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ISOLATION AND SYNTHESIS OF BISHORDENINYL TERPENE ALKALOIDS. SOME EXPERIMENTS RELATING TO THE NATURAL OCCURRENCE OF FORMAL DIELS-ALDER ADDUCTS.

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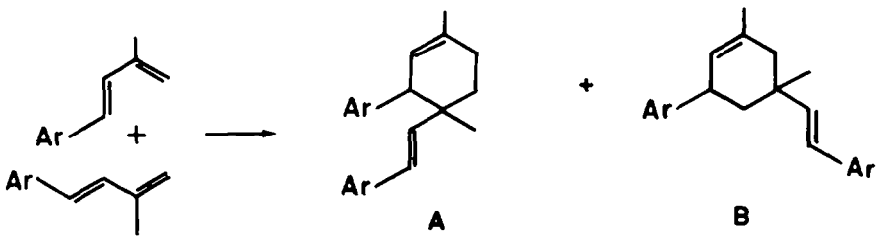
ABSTRACT: Leaves of Zanthoxylum procerum (Rutaceae) yielded two major optically inactive alkaloids, culantraramine and culantraraminol, which were assigned bishordeninyl terpene structures based upon spectral evidence and conversions to known alkaloids. Two minor alkaloids, isomeric with culantraraminol, were also found, along with hordenine and N,N-dimethyltryptamine. Although culantraramine could be viewed as a natural self Diels-Alder adduct of dehydroprenylhordenine, when this diene was prepared and reacted, it yielded instead an alternate adduct. This room temperature Diels-Alder reaction does, however, represent a model for the biosynthesis of some other known isolates considered as natural Diels-Alder adducts. A total synthesis of culantraramine and culantraraminol was instead achieved in high yield from a prenylalcohol precursor under mild acid conditions. The synthetic reaction also yielded the two minor culantraraminol isomers. All four alkaloids were present in similar amounts in both the synthetic mixture and the crude leaf extract. The reaction used in the synthesis of culantraramine and culantraraminol is suggested to be biomimetic for these and certain other dimeric alkaloids.

There has been a gradual accumulation in the literature of reports dealing with the isolation and characterization of 'natural Diels-Alder adducts' from higher plants. Rather diverse genera, particularly from the family Rutaceae, have yielded a number of isolates which can formally be considered as arising from the general reactions given in Schemes I and II. So far, all such isolates have been found to be optically inactive.[1] Occasionally, the presumed diene precursors have also been isolated. Alflabene[2,3,4] (1), cyclobisuberodiene[5] (2), or thamnosine[6] (also 2), and mexolide[7] (3) represent isolates of regiochemistry A (Scheme I), while the two diclausens[8] (4) have regiochemistry B. The paraensidimerins[9] (5) and vepridimerines[10] (6) are pentacyclic alkaloids which could have arisen from Scheme II operating on dehydroprenylated quinolines, followed by cyclization of the formed regioisomer C (Scheme II). Our alfileramine[11,12] (7) could have been formed similarly. No isolates from regiochemistry D (Scheme II) have as yet been reported. Further examples are discussed in two reviews.[13,14]

We report here isolation and synthetic experiments of interest in regard to the natural occurrence of products formally derivable from Schemes I and II. Isolation work was carried out on Zanthoxylum procerum, a Rutaceous tree from the lower Caribbean slopes of the Costa Rican cordillera, and on Z. culantrillo from the central mesa and the deciduous forest of the west coast.

Paper 8 in the series 'Constituents of Zanthoxylum'. Paper 7: J. Grina, M. R. Ratcliff, and F. R. Stermitz, J. Org. Chem., 47, 2648 (1982).

SCHEME I



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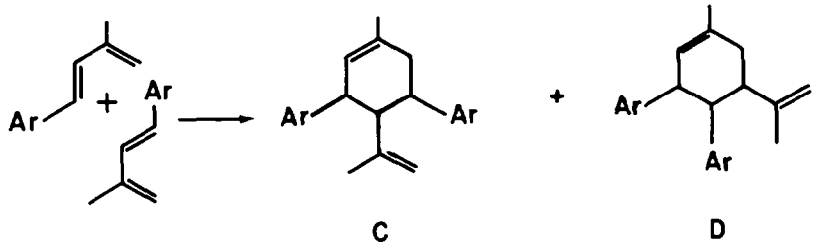

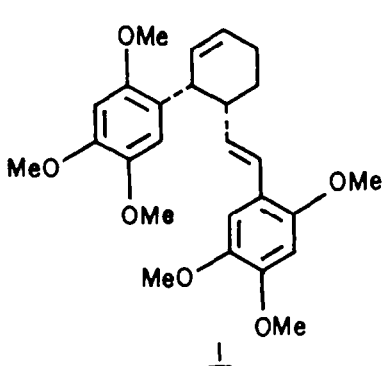

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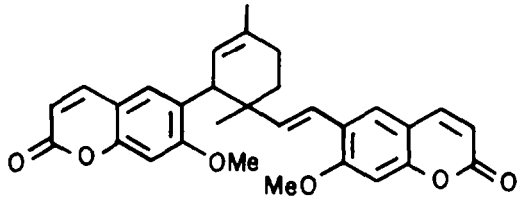

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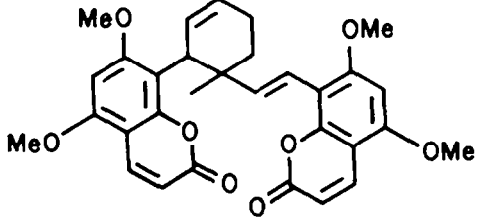

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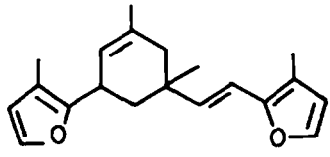

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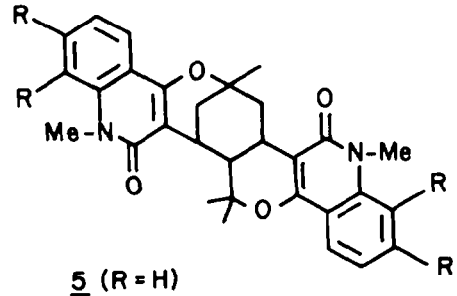

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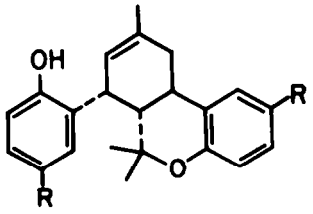
6 (R = OMe)



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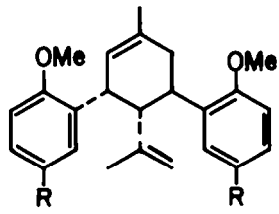
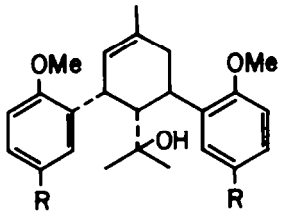


8

R=$CH_2CH_2NMe_2$

in 7-10



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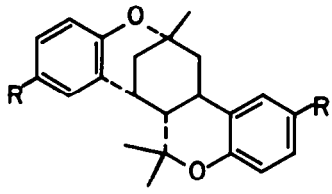

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RESULTS

Isolation and Characterization

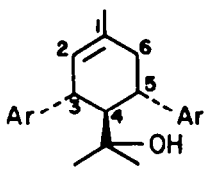
Leaves, but not bark or wood, of Z. progerum yielded two optically inactive major alkaloids, 8 (culantraramine) and 9 (culantraraminol) along with two minor compounds isomeric with 9. (Since the compounds were racemic, the structures are not meant to represent an absolute configuration even though just one enantiomer is depicted.) The exact structures 8 and 9 were determined by a combination of spectral methods and chemical interconversions.

