Assembly of 3a-Arylperhydroindoles by the Intramolecular Cycloaddition of 2-Azaallyl Anions with Alkenes. Total Syntheses of (±)-Crinine, (±)-6-Epicrinine, (−)-Amabiline, and (−)-Augustamine

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The 2-azaallyl anion route to pyrrolidines was used for the concise synthesis of alkaloids featuring the 3a-arylperhydroindole nucleus. The brevity and efficiency of the syntheses described are particularly notable. The key transformations involved the tin−lithium exchange of (2-azaallyl-)stannanes to 2-azaallyl anions, which participated in intramolecular [π4s + π2s] cycloadditions with styrenes to produce the requisite 3a-arylperhydroindoles. (±)-Crinine was synthesized in eight steps in 20% overall yield, with the key cycloaddition producing a single stereoisomer of the perhydroindole in 80% yield. (±)-6-Epicrinine was an intermediate in this synthesis. The key cycloaddition involved the use of a diene as the anionophile. The first asymmetric syntheses of (−)-amabiline and (−)-augustamine were accomplished in overall yields of 43% (in eight steps) and 42% (in nine steps), respectively, confirming or determining the absolute stereochemistry of the natural products. The key cycloadditions produced the perhydroindoles in 83% and 74% yields, respectively, with reasonable stereocontrol. The highly stereoselective cycloaddition leading to a *trans*-dialkoxyperhydroindole in 75% yield was consistent with stereochemical predictions. These studies contribute to a growing body of knowledge on the scope and stereochemistry of 2-azaallyl anion cycloadditions.

Introduction

The 3a-arylperhydroindole nucleus (e.g., **4** in Figure 1) is found in many alkaloids of the Amaryllidaceae family, exemplified by crinine (**1**), amabiline (**2**), augustamine (**3**), and pretazettine.[1] Such alkaloids continue to be of interest as synthetic targets due to their wide range of biological activities.[1] A potentially general strategy for the synthesis of 3a-arylperhydroindoles is shown in Figure 1. An intramolecular cycloaddition of a 2-azaallyl anion **5** onto an alkene may generate the key hydroindole **4**. We now report the details of the concise total syntheses of (±)-crinine (**1**), (−)-amabiline (**2**), and (−)-augustamine (**3**) which were accomplished using this strategy.[2] The syntheses of amabiline and augustamine are the first reported and serve to confirm the absolute configuration of these two alkaloids.

Reports from our laboratories have shown that pyrrolidines may be synthesized by inter- and intramolecular [π4s + π2s] cycloadditions of nonstabilized 2-azaallyl anions with electron-rich alkenes.[3] The anions are generated by tin−lithium exchange of (2-azaallyl)stannanes with *n*-butyllithium. As an extension of this work, we have begun to apply this method to the synthesis of various pyrrolidine-containing alkaloids, e.g., pretazettine[3e] and lepadiformine.[3e] To better understand the scope and stereoselectivity of these cycloadditions, we chose to explore the synthesis of the alkaloids **1**−**3**. Introduction of the starred carbon late in each synthesis would be

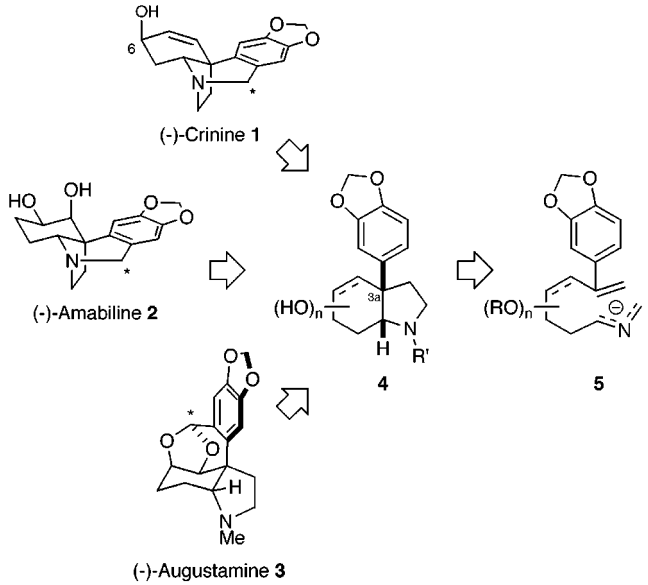

Figure 1. Retrosynthetic analysis of crinine, amabiline, and augustamine.

† Current address: Genetics Institute, 85 Bolton St., Cambridge, MA 02140.

(1) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30; pp 251−376.

(2) Portions of this work have appeared in communication form: (a) Pearson, W. H.; Lovering, F. E. *Tetrahedron Lett.* **1994**, *35*, 9173−9176. (b) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336−12337.

(3) (a) Pearson, W. H.; Szura, D. P.; Harter, W. G. *Tetrahedron Lett.* **1988**, *29*, 761−764. (b) Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329−1345. (c) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1992**, *57*, 6354−6357. (d) Pearson, W. H.; Stevens, E. P. *Tetrahedron Lett.* **1994**, *35*, 2641−2644. (e) Pearson, W. H.; Postich, M. J. *J. Org. Chem.* **1994**, *59*, 5662−5671. (f) Pearson, W. H.; Jacobs, V. A. *Tetrahedron Lett.* **1994**, *35*, 7001−7004. (g) Pearson, W. H.; Barta, N. S.; Kampf, J. W. *Tetrahedron Lett.* **1997**, *38*, 3369−3372. (h) Pearson, W. H.; Mi, Y. *Tetrahedron Lett.* **1997**, *38*, 5441−5444. (i) Pearson, W. H.; Clark, R. B. *Tetrahedron Lett.* **1997**, *38*, 7669−7672.

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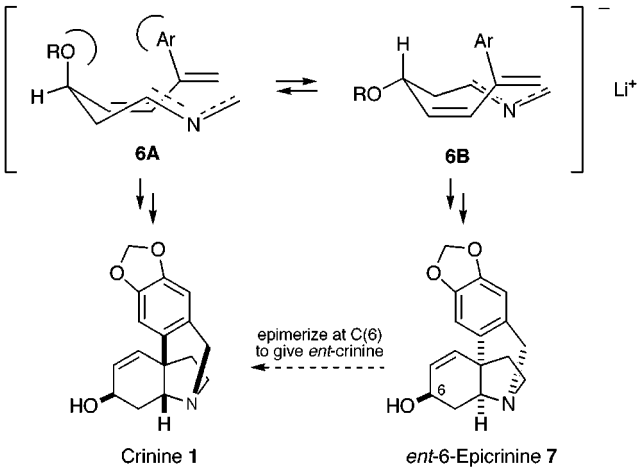


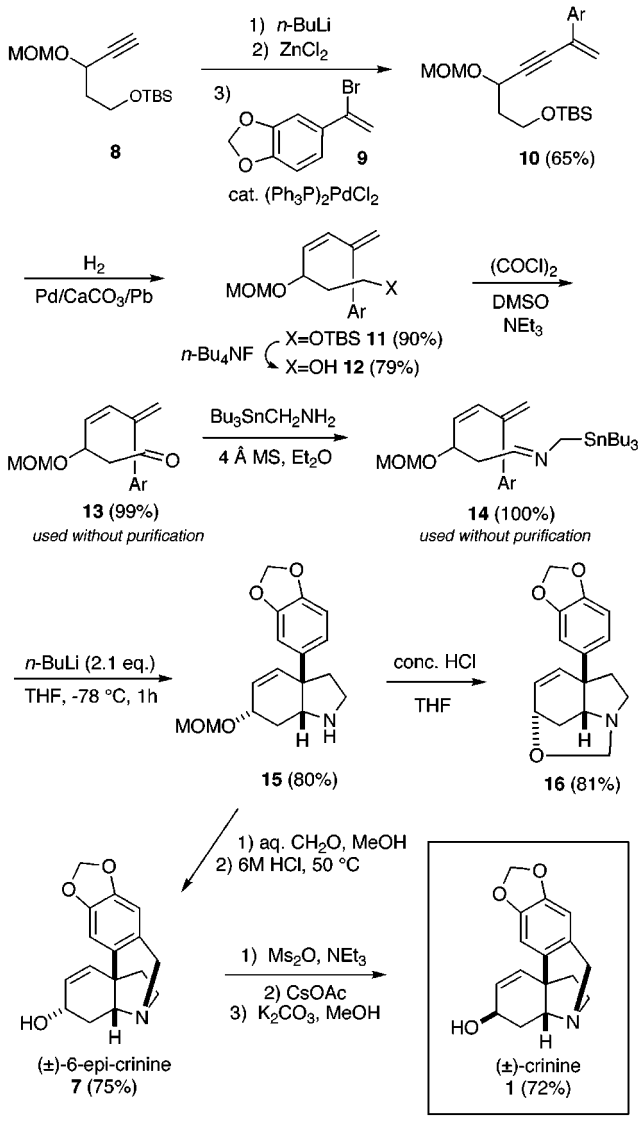
Figure 2. The 2-azaallyl anion cycloaddition required for crinine: diastereoselectivity?

performed by electrophilic aromatic substitution chemistry on a 3a-arylperhydroindole **4** that bears the requisite oxidation pattern in the left hand ring. Construction of **4** by an intramolecular 2-azaallyl anion cycloaddition would require **5**. In addition to extending the scope of the 2-azaallyl anion cycloaddition method, this investigation will provide more information on the diastereoselectivity of such cyclizations in the intramolecular mode, an issue that has not yet been well explored.[3e,g]

Synthesis of (±)-Crinine

Crinine **1** has been the target of synthetic effort in both racemic and optically active forms.[1,4,5] Retrosynthetically, the use of an intramolecular 2-azaallyl anion cycloaddition would require a 1,3-diene as the dienophile (**6** in Figure 2). The single stereocenter at the allylic alkoxy group[6] would be responsible for influencing the relative configuration of the three new stereocenters resulting from the cycloaddition. Examination of molecular models indicates that the *Z*-double bond of the diene exerts a strong influence on the reactive conformation of the cyclization precursor **6**. In conformation **6A**, required for the formation of crinine, a steric interaction between the allylic alkoxy group and the aromatic group is evident. A potentially lower energy conformation **6B** does not have this unfavorable interaction, but would lead ultimately to **7**, the 6-epimer of crinine, a known

Scheme 1. Total Synthesis of (±)-Crinine (1)



compound.[7] This analysis assumes that the cyclization is a concerted [π4s + π2s] cycloaddition and that the cis ring juncture rather than the trans will be formed. While we have obtained evidence that 2-azaallyl anion cycloadditions can be stepwise,[3b,d] most of our work is consistent with a concerted, stereospecific cycloaddition or perhaps a highly stereoselective stepwise process. The assumption of a cis ring juncture seemed sound based on our previous observations in similar cycloadditions leading to octahydro- or hexahydroindoles.[3b,e] Should a cis ring juncture result, we were confident that crinine could be made from either of the two possible diastereomeric cycloadducts, since inversion of the allylic alcohol of **7** should be possible using related chemistry published by Martin.[4f]

The starting material for our crinine synthesis was the known[3e] protected propargyl alcohol **8** (Scheme 1), prepared by the addition of lithium acetylide−TMEDA complex to 3-(*tert*-butyldimethylsilyl)oxypropanal followed by protection of the resultant alcohol (MOMCl, Hünig's base). Formation of the zinc acetylide of **8** followed by palladium-catalyzed coupling with the known

(4) (a) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670. (b) Whitlock, H. W., Jr.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600−3606. (c) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629−6637. (d) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745−9. (e) Martin, S. F.; Campbell, C. L. *Tetrahedron Lett.* **1987**, *28*, 503−506. (f) Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184−3190.

(5) For references to synthetic efforts on alkaloids related to crinine, see ref 4f above.

(6) The analysis given neglects the possible stereoelectronic contributions resulting from the interaction of the alkene with the allylic ether. While the effect of allylic ethers on the stereoselectivity of addition of *electrophiles* to alkenes has been studied extensively, the effect of such a substituent on the stereoselectivity of the addition of *nucleophiles* to alkenes has received much less attention. Studies on the diastereoselectivity of 2-azaallyl anions with simpler allylic ethers are planned in our laboratories. For leading references on the 1,2-asymmetric induction in the addition of electrophiles to alkenes, see: (a) Evans, D. A.; Kaldor, S. W. *J. Org. Chem.* **1990**, *55*, 1698−1700. For leading references on the 1,2-asymmetric induction in the addition of nucleophiles to alkenes, see: (b) Arai, M.; Kawasuji, T.; Nakamura, E. *J. Org. Chem.* **1993**, *58*, 5121−5129.

