Total Synthesis of *Amaryllidaceae* Alkaloids of the 5,11-Methanomorphanthridine Type. Efficient Total Syntheses of (-)-Pancracine and (±)-Pancracine[1]

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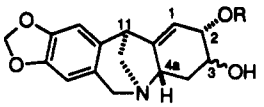
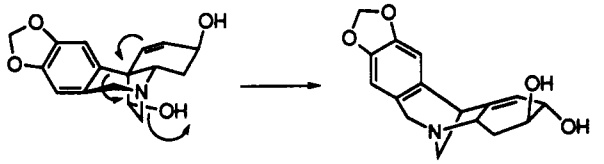
Stereocontrolled total syntheses of the 5,11-methanomorphanthridine alkaloid pancracine in racemic (*rac-1*) and natural levorotatory form (1) are described. The key step is a Lewis acid-mediated aza-Cope rearrangement–Mannich cyclization reaction (9 → 6, Scheme I).

The first members of the subclass of *Amaryllidaceae* alkaloids having the 5,11-methanomorphanthridine skeleton were isolated by Wildman in 1955 from various plant species (*Pancratium amritimum, Narcissus poeticus, and Brunsvigia cooperi*).[2,3] Initially characterized on the basis of spectroscopic data and chemical interconversions,[3] the structure and absolute configuration of (-)-brunsvigine



1 R = H, 3β-OH (-)-pancracine
2 R = H, 3α-OH (-)-brunsvigine
3 R = Me, 3β-OH (-)-montanine

(2) was later secured by single crystal X-ray analysis of the bis(*p*-bromobenzoate) derivative.[4] Biosynthetic labeling studies and chemical transformations support the notion that the rare 5,11-methanomorphanthridine skeleton arises from rearrangement of *Amaryllidaceae* alkaloid precursors having the common 9,10-ethanophenathridine skeleton.[2,5] This relationship is illustrated in eq 1 for the conversion of 11-hydroxyvittatine (normethylhaemanthidine, 4) to (-)-pancracine (1). Weak hypotensive and convulsive activities are reported from members of the 5,11-methanomorphanthridine series having ether functionality at C(2).[6]



11-hydroxyvittatine (4) (-)-pancracine (1) (1

Although massive synthetic effort has been directed toward almost all other types of *Amaryllidaceae* alkaloids, the methanomorphanthridine group has received little attention.[2,7] Only in 1991 were the first total syntheses of members of this alkaloid class reported from our laboratories[8a] and those of Hoshino.[8b-d] In this paper we provide details of our synthesis of (±)-pancracine[8a] and describe the extension of this approach to achieve the first asymmetric total synthesis in this area, that of (-)-pancracine. The synthetic entry to the methanomorphanthridine subclass of *Amaryllidaceae* alkaloids detailed herein is notably concise and fully stereocontrolled.

Results and Discussion

Synthesis Plan. Our basic strategy is outlined in Scheme I. The 1,2-diol functionality of 1 was envisaged to derive from the carbonyl group of 5. This methanomorphanthridine ketone in turn would arise from Pictet-Spengler cyclization of the all *cis*-hydroindolone 6. The heart of this plan is the formation of 6, and the establishment of the critical C(4a)–C(11) stereorelationship, from aza-Cope–Mannich rearrangement of the aminocyclopentanol 9.[9-11] Considerable precedent suggests that the aza-Cope–Mannich reorganization would proceed in a chair topography by way of the intermediate cations 8 and 7.[10,11]

Assembly of the Rearrangement Substrate. Our initial target was the (*E*)-1-alkenyl-2-aminocyclopentanol

(1) Part 25 in the series: Synthesis Applications of Cationic Aza-Cope Rearrangements. For part 24, see: Angle, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W.; Jr., Overman, L. E. *J. Am. Chem. Soc.* **1993**, *116*, 3966-3976.

(2) (a) Wildman, W. C.; Kaufman, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 1248. (b) Inubushi, Y.; Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Org. Chem.* **1960**, *25*, 2153. (c) Wildman, W. C.; Brown, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 6439.

(3) For comprehensive reviews of *Amaryllidaceae* alkaloids, see: Martin, S. F. *Alkaloids* Academic Press: New York, 1987; Vol. 30, p 251 and earlier reviews referenced therein.

(4) Laing, M.; Clark, R. C. *Tetrahedron Lett.* **1974**, 583.

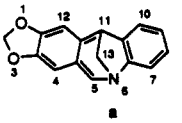
(5) (a) Battersby, A. R.; Fales, H. M.; Wildman, W. C. *J. Am. Chem. Soc.* **1961**, *83*, 4098. (b) Fuganti, C.; Ghiringhelli, D.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1973**, 430. (c) Wildman, W. C.; Olesen, B. *J. Chem. Soc., Chem. Commun.* **1976**, 551. (d) Feinstein, A. I.; Wildman, W. C. *J. Org. Chem.* **1976**, *41*, 2447.

(6) Southon, I. W.; Buckingham, J. *Dictionary of the Alkaloids*; Chapman Hall: New York, 1989; p 229, 735, and 817.

(7) For synthetic approaches, see: (a) Sánchez, I. H.; Larraza, M. I.; Rojas, I.; Breña, F. K.; Flores, H. J.; Jankowski, K. *Heterocycles* **1985**, *23*, 3033. (b) Hoshino, O.; Ishizaki, M.; Saito, K.; Yumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 420.

(8) (a) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005. (b) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079. (c) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *J. Org. Chem.* **1992**, *57*, 7285. (d) Hoshino, O.; Iitaka, Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101.

(9) The common biosynthetic numbering system of Wildman will be used in the Results and Discussion sections of this report. The nomenclature and numbering system of *Chemical Abstracts* is employed in the Experimental Section. The *Chemical Abstracts* numbering for the 6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepine ring system is shown in **a**.



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(10) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629.

(11) For a brief review, see: Overman, L. E.; Ricca, D. J. *Comprehensive Organic Synthesis*; Heathcock, C. H.; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford; Vol. 2, pp 1007-1046.

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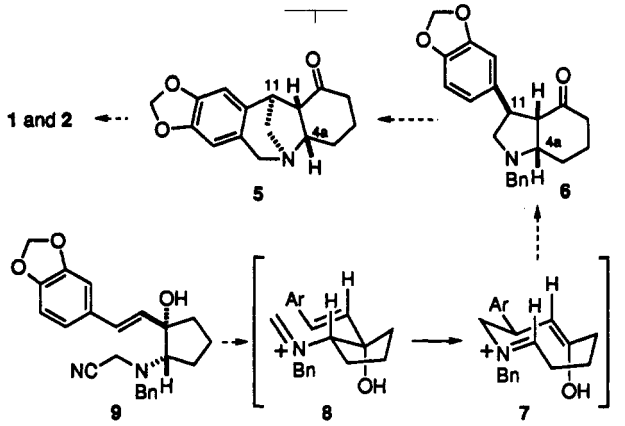
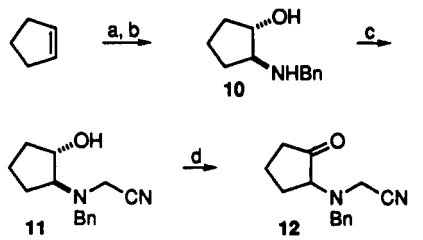
Scheme I



Scheme II[a]

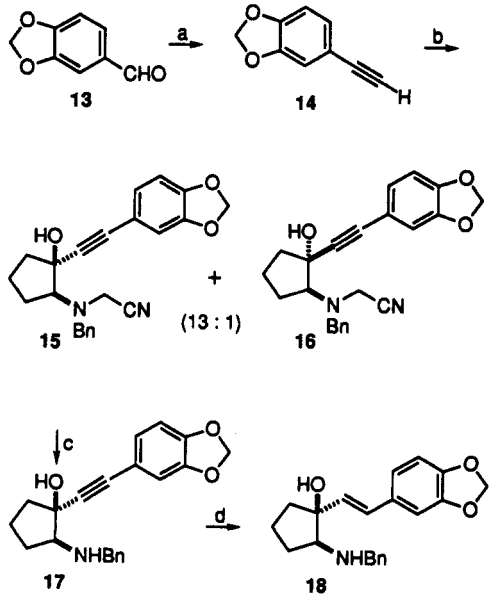


[a] (a) NBS, H_2O (86%); (b) $BnNH_2$, 100 °C (75%); (c) HCHO, KCN, HCl (89%); (d) Swern oxidation[12] (88%).

9 in which nitrogen is protected with benzyl and cyanomethyl groups. This latter group was chosen since it could serve the dual purpose of triggering the aza-Cope–Mannich reorganization and protecting nitrogen during the assembly of 9 from an α-amino ketone precursor.[10,11] Although we had earlier described a three-step synthesis of aminocyclopentanone 12 from diethyl glutarate, this sequence proved difficult to scale up.[10] A slightly longer, though more convenient, sequence for preparing 12 on preparative scales is outlined in Scheme II.

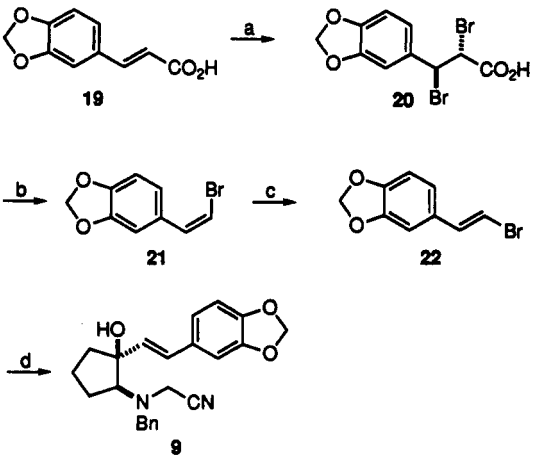
Two methods for attaching the (*E*)-2-[(3,4-methylenedioxy)phenyl]ethenyl moiety to aminocyclopentanone 12 have been developed. The most efficient sequence is summarized in Scheme III. The known arylacetylene 14[13] is best prepared on a large scale from piperonal (13) by the Corey–Fuchs procedure (Scheme III).[14] The alkynylcerium reagent formed from the lithium salt of 14 and $CeCl_3$[15] added to ketone 12 with excellent facial selectivity, without competing enolization of the ketone, to give amino alcohols 15 and 16 in a 13:1 ratio. The less polar major isomer 15 showed characteristic intramolecular hydrogen bonded hydroxyl absorption at 3456 cm^{-1} in the infrared spectrum; this absorption was concentration independent (0.9 to 0.009 M). In contrast, the minor amino alcohol diastereomer 16 showed two signals in the infrared spectrum at high concentration; the absorption at 3588 cm^{-1} disappeared upon dilution (0.8 to 0.008 M). Alcohol 15 could be isolated in 92% yield after purification on silica gel. As discussed later in the context of our asymmetric synthesis of (−)-pancracine, we were not able to reduce the triple bond of 15 while retaining the

Scheme III[a]



[a] (a) Zn, CBr_4, PPh_3, *n*-BuLi (81%); (b) *n*-BuLi; $CeCl_3$; 12 (99%); (c) $AgNO_3$, H_2O, EtOH, sonication (97%); (d) $LiAlH_4$ (94%).

Scheme IV[a]



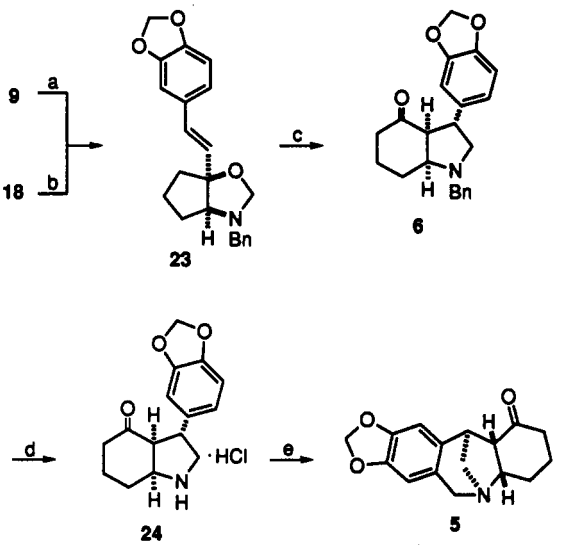
[a] (a) Br_2, PhH (76%); (b) NaN_3, DMF (86%); (c) NBS, hν (73%); (d) *t*-BuLi; ketone 12 (42%).

cyanomethyl group. As a result, the cyanomethyl group of 15 was next removed by treatment with $AgNO_3$ in EtOH, a conversion that proceeded more rapidly when the reaction flask was immersed in an ultrasonic cleaner. Conventional $LiAlH_4$ reduction[16] of 17 then cleanly provided the desired crystalline *E*-allylic alcohol 18 in 84% overall yield from ketone 12.

A more direct, although less efficient, synthesis of the cyanomethyl-protected *E*-allylic alcohol 9 is summarized in Scheme IV. The *E*-styryl bromide 22 was readily accessed from the acid 19 using chemistry described in the *trans*-cinnamic acid series.[17] However, addition of the vinyllithium reagent[18] derived from bromide 22 to cyclopentanone 12 was plagued by competitive enolization of the ketone. Under optimum conditions the isolated yield of the alcohol 9 was 42%. Use of the vinylmagnesium reagent derived from the vinyllithium intermediate and

(12) Swern, D.; Mancuso, A. J.; Huang, S.-L., *J. Org. Chem.* **1978**, *43*, 2480.
(13) Feyerstein, W.; Heimann, M. *Chem. Ber.* **1901**, *34*, 1468. Overman, L. E.; Wild, H. *Tetrahedron Lett.* **1989**, *30*, 647.
(14) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(15) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.
(16) Bates, E. B.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1954**, 1854.
(17) Tanigawa, Y.; Murahashi, S.-I.; Naota, T. *Org. Synth.* **1984**, *62*, 39.
(18) Seebach, D.; Neumann, H. *Tetrahedron Lett.* **1976**, *18*, 4839.

