Synthesis of Plagiochiline N from Santonin

Gonzalo Blay, Luz Cardona, Begoña García, Luisa Lahoz, and José R. Pedro*

Departament de Química Orgànica, Facultat de Química, Universitat de València, E-46100 Burjassot, València, Spain

jose.r.pedro@uv.es

Received June 5, 2001

This article reports the transformation of *O*-acetylisophotosantonin, obtained by photochemical rearrangement of santonin, into plagiochiline N, an *ent*-2,3-secoaromadendrane isolated from *Plagiochila ovalifolia*. The synthesis was carried out in a sequence involving as the key steps (a) the substitution of the lactone moiety by a *gem*-dimethylcyclopropane ring through a synthetic intermediate having a C_6-C_7 double bond and (b) the ozonolysis of the C_2-C_3 bond followed by cyclization to the dihydropyran ring characteristic of plagiochiline N. Spectroscopic data of the synthetic product fully coincided with the reported data for the natural product.

Introduction

The genus *Plagiochila* is one of the largest liverwort genera distributed worldwide.[1] The genus includes more than 3000 species, which are classified into two groups: pungent and nonpungent species.[2] The hot taste of the former is due to the presence of unique *ent*-2,3-secoaromadendrane-type sesquiterpenes, while the nonpungent species produce mainly aromatic compounds such as bibenzyls or different types of sesqui- and diterpenes. These compounds are important not only from the taxonomic point of view but also because some of them have interesting biological activities. Thus, some secoaromadendrane-type compounds have shown insect antifeedant,[3] plant growth inhibitory[4] or neurotrophic[5] properties, as well as strong cytotoxic activity against P-388 murine leukemia.[6] Furthermore, it has been suggested that some relationship may exist between the pungency and biological activity of these products and the occurrence of an actual or latent unsaturated dialdehyde moiety in their molecules, in the same way as in other hot-tasting bioactive compounds such as velleral (**4**) and poligodial (**5**).[7]

The unique structures presented by the *ent*-2,3-secoaromadendranes isolated from *Plagiochila* sp. as well as the difficulties in obtaining sufficient amounts of plant material from some species make the synthesis of these compounds a worthwhile goal. As a continuation of our current synthetic program toward sesquiterpenolides and oxacyclic terpenoids,[8] we report in this paper the first synthesis of plagiochiline N (**3**), a product isolated from *Plagiochila ovalifolia*,[9] whose pyran ring bears a latent unsaturated dialdehyde moiety masked as a cyclic enol ether.

Results and Discussion

Aromadendrane sesquiterpenes are characterized by a tricyclo[6,3,0,$0^{5,7}$]undecane skeleton. Although some methods for the construction of such a system can be found in the literature,[10] they either start from materials not easily available or do not give the proper stereochemistry and functionality for the synthesis of plagiochiline N (**3**). For this reason we envisaged a synthesis of plagiochiline N (**3**) starting from *O*-acetylisophotosantonin (**2**), a compound with a bicyclo[5,3,0]decane skeleton that can be easily obtained by photochemical rearrangement of santonin (**1**) in a well-known procedure.[8,11] Further transformation of compound **2** into plagiochiline N (**3**) should involve the substitution of the lactone moiety by a *gem*-dimethylcyclopropane ring between C_6-C_7 by one hand, and transformation of the cyclopentane ring into a dihydropyran by the other. For the first part, since the stereochemistry of C_7 in compound **2** was the opposite of that of plagiochiline N (**3**), it became necessary to

* Corresponding author. Phone: +34 963864329. Fax: +34 963864328.

(1) Gradstein, S. R.; Reiner-Drehwald, M. E. *Fragmenta Flora et Geobotica* **1995**, *40*, 31−32.

(2) (a) Asakawa, Y. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, E. W., Moore, R. E., Steglich, W., Tamm, C., Eds.; Springer: Wien, 1995; Vol. 65, p 1. (b) Asakawa, Y. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, E. W., Eds.; Springer: Wien, 1982; Vol. 42, p 1.

(3) Asakawa, Y.; Toyoto, M.; Takemoto, T; Kubo, I.; Nakanishi, K. *Phytochemistry* **1980**, *19*, 2147−2154.

(4) Matsuo, A.; Nadaya, K.; Nakayama, M.; Hayashi, S. *Nippon Kagakukai Zasshi* **1981**, 665−770.

(5) Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **1991**, *30*, 4061−4065.

(6) Toyota, M.; Tanimura, K.; Asakawa, Y. *Planta Med.* **1998**, *64*, 462−464.

(7) Hashimoto, T.; Tanaka, H.; Asakawa, Y. *Chem. Pharm. Bull.* **1994**, *42*, 1452−1454.

(8) (a) Bargues, V.; Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *Tetrahedron* **1998**, *54*, 1845−1852. (b) Blay, G.; Bargues, V.; Cardona, L.; Collado, A. M.; García, B.; Muñoz, M. C.; Pedro, J. R. *J. Org. Chem.* **2000**, *65*, 2138−2144. (c) Blay, G.; Cardona, L.; García, B.; Lahoz, L.; Pedro, J. R. *Eur. J. Org. Chem.* **2000**, 2145−2151. (d) Blay, G.; Cardona, L.; García, B.; Lahoz, L.; Monje, B.; Pedro, J. R. *Tetrahedron* **2000**, *56*, 6331−6338. (e) Blay, G.; Bargues, V.; Cardona, L.; García, B.; Pedro, J. R. *J. Org. Chem.* **2000**, *65*, 6703−6707.

