as a yellow oil, which was identical (^{1}H NMR, IR, mass spectrum, TLC) with an authentic sample:[32] ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.77 (ddd, *J* = 2.0, 9.5, 13.5 Hz, 1 H), 2.49 (m, 1 H), 2.50 (s, 3 H), 2.67 (dd, *J* = 7.5, 9.5 Hz, 1 H), 2.95 (m, 1 H), 2.98 (dd, *J* = 9.5, 11.5 Hz, 1 H), 3.44 (s, 3 H), 4.16 (m, 1 H), 4.33 (dd, *J* = 9.5, 11.5 Hz, 1 H), 5.52 (br d, *J* = 11.5 Hz, 1 H), 5.89 (br d, *J* = 11.5 Hz, 1 H), 5.92 (s, 2 H), 6.11 (s, 1 H), 6.87 (s, 1 H); IR ($CHCl_3$) ν 1495, 1270, 1220, 1100, 1050 cm^{-1}; mass spectrum, *m/e* 331, 316, 298, 247 (base), 225, 139, 115; exact mass calcd for $C_{18}H_{21}NO_5$ 331.1420, found 331.1413.

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Registry No. (±)-**2**, 28405-98-3; (±)-**3**, 79068-83-0; **11**, 120-57-0; **12**, 92143-67-4; **13**, 92143-68-5; **14**, 107201-33-2; **16**, 92143-84-5; **17d**, 92143-69-6; (±)-**18a** (isomer 1), 107201-37-6; (±)-**18a** (isomer 2), 107201-39-8; (±)-**18d** (isomer 1), 92143-70-9; (±)-**18d** (isomer 2), 92143-71-0; **19** (X = Br, R = OMe), 107201-34-3; (±)-**22a**, 107201-35-4; (±)-**22b**, 107201-36-5; **26**, 107201-38-7; (±)-**27**, 92143-73-2; (±)-**28**, 92143-74-3; (±)-**32**, 92143-80-1; (±)-**33**, 107222-36-6; (±)-**34**, 92143-81-2; (±)-**35**, 92143-83-4; (±)-**36**, 92143-75-4; (±)-**37**, 92143-76-5; (±)-**45**, 92143-78-7; (±)-**46**, 92143-77-6; (±)-**48**, 92143-79-8; *N*-methylaminoacetaldehyde diethyl acetal, 20677-73-0; *N*-[(allyloxy)carbonyl]-*N*-methylaminoacetaldehyde diethyl acetal, 107201-32-1; diethyl [(benzylideneamino)methyl]phosphonate, 50917-73-2; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; allyl chloroformate, 2937-50-0; benzyl chloroformate, 501-53-1.

Total Synthesis of Isoflavones: Jamaicin, Calopogonium Isoflavone-B, Pseudobaptigenin, and Maxima Substance-B. Friedel-Crafts Acylation Reactions with Acid-Sensitive Substrates†

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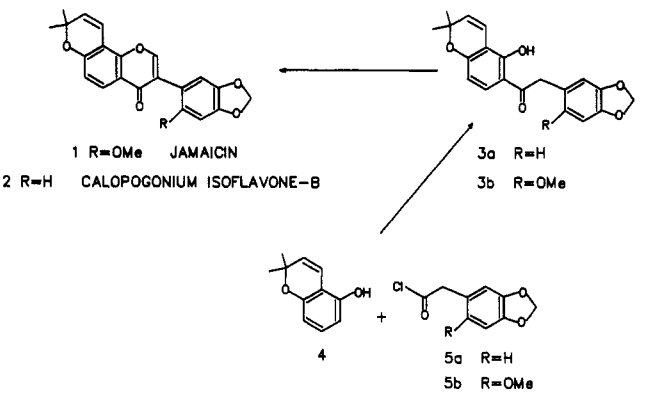
The Friedel-Crafts acylation reaction was studied on several acid-sensitive substrates. Under the proper conditions of varying Lewis acids, solvents, and reaction temperatures, the acylation indeed took place, thus obviating the necessity for functional group protection-deprotection sequences. By use of these procedures, the naturally occurring isoflavones jamaicin (**1**), calopogonium isoflavone-B (**2**), maxima substance-B (**30**), and pseudobaptigenin (**31**) were synthesized and characterized.

We have been examining the scope and limitations of the Lewis acid (titanium tetrachloride and aluminum chloride) mediated Friedel-Crafts acylation reaction using sensitive substrates and acylating agents and have found that, under certain conditions, not only do the reactants survive the process, but the reaction is highly regioselective. As a demonstration of the potential of this methodology for synthesizing heterocycles, we decided to try to synthesize several naturally occurring isoflavones that contain sensitive functionality in a highly efficient manner without resorting to any of the often employed functional group protection-deprotection sequences.

Isoflavones[1] are the most abundant subset of the flavonoid class of compounds which also includes pterocarpans,[2] rotenoids,[3] and coumestans.[4] Structurally, isoflavones are highly substituted and oxygenated derivatives of 3-phenylchromans. Much work on the biosynthesis of isoflavones from phenylpropyl precursors (e.g., shikimic, prephenic, and phenylpyruvic acids and phenylalanine) has been reported,[5] but the complete pathway has not yet been defined.

The highly oxygenated versions of isoflavones often have estrogenic activity.[6] Crude preparations of these compounds have also been used as fish narcotics,[6] insecticides, and antifungals[7] for many years in Central and South America. This wide range of biological properties has stimulated interest in the synthesis of natural and unnatural analogues of isoflavones.

Scheme I



Previous syntheses of isoflavones fall into two main categories: (1) routes deriving from chalcone-based systems[8,9] and (2) syntheses from benzoin precursors.[10-12]

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