Scheme V[a]



[a] (a) $AgNO_3$, EtOH (87%); (b) aqueous HCHO, CSA, Na_2SO_4 (81%); (c) BF_3·OEt_2, CH_2Cl_2, −20 °C (97%); (d) HCl, Pd/C, H_2, MeOH (97%); (e) aqueous HCHO, Et_3N; 6 N HCl (67%).

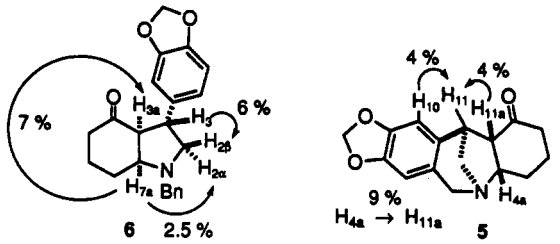


Figure 1. ^1H NOE data of **5** and **6**.

$MgBr_2$ offered no improvement. Addition of cerium chloride prior to reaction of the vinyllithium reagent with ketone **12** resulted in a complex reaction mixture.

Aza-Cope–Mannich Rearrangement and Formation of the 5,11-Methanomorphanthridine Skeleton. The amino alcohols **9** and **18** both afforded oxazolidine **23** in high yield under standard conditions (Scheme V).[10] Heating of **23** in various solvents in the presence of several protic acids did not effect the expected rearrangement to afford **6**. The use of Lewis acids, however, occasioned aza-Cope–Mannich reorganization to give hydroindolone **6** as the sole product (500-MHz ^1H NMR analysis of the crude product mixture). BF_3·OEt_2 was the best of the Lewis acids screened; $SnCl_4$ and Me_3SiOTf were also effective, but the conversion to **6** was slower. The chemical yield of the BF_3·OEt_2-promoted rearrangement of **23** could be improved to 97% by carrying out the reaction at −20 °C at a concentration of 0.05 M.

The structural assignment for the *cis*-octahydroindolone **6** was based on analysis of the ^1H NMR coupling constants: $J_{(3a,7a)}$ = 7.4 Hz and $J_{(3,3a)}$ = 4.5 Hz and ^1H NMR difference NOE experiments: enhancements between H_{3a} and H_{7a} and between H_3 and $H_{2\beta}$ and no enhancement between H_{7a} and H_3 (Figure 1).

The high yielding, completely stereoselective conversion of **23** to **6** provides another demonstration of the utility of aza-Cope–Mannich rearrangements in assembling *cis*-octahydroindolones. The low temperature of the BF_3·OEt_2-promoted rearrangement (−20 °C) further emphasizes the facility of this sequence of iminium ion interconversions. It is noteworthy that the aza-Cope–Mannich reorganization is not undermined by locating the powerful electron-releasing (methylenedioxy)phenyl group at the alkene terminus.

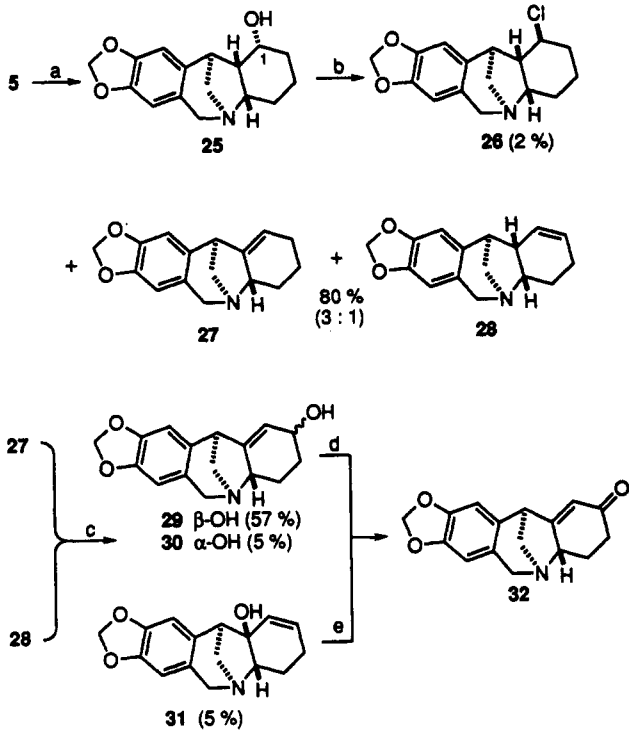
We next turned to the Pictet–Spengler reaction to develop the required fourth ring of the alkaloid targets. Catalytic hydrogenolysis of **6** under acidic condition afforded the crystalline hydrochloride salt **24** in high yield. The free amine, also available by transfer hydrogenolysis, was notably less stable even at −20 °C. When amine salt **24** was basified with Et_3N in the presence of formaldehyde, and the resulting *N*-hydroxymethylamine treated with 6 N HCl the Pictet–Spengler cyclization product **5** was formed in 67% yield.[19] The coupling constants observed in the ^1H NMR spectrum of **5** between H_{4a} and H_{11a} (9.0 Hz) and between H_{11} and H_{11a} (0 Hz) are fully consistent with structural formulation **5** (Figure 1). Molecular mechanics calculations indicate that this tetracyclic ketone would exist in a conformation having the cyclohexanone ring in a boat conformation.[20,21] The dihedral angle between H_{4a} and H_{11} is calculated to be 6°, while that between H_{11} and H_{11a} is calculated to be 88°. The sequence summarized in Scheme V provides the methanomorphanthridine ketone **5** in 51% overall yield from the secondary amine **18** and 54% overall yield from the tertiary cyanomethylamine **9**.

Total Synthesis of (±)-Pancracine. Elaboration of the cyclohexenediol functionality of the carboxylic ring began with reduction of the ketone moiety of **5** with lithium tri-*sec*-butylborohydride to give exclusively the α alcohol **25** (Scheme VI).[22] The epimeric equatorial alcohol was available by reduction of **5** with sodium bromohydride. The coupling constants of the methine hydrogen (H_1) of these two alcohol stereoisomers corroborated these assignments: H_1 of alcohol **25** appeared at δ 4.22 as an apparent triplet (J = 4.3 Hz), while H_1 of the β alcohol epimer of **25** appeared at δ 3.59 as a doublet of triplets (J = 11.0, 6.1 Hz). The axial α alcohol **25** underwent dehydration in the presence of $SOCl_2$ in $CHCl_3$ to afford a 3:1 mixture of tri- and disubstituted alkenes (**27** and **28**) in 80% yield, together with a trace amount of the C(1)-chloride **26** (2%).[23] Alternative dehydration with $POCl_3$–pyridine gave a similar product mixture, however the yield was lower. The two alkene regioisomers could be separated by a combination of chromatography and recrystallization. However, for preparative scale reactions the alkene mixture was directly submitted to allylic oxidation without resolution on silica gel.

Prior to processing the mixture of alkenes **27** and **28**, allylic oxidation was examined on purified samples of each regioisomer. Oxidation of the trisubstituted alkene **27** with SeO_2 in dioxane at 80 °C gave a mixture of the β and α allylic alcohols **29** and **30** in reasonable yield.[24] At short reaction times the β epimer **29** vastly predominated; however, significant amounts (up to 25%) of the α epimer could be isolated from longer reactions. Similar oxidation

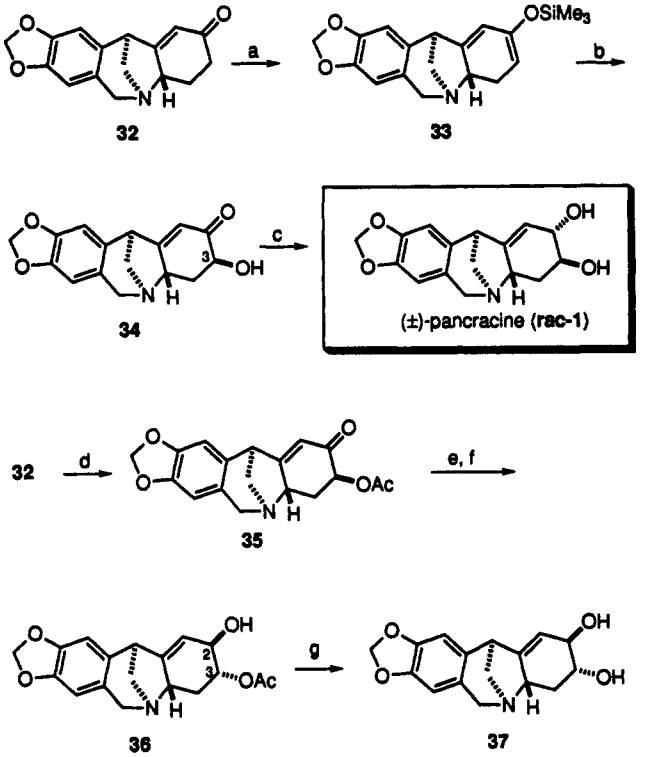
(19) Whitlock, H. W., Jr.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600.
(20) PCMODEL Molecular Modeling Software for the Macintosh II, obtained from Serena Software, Bloomington, IN, was used for these calculations.
(21) For a discussion of the MMX enhanced version of MM2, see: Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. *Advances in Molecular Modeling*; JAP Press: Greenwich, CT; Vol. 2, in press.
(22) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.
(23) Hauser, C. R.; Brasen, W. R.; Skell, P. S.; Kantor, S. W.; Brodhag, A. E. R. *J. Am. Chem. Soc.* **1956**, *78*, 1653.
(24) Cook, J. M.; Cain, M.; Campos, O.; Guzman, F. *J. Am. Chem. Soc.* **1983**, *105*, 907.

Scheme VI[a]



[a] (a) Li(s-Bu)$_3$BH (99%); (b) $SOCl_2$, $CHCl_3$; (c) SeO_2; (d) Swern oxidation (92%); (e) PCC, 4-Å molecular sieve (~40%).

Scheme VII[a]



[a] (a) Me_3SiOTf, Et_3N (91%); (b) OsO_4, NMO (89%); (c) NaBH(OAc)$_3$ (65%); (d) Mn(OAc)$_3$·2H$_2$O, PhH, Δ (86%); (e) DBU; (f) $NaBH_4$, $CeCl_3$·7H$_2$O (75% from 35); (g) NaOH, aqueous EtOH (68%).

of the disubstituted alkene **28** provided a crystalline tertiary allylic alcohol in 56% yield, which was assumed on the basis of steric arguments to be the β isomer **31**. When the crude dehydration product (containing alkenes **27** and **28** and chloride **26**) was oxidized in a similar fashion and the resulting product mixture resolved on silica gel, **29** (57%), **30** (5%), and **31** (5%) were obtained in the indicated overall yields form alcohol **25**. To realize good conversions in this oxidation it was essential to add Celite to the heterogeneous reaction mixture. Stereochemical assignments for **29** and **30** were based on the multiplicity of the C(2) methine hydrogens: **29**: δ 4.07, ddd J = 11, 5.7, 3.0 Hz; **30**: δ 4.18, broad singlet, half-height width = 11 Hz.

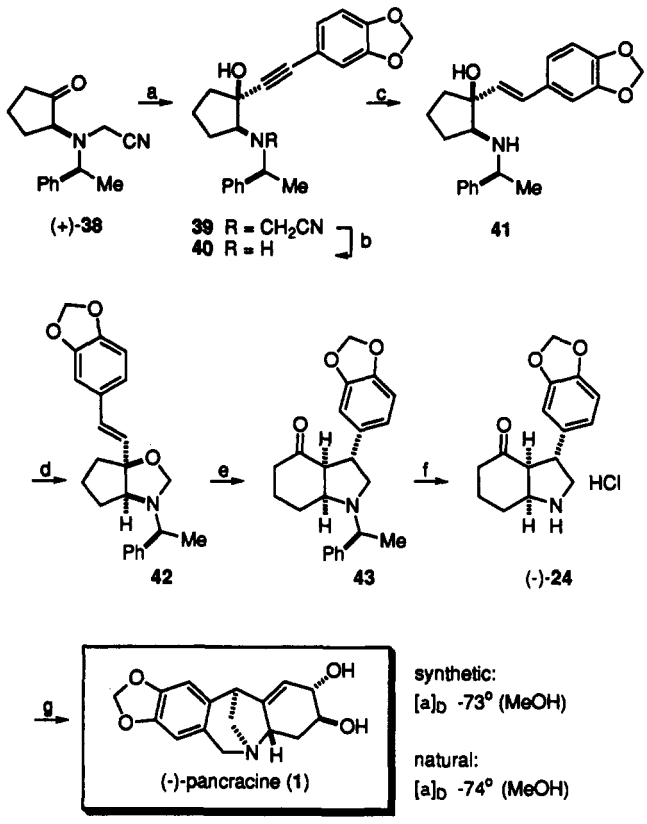
Swern[12] or MnO_2 oxidation converted both secondary alcohol epimers **29** and **30** to the enone **32** in good yield. With MnO_2 the pseudoequatorial alcohol **29** reacted faster than its pseudoaxial counterpart **30**. The tertiary allylic alcohol **31** was also converted to enone **32** upon oxidation with pyridinium chlorochromate in the presence of 4-Å molecular sieves, however the yield was low (~40%).[25]

With enone **32** on hand, we initially examined the direct oxidation of the derived lithium [LDA, LiN(SiMe$_3$)$_2$ or lithium 2,2,6,6-tetramethylpiperidide], sodium [NaN(SiMe$_3$)$_2$], or potassium [KN(SiMe$_3$)$_2$] enolates. Treatment of these enolates with conventional oxidants (Davis' oxaziridines[26] or MoOPH)[27] returned **32** and/or afforded the corresponding N-oxide. However, enolsilylation of **32** with Me_3SiOTf proceeded uneventfully to give the dienoxysilane **33**.[28] Treatment of this intermediate with catalytic OsO_4 in the presence of N-methylmorpholine N-oxide[29] provided the desired α-hydroxy ketone **34** in 82% yield from enone **32**. ^1H NMR analysis of the crude reaction product at 500 MHz showed no trace of the epimeric ketol. However, after purification on silica gel, traces of this epimer could be seen. Finally, reduction of **34** with sodium triacetoxyborohydride[30] afforded racemic pancracine (**1**) in 65% yield after purification on alumina. As detailed in the Experimental Section, this sample showed NMR and chromatographic properties indistinguishable from those of an authentic sample of (−)-pancracine.[31]