(7) Synthesis of 6-epicrinine: Kametani, T.; Kohno, T.; Charubala, R. *Chem. Pharm. Bull.* **1972**, *20*, 1488−1490.

vinyl bromide **9**[4c,8] using a modification of King and Negishi's method[9] gave the enyne **10**. The use of DMF as the solvent in the palladium coupling was found to be superior to THF. The enyne **10** is a sensitive compound that was used immediately after purification. Hence, Lindlar reduction of **10** gave the (*Z*)-diene **11**. Removal of the silyl protecting group gave **12**, which was oxidized to the aldehyde **13** using Swern's method.[10] Condensation of **13** with (aminomethyl)tri-*n*-butylstannane[3c] provided the (2-azaallyl)stannane **14** in quantitative yield. Without purification, **14** was added to *n*-BuLi in THF at −78 °C. Aqueous workup produced the cycloadduct **15** as a single diastereomer in 80% yield. The facility of this cycloaddition process illustrates the potential power of the 2-azaallyl anion method for the synthesis of relatively complex pyrrolidine-containing targets. The stereochemical assignment of **15** was supported by the easy formation of the cyclic aminal **16** upon exposure to aqueous acid. Hence, the cycloaddition of the anion derived from **14** had provided the trans relationship between the allylic oxygen and the ring juncture substituents rather than the cis relationship as required for crinine, as predicted by the above discussion (see **6B** in Figure 2). Completion of the synthesis required the inversion of the allylic stereocenter and a Pictet−Spengler reaction. Although inversion of the allylic alcohol that would be derived from the deprotection of **15** has close literature precedent,[4f] we found that a step could be saved by subjecting **15** directly to Pictet−Spengler conditions. Thus, deprotection of the (methoxy)methoxy group and aminomethylation of the arene occurred in one operation to give (±)-6-epicrinine **7** in good yield, mp 234−235 °C (lit.[7] mp 235−239 °C). Using the conditions developed by Martin for a related inversion,[4f] the allylic alcohol of **7** was converted to the mesylate and inverted with cesium acetate. Without workup or isolation, the resultant acetate was saponified with potassium carbonate and methanol to give (±)-crinine (**1**) in 72% yield, mp 175−177 °C (lit.[4f] mp 172.5−174 °C), which had spectral data in accord with published values.[4f] Hence, the 2-azaallyl anion method has proven its utility for the assembly of a relatively complex alkaloid by allowing the assembly of (±)-crinine in only eight steps from **8** in 20% overall yield. The high efficiency and stereoselectivity of the cycloaddition were particularly promising and led us to attempt the synthesis of the more challenging targets, amabiline (**2**) and augustamine (**3**).

Syntheses of (−)-Amabiline and (−)-Augustamine

Amabiline (**2**) was recently isolated from the bulbs of *Crinum amabile*.[11] Its absolute configuration was assigned as that shown in Figure 1 by comparison of the direction of its optical rotation with that of other alkaloids containing the 5,10-ethanophenanthridine ring system. Augustamine (**2**) has an octahydroindole core similar to that of amabiline. Augustamine was isolated from *Crinum augustum* in 1981 and characterized in 1983,[12] and interest in its pharmacological properties persists.[13] Its absolute configuration was not assigned. We are not aware of any other Amaryllidaceae alkaloids with a similar arrangement of hydroxyl groups in the cyclohexane ring, and no related synthetic studies have been reported.

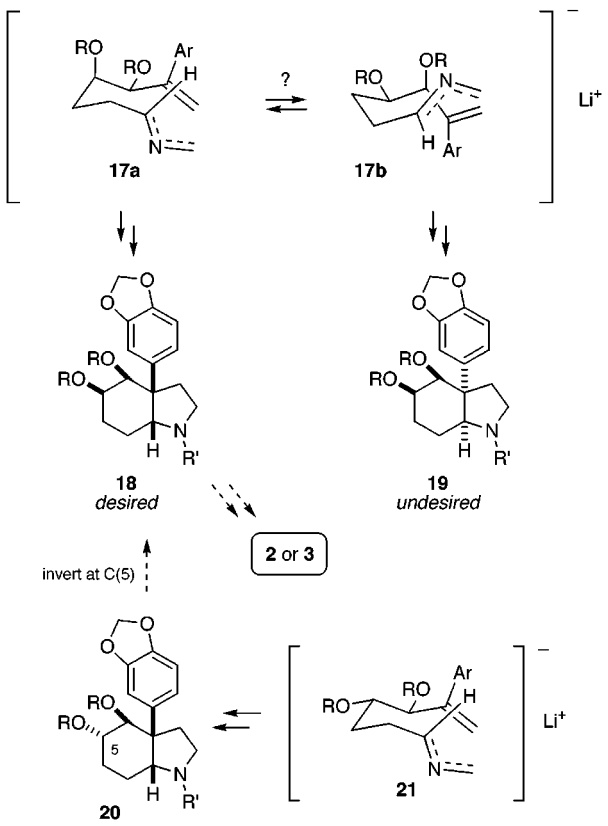
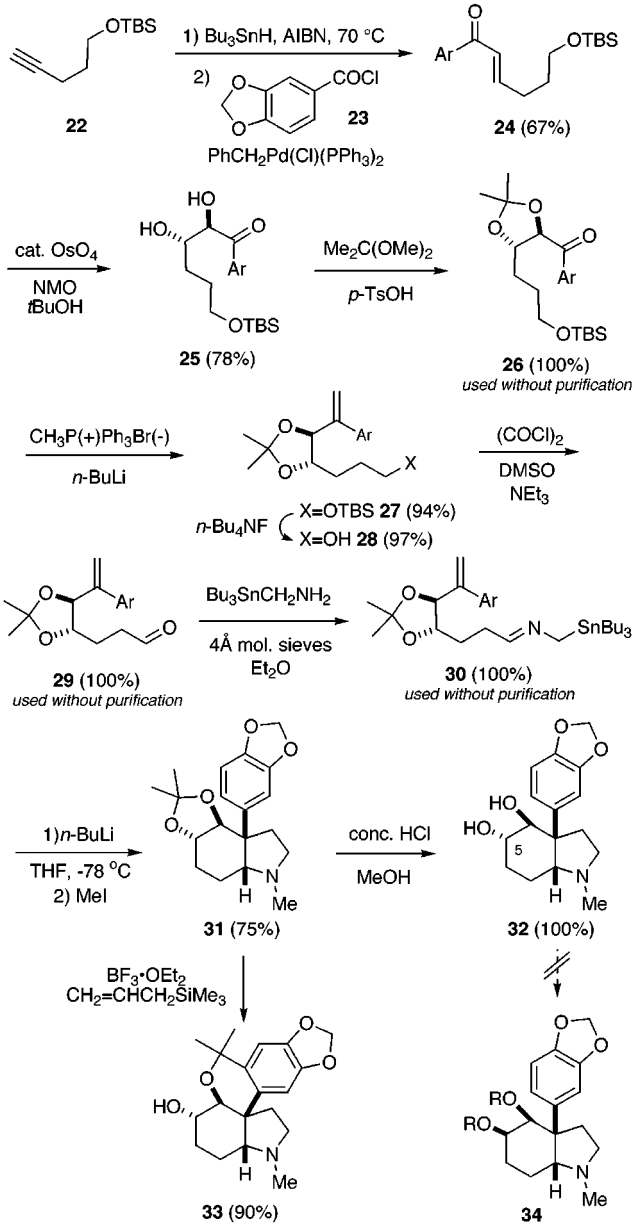


Figure 3. The 2-azaallyl anion cycloaddition required for amabiline and augustamine: diastereoselectivity?

Retrosynthetically, both amabiline and augustamine were proposed to be accessible from a common 4,5-dialkoxy-3a-arylperhydroindole (e.g., **18** in Figure 3). Amabiline would be made from **18** by a Pictet−Spengler reaction, whereas augustamine would be made by generating a dioxolenium ion at the 4- and 5-positions followed by an intramolecular electrophilic aromatic substitution reaction.[14] The perhydroindole **18** would be derived from the 2-azaallyl anion **17**, requiring an intramolecular cycloaddition onto an allylic ether.[6] Assuming that a cis ring juncture would result from the cycloaddition,[3b,e] the two conformations **17a** or **17b** both appeared reasonable, each involving one axial and one equatorial alkoxy group and similar overlap between the anion and anionophile.[6] The diastereomeric anion **21**, which allows both alkoxy groups to occupy equatorial positions, was predicted to give **20** in a stereoselective fashion but would require inversion of a C(5) hydroxy group to afford the desired intermediate **18**. Although a strategy involving the use of a cyclic protecting group for

(8) See also: Newman, M.; Dhawan, B.; Hahem, M.; Khanna, B. K.; Springer, J. M. *J. Org. Chem.* **1976**, *41*, 395.
(9) King, A. O.; Negishi, E. *J. Org. Chem.* **1978**, *43*, 358−360.
(10) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.
(11) Likhitwitayawuid, K.; Angerhofer, C. K.; Chai, H.; Pezzuto, J. M.; Cordell, G. A.; Ruangrungsi, N. *J. Nat. Prod.* **1993**, *56*, 1331−1338.
(12) (a) Ali, A. A.; Kating, H.; Frahm, A. W.; El-Moghazi, A. M.; Ramadan, A. M. *Phytochemistry* **1981**, *20*, 1121−1123. (b) Ali, A. A.; Hambloch, H.; Frahm, A. W. *Phytochemistry* **1983**, *22*, 283−287.
(13) Abd El Hafiz, M. A.; Ramadan, M. A.; Jung, M. L.; Beck, J. P.; Anton, R. *Planta Med.* **1991**, *57*, 437−439.
(14) For a related cyclization, see: Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591−7599.

Scheme 2. Synthesis of Perhydro-3a-arylindoles with *trans*-4,5-Dioxygenation



17 was ultimately successful in producing the desired stereochemical outcome, we also examined the cycloaddition of the diastereomeric system **21**, described below, in the interest of extending our understanding of the stereoselectivity of 2-azaallyl anion cycloadditions as well as possibly providing a successful route to the target alkaloids.

The synthesis of a perhydro-3a-arylindole with trans 4,5-dioxygenation is shown in Scheme 2. Using the ketone synthesis reported by Stille,[15] the known[16] alkyne **22** was hydrostannylated with tri-*n*-butyltin hydride, and the resultant crude *E*-vinyl stannane was coupled with piperonyl chloride **23** to produce the enone **24**. Dihydroxylation of the enone gave the diol **25**, which was protected as the acetonide **26**. Wittig olefination gave **27**, which was deprotected to produce the primary alcohol

(15) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634−4642.

(16) (a) Lin, C. H.; Stein, S. J. *Synth. Commun.* **1976**, 503−508. (b) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856−5866.

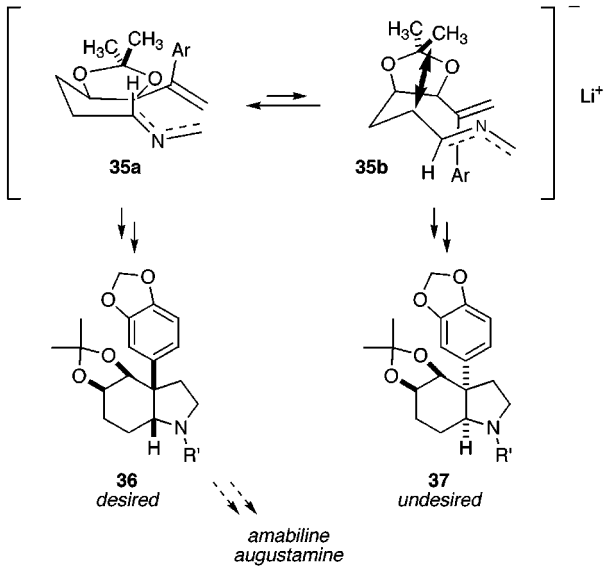


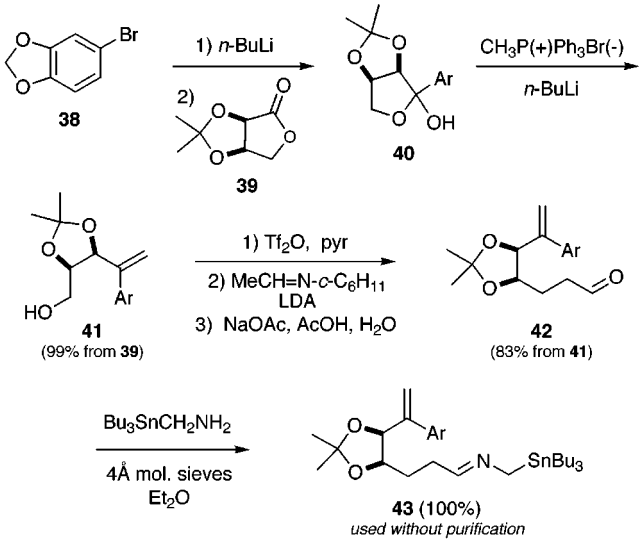
Figure 4. Amabiline and augustamine: diastereoselectivity revisited.

