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# Enantiospecific Total Synthesis of (−)-(*E*)16-Epiaffinisine, (+)-(*E*)16-Epinormacusine B, and (+)-Dehydro-16-epiaffinisine as well as the Stereocontrolled Total Synthesis of Alkaloid G

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An efficient strategy is described for the total synthesis of the sarpagine-related indole alkaloids (−)-(*E*)16-epiaffinisine (**1**), (+)-(*E*)16-epinormacusine B (**2**), and (+)-dehydro-16-epiaffinisine (**4**). A key step employed the chemospecific and regiospecific hydroboration/oxidation at C(16)−C(17); this method has also resulted in the synthesis of (+)-dehydro-16-epinormacusine B (**5**). The oxy-anion Cope rearrangement followed by protonation of the enolate that resulted under conditions of kinetic control has been employed to generate the key asymmetric centers at C(15), C(16), and C(20) in alkaloid G (**7**) in a highly stereocontrolled fashion (>43:1). Conditions that favor control of the sarpagine stereochemistry at C(16) vs the epimeric ajmaline configuration at the same stereocenter have been determined. The formation of the required cyclic ether in **4**, **5**, and **7** was realized with complete control from the top face on treatment of the corresponding alcohols with DDQ/THF or DDQ/aq THF in excellent yields.

## Introduction

The sarpagine alkaloids (−)-(*E*)16-epiaffinisine (**1**), (+)-(*E*)16-epinormacusine B (**2**), and (+)-dehydro-16-epiaffinisine (**4**) were isolated from the leaves and root bark of *Ervatamia hirta* from Malaysia.[1] This plant comprises one of the ingredients in the preparation of poisoned arrows and was also used in traditional medicine for the treatment of ulcerations of the nose.[2] The structures of (−)-(*E*)16-epiaffinisine (**1**), (+)-(*E*)16-epinormacusine B (**2**), and (+)-dehydro-16-epiaffinisine (**4**) were elucidated on the basis of $^1$H NMR and $^{13}$C spectroscopic studies and further supported by analysis of their two-dimensional NMR spectral data as well as chemical correlations.[1] Several other sarpagine-related indole alkaloids in this class (Figure 1) have been isolated from *Gardneria nutans* by Haginiwa and Sakai et al.,[3] including gardnerine (**3**) and gardnutine (**6**). Although dihydro-16-epinormacusine B (**5**) has not yet been isolated from the plant, it is postulated that it may serve as a biogenetic intermediate on the route toward **4**. Alkaloid G (**7**) was isolated from plant cell cultures of *Rauwolfia serpentina* Benth by Stöckigt et al.[4] after feeding experiments with (+)-ajmaline (**8**); the latter alkaloid was isolated from the roots of *R. serpentina* in 1931[5] and is a clinically important indole alkaloid in the cardiovascular area with historical significance.[6]

As illustrated in Figure 1, the common structural features of these indole alkaloids (**1**−**7**) are the asymmetric centers at C-3(*S*), C-5(*R*), C-15(*R*), and C-16(*S*). Alkaloid G (**7**) is of special interest because of the novel C(17)-hemiacetal bond, C(21)-hydroxyl group, and C(20)-ethyl moiety that lies in the *β*-position, whereas the ethylidene double-bond present in alkaloids **1**−**6** [C(19)−C(20)] occupies the less stable (*E*)-configuration. Because of their unique structure and the paucity of alkaloidal material from natural sources, it was decided to prepare them in enantiospecific fashion for biological screening.

## Results and Discussion

No total synthesis of these indole alkaloids (**1**−**6**) has been reported to date. Magnus et al.[7] reported the synthesis of the enantiomer of **2**, which was employed as an intermediate in the total synthesis of (+)-koumine and (+)-taberpsychine. Herein, we wish to describe the first enantiospecific total synthesis of (*E*)16-epiaffinisine (**1**), (*E*)16-epinormacusine B (**2**), and dehydro-16-epiaffinisine (**4**). In addition, dehydro-16-epinormacusine B (**5**) was also prepared by extension of this approach and may provide a route for the synthesis of gardnutine (**6**) in the future.[8]

As shown in Schemes 2 and 3, the (*E*)-ethylidene ketones **9** and **13** were chosen as starting materials, for

(1) Clivio, P.; Richard, B.; Deverre, J.-R.; Sevenet, T.; Zeches, M.; Le Men-Olivier, L. *Phytochemistry* **1991**, *30*, 3785.
(2) Van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A.; Leeuwenberg, A. J. M.; Bisset, N. G. *J. Ethnopharm*. **1984**, *10*, 1.
(3) Haginiwa, J.; Sakai, S.; Kubo, A.; Hamamoto, T. *Yakugaku Zasshi* **1967**, *87*, 1484.
(4) Endress, S.; Takayama, H.; Suda, S.; Kitajima, M.; Aimi, N.; Sakai, S.-I.; Stöckigt, J. *Phytochemistry* **1993**, *32*, 725.
(5) Siddiqui, S.; Siddiqui, R. H. *J. Ind. Chem. Soc.* **1931**, *8*, 667.
(6) Koskinen, A.; Lounasmaa, M. The Sarpagine-Ajmaline Group of Indole Alkaloids. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1983; Vol 43, p 267.
(7) (a) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc*. **1989**, *111*, 786. (b) Magnus, P.; Mugrage, B.; DeLuca, M.; Cain, G. A. *J. Am. Chem. Soc*. **1990**, *112*, 5220.

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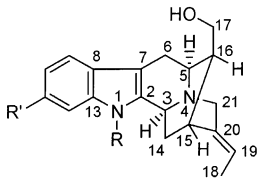
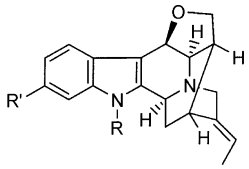
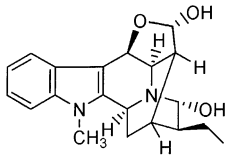


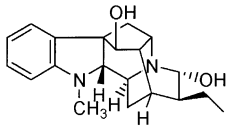
**1** R = $CH_3$, R' = H, (-)-(*E*)16-epiaffinisine
**2** R = H, R' = H, (+)-(*E*)16-epinormacusine B
**3** R = H, R' = $OCH_3$, gardnerine



**4** R = $CH_3$, R' = H, (+)-dehydro-16-epiaffinisine
**5** R = H, R' = H, (+)-dehydro-16-epinormacusine B
**6** R = H, R' = $OCH_3$, gardnutine