Synthesis of (±)-Desmethyl-α-isocrinamine. Entry to 5,11-methanomorphanthridines in the C(3) epimeric series was explored briefly. Oxidation of enone **32** with Mn(OAc)$_3$ in refluxing benzene afforded the axial β-acetoxy derivative **35** in 86% yield.[32] To achieve good conversions in this transformation it was essential that the oxidant was added portionwise. Epimerization to the equatorial α-acetate was readily accomplished at room temperature with DBU. Diagnostic ^1H NMR signals for the C(3) methine hydrogens of these acetate epimers are as follows. **35**: δ 5.25 (broad s). α-Acetoxy epimer of **35**: δ 5.28 (dd, J = 13.0 and 4.7 Hz). The rather unstable α-acetate was not purified but directly reduced under Gemal–Luche conditions[33] to give the hydroxy acetate **36**

(25) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.
(26) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774. (c) Davis, F. A.; Chattopadhyay, Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087.
(27) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(28) Emde, H.; Gotz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643.
(29) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607.
(30) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(31) Kindly provided from the Wildman collection by Dr. Henry M. Fales, NIH.
(32) (a) Watt, D. S.; Kim, M.; Kawada, K.; Gross, R. S. *J. Org. Chem.* **1990**, *55*, 504. (b) Williams, G. J.; Hunter, N. R. *Can. J. Chem.* **1976**, *54*, 3830.
(33) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

Scheme VIII[a]

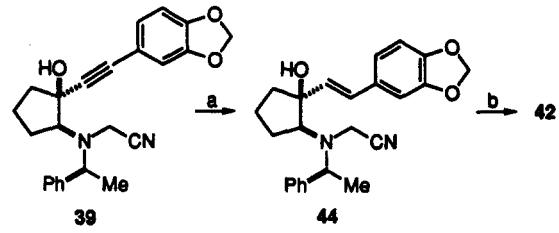


[a] (a) 14, *n*-BuLi; $CeCl_3$ (93%); (b) $AgNO_3$, EtOH, sonication (95%); (c) sodium bis(2-methoxyethoxy)aluminum hydride (100%), or $LiAlH_4$ (89%); (d) aqueous HCHO, CSA, Na_2SO_4 (75%); (e) 2.4 equiv BF_3·OEt_2, 5 °C, 2 h (95%); (f) H_2 (50 psi), HCl, Pd/C, MeOH (99%); (g) seven steps as in Schemes V–VII (25% overall).

as a 7:1 mixture of C(2) epimers in 75% yield. Saponification of **36**, followed by purification of the diol products by preparative TLC, then provided the racemic desmethyl analog **37** of α-isocrinamine in 68% yield. The stereochemistry of **37** was established by single crystal X-ray analysis of the crystalline dihydrate.[34] Conditions for stereoselectively reducing the C(2) carbonyl group of the α-acetoxy epimer of **35** from the β-face to allow efficient entry to the brunsvigine stereoseries were not found in a brief screen of reducing agents.

Enantioselective Synthesis of (−)-Pancracine. Asymmetric entry to the methanomorphanthridine family of *Amaryllidaceae* alkaloids is readily realized from the (*S*)-amino ketone **38** (Scheme VIII). This intermediate is available in enantiomerically pure form in three steps from cyclopentene oxide.[35] The coupling of this ketone with the alkynylcerium reagent derived from alkyne **14** proceeded in near quantitative yield to afford a single amino alcohol **39**. Competitive addition to the nitrile group of **38** was not observed even when 2 equiv of the cerium nucleophile were employed and the reaction solution was allowed to warm to 0 °C. Cleavage of the cyanomethyl group followed by reduction of the propargylic alcohol **40** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) provided the trans-allylic alcohol **41** in 90–95% overall yield from ketone **38**. Aza-Cope–Mannich rearrangement of the derived oxazolidine **42** occurred cleanly at 0–10 °C in the presence of excess BF_3·OEt_2 to afford hydroindolone **43**. To obtain reproducible yields in this conversion it was essential that **42** be filtered through basic Al_2O_3 prior to rearrangement. Removal of the α-methylbenzyl group by catalytic hydrogenation at 50 psi afforded the crystalline hydrochloride salt (−)-**24**, $[\alpha]_D$ −31.1°, in an excellent overall yield of 68% from cyclopentanone **38**.

Scheme IX[a]



[a] (a) Sodium bis(2-methoxyethoxy)aluminum hydride, NaOMe (60%); (b) $AgNO_3$, EtOH (90%).

In order to circumvent the need to cleave the cyanomethyl group prior to reducing the triple bond, we examined the direct reduction of the triple bond of the cyanomethylamino alkyne **39**. Reduction of **39** with chromium(II) reagents[37] or metal/ammonia combinations proceeded without acceptable selectivity or returned **39**. Partial success was realized when Red-Al reduction of the propargylic alcohol was carried out at −25 °C in the presence of NaOMe, an additive employed to convert any electrophilic aluminum hydride species to the corresponding ate complex (Scheme IX). Since the yield of this reduction was only 60%, the two-step synthesis of oxazolidine **42** outlined in Scheme IX was less efficient than the three-step sequence described in Scheme VIII.

The conversion of (−)-**24** to (−)-pancracine (**1**) was realized in seven additional steps using the sequence developed in the racemic series (Schemes V–VII). The melting point of synthetic **1**, mp 270 °C dec and optical rotation $[\alpha]^{25}_D$ −72.6° (*c* = 0.4, MeOH) were in good agreement with those reported for natural (−)-pancracine: mp 272–273 °C, $[\alpha]^{25}_D$ = −74° (*c* 0.02, MeOH).[2]

Conclusion

A concise sequence for preparing *Amaryllidaceae* alkaloids of the 5,11-methanomorphanthridine subclass has been developed. The total synthesis of (±)-pancracine (***rac*-1**) was achieved with complete stereochemical control in 17 chemical operations and 7% overall yield from cyclopentene. The tetracylic methanomorphanthridine enone **32** (Scheme VII) is a potentially useful intermediate for preparing other stereoisomers in this series, as demonstrated in the four-step conversion of **32** into (±)-desmethyl-α-isocrinamine (**37**).

The first asymmetric synthesis of a member of the methanomorphanthridine class of *Amaryllidaceae* alkaloids was recorded in the total synthesis of (−)-pancracine (**1**). The efficient enantioselective total synthesis of (−)-**1** was accomplished in 13 steps and 14% overall yield from the (*S*)-amino ketone **38**. This latter intermediate is available in three steps and 39% yield from 1,2-epoxycyclopentane.

(34) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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The overall efficiency of this first successful entry to this group of *Amaryllidaceae* alkaloids provides a further illustration of the power of the aza-Cope–Mannich reaction in stereocontrolled alkaloid construction.[11,38] Significantly, the formation of the hydroindolone (−)-**24** in enantiopure form by this sequence provides the second demonstration of the use of the aza-Cope–Mannich reaction as the key element of asymmetric alkaloid construction.

Experimental[39] Section

(±)-*trans*-2-(*N*-Benzylamino)cyclopentanol (*rac*-10). A mixture of cyclopentene (51 mL, 0.58 mol), *N*-bromosuccinimide (100 g, 0.56 mol), Et_2O (120 mL), and H_2O (120 mL) was stirred at 0 °C for 23 h. After the mixture was filtered, the aqueous layer was saturated with NaCl and extracted (Et_2O, 100 mL). The combined organic layers were washed with saturated aqueous NaCl solution (50 mL) and dried (Na_2SO_4). Vacuum distillation of the concentrated organic layer gave 80 g (86%) of *trans*-2-bromocyclopentanol as a colorless liquid.

A solution of benzylamine (148 g, 1.4 mol) and a 46 g (0.28 mol) sample of *trans*-2-bromocyclopentanol was heated at 100 °C for 12 h. Excess benzylamine was removed by distillation at reduced pressure (*ca.* 60 °C) and the remaining material was dissolved in H_2O (300 mL). This solution was saturated with solid KOH and the resulting mixture was extracted with Et_2O (3 × 200 mL). The combined extracts were washed with brine (100 mL), dried (K_2CO_3), and concentrated. The crude product was dissolved in a minimum amount of boiling hexane (*ca.* 400 mL), treated with charcoal, and filtered. Upon cooling, ***rac*-10** [10](40 g, 75%) separated as white needles: mp 68–69 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.3–7.1 (m, Ph), 4.0–3.6 (m, 3H), 2.9–2.8 (m, 8H); IR (KBr) 3290, 3170, 3113, 2858, 1086, 860, 752, 702 cm^{-1}; MS (EI) *m/e* 191.1310 (191.1310 calcd for $C_{12}H_{17}NO$, M, 8%), 146 (51%), 100 (23%) 91 (100%).

(±)-*trans*-2-[*N*-Benzyl-*N*-(cyanomethyl)amino]cyclopentanol (*rac*-11). To a solution of ***rac*-10** (42 g, 0.22 mol) and acetone (300 mL) at 23 °C was added concentrated HCl (2.4 mL, 25 mmol) dropwise. When the addition was complete, the solution was concentrated and the residue was dissolved in H_2O (480 mL), cooled to 0 °C, and treated sequentially with KCN (17 g, 0.22 mol) and paraformaldehyde (7.3 g, 0.22 mol). The resulting mixture was stirred at room temperature for 18 h, saturated with solid K_2CO_3, and extracted with ether (3 × 300 mL). The combined organic extracts were washed with brine, dried (K_2CO_3), and concentrated giving 45 g (89%) of ***rac*-11** as a slightly yellow solid.

An analytically pure specimen of ***rac*-11** was prepared by recrystallization from hexane: mp 45–47 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.4–7.1 (m, 5H), 4.2 (br s, CHO), 3.79 (s, 2H), 3.66 (d, *J* = 17.4 Hz, 1H), 3.40 (d, *J* = 17.2 Hz, 1H), 2.95 (m, 1H), 2.2–2.0 (m, 2H), 1.9–1.5 (m, 5H); IR (KBr) 3434, 2695, 1457, 1417, 1075, 746, 699 cm^{-1}; MS (EI) *m/z* 230.1417 (230.1419 calcd for $C_{14}H_{18}N_2O$, M, 3%), 185 (12%), 91 (100%). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.88; H, 7.95; N, 12.05.

(±)-2-[*N*-Benzyl-*N*-(cyanomethyl)amino]cyclopentanone (*rac*-12). According to the general procedure of Swern,[12] ***rac*-11** (18.9 g, 82.0 mmol) was oxidized in CH_2Cl_2 (300 mL) at −78 °C with oxalyl chloride (7.8 mL, 91 mmol), Me_2SO (12 mL, 180 mmol), and Et_3N (50 mL, 0.30 mol). The reaction mixture was allowed to warm to room temperature, diluted with ether (600 mL), and washed with water (3 × 200 mL) and brine (200 mL). The organic phase was dried (K_2CO_3) and concentrated to give 16.5 g (88%) of **rac-12** as a light yellow oil that crystallized upon standing.

An analytical sample was prepared by recrystallization from pentane as white needles (mp 46–48 °C). This material was identical in every respect to the known material.[10] Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.55; H, 7.11; N, 12.24.

5-Ethynyl-1,3-benzodioxole (14). According to the general method of Corey and Fuchs,[14] solid piperonal (13, 22.1 g, 0.150 mol) was added to the mixture prepared from Ph_3P (77 g, 0.29 mol), Zn dust (19 g, 0.29 mol), CBr_4 (97 g, 0.29 mol), and CH_2Cl_2 (1 L). After 5 h at 23 °C, 2 L of hexanes was added and the supernatant solution was decanted through a filter. The brown precipitate was diluted with CH_2Cl_2 (500 mL) and then additional hexane (1.5 L) was added. After decantation, this washing procedure was repeated twice. The combined organic portions were concentrated, the precipitated phosphine oxide was removed by filtration, and the filter cake was washed with hexanes (100 mL). The combined filtrates were concentrated to give 48 g of a yellow oil, which partially solidified upon cooling in a refrigerator. This crude sample of 5-(2,2-dibromoethenyl)-1,3-benzodioxole was used without purification in the next step.

To a 19.3 g sample of this crude dibromide dissolved in THF (300 mL) was added *n*-BuLi (56 mL, 2.65 M, 150 mmol) while maintaining the reaction temperature below −70 °C. After 1 h at −78 °C, the solution was allowed to warm to 23 °C during 30 min, and then maintained at 23 °C for 1 h before quenching with water (300 mL). The aqueous layer was extracted with Et_2O (3 × 200 mL), and the combined organic layers were washed with H_2O (3 × 100 mL) and dried ($MgSO_4$). Concentration and distillation of the residue gave 6.98 g (81%) of **14** as a colorless oil: bp 56–58 °C (1 mmHg); mp 33 °C (reported[13] mp 26–27 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, *J* = 1.6, 8.1 Hz, 1H, Ar), 6.93 (d, *J* = 1.6 Hz, 1H, Ar), 6.75 (d, *J* = 8.1 Hz, 1H, Ar), 5.98 (s, OCH_2O), 2.97 (s, ≡CH); IR (CCl_4) 3315, 2106 cm^{-1}.

