Construction of Quaternary Carbon Centers by Palladium-Catalyzed Intramolecular Alkene Insertions. Total Synthesis of the *Amaryllidaceae* Alkaloids (±)-Tazettine and (±)-6a-Epipretazettine

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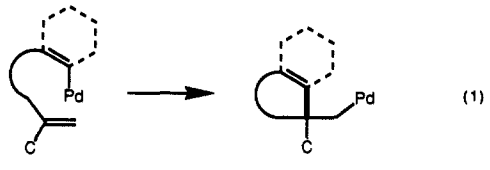
Abstract: Total syntheses of (±)-tazettine (**1**) and (±)-6a-epipretazettine (**3**), which proceed in 11 steps from the known enal **7** (14 steps from commercially available *p*-methoxybenzyl alcohol), are reported. The pivotal step is the palladium-catalyzed cyclization of alkenyl aryl iodide **13**, which proceeded in excellent yield (63–90%) and with high stereoinduction (>20:1) to form **14**.

Background and Synthesis Plan. The insertion of a coordinated π ligand into a metal–carbon σ bond is one of the fundamental transformations of organotransition-metal chemistry.[1] Palladium-catalyzed alkene insertions of aryl and alkenyl halides (Heck reactions) have proven particularly useful in preparative organic chemistry.[2] Although the formation of rings by intramolecular Heck reactions has been known since the mid-1970s,[2] the important utility of this process for forming synthetically demanding quaternary carbon centers was revealed only recently by studies in Grigg's[3] and our[4] laboratories (eq 1). Encouraged by our early



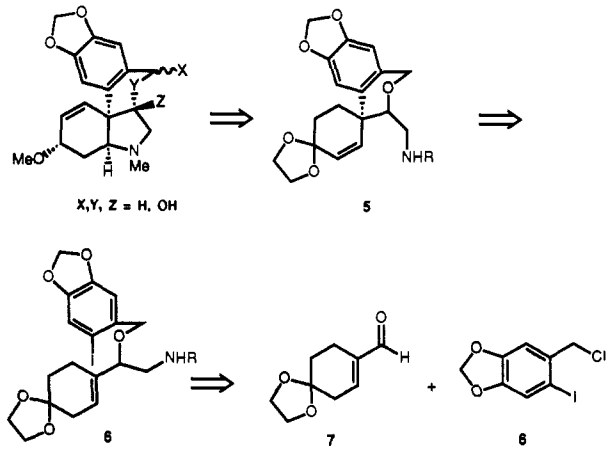
(1)

findings that even *unusually* congested quaternary carbon–carbon centers could be efficiently assembled in this way,[4b] we initiated a broad exploration of this chemistry. One aspect of this program focuses on stereochemical issues, in particular the opportunities for relative[5] and absolute stereocontrol[6] in forming a new quaternary stereogenic center. Surprisingly, this key aspect of intramolecular insertions of organopalladium intermediates had not received attention prior to our recent investigations.[5,6]

As a challenging natural products arena to explore relative stereocontrol in the formation of quaternary carbon centers, we have chosen the [2]benzopyrano[3,4-*c*]hydroindole subgroup of *Amaryllidaceae* alkaloids.[7] These alkaloids, whose structures and chemical interconversions were largely established by incisive investigations by Wildman and Uyeno and their co-workers,[7] include tazettine (**1**),[8] pretazettine (**2**), and 6a-epipretazettine (**3**).[9] One stimulus for our investigations in this area was the numerous disclosures by Furusawa and co-workers of the significant anticancer activity of pretazettine, particularly against Rauscher leukemia, Lewis lung carcinoma, and spontaneous AKR leukemia.[10] Although pretazettine has been convincingly shown to be effective in the Rauscher leukemia system, it has proven less effective in other tumor models.[11]

Since haemanthidine (**4**) can be converted in good yield to pretazettine (**2**) and tazettine (**1**),[9] the pioneering total synthesis of (±)-haemanthidine by Hendrickson and co-workers constitutes the first synthesis achievement in this area.[12] Subsequent significant total synthesis accomplishments in the [2]benzopyrano-[3,4-*c*]hydroindole subclass of *Amaryllidaceae* alkaloids have been recorded by the groups of Tsuda,[13] Danishefsky,[14] White,[15] and Martin.[16,17] Noteworthy are the quite different strategies em-

Scheme I



ployed by these investigators for constructing the quaternary carbon center. Of some note also is the fact that no de novo

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(1) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.

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(3) (a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *45*, 3557.

(4) (a) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. (b) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785.

(5) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.

(6) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.

(7) For reviews, see (a) Martin, S. F. *The Alkaloids* **1987**, *30*, 252. (b) Fuganti, C. *The Alkaloids* **1975**, *15*, 83. (c) Jeffs, P. W. In *MTP International Review of Science, Alkaloids, Organic Chemistry Series one*; Hey, D. H., Wiesner, K. F., Eds.; Butterworths: London; Vol. 9, pp 273–318.

(8) For an X-ray structure of tazettine methiodide, see: Sato, T.; Koyama, H. *J. Chem. Soc. B.* **1971**, 1070.

(9) (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.

(10) See, inter alia: (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.; Lum, M. K. M.; Furusawa, S. *Ibid.* **1981**, *27*, 277. (h) Furusawa, E.; Furusawa, S.; Sokugawa, L. *Ibid.* **1983**, *29*, 294. (i) Furusawa, E.; Furusawa, S. *Onocology* **1988**, *45*, 180.

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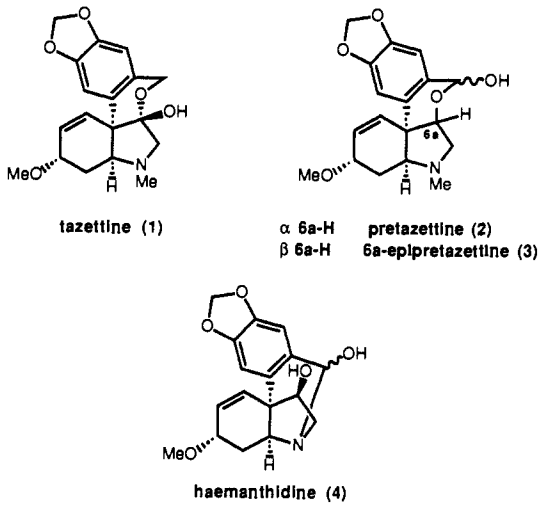


Figure 1. Representative *Amaryllidaceae* alkaloids containing the [2]-benzopyrano[3,4-*c*]hydroindole ring system.