(9) Nagashima, F.; Tanaka, H.; Toyota, M.; Hashimoto, T.; Kan, Y.; Takaoka, S.; Tori, M.; Asakawa, Y. *Phytochemistry* **1994**, *36*, 1425−1430.

(10) (a) Pirrung, M. C.; Morehead, A. T.; Young, B. G. In *The Total Synthesis of Natural Products*; Goldsmith, D., Ed.; John Wiley & Sons: New York, 2000; Vol. 11, pp 163−165. (b) Heathcock, C. H.; Graham, S. C.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; John Wiley & Sons: New York, 1983; Vol. 5, pp 344−347. (c) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; John Wiley & Sons: Ney York, 1973; Vol. 2, pp 417−422.

(11) Barton, D. H. R.; de Mayo, P.; Shafiq, M. *J. Chem. Soc.* **1957**, 929−935.

10.1021/jo010567d CCC: $20.00
Published on Web 10/24/2001

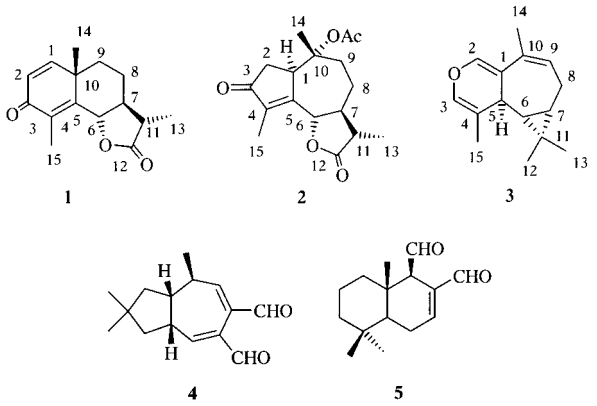


Figure 1. Structures of compounds **1**−**5**.

remove the C_{11}−C_{13} carbon fragment and to introduce the *gem*-dimethylcyclopropane ring later by cyclopropanation of a synthetic intermediate having a C_6−C_7 double bond.

With these ideas in mind, we undertook the synthesis of plagiochiline N (**3**) from *O*-acetylisophotosantonin (**2**). In the first instance (Scheme 1), compound **6b** was obtained in 65% yield by hydrogenation of compound **2** with 10% Pd/C followed by epimerization of C_4 with KOH and relactonization with HCl following a procedure described in the literature.[12] On the other hand, compound **6b** could also be obtained in an improved 86% yield from **2** by a two-step procedure that involved reduction of **2** with NaTeH[8a] to give compound **6a** followed by basic hydrolysis of the acetate group. It should be noted that in both procedures, hydrogenation of the double bond is completely stereoselective and gives the compound with the same configuration at C_5 as that in the target compound. Treatment of compound **6b** with $NaBH_4$ in MeOH gave the major alcohol **7** in 93% yield. The stereochemistry of the resulting alcohol was proposed on the assumption of a preferred attack of the hydride from the less hindered α-side of the molecule.[13]

From compound **7**, the preparation of 2,3-secoaromadendranes required elimination of the C_3-hydroxyl group to give a C_2−C_3 double bond by one hand, and transformation of the lactone ring into a C_6−C_7 double bond by the other. To avoid interference of the C_2−C_3 double bond, elimination of the C_3-hydroxyl group was left for a later stage in the synthetic sequence after the introduction of the cyclopropane ring at the C_6−C_7 position. So, the next steps addressed the removal of the C_{11}−C_{13} carbon fragment of the lactone ring. For this purpose, we decided to introduce a C_7−C_{11} double bond that could be subsequently cleaved by ozonolysis. Prior to this, we needed to protect the hydroxyl groups. Treatment of compound **7** with excess TMSCl protected both hydroxyl groups as TMS ethers. However, the TMS protecting group at the C_3-hydroxyl group was too labile and caused many experimental difficulties during purification of the products. The use of two different protecting groups was much more convenient. Thus, the C_3-hydroxyl group was protected as a TBDMS ether and the C_{10}-hydroxyl group as a TMS ether. Once the hydroxyl groups were protected, we undertook the formation of the C_7−C_{11} double bond. A one-step procedure that uses LDA and dibromoethane failed in our case.[14] This problem was solved by carrying out the oxidation of C_{11} in compound **9** upon treatment of the sodium enolate of the lactone carbonyl group with 2-phenylsulfonyl-3-phenyloxaziridine (Davis' reagent).[15] In this way the 11β-alcohol **10a** was obtained as the major product in 83% yield together with 6% of the α-alcohol **10b**. Mesylation of the alcohol **10a** with MsCl in the presence of triethylamine followed by heating with DBU at a toluene reflux temperature afforded the unsaturated lactone **11** with complete regioselectivity and in 66% overall yield. However, the same treatment with alcohol **10b** gave rise to a complicated mixture and, therefore, this minor alcohol was not used. Once the double bond was introduced at the desired position, we proceeded to cleave it by ozonolysis. This reaction took place smoothly and with a very high yield (94%) when the ozonide was reduced with dimethyl sulfide to give compound **12**.[16] In contrast, the use of hydrides such as $NaBH_4$ or $LiAlH_4$ that usually bring about reduction to the alcohol only led to complex mixtures. The next step was aimed at reducing both the C_7 and C_{12} carbonyl groups to give a *vic*-diol that should allow the regioselective introduction of a double bond in a later step. Reduction of compound **12** yielded the two alcohols **13a** and **13b** in different ratios and yields depending on the reagent. The highest selectivity was found with DIBAH, which gave only compound **13b**, although in a moderate yield (46%); $LiAlH_4$ and Red-Al reagent were less selective, although they gave better yields: **13a**/**13b** in ratios of 27%/40% and 25%/59%, respectively. Finally, $LiBH_4$ inverted the selectivity giving 42% of **13a** and 38% of **13b**. The stereochemistry of C_7 in compounds **13a** and **13b** was inferred from the study of the coupling constants in the ^{1}H NMR spectra and from NOE experiments. Thus, a NOE between H_6 (δ 3.64) and the C_{14} methyl group (δ 1.25), both in the β-side of the molecule, was observed in compound **13a**. This NOE was only possible when the cycloheptane ring adopted a boatlike conformation. In this conformation, H_5 and H_6 were disposed almost anticoplanar. A decoupling experiment involving irradiation on the OH signal at δ 3.39 collapsed the H_6 signal into a triplet ($J_{5,6} \sim J_{6,7} \sim 7.0$ Hz), indicating a similar disposition of H_5 and H_7 with regard to H_6. Therefore, we assigned H_7 the α-disposition in this compound. On the other hand, the coupling constant $J_{5,6}$ in compound **13b** had a value near zero, which indicated a dihedral angle of ∼90° between the C_5−H and C_6−H bonds. This fact indicated a change in the cycloheptane ring conformation compared with compound **13a**, which we assumed to be caused by a hydrogen bond between the C_7−OH group and the C_{10}−O atom, both in the α-side of the molecule. Observation of Dreiding models for this conformation showed an almost syn coplanar disposition of the C_6−H and C_7−H bonds that would account for the observed $J_{6,7}$ = 10.7 Hz, according to the Karplus−Conroy equation.