Mass spectrometry established molecular formulas for 8 and 9, although 9 only showed a good molecular ion under NH_3CI conditions. A facile loss of H_2O for 9 was observed under EI conditions. Culantraramine showed 16 and culantraraminol 14 sp^2 carbons (^{13}C nmr spectra), with the former exhibiting two C-CH_3, (1.78 and 1.38 ppm) singlets and the latter, three C-CH_3 singlets (1.77, 0.68, and 0.64 ppm) in the ^1H nmr spectra. The lower field resonances are typical for the ring vinylic CH_3 of 7 and cannabinoids. A 73.6 ppm singlet in the ^{13}C spectrum of 9 confirmed the tertiary alcohol function for culantraraminol. Culantraraminol was converted in 80% yield to culantraramine by heating with $KHSO_4$ in CH_2Cl_2 and culantraramine was in turn converted to 10 in 70% yield by heating for ten minutes in 48% HBr, followed by basification and extraction. We had previously[12] established the structure of 10 by X-ray crystallography. Treatment of 7 with mild acid in ethanol had given[12] 10. These data assure the structures of 8 and 9, which are also in agreement with complete ^{13}C nmr assignments and detailed analyses of the 360 MHz ^1H nmr spectra with extensive decoupling experiments. The assignments are given in the Experimental Section and details are available in a thesis.[15] Alkaloids 8 and 9 were also previously isolated[16] from leaves of Z. culantrillo, but lack of material and complete high field nmr data at that time did not allow proof of structure for 9. The same situation resulted in postulation of an incorrect isomeric structure for 8.

The two minor alkaloids gave mass spectra exactly as did 9: poor 508 molecular ions, but strong M^+-H_2O ions in the EI mode and strong 509 (M^+ +H) ions in the NH_3CI mode. The ^1H nmr spectra of each showed three C-Me singlets (two aliphatic and one vinylic) in concordance with 9. The other ^1H nmr resonances were also similar to those of 9, as was the ^{13}C nmr spectrum of one. Lack of material precluded obtaining a ^{13}C nmr spectrum for the second minor component. The decision that the minor alkaloids represented stereoisomers (Scheme II, C) rather than regioisomers (Scheme II, D) of 9 was reached by ^1H nmr decoupling experiments centered around the benzylic C-5 proton which appeared at 4.06 ppm in both cases. These experiments clearly showed that proton to be between a methylene and a methine carbon (regioisomer C) and not between two

methine carbons (regioisomer D). The total nmr spectral assignments were also consistent with these formulations.

A closer analysis of the ^1H nmr spectra for the minor alcohols led to tentative stereochemical assignments. The spectra were compared with those of 8 and 9, whose stereochemistries were known from the interconversion experiments. In all of the alcohols, there was no observed coupling between C-2H and C-3H, indicating an approximate 90° relationship and assuring that the two minor alcohols had the same relative stereochemistry at C-3 as did culantraraminol. Thus, differences would only be at C-4 and C-5, and three possible structures need be considered. One minor isomer was the only alkaloid of this series, including 7, with neither of the alkyl C-methyls shielded in the ^1H nmr spectrum (1.21 and 1.26 ppm). In all others at least one C-methyl was in the 0.6 ppm range. We have shown[11,12] that the shielding is a result of the π-cloud of a neighboring aromatic ring and hence, in this isomer, neither hordeninyl side chain is on the same side as the C-4 alkanol group. This suggests 11 for the structure of one minor isomer, which we have dubbed alloculantraraminol. Such an assignment is reinforced by the 11 Hz coupling observed between C-3H and C-4H and lack of coupling between C-4H and C-5H. (The respective dihedral angles are approximately 130° and 90° in a slightly twisted boat conformation, as demonstrated by Dreiding models.)



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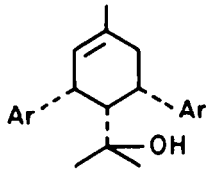

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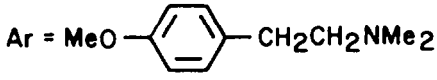

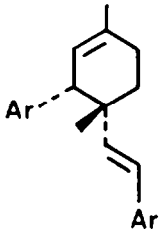

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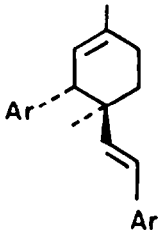


15

In the second alcohol isomer, an 11.2 Hz coupling is observed between C-4H and C-5H. In this case, the two protons must be syn and nearly eclipsed (since the result of the anti relationship is 9). This can be accounted for by assigning structure 12 to this isomer which we have dubbed 5-epiculantraraminol. Again, the proper dihedral angles are achieved in a near boat conformation. The analysis of the cyclohexene ring stereochemistries thus requires assumption of boat conformations with these alcohols, while the standard half-chair conformation is adequate to explain the culantraramine (8) ^1H nmr spectral results. All assignments are provided in the Experimental Section, with further details available separately.[15]

The reported alkaloids were isolated by an extraction process and purification procedure which involved relatively long times and the use of acid and base (see Experimental Section). Since optically inactive alkaloids (in spite of the presence of three asymmetric centers in each) and stereochemical mixtures were found, a rapid plant screening procedure was also used. A small amount of dried leaf material was extracted with MeOH for two minutes, the supernatant was spotted