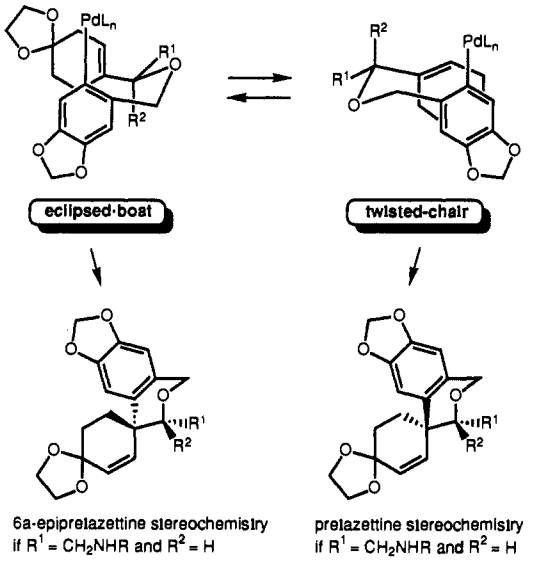
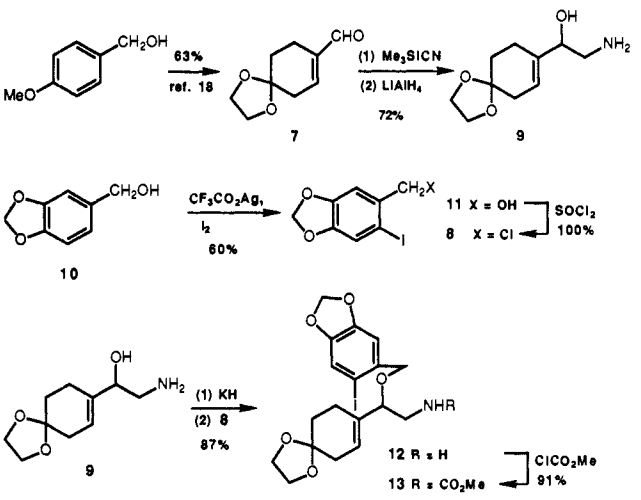


Figure 2. Possible conformations for the insertion step. (The ketal is omitted from the cyclohexene ring of the twisted-chair conformation for clarity.)

synthesis of pretazettine (**2**) has been reported that does not proceed via haemanthidine (**4**) and, thus, not rely on the Wildman protocol for converting **4** → **2**.

The general approach we have employed is outlined in retrosynthetic format in Scheme I. The central step was the projected palladium-catalyzed cyclization of **6** to develop the quaternary

Scheme II



stereocenter and the benzopyran subskeleton. The cyclization substrate **6** can be envisaged to derive from the readily accessible precursors **7**[18] and **8**.[19] The bond to be formed in the key cyclization event is the one presumed to arise in the biosynthesis of these alkaloids through intramolecular oxidative coupling of two phenolic units.[20] The laboratory realization of such a conversion was achieved in White's strikingly short biomimetic synthesis of 6a-epipretazettine.[15]

At the outset of our investigations we considered two limiting conformations for the key insertion step; these are depicted in Figure 2. If the aminomethyl side chain were disposed equatorially, insertion in the eclipsed-boat sense[21] would lead to the 6a-epipretazettine relative orientation of the quaternary carbon stereocenter, while a similar disposition of the side chain in a twisted-chair[21] orientation would evolve to the stereochemistry of pretazettine. Both orientations could result in suprafacial insertion of the alkene into the palladium carbon σ bond, as would be anticipated from the existing precedent in this area.[1] At the outset of our work, little information was available concerning the precise transition-state orientation of the metal–carbon σ bond and the alkene π bond in a suprafacial insertion process.[22] This lack of guidance was, in fact, one of our motivations for examining this issue at the experimental level.

We document here with full experimental detail total syntheses of (±)-tazettine (**1**) and (±)-6a-epipretazettine (**3**). The syntheses proceed in 11 steps from the known,[18] readily available, enal **7** and afford **1** and **3** in overall yields of 6.7% and 8.1%, respectively. A key finding of this study is that the A and C rings[23] of these *Amaryllidaceae* alkaloids can be joined with much greater efficiency (60–90%) by a palladium-catalyzed intramolecular insertion than by a biomimetic protocol.[15] The degree of stereoinduction in forming the quaternary carbon center (Scheme I, **6** → **5**) is high (>20:1) and, like the related biomimetic junction,[15] affords preferentially the 6a-epipretazettine relative stereochemistry.

Results and Discussion

Synthesis of Cyclization Substrate 13. Cyclohexene carboxaldehyde **7** served as a suitable starting point. This aldehyde was prepared on a large scale from 4-methoxybenzyl alcohol in three steps and 63% overall yield by the excellent sequence of Hideo and co-workers.[18] Conversion to amino alcohol **9** was accomplished

(11) Information provided by Dr. Matthew Suffness of the National Products Branch of the Developmental Therapeutics Program at the National Cancer Institute and quoted in ref 7a.

(12) (a) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 5538. (b) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *Ibid.* **1974**, *96*, 7781.

(13) (±)-Haemanthidine and (±)-tazettine: (a) Tsuda, Y.; Isobe, K. *J. Chem. Soc.* **1971**, 1555. (b) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153. (c) Isobe, K.; Taga, J.; Tsuda, Y. *Tetrahedron Lett.* **1976**, 2331.

(14) (±)-Tazettine and (±)-6a-epipretazettine: (a) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838. (b) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *Ibid.* **1982**, *104*, 7591.

(15) 6a-Epipretazettine: White, J. D.; Chong, W. K. M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2300.

(16) (±)-Haemanthidine and (±)-Pretazettine: (a) Martin, S. F.; Davidsen, S. K. *J. Am. Chem. Soc.* **1984**, *106*, 6431. (b) Martin, S. F.; Davidsen, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962.

(17) Formal total syntheses of (±)-tazettine, (±)-6a-epipretazettine, (±)-haemanthidine, and (±)-pretazettine have also been reported: (a) Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647. (b) Ishibashi, H.; Nakatani, H.; Iwami, S.; Sato, T.; Nakamura, N.; Ikeda, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1767.

(18) Isobe, M.; Hideo, I.; Kawai, T.; Goto, T. *Tetrahedron* **1979**, *35*, 946.

(19) Kibayashi, C.; Iida, H.; Yuasa, Y. *J. Org. Chem.* **1979**, *44*, 1074.

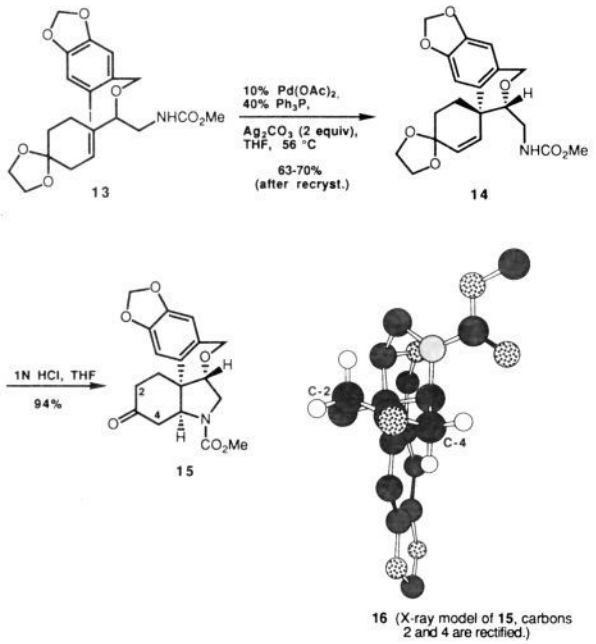
(20) Barton, D. H. R.; Cohen, T. *Festschr. Prof. Dr. Arthur Stoll Siebzigsten Geburtstag 1957* **1957**, 129.