The reduction of *vic*-diols to alkenes is a procedure often used for the regioselective formation of double

(12) Barton, D. H. R.; Levisalles, J. E. D.; Pinhey, J. T. *J. Chem. Soc.* **1962**, 3472−3482.

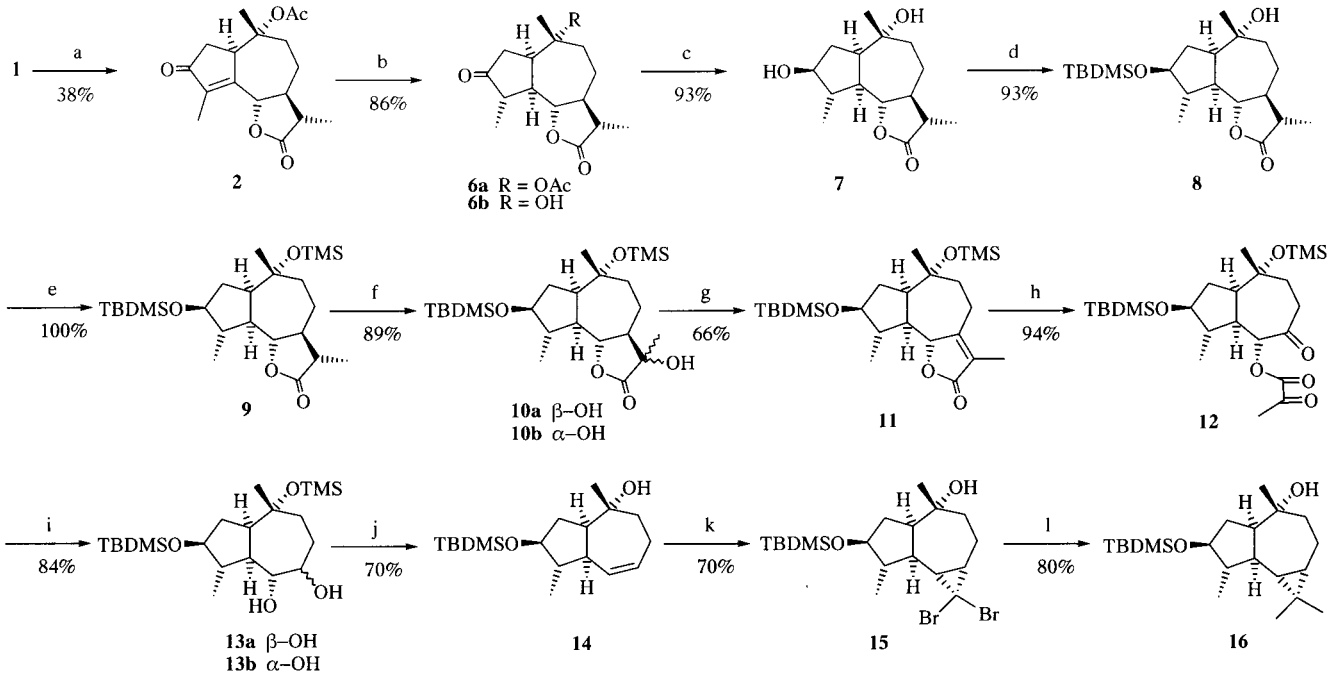
(13) During the preparation of this paper, a paper dealing with the stereochemistry of related alcohols appeared: Garcia-Marrero, B. *Tetrahedron* **2001**, *57*, 1297−1300.