28. Swern oxidation[10] of **28** gave the aldehyde **29**, which was converted to the (2-azaallyl)stannane **30** with (aminomethyl)tri-*n*-butylstannane.[3c] The stannane **30** was added to a cold solution of *n*-butyllithium, and the reaction was quenched with iodomethane to produce the desired perhydroindole **31** as a single stereoisomer in 75% overall yield from the alcohol **28**. The relative configuration of **31** was verified by a fortuitous observation made in an attempt to open the acetonide of **31** with allyltrimethylsilane under Lewis acidic conditions. We had hoped that the allylsilane would intercept the oxonium ion formed in the cleavage of the acetonide in order to convert **31** to a selectively monoprotected diol. Instead, the oxonium ion participated in an intramolecular electrophilic aromatic substitution reaction, producing the dihydrobenzopyran **33** in high yield, thus ensuring that the C(4) oxygen is syn to the C(3a) aryl group. While the high yield and stereoselectivity of the 2-azaallyl anion cycloaddition to produce **31** further illustrates the power of this method for the synthesis of pyrrolidine-containing compounds, this route did not allow access to **34**, and thus to amabiline and augustamine, since we were unable to invert the C(5) alcohol of **32** and related compounds. Hence, we turned to an examination of the less predictable cycloadditions that would lead directly to the desired configuration at C(4) and C(5), as shown in Figure 3.

The difficulty in predicting the stereoselectivity of the cycloadditions of **17a** and **17b** (Figure 3) led us to consider modifying these conformations by using a cyclic protecting group for the C(4) and C(5) alcohols. Examination of molecular models revealed that an acetonide protecting group dominates the conformation of the tether, effectively leading to boatlike transition states. Two of the most reasonable conformations of the 2-azaallyl anion **35** that would lead to the diastereomeric cis-fused perhydroindoles **36** and **37** are shown in Figure 4. In **35b**, one of the acetonide methyl groups has a significant transannular interaction with a methylene group in the tether, as shown. The conformation **35a** has no such interaction and would lead to the desired perhydroindole **36**.

We chose the lactone **39** as the starting material for our synthesis (Scheme 3), since it has the correct relative

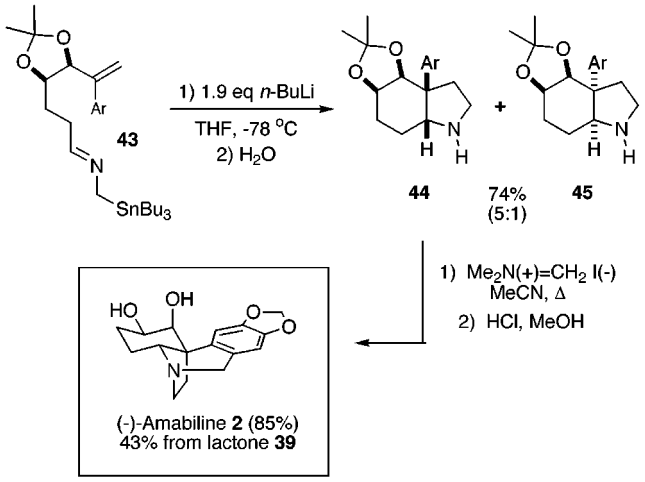
Scheme 3. Synthesis of the (2-Azaallyl)stannane 43



configuration at the two oxygen-bearing stereocenters for amabiline and augustamine. Regarding absolute configuration, natural amabiline is the (−)-isomer, and was assigned the stereostructure shown in Figure 1 on the basis of the known configurations of related (−)-alkaloids.[11] Assuming this assignment is correct, we chose to use the (2*R*,3*R*)-enantiomer of **39**. Although the absolute configuration of natural augustamine was not known, it is also levorotatory. Thus, we hoped that **39** would also translate into the correct enantiomer of synthetic augustamine. The lactone **39** is commercially available (Aldrich) or may be prepared in large quantities from inexpensive D-isoascorbic acid.[17] Lithium−halogen exchange of 4-bromo-1,2-methylenedioxybenzene **38** (Aldrich) with *n*-butyllithium in THF gave the aryllithium, which was added to the lactone **39**. Without purification, the resultant lactol **40** was subjected to Wittig methylenation to give the alcohol **41** in nearly quantitative yield for the two-step sequence. Chain extension of **41** to the aldehyde **42** was accomplished in an efficient manner using metalloenamine chemistry.[18] Thus, the alcohol **41** was converted to its triflate and then treated with the metalloenamine derived from *N*-(cyclohexyl)acetaldimine and LDA. The resultant imine was hydrolyzed under mildly acidic conditions to give aldehyde **42** in 83% yield from the alcohol **41**, a sequence requiring no purification of intermediates. The aldehyde **42** was then condensed with (aminomethyl)tri-*n*-butylstannane[3c] to give the (2-azaallyl)stannane **43**, which was used without purification.

Addition of the (2-azaallyl)stannane **43** to a solution of *n*-butyllithium in THF at −78 °C effected transmetalation to the 2-azaallyl anion, which participated in an intramolecular cycloaddition with the alkene (Scheme 4). Quenching the resultant *N*-lithiopyrrolidine with water afforded a 74% yield (from **42**) of the two diastereomeric cycloadducts **44** and **45** (5:1) ratio. While exposure of **44**

Scheme 4. Synthesis of (−)-Amabiline (2)



to classic Pictet−Spengler conditions (HCl, formaldehyde) did not promote the desired transformation, treatment of **44** with Eschenmoser's salt[19] in refluxing acetonitrile followed by removal of the acetonide under acidic conditions gave (−)-amabiline **2** in 85% yield. The spectral data of synthetic (−)-amabiline were consistent with those provided by Professor Cordell.[20] The magnitude and direction of the optical rotation, $[\alpha]^{20}_D$ −31.6 (*c* = 0.28, EtOH), matched the literature value of $[\alpha]^{20}_D$ −32 (*c* = 0.3, EtOH),[11] verifying the absolute configuration of the natural alkaloid. The synthesis of (−)-amabiline required eight steps from the lactone **39**, required only four purifications, and proceeded in 43% overall yield.

For the synthesis of (−)-augustamine (**3**), the imine **43** was used in a 2-azaallyl anion cycloaddition as described above, except that the reaction was quenched with iodomethane to provide a 4.3:1 ratio of **46** and **47** in 82% combined yield overall from the aldehyde **42** (Scheme 5). Removal of the acetonide of **46** with methanolic HCl provided the diol (not shown). Initial attempts to form the bicyclic ketal of augustamine directly using a related protocol developed by Danishefsky et al.[14] in their work on tazettine and pretazettine (PPA, trimethylorthofomate, reflux) proved unsuccessful. However, a stepwise approach proceeding through the ortho ester **48** was fruitful. Evaporation of the reaction mixture resulting from the HCl cleavage of **46** left the hydrochloride salt of the diol, which was mixed with trimethylorthoformate to produce **48**. Without purification, **48** was treated with methanesulfonic acid to afford (−)-augustamine **2** in 76% yield from **46**. The spectral data of synthetic (−)-augustamine matched that reported in the literature.[11b] The optical rotation of synthetic **2**, $[\alpha]^{20}_D$ −80.1 (*c* = 1.42, $CHCl_3$), was also consistent with the literature value of $[\alpha]^{20}_D$ −83 (*c* = 1.4, $CHCl_3$),[11b] thus proving the absolute configuration of the natural product. The synthesis of (−)-augustamine required nine steps from the lactone **39**, required only four purifications, and proceeded in 42% overall yield.

Conclusion

The 2-azaallyl anion route to pyrrolidines has proven to be useful for the concise synthesis of alkaloids featur-

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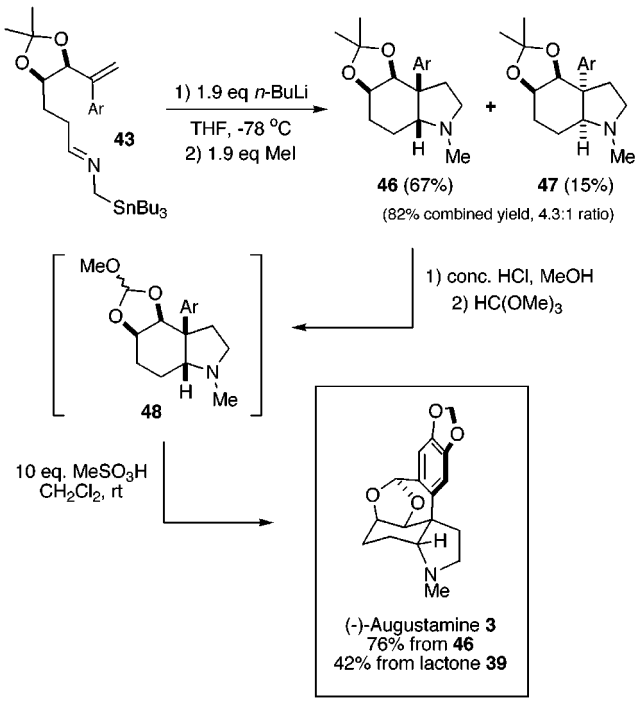
(18) (a) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178−2179. (b) Wittig, G.; Frommeld, H. D.; Suchanek, P. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 683. (c) Wittig, G.; Hesse, A. In *Organic Syntheses*; W. E. Noland, Ed.; Wiley: New York, 1988; Collec. Vol. VI., pp 901−905.

(19) Keck, G. E.; Webb, R. R., II. *J. Am. Chem. Soc.* **1981**, *103*, 3173−3177.

(20) We thank Professor G. A. Cordell (University of Illinois at Chicago) for supplying us with the ^{1}H NMR, ^{13}C NMR, IR, and mass spectra of natural amabiline for comparison.

Scheme 5. Synthesis of (−)-Augustamine (3)



ing the 3a-arylperhydroindole nucleus. (±)-Crinine (**1**) was synthesized in eight steps from **8** in 20% overall yield, with the key cycloaddition producing a single stereoisomer of the perhydroindole in 80% yield. Of interest in this cycloaddition is the use of a diene as the anionophile. The first asymmetric syntheses of (−)-amabiline (**2**) and (−)-augustamine (**3**) were accomplished in overall yields of 43% (in eight steps) and 42% (in nine steps), respectively, confirming or determining the absolute configuration of the natural products. The key cycloadditions produced the perhydroindoles in 83% and 74% yields, respectively, with reasonable stereocontrol. The highly stereoselective cycloaddition leading to the *trans*-dialkoxyperhydroindole **31** in 75% yield was consistent with our predictions. These studies contribute to a growing body of knowledge on the scope and stereoselectivity of 2-azaallyl anion cycloadditions. Applications to different classes of alkaloids are underway in our laboratories, each meant to further extend the scope of the 2-azaallyl anion chemistry.

Experimental Section

General. Methods. Reagents and starting materials were obtained from commercial suppliers and used without further purification unless otherwise noted. The lactone **39** is available from Aldrich Chemical Co. or may be conveniently prepared from isoascorbic acid by the literature procedure.[17] Methylene chloride (CH_2Cl_2), triethylamine, dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and benzene were distilled from calcium hydride under a nitrogen atmosphere. Methanol (MeOH) was distilled from magnesium turnings under a nitrogen atmosphere. Tetrahydrofuran (THF) and ether were distilled from sodium/benzophenone ketyl under a nitrogen atmosphere. Chloroform was filtered through basic alumina. Alkyllithiums were titrated either by the method of Gilman and Haubein[21] or by that of Ronald, Winkle, and Lansinger.[22] All reactions were conducted in oven- or flame-dried glassware under an anhydrous nitrogen atmosphere with standard precautions taken to exclude moisture. Chromatography refers to flash chromatography on silica gel (230−400 mesh) unless otherwise noted. Radial chromatography was performed on a Harrison Research Chromatotron with Merck 60 PF254 silica or Merck 60 GF254 aluminum oxide. Thin-layer chromatography (TLC) was performed on 0.25 mm Merck precoated silica plates (60 F-254).