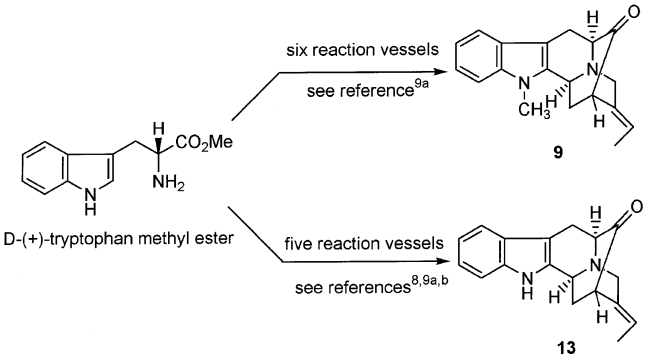
**7** alkaloid G



**8** ajmaline

**FIGURE 1.**

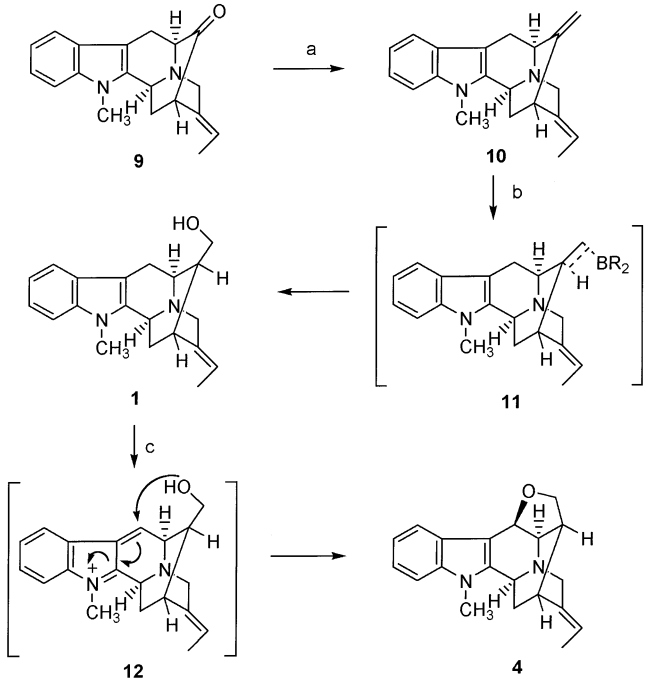
**SCHEME 1**




they were readily available from the D-(+)-tryptophan methyl ester via the asymmetric Pictet−Spengler reaction (>98% ee), the Dieckmann cyclization, and the enolate-mediated palladium-catalyzed intramolecular cyclization (Scheme 1). The stereocenters at C(3), C(5), and C(15) as well as the C(19)−C(20) (*E*)-ethylidene function were controlled in a stereospecific fashion.[8,9]

The ketone **9** was available in enantiospecific fashion in six reaction vessels from D-(+)-tryptophan methyl ester employed for the total synthesis $N_a$-methylvellosimine (Scheme 1).[9a] The ketone **9** was stirred with methyltriphenylphosphonium bromide in benzene in the presence of potassium *tert*-butoxide (Scheme 2) to provide the olefin **10**; the Wittig reaction took place in 90% yield. Hydroboration/oxidation was employed to solve the problem of chemoselectivity between the olefinic centers. It was felt that the less hindered C(16)−C(17) double bond, relative to the C(19)−C(20) site, would be attacked more readily by selective hydroborating agents. It had been documented that the C(19)−C(20) double bond of the enantiomer of **9** reacted with both $BH_3$·DMS and $BH_3$·THF; however, this olefin did not react with thexyl borane or 9-BBN.[10] Certainly, a key issue rested on the

**SCHEME 2**[a]




[a] Reagents and conditions: (a) $PPh_3CH_3Br$, KO-*t*-Bu, benzene, rt, 4 h, 92%. (b) $Sia_2BH$; $NaOH/H_2O_2$, rt or 9-BBN; $NaOH/H_2O_2$, rt, 75−80%. (c) DDQ, THF, reflux, 1 h, 95%.

regiopreference for the desired attack at the C(16)−C(17) double bond in contrast to the C(19)−C(20) bond. Importantly, Magnus et al.[7] had previously demonstrated that C(17) of the C(16)−C(17) olefinic site could be selectively hydroborated to provide the 16(*S*) alcohol in the synthesis of (+)-koumine. From examination of the possible transition states,[11] attack from the convex face seemed more favorable, although it would be difficult to distinguish the outcome solely on the basis of steric factors. Gratifyingly, (*E*)16-epiaffinisine (**1**) was obtained as the only detectable diastereomer when the hindered diisoamyl-

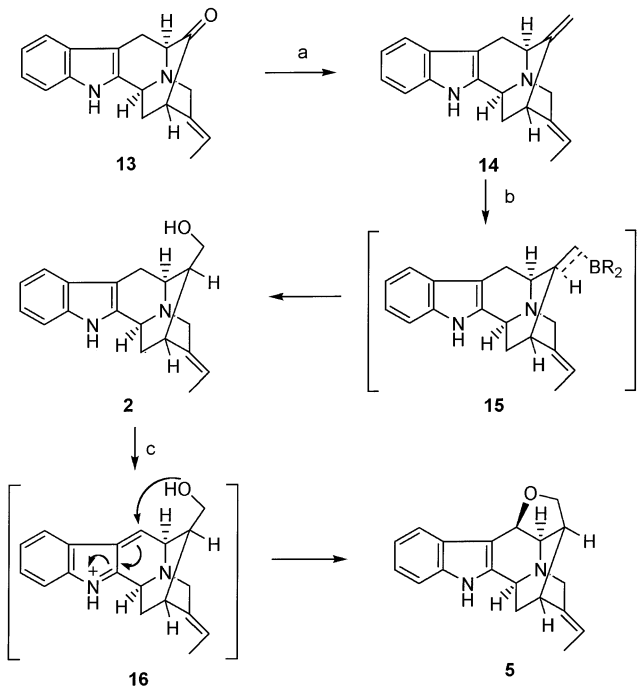
(8) Preliminary communication: Yu, J.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 4681.

(9) (a) Yu, J.; Wearing, X.; Cook, J. M. *Tetrahedron Lett.* **2003**, *44*, 543. (b) Wang, T.; Cook, J. M. *Org. Lett.* **2000**, *2*, 2057. (c) Zhao, S.; Liao, X.; Cook, J. M. *Org. Lett.* **2002**, *4*, 687. (d) Liu, X.; Zhang, C.; Liao, X.; Cook, J. M. *Tetrahedron Lett.* **2002**, *43*, 7373. (e) Yu, P.; Wang, T.; Li, J.; Cook, J. M. *J. Org. Chem.* **2000**, *65*, 3173.

(10) Liu, X. Ph.D. Thesis, University of Wisconsin−Milwaukee, Milwaukee, WI, 2002.

(11) Brown, H. C.; Keblys, K. A. *J. Am. Chem. Soc.* **1964**, *86*, 1791.

**SCHEME 3**[a]




[a] Reagents and conditions: (a) $PPh_3CH_3Br$, KO-*t*-Bu, benzene, rt, 4 h, 92%. (b) $Sia_2BH$; $NaOH/H_2O_2$, rt, or 9-BBN; $NaOH/H_2O_2$, rt, 75−80%. (c) DDQ, THF, reflux, 1 h, 95%.

borane or 9-BBN was employed as a hydroborating agent, followed by oxidative workup. Further oxidative cyclization of **1** affected by DDQ in THF afforded dehydro-16-epiaffinisine (**4**) in 98% yield in stereospecific fashion. Although the vinylogous iminium ion **12** is depicted here as an intermediate, a number of other mechanisms for the generation of **4** are possible.[12−21] The spectroscopic properties and optical rotations of synthetic **1** and **4** agree in all respects with those reported for the natural products.[1] Thus, a concise and stereospecific total synthesis of **1** and **4** has been carried out from commercially available D-(+)-tryptophan methyl ester that involved only seven reaction vessels for **1** (25% overall yield) and eight reaction vessels for **4** (24% overall yield).