(14) Delair, P.; Kann, N.; Greene, A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1651−1652.

(15) Lauridsen, A.; Cornett, C.; Vulpius, T.; Moldt, P.; Christensen, S. B. *Acta Chem. Scand.* **1996**, *50*, 150−157.

(16) Lin, J.; Nikaido, M. M.; Clark, G. *J. Org. Chem.* **1987**, *52*, 3745−3752.

Scheme 1[a]

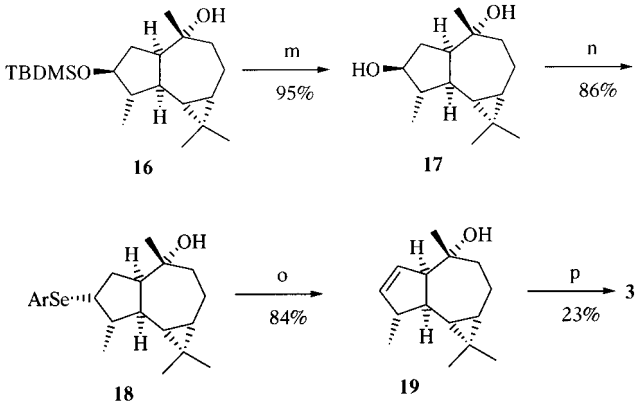


[a] Key: (a) *hν*/AcOH; (b) (1) NaTeH, (2) KOH, (3) HCl; (c) $NaBH_4$; (d) TBDMSCl−imidazole; (e) TMSCl−Et_3N; (f) $Na(Me_3Si)_2$−Davis' reagent; (g) (1) MsCl, (2) DBU; (h) (1) O_3, (2) Me_2S; (i) RedAl reagent; (j) (1) Ph_2PCl−I_2, (2) H_2O−AcOH−THF; (k) $HCBr_3$−Na *tert*-amylate; (l) MeLi−MeI.

bonds.[17] However in our case, this transformation was not straightforward and many procedures were tested.[18] All these procedures failed due to different reasons, and eventually, it was only possible to achieve the reduction of diol **13b** with chlorodiphenylphosphine and iodine.[19] In this way, and after deprotection of the C_{10}−TMS group with H_2O−AcOH−THF, compound **14** was obtained in 70% overall yield from **13b**. In contrast, it was not possible for us to transform compound **13a** into **14** under any of the attempted conditions, and hence the election of Red-Al reagent as the reducing agent in the preceding step is very important since it affords **13b** with the highest yield.

Once the C_6−C_7 double was obtained, the introduction of the *gem*-dimethylcyclopropane ring was accomplished in two steps.[20] The first step was the introduction of a *gem*-dibromocyclopropane ring by reaction with dibromocarbene, prepared from bromoform and sodium *tert*-amylate. The resulting product was then treated with MeLi and MeI to give compound **16**, which possesses a complete aromadendrane carbon skeleton. The cyclopropanation reaction was completely stereoselective, and only one of the two possible stereoisomers was obtained. The stereochemistry of compound **16** was assigned on the basis of a favorable attack of the carbene from the less hindered α-side of the molecule and was confirmed by NOE experiments. Thus, irradiation at H_6 (0.30 ppm) gave NOE with H_{14} (1.47 ppm), H_7 (0.55 ppm), and H_{12} (1.03 ppm). Equally, H_7 showed NOE with H_6, H_{12}, and H_{14}. These results indicated that H_6 and H_7 were on the same side of the molecule as the C_{14} methyl group, which is *β*-oriented, and therefore the cyclopropane ring must be α-oriented.

Scheme 2[a]



[a] Key: (m) HF/THF; (n) *o*-$NO_2C_6H_4SeCN$−Bu_3P; (o) H_2O_2; (p) (1) O_3, (2) Me_2S, (3) TsOH.

With compound **16** available, we undertook the modification of the A-ring, which should involve cleavage of the C_2−C_3 bond to give a 2,3-secoaromadendrane derivative (Scheme 2). First, the TBS protecting group was removed by treatment with 45% aqueous HF in THF to give diol **17** in 95% yield. The election of the reaction solvent was critical in this reaction as it was found that when the reaction was carried out in the usual solvent acetonitrile, elimination of the tertiary alcohol took place.

(17) Block, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984; Vol. 30.

(18) (a) Vedjes, E.; Wu, E. S. C. *J. Org. Chem.* **1974**, *39*, 3641−3648. (b) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979−1982. (c) Barton, D. H. R.; Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1773−1776. (d) Rao, A. V. R.; Mysorekar, S. V.; Gurjar, M. K.; Yadav, J. S. *Tetrahedron Lett.* **1987**, *19*, 2183−2186. (e) Barrett, A. G. M.; Barton, D. H. R.; Bielski, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2378−2381. (f) Barua, N. C.; Sharma, R. P. *Tetrahedron Lett.* **1982**, *23*, 1365−1366. (g) Bargues, V.; Blay, G.; Fernández, I.; Pedro, J. R. *Synlett* **1996**, 655−656.

(19) Liu, Z.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1990**, *55*, 4273−4275.

(20) Jenninskens, L. H. D.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1991**, *56*, 6585−6591.