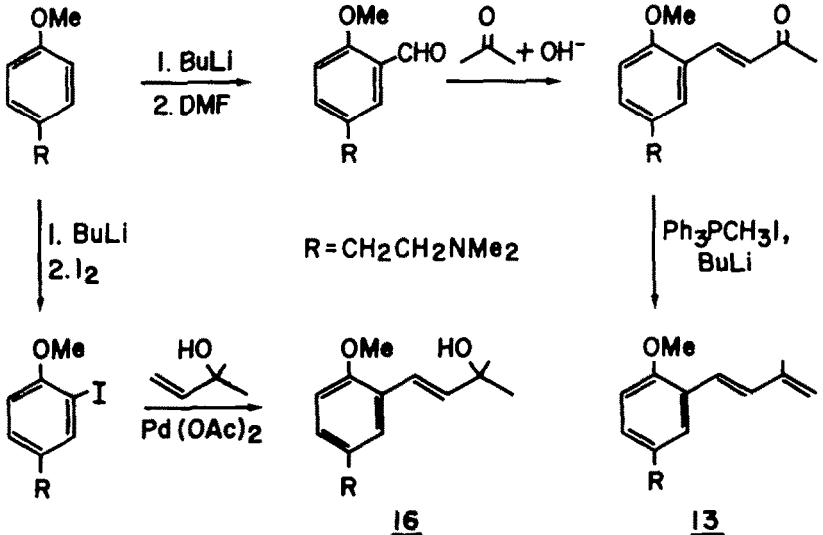
directly on Si gel and a chromatogram developed rapidly in MeOH/EtOAc/H_2O/NH_4OH (14:4:4:1). Visualization showed spots of essentially equal intensity for 8 and 9, the minor components not being of sufficient concentration for visibility. Dried leaves of Z. culantrillo (Honduras) from the previous isolation[16] were also available and the same procedure again resulted in identification of 8 and 9. Thus, the products are not likely artifacts of the isolation-purification process, although their formation during plant drying was still of concern. This possibility was ruled out for Z. culantrillo since we were able to perform direct extractions on fresh leaves in Costa Rica in January 1985. The leaves were placed in EtOH, OH^- immediately upon collection and the mixture triturated together with $CHCl_3$. Direct tlc from the $CHCl_3$ as well as later ^1H nmr spectroscopy of the residue left upon evaporation of the $CHCl_3$ showed the presence of 8 and 9. We were unfortunately not able to obtain proper leaf samples of Z. procerum on which to conduct the same experiment.

Synthesis

The structure of 8 and its lack of optical activity suggested a possible origin as a natural Diels-Alder adduct (Scheme II). The literature surprisingly did not yield information on arylisoprene reactivity, although 1-phenyl-1,3-butadiene was known[2,17] to react in the sense of Scheme I rather than Scheme II. The requisite diene 13 was prepared according to Scheme III. When 13 was allowed to stand ten days in xylene at room temperature it was gradually, but completely converted to products, with at least 90% representing a separable 3:2 mixture of 14 and 15.[18] These were clearly diastereomers of regiochemistry A (Scheme I) rather than B according to analysis of their ^1H nmr spectra (see Experimental Section). A distinction between 14 and 15 could be made since the C-Me resonance of 14 was at 1.14 ppm, while that of 15 was shielded at 0.85 ppm and must therefore have the C-Me cis to the neighboring aryl substituent.

Culantraramine (8) and culantraraminol (9) synthesis was, however achieved in high yield from 16, prepared as in Scheme III. When 16 was treated with 48% HBr in EtOH at 25° for 15 minutes, it was converted in 80% yield to 8, along with minor alkaloidal products.[19] Treatment of 16 for 30 min with 1M HCl again gave a high yield of alkaloid products, this time composed of 55% 8, 25% 9, and about 8% each of 11 and 12. Comparison of the ^1H nmr spectrum of this mixture before separation, with the ^1H nmr spectrum of the crude isolated base fraction from Z. procerum leaves, showed them to be remarkably similar. The OMe and C-Me signals of the various components are distinctive and each could be clearly seen in the reaction mixture and the isolate mixture nmr spectra. The only real difference was the ratio of 8 to 9, but it seems clear from the synthetic experiments described that this ratio will be highly dependent upon exact reaction conditions.

SCHEME III



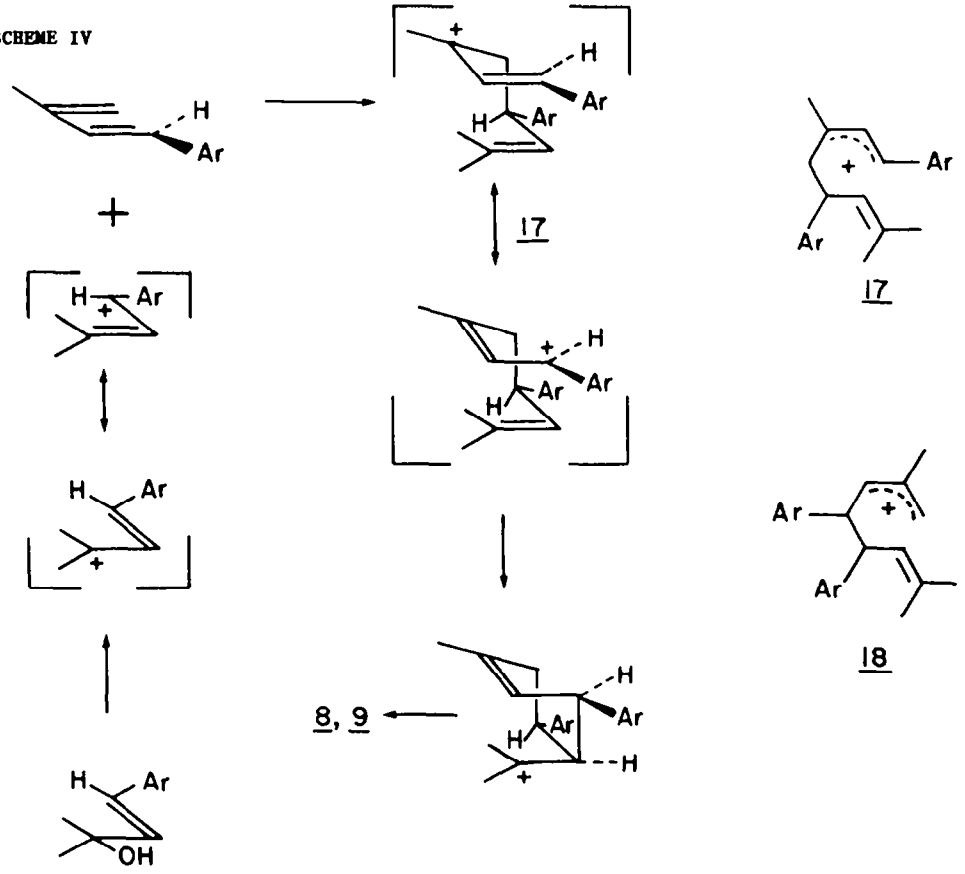
Since it seemed plausible that 16 yielded a cation and diene 13, which then reacted together,[21] a 50:50 mixture of 13 and 16 was reacted with mild acid catalysis. Both 13 and 16 were completely transformed and the product mixture was the same as obtained above. We found only what appeared to be acyclic polymers and no 8 or 9 when diene 13 was treated by itself with dilute acid under a variety of conditions.

DISCUSSION

The two high yield ambient temperature syntheses reported here represent viable ones to consider as biomimetic for isolates such as 1-9 if it can be proven that these substances occur as such in the living plant. Before addressing this point, some additional discussion of the results is necessary.

The particular regio- and stereochemical results observed in the reaction leading to 8 and 9 can probably best be explained by considering the process to be either a particularly facile stepwise one as depicted in Scheme IV or a concerted analog bypassing 17 as an intermediate. In order to provide 8 and 9 as the major products, the process would have to mainly take place with configuration retention of the allylic cation intermediates. The mechanism could approach a nonsynchronous [4+2] cycloaddition[22] and, indeed, application[15] of FMO theory is also consistent with the regiochemistry and stereochemistry observed.