7-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-(3,4-methylenedioxy)phenyl-5-(methoxy)methoxy-1-heptene-3-yne (10). By using a modification of the method of King and Negishi,[9] *n*-butyllithium (2.16 mL of a 2.69 M solution in hexanes, 5.8 mmol) was added to a solution of the known[3e] alkyne **8** (1.5 g, 5.8 mmol) in THF (6 mL) at −78 °C. The solution was warmed to 0 °C for 10 min and then treated with a solution of anhydrous $ZnCl_2$ (0.79 g, 5.8 mmol) in THF (6 mL). After being allowed to stand 20 min at room temperature and being recooled to 0 °C, the mixture was treated with a solution of the known[4f,8] vinyl bromide **9** (1.44 g, 6.38 mmol) in DMF (15 mL), followed by bis(triphenylphosphine)palladium(II) chloride (0.122 g, 0.174 mmol). After 10 min, the dark brown reaction mixture was taken up in ether (100 mL) and washed first with a 1:1 mixture of saturated aqueous ammonium chloride and 30% aqueous ammonium hydroxide (2 × 15 mL) and then with brine (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Radial chromatography (silica, 4 mm plate, 5% EtOAc/hexanes) afforded 1.53 g (65%) of the title compound as a colorless oil. This compound must be carried on immediately to the next step. R_f = 0.51 (10% EtOAc/hexanes); IR (neat) 2953 (s), 2885 (s), 1489 (s), 1236 (s), 1097 (s), 1035 (s), 939 (w), 835 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.12, 1.87 Hz, 1 H), 7.10 (d, J = 1.83 Hz, 1H), 6.77 (d, J = 8.15 Hz, 1H), 5.97 (s, 2H), 5.78 (s, 1H), 5.56 (s, 1H), 4.98 (d, J = 6.7 Hz, 1H), 4.74 (t, J = 6.5 Hz, 1H), 4.65 (d, J = 6.7 Hz, 1H), 3.83 (m, 2H), 3.43 (s, 3H), 2.04 (m, 2H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.0, 131.7, 129.7, 120.5, 119.8, 108.2, 106.4, 101.5, 94.6, 89.1, 85.0, 63.3, 59.3, 55.9, 39.3, 26.1, 26.0, 18.5, −5.1; MS (EI) *m*/*z* (rel intensity) 404 (0.8, M^+), 317 (35), 211 (37), 155 (13), 131 (100), 119 (60), 101 (27), 45 (51); HRMS calcd for $C_{22}H_{32}O_5SiH$ [$(M + H)^+$] 405.2097, found 405.2094.

(3*Z*)-7-[(1,1-Dimethylethyl)dimethylsilyl]oxy-2-(3,4-methylenedioxy)phenyl-5-(methoxy)methoxy-1,3-heptadiene (11). Palladium on calcium carbonate (0.4 g, poisoned with lead) was added to a solution of **10** (1.25 g, 3.07 mmol) and quinoline (70 μL, 0.61 mmol) in EtOAc (55 mL). The flask was evacuated and purged with dry nitrogen three times and then placed under an atmosphere of hydrogen (5 psi) in a Parr shaker. After 10 min, the reaction mixture was filtered through Celite and concentrated. Radial chromatography (silica, 4 mm plate, 6% EtOAc/hexanes) afforded 1.13 g (90%) of the title compound as a colorless oil. R_f = 0.50 (10% EtOAc/hexanes); IR (neat) 2928 (s), 1488 (s), 1247 (s), 1096 (s), 1036 (s), 836 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.92 (d, J = 1.75 Hz, 1H), 6.88 (dd, J = 8.1, 1.8 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 6.23 (d, J = 11.5 Hz, 1H), 5.97 (s, 2H), 5.64 (dd, J = 11.5, 9.53 Hz, 1H), 5.45 (d, J = 1.2 Hz, 1H), 5.31 (d, J = 1.2 Hz, 1H,), 4.72 (dt, J = 9.3, 4.2 Hz, 1H), 4.64, 4.53 (ABq, J_{AB}= 6.6 Hz, 2H), 3.72 (m, 2H,), 1.9−1.7 (m, 2H,), 0.9 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.9, 147.5, 143.0, 134.8, 134.6, 131.7, 120.6, 114.5, 108.2, 107.1, 101.3, 94.7, 69.4, 55.6, 39.3, 31.8, 26.1, 26.0, 22.9, 18.4, −5.14, −5.17; MS (EI) *m*/*z* (rel intensity) 406 (17, M^+), 287 (25), 229 (10), 213 (58), 200 (22), 187 (23), 119 (38), 89 (100), 73 (56), 59 (26); HRMS calcd for $C_{22}H_{34}O_5Si$ 406.2176, found 406.2175.

(4*Z*)-6-(3,4-Methylenedioxy)phenyl-3-(methoxy)-methoxy-4,6-heptadiene-1-ol (12). Tetra-*n*-butylammonium fluoride (2.84 mL of a 1 M solution in THF, 2.84 mmol) was added to a solution of the diene **11** (1.10 g, 2.71 mmol) in THF (5 mL) at 0 °C. After 6 h, the mixture was diluted with

(21) Gilman, H.; Haubein, R. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515.
(22) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 87.
(23) Kametani, T.; Kohno, T.; Charubala, R. *Chem. Pharm. Bull.* **1972**, *20*, 1488−1490.

ether (50 mL), washed with brine (2 × 10 mL), and dried (Na_2SO_4), filtered, and concentrated. Chromatography (35% EtOAc/hexanes) afforded 0.633 g (79%) of the title compound as a pale yellow oil. R_f = 0.2 (30% EtOAc/hexanes); IR (neat) 3450 (br), 2886 (s), 1488 (s), 1246 (s), 1035 (s), 927 (w) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.89 (d, J = 1.77 Hz, 1H), 6.85 (dd, J = 8.15, 1.7 Hz, 1H), 6.76 (d, J = 8.06 Hz, 1H), 6.29 (d, J = 11.5 Hz, 1H), 5.97 (s, 2H), 5.64 (dd, J = 11.5, 9.4 Hz, 1H), 5.47 (s, 1H), 5.06 (s, 1H), 4.78 (dt, J = 9.0, 5.0 Hz, 1H), 4.64, 4.52 (ABq, J_{AB} = 6.6 Hz, 2H), 3.78 (m, 2H,), 3.33 (s, 3H), 2.35 (br s, 1H), 2.1−1.72 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.0, 147.6, 143.2, 133.6, 132.3, 120.5, 114.5, 108.3, 107.0, 101.3, 94.5, 71.7, 60.5, 55.8, 38.2; MS (EI) m/z (rel intensity) 292 (29, M^+), 230 (24), 185 (35), 175 (28), 173 (35), 149 (18), 145 (23), 128 (14.7), 115 (29), 73 (47), 45 (100); HRMS calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1320.

(4*Z*)-6-(3,4-Methylenedioxy)phenyl-3-(methoxy)-methoxy-4,6-heptadienal (13). DMSO (0.300 mL, 4.27 mmol) was added to a solution of oxalyl chloride (0.186 mL, 2.14 mmol) in CH_2Cl_2 (7 mL) at −78 °C. After 15 min, the diene **12** (0.52 g, 1.78 mmol) was added as a solution in CH_2Cl_2 (2 mL). After 15 min, the mixture was warmed to −60 °C and then treated with triethylamine (1.24 mL, 8.90 mmol). After 20 min, the mixture was allowed to warm to room temperature over 45 min, diluted with ether (100 mL), washed with saturated aqueous ammonium chloride (3 × 10 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated to afford 0.484 g (99%) the title compound as a pale yellow oil. IR (neat) 2891 (s), 1727 (s), 1489 (s), 1246 (s), 1098 (m), 1036 (s), 920 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.22 (dd, J = 2.95, 1.7 Hz, 1H), 6.9 (d, J = 1.67 Hz, 1H), 6.85 (dd, J = 8.1, 1.8 Hz, 1H), 6.77 (dd, J = 8.1, 0.3 Hz, 1H), 6.33 (d, J = 11.5 Hz, 1H), 5.95 (s, 2H), 5.65 (dd, J = 11.5, 9.4 Hz, 1H), 5.5 (s, 1H), 5.06 (s, 1H), 4.99 (app dt, J = 11.2, 4.45 Hz, 1H), 5.84 (dd, J = 51.3, 6.8 Hz, 2H), 3.3 (s, 3H), 2.7 (ddd, J = 16.1, 8.8, 3.0 Hz, 1H), 2.49 (ddd, J = 16, 3.9, 1.7 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202, 148.1, 148.0, 143.2, 134.1, 133.1, 132.4, 120.6, 114.8, 108.3, 107.0, 101.4, 94.5, 67.9, 55.8, 49.5; MS (EI) m/z (rel intensity) 290 (25, M^+), 245 (12.1), 202 (50), 199 (13), 186 (38), 173 (40), 141 (19), 128 (16), 115 (31), 45 (100); HRMS calcd for $C_{16}H_{18}O_5$ 290.1154, found 290.1165.

***N*-(Tri-*n*-butylstannyl)methyl-(4*Z*)-6-(3,4-methylenedioxy)phenyl-3-(methoxy)methoxy-4,6-heptadienaldimine (14).** Hydrazine monohydrate (6.10 g, 126 mmol) was added to a solution of *N*-(tri-*n*-butylstannyl)methylphthalimide (1.07 g, 2.52 mmol)[3c] in absolute ethanol (10 mL), and the resultant mixture was heated to 75 °C. After 25 min, the clear solution was brought to room temperature, concentrated, and diluted with ether (100 mL). The organic layer was washed with water (3 × 10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated. The crude amine was mixed with ether (3 mL) and 4 Å molecular sieves (0.3 g), and then a solution of the aldehyde **13** (0.67 g, 2.3 mmol) in ether (3 mL) was added. After 18 h, the mixture was filtered through Celite and concentrated to afford 1.20 g (100%) of the title compound as an orange oil which was used without further purification. IR (neat) 2925 (s), 1640 (w), 1489 (s), 1443 (m), 1246 (s), 1037 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.35 (t, J = 5.2 Hz, 1H), 6.92 (d, J = 1.68 Hz, 1H), 6.87 (dd, J = 8.1, 1.8 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 6.3 (d, J = 11.6 Hz, 1H), 5.97 (s, 2H), 5.66 (dd, J = 11.5, 9.5 Hz, 1H), 4.71 (ddd, J = 9.5, 7.2, 5.4 Hz, 1H), 4.63, 4.54 (ABq, J = 6.7 Hz, 2H), 3.55 [s, 2H, $^2J(^{117/119}Sn-^1H)$ = 43.8 Hz], 3.31(s, 3H), 2.6−2.4 (m, 2H), 1.55−1.43 (m, 6H), 1.35−1.25 (m, 6H), 0.95−0.75 (m, 15H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 155.7, 147.8, 142.9, 133.4, 132.0, 128.3, 120.3, 114.0, 108.0, 106.8, 101.0, 94.2, 70.3, 55.3, 47.2, 42.0, 29.0, 27.3, 13.7, 9.2; MS (EI) m/z (rel intensity) 593 (4, M^+), 528 (10), 474 (11), 394 (13), 251 (32), 179 (88), 175 (61), 149 (20), 94 (17), 73 (14), 45 (100); HRMS calcd for $C_{29}H_{47}NO_4Sn$ 593.2527, found 593.2541.

(3a*R,6*R**,7a*S**)-2,3,3a,6,7,7a-Hexahydro-6-(methoxy)methoxy-3a-(3,4-methylenedioxy)phenylindole (15).** A solution of the imine **14** (1.2 g, 2.3 mmol) was added to a solution of *n*-BuLi (1.76 mL of a 2.75 M solution in hexanes, 4.85 mmol) in THF (200 mL) at −78 °C over 20 min. After 1 h at −78 °C, the dark burgundy solution was quenched by the addition of a solution of water (10 mL) in THF (30 mL). The mixture was warmed to room temperature and concentrated. The residue was diluted with $CHCl_3$ (100 mL) and washed with brine (3 × 10 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 30 mL), and the organic extract was washed with brine (2 × 8 mL). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated. Radial chromatography (alumina, 2 mm plate, gradient elution with CH_2Cl_2 to 8% MeOH/CH_2Cl_2) afforded 0.53 g (80%) of the title compound as a yellow oil. R_f = 0.35 (20% MeOH/$CHCl_3$); IR (neat) 3367 (w), 2942 (s), 1486 (s), 1240 (s), 1240 (s), 1034 (s), 921 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.83 (dd, J = 1.5, 0.4 Hz, 1H), 6.76 (d, J = 1.5 Hz, 1H), 6.75 (d, J = 0.4 Hz, 1H), 6.24 (dd, J = 10.2, 4.56 Hz, 1H), 5.93 (s, 2H), 5.79 (d, J = 10.2 Hz, 1H), 4.70 (dd, J = 14.2, 6.9 Hz, 2H), 4.12 (br s, 1H), 3.39 (br s, 1H), 3.15 (m, 2H), 2.45 (app td, J = 13.1, 8.33, 1H), 2.13 (dd, J = 15.1, 1.9 Hz, 1H), 2.02 (ddd, J = 12.7, 7.4, 5.1 Hz, 1H), 1.76 (ddd, J = 15.1, 5.0, 3.4 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.9, 146.4, 138.8, 135.6, 126.6, 120.0, 108.1, 107.4, 101.2, 95.5, 67.8, 64.5, 55.6, 51.0, 45.6, 41.3, 27.5; MS (EI) m/z (rel intensity) 303 (20, M^+), 258 (32), 248 (11), 242 (16), 189 (31), 186 (14), 148 (14), 56 (100); HRMS calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1474.