Next, we considered the elimination of the hydroxyl group at C_3 to give the less substituted C_2-C_3 double bond. For this purpose, alcohol **17** was treated with *o*-nitrophenylselenocyanate and tri-*n*-butylphosphine to give selenide **18** with inversion of the configuration at C_3, which upon oxidation with H_2O_2 afforded only one alkene **19** with total regioselectivity. Probably both the higher substitution[21] at C_4 and the impossibility of the selenoxide undertaking a syn elimination toward C_4 because of its anti orientation with H_4 account for the high regioselectivity of this reaction.

The final transformations in the synthetic sequence involved cleavage of the C_2-C_3 bond and the construction of the pyran ring. Cleavage of the double bond was brought about by ozonolysis followed by reduction of the ozonide with Me_2S. This reaction was expected to yield a 2,3-dialdehyde. However, the resulting mixture showed a complex TLC. ^{1}H NMR analysis of the mixture showed two signals of aldehyde protons together with other signals of protons geminal to oxygen, which were attributed to the presence of hemiacetal intermediates in the cyclization to the divinyl ether. Consequently, we decided to carry out the cyclization with the ozonolysis mixture without isolation and purification of the aldehyde. Therefore, compound **19** was treated with ozone and reduced with Me_2S, and the resulting mixture was heated at a benzene reflux temperature in the presence of TsOH. From the reaction mixture was isolated plagiochiline N (**3**) in 23% yield as a volatile compound with the same spectroscopic and optical rotation features as those of the natural product isolated from *P. ovalifolia*.[22] This synthesis gives chemical evidence of the structure and absolute stereochemistry of plagiochiline N (**3**).

Experimental Section

General Procedures. All melting points are uncorrected. Column chromatography was performed on silica gel (SDS, silica gel 60, 0.035−0.070 mm particle size). Pyridine (10 drops/100 mL) was added to the solvents for chromatography of compounds containing the TMS protecting group. Commercial reagents and solvents were analytical grade or purified by standard procedures prior to use.[23] All reactions involving air- or moisture-sensitive materials were carried out under an argon atmosphere. Specific rotations were measured in $CHCl_3$. IR spectra were recorded as liquid films in NaCl for oils and as KBr disks for solids. NMR experiments were run in $CDCl_3$ at 399.94 MHz for ^{1}H NMR and at 50.3, 75.43, or 100.58 MHz for ^{13}C NMR and referenced to the solvent as the internal standard. The carbon type was determined by DEPT experiments. EIMS experiments were run at 70 eV. Methane was used as an ionizing gas for CIMS experiments. FABMS experiments were run at 30 kV in an MNBA matrix.

10α-Hydroxy-3-oxo-1,5,7α*H*,4,6,11*βH*-guaian-6,12-olide (6b): Procedure A. Compound **6b** was obtained by hydrogenation of *O*-acetylisophotosantonin (**2**)[8,11] over 10% palladium adsorbed onto carbon in EtOH, followed by basic treatment as described in the literature.[12]

Procedure B. A solution of compound **6a** (370 mg, 1.21 mmol), obtained upon reduction of *O*-acetylisophotosantonin (**2**) with NaTeH (92% yield),[8a] in EtOH (4.9 mL) was treated with 5% aqueous KOH (66 mL) overnight. After this time, 18% aqueous HCl was added until a pH of 2 was reached, and the mixture was stirred for 30 min. The mixture was extracted with EtOAc (3 × 100 mL), washed with brine until neutrality was reached, and dried with Na_2SO_4. Evaporation of the solvent and chromatography (from 8:2 to 1:1 hexanes−EtOAc mixtures) gave 302 mg (94%) of compound **6b**: mp 137−138 °C (hexanes−EtOAc) (lit.[12] 150−152 °C (EtOAc)); $[\alpha]^{24}_D$ +36 (*c* 1.2) (lit.[12] $[\alpha]^{24}_D$ +39 (*c* 2.49)); MS (EI) *m*/*z* 266.1510 (M^+, 77, $C_{15}H_{22}O_4$ required 266.1518), 248 (17), 208 (20), 195 (48), 193 (67), 97 (100); IR (KBr) ν_{max} 3460, 1760 cm^{-1}; ^{1}H NMR δ 4.11 (1H, t, J = 9.6 Hz), 2.73 (1H, ddd, J = 19.4, 5.2, 2.0 Hz), 2.59 (1H, ddd, J = 9.0, 8.4, 5.2 Hz), 2.39 (1H, dd, J = 19.4, 9.0 Hz), 2.37−2.20 (3H, m), 2.11−2.02 (2H, m), 1.98 (1H, td, J = 13.8, 4.8 Hz), 1.69 (1H, tdd, J = 9.7, 5.2, 4.9 Hz), 1.45 (1H, br q, J = 9.7 Hz), 1.25 (3H, d, J = 6.8 Hz), 1.21 (3H, d, J = 6.8 Hz), 1.17 (3H, s); ^{13}C NMR δ 220.1 (s), 178.5 (s), 86.5 (d), 73.8 (s), 50.0 (d), 48.4 (d), 48.3 (d), 45.5 (d), 42.1 (d), 42.1 (t), 39.8 (t), 26.5 (t), 25.5 (q), 15.3 (q), 12.9 (q).