(±)-*cis*- and *trans*-2-[*N*-Benzyl-*N*-(cyanomethyl)amino]-1-[2-(1,3-benzodioxol-5-yl)ethynyl]cyclopentanols (*rac*-15 and *rac*-16). According to the general procedure of Imamoto,[15] "anhydrous $CeCl_3$" was freshly prepared from 13.6 g of $CeCl_3 \cdot 7H_2O$ (36.5 mmol) by heating at 135 °C (0.2 mmHg) without stirring for 1 h, followed by heating at 135 °C for 1 h with stirring, and then allowed to cool to 23 °C under Ar. Freshly distilled THF (50 mL) was added rapidly to the cooled $CeCl_3$ at 0 °C and the resulting slurry was stirred at 23 °C for 2 h. In a separate flask containing 5.41 g (37.0 mmol) of alkyne **14** and 50 mL of THF was added 12.0 mL of *n*-BuLi (2.48 M in hexane, 29.8 mmol) dropwise at 0 °C and the resulting solution was maintained for 30 min at 0 °C. This solution was then cooled to −78 °C and transferred to the precooled $CeCl_3$ slurry in THF at −78 °C via a cannula. The resulting mixture was stirred for 1 h at −78 °C before a solution of ***rac*-12** (4.18 g, 18.3 mmol) in 30 mL of THF was added dropwise at −78 °C. The resulting mixture was stirred for 6 h and then quenched by adding 10 mL of aqueous THF (50%). Saturated aqueous KH_2PO_4 solution (100 mL) was added and the mixture was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$ solution (50 mL) and water (50 mL) and dried (K_2CO_3). Concentration gave 10.2 g of a slightly yellow oil. Flash column chromatography (1:1 hexane–CH_2Cl_2 to CH_2Cl_2 to 1:1 CH_2Cl_2–Et_2O) afforded 2.55 g of recovered alkyne **14**, 6.34 g (92%) of ***rac*-15** and 0.49 g (7%) of **rac-16**.

An analytical sample of ***rac*-15** was prepared by flash column chromatography (1:4 ethyl acetate–hexanes) as a yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.39 (m, 5H, Ph), 6.92 (dd, *J* = 1.6, 8.1 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 5.95 (s, 2H, OCH_2O), 4.07 (AB q, *J* = 13.2 Hz, $\Delta\nu_{AB}$ = 175 Hz, NCH_2N), 3.72 (s, 1H, OH), 3.71 (AB q, *J* = 17.6 Hz, $\Delta\nu_{AB}$ = 282 Hz, NCH_2Ph), 3.34 (dd, *J* = 6.9, 10.7 Hz, CHN), 1.78–2.32 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) 147.8, 147.2, 136.4, 128.9, 128.7, 127.9, 126.0, 115.4, 115.1, 111.3, 108.2, 101.1, 90.8, 84.3, 72.2, 71.2, 56.6, 40.7, 39.6, 28.6, 20.0 ppm; IR (CH_2Cl_2) 3459, 2977, 2222, 1604, 1498 cm^{-1}; MS (CI) *m/z* 375 (MH), 348 (MH − HCN); 374.1644 (374.1630 calcd for $C_{23}H_{22}NO_3$, M). Anal. Calcd for $C_{23}H_{22}NO_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.53; H, 5.87; N, 7.40.

An analytically pure sample of ***rac*-16** was prepared by recrystallization from diethyl ether–pentane (2:1): mp 144–146 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.46 (m, 5H, Ph), 6.93 (dd, *J* = 1.4, 7.9 Hz, 1H), 6.84 (d, *J* = 1.4 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 5.98 (s, OCH_2O), 3.99 (AB q, *J* = 13.7 Hz, $\Delta\nu_{AB}$ = 61.5 Hz, NCH_2N), 3.66 (AB q, *J* = 17.5 Hz, $\Delta\nu_{AB}$ = 148 Hz, NCH_2Ph), 3.16 (dd, *J* = 7.3, 9.9 Hz, CHN), 2.35 (s, OH), 1.81–2.32 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) 147.9, 147.3, 137.7, 128.7, 128.5, 127.5, 126.2, 115.9, 115.7, 111.5, 108.3, 101.2, 88.2, 86.7,

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(39) General experimental details were described in: Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 2630.

77.7, 71.5, 56.0, 41.5, 40.3, 27.5, 18.7 ppm; IR (KBr) 3432, 2873, 2266, 1507 cm^{-1}; MS (EI) *m/z* 374.1624 (374.1630 calcd for $C_{23}H_{22}NO_3$, M, 5%. Anal. Calcd for $C_{23}H_{22}NO_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.65; H, 5.93; N, 7.43.

(±)-*cis*-(*N*-Benzylamino)-1-[2-(1,3-benzodioxol-5-yl)ethynyl]cyclopentanol (*rac*-17). To a solution of ***rac*-15** (1.94 g, 5.19 mmol) in 400 mL of absolute EtOH at 23 °C was added 0.97 g of $AgNO_3$ (5.7 mmol). The mixture soon formed a precipitate while being stirred at 23 °C. After 10 h at 23 °C, the precipitate was filtered and 50 mL of water was added to the supernatant. The resulting solution was placed in an ultrasonic bath at 30 °C for 100 min and then concentrated. The residue was extracted with $CHCl_3$ (3 × 30 mL) and the combined organic extracts were washed with aqueous ammonia (3 mL) and dried (K_2CO_3). The organic layer was concentrated to give a dark oil, which was purified by flash column chromatography (1:2 ethyl acetate–hexanes) to give 1.69 g (97%) of an oil, which solidified upon standing.

An analytically pure sample of ***rac*-17** was prepared by recrystallization from CH_2Cl_2–hexanes (2:1): mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.36 (m, 5H, Ph), 6.95 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.87 (d, *J* = 1.6 Hz, 1H), 6.74 (d, *J* = 8.0, 1H), 5.96 (s, OCH_2O), 4.05 (AB q, *J* = 13.4 Hz, $\Delta\nu_{AB}$ = 42.1 Hz, CH_2Ph), 3.36 (app t, *J* = 8.7 Hz, CHN), 1.46–2.20 (m, 6H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 147.5, 147.2, 139.9, 128.4, 128.0, 127.0, 125.9, 116.2, 111.4, 108.2, 101.1, 91.5, 82.5, 71.8, 67.0, 52.4, 39.8, 30.4, 20.7 ppm; IR (film) 3392, 2946, 2220, 1737, 1489, 1217 cm^{-1}; MS (EI) *m/z* 335.1517 (335.1521 calcd for $C_{21}H_{21}NO_3$, M, 4%). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.06; H, 6.34; N, 4.12.

(±)-*cis*-2-(*N*-Benzylamino)-1-[(*E*)-2-(1,3-benzodioxol-5-yl)]ethenyl]cyclopentanol (*rac*-18). According to the general procedure of Bates,[16] a solution of amino alcohol ***rac*-17** (1.20 g, 3.60 mmol) and 15 mL of Et_2O was added dropwise to a cooled slurry of $LiAlH_4$ (0.46 g, 12 mmol) in 10 mL of Et_2O at −20 °C. After gas evolution subsided, the mixture was heated at reflux for 4 h. After cooling to room temperature, excess hydride was destroyed with water (3 mL) and the mixture was acidified with 1 N HCl solution (60 mL). The aqueous solution was extracted with $CHCl_3$ (3 × 100 mL), and the extracts were washed with 50 mL of 1 N NaOH solution. After drying over K_2CO_3, the organic layer was concentrated to give 1.15 g (94%) of an oil, which was homogeneous by TLC and ^{1}H NMR analysis.

A pure sample of ***rac*-18** was prepared by recrystallization from hexane–$CHCl_3$ (4:1): mp 68–69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.34 (m, 5H, Ph), 6.93 (d, *J* = 1.7 Hz, 1H), 6.83 (dd, *J* = 1.7, 8.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.73 (d, *J* = 15.8 Hz, ArCH=C), 6.05 (d, *J* = 15.7 Hz, ArC=CH), 5.94 (s, OCH_2O), 3.77 (AB q, *J* = 13.4 Hz, $\Delta\nu_{AB}$ = 25.0 Hz, CH_2Ph), 3.02 (app t, *J* = 8.6 Hz, CHN), 1.65–2.02 (m, 6H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) 147.8, 146.7, 140.0, 134.1, 131.7, 128.3, 127.8, 127.2, 127.0, 120.7, 108.1, 105.6, 100.8, 79.2, 65.6, 52.5, 38.5, 30.7, 20.8 ppm; IR (film) 3346, 2960, 1605, 1505 cm^{-1}; MS (EI) 337.1683 (337.1678 calcd for $C_{21}H_{23}NO_3$, M, 25%), 319 (61%), 228 (42%), 146 (68%), 106 (65%), 91 (100%).

(±)-*cis*-2-[*N*-Benzyl-*N*-(cyanomethyl)amino]-1-[(*E*)-2-(1,3-benzodioxol-5-yl)ethenyl]cyclopentanol (*rac*-9). A solution of bromide **22** (229 mg, 1.00 mmol) was treated dropwise with *t*-BuLi (1.31 mL, 1.95 mmol, 1.49 M in pentane) at −95 °C in THF, and the resulting solution was kept for 1 h at −90 to −100 °C. A solution of ***rac*-12** (217 mg, 0.95 mmol) and THF (1 mL) was then added at −95 °C and the resulting solution was allowed to warm to 23 °C. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 30 mL). The ether extracts were dried ($MgSO_4$) and concentrated to give an oil, which was purified by flash chromatography (CH_2Cl_2) to give 150 mg (42%) of ***rac*-9** as an oil, which crystallized upon standing.

An analytical sample of ***rac*-9** was obtained by recrystallization from ethyl acetate–hexanes (1:4): mp 98–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H, Ph), 6.93 (d, *J* = 1.4 Hz, 1H), 6.86–6.72 (m, 3H, ArH and ArCH=), 6.20 (d, *J* = 15.8 Hz, 1H, ArC=CH), 3.96 (d, *J* = 13.1 Hz, 1H), 3.74 (d, *J* = 13.1 Hz, 1H), 3.63 (d, *J* = 12.3 Hz, 1H), 3.34 (d, *J* = 17.6 Hz, 1H), 3.30 (s, 1H, OH), 3.10 (dd, *J* = 10.4, 7.0 Hz, CHN), 2.21–1.63 (m, 6H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) 147.8, 146.8, 136.4, 134.2, 131.0, 128.8, 128.6, 127.8, 126.7, 120.7, 114.9, 108.0, 105.5, 100.8, 79.5, 70.1, 56.6, 39.5, 39.4, 29.2, 19.8 ppm; IR (film) 511, 802, 875, 1029, 1038, 1129, 1255, 1506, 1605, 2860, 3478 cm^{-1}; MS (EI) *m/z* 376.1763 (376.1787 calcd for $C_{23}H_{24}N_2O_3$, M, 1%), 349 (20%), 306 (19%), 278 (30%), 91 (100%).

Preparation of (±)-*cis*-*N*-Benzyl-6a-[(*E*)-2-(1,3-benzodioxol-5-yl)ethenyl]-1-oxa-3-azabicyclo[3.3.0]octane (*rac*-23) from Amino Alcohol *rac*-9. A mixture of alcohol ***rac*-9** (54 mg, 0.14 mmol), silver nitrate (31 mg, 0.18 mmol), and ethanol (7 mL) was stirred at 23 °C for 16 h. The reaction mixture then was filtered, the filtrate was concentrated, and the residue was taken up in 1 mL of aqueous ammonia and then extracted with Et_2O (2 × 20 mL). The organic portion was washed with brine (2 × 10 mL) and dried (Na_2SO_4). Concentration gave 52 mg of an oil that was purified by flash chromatography (1:4 ethyl acetate–hexanes) to give 44 mg (87%) of a clear oil, which was homogeneous by TLC analysis and solidified upon standing at 23 °C.

Recrystallization from THF–hexanes (1:1) gave an analytical sample of ***rac*-23**: mp 62–64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H, Ph), 6.98 (d, *J* = 1.4 Hz, 1H), 6.83 (dd, *J* = 1.4, 8.0 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 15.0 Hz, ArCH=C), 6.21 (d, *J* = 15.0 Hz, ArC=C*H*), 5.97 (s, OCH_2O), 4.48 (AB q, J_{AB} = 5.1 Hz, $\Delta\nu_{AB}$ = 54.0 Hz, NCH_2CN), 3.81 (AB q, J_{AB} = 13.3 Hz, $\Delta\nu_{AB}$ = 32.0 Hz, OCH_2N), 3.31–3.29 (m, CHN), 2.0–1.2 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$), 147.8, 146.8, 138.9, 132.0, 130.4, 128.4, 128.1, 126.8, 125.5, 120.7, 108.1, 105.4, 100.8, 91.2, 86.2, 73.4, 55.8, 38.1, 24.2 ppm; IR (film) 2594, 2877, 1606, 1505, 1251, 1038, 830, 699 cm^{-1}; MS (EI) *m/z* 349.1661 (349.1678 calcd for $C_{22}H_{23}NO_3$, M, 35%), 306 (25%), 278 (37%), 91 (100%). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.38; H, 6.67; N, 4.07.

Preparation of *rac*-23 from *rac*-18. A mixture containing ***rac*-18** (0.48 g, 1.4 mmol), formalin solution (0.24 g, 37% in water, 3.0 mmol), anhydrous Na_2SO_4 (0.68 g, 4.8 mmol), camphorsulfonic acid (71 mg, 0.3 mmol) and CH_2Cl_2 (14 mL) was stirred at 23 °C for 8 h. The mixture then was filtered and the filtrate was washed with 1 N NaOH solution (5 mL) and water (5 mL) and dried ($MgSO_4$). Concentration gave 0.47 g of an oil, which was purified by radial chromatography (silica gel, 1:5 EtOAc–hexanes) to give 0.40 g (81%) of ***rac*-23** as an oil that crystallized upon standing.