Analogous to the preparation of ketone **9**, the synthesis of the key (*E*)-ethylidene ketone **13** was completed via an efficient enolate-driven palladium-catalyzed cyclization as a key step (Scheme 1).[8,9a,b] The synthesis of **2** was completed via a Wittig reaction coupled with a chemospecific, regiospecific hydroboration/oxidation (74% yield for the two steps) sequence, as depicted in Scheme 3. (*E*)-

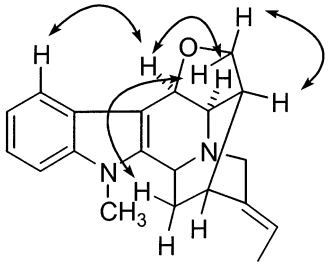


**FIGURE 2.** Selected NOESYs of (+)-dehydro-16-epiaffinisine (**4**).

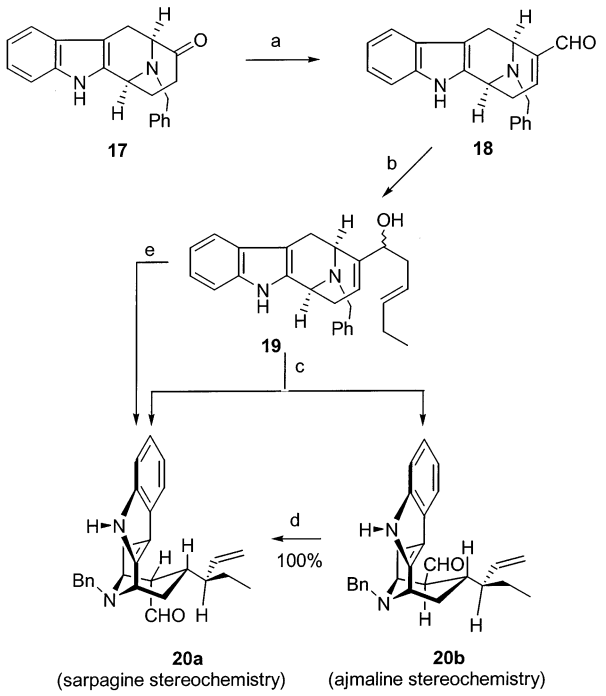
16-Epinormacusine B (**2**) was obtained as the sole diastereomer from this sequence; consequently, (*E*)16-epinormacusine B (**2**) could be prepared in a short synthetic sequence from D-(+)-tryptophan methyl ester in eight reaction vessels in 26% overall yield. The spectroscopic properties and optical rotation of synthetic **2** were in good agreement with the natural product.[1] Finally, oxidative cyclization of alcohol **2** by treatment with DDQ in THF afforded the dehydro-16-epinormacusine B (**5**) in 95% yield (Scheme 3). The stereochemistry of the chiral centers in both **4** and **5** was determined by two-dimensional NOESY experiments; they were present in the correct configuration at C(3), C(5), C(6), C(15), and C(16), as depicted in Figure 2.

The total synthesis of alkaloid G (**7**) was first reported by Li and Cook,[22] and an improved route appeared later.[23] The chiral centers of C(15), C(16), and C(20) were established selectively in an earlier work based on a Barbier−Grignard process[22−24] (Mg metal) with a seven-carbon atom pseudosymmetric carbanion, followed by an oxy-anion Cope rearrangement. This approach resulted in the formation of several diastereomers at C(20), the majority of which could be employed in the synthesis of (+)-**8**. Recently, this seven-carbon fragment has been replaced with a five-carbon unit (*trans*-1-bromo-2-pentene) employing the barium chemistry of Yamamoto.[25,26] This provided a homoallylic alcohol that underwent the oxy-anion Cope rearrangement with high diastereoselectivity. Kinetic protonation of the enolate that resulted gave the desired intermediate with the correct asymmetric centers at C(15), C(16), and C(20) with high diastereoselectivity (43:1). This improvement also provided the first facile entry into the desired absolute configuration of the ethyl group at C(20) of the ajmaline base, alkaloid G (**7**), and resulted in an improved enantiospecific total synthesis of alkaloid G (**7**), the details of which follow below.

The $N_a$-H, $N_b$-benzyl tetracyclic ketone **17** was chosen as the starting material (Scheme 4).[9] Conversion of the carbonyl function of (−)-**17** into the α,β-unsaturated aldehyde moiety of **18** was achieved through the spirooxiranophenylsulfoxide[27,28] in 87% yield. A key improve-

(12) Pinchon, T.-M.; Nuzillard, J.-M.; Richard, B.; Massiot, G.; Le Men-Olivier, L.; Sevenet, T. *Phytochemistry* **1990**, *29*, 3341.
(13) Oikawa, Y.; Yonemitsu, O. *J. Org. Chem*. **1977**, *42*, 1213.
(14) Oikawa, Y.; Yoshioka, T.; Mohri, K.; Yonemitsu, O. *Heterocycles* **1979**, *12*, 1457.
(15) Campos, O.; DiPierro, M.; Cain, M.; Mantei, R.; Gawish, A.; Cook, J. M. *Heterocycles* **1980**, *14*, 975.
(16) Cain, M.; Mantei, R.; Cook, J. M. *J. Org. Chem*. **1982**, *47*, 4933.
(17) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M. *Org. Lett*. **2001**, *3*, 345.
(18) Walker, D.; Hiebert, J. D. *Chem. Rev*. **1967**, *67*, 153.
(19) Braude, E. A.; Jackman, L. M.; Linstead, R. P. *J. Chem. Soc*. **1954**, 3548.
(20) Jackman, L. M. *Adv. Org. Chem*. **1960**, *2*, 329.
(21) Bergman, J.; Carlsson, R.; Misztal, S. *Acta Chem. Scand. B* **1976**, *30*, 853.
(22) (a) Li, J.; Cook, J. M. *J. Org. Chem*. **1998**, *63*, 4166. (b) Li, J.; Wang, T.; Yu, P.; Peterson, A.; Weber, R.; Soerens, D.; Grubisha, D.; Bennett, D. Cook, J. M. *J. Am. Chem. Soc*. **1999**, *121*, 6998.
(23) Wang, T.; Xu, Q.; Yu, P.; Liu, X.; Cook, J. M. *Org. Lett*. **2001**, *3*, 345.
(24) Fu, X.; Cook, J. M. *J. Am. Chem. Soc*. **1992**, *114*, 6910.
(25) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc*. **1991**, *113*, 8955.
(26) Yanagisawa, A.; Yamamoto, H. *Active Metals*; Fürster, A., Ed.; VCH Verlagsgesellschaft: Weinheim, 1996; p 61.
(27) Taber, D. F.; Guun, B. P. *J. Org. Chem*. **1979**, *16*, 1377.

**SCHEME 4**[a]




[a] Reagents and conditions: (a) $ClCH_2SOPh$, LDA/THF, −78 °C, KOH (aq), rt, $LiClO_4$/dioxane, reflux 24 h, on 50 g scale, 87% overall yield. (b) Li/biphenyl/$BaI_2$/THF, −78 °C, **18** and *trans*-1-bromo-2-pentene, 90%. (c) KH/dioxane/18-crown-6, 100 °C, 14 h, 85%. (d) NaOMe/MeOH, 95%. (e) KH/dioxane/18-crown-6, 100 °C, 14 h; $CH_3OH$, 0 °C to room temperature, 4 h, 85%.

ment in the synthesis of **7** came on conversion of aldehyde **18** into the allylic alcohol **19** employing a modification of the chemistry of Yamamoto.[25,26] When *trans*-1-bromo-2-pentene was stirred with barium metal under normal reaction conditions, none of the desired olefinic alcohol **19** was observed. However, when aldehyde **18** and *trans*-1-bromo-2-pentene were premixed and added to a solution of preformed barium metal at −78 °C, analogous to a Barbier−Grignard process, a 90% yield of the desired homoallylic alcohol **19** was obtained. Allylic rearrangement of the barium-stabilized carbanion did not occur at −78 °C.