3*β*,10α-Dihydroxy-1,5,7α*H*,4,6,11*βH*-guaian-6,12-olide (7). A solution of ketolactone **6b** (3.26 g, 12.2 mmol) in MeOH (50 mL) was treated with $NaBH_4$ (355 mg, 9.3 mmol) at 0 °C. After 20 min, the reaction was quenched with saturated aqueous NH_4Cl (50 mL), MeOH was removed under reduced pressure, and water (100 mL) was added; the mixture was then extracted with EtOAc (3 × 100 mL). The organic layers were washed with brine until neutrality was reached and dried with Na_2SO_4, and the solvent was removed under reduced pressure. Column chromatography, eluting with 1:9 hexanes−EtOAc, gave 3.05 g (93%) of **7** as a white foam: $[\alpha]^{24}_D$ +3 (*c* 1.4); MS (EI) *m*/*z* 268.1675 (M^+, 3, $C_{15}H_{24}O_4$ required 268.1675), 250 (19), 240 (5), 222 (5), 192 (43), 169 (100); IR (KBr) ν_{max} 2530−3275, 1757 cm^{-1}; ^{1}H NMR δ 4.17 (1H, t, J = 9.6 Hz), 3.65 (1H, q, J = 7.4 Hz), 2.29 (2H, m), 2.20 (1H, dq, J = 12.0, 6.8 Hz), 2.01−1.91 (2H, m), 1.88−1.75 (3H, m), 1.68−1.58 (2H, m), 1.36 (1H, m), 1.24 (3H, s), 1.21 (3H, d, J = 6.8 Hz), 1.13 (3H, d, J = 6.4 Hz); ^{13}C NMR δ 178.8 (s), 85.5 (d), 74.7 (s), 77.7 (d), 50.2 (d), 49.9 (d), 47.5 (d), 46.8 (d), 42.0 (d), 41.7 (t), 36.0 (t), 26.1 (t), 25.5 (q), 17.4 (q), 12.9 (q).

3*β*-*tert*-Butyldimethylsilyloxy-10α-hydroxy-1,5,7α*H*,4,6,-11*βH*-guaian-6,12-olide (8). A solution of compound **7** (2.64 g, 9.85 mmol), imidazole (2.49 g, 36.6 mmol), and TBSCl (3.15 g, 20.3 mmol) in DMF (60 mL) was stirred at room temperature for 2 h. After this time, the reaction mixture was diluted with EtOAc (300 mL), washed with water (200 mL) and brine (200 mL), and dried with anhydrous Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the resulting residue was chromatographed on silica gel (1:1 hexane−EtOAc) to give 3.48 g (93%) of compound **8**: mp 141−143 °C (hexanes−EtOAc); $[\alpha]^{24}_D$ +28 (c 0.8); MS (CI) *m*/*z* 383.2611 (M^+ + 1, 8, $C_{21}H_{39}O_4Si$ required 383.2618), 365 (29), 307 (23), 263 (24), 233 (100); IR (KBr) ν_{max} 1771 cm^{-1}; ^{1}H NMR δ 4.15 (1H, t, J = 9.8 Hz), 3.53 (1H, q, J = 7.6 Hz), 2.27 (1H, q, J = 8.8 Hz), 2.19 (1H, dq, J = 12.0, 7.2 Hz), 2.13 (1H, m), 2.00 (2H, m), 1.80−1.69 (3H, m), 1.66−1.57 (2H, m), 1.39 (1H, m), 1.24 (3H, s), 1.21 (3H, d, J = 7.2 Hz), 1.07, (3H, d, J = 6.4 Hz), 0.89 (9H, s), 0.09 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 178.6 (s), 85.6 (d), 78.2 (d), 75.0 (s), 50.2 (d), 49.8 (d), 47.7 (d), 47.1 (d), 42.3 (t), 36.7 (t), 42.1 (d), 26.2 (t), 25.8 (q), 25.6 (q), 18.1 (s), 17.4 (q), 13.0 (q), −3.6 (q), −4.6 (q).

3*β*-*tert*-Butyldimethylsilyloxy-10α-trimethylsilyloxy-1,5,7α*H*,4,6,11*βH*-guaian-6,12-olide (9). To a stirred solution of compound **8** (2.49 g, 6.5 mmol), triethylamine (7.3 mL, 57.2 mmol), and 4-DMAP (157 mg, 1.29 mmol) was added TMSCl (12.8 mL, 91.9 mmol) at room temperature. After 4 h, additional triethylamine (7.6 mL, 55.2 mmol) and TMSCl (2.6 mL, 20.6 mmol) were added, and stirring was continued overnight. The reaction mixture was concentrated under reduced pressure and the residue chromatographed (9:1 hexane−EtOAc) to give 3.41 g (100%) of compound **9**: mp 60−63 °C (hexanes−EtOAc); $[\alpha]^{24}_D$ +13 (*c* 1.4); MS (CI) *m*/*z* 455.3020 (M^+ + 1, 56, $C_{24}H_{47}O_4Si_2$ required 455.3013), 395 (10), 365 (100), 323 (9); IR (KBr) ν_{max} 1776 cm^{-1}; ^{1}H NMR δ 4.20 (1H, t, J = 10.0 Hz), 3.60 (1H, q, J = 6.8 Hz), 2.23 (1H, q, J = 10.8 Hz), 2.17 (1H, dq, J = 11.6, 7.2 Hz), 2.10−1.80 (5H, m), 1.66−1.57 (2H, m), 1.51 (1H, ddd, J = 13.2, 10.8, 6.8 Hz), 1.29 (1H, m), 1.24 (3H, s), 1.19 (3H, d, J = 7.2 Hz), 1.04, (3H, d, J = 6.8

(21) (a) Blay, G.; Cardona, L.; García, B.; Pedro, J. R. *Can. J. Chem.* **1992**, *70*, 817−822. (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697−1705.