(21) Eclipsed or twisted refers to the relative orientation of the aryl palladium σ bond and the cyclohexene π bond; the second descriptor (chair or boat) refers to the conformation adopted by the forming benzopyran ring.

(22) Some stereochemical results consistent with an eclipsed orientation arose from our contemporaneous exploratory studies of sequential insertion reactions.[5]

(23) We employ the designation originally suggested by Wildman[9] in the narrative part of this paper.

Scheme III

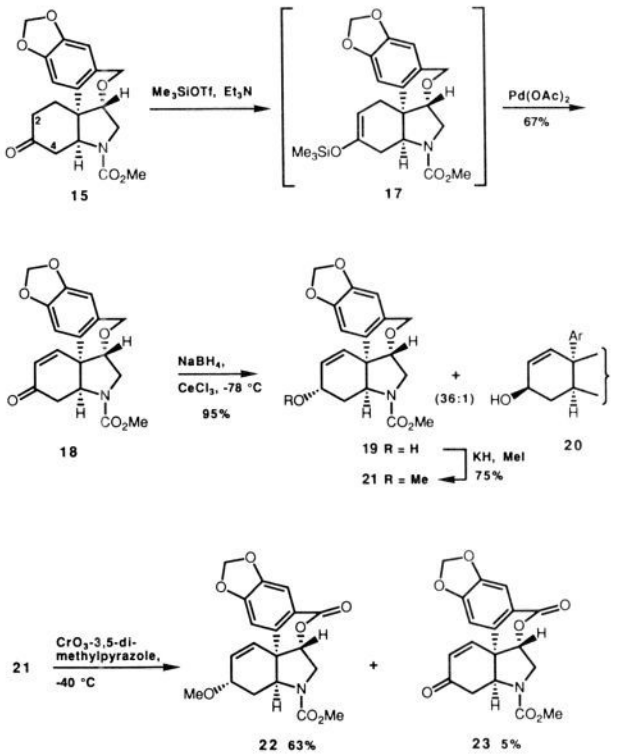


in good yield by lithium aluminum hydride reduction of the trimethylsilyl cyanohydrin derivative of **7**.[24] The aryl iodide **8** was conveniently assembled in two steps from commercially available piperonyl alcohol (**10**). The procedure reported[25] for electrophilic iodination of *o*-dimethoxybenzene (veratrole) afforded directly the desired iodide **11**[26] from **10** in 60% yield after recrystallization. Conversion to the crystalline chloride[19] **8** was straightforward.

Selective O-alkylation[27] of amino alcohol **9** with the benzylic electrophile **8** was achieved at 0 °C in THF by way of the potassium salt of the alcohol. In this way the benzylic ether **12** was obtained in yields as high as 87%. Conventional acylation of **12** provided the carbamate derivative **13**. The sequence summarized in Scheme II delivered **13** on multigram scales in three steps and 57% yield from **7** (seven steps and 36% overall yield from commercially available 4-methoxybenzyl alcohol).

Palladium-Catalyzed Cyclization and Conversion to the [2]Benzopyrano[3,4-*c*]hydroindole 15. Both we[4a] and Hallberg[28] have recently detailed significant advantages of performing Heck reactions in the presence of stoichiometric amounts of silver(I) salts. By use of the conditions developed in our laboratories,[4a] aryl iodide **13** was cleanly cyclized in the presence of 10 mol % $Pd(OAc)_2$, 40 mol % Ph_3P, and 2 equiv of Ag_2CO_3 to afford **14** as the sole product. Pentacycle **14** was isolated in crystalline form in 90% yield (Scheme III). After recrystallization, analytically pure **14** was obtained in 63–70% yield. Examination of the crude cyclization product by ^1H NMR at 500 MHz failed to reveal the presence of a stereoisomer, suggesting that stereoselection in the formation of **14** was at least 20:1. Treatment of **14** with a 6:1 mixture of tetrahydrofuran (THF) and 2 N HCl resulted in cleavage of the ketal and concomitant cyclization to afford the crystalline [2]benzopyrano[3,4-*c*]hydroindole **15** in nearly quantitative yield. This pentacyclic intermediate proved amenable to single-crystal X-ray diffraction analysis and the results of this study are depicted in representation **16**. *The key intramolecular insertion step, thus occurred preferentially to enter the 6a-epi-*

Scheme IV



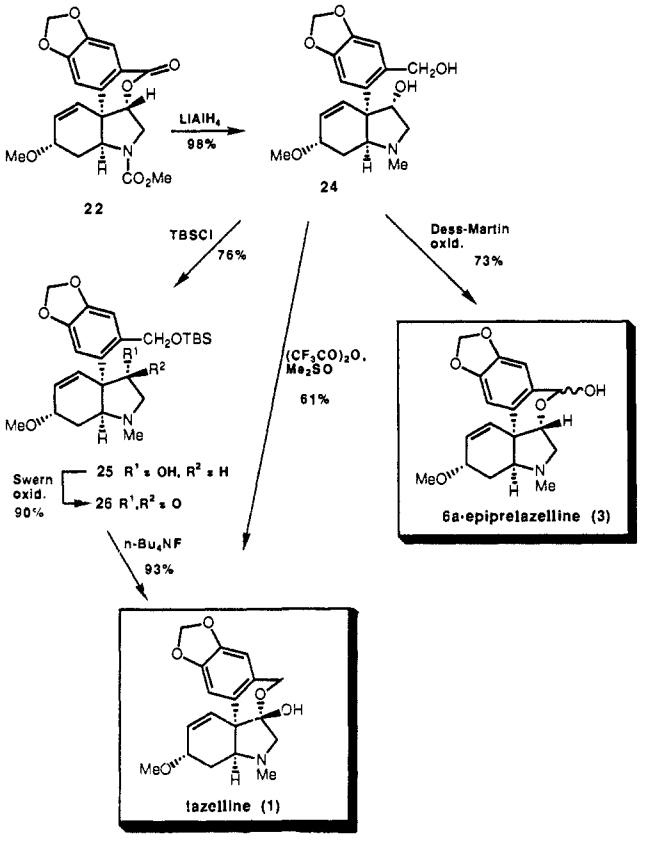
pretazettine stereoseries. This result is consistent with cyclization occurring in the eclipsed-boat sense with the aminomethyl side chain adopting an equatorial orientation (Figure 2; $R^1 = CH_2NHCO_2Me$, $R^2 = H$).[29]

Conversion of 15 to (±)-Tazettine and (±)-6a-Epipretazettine. Conversion of **15** to the target alkaloids entailed developing the allylic ether functionality of the C ring and increasing the oxidation state of the B and D rings to the hemiacetal level. The X-ray model **16** of this starting material suggested that the axial hydrogen at C-4 might be protected from removal by an external base by the 1,3 related axial aryl group. Irrespective of the validity of this rationale,[30] enolization of **15** with trimethylsilyl triflate and Et_3N afforded cleanly the desired silyl enol ether **17** (Scheme IV). This intermediate was not purified but rather immediately subjected to Saeguza–Ito oxidation[31] to provide the $\Delta^{1,2}$ enone **18** in 67% overall yield.