SCHEME IV



Schemes I and II represent nonoverlapping alternatives both in the isolations reported so far and in our synthetic work. Although there have been numerous isolations of formal adducts A-C from widely differing plants, in no case have both Scheme I and Scheme II adducts been reported from the same plant. Similarly, in our syntheses only Scheme I products were found from the 13 diene and only Scheme II, C products resulted from the 16 alcohol. Thus, isolates A and B likely arise from a 'true' Diels-Alder reaction, while isolates such as C arise from a cation-diene process we propose.[23] The failure so far to find regiochemistry D isolates is clear if the

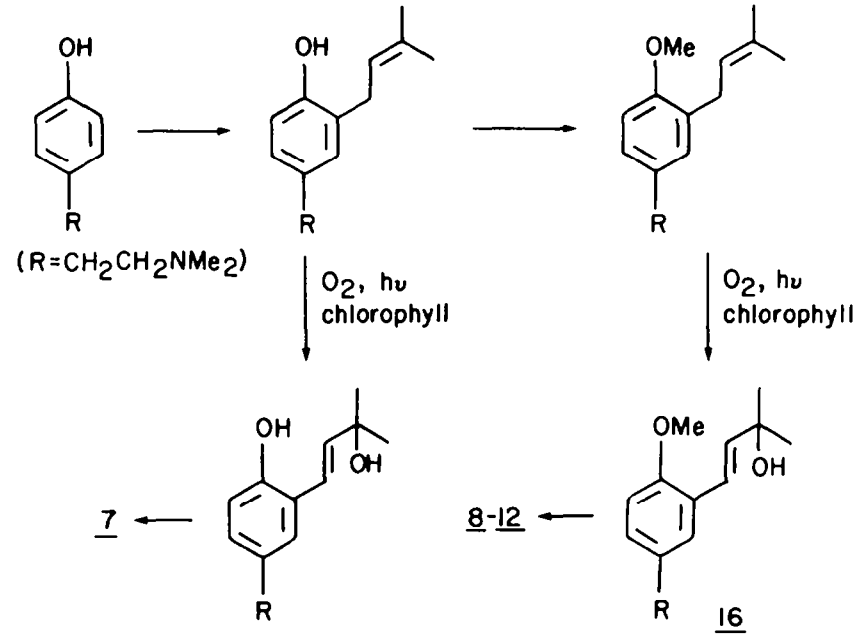
mechanism of Scheme IV is operative. To get D products would require formation of cation 18, which is much less stable than 17.

Our failure to find cyclization products from treatment of 13 with acid correlates with similar problems encountered by Gassman (footnote 17 in Reference 23). It seems as if a carbocation can initiate the process, while a simple proton cannot.

Although some authors have concerned themselves with the possible artifactual nature of the isolates we are considering here, none, as far as we are aware, have reported attempts at direct isolations from living plant material. We have now accomplished this with Z. culantrillo and were able to isolate the dimeric alkaloids from fresh leaves under conditions where the proposed intermediate 16 is stable. Similar experiments should certainly be done for each of the many literature cases quoted.[2-10,13,14]

It remains to be considered whether or not 16 represents a reasonable plant product itself. The rather puzzling fact that bishordeninyl terpenes have only been found in leaves suggests a logical sequence for 16 formation (Scheme V). Prenylation ortho to a phenol is ubiquitous in the Rutaceae and the suggested singlet oxygen ene reaction with chlorophyll sensitization to form 16 also has excellent precedence.[24-26] Scheme V suggests that isolation work on buds or freshly emerged leaves of Z. procerum (which puts out new growth in May-June, a time of constant clouds and rain in the Costa Rican Caribbean area) should result in finding the proposed prenylated hordenine precursor. Such experiments are planned.

SCHEME V



EXPERIMENTAL SECTION

General Procedure

Melting points were obtained with a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on either a Beckmann 4200 or a Beckmann Acculab spectrophotometer. 60 MHz ^{1}H NMR spectra were recorded on either a Varian Model EM360 or a Varian Model T-60 spectrometer using Me_4Si as an internal standard and are reported in δ. All ^{13}C NMR spectra were recorded on a JEOL JNM FX-100 Fourier Transform spectrometer. High field NMR spectra were recorded on Nicolet NT360 or Bruker-IBM Model WP-270 spectrometers. Mass spectra were recorded on a V. G. Micromass 16F spectrometer. Exact mass spectra were obtained at Midwest Center for Mass Spectroscopy, University of Nebraska, Lincoln, NE.

Chromatographic isolations were accomplished by either medium-pressure liquid chromatography (MPLC), using a Michel-Miller column (37 mm x 350 mm) packed with Merck Silica Gel-60 (230-400 mesh), or by flash and preparative layer chromatography. Products isolated by MPLC were detected with an ISCO Model UA-5 absorbance-fluorescence monitor at wavelength 254 nm.

Analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Isolation and Purification

Collection and identification data on *Z. procerum* Donn. Sm. has been reported previously[27] This work[27] described isolation and identification of bark and wood components. In addition, there was preliminary data on isolation of a crude base fraction from leaves which showed the presence (by tlc) of the two major and two minor alkaloids which have been characterized in this study. For the present work, 1128 g of leaves which had been allowed to dry at room temperature were extracted with hexane (Soxhlet) and then MeOH (Soxhlet). The MeOH was evaporated *in vacuo* to leave 240 g of wet, gummy residue. Of this, 60 g was distributed between 1M H_2SO_4 and $CHCl_3$. The acidic layer was made basic to pH 9 (NH_4OH), extracted with $CHCl_3$ three times, the extracts combined, dried over Na_2SO_4 and evaporated to yield 1.5 g of crude alkaloid extract. The crude base fraction showed mainly the same four alkaloids, two major and two minor, whose tlc data was previously reported.[27] The 60 MHz ^1H NMR spectrum of the crude showed peaks at 0.64, 1.20, 1.25, 1.35, 1.65, 1.80 ppm in the C-Me region and 3.50, 3.62, 3.68, 3.71, 3.75, and 3.80 ppm in the OMe region.

In a typical purification, 350 mg of the crude base was subjected to flash chromatography (Si gel; EtOAc/EtOH/H_2O/HCOOH 12:6:4:1). This provided the alkaloids as their formate salts, with pure samples of **8** (70 mg) and **9** (50 mg) resulting. Spectral data was obtained on these salts and on samples converted to the free base. Two minor components which could be isolated from the chromatography in less pure state were **12** (10 mg) and **11** (5 mg). For the spectral data given below it was necessary to repurify the minor compounds by a second chromatography. Finally, two additional minor components were identified as hordenine[16] and N,N-dimethyltryptamine[28] by spectral and tlc comparisons with samples previously isolated and characterized.