When the homoallylic alcohol **19** was heated to 100 °C under the conditions of the oxy-anion Cope rearrangement (KH, 18-crown-6, dioxane), the process took place from the desired α-face of the olefinic system to furnish the desired stereochemistry at C(15) and C(20) with high diastereoselectivity (>30:1). Only a trace of the epimeric diastereomer at C(15) was ever observed; moreover, the correct chirality of the ethyl function (20(*S*)) required for **7** was also established. The two epimers **20a** and **20b** at C(16), originally isolated as a 4:1 mixture, could be converted entirely into the sarpagine stereochemistry at C(16) on treatment with base under thermodynamic control.[9e]

From examination of MM2[29] calculations and epimerization experiments, it was clear that epimer **20b** with the ajmaline aldehydic stereochemistry at C(16) was the thermodynamically less stable epimer. In earlier work,

(28) Reutrakul, V.; Kanghae, W. *Tetrahedron Lett.* **1977**, *16*, 1377.
(29) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

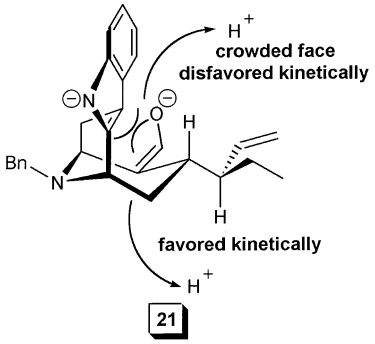



**FIGURE 3.**

**TABLE 1. Kinetic Protonation versus Thermodynamic Equilibration**

| entry | solvent | temp | reagent for quench | ratio of **20a**:**20b**[a] |
|---|---|---|---|---|
| 1 | dioxane | 0 °C | $CH_3OH$, 0 °C→rt, 4 h | 100:0 |
| 2 | dioxane | 0 °C | $CH_3OH$ | 4:1 |
| 3 | dioxane | 0 °C | 2, 6-diisopropylphenol | 3:2 |
| 4 | dioxane | 0 °C | 1N HCl (aq) | 5:6 |
| 5 | dioxane | −78 °C | 1N HCl (aq) | 1:7 |
| 6 | dioxane/THF | −78 °C | 1N TFA (THF solution) | 1:27 |
| 7 | dioxane/THF | −100 °C | 1N TFA (THF solution) | 1:43 |

[a] Ratio was determined by integration of the $^1H$ NMR spectrum of the crude product. **20a**: sarpagine stereochemistry. **20b**: ajmaline stereochemistry.

epimerization of the aldehydic group at C(16) from the *R* to the *S* (ajmaline) configuration was reported as 43:7 to 7:3,[30−32] where the desired (ajmaline)16(*S*) material was the minor component. A study of the structure of the enolate (see **21**, Figure 3) indicated that protonation from the less hindered (bottom) face (kinetic protonation) might provide the desired 16(*S*) stereochemistry directly in a one-pot fashion. Consequently, a number of experiments were carried out to study the effect of kinetic protonation in this system (see **21**). The initial factor considered was the steric bulk of the proton donor. Attack on the enolate from the crowded *β*-face with a bulky reagent should be retarded and provide a higher ratio of 16(*S*) to 16(*R*). However, when diisopropylphenol was employed to quench the reaction, the ratio only increased from 1:4 to 2:3 (compare entries 2 and 3, Table 1). The second factor considered was based on kinetic control of the protonation. A higher concentration of the proton donor should favor kinetic protonation. As shown in entry 4 (Table 1), when the enolate **21** was quenched under acidic conditions, the ratios of the desired **20b** (16(*S*)) to **20a** began to increase in favor of the desired aldehyde **20b**. The third factor considered was temperature. A lower temperature was believed to favor the kinetic process; moreover, the rate of epimerization of the aldehyde from the 16(*S*) to the 16(*R*) stereochemistry would be retarded. When the enolate was quenched at −78 °C, the ratio of **20b** (16(*S*)) to **20a** was altered to 7:1 (entry 5, Table 1). One problem involved in this process arose because the melting point of dioxane was higher than −78 °C; consequently, the actual temperature of the quench was much higher than this.

(30) Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sarkar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506.
(31) Mashimo, K.; Sato, Y. *Tetrahedron Lett.* **1969**, 901.
(32) Van Tamelen, E. E.; Oliver, L. K. *Bioorg. Chem.* **1976**, *5*, 309.

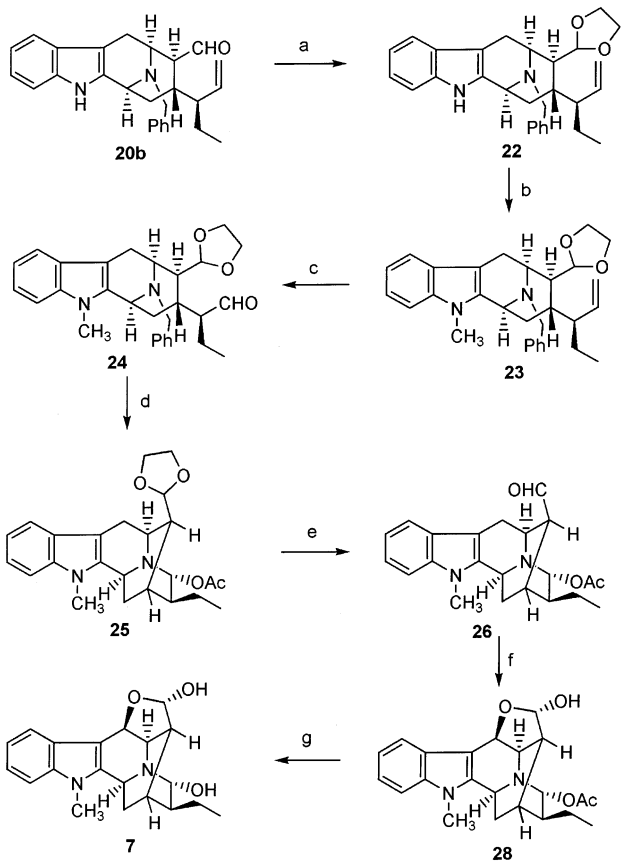
To solve this problem, the mixture was diluted with dry THF after the oxy-anion Cope process had been completed (entries 6 and 7, Table 1). At the same time, another factor was considered. It was decided to quench the enolate by adding it to a cold solution of TFA/THF in order to maintain an excess of acid at all times. This would retard the epimerization of the aldehyde from the crowded *β*-face to the thermodynamically stable α-face. As shown in entry 7 (Table 1), when the enolate was quenched by pouring it (**21**, THF/dioxane, −100 °C) into a (1 N) TFA/THF solution at −100 °C, the ratio of **20b** to **20a** improved dramatically to greater than 43:1. This one-pot conversion of **19** into **20b** can now be accomplished in high yield. This, for the first time, provided a highly stereocontrolled route to the key chiral centers at C(15), C(16), and C(20) of the ajmaline series.

The enantiospecific total synthesis of alkaloid G (**7**) (from **20b**) was completed as follows. The aldehydic group in **20b** was protected as the acetal **22** with ethylene glycol/*p*-TSA with no epimerization at C(16). This provided a stable stereocenter at C(16), which permitted the conversion (NaH, $CH_3I$) of $N_a$-H analogue **22** into the $N_a$-methyl derivative **23** in 94% yield. This improvement resulted in the replacement of $N_a$-methyl-(D)-tryptophan with the cheaper D-(+)-tryptophan employed in the improved asymmetric Pictet−Spengler reaction.[9e] Oxidative removal of the methylene group of the latent aldehyde in **23** with $OsO_4/NaIO_4$ furnished aldehyde **24** in 91% yield (Scheme 5). Analogous to the chemistry of Li[22] previously reported from our laboratory, catalytic removal of the benzyl function (Pd/C, $H_2$) and acetylation of the resulting carbinolamine resulted in a one-pot process to provide acetate **25**. The acetal moiety of **25** was removed under standard conditions to release the aldehyde **26**. This aldehyde was oxidized at C(16) employing the conditions of Yonemitsu[13,14] later modified in our laboratory (DDQ, aq THF)[15,16] to provide the acetal **28** stereospecifically (94%). One possible mechanism for the generation of **28** is depicted in Scheme 6. It has been proposed in the $N_a$-H indole system that indolenine/diene intermediates such as **27** are involved.[12−21] Although higher in energy, by analogy it is conceivable that the $N_a$-methyl-substituted indolenine **27** was involved, which could only be attacked by the aldehyde moiety from the top face of the olefinic system. This would provide the stereochemistry at C(6) illustrated in **27**. Hydrolysis of **28** under standard conditions provided **7** in enantiospecific fashion and in 36% overall yield (from **17**). The proton and $^{13}C$ NMR spectrum of **7** were identical to those reported for the natural product by Stöckigt and Sakai.[4]