Conversion of **18** to the desired α equatorial alcohol **19** was cleanly accomplished (in 95% yield) by Luche reduction[32] at −78 °C. The stereoselectivity of this transformation was strongly temperature dependent, providing a 36:1 ratio of **19** and **20** at −78 °C, while only a 7:1 ratio was realized at 0 °C. The stereochemistries assigned to **19** and **20**, initially on the basis of precedent,[32a] were confirmed by ^1H NMR analysis of these epimers at 100 °C in toluene-d_8 (to collapse carbamate stereoisomers). Particularly diagnostic was $J_{2,3}$, which was 4.9 Hz for the minor alcohol stereoisomer **20** and <1 Hz for the major isomer **19**. These vicinal couplings would be expected if **19** (axial C-3 methine hydrogen) and **20** (equatorial C-3 methine hydrogen) adopted the conformation found by X-ray analysis for tazettine methiodide.[8] O-Methylation of **19** followed by benzylic oxidation of ether **21** at −40 °C with the chromium trioxide–3,5-di-

(24) Evans, D. A.; Truesdale, C. K.; Carroll, G. L. *J. Org. Chem.* **1974**, *39*, 914.
(25) Wilson, C. V.; Janssen, D. E. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 547.
(26) Kobayashi, S.; Kihara, M.; Yamahara, Y. *Chem. Pharm. Bull.* **1978**, *26*, 3113.
(27) Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622.
(28) (a) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (b) Karabelas, K.; Hallberg, A. *Ibid.* **1986**, *51*, 5286.
(29) The alternative possibility that cyclization takes place in a twisted-chair conformation with the (acylamino)methyl substituent in an axial conformation, although deemed by us less likely, is not rigorously ruled out.
(30) Although this argument assumes kinetic control in the enolization, we have no direct experimental evidence pertinent to this point in the successful conversion of **15** → **17**.
(31) Saeguza, T.; Ito, Y.; Hirao, T. *J. Org. Chem.* **1978**, *43*, 1011.
(32) (a) Luche, J. L.; Rodrigues, Hanz, L.; Cragge, P. *J. Chem. Soc., Chem. Commun.* **1978**, 601. (b) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

Scheme V



methylpyrazole complex[33] provided the important lactone intermediate **22** (47% overall yield from **19**). It was essential that the benzylic oxidation be accomplished below 0 °C or else major amounts of the enone byproduct **23** were produced.

The conversion of lactone carbamate **22** to (±)-tazettine and (±)-6a-epipretazettine is summarized in Scheme V. Reduction of **22** with $LiAlH_4$ at room temperature provided tazettine diol **24** in 98% yield. This diol was a late intermediate in the Danishefsky[14] synthesis of (±)-tazettine and our sample exhibited the expected spectroscopic characteristics. Tazettine diol **24** could be converted to (±)-tazettine in two ways. The first sequence employed the Danishefsky protocol,[14] which involves selective silylation of **24** to afford **25**, oxidation of this latter intermediate to the 6a ketone **26** followed by desilylation of **26** to afford (±)-tazettine. In our hands the oxidation of **25** was most efficient with the Swern reagent,[34] and this slight modification allowed (±)-tazettine to be obtained in 65% overall yield from diol **24**. Alternatively, **24** could be converted directly to (±)-tazettine in 61% yield by oxidation with the dimethyl sulfoxide–trifluoroacetic anhydride reagent. The utility of this reagent mixture for oxidizing hindered secondary alcohols and for the selective oxidation of secondary alcohols in the presence of a primary benzylic hydroxyl group had previously been described.[35] Synthetic (±)-tazettine, mp 173–175 °C (lit.[14] mp 175–176 °C),[36] prepared in either fashion showed a 500-MHz ^1H NMR spectrum that was indistinguishable from that of an authentic sample kindly provided by Professor Martin.

Although in principle it would be possible to access 6a-epipretazettine (**3**) from lactone **22** without proceeding through tazettine diol, such conversions were not pursued. Instead we chose to prepare (±)-6a-epipretazettine from diol **24** by selective oxidation of the benzylic alcohol functionality.[37] Kobayashi had earlier accomplished this conversion, albeit in low yield, with MnO_2. A more satisfactory oxidant is the Dess–Martin periodinane reagent,[38] which delivers (±)-6a-epipretazettine (**3**) as the sole isolated product in 73% yield.[39]

Conclusion

Employing an intramolecular palladium-catalyzed alkene arylation as the central step, stereocontrolled total syntheses of the *Amaryllidaceae* alkaloids (±)-tazettine (**1**) and (±)-6a-epipretazettine (**3**) have been accomplished by efficient, short sequences. Starting from the known enal **7**, 11 steps are required and the overall yields of **1** and **3** are 6.7% and 8.1%, respectively. The overall yields from commercially available *p*-methoxybenzyl alcohol are 3.8% and 4.6%, respectively.

The efficient palladium-catalyzed cyclization of **13** introduces a new strategy for forming the quaternary carbon–aryl bond common to a wide variety of *Amaryllidaceae* alkaloids. The sense of stereoinduction observed in this step suggests that the insertion event occurs preferentially through a conformer having an eclipsed orientation of the alkene π bond and aryl palladium σ bond. This observation should be of general utility in planning stereocontrolled synthetic strategies that employ intramolecular transition-metal-catalyzed insertions as central steps.

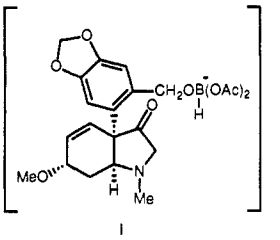
Experimental Section[41]

α-(Aminomethyl)-4,4-(ethylenedioxy)-1-cyclohexenemethanol (9). A modification of a general procedure was employed.[24] A solution of aldehyde **7** (5.00 g, 29.7 mmol) in dry CH_2Cl_2 (50 mL) was treated with trimethylsilyl cyanide (8.0 mL, 60 mmol) and a catalytic amount (ca. 10 mg) of the potassium cyanide–18-crown-6 ether complex. After 30 min at room temperature, solvent and excess trimethylsilyl cyanide were removed in vacuo to provide the crude silyl cyanohydrin.