Formation of Aminal 16 from 15. Four drops of concentrated HCl were added to a solution of the cycloadduct **15** (0.075 g, 0.25 mmol) in THF (3 mL). After 24 h, the reaction mixture was basified with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with chloroform (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 3 mL) and brine (5 mL). The combined aqueous layers were again extracted with chloroform (3 × 8 mL), and the organic extracts were washed with brine (2 × 3 mL). All organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. Radial chromatography (silica, 1 mm, gradient elution, CH_2Cl_2 to 5% MeOH/CH_2Cl_2) afforded 0.062 g (81%) of the title compound as a pale yellow oil. R_f = 0.6 (20% MeOH/$CHCl_3$); IR (neat) 2875 (s), 1486 (s), 1242 (s), 1039 (s), 929 (m), 809 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.89 (d, J = 1.68 Hz, 1H), 6.82 (dd, J = 8.1, 1.8 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 6.25 (ddd, J = 9.9, 5.9, 1.3 Hz, 1H), 5.93 (s, 2H), 5.7 (dd, J = 9.9, 1.6 Hz, 1H), 4.82 (d, J = 10.5 Hz, 1H), 4.29 (ddd, J = 7.7, 4.0, 2.1 Hz, 1H), 4.10 (d, J = 10.5 Hz, 1H), 3.54 (d, J = 3.7 Hz, 1H), 3.13 (m, 2H), 2.35 (m, 2H), 1.83 (dd, J = 12.2, 5.5 Hz, 1H), 1.59 (d, J = 14.4 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.2, 146.6, 136.5, 133.4, 131.2, 120.4, 108.4, 107.7, 101.3, 74.9, 62.7, 61.0, 51.6, 50.0, 36.0, 22.0; MS (EI) m/z (rel intensity) 271 (100, M^+), 243 (25), 228 (22), 217 (92), 201 (24), 187 (25), 141 (20), 128 (30), 115 (30), 73 (58); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1200.

6-Epicrinine (7). A 37% solution of formaldehyde (0.9 mL) was added to a solution of the cycloadduct **15** (0.1 g, 0.35 mmol) in methanol (0.6 mL). After 5 min, 6 M HCl (25 mL) was added. The mixture was warmed to 50 °C for 15 h, cooled, and then basified by the addition of solid K_2CO_3. The resultant mixture was extracted with EtOAc (5 × 10 mL), and then the organic layer was dried (Na_2SO_4), filtered, and concentrated. Radial chromatography (alumina, 1 mm, gradient elution from 0.5 to 5% MeOH/CH_2Cl_2) of the residue afforded 0.071 g (75%) of the title compound as a colorless solid which was recrystallized from acetone to give colorless crystals, mp 234−235 °C (lit. mp 235−239 °C[23]). R_f = 0.25 (20% MeOH/$CHCl_3$); IR (KBr) 3146 (br), 2917 (s), 2813 (m), 2710 (w), 1489 (s), 1230 (s), 1039 (s), 932 (s), 863 (m) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.49 (s, 1H) 6.39 (dd, J = 10.2, 2.2 Hz, 1H), 5.89 (dd, J = 7.3, 1.4 Hz, 2H), 5.78 (d, J = 10.2 Hz, 1H,), 4.49 (m, 1H), 4.41 (d, J = 16 Hz, 1H), 3.82 (d, J = 16 Hz, 1H), 3.50 (ddd, J = 14.3, 10.9, 4.79 Hz, 1H), 3.28 (dd, J = 13.4, 3.65 Hz, 1H), 2.95 (ddd, J = 14.4, 8.95, 5.85 Hz, 1H), 2.21−2.1 (m, 3H), 1.64 (ddd, J = 13.1, 12.0, 10.5 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.9, 146.6, 138.5, 132.0, 128.5, 125.4, 107.2, 103.1, 101.1, 67.7, 66.9, 62.1, 53.4, 45.0, 44.7, 34.9; MS (EI) m/z (rel intensity) 271 (100, M^+), 254 (10), 228 (22), 199 (52), 173 (21), 128 (20), 115 (25), 77 (14); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1214.

(±)-Crinine (1). Following the procedure developed by Martin et al.,[4f] methanesulfonic anhydride (recrystallized from ether, 0.096 g, 0.55 mmol) was added to a solution of triethylamine (0.077 mL, 0.55 mmol) and the amine **7** (0.029 g, 0.11 mmol) in THF (2 mL) at 0 °C. After 1 h, DMF (2 mL) was added, and the THF was removed by passing a stream of nitrogen over the reaction mixture. Cesium acetate (0.32 g, 1.7 mmol) was then added. After 38 h at room temperature, the resulting ester was cleaved by the addition of a solution of K_2CO_3 (0.25 g) in MeOH (5 mL). After 1 h, the methanol was removed on a rotatory evaporator, and the residue was diluted with $CHCl_3$ (3 mL), washed with saturated aqueous $NaHCO_3$ (2 × 0.5 mL), dried (Na_2SO_4), filtered, and concentrated. Radial chromatography (silica, 1 mm, gradient elution from 10% to 30% MeOH/CH_2Cl_2) afforded 0.021 g (72%) of the title compound as a colorless solid which was recrystallized from acetone/CH_2Cl_2 to give fine colorless crystals, mp 175−177 °C (lit. 172.5−174 °C[4f]). R_f = 0.18 (20% MeOH/$CHCl_3$); IR (neat) 3200 (br), 2882 (s), 2803 (w), 1478 (s), 1232 (s), 1036 (s), 932 (s), 726 (s) cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.57 (d, J = 9.9 Hz, 1H), 6.44 (s, 1H), 5.94 (dd, J = 9.9, 5.3 Hz, 1H), 5.88 (dd, J = 5.6, 1.4 Hz, 2H), 4.36 (d, J = 17 Hz, 1H), 4.33 (m, 1H), 3.72 (d, J = 17 Hz, 1H), 3.35 (m, 2H), 2.89 (ddd, J = 13.1, 9.1, 6.0 Hz, 1H), 2.35 (br s, 1H), 2.15 (ddd, J = 12.6, 9.2, 4.4 Hz, 1H), 1.98 (dm, J = 13.8 Hz, 1H), 1.89 (ddd, J = 12.2, 10.8, 6.1 Hz, 1H), 1.71 (dt, J = 13.5, 4.1 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.6, 146.1, 138.6, 132.4, 127.8, 126.6, 107.2, 103.1, 101.0, 64.3, 63.1, 62.7, 53.8, 44.5, 33.0; MS (EI) *m*/*z* (rel intensity) 271 (100, M^+), 254 (12), 228 (19), 201 (14), 199 (37), 187 (34), 174 (10), 129 (12), 115 (15); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1208, found 271.1205. The spectral data matched those reported by Martin et al.[4f]

6-[(1,1-Dimethylethyl)dimethylsilyl]oxy-1-(3,4-methylenedioxy)phenyl-2-hexene-1-one (24). AIBN (0.020 g, 0.12 mmol) was added to a neat mixture of tri-*n*-butyltin hydride (18.1 g, 62 mmol) and the alkyne **22** (11.68 g, 59 mmol).[16] After 2 h at 70 °C, the mixture was cooled to room temperature and diluted with chloroform (60 mL). The acid chloride **23** (9.9 g, 59 mmol, Aldrich) and *trans*-benzyl(chloro)bis(triphenylphosphine)palladium(II) (0.008 g, 0.01 mmol) were then added. After 18 h at 70 °C, the reaction mixture was diluted with ether (400 mL), washed with saturated aqueous $NaHCO_3$ (1 × 100 mL) and brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated. Chromatography (5% EtOAc/hexanes) afforded 13.7 g (67%) of the title compound as colorless crystals, mp 135.0−135.5 °C. R_f = 0.23 (10% EtOAc/hexanes); IR (film) 2929 (s), 1667 (s), 1662 (s), 1664 (s), 1437 (s), 1256 (s), 1079 (s), 1034 (s), 832 (s); ^1H NMR (360 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.16, 1.74 Hz, 1H), 7.45 (d, J = 1.68 Hz, 1H), 7.06 (td, J = 15.27, 6.88 Hz, 1H), 6.86 (td, J = 15.31, 1.38 Hz, 1H), 6.85 (d, 8.2 J = Hz, 1H), 6.05 (s, 2H), 3.66 (t, J = 6.19 Hz, 2H), 2.38 (ddd, J = 15.1, 7.0, 1.25 Hz, 2H), 1.73 (ddd, J = 15.33, 7.56, 6.36 Hz, 2H), 0.9 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 188.5, 151.7, 148.9, 148.4, 132.8, 125.7, 124.8, 108.6, 107.9, 101.9, 62.4, 31.5, 29.4, 26.1, 18.4, −5.1; MS (EI) *m*/*z* (rel intensity) 292 (31), 291 (100), 149 (34), 135 (38), 124 (20), 75 (57), 73 (19), 65 (10), 41 (20); HRMS calcd for $C_{19}H_{28}O_4SiH$ 349.1835 [$(M + H)^+$], found 349.1832. Anal. Calcd for $C_{19}H_{28}O_4Si$: C, 65.48; H, 8.10. Found: C, 65.37; H, 7.93.

(2*R,3*S**)-6-[(1,1-Dimethylethyl)dimethylsilyl]oxy-1-(3,4-methylenedioxy)phenyl-2,3-dihydroxyhexan-1-one (25).** *N*-Methylmorpholine *N*-oxide (4.0 g, 40 mmol) was added to a solution of the ketone **24** (6.00 g, 17.2 mmol) in THF (18 mL) and water (4 mL). Osmium tetroxide (6 mL of a 0.05 M solution in *t*-BuOH, 0.3 mmol) was added at 0 °C. After 5 h at room temperature, $NaHSO_3$ (20 mL of a 5% aqueous solution) was added. After 15 min, the mixture was diluted with EtOAc (200 mL) and washed with brine (2 × 40 mL), and the aqueous washes were re-extracted with EtOAc (7 × 20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. Chromatography (25% EtOAc/hexanes) afforded 5.2 g (78%) of the title compound as a colorless oil. R_f = 0.25 (25% EtOAc/hexanes); IR (film) 3458 (br, s) 2929 (s), 1673 (s), 1445 (s), 1258 (s), 1097 (s); ^1H NMR (360 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.7, 1.7 Hz, 1H), 7.41 (d J = 1.7 Hz, 1H), 6.8 (d, J = 8.21 Hz, 1H), 6.05 (s, 2H), 4.89 (dd, J = 5.85, 1.76 Hz, 1H), 3.93 (m, 2H), 3.62 (m, 2H), 2.58 (d, J = 5.68 Hz, 1H), 1.80−1.63 (m, 4H), 0.82 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 198.3, 153.1, 149.2, 138.7, 128.9, 125.2, 108.6, 108.3, 102.2, 75.7, 73.2, 63.2, 31.5, 29.3, 26.1, 18.4−5.2; MS (EI) *m*/*z* (rel intensity) 237 (23), 180 (14), 149 (86), 145 (61), 127 (12), 121 (27), 75 (100), 73 (18), 65 (18), 41 (16); HRMS calcd for $C_{19}H_{30}O_5SiH$ 383.1890 [$(M + H)^+$], found 383.1883.

(2*R,3*S**)-2,3-*O*-Isopropylidenedioxy-6-[(1,1-dimethylethyl)dimethylsilyl]oxy-1-(3,4-methylenedioxy)phenylhexan-1-one (26).** 2,2-Dimethoxypropane (2.4 mL, 19.6 mmol) and toluenesulfonic acid (0.02 g) were added to a solution of the diol **25** (2.50 g, 6.54 mmol) in THF (25 mL). After 18 h, the solution was concentrated, and the residue was dissolved in ether (100 mL), washed with $NaHCO_3$ (2 × 20 mL), and dried over $MgSO_4$, filtered, and concentrated to afford 2.65 g (100%) of the title compound as a colorless oil that was sufficiently pure to be used in the next step without purification. R_f = 0.22 (10% EtOAc/hexanes); IR (film) 2930 (s), 1680 (s), 1444 (s), 1253 (s), 1096 (s), 835 (s); ^1H NMR (360 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.24, 1.7 Hz, 1H), 7.57 (d, J = 1.74 Hz, 1H), 6.87 (d, J = 8.17 Hz, 1H), 6.05 (s, 2H), 4.68 (d, J = 7.17 Hz, 1H), 4.44 (dt, J = 7.12, 4.82 Hz, 1H), 3.63 (t, J = 5.9 Hz, 2H), 1.8−1.6 (m, 4H), 1.5 (s, 3H), 1.36 (s, 3H), 0.85 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 195.3, 152.2, 148.5, 131, 126.9, 111, 109, 108.2, 102.1, 82.2, 78.1, 63.0, 30.2, 29.3, 27.6, 26.4, 26.2, 18.6, −5.1; MS (EI) *m*/*z* (rel intensity) 365 (19), 308 (12), 307(45), 215 (30), 149 (100), 145 (72), 121 (15), 86 (30), 73 (55), 49 (50); HRMS calcd for $C_{22}H_{34}O_6SiH$ 423.2203 [$(M + H)^+$], found 423.2214.