## Conclusion

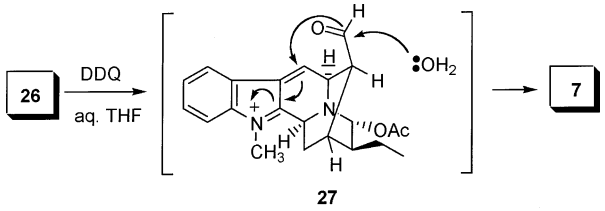
The first stereospecific total synthesis of (−)-(*E*)16-epiaffinisine (**1**), (+)−(*E*)16-epinormacusine B (**2**), and (+)-dehydro-16-epiaffinisine (**4**) has been accomplished from commercially available D-(+)-tryptophan methyl ester via the asymmetric Pictet−Spengler reaction. A stereocontrolled intramolecular enolate-driven palladium-mediated cross-coupling reaction, as well as a chemospecific and regiospecific hydroboration/oxidation, were also key steps in this approach. In these syntheses, the stereochemistries at C(3), C(5), C(6), C(15), and C(16) and the geometry of the C(19)−C(20) (*E*)-ethylidene were controlled completely. The synthesis of (+)-dehydro-16-epinormacusine B (**5**) was also completed and provides a model route to reliably access other sarpagine-related alkaloids, including gardnutine (**6**). The oxy-anion Cope rearrangement of **19**, followed by quenching of the enolate under kinetically controlled conditions at −100 °C, has provided the C(15), C(16), and C(20) asymmetric centers in **20b** in a highly stereoselective manner. The homoallylic alcohol **19** was prepared by a Barbier modification of the barium chemistry of Yamamoto again in high yield. The combination of the cyclization reactions described above has permitted the use of (D)-(+)-tryptophan as both the chiral auxiliary and the starting material in the synthesis of **1**, **2**, **4**, **5**, and **7** with extremely high stereocontrol.

**SCHEME 5**[a]




[a] Reagents and conditions: (a) ethylene glycol/*p*-TSA/benzene, Δ, 20 h, 92%. (b) NaH/THF, $CH_3I$, 94%. (c) $OsO_4$/py/THF, 0 °C, 16 h; $NaHSO_3$ (aq), rt, 4 h; $NaIO_4/CH_3OH/H_2O$, 0 °C 16 h, 91%. (d) $Pd/C/H_2$, DME, 2 days; $Ac_2O$/DMAP, 2 h, 91%. (e) *p*-TSA/acetone, rt, 12 h, 89%. (f) DDQ/THF/$H_2O$, rt, 94%. (g) $CH_3OH$, $K_2CO_3$ (20% aq), 0 °C, 2 h, 92%.

**SCHEME 6**



## Experimental Section

**General Methods.** Reagent and solvent purification, workup procedures, and analyses were performed in general as described previously.[22]

**Conversion of the Pentacyclic Ketone (9) into (+)-3-Ethylidene-12-methyl-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methano-13-methylene-indole[2,3-*a*]quinolizine (10) via the Wittig Reaction.** A mixture of anhydrous potassium *tert*-butoxide (3.24 g, 2.75 mmol) and methyltriphenylphosphonium bromide (8.93 g, 2.5 mmol) in dry benzene (150 mL) was allowed to stir at room temperature for 1 h. The pentacyclic ketone **9** (1.46 g, 0.50 mmol) in THF (50 mL) was then added into the above orange-colored solution dropwise at room temperature. The mixture that resulted was stirred at room temperature for 4 h. The mixture was diluted with EtOAc (500 mL), washed with $H_2O$ (3 × 50 mL) and brine (100 mL), and dried ($K_2CO_3$). The solvent was removed under reduced pressure, and the oil that resulted was chromatographed (silica gel, $CHCl_3$/MeOH = 40:1) to provide the olefin **10** (1.30 g, 90%): FTIR ($CHCl_3$) 3439 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.67 (3 H, dt, $J$ = 6.8, 1.8 Hz), 1.87 (1 H, dt, $J$ = 9.2, 2.8 Hz), 2.25 (1 H, ddd, $J$ = 11.8, 10.0, 1.7 Hz), 3.02 (1 H, dd, $J$ = 15.4, 1.3 Hz), 3.24 (1 H, dd, $J$ = 15.5, 5.2 Hz), 3.35 (1 H, m), 3.60 (3 H, s), 3.84 (2 H, m), 3.93 (1 H, m), 4.35 (1 H, dd, $J$ = 9.9, 2.3 Hz), 4.86 (2 H, t, $J$ = 2.4 Hz), 5.34 (1 H, q, $J$ = 7.0 Hz), 7.08 (1 H, td, $J$ = 6.9, 1.2 Hz), 7.20 (1 H, td, $J$ = 6.9, 1.1 Hz), 7.27 (1 H, d, $J$ = 7.6 Hz), 7.50 (1 H, td, $J$ = 7.6 Hz); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 12.4, 26.2, 29.2, 35.3, 36.3, 49.6, 56.1, 56.8, 103.8, 105.4, 108.7, 115.4, 118.1, 118.8, 120.9, 127.0, 136.4, 137.3, 138.2, 151.6; EIMS (*m*/*z*, relative intensity) 290 ($M^+$, 100), 275 (13), 182 (76). Anal. Calcd for $C_{20}H_{22}N_2$: C, 82.72; H, 7.04; N, 9.65. Found: C, 82.84; H, 7.29; N, 9.46.

**Hydroboration of (+)-3-Ethylidene-12-methyl-1,3,4,7,-12,12b-hexahydro-2*H*,6*H*-2,6-methano-13-methylene-indole[2,3-*a*]quinolizine (10) Followed by Oxidation to Provide (−)-(*E*)16-Epiaffinisine (1).** A solution of commercially available $BH_3$−THF (1.0 M in THF, 5 mL) was treated with 2-methyl-2-butene (2.0 M in THF, 10 mL) at −5 °C to give a solution of diisoamylborane in THF. A solution of olefin **10** (290 mg, 1.0 mmol) in THF (12 mL) was added to the diisoamylborane at 0 °C. The solution was warmed to room temperature and stirred for 5 h. To the solution was then added 10% aq NaOH (2 mL), followed by addition of 30% $H_2O_2$ (4 mL). The mixture was stirred for 2 h at room temperature, diluted with $CH_2Cl_2$ (200 mL), washed with $H_2O$ (3 × 50 mL) and brine (100 mL), and dried ($K_2CO_3$). The solvent was removed under reduced pressure, and the residue that resulted was chromatographed (silica gel, $CHCl_3$/MeOH = 9:1) to provide the alcohol **1** (246 mg, 80%): FTIR ($CHCl_3$) 3350, 2918 $cm^{-1}$; $[\alpha]_D = -14.04°$ (*c* 0.50, MeOH) {lit.[1] $[\alpha]_D = -18°$ (*c* 0.50, MeOH)}; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.66 (3 H, dt, $J$ = 6.8, 1.9 Hz), 1.77 (1 H, dt, $J$ = 13.0, 3.4 Hz), 1.96 (1 H, m), 2.22 (1 H, m), 2.98 (2 H, m), 3.05 (1 H, dd, $J$ = 16.2, 5.7 Hz), 3.25 (1 H, t, $J$ = 8.8 Hz), 3.51−3.70 (5 H, m), 3.78 (2 H, m), 4.28 (1 H, dd, $J$ = 10.2, 2.8 Hz), 5.33 (1 H, q, $J$ = 6.8 Hz), 7.11 (1 H, td, $J$ = 6.9, 1.1 Hz), 7.22 (1 H, td, $J$ = 6.9, 1.1 Hz), 7.29 (1 H, d, $J$ = 7.7 Hz), 7.49 (1 H, d, $J$ = 7.7 Hz); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 12.8, 22.5, 26.0, 26.5, 29.2, 42.0, 48.9, 52.4, 56.5, 61.1, 105.0, 108.7, 114.4, 118.2, 118.9, 121.1, 125.9, 137.3, 137.6, 138.8; EIMS (*m*/*z*, relative intensity) 308 ($M^+$, 77), 277 (35), 183 (100). Anal. Calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 78.02; H, 7.79; N, 8.83.