A slurry of $LiAlH_4$ (2.8 g, 74 mmol) in dry ether (150 mL) was cooled to 0 °C, and a solution of the crude silyl cyanohydrin in dry ether (50 mL) was added dropwise. The resulting brown mixture was allowed to warm to room temperature and maintained there for 16 h. The reaction was then quenched with H_2O (3.4 mL), 15% NaOH (3.4 mL), and H_2O (10 mL), and the resulting mixture was filtered. The solid residue was washed well with $CHCl_3$, the combined organic phases were concentrated, and the residue was purified on silica gel (5:1:0.1 $CHCl_3$–MeOH–NH_4OH) to give 4.26 g (72%) of amino alcohol **9** as a light yellow solid: mp 91.5–92.5 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (app br s, 1 H, CH=), 3.9–4.0 (m, 1 H, C*H*OH), 3.94 (app s, 4 H, OCH_2CH_2O), 2.80 (dd, J = 4.1, 12.7 Hz, 1 H, C*H*HN), 2.68 (dd, J = 7.5, 12.7 Hz, 1 H, CH*H*N), 2.55 (br s, 3 H, OH, NH_2), 2.12–2.26 (m, 4 H, CH_2C=), 1.74 (app t, J = 6.6 Hz, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 120.4, 108.4, 75.8, 64.7, 46.1, 35.8, 31.2, 24.0; IR (CCl_4) 3684, 3600, 1113, 1061, 868 cm^{-1}; MS (CI) m/z 200 (MH) 182, 169, 153, 141, 123, 109, 99, 86, 80; HRMS (EI) m/z 199.1211 (199.1207 calcd for $C_{10}H_{17}NO_3$).

6-Iodo-1,3-benzodioxole-5-methanol (11). An adaptation of a published procedure was employed.[25] To a solution of piperonyl alcohol **10** (8.25 g, 54.2 mmol), CF_3CO_2Ag (15.6 g, 70.5 mmol), and dry $CHCl_3$

(33) McDonald, E.; Suksamrarn, A. *Tetrahedron Lett.* **1975**, 4425. Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(34) Swern, D.; Mancuso, A.; Huang, S. *J. Org. Chem.* **1978**, *43*, 2480.
(35) (a) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957. (b) Huang, S. L.; Omura, K.; Swern, D. *Ibid.* **1976**, *41*, 3329.
(36) A melting point of 237–238 °C was reported for (±)-tazettine by Tsuda and co-workers.[13b]
(37) Kobayashi, S.; Kihara, M. *Heterocycles* **1979**, *12*, 1547.
(38) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(39) In accord with the results of earlier investigators,[14,16] we were unable to reduce **26** from the α face with acceptable selectivity to afford a potential direct precursor or pretazettine. Attempted reduction of (±)-tazettine with $Me_4NBH(OAc)_3$[40] at temperatures up to 115 °C returned only starting **1**. These experiments were conducted on the outside chance that acyloxy borohydride **i** would be generated and then suffer intramolecular reduction stereoselectively from the α face.



i

(40) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(41) General experimental details were recently described.[42] Commercial KH in mineral oil was washed with dry THF in an oxygen-free drybox prior to use.
(42) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

(130 mL) at −5 °C was added I_2 (17.9 g, 70.5 mmol) in one portion. The resulting yellow mixture was maintained at −5 °C for 5 min, whereupon it was filtered. The filtrate was washed with 20% $Na_2S_2O_3$ (40 mL), dried ($MgSO_4$), and concentrated to give a pale yellow solid. Recrystallization from $CHCl_3$ afforded 9.0 g (60%) of **11** as white needles: mp 110–11 °C (lit.[26] mp 106–107 °C, from benzene).

5-(Chloromethyl)-6-iodo-1,3-benzodioxole (8). To a solution of alcohol **11** (8.15 g, 29.3 mmol), triethylamine (4.4 mL, 31 mmol), and dry benzene (100 mL) at 5 °C was added dropwise a solution of $SOCl_2$ (2.9 mL, 44 mmol) in benzene (40 mL). The resulting yellow solution was allowed to warm to room temperature. After 2 h the reaction was cooled to 5 °C, washed successively with H_2O (3 × 20 mL), 10% 2 N HCl (20 mL), saturated aqueous $NaHCO_3$ (30 mL), and H_2O (20 mL) and then dried ($MgSO_4$). Concentration and recrystallization of the residue from ether–hexane afforded 8.8 g (100%) of the known chloride **8**[9] as a white solid: mp 65–66 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 1 H, ArH), 6.98 (s, 1 H, ArH), 6.01 (s, 2 H, OCH_2O), 4.63 (s, 2 H, CH_2).

5-[[(Aminomethyl)[4,4-(ethylenedioxy)cyclohex-1-enyl]methoxy]methyl]-6-iodo-1,3-benzodioxole (12). To a suspension of KH (230 mg, 5.7 mmol)[41] in dry THF (35 mL) at 0 °C under an argon atmosphere was added dropwise a solution of amino alcohol **9** (590 mg, 2.96 mmol) in dry THF (35 mL). The resulting brown mixture was allowed to warm to room temperature, maintained there for 1 h, and then cooled to 0 °C. A solution of **8** (880 mg, 2.96 mmol) in dry THF (20 mL) was added via a syringe pump (over 3 h), and the resulting mixture was allowed to warm to room temperature. After 6 h, the reaction was quenched with aqueous saturated $NaHCO_3$ (30 mL). The organic phase was separated, and the aqueous phase was washed with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified on silica gel (20:1:0.1 $CHCl_3$–MeOH–NH_4OH) to provide 1.18 g (87%) of ether **12** as a light red thick oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 1 H, ArH), 6.92 (s, 1 H, ArH), 5.94 (s, 2 H, OCH_2O), 5.63 (br s, 1 H, CH=), 4.30 (AB q, $\Delta\nu$ = 45.2 Hz, J = 11.9 Hz, 2 H, $ArCH_2$), 3.95 (s, 4 H, OCH_2CH_2O), 3.69 (dd, J = 4.8, 7.6 Hz, 1 H, OCH), 2.85 (dd, J = 7.8, 13.1 Hz, 1 H, C*H*HN), 2.71 (dd, J = 4.7, 13.1 Hz, 1 H, CH*H*N), 2.0–2.4 (m, 4 H, CH_2C=), 1.7–1.8 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 147.7, 134.9, 134.1, 123.6, 118.4, 109.6, 107.9, 101.5, 86.3, 85.2, 73.9, 64.3 (2 C), 45.1, 35.6, 30.8, 22.6; IR (CCl_4) 2879, 1504, 1490, 1444, 1251, 1044 cm^{-1}; MS (CI) m/z 460 (MH) 334, 261, 198, 182, 169, 151, 135; HRMS (CI) m/z 460.0621 (460.0603 calcd for $C_{18}H_{22}INO_5$).