(±)-(3*R,3a*S**,7a*S**)-*N*-Benzyl-3-(1,3-benzodioxol-5-yl)-4-oxooctahydroindole (*rac*-6).** A solution of ***rac*-23** (120 mg, 0.34 mmol) in CH_2Cl_2 (8.2 mL) was allowed to react with BF_3·OEt_2 (0.11 mL, 0.81 mmol) at −20 °C for 30 min and then the reaction solution was allowed to warm to 23 °C. After 15 min, the resulting solution was quenched with 1.0 N NaOH solution (4 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic portions were dried (K_2CO_3) and concentrated to give 116 mg (97%) of a light yellow oil, which crystallized upon standing. The product was homogeneous by TLC analysis.

Recrystallization from Et_2O gave an analytical specimen of ***rac*-6**: mp 91–92 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 7.23–7.09 (m, 5H, Ph), 6.73 (d, *J* = 1.7 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.55 (dd, *J* = 1.7, 8.0 Hz, 1H), 5.33 (AB q, *J* = 1.3 Hz, $\Delta\nu_{AB}$ = 5.1 Hz, OCH_2O), 3.94 (dt, *J* = 8.6, 4.7 Hz, H_3), 3.71 (d, *J* = 13.1 Hz, C*H*HPh), 3.17 (app t, *J* = 8.7 Hz, 1H, H_2), 2.79 (d, *J* = 13.0 Hz, 1H, CH*H*Ph), 2.65 (dt, *J* = 7.4, 4.5 Hz, H_{7a}), 2.35 (dd, *J* = 7.4, 4.8 Hz, H_{3a}), 2.32–2.28 (m, 1H), 1.96 (app t, *J* = 9.1 Hz, 1H, H_2), 1.90–1.83 (m, 1H), 1.73–1.70 (m, 1H), 1.45–1.26 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 210.9, 147.5, 145.8, 138.7, 137.8, 128.5, 128.1, 126.9, 120.5, 108.0, 107.9, 100.7, 65.1, 61.0, 59.5, 57.2, 41.8, 40.5, 26.3, 19.9 ppm; IR (KBr) 1038, 1251, 1489, 1702, 1708, 2940 cm^{-1}; MS (EI) *m/z* 349.1688 (349.1678 calcd for $C_{22}H_{23}NO_3$, M, 85%), 321 (13%), 306 (45%), 279 (42%). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.54; H, 6.69; N, 3.98.

(±)- and [6a*S*-(6α,6aβ,10aβ,11α)]-5,6a,7,8,9,10,10a,11-octahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-10-one (*rac*-5 and (−)-5). A solution of 0.28 g (0.80 mmol) of ***rac*-6** in MeOH (15 mL) was acidified with concd HCl (0.07 mL, 12 N in H_2O, 0.85 mmol). Pd/C (10%, 60 mg) was added, and the mixture was degassed and stirred under 1 atm of hydrogen gas for 6 h. The catalyst was then removed by filtration and the filtrate was concentrated to *ca.* 2 mL. Freshly distilled THF (10 mL) was added to the solution to facilitate crystallization and then the solvent was removed under vacuum. The resulting white powder of ***rac*-24**, 0.23 g (97%), was used in the next step without further purification: mp 208–210 °C; ^{1}H

NMR (500 MHz, DMSO-d_6) δ 6.61 (s, 1H, ArH), 6.52 (s, 2H, ArH), 5.72 (s, OCH_2O), 4.03 (m, 1H), 3.66 (q, 1H), 3.45 (m, 1H), 3.04 (m, 1H), 2.80 (t, 1H), 2.36 (br s, 1H), 1.57–2.24 (m, 6H, CH_2).

The general Pictet–Spengler procedure of Whitlock was followed.[19] To a solution of a comparable sample of this salt (295 mg, 1.0 mmol), 4.0 mL of formalin (37%, 50 mmol), and 4 mL of CH_3OH was added 0.30 mL of NEt_3 (2.0 mmol). After 5 min at 23 °C, the mixture was extracted with $CHCl_3$ (3 × 20 mL), the organic layer was concentrated, and the resulting residue was used without further purification. Characteristic data for the *N*-(hydroxymethyl) intermediate produced at this stage are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (d, J = 7.9 Hz, 1H), 6.69 (d, J = 1.7 Hz, 1H), 6.65 (dd, J = 1.7, 7.9 Hz, 1H), 5.94 (s, OCH_2O), 4.44 (br s, OH), 4.26 (dd, J = 8.9, 13.9 Hz, 1H), 2.60–2.58 (m, 1H), 2.51–2.48 (m, 1H), 2.20–2.15 (m, 1H), 1.95–1.92 (m, 2H), 1.51–1.45 (m, 1H), 1.30–1.18 (m, 2H); M/S (EI) m/z 273 (2%, MH - H_2O).

Aqueous HCl (6 N, 100 mL) was added to a solution of this residue and MeOH (2.0 mL), and the resulting solution was maintained at 23 °C for 10 h before carefully quenching with 50 mL of aqueous ammonia (while maintaining the temperature below 40 °C). The basic solution was extracted with $CHCl_3$ (5 × 25 mL) and the combined organic layer was concentrated to give 304 mg of an oil. Column chromatography (3:1 $CHCl_3$–methanol) of this material gave 183 mg (67% from ***rac*-24**) of ***rac*-5** as a white solid.

An analytical sample of ***rac*-5** was obtained by recrystallization from $CHCl_3$–hexane (3:1): mp 101–103 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 6.41 (s, H_{12}), 6.23 (s, H_4), 5.33 (dd, J = 1.3, 16.9 Hz, H_2), 3.69 (AB q, J = 16.9 Hz, $\Delta\nu_{AB}$ = 310 Hz, H_5), 3.64 (d, J = 2.2 Hz, H_{10}), 3.00 (ddd, only six lines visible, J = 6.1, 9.0, 10.4 Hz, H_{6a}), 2.65 (dd, J = 2.7, 11.7 Hz, 1H, H_{13}), 2.62 (d, 11.7 Hz, 1H, H_{13}), 2.46 (dd, J = 1.3, 9.0 Hz, H_{10a}), 1.79–1.98 (m, 3H), 0.91–1.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 211.1, 146.4, 145.6, 125.7, 107.2, 106.3, 100.6, 86.9, 67.1, 63.2, 60.4, 54.0, 39.7, 37.9, 29.4, 18.5 ppm; IR ($CDCl_3$) 3690, 2954, 2188, 1704, 1602, 1230 cm^{-1}; MS (EI) m/z 271.1203 (271.1208 calcd for $C_{16}H_{17}NO_3$, M, 100%), 242 (37%), 228 (31%), 215 (13%), 175 (55%). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.70; H, 6.38; N, 5.21.

The levorotatory hydroindolone hydrochloride (–)-**24** was prepared from (+)-**43** (0.57 g, 1.57 mmol), Pd/C (10%, 120 mg), concentrated HCl (0.2 mL), and MeOH (25 mL) by hydrogenolysis at 50 psi H_2 in a Parr shaker for 24 h to give 0.46 g (99%) of (–)-**24**: $[\alpha]^{25}_D$ = –31.1° (c = 1.2, MeOH). Pictet–Spengler cyclization of this intermediate, as in the racemic series, with Et_3N (0.33 mL), aqueous formaldehyde (4.5 mL, 37%), MeOH (4.8 mL), and 6 N HCl (95 mL) afforded, after chromatographic purification, 213 mg (67%) of (–)-**5**: $[\alpha]^{25}_D$ = –54.1° (c = 2.1, MeOH).

(±)- and [6a*S*-(6α,6aβ,10aβ,10α,11α)]-5,6a,7,8,9,10,10a,11-octahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-10-ol (*rac*-25 and (–)-25). Lithium tri-*sec*-butylborohydride (L-Selectride, 2.5 mL, 1 M in THF, 2.5 mmol) was added to a solution of ***rac*-5** (344 mg, 1.27 mmol) in THF (4 mL) at –78 °C.[22] After 1 h at –78 °C, the reaction mixture was allowed to warm to 23 °C and then recooled to –78 °C before being quenched with aqueous THF. After concentration, the residue was partitioned between saturated aqueous $NaHCO_3$ (5 mL), and $CHCl_3$ (10 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL), and the combined organic layers were dried (K_2CO_3) and concentrated. Flash chromatography (1:10:100 aqueous ammonia–methanol–$CHCl_3$) gave 345 mg (99%) of crystalline ***rac*-25**.

A pure sample of ***rac*-25** was prepared by recrystallization from chloroform: mp 214–216 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.50 (s, H_{12}), 6.45 (s, H_4), 5.86 (s, H_2), 4.04 (ABq, J = 17.0 Hz, $\Delta\nu_{AB}$ = 29.4 Hz, H_5), 4.21 (app q, J = 3.8 Hz, H_{10}), 3.43 (dd, J = 3.1, 11.1 Hz, 1H, H_{13}), 3.10 (ddd, six lines visible, J = 9.5, 6.5, 2.7 Hz, H_{6a}), 3.03 (d, J = 3.1 Hz, H_{11}), 2.85 (d, J = 11.1 Hz, 1H, H_{13}), 2.18 (dd, J = 4.3, 8.5 Hz, H_{10a}), 1.83–1.75 (m, 3H), 1.67–1.65 (m, 1H), 1.51–1.46 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 145.8, 145.4, 138.0, 125.4, 106.5, 106.1, 100.4, 69.2, 65.9, 60.2, 54.5, 54.0, 42.8, 27.5, 25.2, 16.7 ppm; MS (EI) m/z 273.1368 (273.1365 calcd for $C_{16}H_{19}NO_3$, M), 256 (5%), 230 (5%), 202 (5%), 175 (100%); IR (KBr) 933, 1038, 1225, 1481, 2863, 3135 cm^{-1}.

The levorotatory alcohol (–)-**25** was prepared from (–)-**5** (69 mg, 0.25 mmol) and L-Selectride (0.5 mL, 0.5 mmol) in an identical fashion to give 69 mg (99%) of (–)-**25**: $[\alpha]^{25}_D$ = –27.0° (c = 1.0, MeOH).

(±)- and [6a*S*-(6α,6aβ,11α)]-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepine (*rac*-27 and (–)-27), (±)-[6a*S-(6α,6aβ,10aβ,11α)]-5,6a,7,8,10a,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo-[5,6-*c*][1]-benzazepine (*rac*-28), and (±)-[6a*S**-(6α,6aβ,10β,10aβ,11α)]-10-chloro-5,6a,7,8,9,10,10a,11-octahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepine (*rac*-26).** According to the general method of Hauser,[23] ***rac*-25** (167 mg, 0.610 mmol) in $CHCl_3$ (7 mL) was added dropwise to cold $SOCl_2$ (0.60 mL, 8.1 mmol) at –30 °C. The resulting solution was allowed to warm to 23 °C and maintained at 23 °C for 20 h before volatile materials were removed under reduced pressure. The residue was partitioned between 1 N NaOH (3 mL) and $CHCl_3$ (6 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were dried (K_2CO_3) and concentrated to give 138 mg of a slightly yellow oil, which was purified by flash chromatography (1:10:100 aqueous ammonia–CH_3OH–$CHCl_3$) to give 3 mg (2%) of ***rac*-26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, H_{12}), 6.43 (s, H_4), 5.87 (s, H_2), 4.00 (AB, q, J = 16.9 Hz, $\Delta\nu_{AB}$ = 274 Hz, H_5), 3.93 (dt, J = 11.8, 5.8 Hz, H_{10}), 3.21–3.16 (m, H_{6a}), 3.11 (d, J = 2.6 Hz, H_{11}), 3.06 (dd, J = 2.6, 11.7 Hz, H_{13}), 2.94 (d, J = 11.7 Hz, H_{13}), 2.42 (dd, J = 8.1, 12.0 Hz, H_{10a}), 2.19–2.12 (m, 1H), 1.76–1.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.2, 145.7, 135.7, 125.1, 107.0, 106.2, 100.5, 66.1, 60.4, 59.8, 58.5, 52.4, 43.2, 30.6, 25.1, 18.7 ppm; IR (film) 1044, 1238, 1481, 1675, 2944 cm^{-1}; MS (EI) m/z 291.1024 (291.1026 calcd for $C_{16}H_{18}{}^{35}ClNO_2$, M, 49%), 293.1010 (293.0996 calcd for $C_{16}H_{18}{}^{37}ClNO_2$, 17%) 256 (100%).

Further elution gave a 3:1 mixture of ***rac*-27** and ***rac*-28** (126 mg, 80%): Crystallization from $CHCl_3$–hexanes (1:2) gave 55 mg of ***rac*-27**: mp 101–103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, H_{12}), 6.47 (s, H_4), 5.87 (ABq, J = 1.4 Hz, $\Delta\nu_{AB}$ = 15.1 Hz, H_2), 5.49 (q, J = 2.7 Hz, H_{10}), 4.06 (ABq, J = 16.6 Hz, $\Delta\nu_{AB}$ = 260 Hz, H_5), 3.22 (br s, H_{11}), 3.12 (ddd, J = 11.3, 4.6, 2.5 Hz, H_{6a}), 2.97 (br s, 2H, H_{13}), 2.09–2.00 (m, 3H), 1.85–1.81 (m, 1H), 1.52–1.47 (m, 1H), 1.27–1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.4, 146.3, 145.7, 133.2, 124.8, 114.8, 107.0, 106.7, 100.5, 63.3, 61.1, 55.2, 45.8, 28.5, 24.2, 21.0 ppm; IR (film) 938, 1038, 1223, 1236, 1483, 1503, 2934 cm^{-1}; MS (EI) m/z 255.1271 (255.1259 calcd for $C_{16}H_{17}NO_2$, M, 82%), 227 (54%), 185 (100%).