(3*R,4*R**)-3,4-*O*-Isopropylidenedioxy-7-[(1,1-dimethylethyl)dimethylsilyl]oxy-2-(3,4-methylenedioxy)phenyl-1-heptene (27).** *n*-BuLi (2.83 mL of a 2.75 M solution in hexanes, 7.8 mmol) was added to a slurry of methyltriphenylphosphonium bromide (2.78 g, 7.8 mmol) in THF (35 mL) at −78 °C. After being warmed to 0 °C for 30 min, the orange solution was recooled to −78 °C and treated with a solution of the ketone **26** (2.65 g, 6.5 mmol) in THF (5 mL). After 30 min, the mixture was warmed to room temperature over 1 h, diluted with ether (200 mL), and washed with brine (2 × 30 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. Ether (20 mL) was added, the liquid phase was decanted, and the remaining solid was triturated with hexanes. The combined solutions were concentrated. Chromatography (5% EtOAc/hexanes) of the residue afforded 2.47 g (94%) of the title compound as a colorless oil. R_f = 0.32 (10% EtOAc/hexanes); IR (film) 2983 (s), 1488 (s), 1435 (m), 1370 (m), 1232 (s), 1085 (s), 1041 (s); ^1H NMR (360 MHz, $CDCl_3$) δ 6.92 (d, J = 1.68 Hz, 1H), 6.86 (dd, J = 8.04, 1.74 Hz, 1H), 6.75 (d, J = 7.99 Hz), 5.95 (s, 2H), 5.42 (t, J = 2 Hz, 1H), 5.27 (d, J = 2 Hz, 1H), 4.41 (dd, J = 7.6, 0.82 Hz, 1H), 3.7 (ddd, J = 7.80, 7.75, 4.16 Hz, 1H), 3.54 (m, 2H), 1.6−1.54 (m, 4H), 1.46 (s, 3H), 1.42 (s, 3H), 0.35 (s, 9H), −0.9 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.4, 147.2, 145.7, 133.6, 120.9, 115.9, 108.4, 108.1, 108.0, 101.0, 83.3, 80.8, 62.8, 29.0, 28.8, 27.4, 26.9, 25.9, 18.2, −5.4; MS (EI) *m*/*z* (rel intensity) 306 (24), 305 (100), 218 (45), 213 (92), 203 (65), 187 (75), 147 (97), 127 (33), 75 (94); HRMS calcd for $C_{23}H_{36}O_5Si$ 420.2332, found 420.2353.

(3*R,4*R**)-3,4-*O*-Isopropylidenedioxy-2-(3,4-methylenedioxy)phenyl-1-heptene-7-ol (28).** *n*-Bu_4NF (5.05 mL of a 1 M solution in THF, 5.05 mmol) was added to a solution of the alkene **27** (2.02 g, 5.00 mmol) in THF (15 mL) at 0 °C. After 2 h, the solution was dissolved in ether (200 mL), washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered, and concentrated. Chromatography (30% EtOAc/hexanes) afforded 1.4 g (97%) of the title compound as a colorless oil. R_f = 0.11 (25% EtOAc/hexanes); IR (film) 3442 (br), 2880 (s), 1488 (s), 1232 (s), 1039 (s); ^1H NMR (360 MHz, $CDCl_3$) δ 6.91 (d, J = 1.65 Hz, 1H), 6.87 (dd, J = 8.02, 1.73 Hz, 1H), 6.77 (d, J = 7.99 Hz, 1H), 5.97 (s, 2H), 5.41 (t, J = 0.89 Hz, 1H), 5.29 (d, J = 1.4 Hz, 1H), 4.41 (d, J = 8.06 Hz, 1H), 3.72 (td, J = 8.33, 3.42 Hz, 1H), 3.59 (m, 2H), 2.12 (br s, 1H), 1.62 (m, 2H), 1.51 (m, 2H), 1.48 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.7, 147.5, 145.5, 133.7, 121.2, 116.18, 108.9, 108.3, 108.2,

101.3, 83.6, 81.0, 62.8, 29.5, 29.2, 27.6, 27.2; MS (EI) *m*/*z* (rel intensity) 306 (25, M^+), 218 (97), 204 (22), 203 (100), 187 (18), 175 (19), 159 (23), 147 (60), 102 (31), 59 (38); HRMS calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1461.

(4*R,5*R**)-4,5-*O*-Isopropylidenedioxy-6-(3,4-methylenedioxy)phenyl-6-heptenal (29).** DMSO (0.51 mL, 7.2 mmol) was added to a solution of oxalyl chloride (0.31 mL, 3.6 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After 15 min, a solution of the alcohol **28** (0.87 g, 3.0 mmol) in CH_2Cl_2 (2 mL) was added. After being warmed to room temperature, the mixture was dissolved in ether (200 mL), washed with saturated aqueous ammonium chloride (3 × 30 mL) and brine (1 × 30 mL), dried over $MgSO_4$, filtered, and concentrated to afford 0.86 g (100%) of the title compound as a slightly pale yellow oil, which was used immediately in the next step without purification. R_f = 0.29 (25% EtOAc/hexanes); IR (film) 2985 (m), 2888 (m), 1724 (s), 1488 (s), 1436 (m), 1379 (m), 1232 (s), 1038 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.71 (t, J = 1.4 Hz, 1H), 6.91 (d, J = 1.67 Hz, 1H), 6.86 (dd, J = 8.0, 1.75 Hz, 1H) 6.76 (d, J = 8.0 Hz, 1H), 5.97 (s, 2H), 5.42 (t, J = 1.18 Hz, 1H), 5.31 (d, J = 1.38 Hz, 1H), 4.42 (dd, J = 8.35, 0.73 Hz, 1H), 3.69 (dt, J = 8.28, 3.68 Hz, 1H), 2.51 (m, 2H), 1.71 (m, 2H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.7, 147.7, 147.5, 145.4, 133.5, 121.1, 115.8, 108.9, 108.2, 108.1, 101.2, 83.2, 79.9, 40.3, 27.4, 27.1, 24.9; MS *m*/*z* (rel intensity) 304 (40, M^+), 246 (21), 218 (82), 203 (100), 189 (33), 187 (17), 159 (22), 148 (22), 147 (42), 102 (28), 70 (50); HRMS calcd for $C_{17}H_{20}O_5$ 304.1311, found 304.1302.

(4*R,5*R**)-*N*-(Tri-*n*-butylstannyl)methyl-4,5-*O*-isopropylidenedioxy-6-(3,4-methylenedioxy)phenyl-6-heptenaldimine (30).** Hydrazine hydrate (6.10 g, 126 mmol) was added to a solution of *N*-(tri-*n*-butylstannyl)methylphthalimide[3c] (1.29 g, 3.03 mmol) in absolute ethanol (10 mL), and the mixture was heated at 75 °C for 25 min. The clear solution was then cooled to room temperature, concentrated, dissolved in ether (100 mL), washed with water (3 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude amine was mixed with ether (3 mL) and 4 Å molecular sieves (0.5 g) and then mixed with a solution of the aldehyde **29** (0.86 g, 3.0 mmol) in ether (3 mL). After 18 h, the mixture was filtered through Celite and concentrated to afford 1.82 g (100%) of the title compound as an orange oil which was used without further purification. IR (film) 2924 (s), 1651 (m), 1488 (s), 1370 (m), 1232 (s), 1040 (s), 812 (m); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.46 (t, J = 4.36 Hz, 1H), 6.92 (d, J = 1.68 Hz, 1H), 6.86 (dd, J = 8.04, 1.73 Hz, 1H), 6.75 (d, J = 8.03 Hz, 1H), 5.96 (s, 2H), 5.40 (t, J = 1.05 Hz, 1H), 5.29 (d, J = 1.41 Hz, 1H), 4.42 (dd, J = 8.33, 0.7 Hz, 1H), 3.72 (ddd, J = 8.31, 6.76, 5.76 Hz, 1H), 3.52 [s, 2H, ^2J ($^{117/119}$Sn−^{1}H) = 21.3 Hz], 2.32−2.13 (m, 2H), 1.45 (m, 8H), 1.33 (m, 6H), 0.89 (m, 15H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.4, 147.7, 147.5, 145.7, 133.8, 121.3, 116.4, 108.9, 108.5, 108.2, 101.3, 83.7, 80.4, 47.1, 32.3, 29.5, 29.4, 29.3, 29.2, 27.6, 27.3, 13.9, 9.4; MS (EI) *m*/*z* (rel intensity) 492 (11), 316 (16), 291 (39), 289 (31), 287 (18), 269 (20), 259 (30), 235 (62), 179 (100), 70 (69); HRMS calcd for $C_{30}H_{49}NO_4SnH$ 608.2762 [(M + H)$^+$], found 608.2733.

(3a*R,4*R**,5*R**,7a*S**)-Octahydro-1-methyl-4,5-*O*-isopropylidenedioxy-3a-(3,4-methylenedioxy)phenylindole (31).** A solution of the imine **30** (1.82 g, 3.00 mmol) was added to a solution of *n*-BuLi (2.37 mL of a 2.4 M solution in hexanes, 5.7 mmol) in THF (200 mL) at −78 °C over 15 min. After 1 h at −78 °C, the resulting light orange solution was quenched with MeI (0.37 mL, 6.0 mmol). After 10 min at −78 °C, ammonium hydroxide was added (5 mL), and the mixture was warmed to room temperature and concentrated. The residue was dissolved in $CHCl_3$ (50 mL) and washed with brine (2 × 10 mL). The aqueous layers were combined and extracted with $CHCl_3$ (5 × 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Radial chromatography (silica, 4 mm plate, gradient 1% MeOH/CH_2Cl_2 to 10% MeOH/CH_2Cl_2) afforded 0.74 g (75%) of the title compound as a colorless oil. R_f = 0.22 (5% MeOH/CH_2Cl_2); IR (film) 2949 (m), 2767 (m), 1490 (s), 1440 (m), 1380 (m), 1232 (s), 1086 (s), 1035 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.95 (d, J = 1.83 Hz, 1H), 6.81 (dd, J = 8.2, 1.82 Hz, 1H), 6.72 (d, J = 8.13 Hz, 1H), 6.72 (d, J = 8.13 Hz, 1H), 5.93 (dd, J = 5.18, 1.43 Hz, 2H), 3.88 (d, J = 9.64 Hz, 1H), 3.27 (dt, J = 9.33, 3.99 Hz, 1H), 3.2 (m, 1H), 2.67 (d, J = 2.22 Hz, 1H), 2.52 (ddd, J = 12.80, 8.60, 7.55 Hz, 1H), 2.29 [(s, 3H) on top of (m, 1H)], 2.11 (dm, J = 13 Hz, 1H), 1.95 (m, 1H), 1.89−1.67 (m, 4H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.9, 145.6, 136.9, 121.1, 110.2, 108.6, 107.1, 100.9, 84.9, 75.23, 69.9, 54.9, 52.5, 40.9, 36.4, 27.4, 26.9, 26.3, 23.1; MS (EI) *m*/*z* (rel intensity) 245 (27), 230 (22), 217 (31), 216 (34), 204 (20), 203 (70), 164 (17), 94 (10), 84 (21), 44 (100); HRMS calcd for $C_{19}H_{25}NO_4$ 331.1784, found 331.1779.

(3a*R,4*R**,5*R**,7a*S**)-Octahydro-1-methyl-4,5-dihydroxy-3a-(3,4-methylenedioxy)phenylindole (32).** Concentrated HCl (0.5 mL) was added to a solution of the octahydroindole **31** (0.15 g, 0.45 mmol) in MeOH (1.5 mL). After 1.5 h, the mixture was basified with solid K_2CO_3 and dissolved in water (1 mL). The solution was extracted with EtOAc (8 × 2 mL), dried (Na_2SO_4), filtered, and concentrated to afford 0.135 g (100%) of the title compound as a colorless oil. R_f = 0.08 (10% MeOH/CH_2Cl_2); IR (film) 3362 (br), 2948 (m), 2771 (m), 1489 (s), 1235 (s), 1040 (s); ^{1}H NMR (360 MHz, CD_3OD) δ 7.06 (d, J = 1.82 Hz, 1H), 6.93 (dd, J = 8.24, 1.86 Hz, 1H), 6.72 (d, J = 8.26 Hz, 1H), 5.9 (s, 2H), 3.63 (d, J = 9.97 Hz, 1H), 3.38 (td, J = 10.42, 4.57 Hz, 1H), 2.73 (dt, J = 9.14, 4.52 Hz, 1H), 2.68 (br s, 1H), 2.56 (ddd, J = 12.9, 8.74, 7.04 Hz, 1H) 2.41 (dd, J = 16.9, 10.0 Hz, 1H), 2.33 (s, 3H), 1.97 (m, 2H), 1.87 (ddd, J = 13.0, 10.6, 4.65 Hz, 1H), 1.8−1.65 (m, 2H); ^{13}C NMR (90 MHz, CD_3OD) δ 148.4, 147.1, 138.7, 122.8, 111.8, 107.9, 102.2, 79.7, 72.9, 71.8, 55.7, 55.5, 41.3, 38.5, 30.0, 23.7; MS (EI) *m*/*z* (rel intensity) 290 (17), 274 (26), 273 (64), 232 (16), 216 (25), 204 (28), 203 (100), 112 (15), 96 (12), 70 (58); HRMS calcd for $C_{16}H_{21}NO_4H$ 292.1549 [(M + H)$^+$], found 292.1543.