Carbamate 13. To a mixture of ether **12** (1.18 g, 2.56 mmol), dry CH_2Cl_2 (80 mL), and K_2CO_3 (1.8 g) was added methyl chloroformate (1.0 mL, 13 mmol). The resulting mixture was maintained at room temperature for 8 h, and then ether (50 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added. The aqueous layer was separated and washed with Et_2O (2 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated. The resulting residue was purified on silica gel (1:2 EtOAc–hexane) to give 1.2 g (91%) of carbamate **13** as a thick yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$)[43] δ 7.23 (s, 1 H, ArH), 6.89 (s, 1 H, ArH), 5.96 (s, 2 H, OCH_2O), 5.68 (app br s, 1 H, CH=), 5.13 (br s, 1 H, NHCO), 4.30 (AB q, $\Delta\nu$ = 47.2 Hz, J = 11.8 Hz, 2 H, $ArCH_2$), 3.97 (app s, 4 H, OCH_2CH_2O), 3.83 (dd, J = 3.5, 8.4 Hz, 1 H, OCH), 3.64 (s, 3 H, OCH_3), 3.15–3.48 (m, 2 H, CH_2N), 2.15–2.4 (m, 4 H, CH_2C=), 1.6–1.8 (m, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 148.0, 147.5, 133.9, 133.5, 123.8, 118.1, 109.3, 107.5, 101.3, 86.1, 81.4, 73.6, 64.0 (2 C), 51.6, 43.7, 35.3, 30.5, 22.5; IR ($CHCl_3$) 3456, 1717, 1518, 1504, 1478, 1228, 1041 cm^{-1}; MS (CI) m/z 518 (MH) 256, 240; HRMS (CI) m/z 518.0675 (518.0650 calcd for $C_{20}H_{24}O_7IN$).

[7α,8α]-Dispiro[1,3-dioxolane-2,1′-cyclohex-2′-ene-4′,8″-7″[(methoxycarbonyl)aminomethyl][5*H*-1,3]dioxo[4,5-*g*][2]benzopyran] (14). A mixture of carbamate **8** (530 mg, 1.02 mmol), $Pd(OAc)_2$ (23 mg, 0.10 mmol), Ph_3P (110 mg, 0.41 mmol), Ag_2CO_3 (565 mg, 2.05 mmol), and dry THF (30 mL) was heated at reflux for 15 h and then allowed to cool to room temperature. Ether (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added, the organic phase was separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The residue was filtered through silica gel (1:1 hexane–EtOAc) and concentrated to afford 360 mg (91%) of **14** as a white solid. Recrystallization from ether gave 248 mg (63%) of **12** as colorless fine needles: mp 138–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (s, 1 H, ArH), 6.40 (s, 1 H, ArH), 5.90 (s, 2 H, OCH_2O), 5.76 (AB q, $\Delta\nu$ = 81.8 Hz, J = 10.1 Hz, 2 H, CH=CH), 5.06 (br s, 1 H, NHCO), 4.67 (br s, 2 H, $ArCH_2$), 4.03–3.94 (m, 4 H, OCH_2CH_2O), 3.82 (dd, J = 2.8, 10.8 Hz, 1 H, OCH), 3.67 (s, 3 H, OCH_3), 3.52–3.12 (m, 2 H, CH_2N), 1.85–2.0 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9, 146.7, 146.2, 134.0, 132.7, 130.1, 125.7, 107.7, 104.5, 103.5, 100.8, 77.5, 64.6, 64.5 (2 C), 52.0, 40.3, 40.0, 32.7, 30.7; IR (CCl_4) 3450, 2956, 2881, 1731, 1506, 1481, 1244, 944, 913 cm^{-1}; MS (CI) m/z 390 (MH) 117, 99; HRMS (CI) m/z 390.1555 (390.1551 calcd for $C_{20}H_{24}NO_7$). Anal. Calcd for $C_{20}H_{24}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.60; H, 5.95; N, 3.57.

(±)-(6aβ)-5-Demethyl-6a-deoxydihydro-5-(methoxycarbonyl)tazettinone (15). A solution of spiroketal **14** (240 mg, 0.616 mmol), THF (8 mL), and 2 N HCl (1.5 mL was heated at reflux for 2 h. After being cooled to room temperature, the reaction was quenched by adding solid $NaHCO_3$. The resulting layers were separated and the aqueous layer was extracted with ether (2 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated and the residue was purified on silica gel (1:1 hexane–EtOAc) to give 200 mg (94%) of **15** as a white solid: mp 144–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$)[43] δ 6.81 (br s, 1 H, ArH), 6.48 (s, 1 H, ArH), 5.94 (s, 2 H, OCH_2O), 4.65 (s, 2 H, $ArCH_2$), 4.27 (br s, 1 H, CHN), 4.11 (br s, 1 H), 3.8–4.0 (m, 1 H), 3.65 (s, 3 H, OCH_3), 3.60–3.65 (m, 1 H), 2.9–3.2 (m, 1 H), 2.80 (dd, J = 4.0, 16.8 Hz, CH*H*CO), 2.30–2.60 (m, 3 H), 2.02 (m, 1 H); IR (film) 1720, 1709, 1485, 1452, 1239, 1044, 943 cm^{-1}; MS (CI) m/z 346 (MH) 229, 118; HRMS (EI) m/z 345.1194 (345.1212 calcd for $C_{18}H_{19}NO_6$). Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.54; N, 4.06. Found: C, 62.42; H, 5.57; N, 4.04.

(±)-(6aβ)-5-Demethyl-6a-deoxy-5-(methoxycarbonyl)tazettinone (18). To a solution of ketone **15** (100 mg, 0.290 mmol), dry CH_2Cl_2 (10 mL), and Et_3N (0.80 mL, 5.8 mmol) at 0 °C was added trimethylsilyl triflate (0.56 mL, 2.9 mmol) dropwise via syringe. The solution was maintained at 0 °C for 30 min, then cold pentane (15 mL) was added, and the solution was washed with cold saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with cold pentane (2 × 10 mL). The combined organic layers were dried (K_2CO_3) and concentrated at reduced pressure to give crude silyl enol ether **19** as a pale yellow oil.