Flash chromatography of the mother liquor provided a pure sample of ***rac*-28** as a solid: mp 94–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, H_{12}), 6.46 (s, H_4), 5.93 (m, H_{10}), 5.88 (s, H_2), 5.66 (dt, J = 10.0, 2.7 Hz, H_9), 4.03 (AB q, J = 16.5 Hz, $\Delta\nu_{AB}$ = 235 Hz, H_5), 3.24 (m, H_{6a}), 2.97 (dd, J = 2.5, 11.1 Hz, 1H, H_{13}), 2.86 (br s, H_{10a}), 2.83 (d, J = 11.1 Hz, 1H, H_{13}), 2.72 (d, 2.5 Hz, H_{11}), 2.13–2.02 (m, 1H), 2.00–1.93 (m, 2H), 1.60–1.54 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 146.3, 145.7, 134.9, 130.1, 129.3, 125.1, 107.3, 106.5, 100.5, 62.1, 61.0, 54.4, 49.6, 46.0, 27.6, 20.4 ppm; IR (film) 935, 1040, 1232, 1482, 1505, 2925 cm^{-1}; MS (EI) m/z (255.1274 (255.1259 calcd for $C_{16}H_{17}NO_2$, M, 28%), 200 (26%), 175 (87%), 148 (100%).

Dehydration of (–)-**25** (111 mg, 0.41 mmol) with $SOCl_2$ (0.5 mL) and chloroform (6 mL) gave a 3:1 mixture of (–)-**27** and (–)-**28** (102 mg) from which a pure sample of crystalline (–)-**27** was isolated by crystallization: $[\alpha]^{25}_{577}$ = –96.6°, $[\alpha]^{25}_{546}$ = –131.4°, $[\alpha]^{25}_{435}$ = –262.5°, $[\alpha]^{25}_{405}$ = –326.5° (c = 0.21, $CHCl_3$).

(±)-[6a*S-(6α,6aβ,9β,11α)]-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-9-ol (*rac*-29) and (±)-[6a*S**-(6a,6aβ,9α,11α)]-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-9-ol (*rac*-30).** According to the general method of Cook,[24] a mixture of SeO_2 (63 mg, 0.57 mmol), ***rac*-27** (57 mg, 0.22 mmol) and dry dioxane was heated at 85 °C for 6 h. The resulting dark mixture was treated with 2 mL of saturated aqueous $KHCO_3$ solution. The mixture was then extracted with CH_2Cl_2 (5 × 20 mL) and the combined organic layer was dried (K_2CO_3) and concentrated to give a yellow oil (79 mg). Flash chromatography (1:10:500 aqueous ammonia–MeOH–$CHCl_3$) gave ***rac*-29** (30 mg, 50%) as a chromatographically homogeneous oil, which solidified upon standing.

A pure specimen of ***rac*-29** was prepared by recrystallization from 3:1 chloroform–hexanes: mp 220–222 °C dec; ^{1}H NMR (500

MHz, C_6D_6) δ 6.34 (s, H_{12}), 6.18 (s, H_4), 5.35 (br t, J = 2.5 Hz, H_{10}), 5.30 (AB q, J = 16.7 Hz, $\Delta\nu_{AB}$ = 11.7 Hz, H_2), 4.07 (ddd, J = 3.0, 5.7, 11.9 Hz, H_9), 3.77 (AB q, J = 16.7 Hz, $\Delta\nu_{AB}$ = 297 Hz, H_5), 2.96 (dd, J = 1.8, 10.9 Hz, H_{6a}), 2.70 (d, J = 2.4 Hz, H_{11}), 2.66 (dd, J = 2.4, 11.0 Hz, 1H, H_{13}), 2.58 (d, J = 11.0 Hz, 1H, H_{13}), 1.98–1.91 (m, 2H), 1.30–1.10 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.6, 146.6, 145.8, 131.9, 124.4, 117.9, 107.4, 106.6, 100.6, 67.7, 63.5, 60.8, 54.8, 45.4, 32.9, 30.2 ppm: IR (KBr pellet) 1027, 1037, 1239, 1490, 2890, 3128 cm^{-1}; MS (CI) m/z 272.1190 (272.1208 calcd for $C_{16}H_{18}NO_3$, MH), 254.1170 (MH – H_2O).

Further elution gave 15 mg of ***rac*-30** (0.06 mmol, 25%) as a yellow solid. A pure sample of ***rac*-30** was obtained by recrystallization from chloroform: mp 219–221 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.56 (s, H_{12}), 6.48 (s, H_4), 5.87 (AB q, J = 1.4 Hz, $\Delta\nu_{AB}$ = 14.2 Hz, H_2), 5.60 (br s, H_{10}), 4.18 (broad s, half-height width = 11 Hz, H_9), 4.09 (AB q, J = 16.7 Hz, $\Delta\nu_{AB}$ = 266 Hz, H_5), 3.25 (d, J = 2.2 Hz, H_{11}), 3.07–2.98 (m, H_{13}, H_{6a}), 1.93–1.89 (m, 1H), 1.77–1.68 (m, 2H), 1.45–1.41 (m, 1H), 1.77–1.68 (m, 2H), 1.45–1.41 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.5, 146.6, 145.9, 132.3, 124.5, 116.6, 107.2, 106.7, 100.7, 64.0, 63.7, 61.0, 55.6, 45.6, 30.9, 23.6 ppm; IR (KBr) 1027, 1041, 1237, 1490, 2945, 3170 cm^{-1}; MS (CI) m/z 272.1281 (272.1287 calcd for $C_{16}H_{18}NO_3$, MH), 254.1172 (MH – H_2O); MS (EI) m/z 271 (23%), 254 (7%), 149 (51%).

(±)-[6a*S-(6α,6aβ,10aβ,11α)]-5,6a,7,8,10a,11-hexahydro-6,-11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-10a-ol (*rac*-31).** In a similar manner, ***rac*-28** (5 mg, 20 μmol) was oxidized to give the tertiary allylic alcohol ***rac*-31** (3 mg, 55%) as a colorless solid: mp 208–210 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, H_{12}), 6.55 (s, H_4), 6.15 (ddd, J = 1.3, 6.0, 10.2 Hz, H_{10}), 5.93 (s, H_2), 5.79 (dt, J = 10.2, 1.3 Hz, H_9), 4.04 (AB, q, J = 16.5 Hz, $\Delta\nu_{AB}$ = 129 Hz, H_5), 3.07 (dd, J = 2.4, 12.6 Hz, 1H, H_{13}), 2.82 (d, J = 12.6 Hz, 1H, H_{13}), 2.82 (s, OH), 2.60 (d, J = 2.4 Hz, H_{11}), 2.13 (app, dq, J = 12.2, 2.5 Hz, H_{6a}), 2.09–2.06 (m, 1H), 1.97–1.85 (m, 2H), 1.70–1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 147.2, 145.8, 132.2, 130.7, 129.7, 126.6, 109.8, 107.0, 100.8, 82.8, 68.9, 62.1, 55.0, 49.8, 25.2, 20.3 ppm; IR (film) 733, 931, 1058, 1235, 1484, 2925, 3364 cm^{-1}; MS (CI) m/z 272.1271 (272.1287 calcd for $C_{16}H_{18}NO_3$, MH), 271.1200 (271.1208 calcd for $C_{16}H_{17}NO_3$, M), 254.1171 (MH – H_2O).

Preparative Scale Allylic Oxidation of the Mixture of Alkenes *rac*-27 and *rac*-28. A 3:1 mixture of alkenes ***rac*-27** and ***rac*-28** [597 mg, containing a trace amount of ***rac*-26**, derived directly from dehydration of ***rac*-25** (610 mg, 2.23 mmol)] was oxidized with SeO_2 (730 mg initial charge, 330 mg added after 1.5 h) in dioxane at 85 °C for 3 h. The resulting mixture was concentrated, the residue was basified with 20 mL of saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with $CHCl_3$ (3 × 40 mL). The combined organic layers were dried (K_2CO_3) and concentrated to give 639 mg of an oil, which was purified by chromatography to give ***rac*-29** (344 mg, 57%), ***rac*-30** (32 mg, 5%), and ***rac*-31** (31 mg, 5%).

Preparation of (±)-[6a*S-(6α,6aβ,11α)]-5,6a,7,8,9,11-hexahydro-11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-9-one (*rac*-32).** According to the general method of Swern,[12] ***rac*-29** (41 mg, 0.15 mmol) in 0.45 mL of Me_2SO was added dropwise to the cooled solution derived from the reaction of Me_2SO (28 mg, 0.33 mmol) and oxalyl chloride (21 mg, 0.17 mmol) in CH_2Cl_2 (1.3 mL) at –78 °C. The resulting solution was maintained at –78 °C for 15 min and 0.9 mL of Et_3N was added, and then the resulting solution was allowed to warm to 23 °C before water (2.0 mL) was introduced. This mixture was extracted ($CHCl_3$, 3 × 20 mL) and combined organic layers were dried (Na_2SO_4) and concentrated to give 38 mg (93%) of ***rac*-32** as a solid, which was homogeneous by TLC analysis: mp 170–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, H_{12}), 6.51 (s, H_4), 5.91 (AB q, J = 1.4 Hz, $\Delta\nu_{AB}$ = 13.8 Hz, H_2), 5.90 (br s, H_{10}), 4.14 (AB, q, J = 16.9 Hz, $\Delta\nu_{AB}$ = 261 Hz, H_5), 3.57 (m, H_{6a}), 3.45 (d, J = 2.0 Hz, H_{11}), 3.21 (dd, J = 2.0, 11.5 Hz, 1H, H_{13}), 3.16 (dd, J = 1.7, 11.5 Hz, 1H, H_{13}), 2.53–2.51 (m, 1H), 2.37–2.30 (m, 2H), 1.88–1.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 198.6, 176.1, 147.3, 146.2, 130.0, 124.3, 117.2, 107.5, 106.7, 100.8, 64.5, 60.6, 54.7, 46.0, 37.0, 30.5 ppm; IR (film) 754, 1038, 1236, 1484, 1660, 1673, 2881, 2949 cm^{-1}; MS (EI) m/z 269.1032 (269.1052 calcd for $C_{16}H_{15}NO_3$, M, 100%), 241 (9%), 212 (20%), 151 (52%).

Preparation of (±)-[6a*S-(6α,6aβ,11α)]-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-9-one (*rac*-32) by MnO_2 Oxidation of the Mixture of Allylic Alcohols *rac*-29 and *rac*-30.** A mixture of the allylic alcohols ***rac*-29** and ***rac*-30** (121 mg, 0.45 mmol) was oxidized with MnO_2 (activated, Aldrich, 1.13 g) in $CHCl_3$ (5 mL) at 23 °C. After 2 h, the filtered solution was concentrated to give 110 mg of enone ***rac*-32** (0.41 mmol, 91%), which was sufficiently pure for use in the next step.

Preparation of (–)-[6a*S*-(6α,6aβ,11α)]-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-9-ol ((–)-32) by Sequential Oxidation of the Mixture of Alkenes (–)-27 and (–)-28 with SeO_2 and MnO_2. A 3:1 mixture of (–)-**27** and (–)-**28**, derived from 80 mg (0.29 mmol) of (–)-**25**, was oxidized as described above with SeO_2 (205 mg), Celite (150 mg), and dioxane (5 mL) at 85 °C for 4 h. The reaction mixture was filtered through Celite and the eluent was concentrated. The residue was oxidized with MnO_2 (350 mg) in chloroform (10 mL) at room temperature for 10 h. Filtration of the crude product through Celite and purification of the concentrated eluent by flash column chromatography (aqueous ammonia–methanol–chloroform 1:10:100) afforded 60 mg (0.22 mmol, 76% overall from (–)-**25**) of (–)-**32**: $[\alpha]^{25}_D$ = –133° (*c* = 1.6, MeOH).

(±)- and [6a*S*-(6α,6aβ,8β,11α)]-8-hydroxy-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]-benzazepin-9-one (*rac*-34 and (–)-34). According to the method of Emde,[28] neat Me_3SiOTf (0.75 mL, 7.9 mmol) was added dropwise at *ca.* –60 °C (external bath temperature) to a solution containing the racemic enone ***rac*-32** (132 mg, 0.49 mmol), Et_3N (2.2 mL, 16 mmol), and Et_2O (22 mL). After 5 min, the reaction mixture was put in an ice bath before being quenched with cold saturated aqueous $NaHCO_3$ (30 mL). Extraction (Et_2O, 3 × 30 mL) and drying (Na_2SO_4) was followed by concentration to give 151 mg of a yellow solid, which was homogeneous by ^{1}H NMR analysis. This crude dienoxysilane ***rac*-33** was used without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.53 (s, H_{12}), 6.45 (s, H_4), 5.89 (AB q, J_{AB} = 1.4 Hz, $\Delta\nu_{AB}$ = 8.2 Hz, H_2), 5.51 (t, J = 2.0 Hz, H_{10}), 4.74 (ddd, J = 6.6, 2.3, 2.0 Hz, H_8, only six lines visible), 4.05 (AB q, J_{AB} = 16.8 Hz, $\Delta\nu_{AB}$ = 286 Hz, H_5), 3.56 (dd, J = 7.6, 16.8 Hz, H_{6a}), 3.34 (dd, J = 2.6, 11.0 Hz, 1H, H_{13}), 3.31 (d, J = 2.1 Hz, H_{11}), 3.10 (dd, J = 1.1, 11.0 Hz, 1H, H_{13}), 2.32 (app quintet, J = 7.6 Hz, $H_{7\beta}$), 2.16 (dt, J = 17.4, 2.3 Hz, $H_{7\alpha}$), 0.16 (s, $SiMe_3$).