Dried leaves of *Z. culantrillo* from a previous collection[16] were submitted to a rapid two minute extraction with methanol, work up and tlc as indicated for *Z. procerum* at the end of the Results section. As was the case with *Z. procerum*, essentially a 1:1 ratio of **8** to **9** was found by this procedure. In January 1985, fresh leaves of *Z. culantrillo* were obtained from two locations in Costa Rica: (1) near the Jicaral turnoff in Santa Rosa National Park, Guanacaste Province with the assistance of D. R. Janzen and (2) from the Faubio Baudrit Experiment Station west of Alajuela with the assistance of L. Poveda. Small portions of fresh leaves (1 g) were triturated well with 10:1 MeOH/5% aq. Na_2CO_3 and 20 mls of $CHCl_3$ was added. The layers were separated, and the organic layer evaporated to dryness. This was taken up in a little MeOH, spotted on neutral Si gel tlc plates and developed in 8:1 EtOH/6M NH_4OH. Spots for **8** and **9** were visualized with iodoplatinate at R_f 0.30 and 0.20, identical with R_f values of the standards. For a large isolation, 83 g of fresh, new leaves from Faubio Baudrit were stirred for 5 min in 150 mls of MeOH, 5 mls of 5% Na_2CO_3 was added and the mixture allowed to stand overnight. Most of the MeOH was removed *in vacuo* and 100 mls of $CHCl_3$ added. The $CHCl_3$ layer was separated and evaporated to dryness to leave 1 g of residue. Tlc showed **8** and **9**. The 270 MHz ^1H nmr spectrum of the crude showed mainly peaks due to the two previously isolated[16] lignans eudesmin and epieudesmin, but the C-Me, NMe_2, and OMe peaks due to **8** and **9** were clearly visible at 0.64, 0.68, 1.8, 2.28-2.32, and 3.68-3.78.

Spectral Data

Culantraramine (8). Semisolid or oil as formate salt or free base, but both pure by tlc and 360 MHz ^1H nmr spectrum. MS data (including HRMS) given previously.[16] Optically inactive, contrary to results[16] on a very small and apparently less pure sample. For the ^1H and ^{13}C NMR data which follow, the individual resonances for the two hordeninyl moieties cannot be assigned specifically to one or the other. ^1H NMR ($CDCl_3$, 360 MHz, formate salt), (1) hordeninyl moiety resonance at 7.08(d, J=2.2Hz, 1H), 7.01(dd, J=2.2 and 8.6Hz, 1H), 6.93(dd, J=1.8 and 8.3Hz, 1H), 6.89(d, J=1.8Hz, 1H), 6.72(d, J=8.6Hz, 1H), 6.70(d, J=8.3Hz, 1H), 3.75(s, 3H, OMe), 3.68(s, 3H, OMe), 2.95(m, 8H, CH_2CH_2 twice), 2.79(s, 6H, NMe_2), 2.70 ppm (s, 6H, NMe_2) and (2) terpene resonances at 5.45(d, J=4.0Hz, 1H), 4.26(m, 1H), 4.25(m, 2H), 2.45(m, 1H), 2.35(dd, 1H), 2.15(m, 1H), 1.83(s, 3H), 1.38 ppm (s, 3H). ^1H NMR ($CDCl_3$, 360 MHz, free base), (1) hordeninyl moiety resonances at 7.13(d, J=2Hz, 1H), 6.98(dd, J=2 and 8Hz, 1H), 6.90(m, 2H), 6.68(m, 2H), 3.75(s, 3H, OMe), 3.68(s, 3H, OMe), 2.70 and 2.50(m, 4H each, CH_2CH_2), 2.32(s, 6H, NMe_2), 2.26 ppm (s, 6H, NMe_2). The terpene ring resonances could be completely assigned by double resonance experiments:

Proton	Multiplicity	Shift (ppm)	Coupling
C-2H	d	5.45	4Hz to C-3H
C-3H	dd	4.25	4Hz to C-2H, 7Hz to C-4H
C-4H	dd	2.95	7Hz to C-3H, 13Hz to C-5H
C-5H	m	3.60	13Hz to C-4H, 10Hz to C-6β, 5Hz to C-6α
C-6β	dd	2.35	10Hz to C-5H, 17.6Hz to C-6α
C-6α	dd	2.15	5Hz to C-6H, 17.5Hz to C-6β

^{13}C NMR ($CDCl_3$, 25MHz, formate salt): (1) hordeninyl moiety resonances at: 156.9s, 155.5s, 134.4s, 134.2s, 130.5d, 128.0d, 127.8s, 126.9s, 126.7d, 126.1d, 110.4d, 109.9d, 58.8t (CH_2N), 58.7t (CH_2N), 55.2q (OMe), 54.7q (OMe), 42.5q (4 NMe_2), 30.1t ppm (2 $\underline{C}H_2CH_2N$) and (2) terpene resonances at 144.6s (C-1), 131.1s, ($CH_2\underline{C}=CH_2$), 123.3d (C-2), 110.4t ($C=\underline{C}H_2$), 48.5d (C-3), 39.1t (C-6), 36.7d (C-4), 32.1d (C-5), 23.3q (C-Me), 23.1q (C-Me).

Culantraraminol (9). Isolated as an oil or semi-solid as the formate salt and the free base, but both pure by tlc and 360 MHz ^{1}H nmr spectrum. Optically inactive. HREIMS m/z 490.3494 (Calc. for $C_{32}H_{46}N_2O_2$: 490.3558; M^+-H_2O); CIMS M^++1 509 (HRMS not available); EIMS 508, 490, 451, 450, 449, 246, 245, 244, 243, 201, 58(100). For the NMR data which follow, the individual resonances for the two hordeninyl moieties cannot be assigned specifically to one or the other. ^{13}C NMR ($CDCl_3$, 25 MHz, formate salt): (1) hordeninyl moiety resonances at 159.9s, 155.0s, 133.1s, 132.2s, 131.4d, 129.5d, 128.7s, 127.9s, 127.2d (2), 110.8d, 110.6d, 58.5t (2 $\underline{C}H_2NMe_2$), 55.4q (OMe), 55.0q (OMe), 42.6q (2 NMe_2), 42.5q (2 NMe_2), 30.2t (2 $ArCH_2$), and (2) terpene resonances at 134.5s (C1), 124.5d (C2), 73.6s ($Me_2\underline{C}OH$), 50.5d (C3), 36.7t (C6), 33.9d (C5), 30.4q ($C\underline{Me}_2$), 26.1q (C1-$\underline{Me}$), 23.0d ppm (C4). ^{1}H NMR ($CDCl_3$, 360 MHz, formate salt): (1) hordeninyl moiety resonances at 7.21-6.74(m, 6H, aromatic H), 3.81(s, 3H, OMe), 3.74(s, 3H, OMe), 3.2-2.83(m, 8H, 2 $ArCH_2CH_2N$), 2.73(s, 6H, NMe_2), 2.70 ppm (s, 6H, NMe_2), and terpene resonances at 5.56(br s, 1H, C-2H), 4.10(br s, 1H, C-3H), 1.82(s, 3H, C=CMe), 0.72 ppm (s, 3H, 2 CMe), with nontabulated resonances obscured. ^{1}H NMR ($CDCl_3$, 360 MHz, free base): (1) hordeninyl moiety resonances at 7.30-6.76(m, 6H, aromatic H), 3.80(s, 3H, OMe), 3.79(s, 3H, OMe), 2.4-2.8(m, 8H, $ArCH_2CH_2N$), 2.32(s, 6H, NMe_2), 2.28 ppm (s, 3H, NMe_2), and (2) terpene moiety resonances at 5.53(br d, 1H, C-2H), 4.20(br s, 1H, C-3H), 1.77(s, 3H, C=CMe), 0.68(s, 3H, CMe), 0.64(s, 3H, CMe) with nontabulated resonances obscured.