Following the general procedure of Saeguza,[31] a mixture of this crude enol ether, $Pd(OAc)_2$ (84 mg, 0.37 mmol), and CH_3CN (10 mL) was stirred at room temperature for 10 h. The mixture was then concentrated and the brown residue was purified on silica gel (2:1 hexane–EtOAc) to afford 67 mg (67%) of enone **18** as a thick oil: ^{1}H NMR (500 MHz, toluene-d_8, 90 °C) δ 6.67 (s, 1 H, ArH), 6.30 (s, 1 H, ArH), 6.00 (AB q, $\Delta\nu$ = 86.2 Hz, J = 10.1 Hz, 2 H, CH=CH), 5.58 (s, 2 H, OCH_2O), 4.51 (AB q, $\Delta\nu$ = 15.6 Hz, J = 14.8 Hz, 2 H, $ArCH_2$), 4.32 (br s, 1 H, CHN), 3.90–4.02 (m, 1 H), 3.60–3.70 (m, 1 H, OCH), 3.58 (s, 3 H, OCH_3), 3.5–3.55 (m, 1 H), 3.38 (app dd, J = 3.5, 12.2 Hz, 1 H, CH*H*N), 2.59 (dd, J = 3.7, 17.3 Hz, 1 H, CH*H*CO); IR (film) 1696, 1504, 1486, 1449, 1384, 1352, 1249, 1223, 1126 cm^{-1}; MS (CI) m/z 434 (MH) 173, 115; HRMS (EI) m/z 343.1050 (343.1056 calcd for $C_{18}H_{17}NO_6$).

(±)-(3α,6aβ)-3-Demethoxy-5-demethyl-6a-deoxy-3-hydroxy-5-(methoxycarbonyl)tazettine (19). To a solution of enone **18** (40.0 mg, 0.117 mmol), $CeCl_3{\cdot}7H_2O$ (43.4 mg, 0.117 mmol) and dry CH_3OH (3 mL) at −78 °C was added $NaBH_4$ (11 mg, 0.29 mmol).[32] The reaction was maintained at −78 °C for 10 min, whereupon H_2O (1 mL) was added and the resulting mixture was allowed to warm to room temperature. The resulting mixture was filtered and the filtrate concentrated to give 40 mg (95%) of allylic alcohol **19** as a white solid: mp 218–219 °C; ^{1}H NMR (500 MHz, toluene-d_8, 100 °C) δ 7.01 (s, 1 H, ArH), 6.30 (s, 1 H, ArH), 6.02 (br d, J = 10.3 Hz, 1 H, =CH), 5.58 (br s, 2 H, OCH_2O), 5.16 (ddd, J = 1.3, 2.1, 10.2 Hz, 1 H, CH=), 4.56 (AB q, $\Delta\nu$ = 18.0 Hz, J = 14.7 Hz, 2 H, $ArCH_2$), 4.26–4.31 (m, 1 H), 4.21 (br s, 1 H), 3.95–4.1 (m, 1 H), 3.69 (s, 3 H, OCH_3), 3.60 (d, J = 3.4 Hz, 1 H, HCO), 3.46 (dd, J = 3.4, 11.9 Hz, 1 H, CH*H*N), 3.10 (br s, 1 H), 1.74 (ddd, J = 2.5, 10.4, 13.1 Hz, 1 H); IR (film) 3375, 2925, 1696, 1677, 1485, 1387, 1038 cm^{-1}; MS (CI) m/z 346 (MH) 328, 211, 118; HRMS (EI) m/z 345.1210 (345.1212 calcd for $C_{18}H_{19}NO_6$).

Spectral data for epimer **20** (isolated from a reduction conducted at 23 °C): ^{1}H NMR (500 MHz, toluene-d_8, 100 °C) δ 6.70 (s, 1 H, ArH), 6.31 (s, 1 H, ArH), 6.16 (dd, J = 4.9, 10.1 Hz, 1 H, =CH), 5.59 (s, 2 H, OCH_2O), 5.29 (d, J = 10.0 Hz, 1 H, CH=), 4.56 (AB q, $\Delta\nu$ = 24.4 Hz, J = 14.8 Hz, 2 H, $ArCH_2$), 4.20 (app br t, 1 H), 4.25 (app br m, 1 H), 3.98 (d, J = 11.5 Hz, 1 H), 3.66 (s, 3 H, OCH_3), 3.64 (d, J = 3.7 Hz, 1 H, HCO), 3.60 (dd, J = 3.6, 11.8 Hz, 1 H, CH*H*N), 3.04 (br d, J = 15.4 Hz, 1 H), 1.94 (ddd, J = 3.1, 5.0, 15.4 Hz, 1 H).

(±)-(6aβ)-5-Demethyl-6a-deoxy-5-(methoxycarbonyl)tazettine (21). To a suspension of KH (40 mg, 1 mmol) in dry THF (1.4 mL) was added a solution of alcohol **19** (40 mg, 0.12 mmol) and THF (1.5 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature. After 1 h, the pale yellow mixture was cooled to 0 °C and CH_3I (0.32 mL, 5.1 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature where it was maintained for 5 h. Excess KH was

(43) NMR signals for this compound are broadened by the presence of amide conformational isomers.

then destroyed by adding CH_3OH (0.5 mL), the heterogenous mixture was filtered, and the filtrate was concentrated. The residue was purified by radial chromatography (1:2 EtOAc–hexane) to afford 31 mg (75%) of **21** as a white solid: mp 168.5–170 °C; ^1H NMR (500 MHz, toluene-d_8, 100 °C) δ 7.05 (s, 1 H, ArH), 6.31 (s, 1 H, ArH), 6.20 (dt, J = 10.3, 1.6 Hz, 1 H, CH), 5.58 (app d, J = 1.6 Hz, 2 H, OCH_2O), 5.24 (ddd, J = 1.6, 2.1, 10.3 Hz, 1 H, =CH), 4.58 (AB q, $\Delta\nu$ = 11.0 Hz, J = 14.8 Hz, 2 H, $ArCH_2$), 4.27 (br s, 1 H, CHN), 4.0–4.1 (m, 2 H, C*H*HN and C*H*OCH_3), 3.67 (s, 3 H, $COOCH_3$), 3.64 (d, J = 3.4 Hz, 1 H, HCO), 3.51 (dd, J = 3.5, 11.9 Hz, 1 H, CH*H*N), 3.39 (s, 3 H, OCH_3), 3.30 (m, 1 H), 1.90 (ddd, J = 2.5, 10.3, 13.1 Hz, 1 H); IR (film) 2936, 1702, 1485, 1385, 1247, 1104, 1034 cm^{-1}; MS (CI) m/z 360 (MH), 211, 118; HRMS (EI) m/z 359.1368 (359.1369 calcd for $C_{19}H_{21}NO_6$). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.89. Found: C, 63.35; H, 5.91; N, 3.95.