Following the general procedure of McCormick,[29] a solution of this sample of ***rac*-33** (151 mg) and *tert*-butyl alcohol (4.5 mL) was added in one portion at –5 °C to a solution of water (0.1 mL), pyridine (0.1 mL), OsO_4 (*ca.* 5 mg), *N*-methylmorpholine *N*-oxide monohydrate (121 mg, 0.90 mmol), and *tert*-butyl alcohol (1.5 mL). The reaction mixture was allowed to warm to 23 °C and was maintained at this temperature for 5 h. Sodium hydrosulfite (230 mg, 1.30 mmol) and Florisil (340 mg) were then added sequentially. The resulting mixture was filtered, the filtrate was concentrated, and the residue was purified by flash column chromatography (1:10:300 aqueous ammonia–MeOH–$CHCl_3$) to give 17 mg of recovered ***rac*-32** and 114 mg (82%) of ***rac*-34** as a chromatographically homogeneous oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.57 (s, H_{12}), 6.49 (s, H_4), 5.91 (AB q, J_{AB} = 1.4 Hz, $\Delta\nu_{AB}$ = 13.0 Hz, H_2), 5.91 (br s, H_{10}), 4.14 (AB q, J_{AB} = 16.9 Hz, $\Delta\nu_{AB}$ = 241 Hz, H_5), 4.10 (br s, H_8), 3.92–3.87 (m, 1H), 3.46 (d, J = 0.7 Hz, 1H, H_{11}), 3.18 (br s, 2H, H_{13}), 2.56 (ddd, J = 13.8, 4.8, 2.1 Hz, H_{6a}), 1.94 (ddd, J = 13.3, 11.9, 4.0 Hz, $H_{7\alpha}$), 1.68 (br s, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) 197.2, 177.7, 147.6, 146.3, 129.9, 124.6, 115.0, 107.6, 107.0, 101.0, 70.3, 60.6, 59.7, 54.6, 46.4, 36.7 ppm; IR (film) 1038, 1237, 1482, 1654, 3425 cm^{-1}; MS (EI) m/z 285.0985 (285.0977 calcd for $C_{16}H_{15}NO_4$, M, 100%), 212 (23%), 162 (17%).

The levorotatory α-hydroxy ketone (–)-**34** was prepared in an identical fashion from (–)-**32** (20 mg, 74 μmol) to give 17 mg (81%): $[\alpha]^{25}_{546}$ = –47.7°, $[\alpha]^{25}_{435}$ = –91.2° (*c* = 0.10, MeOH).

(±)- and [6a*S*-(6α,6aβ,8β,9α,11α)]-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepine-8,9-diol ((±)- and (–)-pancracine, *rac*-1 and (–)-1). According to the method of Evans,[30] a solution of ***rac*-34** (29 mg, 0.10 mmol) and CH_3CN (0.8 mL) was added dropwise to the reagent derived from $NaBH_4$ (74 mg, 2 mmol), CH_3CN (0.8 mL), and AcOH (0.8 mL) at –40 °C, and the resulting solution was maintained at this temperature for 6 h. Another portion of the acetoxy borohydride reagent derived from $NaBH_4$ (74 mg, 2 mmol), CH_3CN (0.8 mL),

and AcOH (0.8 mL) was added at −35 °C. After an additional 13 h at −30 to −40 °C, the reaction mixture was treated with aqueous NH_4OH (1 mL). When gas evolution subsided, aqueous NaOH (10 N, 0.5 mL) was added, and the resulting solution was put directly on an alumina column (Brockmann activity II) and eluted (1:10:100 aqueous ammonia–MeOH–$CHCl_3$) to afford 19 mg (65%) of (±)-pancracine (***rac*-1**) as a colorless oil that slowly solidified: ^1H NMR (500 MHz, DMSO-d_6) δ 6.78 (s, H_{12}), 6.69 (s, H_4), 6.00 (AB q, J = 1.0 Hz, $\Delta\nu_{AB}$ = 16.1 Hz, H_2), 5.47 (s, H_{10}), 4.84 (br s, OH), 4.80 (br s, OH), 4.24 (d, J = 16.7 Hz, H_5), 3.84 (s, H_9), 3.76 (s, H_8), 3.74 (d, J = 16.7 Hz, H_5), 3.35 (s, H_{13}), 3.31 (ddd, J = 11.5, 4.5, 1.8 Hz, H_{6a}), 2.96 (br s, H_{13}), 1.95 (ddd, J = 4.5, 3.8, 1.0 Hz, $H_{7\beta}$), 1.46 (ddd, J = 12.0, 11.5, 2.3 Hz, $H_{7\alpha}$); ^{13}C NMR (125 MHz, DMSO-d_6) 152.6, 146.0, 145.3, 133.0, 125.4, 115.9, 107.3, 106.8, 100.4, 71.0, 68.9, 60.8, 58.0, 55.2, 44.9, 31.3 ppm. Synthetic (±)-pancracine was spectroscopically (500-MHz ^1H NMR and 125-MHz ^{13}C NMR in DMSO-d_6) and chromatographically (silica gel TLC, triple elution with 1:10:100 aqueous NH_4OH–methanol–$CHCl_3$, single elution with 1:30:100 aqueous NH_4OH–methanol–$CHCl_3$ and with 1:20:100 aqueous NH_4OH–methanol–CH_2Cl_2; on alumina TLC with 1:10:100 aqueous NH_4OH–methanol–$CHCl_3$) indistinguishable from an authentic sample.

Enantiomerically pure (−)-pancracine ((−)-**1**) was prepared in an identical fashion from (−)-**34** (25 mg, 84.2 μmol) to give a solid (17 mg, 62%): mp 270 °C dec, (lit.[3] mp 272–273 °C); $[\alpha]^{25}_D$ = −72.6°, $[\alpha]^{25}_{577}$ = −103.9°, $[\alpha]^{25}_{546}$ = −110.5°, $[\alpha]^{25}_{435}$ = −226.2°, $[\alpha]^{25}_{405}$ = −283.3° (*c* = 0.4, CH_3OH). Optical rotations we measured on an authentic sample[31] are as follows: $[\alpha]^{25}_{577}$ = −108.4°, $[\alpha]^{25}_{546}$ = −115.0°, $[\alpha]^{25}_{435}$ = −227.5°, $[\alpha]^{25}_{405}$ = −281.1° (*c* = 0.3, MeOH); reported optical rotation:[3] $[\alpha]^{25}_D$ = −74.0° (*c* = 0.02, MeOH).

(±)-[6a*S-(6α,6aβ,8β,11α)]-8-acetoxy-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-9-one (*rac*-35).** A solution of ***rac*-32** (162 mg, 0.60 mmol) and benzene (160 mL) was heated at reflux in a Dean–Stark apparatus filled with 4-Å molecular sieves. To this solution was added portionwise $Mn(OAc)_3 \cdot 2H_2O$ (200 mg added every 2 h; total 2.2 g, 8.4 mmol). The reaction mixture was then concentrated and the residue was partitioned between $CHCl_3$ (100 mL) and saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with $CHCl_3$ (100 mL × 3) and the combined organic phase was washed with H_2O (10 mL), dried (K_2CO_3) and concentrated to give 169 mg of crude ***rac*-35** as a dark oil.

A chromatographically homogeneous sample of ***rac*-35** was prepared by preparative TLC (silica gel 1:10:100 aqueous ammonia–CH_3OH–$CHCl_3$) as a slightly yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, H_{12}), 5.96 (d, J = 0.9 Hz, H_{10}), 5.88 (d, J = 11.3 Hz, H_2), 5.25 (br s, H_8), 4.13 (AB q, J = 16.9 Hz, $\Delta\nu_{AB}$ = 257 Hz, H_5), 3.74 (dd, J = 11.6, 4.1 Hz, H_{6a}), 3.47 (s, H_{11}), 3.17 (br s, H_{13}), 2.53 (ddd, J = 13.8, 4.8, 2.2 Hz, $H_{7\beta}$), 2.05 (s, CH_3), 1.99 (ddd, J = 13.6, 12.3, 3.9 Hz, $H_{7\alpha}$); ^{13}C NMR (125 MHz, $CDCl_3$) 192.1, 177.7, 169.5, 147.5, 146.3, 129.7, 124.3, 116.0, 107.5, 106.8, 100.9, 70.8, 60.6, 59.6, 54.4, 49.4, 35.5, 20.8 ppm; MS (CI) *m*/*z* 328.1156 (328.1185 calcd for $C_{18}H_{18}NO_5$, MH), 270; IR (film) 732, 1038, 1234, 1373, 1483, 1506, 1679, 1745, 2973 cm^{-1}.

(±)-[6a*S-(6α,6aβ,8α,9β,11α)]-9-acetoxy-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepin-8-ol (*rac*-36).** To a solution of ***rac*-35** (9 mg, 28 μmol) and acetone (1.0 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.10 mL, 102 mg, 0.67 mmol) at 23 °C. After 5 min, 2 N HCl (0.35 mL) was added to the reaction mixture and the volatile solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ (5 mL × 2), and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), and concentrated. This crude material was used without purification; partial ^1H NMR (300 MHz, $CDCl_3$) δ 6.57 (s, H_{12}), 6.51 (s, H_4), 6.02 (d, J = 2.0 Hz, H_{10}), 5.93 (AB q, J_{AB} = 1.2 Hz, $\Delta\nu_{AB}$ = 5.9 Hz, H_2), 5.28 (dd, J = 13.0, 4.7 Hz, H_8), 4.14 (AB q, J_{AB} = 17.1 Hz, $\Delta\nu_{AB}$ = 150 Hz, H_5), 3.72–3.78 (m, H_{6a}), 3.45 (br s, H_{13}), 2.17 (s, $COCH_3$).

A solution of this crude sample of the α-acetoxy enone, $NaBH_4$ (10 mg), $CeCl_3 \cdot 7H_2O$ (11 mg) and 2 mL of 1:1 methanol–H_2O was maintained at room temperature for 10 min. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (2.0 mL) and extracted with $CHCl_3$ (10 mL × 2). The combined organic phases were washed with saturated aqueous $NaHCO_3$ solution (3 mL) and dried (Na_2SO_4). After filtration the solution was concentrated and the residue purified by flash column chromatography (aqueous ammonia–methanol–chloroform 1:10:100) to give 7 mg (75%) of ***rac*-36**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, H_{12}), 6.47 (s, H_4), 5.90 (AB q, J_{AB} = 1.3 Hz, $\Delta\nu_{AB}$ = 5.8 Hz, H_2), 5.64 (dd, J = 2.5, 3.8 Hz, H_{10}), 4.78 (ddd, J = 12.3, 6.6, 4.1 Hz, H_8), 4.31 (ddd, J_{AB} = 6.4, 4.2, 2.3 Hz, H_9, only seven lines visible), 4.12 (AB q, J_{AB} = 16.6 Hz, $\Delta\nu_{AB}$ = 149.1 Hz, H_5), 3.52 (ddd, J = 9.3, 4.3, 2.0 Hz, H_{6a}), 3.33 (br s, H_{11}), 3.11 (br s, H_{13}), 2.45 (ddd, J = 11.3, 7.6, 4.1 Hz, $H_{7\beta}$), 2.11 (s, $COCH_3$), 1.66 (app q, J = 11.9 Hz, $H_{7\alpha}$); ^{13}C NMR (125 MHz, $CDCl_3$) 171.8, 154.4, 146.8, 145.9, 131.4, 124.2, 115.5, 107.6, 106.7, 77.7, 72.1, 62.0, 60.9, 55.4, 45.1, 35.3, 21.2 ppm; MS (CI) *m*/*z* 330.1315 (330.1341 calcd for $C_{18}H_{19}NO_5$, MH), 312.1240 (312.1236 calcd for $C_{18}H_{17}NO_4$, MH − H_2O); IR (film) 1037, 1237, 1483, 1637, 1733, 2925, 3364 cm^{-1}.

(±)-[6a*S-(6α,6aβ,8α,9β,11a)]-5,6a,7,8,9,11-hexahydro-6,11-methano-6*H*-1,3-benzodioxolo[5,6-*c*][1]benzazepine-8,9-diol (*rac*-37, (±)-desmethyl-α-isocrinamine).** To a solution of ***rac*-36** (5 mg, 15 μmol) and methanol (1 mL) was added a saturated solution of K_2CO_3 in methanol (0.3 mL) in one portion. After 1 min the solvent was removed under reduced pressure, the resulting residue was triturated with methanol–$CHCl_3$ (1:10), and the extract was concentrated. This residue was purified by preparative TLC (silica gel, 1:10:100 aqueous ammonia–methanol–chloroform) to afford 3 mg (69%) of ***rac*-37** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 6.54 (s, H_{12}), 6.46 (s, H_4), 5.88 (AB q, J_{AB} = 1.3 Hz, $\Delta\nu_{AB}$ = 10.5 Hz, H_2), 5.54 (app t, J = 2.9 Hz, H_{10}), 4.16 (dt, J = 7.1, 3.1, Hz, H_9), 4.03 (AB q, J_{AB} = 16.6 Hz, $\Delta\nu_{AB}$ = 249.2 Hz, H_5), 3.72 (ddd, J = 3.5, 7.3, 11.9 Hz, H_8), 3.39–3.41 (m, H_{6a}), 3.23 (br s, H_{11}), 3.02 (br s, H_{13}), 2.31 (dt, J = 11.3, 4.0 Hz, $H_{7\beta}$), 2.30 (br s, OH), 1.66 (app q, J = 11.8 Hz, $H_{7\alpha}$); ^{13}C NMR (125 MHz, $CDCl_3$) 154.0, 146.7, 145.9, 131.5, 124.3, 116.2, 107.5, 106.7, 100.7, 75.2, 74.6, 63.0, 61.0, 55.5, 45.1, 37.8 ppm; IR (film) 756, 1031, 1238, 1338, 1488, 1506, 2935, 3350 cm^{-1}; MS (CI) *m*/*z* 288 (MH), 270.1121 (270.1108 calcd for $C_{16}H_{16}NO_3$, MH − H_2O).