Cyclic Ether 33. A solution of $BF_3{\cdot}OEt_2$ (0.0075 mL, 0.18 mmol) in CH_2Cl_2 (0.2 mL) was added to a solution of the octahydroindole **31** (0.02 g, 0.06 mmol) and allyltrimethylsilane (0.096 mL, 0.6 mmol) in CH_2Cl_2 (1 mL) at −50 °C. After being stirred at room temperature overnight, the mixture was dissolved in $CHCl_3$ (5 mL) and washed with saturated $NaHCO_3$ (1 mL) and brine (1 mL). The aqueous layers were combined and extracted with $CHCl_3$ (5 × 2 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Chromatography (7% MeOH/CH_2Cl_2) afforded 0.018 g (90%) of the title compound as a colorless oil. R_f = 0.13 (5% MeOH/CH_2Cl_2); IR (film) 2995 (s), 1500 (s), 1227 (s), 1100 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.78 (s, 1H), 6.58 (s, 1H), 5.93 (s, 2H), 3.92 (d, J = 7.0 Hz, 1H), 3.75 (t, J = 5.8 Hz, 1H), 3.30 (t, J = 9.0 Hz, 1H), 2.61 (br s, 1H), 2.5−2.4 (m, 2H), 2.34 (s, 3H), 1.94 (br d, J = 6.6 Hz, 1H), 1.58−1.57 (m, 4H), 1.55 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.9, 146.2, 136.4, 105.6, 104.8, 101.2, 77.1, 73.6, 71.8, 69.2, 55.6, 46.7, 40.0, 38.8, 31.5, 26.3, 18.9; MS (EI) *m*/*z* (rel intensity) 316 (22), 274 (40), 273 (20), 272 (25), 259 (10), 246 (13), 244 (22), 243 (19), 187 (15), 100 (25), 85 (25); HRMS calcd for $C_{19}H_{25}NO_4$ 331.1784, found 331.1773.

(3*R*,4*R*)-3,4-*O*-Isopropylidenedioxy-2-(3,4-methylenedioxy)phenyl-1-hydroxytetrahydrofuran (40). *n*-BuLi (2.45 M in hexanes, 13.56 mL, 33.22 mmol) was added to a solution of 3,4-methylenedioxybromobenzene (3.8 mL, 31.65 mmol, Aldrich) in THF (100 mL) at −78 °C. After 1.5 h, the off-white slurry was transferred via cannula to a solution of the lactone **39** (5.0 g, 31.65 mmol) in THF (100 mL) at −78 °C. After 1 h, the light yellow solution was quenched with saturated aqueous ammonium chloride (5 mL), warmed to room temperature, and extracted with ether (700 mL). The organic extract was washed with brine (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated to give 8.8 g (100%) of the title compound as a white powder, which was used without further purification. An analytical sample was recrystallized from EtOAc/hexanes to give colorless crystals, mp 132−134 °C. $[\alpha]^{20}_D$ −92.9 (c = 0.73, $CHCl_3$); R_f = 0.15 (25% EtOAc/hexanes); IR (KBr) 3384 (br, s), 2987 (m), 1490 (s), 1225 (s), 1042 (s), 746 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.05 (dd, 1.7, 8.1 Hz, 1H), 7.01 (d, 1.6 Hz, 1H), 6.77 (d, 8.0 Hz, 1H), 6.00 (ABq, 1.5, 2.9 Hz, 2H), 4.95 (ddd, 0.4, 3.9, 5.8 Hz, 1H), 4.53 (d, 5.8 Hz, 1H), 4.18 (dd, 3.9, 10.2 Hz, 1H), 4.08 (d, 10.1 Hz, 2H), 1.4 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.0, 147.4, 133.4, 120.6, 112.8, 108.1, 107.9, 107.0, 101.4, 85.0, 80.9, 71.2, 26.4, 24.8;

MS (EI) *m*/*z* (rel intensity) 167 (17), 166 (100), 165 (24), 149 (87), 131 (37), 121 (18), 85 (23), 65 (18), 59 (81), 43 (39); HRMS calcd for $C_{14}H_{16}O_6$ (M^+) 280.0947, found 280.0956. Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.68; H, 5.84.

(2*R*,3*S*)-2,3-*O*-Isopropylidenedioxy-4-(3,4-methylenedioxy)phenyl-4-pentene-1-ol (41). *n*-BuLi (2.45 M in hexanes, 38.4 mL, 87 mmol) was added to a solution of methyltriphenylphosphonium bromide (31.0 g, 86.7 mmol) in THF (200 mL) at −78 °C. After 30 min at 0 °C, the light orange solution was recooled to −78 °C and treated with a solution of the lactol **40** (8.10 g, 28.9 mmol) in THF (10 mL). After warming to −10 °C over 3 h, the reaction was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ether (200 mL). The organic extract was washed with brine (2 × 30 mL). The combined aqueous layers were extracted with ether (200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (25% EtOAc/hexanes) afforded 8.0 g (99%) of the title compound as a colorless oil. R_f = 0.18 (25% EtOAc/hexanes); $[\alpha]^{20}_D$ −13.96 (*c* = 1.10, $CHCl_3$); IR (film) 3451 (br), 2935 (m), 1493 (s), 1230 (s), 1037 (s), 907 (w); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.90 (d, 1.8 Hz, 1H), 6.85 (dd, 1.8, 8.1 Hz, 1H), 6.77 (d, 8.1 Hz, 1H), 5.95 (s, 2H), 5.48 (t, 1.5 Hz, 1H), 5.42 (t, 1.0 Hz, 1H), 5.19 (d, 6.6 Hz, 1H), 4.28 (ddd, 3.9, 6.6, 8.53 Hz, 1H), 3.40 (ddd, 3.3, 8.7, 11.8 Hz, 1H), 3.24 (ddd, 3.9, 9.1, 12.9 Hz, 1H), 1.81 (dd, 3.4, 9.1 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.2, 147.8, 141.6, 133.1, 119.6, 113.0, 108.8, 108.6, 106.8, 101.5, 77.8, 77.1, 62.6, 28.2, 25.8; MS (EI) *m*/*z* (rel intensity) 278 (35), 220 (73), 203 (90), 190 (71), 178 (79), 147 (59), 131 (61), 103 (50), 89 (40), 59 (100); HRMS calcd for $C_{15}H_{18}O_5$ (M) 278.1154, found 278.1161.

(4*R*,5*S*)-4,5-*O*-Isopropylidenedioxy-6-(3,4-methylenedioxy)phenyl-6-heptenal (42). Pyridine (1.05 mL, 10.3 mmol) was added to a solution of trifluoromethanesulfonic anhydride (2.02 mL, 10.2 mmol) in CH_2Cl_2 (30 mL) at −50 °C, followed by a solution of the alcohol **41** (2.78 g, 10.0 mmol) in CH_2Cl_2 (10 mL). After 15 min, the mixture was then filtered through Celite and concentrated, affording 4.1 g (100%) of the triflate as a colorless oil, which was used immediately without purification. R_f = 0.52 (25% EtOAc/hexanes); IR (film) 2990 (m), 1490 (s), 1417 (s), 1246 (s), 1040 (s), 962 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.92 (d, 1.7 Hz, 1H,), 6.86 (dd, 1.7, 8.1 Hz, 1H), 6.82 (d, 8.1 Hz, 1H,), 6.05 (d, 1.7 Hz, 2H), 5.59 (dd, 1.0, 1.6 Hz, 1H), 5.51 (t, 1.1 Hz, 1H), 5.30 (dd, 1.4, 6.4 Hz, 1H), 4.47 (ddd, 3.6, 6.6, 7.8 Hz, 1H), 4.25 (dd, 8.0, 10.5 Hz, 1H), 4.16 (dd, 3.6, 10.5 Hz, 1H), 1.62 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 148.6, 148.3, 140.4, 132.2, 119.6, 118.9 (q, J_{C-F} = 452 Hz), 113.8, 110.0, 108.8, 106.6, 101.6, 76.7, 75.7, 74.5, 27.8, 25.7; MS (EI) *m*/*z* (rel intensity) 86 (28), 84 (41), 69 (27), 64 (15), 60 (33), 58 (40), 51 (19), 49 (50), 43 (100), 38 (34). Satisfactory elemental analysis and HRMS could not be obtained on this compound.

n-BuLi (2.45 M in hexanes, 4.9 mL, 18 mmol) was added to a solution of diisopropylamine (1.68 mL, 18.0 mmol) in THF (40 mL) at −78 °C. The solution was stirred at 0 °C for 20 min and then recooled to −78 °C, after which *N*-cyclohexylethanaldimine[18] (1.5 g, 12 mmol) was added. After 20 min at 0 °C, the mixture was recooled to −78 °C and treated with the triflate from above (4.1 g, 10 mmol) as a solution in THF (10 mL). After being stirred at −50 °C for 1.5 h, the mixture was quenched with a solution of NaOAc (33 g), HOAc (60 mL), and water (50 mL). After being stirred for 20 min at room temperature, the mixture was extracted with ether (300 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 30 mL) and brine (2 × 30 mL), dried over $MgSO_4$, filtered, and concentrated. Chromatography (20% EtOAc/hexanes) gave 1.78 g (83% overall from **41**) of the title compound as a colorless oil. R_f = 0.31 (25% EtOAc/hexanes); $[\alpha]^{20}_D$ 18.92 (*c* = 1.67, $CHCl_3$); IR (film) 2986 (m), 2898 (m), 1722 (s), 1490 (s), 1233 (s), 1038 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.70 (t, 1.5 Hz, 1H), 6.90 (d, 1.7 hz, 1H), 6.84 (dd, 1.8, 8.1 Hz, 1H), 6.76 (d, 8.1 Hz, 1H), 6.0 (s, 2H), 5.47 (t, 1.5 Hz, 1H), 5.43 (t, 1.2 Hz, 1H) 5.17 (dt, 1.2, 6.3 Hz, 1H), 4.18 (ddd, 3.1, 6.3, 9.4 Hz, 1H), 2.51 (dddd, 1.6, 5.6, 7.8, 17.8 Hz, 1H), 2.39 (dddd, 1.4, 6.7, 6.8, 17.8 Hz, 1H), 1.63 (dddd, 5.6, 8.2, 14.2, 16.9 Hz, 1H), 1.55 (s, 3H, CH_3), 1.45 (s, 3H), 1.41 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 202.3, 148.2, 147.7, 142.4, 133.3, 119.7, 113.2, 108.5, 108.3, 106.8, 101.4, 78.3, 76.9, 40.6, 28.2, 25.8, 24.0; MS (EI) *m*/*z* (rel intensity) 304 (38), 246 (60), 218 (71), 203 (100), 147 (50), 102 (30), 85 (26), 70 (40), 43 (52); HRMS calcd for $C_{17}H_{20}O_5$ (M^+) 304.1311, found 304.1309.

(4*R*,5*S*)-*N*-(Tri-*n*-butylstannyl)methyl-4,5-*O*-isopropylidenedioxy-6-(3,4-methylenedioxy)phenyl-6-heptenaldimine (43). Hydrazine monohydrate (15 mL) was added to a solution of *N*-(tri-*n*-butylstannyl)methylphthalimide[3c] (2.52 g, 5.9 mmol) in absolute ethanol (20 mL), and the resultant mixture was heated to 75 °C. After 25 min, the clear solution was cooled to room temperature and concentrated, and the residue was extracted with ether (100 mL). The organic extract was washed with water (3 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude amine was mixed with ether (4 mL) containing 4 Å molecular sieves (0.5 g) and treated with a solution of the aldehyde **42** (1.56 g, 5.65 mmol) in ether (3 mL). After 18 h, the mixture was filtered through Celite and concentrated to afford 3.4 g (100%) of the title compound as an orange oil which was used without further purification. IR (film) 2960 (s), 1640 (m), 1495 (s), 1230 (s), 1035 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43 (t, 4.8 Hz, 1H), 6.90 (d, 1.8 Hz, 1H), 6.83 (dd, 1.84, 8.12 Hz, 1H), 6.76 (d, 8.1 Hz, 1H), 5.98 (s, 2H), 5.46 (t, 1.5 Hz, 1H), 5.14 (d, 6.3 Hz, 1H), 4.20 (ddd, 3.0, 6.2, 9.2 Hz, 1H), 3.40 [s, 2H, $^2J(^{117/119}Sn-^1H)$ = 21.7 Hz], 2.32 (ddd, 5.6, 10.3, 15.9 Hz, 1H), 1.45 (m, 8H), 1.34 (m, 6H), 0.89 (15H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 158.7, 148.1, 147.6, 142.7, 133.5, 119.6, 113.0, 108.3, 108.0, 106.9, 101.3, 78.5, 77.5, 47.0, 32.4, 29.3, 28.3, 27.5, 25.9, 13.9, 9.3; MS (EI) *m*/*z* (rel intensity) 494 (15), 490 (26), 478 (47), 304 (24), 291 (43), 235 (72), 233 (53), 179 (100), 175 (47), 70 (59); HRMS calcd for $C_{30}H_{49}NO_4SnH$ (M + 1) 608.2761, found 608.2753.