(±)-(6aβ)-5-Demethyl-6a-deoxy-5-(methoxycarbonyl)-8-oxotazettine (22). To a suspension of CrO_3 (500 mg, 5.00 mmol) and 3,5-dimethylpyrazole (481 mg, 5.00 mmol)[33] in CH_2Cl_2 (12 mL) at 50 °C was added dropwise a solution of **21** (80 mg, 0.22 mmol) and CH_2Cl_2 (5 mL). The resulting red mixture was maintained between −40 and −45 °C for 6 h, whereupon 2 N NaOH (10 mL) was added, the resulting mixture was allowed to warm to room temperature, and the layers were separated. The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined organic layers were washed with 2 N HCl (15 mL). The pale green organic phase was dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (4:1 Et_2O–hexane) to give 52 mg (63%) of **22** and 4.3 mg (5.4%) of **23**, both as white solids. For **22**: mp 214.5–215.5 °C; ^1H NMR (500 MHz, toluene-d_8, 100 °C) δ 7.81 (s, 1 H, ArH), 6.83 (s, 1 H, ArH), 6.19 (br d, J = 10.2 Hz, 1 H, =CH), 5.50 (AB q, $\Delta\nu$ = 11.6 Hz, J = 1.2 Hz, 2 H, OCH_2O), 5.05 (br d, J = 10.2 Hz, 1 H, CH=), 4.22 (d, J = 3.3 Hz, 1 H), 4.12–4.18 (m, 1 H), 3.98–4.08 (m, 1 H), 3.88–3.94 (m, 1 H), 3.43 (dd, J = 3.3, 12.3 Hz, 1 H, CH*H*N), 3.15 (m, 1 H), 1.64 (m, 1 H); IR (film) 1711, 1702, 1380, 1276, 1029; MS (CI) m/z 374 (MH); HRMS (CI) m/z 374.1221 (374.1239 calcd for $C_{19}H_{19}NO_7$). Anal. Calcd for $C_{19}H_{19}NO_7$: C, 61.12; H, 5.13; N, 3.75. Found: C, 61.11; H, 5.17; N, 3.78.

(±)-Tazettine Diol 24. To a suspension of $LiAlH_4$ (60 mg, 1.6 mmol) in dry Et_2O (2.5 mL) at room temperature under an argon atmosphere was added a solution of lactone **22** (40 mg, 0.11 mmol) and THF (2.5 mL). The resulting mixture was kept at room temperature for 5 h and excess hydride was quenched by Rocelle's salt solution (0.5 mL). The resulting mixture was stirred at room temperature for 3 h, the layers were separated, and the milky aqueous layer was extracted several times with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified by radial chromatography (10:1 $CHCl_3$–CH_3OH) to afford 35 mg (98%) of tazettine diol as a thick oil. The spectral properties of this material were in accord with the characterization data reported by Danishefsky.[14]

(3α,3aα,6α,7aα)-3a,6,7,7a-Tetrahydro-3a-[2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4,5-(methylenedioxy)phenyl]-6-methoxy-1-methyl-3-indolinone (26). Following the general procedure of Swern,[34] to a solution of oxalyl chloride (5 μL, 0.06 mmol) in dry CH_2Cl_2 (0.3 mL) at −78 °C was added Me_2SO (5 μL, 0.07 mmol, distilled from CaH_2 and stored over 4A molecular sieves) dropwise over 30 s. The resulting mixture was maintained at −78 °C for 10 min and a solution of silyl alcohol **25** (9.0 mg, 0.02 mmol, prepared from **24** as described[14]) and CH_2Cl_2 (0.2 mL) was added dropwise over 1 min. The reaction was kept at −78 °C for an additional 40 min and then Et_3N (20 μL, 0.15 mmol) was added dropwise over 1 min. The resulting slurry was kept at −78 °C for 10 min and then allowed to gradually warm (20 min) to room temperature. The reaction was quenched with 5% Na_2CO_3 (0.3 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (1:6 EtOAc–hexane) to give 8.0 mg (90%) of the known[14] ketone **25** as a white solid: mp 131–132.5 °C (lit.[14] mp 131–133 °C).

Preparation of (±)-Tazettine (1) by Selective Oxidation of Tazettine Diol. To a solution of Me_2SO (15 μL, 0.22 mmol, distilled from CaH_2 and stored over 4A molecular sieves) in dry CH_2Cl_2 (0.4 mL) at −78 °C was added trifluoroacetic anhydride (41 μL, 0.29 mmol).[35] The resulting solution was maintained at −78 °C for 15 min and a solution of diol **24** (12 mg, 0.036 mmol) and CH_2Cl_2 (0.5 mL) was added dropwise. The reaction was maintained at −78 °C for 5 min and then allowed to warm to room temperature. After 2 h, Et_3N (73 μL, 0.54 mmol) was added dropwise. The resulting slurry was kept at room temperature for an additional 2 h, the reaction was then quenched with H_2O (0.5 mL), and the aqueous layer was extracted with Et_2O (2 × 2 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified on silica gel (1:2 EtOAc–hexane) to give 7.3 mg (61%) of (±)-tazettine, mp 173–175 °C (benzene). Synthetic (±)-tazettine was in all respects (500-MHz ^1H NMR, MS, TLC mobility in three solvent systems) identical with an authentic sample of (±)-tazettine provided by Professor S. Martin.

Preparation of (±)-6a-Epipretazettine (3) by Selective Oxidation of Tazettine Diol. An adaptation of a general procedure was employed.[38] A solution of diol **24** (7.0 mg, 0.021 mmol) and CH_2Cl_2 (0.1 mL) was added at room temperature to a CH_2Cl_2 (0.2 mL) solution of the Dess–Martin periodinane (27 mg, 0.063 mmol). After 2 h, the heterogeneous mixture was diluted with Et_2O (2 mL) and the resulting solution poured into a solution of saturated aqueous $NaHCO_3$ containing excess $Na_2S_2O_3$. The resulting mixture was stirred to dissolve the residual solid and the layers were then separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (0.5 mL) and H_2O (0.5 mL) and finally dried ($MgSO_4$). Concentration and purification of the residue on silica gel (EtOAc) afforded 5.0 mg (73%) of **3**. The 500-MHz ^1H NMR spectrum of this sample was in complete agreement with the 300-MHz ^1H NMR reported[14b] for 6a-epipretazettine.

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Registry No. (±)-**1**, 28405-99-4; (±)-**3**, 86064-46-2; **7**, 72445-22-8; **8**, 65673-83-8; (±)-**9**, 128135-13-7; **10**, 495-76-1; **11**, 69048-76-6; (±)-**12**, 128135-14-8; (±)-**13**, 128135-15-9; (±)-**14**, 128135-16-0; (±)-**15**, 128135-17-1; (±)-**18**, 128135-18-2; (±)-**19**, 128164-07-8; (±)-**20**, 128135-19-3; (±)-**21**, 128164-08-9; (±)-**22**, 128190-33-0; (±)-**23**, 128135-20-6; (±)-**24**, 74165-11-0; (±)-**25**, 74120-55-1; (±)-**26**, 128135-21-7.

Supplementary Material Available: Details of the single-crystal X-ray structure of **15** including an ORTEP plot and tables of atomic coordinates, interatomic distances, interatomic angles, and anisotropic displacement coefficients (8 pages). Ordering information is given on any current masthead page.