Trituration with hexane provided X-ray quality crystals of the dihydrate.[34]

(1*S*,2*S*)-*N*-[(1*S*)-methylbenzyl]-*N*-(cyanomethyl)-1-[(1,3-benzodioxol-5-yl)ethynyl]-2-aminocyclopentanol ((+)-39). According to the method of Imamoto,[15] $CeCl_3 \cdot 7H_2O$ (45.2 g, 0.12 mol) was dried at 140 °C (0.3 mmHg) for 2 h and the resulting powder was allowed to cool to 23 °C. THF (80 mL) was added to the powder and the resulting slurry was stirred for 12 h at 23 °C. A solution of the lithium salt of alkyne **14** [prepared at 0 °C from 11.4 g (78.0 mmol) of **14** and *n*-BuLi (8.0 mL, 8.2 M in hexanes, 65 mmol)] in THF was introduced to the cerium chloride slurry via a cannula at −78 °C. After 30 min at −78 °C, a solution of ketone (+)-**38** (9.38 g, 38.8 mmol)[35] and THF (70 mL) was added dropwise while maintaining the temperature below −70 °C. After 2 h at −78 °C, the reaction mixture was allowed to warm to 0 °C and then was quenched with saturated aqueous KH_2PO_4 (100 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (30 mL) and dried ($MgSO_4$). Concentration gave 11.8 g (78%) of (+)-**39** as slightly yellow crystals. The mother liquor was concentrated and the residue purified by column chromatography (1:4 ethyl acetate–hexanes) to provide additional (+)-**39** (2.3 g, 15%) as a solid.

An analytical sample of (+)-**39** was prepared by recrystallization from diethyl ether: mp 118–120 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42–7.26 (m, Ph), 6.96 (dd, J = 1.5, 8.1 Hz, 1H), 6.88 (d, J = 1.5 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 5.94 (s, OCH_2O), 4.40 (q, J = 7.0 Hz, $CHCH_3$), 3.72 (AB q, $\Delta\nu_{AB}$ = 304 Hz, J = 18.0 Hz, CH_2CN), 3.63 (dd, J = 11.2, 6.8 Hz, CHN), 3.58 (br s, OH), 2.29 (app t, J = 7.7 Hz, CH_2), 1.74–2.18 (m, 2 CH_2), 1.67 (d, J = 7.0 Hz, $CHCH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) 147.8, 147.1, 141.1, 128.6, 127.8, 126.2, 117.8, 115.6, 111.5, 108.3, 101.4, 90.8, 84.1, 72.3, 68.9, 58.3, 40.6, 35.7, 28.5, 20.3, 14.0 ppm (one carbon not resolved); MS (CI) *m*/*z* 389.1830 (389.1865 calcd for $C_{24}H_{25}N_2O_3$, MH), 362.1735 (MH − HCN); IR (KBr) 1218, 1483, 2223, 2358, 3477 cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.08; H, 6.18; N, 7.17; $[\alpha]^{25}_D$ = 67.7°, $[\alpha]^{25}_{577}$ = 69.1°, $[\alpha]^{25}_{546}$ = 79.7°, $[\alpha]^{25}_{435}$ = 155.0°, $[\alpha]^{25}_{405}$ = 196.6° (*c* = 1.02, $CHCl_3$).

(1*S*,2*S*)-*N*-[(1*S*)-methylbenzyl]-1-[2-(1,3-benzodioxol-5-yl)ethynyl]-2-aminocyclopentanol ((-)-40). A solution of (+)-**39** (5.0 g, 12.9 mmol) in 100 mL of 95% EtOH was stirred with $AgNO_3$ (2.41 g, 14.2 mmol) at 23 °C for 2 h and then the resulting mixture was placed in sonication bath for 48 h. The mixture was then filtered through Celite and the filtrate concentrated to a thick paste. This residue was extracted with $CHCl_3$ (3 × 200 mL) and the combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL). The dried (K_2CO_3) organic portion was concentrated and chromatographed (hexanes–EtOAc 4:1) to give alcohol (-)-**40** (2.35 g, 52%) and 2.24 g (48%) of the corresponding oxazolidine. The oxazolidine was further sonicated in aqueous EtOH (50%, 160 mL) containing 0.40 mL of nitric acid for 72 h to give an additional 1.93 g of (-)-**40**. The total yield of (-)-**40** was 4.49 g (95%).

An analytical sample of (-)-**40** was prepared by column chromatography (1:3 ethyl acetate–hexanes) as a slightly yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.25 (m, Ph), 6.97 (dd, J = 1.5, 8.0 Hz, 1H), 6.89 (d, J = 1.4 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.98 (s, OCH_2O), 4.24 (q, J = 6.8 Hz, C*H*CH_3), 3.09 (app t, J = 8.6 Hz, CHN), 2.23–2.14 (m, 1 H), 2.01–1.74 (m, 3H), 1.58–1.55 (m, 1H), 1.39 (d, J = 6.8 Hz, CHC*H*$_3$), 1.36–1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 147.5, 147.2, 145.2, 128.4, 126.9, 126.1, 125.9, 116.4, 111.4, 108.3, 101.1, 92.0, 82.2, 71.2, 65.0, 56.3, 40.2, 31.4, 24.6, 20.8 ppm; IR (film) 1039, 1489, 1505, 1616, 2219, 2967, 3325 cm^{-1}; MS (CI) m/z 350.1737 (350.1756 calcd for $C_{22}H_{25}NO_3$, MH), 332, 244, 181, 131. Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.52; H, 6.63; N, 4.01; $[\alpha]^{25}_D$ = -212.3°, $[\alpha]^{25}_{577}$ = -224.4°, $[\alpha]^{25}_{546}$ = -258.5° (c = 1.9, $CHCl_3$).

Preparation of (1*S*,2*S*)-*N*-[(1*S*)-Methylbenzyl]-1-[2-(1,3-benzodioxol-5-yl)ethenyl]-2-aminocyclopentanol ((-)-41) by $LiAlH_4$ Reduction of (-)-40. To a solution of propargyl alcohol (-)-**40** (1.90 g, 5.4 mmol) and dry diethyl ether (46 mL) was added a solution of $LiAlH_4$ (1.0 M in diethyl ether, 15 mL, 15 mmol) at 23 °C. After 9 h, the resulting solution was quenched with aqueous NaOH (30%, *ca.* 0.9 mL) at -78 °C. After the vigorous gas evolution subsided, aqueous HCl (12 N, 20 mL) was added to the resulting mixture. The aqueous layer was then extracted with $CHCl_3$ (3 × 70 mL) and the combined organic phases were washed with saturated aqueous $NaHCO_3$ (10 mL) and then dried (K_2CO_3). Concentration gave 1.78 g (89%) of (-)-**41** as a yellow oil that contained ~5% of the (*Z*)-alkene isomer as an impurity (by ^{1}H NMR analysis).

A chromatographically homogeneous sample of (-)-41 was obtained by column chromatography (1:4 ethyl acetate–hexanes) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13–7.36 (m, Ph), 6.95 (d, J = 1.4 Hz, 1H), 6.85 (dd, J = 1.5, 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 15.8 Hz, 1H), 5.97 (d, J = 15.6 Hz, 1H), 5.96 (ABq, J_{AB} = 1.2 Hz, $\Delta\nu_{AB}$ = 3.2 Hz, OCH_2O), 3.79 (q, J = 6.7 Hz, C*H*CH3), 3.40 (s, OH), 2.80 (app t, J = 8.3 Hz, CHN), 1.44–1.89 (m, 3 CH_2), 1.26 (d, J = 6.7 Hz, CHC*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 147.9, 146.6, 145.3, 134.8, 131.8, 128.4, 126.8, 126.4, 126.0, 120.7, 108.2, 105.5, 100.8, 78.6, 63.7, 56.3, 38.8, 31.7, 24.6, 20.9 ppm; IR (film) 931, 1040, 1251, 1491, 1504, 2961, 3347 cm^{-1}; MS m/z 352.1892 (352.1912 calcd for $C_{22}H_{26}NO_3$, MH), 351.1821 (351.1834 calcd for $C_{22}H_{25}NO_3$), 246, 105; $[\alpha]^{25}_D$ = -57.7°, $[\alpha]^{25}_{577}$ = -80.1°, $[\alpha]^{25}_{546}$ = -87.6° (c = 2.50, CH_3OH).

Preparation of (-)-41 from (-)-40 by Using Sodium Bis(2-methoxyethoxy)aluminum Hydride. To a solution of propargyl alcohol (-)-**40** (40 mg, 0.12 mmol) and dry diethyl ether (8 mL) was added dropwise sodium bis(2-methoxyethoxy)-aluminum hydride (3.4 M in toluene, 0.56 mL, 1.9 mmol) at 23 °C. After 30 min, the resulting solution was poured into 2 N HCl solution (2 mL). The aqueous layer was extracted with $CHCl_3$ (5 mL × 2) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (2 mL) and then dried (K_2CO_3). Concentration gave 41 mg (100%) of (-)-41 as a yellow oil that was homogeneous by TLC analysis.

(3a*S*,6a*S*)-*N*-[(1*S*)-Methylbenzyl]-6a-[(*E*)-2-(1,3-benzodioxol-5-yl)ethenyl]-1-oxa-3-azabicyclo[3.3.0]octane ((-)-42). A mixture of (-)-41 (1.57 g, 4.47 mmol), formaldehyde (1.0 mL, 37%, 12 mmol), Na_2SO_4 (1.5 g, 11 mmol), camphorsulfonic acid (250 mg, 1.1 mmol) and CH_2Cl_2 (70 mL) was stirred at 23 °C for 2 h. The mixture was then filtered, the filtrate was washed with saturated aqueous $NaHCO_3$ (10 mL), and the aqueous solution was extracted with CH_2Cl_2 (10 mL × 2). The combined organic layers were dried (K_2CO_3) and concentrated. The resulting residue was purified by flash column chromatography (hexanes–EtOAc 4:1) to afford 1.22 g (75%) of (-)-**42** as a slightly yellow oil that was chromatographically homogeneous: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.24–7.33 (m, Ph), 6.93 (d, J = 1.5 Hz, 1H), 6.81 (dd, J = 1.5, 8.0 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.54 (d, J = 15.9 Hz, 1H), 6.10 (d, J = 16.0 Hz, 1H, vinyl), 5.96 (s, OCH_2O), 4.64 (AB q, $\Delta\nu_{AB}$ = 3.7 Hz, J_{AB} = 5.6 Hz, OCH_2N), 3.74 (q, J = 6.5 Hz, C*H*CH_3), 3.21 (dd, J = 4.1, 7.6 Hz, CHN), 1.35–2.40 (m, 6H, 3CH_2), 1.34 (d, J = 6.5 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) 147.9, 146.8, 144.9, 131.8, 131.5, 128.3, 127.5, 120.8, 108.2, 105.5, 100.9, 90.8, 83.4, 71.9, 61.2, 39.1, 32.7, 24.2, 22.9 ppm; IR (film) 703, 930, 1251, 1481, 1505, 2872, 2968 cm^{-1}; MS (CI) m/z 364.1893 (364.1913 calcd for $C_{23}H_{26}NO_3$, MH), 363.1841 (363.1834 calcd for $C_{23}H_{25}NO_3$, M), 334, 292; $[\alpha]^{25}_D$ = -169.4° (c = 1.15, CH_3OH).

(3*R*,3a*S*,7a*S*)-*N*-[(1*S*)-Methylbenzyl]-3-(1,3-benzodioxol-5-yl)-4-oxooctahydroindole ((+)-43). To a solution of (-)-**42** (166 mg, 0.46 mmol) in CH_2Cl_2 (10 mL), which had been filtered through basic alumina (Brockmann activity I), was added BF_3·OEt_2 (0.16 g, 1.1 mmol) at -10 °C. The cooling bath was changed to an ice bath (5 °C), and after 2 h at 5 °C, saturated aqueous $NaHCO_3$ solution (3 mL) was added. The aqueous layer was then extracted with $CHCl_3$ (2 × 5 mL) and the combined organic phase was dried (K_2CO_3). Concentration gave 157 mg (95%) of (+)-**43** as a yellow solid.

An analytically pure sample (+)-**43** was prepared by recrystallization from hexanes–chloroform (1:1) as slightly yellow needles: mp 117–118 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.23–7.37 (m, Ph), 6.74 (d, J = 1.0 Hz, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.66 (dd, J = 8.0, 1.5 Hz, 1H), 5.91 (s, OCH_2O), 3.82 (q, J = 6.6 Hz, C*H*CH_3), 3.59 (app q, J = 8.1 Hz, H_3), 3.44–3.48 (m, H_{7a}), 3.12 (app t, J = 8.7 Hz, 1H, H_2), 2.82 (app t, J = 7.7 Hz, H_{3a}), 2.54 (app, t, J = 8.9 Hz, 1H, H_2), 2.44–2.27 (m, H_4), 1.97–1.58 (m, H_6, H_7), 1.36 (d, J = 6.6 Hz, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) 211.2, 147.6, 145.9, 144.6, 136.6, 128.0, 127.2, 126.7, 120.4, 107.9, 107.6, 100.7, 63.1, 59.6, 58.7, 56.5, 43.8, 39.4, 26.3, 26.6, 12.8 ppm; IR (KBr) 927, 1034, 1248, 1492, 1702, 2934 cm^{-1}; MS (CI) 364.1891 (364.1913 calcd for $C_{23}H_{26}NO_3$, MH), 363.1826 (363.1834 calcd for $C_{23}H_{25}NO_3$, M), 348, 320, 293. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.00; H, 6.96; N, 3.90; $[\alpha]^{25}_D$ = 34.6°, $[\alpha]^{25}_{577}$ = 34.6°, $[\alpha]^{25}_{546}$ = 38.1°, $[\alpha]^{25}_{435}$ = 60.2°, $[\alpha]^{25}_{405}$ = 65.1° (c = 0.65, $CHCl_3$).

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Supplementary Material Available: Complete experimental details and characterization data for the preparation of ***rac*-20, 21, 22**, and (+)-**44** from (+)-**39**, and copies of ^{13}C NMR spectra for compounds **18, 25–32, 34–37**, and **42** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.