**Oxidative Cyclization of Alcohol 1 to Provide (+)-Dehydro-16-epiaffinisine (4).** To a solution of alcohol **1** (62 mg, 0.20 mmol) in THF (2 mL) was added DDQ (93 mg, 0.40 mmol). The mixture that resulted was heated to reflux for 1 h. The mixture was then diluted with $CH_2Cl_2$ (25 mL), washed with 0.5 M $NaHCO_3$ (10 mL) and brine (2 × 10 mL), and dried ($K_2CO_3$). The solvent was removed under reduced pressure, and the residue that resulted was chromatographed (silica gel, $CHCl_3$/MeOH = 20:1) to provide the cyclic ether **4** (60 mg, 98%): FTIR ($CHCl_3$) 2933, 1468 $cm^{-1}$; $[\alpha]_D = +60.40°$ (*c* 0.30, MeOH) {lit.[1] $[\alpha]_D = +58.80°$ (*c* 0.25, MeOH)}; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.66 (3 H, dt, $J$ = 6.8, 1.9 Hz), 1.83−2.00 (2 H, m), 2.32 (1 H, m), 2.85 (1 H, q, $J$ = 3.0 Hz), 3.48 (1 H, t, $J$ = 11.6 Hz), 3.64 (3 H, s), 3.76−3.87 (4 H, m), 4.11 (1 H, dd, $J$ = 9.7, 3.8 Hz), 5.36 (1 H, q, $J$ = 6.7 Hz), 5.66 (1 H, d, $J$ = 7.5 Hz), 7.16 (1 H, td, $J$ = 7.9, 1.2 Hz), 7.24 (1 H, td, $J$ = 7.9, 1.2 Hz), 7.33 (1 H, d, $J$ = 7.3 Hz), 7.72 (1 H, d, $J$ = 7.3 Hz); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 12.8, 27.0, 27.4, 29.1, 38.8, 47.5, 56.1, 59.6, 64.8, 71.4, 103.6, 108.8, 113.9, 118.8, 119.6, 121.3, 126.2, 137.3, 138.9, 143.3; EIMS (*m*/*z*, relative intensity) 306 ($M^+$, 60), 196 (30), 182 (100). Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.04; H, 7.03; N, 8.86.

**Conversion of the Pentacyclic Ketone (13) into (+)-3-Ethylidene-12-H-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methano-13-methylene-indole[2,3-*a*]quinolizine (14) via the Wittig Reaction.** A mixture of anhydrous potassium *tert*-butoxide (300 mg, 0.225 mmol) and methyltriphenylphosphonium bromide (958 mg, 0.20 mmol) in dry benzene (10 mL) was allowed to stir at room temperature for 1 h. The pentacyclic ketone **13** (110 mg, 0.04 mmol) in THF (5 mL) was then added into the above orange-colored solution dropwise at room temperature. The mixture that resulted was stirred at room temperature for 4 h. The mixture was diluted with EtOAc (50 mL), washed with $H_2O$ (3 × 10 mL) and brine (25 mL), and dried ($K_2CO_3$). The solvent was removed under reduced pressure, and the oil that resulted was chromatographed (silica gel, $CHCl_3$/MeOH = 15:1) to provide the olefin **14** (100 mg, 92%): FTIR ($CHCl_3$) 2960, 1739, 1246 $cm^{-1}$; $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.61 (3 H, d, $J$ = 6.8 Hz), 1.75 (1 H, dt, $J$ = 6.3, 2.7 Hz), 2.07 (1 H, dd, $J$ = 11.5, 7.2 Hz), 2.89 (2 H, m), 3.32 (1 H, m), 3.60 (3 H, m), 4.10 (1 H, d, $J$ = 8.0 Hz), 4.78 (2 H, m), 5.20 (1 H, q, $J$ = 6.8 Hz), 6.92 (1 H, td, $J$ = 7.7, 1.1 Hz), 7.24 (1 H, td, $J$ = 7.7, 1.1 Hz), 7.26 (1 H, d, $J$ = 7.4 Hz), 7.35 (1 H, d, $J$ = 7.9 Hz), 10.72 (1 H, s); $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 12.6, 26.4, 36.5, 36.9, 50.1, 55.6, 56.4, 103.4, 104.8, 111.3, 113.8, 117.8, 118.52, 120.6, 127.3, 136.4, 139.0, 139.3, 154.3; EIMS (*m*/*z*, relative intensity) 276 ($M^+$, 61), 168 (100). This material was used directly in a later step.

**Hydroboration of (+)-3-Ethylidene-12-H-1,3,4,7,12,12b-hexahydro-2*H*,6*H*-2,6-methano-13-methylene-indole[2,3-*a*]quinolizine (14) Followed by Oxidation to Provide (+)-(*E*)16-Epinormacusine B (2).** A solution of commercially available $BH_3$−THF (1.0 M in THF, 5 mL) was treated with 2-methyl-2-butene (2.0 M in THF, 10 mL) at −5 °C to give a solution of diisoamylborane in THF. A solution of olefin **14** (276 mg, 1.0 mmol) in THF (12 mL) was added to the diisoamylborane at 0 °C. The solution was warmed to room temperature and stirred for 5 h. To the solution was then added 10% aq NaOH (2 mL), followed by addition of 30% $H_2O_2$ (4 mL). The mixture that resulted was stirred for 2 h at room temperature, diluted with $CH_2Cl_2$ (200 mL), washed with $H_2O$ (3 × 50 mL) and brine (100 mL), and dried ($K_2CO_3$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, $CHCl_3$/MeOH = 9:1) to provide the alcohol **2** (229 mg, 78%): FTIR ($CHCl_3$) 3200, 2918 $cm^{-1}$; $[\alpha]_D = +6.92°$ (*c* 0.25, MeOH) {lit.[1] $[\alpha]_D = +3°$ (*c* 0.25, MeOH)}; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.64 (3 H, dt, $J$ = 6.8, 1.8 Hz), 1.84 (2 H, m), 2.24 (1 H, m), 2.89 (1 H, q, $J$ = 2.8 Hz), 3.01 (2 H, m), 3.27 (1 H, dd, $J$ = 10.5, 8.5 Hz), 3.48−3.76 (4 H, m), 4.22 (1 H, dd, $J$ = 9.0, 4.2 Hz), 5.23 (1 H, q, $J$ = 6.8 Hz), 7.08 (1 H, td, $J$ = 7.1, 1.3 Hz), 7.16 (1 H, td, $J$ = 7.1, 1.3 Hz), 7.36 (1 H, d, $J$ = 7.3 Hz), 7.49 (1 H, d, $J$ = 7.3 Hz), 8.60 (1 H, s); $^{13}C$ NMR (75.5 MHz, $CDCl_3$) $\delta$ 12.7, 22.3, 26.1, 27.0, 41.8, 50.1, 52.8, 55.9, 60.9, 105.6, 111.2, 114.9, 118.1, 119.3, 121.7, 126.0, 135.6, 136.4, 137.4; EIMS (*m*/*z*, relative intensity) 306 ($M^+$, 100). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.80; H, 7.79; N, 9.34.