5-Epiculantraraminol (12). Semisolid or oil as formate salt and free base, but pure by tlc and 360 MHz ^{1}H nmr spectrum. EIMS m/z 508(.2), 507(.5), 506(.9), 463(1.9), 368(2.1), 236(4.4), 58(100) and NH_3CIMS m/z 509(19), 491(17), 300(13), 248(17), 247(15), 246(77), 208(13), 58(100). HREIMS: Calc. for M^+-H_2O, $C_{32}H_{46}N_2O_2$: 490.3559; Found: 490.3559. Optical activity not measured. ^{13}C NMR ($CDCl_3$, 25 MHz, formate salt): (1) hordeninyl moiety resonances at 155.5, 154.5, 133.5, 131.6, 129.4(2), 128.4, 127.6, 127.0, 126.4, 110.2, 110.0, 59.6, 59.4, 55.6, 55.0, 43.3(2), 43.1(2), 31.2, 30.9 ppm and (2) terpene resonances at 134.5, 124.3, 70.2, 52.4, 49.2, 35.8, 34.7, 29.7, 23.6, and 22.8 ppm. Insufficient material was available so that a useful off-resonance spectrum could be obtained and hence many of the signals are ambiguous as to exact assignment. There are, however, exactly the right number and general chemical shifts expected for an isomer of 9. ^{1}H NMR ($CDCl_3$, 360 MHz, formate salt): (1) aromatic hordeninyl moiety proton resonances at 7.08(d, J=2Hz, 1H), 6.99(d, J=2Hz, 1H), 6.90(dd, J=2Hz and J=9Hz, 1H), 6.87(dd, J=2 and 9Hz, 1H), 6.58(d, J=9Hz, 1H), 6.55 ppm (d, J=9Hz, 1H), (2) other hordeninyl resonances at 3.68(s, 3H, OMe), 3.59(s, 3H, OMe), 3.19-3.00(m, 8H, 2 $ArCH_2CH_2N$), 2.81(s, 6H, NMe_2), 2.75 ppm (s, 6H, NMe_2), and (3) terpene moiety resonances at 5.00(s, 1H, C-2H), 4.83(d, J=4Hz, 1H, C-3H), 3.84(br dd with fine splitting, J=1, 2.5, and 11.2Hz, 1H, C-5H), 2.25(dd, J=4.0 and 11.2Hz, 1H, C-4H), 2.13(dd, J=2.5 and 17.3Hz, 1H, C-6H), 1.63(s, 3H, C=CMe), 1.47(br d, J=17.3Hz, C-6H), 1.18(s, 3H, CMe) and 0.81 ppm (s, 3H, CMe). ^{1}H NMR ($CDCl_3$, 360 MHz, free base): (1) aromatic hordeninyl moiety resonances at 7.03(d, J=2.1Hz, 2H overlapping), 6.94(dd, J=2.1 and 8.3Hz, 1H), 6.89(dd, J=2.1Hz and 8.3Hz, 1H), 6.68(d, J=8.3Hz, 1H), 6.53(d, J=8.3Hz, 1H), (2) other hordeninyl resonances at 3.78(s, 3H, OMe), 3.52(s, 3H, OMe), 2.70(m, 4H, CH_2N), 2.50(m, 4H, $ArCH_2$), 2.33(s, 6H, NMe_2), 2.29 ppm (s, 6H, NMe_2), and (3) terpene resonances at 5.15 (s, 1H, C-2H), 4.75(d, J=2.9Hz, 1H, C-3H), 4.06(br d, J=2 and 11.2Hz, 1H, C-5H), 2.23(dd, J=2.9 and 11.2Hz, 1H, C-4H), 2.12(br d, J=2 and 17.2Hz, 1H, C-6H), 1.65(s, 3H, C=CMe), 1.41(br dd, J=1 and 17.2Hz), 1.20(s, 3H, CMe) and 0.61 ppm (s, 3H, CMe).

Alloculatraraminol (11). Isolated as an oil as either the formate salt or free base. NH_3CIMS m/z 509(11), 493(8), 491(14), 399(4), 300(24), 246(100), 208(24), 58(97) and EIMS m/z 507(0.4), 490(0.5), 464(1.3), 446(0.8), 301(1), 81(7), 69(13), and 58(100); HREIMS: Calc. for M^+-H_2O, $C_{32}H_{46}N_2O_2$: 490.3559; Found: 490.3559. Optical activity not measured. ^{1}H NMR ($CDCl_3$, 360 MHz, free base): (1) aromatic hordeninyl resonances at 6.66(m, 3H), 6.49(d, J=1.4Hz, 1H), 6.47(d, J=8.3Hz, 1H), 6.38 ppm (d, J=1.4Hz, 1H), (2) other hordeninyl resonances at 3.88(s, 3H, OMe), 3.71(s, 3H, OMe), 2.3-2.4(m, 8H, 2 CH_2CH_2), 2.27(s, 6H, NMe_2), 2.23 ppm (s, 6H, NMe_2) and (3) terpene resonances at 5.34(d, J=11.2Hz, 1H, C-3H), 5.01(s, 1H, C-2H), 4.06(br d, 1H, C-5H), 3.12(d, J=11.2Hz, 1H, C-4H); 2.21(dd, J=7 and 15Hz, 1H, C-6H), 1.67(dd, J=2 and 15Hz, 1H, C-6H), 1.64(s, 3H, C=CMe), 1.26(s, 3H, CMe), and 1.20 ppm (s, 3H, CMe).

Interconversions

Dehydration of Culantraraminol (9) to Culantraramine (8). A solution containing 25 mg (0.049 mmol) of 9 and 20 mg $KHSO_4$ in 10 ml of dry CH_2Cl_2 was heated at reflux for 5 hours, at which time no starting material remained (tlc). The organic layer was washed three times with H_2O and the CH_2Cl_2 evaporated under reduced pressure to yield 19 mg (0.039 mmol, 80%) of 8 as virtually the only product (360 MHz ^{1}H nmr, tlc).