(3a*S*,4*S*,5*R*,7a*R*)-Octahydro-4,5-*O*-isopropylidenedioxy-3a-(3,4-methylenedioxy)phenylindole (44) and (3a*R*,4*S*,5*R*,7a*S*)-Octahydro-4,5-*O*-isopropylidenedioxy-3a-(3,4-methylenedioxy)phenyldihydroxyindole (45). A solution of the imine **43** (3.40 g, 5.65 mmol) in THF (20 mL) was added to a solution of *n*-BuLi (2.45 M in hexanes, 4.27 mL, 10.7 mmol) in THF (200 mL) at −78 °C over 20 min. After 25 min, the pale orange solution was treated with water (10 mL) in THF (30 mL). The mixture was then warmed to room temperature and concentrated. The residue was mixed with $CHCl_3$ (100 mL), and the organic phase was washed with brine (3 × 10 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 20 mL), and the resultant organic layer was washed with brine (2 × 8 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. Chromatography (alumina, gradient CH_2Cl_2 to 5% MeOH/CH_2Cl_2) afforded 1.33 g (74%) of the title compounds as a 5:1 mixture of diastereomers. Radial chromatography (alumina, 1 mm plate, gradient CH_2Cl_2 to 3% MeOH/CH_2Cl_2) of the mixture of diastereomers afforded an analytical sample of **44** as a colorless oil, as well as a sample enriched in **45**. Fractions were combined to carry on to the next step, which resulted in a 10:1 mixture of **44**/**45**. Data for **44**: R_f = 0.22 (20% MeOH/$CHCl_3$); $[\alpha]^{20}_D$ +34.3 (*c* = 1.80, $CHCl_3$); IR (film) 3450 (w), 2950 (s), 1510 (s), 1230 (s), 1035 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.99 (d, 1.8 Hz, 1H), 6.90 (dd, 1.7, 8.2 Hz, 1H), 6.77 (d, 8.2 Hz, 1H), 5.95 (s, 2H), 4.56 (d, 5.5 Hz, 1H), 4.31 (dd, 5.2, 11.5 Hz, 1H), 3.75 (dd, 4.9, 6.4 Hz, 1H), 3.00 (t, 9.1, 1H), 2.80 (dt, 10.3, 7.2 Hz), 2.55 (br s, 1H), 2.04 (dd, 5.8, 12.5 Hz, 1H), 1.95−1.80 (m, 2H), 1.59 (m, 1H), 1.39 (s, 3H), 1.37 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.8, 145.9, 138.9, 119.8, 108.1, 107.8, 107.7, 101.1, 78.0, 73.6, 58.7, 51.9, 42.8, 37.2, 27.9 27.3, 26.0, 25.4; MS (EI) *m*/*z* (rel intensity) 318 (22), 302 (26), 259 (100), 242 (23), 230 (37), 202 (47), 189 (27), 84 (32), 56 (36); HRMS calcd for $C_{18}H_{23}NO_4$ (M) 317.1627, found 317.1640. Data for **45** (obtained on a 3:2 mixture of **45**/**44**): R_f = 0.21 (20% MeOH/$CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (d, 1.8 Hz, 1H), 7.11 (dd, 2.0, 8.4 Hz, 1H), 6.76 (d, 8.3 Hz, 1H), 5.92 (ABq, 1.5 Hz, 2H), 4.39 (dd, 9.6, 17.6 Hz, 1H), 4.19 (d, 8.1 Hz, 1H), 3.18 (dt, 2.0, 9.4 Hz, 1H), 3.02 (dd, 9.5, 20.0 Hz, 1H), 2.91 (dt, 9.5, 11.5 Hz, 1H), 2.26 (ddd, 2.0, 7.5, 12.5 Hz, 1H), 1.95−1.8 (m,

4H), 1.41 (s, 3H), 1.35 (m, 1H), 1.33 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) d 146.8, 145.6, 134.6, 122.3, 110.9, 107.9, 107.1, 100.8, 84.6, 74.9, 62.8, 52.2, 45.7, 44.5, 24.4, 23.8, 23.1, 21.9.

(−)-Amabiline (2). *N*,*N*-Dimethylmethyleneammonium iodide (Eschenmoser's salt, 0.42 g, 2.3 mmol) was added to a solution of the amine **44** (0.090 g, 0.28 mmol, a 10:1 mixture of diasteromers) in CH_3CN (10 mL). The mixture was heated at reflux for 58 h and concentrated. Methanol (5 mL) was added to the residue, followed by 12 M HCl (1 mL). This mixture was stirred for 3 h and concentrated, and the excess HCl was removed by addition and evaporation of MeOH/benzene. The resultant hydrochloride salt was converted to the free amine by passing it through an ion-exchange resin (3 g, Dowex 1 × 8−200, OH^- form). Concentration of the filtrate followed by radial chromatogaphy (alumina, 1 mm plate, 1% to 4% MeOH/CH_2Cl_2) of the residue afforded 0.063 g (85%) of (−)-amabiline as colorless crystals, mp 250 °C (dec) [lit. mp 210 °C (dec)[11]]. R_f = 0.10 (20% MeOH/$CHCl_3$); $[\alpha]^{20}_D$ −31.6 (*c* = 0.28, EtOH) [lit. −32 (*c* = 0.30, EtOH)[11]]; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.48 (s, 1H), 5.89 (ABq, 1.4, 5.3 Hz, 2H), 4.56 (d, 2.6 Hz, 1H), 4.30 (d, 16.6 Hz, 1H), 4.08 (ddd, 2.9, 5.9, 7.9 Hz, 1H), 3.68 (d, 16.7 Hz, 1H), 3.3−3.2 (m, 2H), 2.78 (ddd, 6.2, 8.8, 13.1 Hz, 1H), 2.05 (ddd, 6.3, 11.8, 12.1 Hz, 1H), 1.89−1.71 (m, 4H), 1.34 (app ddd, 3.9, 13.1, 17.5 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.8, 146.2, 137.3, 126.9, 107.1, 104.0, 101.0, 69.8, 69.0, 63.3, 62.0, 50.9, 49.8, 37.9, 27.0, 25.8. Measurement of the ^{1}H NMR and ^{13}C NMR spectra of synthetic (−)-amabiline in DMSO-d_6 allowed comparison with the spectroscopic data on natural (−)-amabiline provided by Professor Cordell (University of Chicago at Illinois), revealing an exact match.[20]

(3a*S*,4*S*,5*R*,7a*R*)-Octahydro-4,5-*O*-isopropylidenedioxy-1-methyl-3a-(3,4-methylenedioxy)phenylindole (46) and (3a*R*,4*S*,5*R*,7a*S*)-Octahydro-4,5-*O*-isopropylidenedioxy-1-methyl-3a-(3,4-methylenedioxy)phenylindole (47). A solution of the imine **43** (2.11 g, 3.48 mmol) in THF (10 mL) was added to a solution of *n*-BuLi (2.45 M in hexanes, 2.7 mL, 6.6 mmol) in THF (200 mL) at −78 °C over 15 min. After the resulting orange solution was stirred for 1 h at −78 °C, iodomethane (0.48 mL, 6.6 mmol) was added in a dropwise fashion. The mixture was allowed to warm to room temperature, quenched by the addition of ammonium hydroxide, and concentrated, and the residue was extracted with EtOAc (100 mL). The organic layer was washed with brine (3 × 10 mL), and the aqueous layers were combined and extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Chromatography (5% MeOH/CH_2Cl_2) afforded 0.700 g of **46** and 0.162 g of **47** (82% total) as colorless foams. Data for **46**: R_f = 0.20 (5% MeOH/$CHCl_3$); $[\alpha]^{20}_D$ 31.04 (*c* = 0.73, $CHCl_3$); IR (film) 2943 (s), 1504 (s), 1239 (s), 1030 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.93 (d, 1.9 Hz, 1H), 6.84 (dd, 2.0, 8.3 Hz, 1H), 6.77 (d, 8.3 Hz, 1H), 5.95 (s, 2H), 4.51 (d, 6.77 Hz, 1H), 4.42 (m, 1H), 3.05 (br t, 3 Hz, 1H), 2.85 (m, 1H), 2.48 (s, 3H), 2.39 (m, 1H), 2.1−1.8 (m, 4H), 1.55 (dm, 12.3 Hz, 1H), 1.44 (dm, 14.1 Hz, 1H), 1.36 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 147.6, 145.6, 140.6, 120.4, 108.8, 107.5, 107.0, 101.1, 77.9, 73.3, 65.9, 52.6, 50.6, 40.6, 38.2, 26.8, 24.5, 24.1, 22.8; MS (EI) *m*/*z* (rel intensity) 331 (74), 330 (78), 273 (76), 216 (58), 203 (76), 86 (58), 70 (49), 49 (100), 44 (94); HRMS calcd for $C_{18}H_{25}NO_4$ (M^+) 331.1783, found 331.1773. Data for **47**: R_f = 0.27 (5% MeOH/$CHCl_3$); $[\alpha]^{20}_D$ 99.88 (*c* = 1.33, $CDCl_3$); IR (film) 2677 (s), 1487 (s), 1234 (s), 1441 (s); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54 (d, 1.8 Hz, 1H), 7.44 (dd, 1.9, 8.4 Hz, 1H), 6.69 (d, 8.4 Hz, 1H), 3.75 (ddd, 6.45, 8.1, 10.8 Hz, 1H), 4.2 (d, 8.2 Hz, 1H), 3.19 (dd, 7.7, 17.4 Hz, 1H), 2.35 (m, 1H), 2.35 (s, 3H), 2.13 (t, 9.0 Hz, 1H), 2.03 (m, 2H), 1.87 (ddt, 5.7, 9.5, 18.0 Hz, 1H), 1.75 (m, 2H), 1.65 (dd, 10.5, 20.7 Hz), 1.49 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.4, 145.2, 137.1, 122.8, 110.8, 108.6, 106.9, 100.6, 85.6, 75.4, 70.3, 55.6, 51.8, 42.1, 41.9, 26.1, 25.0, 23.7, 21.2; MS (EI) *m*/*z* (rel intensity) 330 (100), 316 (21), 217 (54), 216 (52), 203 (52), 202 (49), 85 (75), 70 (78), 44 (93); HRMS calcd for $C_{18}H_{25}NO_4$ (M^+) 331.1783, found 331.1773.

(−)-Augustamine (3). Concentrated HCl (2 mL) was added to a solution of the octahydroindole **46** (0.162 g, 0.490 mmol) in methanol (4 mL). After 4 h, the solvent was removed in vacuo, the residue was dissolved in methanol (0.5 mL) and benzene (2 mL), and the solvent was removed in vacuo once again. This process was repeated twice to produce an off-white foam, which was dissolved in CH_2Cl_2 (2 mL) and treated with trimethylorthoformate (3 mL). After 18 h, the solution was concentrated, the residue was dissolved in CH_2Cl_2 (1 mL) and benzene (2 mL), and the solution was then concentrated in vacuo. This process was repeated twice to produce an off-white foam which was dissolved CH_2Cl_2 (3 mL) and treated with methanesulfonic acid (0.35 mL, 5.36 mmol). After 3 h, $CHCl_3$ (20 mL) was added, and the solution was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL) and brine (1 × 5 mL). The aqueous layer was extracted with $CHCl_3$ (10 mL), and this organic layer was washed with $NaHCO_3$ (1 × 5 mL) and brine (1 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography (gradient, 1 to 5% MeOH/CH_2Cl_2) of the residue gave 0.11 g (76%) of (−)-augustamine **3** as colorless crystals, mp 167−170 °C [lit. mp 170−175 °C[11b]]. R_f = 0.5 (10% MeOH/$CHCl_3$); $[\alpha]^{20}_D$ −80.1 (*c* = 1.42, $CHCl_3$) [lit. −83 (*c* = 1.4, $CHCl_3$)[11b]]. The ^{1}H NMR and ^{13}C NMR spectra matched those reported by Ali. et al.[11b]

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Supporting Information Available: Photocopies of ^{1}H NMR and ^{13}C NMR spectra of new compounds without elemental analysis (60 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.

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