**Oxidative Cyclization of Alcohol 2 to Provide (+)-Dehydro-16-epinormacusine B (5).** To a solution of alcohol **2** (27 mg, 0.09 mmol) in THF (2 mL) was added DDQ (42 mg, 0.18 mmol). The mixture that resulted was heated to reflux

for 1 h. The mixture was then diluted with $CH_2Cl_2$ (15 mL), washed with 0.5 M aq $NaHCO_3$ (10 mL) and brine (2 × 10 mL), and dried ($K_2CO_3$). The solvent was removed under reduced pressure, and the residue was chromatographed (silica gel, $CHCl_3$/MeOH = 15:1) to provide the cyclic ether **5** (25 mg, 95%): FTIR 3164, 2938 $cm^{-1}$; $[\alpha]_D = +131.58°$ (*c* 0.19, $CHCl_3$); $^1H$ NMR (300 MHz, DMSO-$d_6$) $\delta$ 1.60 (3 H, d, $J$ = 6.7 Hz), 1.71 (1 H, t, $J$ = 10.9 Hz), 1.89 (1 H, dt, $J$ = 10.1, 3.1 Hz), 2.11 (1 H, m), 2.78 (1 H, q, $J$ = 2.8 Hz), 3.30 (1 H, m), 3.63 (4 H, m), 3.93 (1 H, dd, $J$ = 10.2, 3.0 Hz), 5.24 (1 H, q, $J$ = 6.7 Hz), 5.38 (1 H, d, $J$ = 7.5 Hz), 6.98 (1 H, td, $J$ = 7.2, 1.1 Hz), 7.07 (1 H, td, $J$ = 7.2, 1.1 Hz), 7.30 (1 H, d, $J$ = 7.8 Hz), 7.46 (1 H, d, $J$ = 7.5 Hz), 10.87 (1 H, s); $^{13}C$ NMR (75.5 MHz, DMSO-$d_6$) $\delta$ 13.1, 27.2, 28.1, 38.9, 48.3, 55.4, 59.4, 64.3, 70.9, 103.2, 111.6, 112.9, 118.4, 119.2, 121.0, 126.5, 136.1, 140.6, 143.7; EIMS (*m*/*z*, relative intensity) 292 (49), 168 (100). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 78.42; H, 6.50; N, 9.32.

**General Procedure for Quenching the Enolate 21 Formed during the Oxy-anion Cope Rearrangement at Low Temperature to Provide the Ajmaline (16(*S*)) Stereochemistry.** The oxy-anion Cope rearrangement was run with the mixture of both diastereomers of allylic alcohol *trans*-**19** (100 mg, 0.25 mmol). After analysis by TLC indicated the disappearance of *trans*-**19**, the reaction mixture was allowed to cool to the required temperature depicted in Table 1, after which the reaction was quenched by careful addition of a proton source or by pouring the precooled reaction mixture into the cooled solution of the proton source. The mixture that resulted was brought to pH 8 with a saturated solution of cold aq $NaHCO_3$ and extracted with $CH_2Cl_2$. The combined organic extracts were washed with water and brine, dried ($K_2CO_3$), and concentrated under reduced pressure. The residue was analyzed by $^1H$ NMR spectroscopy and compared to authentic samples of **20a** and **20b**. The ratios and yields are illustrated in Table 1.

**One-Pot Oxy-anion Cope Rearrangement to Convert (6*S*,9*R*,10*S*)-9-(1′-Hydroxy-3′-hexenyl)-12-benzyl-6,7,10,-11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]-indole (*trans*-19) into (6*S*,9*S*,10*S*)-8-(1′-Ethyl-2′-propenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-9-carboxaldehyde (20b).** The oxy-anion Cope rearrangement was run with a mixture of both diastereomers of allylic alcohol *trans*-**19** (100 mg, 0.24 mmol). After analysis by TLC indicated the disappearance of *trans*-**19**, the reaction mixture was allowed to cool to 0 °C and diluted with cold dry THF. The mixture was then further cooled to −100 °C, after which it was quenched by pouring the precooled reaction mixture into a precooled 2 N solution of TFA in THF at −100 °C. The cold mixture that resulted was then brought to pH 8 with a cold saturated solution of aq $NaHCO_3$ at low temperature and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic extracts were washed with cold $H_2O$ (10 mL) and cold brine (10 mL), dried ($Na_2SO_4$), and concentrated under reduced pressure. Examination of the integration of the $^1H$ NMR spectrum of the crude product indicated that the ratio of **20b** to **20a** was greater than 43:1. The residue that resulted was rapidly chromatographed on silica gel (EtOAc/hexane = 1:4) to provide alkenic aldehyde **20b** (83 mg, 83%): FTIR (NaCl) 3396, 2958, 2913, 1709 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.78 (3 H, t, $J$ = 7.2 Hz), 0.85−1.30 (2 H, m), 1.35−1.50 (1 H, m), 1.70−2.05 (3 H, m), 2.57 (1 H, d, $J$ = 17.0 Hz), 2.91 (1 H, dt, $J$ = 11.9, 4.1 Hz), 3.08 (1 H, dd, $J$ = 17.1, 6.7 Hz), 3.62 (1 H, t, $J$ = 6.1 Hz), 3.70 (2 H, q, $J$ = 9.4 Hz), 3.89 (1 H, t, $J$ = 3.1 Hz), 4.88−5.03 (2 H, m), 5.30−5.50 (1 H, m), 7.14−7.39 (8 H, m), 7.53 (1 H, dd, $J$ = 6.6, 1.8 Hz), 7.71 (1 H, s), 9.75 (1 H, d, $J$ = 3.5 Hz); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 12.4, 19.0, 22.4, 32.3, 33.1, 49.0, 51.5, 53.3, 56.6, 57.1, 107.3, 111.0, 116.9, 118.2, 119.6, 121.6, 127.0, 127.2, 128.4, 128.6, 133.4, 135.9, 139.0, 140.3, 205.8; CIMS (*m*/*e*, relative intensity) 399 ($M^+ + 1$, 100). Anal. Calcd for $C_{27}H_{30}N_2O \cdot 0.1H_2O$: C, 81.00; H, 7.60; N, 7.00. Found: C, 80.78; H, 7.51; N, 6.65.

**Conversion of (6*S*,9*S*,10*S*)-8-(1′-Ethyl-2′-propenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-9-carboxaldehyde (20b) into Ethylene Acetal 22.** The alkenic aldehyde **20b** (100 mg, 0.25 mmol, 16(*S*)) was dissolved in benzene (5 mL) and added to a solution of dry ethylene glycol (100 mg, 1.61 mmol) in benzene (10 mL) that contained dry *p*-toluenesulfonic acid (5.00 mg, 0.029 mmol). The mixture that resulted was heated to reflux for 20 h, accompanied by removal of water via a Dean Stark trap (DST). Analysis of the mixture by TLC (silica gel, EtOH/$CHCl_3$ = 1:20) indicated the absence of starting material **20b** at this time. The mixture was allowed to cool to room temperature and poured into an aq solution of $NH_4OH$ (10%, 10 mL). The aqueous layer was separated and then extracted with EtOAc (3 × 30 mL). The combined benzene and EtOAc layers were washed with $H_2O$ (2 × 10 mL) and brine and dried ($K_2CO_3$). The solvent was removed under reduced pressure and chromatographed (hexane/EtOAc = 4:1) to provide the ethylene acetal **22** (100 mg, 92%): IR (KBr) 2934 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.79 (3 H, t, $J$ = 7.3 Hz), 1.10−1.20 (1 H, m), 1.55−1.75 (4 H, m), 2.22 (1 H, t, $J$ = 7.1 Hz), 2.30−2.40 (1 H, m), 2.73 (1 H, d, $J$ = 17.0 Hz), 3.00 (1 H, dd, $J$ = 7.0, 17.0 Hz), 3.50−3.60 (2 H, m), 3.67 (1 H, d, $J$ = 13.7 Hz), 3.70−4.00 (5 H, m), 4.75−4.82 (2 H, m), 5.40−5.55 (1 H, m), 7.05−7.30 (8 H, m), 7.48−7.60 (2 H, m); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 12.6, 14.2, 31.2, 34.8, 44.9, 46.0, 51.3, 53.5, 57.2, 63.9, 64.9, 105.7, 108.2, 110.8, 114.7, 118.0, 119.1, 121.0, 126.7, 127.2, 128.2, 128.5, 133.7, 135.7, 139.7, 141.4; CIMS (*m*/*e*, relative intensity) 443 ($M^+ + 1$, 100). This material was employed directly in the next step.