(22) Copies of NMR spectra in $CDCl_3$ of natural plagiochiline N were available for comparison with our synthetic product.

(23) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.

Hz), 0.87 (9H, s), 0.10 (9H, s), 0.05 (6H, s); ^{13}C NMR δ 179.1 (s), 85.2 (d), 78.8 (d), 77.8 (s), 51.0 (d), 49.3 (d), 48.7 (d), 46.7 (d), 43.0 (d,), 37.8 (t, two signals), 28.6 (q), 26.2 (t), 25.8 (q), 18.3 (q), 18.0 (s), 13.1 (q), 2.5 (s), −4.7 (q), −4.6 (q).

3*β*-*tert*-Butyldimethylsilyloxy-11*β*-hydroxy-10α-trimethylsilyloxy-1,5,7α*H*,4,6*β*H-guaian-6,12-olide (10a) and 3*β*-*tert*-Butyldimethylsilyloxy-11α-hydroxy-10α-trimethylsilyloxy-1,5,7α*H*,4,6*β*H-guaian-6,12-olide (10b). To a solution of compound **9** (1.98 g, 4.36 mmol) in 44 mL of THF at −78 °C under argon was added dropwise a 1 M solution of $NaN(SiMe_3)_2$ in THF (13.7 mL). The resulting solution was stirred at this temperature for 30 min and then at room temperature for 30 min and was cooled again to −78 °C. A solution of Davis' reagent[24] (1.29 g, 4.94 mmol) in THF (40 mL) was injected into the reaction flask, and after 15 min, the reaction was quenched with saturated aqueous NH_4Cl (80 mL) and extracted with EtOAc (3 × 80 mL). The usual treatment was followed by chromatography (from 8:2 to 1:1 hexane−EtOAc mixtures) that successively eluted 1.70 g (83%) of compound **10a** and 123 mg (6%) of compound **10b**.

Compound 10a: mp 175−176 °C (hexanes−EtOAc); $[\alpha]^{21}_D$ +39 (*c* 1.5); MS (CI) *m*/*z* 471.2945 ($M^+ + 1$, 10, $C_{24}H_{47}O_5Si_2$ required 471.2962), 427 (9), 381 (100), 339 (17), 249 (44); IR (KBr) ν_{max} 3450, 1760 cm^{-1}; ^{1}H NMR δ 4.49 (1H, t, *J* = 10.4 Hz), 3.61 (1H, q, *J* = 6.7 Hz), 2.19 (1H, dt, *J* = 11.6, 7.6 Hz), 2.10−1.90 (2H, m), 1.90−1.50 (6H, m), 1.49 (1H, ddd, *J* = 13.0, 10.5, 6.8 Hz), 1.37 (3H, s), 1.23, (3H, s), 1.03 (3H, d, *J* = 7.2 Hz), 0.86 (9H, s), 0.09 (9H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR δ 177.9 (s), 84.7 (d), 79.3 (d), 77.9 (s), 74.8 (s), 51.6 (d), 50.8 (d), 49.9 (d), 47.0 (d), 38.2 (t, two signals), 26.1 (q, two signals), 22.4 (q), 18.9 (q), 18.3 (t), 18.3 (s), 2.8 (q), −4.3 (q), −4.4 (q).

Compound 10b: mp 114−115 °C (hexanes−EtOAc); $[\alpha]^{21}_D$ +84 (*c* 2.0); MS (CI) *m*/*z* 471.2953 ($M^+ + 1$, 10, $C_{24}H_{47}O_5Si_2$ required 471.2962), 427 (12), 381 (100), 339 (32), 249 (48); IR (KBr) ν_{max} 3430, 1780 cm^{-1}; ^{1}H NMR δ 4.12 (1H, t, *J* = 10.3 Hz), 3.51 (1H, q, *J* = 7.0 Hz), 2.40−2.20 (2H, m), 2.00−1.50 (9H, m), 1.22 (3H, s), 1.15 (3H, s), 0.98 (3H, d, *J* = 7.0 Hz), 0.83 (9H, s), 0.05 (9H, s), −0.01 (3H, s), −0.02 (3H, s); ^{13}C NMR δ 180.2 (s), 84.2 (d), 79.4 (s), 75.4 (s), 78.9 (d), 51.2 (d), 49.4 (d), 47.3 (d, four signals), 37.9 (t, two signals), 27.5 (q), 26.2 (q), 21.1 (t), 19.8 (q), 18.4 (s), 18.1 (q), 3.0 (q), −4.1 (q), −4.3 (q).