Conversion of Culantraramine (8) to Isoalfileramine (10). A solution containing 25 mg (0.051 mmol) 8 in 12.5 ml EtOH and 2.5 ml 48% HBr was heated under reflux for 10 minutes, at which time no starting material remained (tlc). The reaction mixture was basified, extracted with $CHCl_3$, and the organic layer evaporated under reduced pressure to yield an oily residue. The residue was purified by prep tlc on Si gel (15:15:4:3 EtOAc/Et_2O/EtOH/NH_4OH) to yield 16 mg (0.035 mmol, 70% purified) of 10, identical with previously prepared material.[12]

Culantraramine and Culantraraminol from 16. A solution containing 75 mg (0.36 mmol) of 16 in 0.5 ml of 1M HCl was allowed to stand at room temperature for 30 minutes, at which time no starting material remained (tlc). The reaction mixture was made basic with 1M NaOH solution and extracted with $CHCl_3$. A 270 MHz ^1H NMR spectrum of the $CHCl_3$ extract showed total conversion to a mixture of cycloadducts with CMe peaks at 0.61, 0.65, 1.19, 1.24, 1.36, 1.65, 1.71, 1.79 ppm and OMe peaks at 3.50, 3.62, 3.69, 3.75, 3.70, 3.75, and 3.84. This compared closely to the crude isolated mixture from Z. procerum (see above). The analysis indicated the presence of about 55% culantraramine (8), 25% culantraraminol (9), 8% each of both 5-epiculantraraminol (12) and alloculantraraminol (11) and several trace substances. The residue was purified by flash chromatography on Si gel (6:6:4:1 EtOAc/EtOH/H_2O/HCO_2H) and by prep tlc (10:2:1 EtOAc/EtOH/NH_4OH) to yield 31 mg (.063 mmol, 35% purified) of 8, 14 mg (.027 mmol, 15% purified) of 9, 4 mg (.007 mmol, 4%, still slightly impure) of 12, and 3 mg (.005 mmol, 3%, still slightly impure) of 11. Comparisons were made with natural isolates by tlc and ^1H NMR at 360 MHz.

A solution containing 60 mg (0.29 mmol) of 16 and 27 mg (0.35 mmol, 1.2 eq) of acetyl chloride in 2 ml $CDCl_3$ was allowed to stand at room temperature for one hour in an nmr tube. At the end of this time, the 270 MHz ^1H NMR spectrum of the reaction mixture showed total conversion to the HCl salt of culantraramine (peaks compared to a standard), along with several minor products. The analysis indicated about 80% culantraramine and 2-5% each of the minor products. The solution was made basic with NaOH, extracted with $CHCl_3$, and the combined $CHCl_3$ layers evaporated to yield an oily residue. This was purified by prep tlc on Si gel (20:4:1 EtOAc/EtOH/NH_4OH) to yield 44 mg (0.09 mmol, 62% purified) of culantraramine (8).

In a similar manner, the conversion was accomplished by letting a solution of 20 mg (0.076 mmol) of 16 in 1.5 ml of EtOH and 0.5 ml 48% HBr stand at room temperature for 15 minutes. The results were essentially the same as those described above.

Synthesis

Methoxyhordenine. To a round-bottomed flask containing 25 g (165 mmol) of p-methoxyphenethylamine was added 29.5 g (364 mmol, 2.2 eq) of 37% formaldehyde, which initiated an immediate reaction. To this mixture was added 43.3 g (830 mmol, 5 eq) of 88% formic acid, which caused evolution of CO_2. The flask was allowed to stand overnight and then heated at reflux for 3 hours. One eq of conc HCl was added and the volatiles removed by evaporation under reduced pressure. The amine salt residue was converted to the free base with NaOH and the aqueous layer extracted with $CHCl_3$. The $CHCl_3$ layers were combined and the $CHCl_3$ removed under reduced pressure to yield 27.6 g (154 mmol, 93%) of methoxyhordenine[29] as an oil. Mp of HCl salt: 167-168.5°.

2-Formylmethoxyhordenine. To a solution of 36.5 g (204 mmol) of methoxyhordenine in 400 ml of dry Et_2O at room temperature under argon was added 107 ml (224 mmol, 1.1 eq) of 2.1 M BuLi dropwise with stirring. After stirring 30 hrs, 16.4 g (224 mmol, 1.1 eq) of dimethylformamide was added dropwise and the solution was allowed to stir an additional 5 hrs. The reaction mixture was quenched with two eq of 1M HCl, extracted twice with Et_2O (discarded), then basified with NaOH and extracted three times with $CHCl_3$. The $CHCl_3$ was removed under reduced pressure and the residue purified by bulb-to-bulb vacuum distillation to yield 29.1 g (141 mmol, 69%) of 2-formylmethoxyhordenine. ^1H NMR ($CDCl_3$, 360 MHz): 10.45(s, 1H), 7.66(d, J=2.2Hz, 1H), 7.40(dd, J=2.2Hz, J=8.3Hz, 1H), 6.92(d, J=8.3Hz, 1H), 3.91(s, 3H), 2.74(t, 2H), 2.51(t, 2H), 2.28 ppm (s, 6H); ^{13}C NMR ($CDCl_3$) 189.28d, 159.96s, 135.85d, 132.29s, 127.68d, 124.23s, 111.51d, 61.06t, 55.46q, 45.30q(2), 32.98t. Mp of HCl salt: 188-192°. Anal. Calcd. for $C_{12}H_{18}NO_2Cl \cdot 1/2 H_2O$: C, 57.02; H, 7.57; N, 5.54. Found: C, 56.78; H, 7.16; N, 5.55.

4-(2'-Methoxyhordeninyl)-(E)-but-3-en-2-one. To a solution of 1.0 g (4.8 mmol) of 2-formylmethoxyhordenine in 100 ml of acetone was added 17 ml of H_2O and 5 ml of 1M NaOH. This mixture was allowed to stir overnight under argon at room temperature. After neutralization to pH 7 with 1M HCl, the acetone was evaporated under reduced pressure and the remaining aqueous solution extracted with $CHCl_3$. The combined $CHCl_3$ layers were evaporated and the residue purified by flash chromatography on Si gel (10:10:1 EtOAc/Et_2O/NH_4OH) to yield 0.96 g (3.9 mmol, 81%) of the butenone as a viscous oil. The oil was converted to the hydrochloride (mp 172-173°) for characterization. Anal. Calcd. for $C_{15}H_{22}NO_2Cl \cdot 1/2 H_2O$: C, 61.53; H, 7.92; N, 4.78. Found: C, 61.52; H, 7.92; N, 4.66. ^1H NMR ($CDCl_3$, 360 MHz): 7.82(d, J=16.6Hz, 1H), 7.44(d, J=1.8Hz, 1H), 7.28(dd, J=1.8Hz, J=8.3Hz, 1H), 6.88(d, J=8.3Hz, 1H), 6.76(d, J=16.6Hz, 1H), 3.88(s, 3H), 3.22(m, 4H), 2.88(s, 6H), 2.38 ppm (s, 3H).