**$N_a$-Methylation of (16(*S*)) Olefinic Acetal 22 to Provide (6*S*,9*S*,10*S*)-5-methyl-8-(1′-ethyl-2′-propenyl)-12-benzyl-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]-indolyl-9-acetal (23).** A solution of the olefinic acetal (16(*S*)) **22** (100 mg, 0.23 mmol) in dry THF (5 mL) was added to a suspension of NaH (10 mg, 60% NaH in mineral oil) in dry THF (5 mL) in a round-bottom flask (25 mL) at 0 °C. The slurry that resulted was allowed to stir at room temperature for 1 h before it was cooled to 0 °C. Methyl iodide (65 mg, 0.40 mmol) was added to the above solution at 0 °C, and the reaction mixture that resulted was stirred at 0 °C for 2 h and then at room temperature for 6 h. The reaction was quenched by careful addition of $CH_3OH$ (1 mL), and the solution was then brought to pH = 7 with an aqueous solution of $NH_4Cl$ and extracted with EtOAc. The combined organic layers were washed with brine and dried ($K_2CO_3$). After the solvent was removed under reduced pressure, the residue was chromatographed (silica gel, EtOAc/hexane = 1:4) to provide the $N_a$-methyl olefinic acetal **23** (97 mg, 94%): IR (KBr) 2935, 1470 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 0.81 (3 H, t, $J$ = 7.2 Hz), 1.07 (1 H, m), 1.25 (2 H, m), 1.60 (4 H, m), 2.15 (1 H, m), 2.35 (1 H, m), 2.72 (1 H, d, $J$ = 17.0 Hz), 3.02 (1 H, dd, $J$ = 17.0, 7.1 Hz), 3.48 (3 H, s), 3.53 (1 H, d, $J$ = 14.0 Hz), 3.67 (1 H, d, $J$ = 14.0 Hz), 3.60 (1 H, m), 3.81 (2 H, m), 3.93 (2 H, m), 4.76 (2 H, m), 5.46 (1 H, m), 7.20 (8 H, m), 7.53 (1 H, d, $J$ = 7.6 Hz); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 12.7, 18.5, 20.0, 28.9, 30.8, 34.7, 45.1, 46.1, 50.2, 53.6, 57.4, 64.0, 65.0, 106.1, 107.49, 108.8, 114.7, 118.1, 118.6, 120.5, 126.8, 128.2, 128.7, 135.1, 137.1, 139.6, 141.4; EIMS (*m*/*e*, relative intensity) 456 ($M^+$, 100). Anal. Calcd for $C_{30}H_{36}N_2O_2$: C, 78.90; H, 7.95; N, 6.14. Found: C, 78.57; H, 7.70; N, 6.25.

**$OsO_4$-Mediated Oxidation of Aldehyde 23 to Provide (6*S*,8*S*,9*S*,10*S*,1′*S*)-5-Methyl-8-(1′-ethyl-oxomethyl)-9-(1′,3′-dioxolan-2′-yl)-12-benzyl-6,7,8,9,10,11-hexa-hydro-6,10-imino-5*H*-cyclooct[*b*]indole (24).** Alkenic ethylene acetal **23** (169 mg, 0.37 mmol) was dissolved in a solution of dry THF (8 mL) and pyridine (freshly distilled, 0.7 mL). The solution that resulted was added at 0 °C to a lightly yellow-colored premixed solution of $OsO_4$ (95 mg, 0.37 mmol) in dry THF (5 mL) that contained freshly distilled pyridine (1 mL). The black-colored mixture that resulted was stirred at 0 °C for 16 h under an atmosphere of argon. An aqueous solution of sodium bisulfite

(1.5 g dissolved in 6 mL of $H_2O$) was then added, and the slurry that resulted was stirred at room temperature for 4 h. The mixture was diluted with EtOAc (20 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (5 × 50 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried ($K_2CO_3$). The solvent was removed under reduced pressure to provide the crude product as a lightly black-colored oil. The oil was chromatographed to provide the desired diols (150 mg). Both diols, without further separation, were employed directly for the sodium periodate oxidative cleavage of the *cis*-diol function.

The mixture of diols (150 mg, 0.306 mmol) was dissolved in dry distilled $CH_3OH$ (3 mL) in a round-bottom flask (10 mL) that was coated with aluminum foil to exclude light. The solution that resulted was cooled to 0 °C, and an aqueous solution of $NaIO_4$ (140 mg, 0.66 mmol, in 2 mL of $H_2O$) was added to the chilled solution. The mixture was stirred at 0 °C for 16 h. Examination of the mixture by TLC (silica gel, EtOAc/hexane = 1:1) indicated the presence of a new component ($R_f$ = 0.71) that was active to 2,4-DNP spray reagent, and starting material had disappeared. Methanol was removed under reduced pressure, and the residue that resulted was dissolved in EtOAc/water (2:1). The two layers were separated, and the aqueous layer was extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with water and brine and dried ($Na_2SO_4$). The solvent was removed under reduced pressure to provide the aldehydic acetal **24** (151 mg, 91%). Do not subject the aldehyde to silica gel chromatography (it will epimerize); use it directly in the next step: FTIR (KBr) 2998, 1722, 1468, 744 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.87 (3 H, t, $J$ = 7.3 Hz), 1.24 (1 H, m), 1.47 (1 H, m), 1.60 (1 H, m), 1.79 (1 H, dt, $J$ = 12.61 4.1 Hz), 2.21 (1 H, m), 2.36 (1 H, dt, $J$ = 11.8, 4.9 Hz), 2.60 (1 H, bd, $J$ = 10.5 Hz), 2.79 (1 H, d, $J$ = 17.2 Hz), 3.07 (1 H, dd, $J$ = 17.0, 7.1 Hz), 3.44 (3 H, s), 3.53 (1 H, d, $J$ = 13.6 Hz), 3.57 (1 H, dd, $J$ = 6.8, 4.5 Hz), 3.67 (1 H, d, $J$ = 13.6 Hz), 3.80 (1 H, dd, $J$ = 12.7, 6.3 Hz), 3.85 (2 H, m), 3.92 (1 H, dd, $J$ = 12.1, 6.9 Hz), 3.98 (1 H, dd, $J$ = 12.7, 6.5 Hz), 4.74 (1 H, d, $J$ = 5.1 Hz), 7.11 (1 H, t, $J$ = 7.5 Hz), 7.19 (1 H, t, $J$ = 7.8 Hz), 7.27 (6 H, m), 7.53 (1 H, d, $J$ = 7.7 Hz), 9.36 (1 H, s); $^{13}C$ NMR (125.75 MHz, $CDCl_3$) $\delta$ 13.0, 15.9, 18.2, 28.9, 29.0, 31.9, 45.9, 49.7, 53.6, 54.8, 57.3, 63.8, 65.0, 105.8, 107.3, 109.0, 118.1, 118.8, 120.8, 126.6, 126.9, 128.2, 128.6, 134.3, 137.1, 139.3, 205.2; EIMS (*m*/*e*, relative intensity) 460 ($M^+$ + 2, 34), 459 ($M^+$ + 1, 26), 458 ($M^+$, 92), 274 (18), 273 (52), 255 (20), 253 (29), 225 (38), 224 (57), 183 (37), 182 (100), 181 (31). Anal. Calcd for $C_{29}H_{34}N_2O_3 \cdot 0.5H_2O$: C, 74.52; H, 7.49; N, 6.00. Found: C, 74.88; H, 7.60; N, 5.92. This material was converted into alkaloid G analogous to steps reported in the literature.[22]

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**Supporting Information Available:** $^1H$ NMR spectra of **1**, **2**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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