1-(2'-Methoxyhordeninyl)-3-methyl-1,3-butadiene (13). To a cooled (0°) suspension of 1.71 g (4.2 mmol) of methyltriphenylphosphonium iodide in 60 ml of THF under argon was added 2.0 ml (4.2 mmol) of 2.1 M BuLi dropwise with stirring. This solution was stirred for 1/2 hr, cooled to -78°, and a solution of 1.04 g (4.2 mmol) of the above butenenone in 20 ml THF was added slowly with stirring. After 30 min, the mixture was diluted with $CHCl_3$, extracted three times with H_2O and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography on Si gel (1:1 EtOAc/Et_2O) to afford 0.69 g (2.73 mmol, 65%) of diene 13 as an oil, pure by tlc and 360 MHz ^1H nmr. HREIMS (m/z) Calcd. for $C_{16}H_{23}NO$: 245.1774. Found: 245.1770. ^1H NMR: ($CDCl_3$, 360 MHz): 7.35(d, J=1.8Hz, 1H), 7.07(dd, J=1.8Hz, J=9.1Hz, 1H), 6.90(d, J=16.2Hz, 1H), 6.84(d, J=16.2Hz, 1H), 6.80(d, J=9.1Hz, 1H), 5.12(s, 1H), 5.01(s, 1H), 3.83(s, 3H), 2.91(t, 2H), 2.80 (t, 2H), 2.52(s, 6H), 1.98 ppm (s, 3H); ^{13}C NMR ($CDCl_3$): 155.17s, 142.27s, 132.00d, 130.01s, 128.38d, 126.16s, 126.16d, 122.72d, 116.88t, 110.86d, 60.65t, 55.51q, 44.48q(2), 32.10t, 18.61q.

Dimerization of 13 to 14 and 15. A solution of 30 mg (0.12 mmol) of diene 13 in 2 ml xylene was allowed to stand at room temperature for 10 days, at which time no starting material remained (tlc). The xylene was evaporated at reduced pressure to give a residue whose 360 MHz ^1H NMR

spectrum showed it to be a 3:2 mixture of 14 and 15. The mixture was separated by prep tlc (10:2:1 EtOAc/EtOH/NH_4OH) to yield (top band) 7 mg (0.014 mmol, 24% purified) of 15. HREIMS (m/z) Calcd. for $C_{32}H_{46}N_2O_2$: 490.3557. Found: 490.3567. ^1H NMR ($CDCl_3$, 360 MHz): 6.90(m, 4H, aromatics), 6.40(m, 3H, aromatics), 6.54(d, J=16Hz, 1H, styryl olefin), 6.34(d, J=16Hz, 1H, styryl olefin), 5.30(s, 1H, vinyl), 4.05(s, 1H, C-3H), 3.78(s, 3H, OMe), 3.71(s, 3H, OMe), 2.75(m, 4H, $ArCH_2CH_2N$), 2.60(m, 4H, $ArCH_2CH_2N$), 2.38(s, 12H, $2NMe_2$), 2.12(m, 1H), 1.88(m, 1H), 1.78(s, 3H, C=CMe), 0.85 ppm (s, 3H, C-Me).

A lower band yielded 10 mg (0.021 mmol, 36% purified) of 14. HREIMS (m/z) Calcd. for $C_{32}H_{46}N_2O_2$: 490.3557. Found: 490.3514. ^1H NMR ($CDCl_3$, 360 MHz): 7.05-6.70(m, 6H, aromatics), 6.34(d, J=15Hz, 1H, styryl olefin), 6.16(d, J=15Hz, 1H, styryl olefin), 5.32(s, 1H, vinyl), 4.02(s, 1H, C-3H), 3.73(s, 3H, OMe), 3.71(s, 3H, OMe), 2.31(s, 6H, NMe_2), 2.19(s, 6H, NMe_2), 1.80(s, 3H, C=CMe), 1.20(s, 3H, C-Me).

2-Iodomethoxyhordenine. To a solution of 3.8 g (21.1 mmol) of methoxyhordenine in 35 ml of dry Et_2O was added 11.1 ml (23.3 mmol, 1.1 eq) of 2.1M BuLi dropwise with stirring. After stirring 30 hrs, 5.38 g (21.2 mmol) of I_2 in 40 ml Et_2O was added dropwise. The iodine color was discharged immediately upon contact with the solution. Addition was continued until the iodine color persisted. The mixture was poured into H_2O, the Et_2O removed at reduced pressure and the H_2O extracted with $CHCl_3$. The organic layer was washed with saturated Na_2SO_4 solution and the $CHCl_3$ evaporated under reduced pressure. The residue was purified by flash chromatography on Si gel (1:1 $CHCl_3$/EtOH) to yield 5.24 g (17.2 mmol, 81%) of 2-iodomethoxyhordenine. ^1H NMR ($CDCl_3$, 360 MHz): 7.61(d, J=2.2Hz, 1H), 7.14(dd, J=2.2Hz, J=8.3Hz, 1H), 6.74(d, J=8.3Hz, 1H), 3.85(s, 3H), 2.68(t, 2H), 2.49(t, 2H), 2.28 ppm (s, 6H). EIMS (m/z, %): 305(0.3), 303(1.5), 288(1.5), 261(0.9), 260(1.3), 247(1.2), 134(2.2), 58(100). Characterized as the HCl salt (mp 226°). Anal. Calcd. for $C_{11}H_{17}NOCl$: C, 38.67; H, 5.02; N, 4.10. Found: C, 38.82; H, 4.92; N, 3.96.

4-(2'-Methoxyhordeninyl)-(E)-2-methylbut-3-en-2-ol (16). To a test tube fitted with a vacuum apparatus was added 2.25 g (7.39 mmol) of 2-iodomethoxyhordenine, 0.86 g (10 mmol) of 2-methyl-3-buten-2-ol (Aldrich Chemical Company), 8.6 mg (0.025 mmol) of palladium(II) acetate and 2.2 ml of dry acetonitrile. The tube was evacuated, filled with argon and then heated at 100° in an oil bath for 4 hrs with stirring. The reaction mixture was made basic with 1M NaOH solution and extracted with $CHCl_3$. The organic layer was evaporated under reduced pressure and the residue purified by bulb-to-bulb vacuum distillation to yield 1.42 g (4.65 mmol, 63%) of 16 as a clear oil. CIMS m/z: 264(M^+ +1; 12), 246(M^+ +1-H_2O; 100). HRMS not obtainable. ^1H NMR ($CDCl_3$, 360 MHz): 7.26(d, J=2.2Hz, 1H, C-3H), 7.04(dd, J=2.2Hz, J=8.6Hz, 1H, C-5H), 6.88(d, J=16.2Hz, 1H, C-1'H styryl), 6.78(d, J=8.6Hz, 1H, C-6H), 6.36(d, J=16.2Hz, 1H, C-2'H styryl), 3.81(s, 3H, OMe), 2.74(m, 2H, $ArCH_2$), 2.56(m, 2H, CH_2N), 2.33(s, 6H, NMe_2), 1.43 ppm (s, 6H, 2C-Me); ^{13}C NMR ($CDCl_3$): 155.17s(C-1), 138.32d(C-3), 132.23s(C-2), 128.16d(C-C-1')*, 126.74d(C-5)*, 126.02s(C-4), 120.97d(C-2'), 111.10d(C-6), 70.55s(C-3'), 61.36t(CH_2N), 55.43q(OMe), 45.02q(NMe_2), 33.02t($ArCH_2$), 29.80q(2C-Me). The starred assignments may be interchanged. Combustion analyses were outside acceptable limits, but both the ^1H and ^{13}C nmr spectra showed essentially no organic impurities. The alcohol was stable to distillation at reduced pressure (see above) and to treatment with base.

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