3*β*-*tert*-Butyldimethylsilyloxy-10α-trimethylsilyloxy-1,5α*H*,4,6*β*H-guai-7(11)-en-6,12-olide (11). A solution of compound **10a** (500 mg, 1.06 mmol) and triethylamine (0.75 mL, 5.4 mmol) in THF (14 mL) at 0 °C under argon was treated with MsCl (0.16 mL, 2.1 mmol) for 2.5 h. After this time, the reaction mixture was filtered through silica gel and eluted with 200 mL of ether. The solvent was removed under reduced pressure, and the resulting residue was dissolved with toluene (35 mL) under argon; DBU (1 mL) was then added, and the mixture was heated under reflux for 20 min. The cold reaction mixture was diluted with CH_2Cl_2 (120 mL), washed with water (50 mL) and brine (50 mL), and dried with Na_2SO_4. Solvent evaporation and chromatography (9:1 hexane−EtOAc) gave 320 mg (66%) of compound **11**: mp 61−62 °C (hexanes−EtOAc); $[\alpha]^{22}_D$ +29 (*c* 1.2); MS (CI) *m*/*z* 453.2853 ($M^+ + 1$, 100, $C_{24}H_{45}O_4Si_2$ required 453.2856), 438 (10), 396 (15); IR (KBr) ν_{max} 1758, 1675 cm^{-1}; ^{1}H NMR δ 5.08 (1H, dq, *J* = 11.0, 1.2 Hz), 3.81 (1H, ddd, *J* = 11.0, 7.0, 1.8 Hz), 2.87 (1H, ddd, *J* = 19.0, 12.0, 4.5 Hz), 2.43 (1H, q, *J* = 7.2 Hz), 2.31 (1H, br d, *J* = 19.0 Hz), 2.15 (2H, m), 1.96 (1H, ddd, *J* = 12.5, 12.0, 4.5 Hz), 1.73 (3H, *J* = 1.2 Hz), 1.60 (1H, dt, *J* = 12.5, 4.5 Hz), 1.45 (2H, m), 1.26 (3H, s), 0.95 (3H, d, *J* = 7.2 Hz), 0.84 (9H, s), 0.05 (9H, s), 0.01 (6H, s); ^{13}C NMR δ 175.0 (s), 165.0 (s), 121.1 (s), 83.2 (d), 79.2 (d), 75.4 (s), 52.1 (d), 50.8 (d), 46.5 (d), 38.0 (t), 31.9 (q), 31.4 (t), 25.8 (q), 22.6 (t), 17.9 (s), 19.2 (q), 8.2 (q), 2.5 (q), −4.7 (q), −4.9 (q).

Compound 12. Ozone-enriched oxygen was bubbled through a solution of compound **11** (240 mg, 0.53 mmol) in 9 mL of CH_2Cl_2 at −78 °C until a blue color appeared in the solution. The excess ozone was removed with an argon purge, and dimethyl sulfide (2 mL) was added. The cooling bath was removed, and the temperature was allowed to rise to room temperature. After 2 h, additional dimethyl sulfide (2 mL) was added and the mixture stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue chromatographed (9:1 hexanes−EtOAc) to give 240 mg (94%) of compound **12**: colorless oil; $[\alpha]_D^{23}$ +27 (*c* 1.8); MS (CI) *m*/*z* 485.2762 ($M^+ + 1$, 8, $C_{24}H_{45}O_6Si_2$ required 485.2755), 427 (13), 395 (49), 249 (32), 175 (100); IR (NaCl) ν_{max} 1750−1730 cm^{-1}; ^{1}H NMR δ 5.35 (1H, d, *J* = 12.5 Hz), 3.78 (1H, m), 2.55 (1H, ddd, *J* = 17.0, 12.0, 6.5 Hz), 2.40−2.00 (5H, m), 1.95 (1H, dd, *J* = 12.0, 7.0 Hz), 1.69 (1H, dd, *J* = 16.0, 6.0 Hz), 1.49 (1H, td, *J* = 12.5, 5.0 Hz), 2.42 (3H, s), 1.29 (3H, s), 0.99 (3H, d, *J* = 7.5 Hz), 0.79 (9H, s), 0.05 (9H, s), 0.01 (3H, s), −0.05 (3H, s); ^{13}C NMR δ 204.5 (s), 191.1 (s), 160.0 (s), 79.8 (d), 78.9 (d), 75.3 (s), 50.8 (d), 46.5 (d), 45.9 (d), 37.5 (t), 37.2 (t), 31.8 (q), 28.7 (t), 26.8 (s), 25.7, (q), 18.8 (q), 17.8 (s), 2.2 (q), −4.9 (q).

Diols 13a and 13b. To a solution of compound **12** (33 mg, 0.068 mmol) in THF (2 mL) under argon at 0 °C was added via syringe 65% Red-Al reagent in toluene (0.16 mL, 0.53 mmol). After 15 min, the reaction mixture was diluted with ether (50 mL) and washed with brine (15 mL). The major part of the solvent was evaporated under reduced pressure, diluted with EtOAc (50 mL), and washed again with brine (2 × 15 mL). The aqueous layers were extracted with EtOAc, and the organic layers were dried with Na_2SO_4. Evaporation of the solvents and chromatography (8:2 hexanes−EtOAc) afforded 7 mg (25%) of compound **13a** and 16.5 mg (59%) of compound **13b**.

Compound 13a: colorless oil; $[\alpha]_D^{23}$ +20 (*c* 0.6); MS (FAB) *m*/*z* 439.2663 (M^+ + Na, 13, $C_{21}H_{44}O_4NaSiO_2$ required 439.2676), 304 (25), 246 (32), 190 (34), 172 (100), 154 (45); IR (NaCl) ν_{max} 3390 cm^{-1}; ^{1}H NMR δ 3.83 (1H, m), 3.64 (1H, q, *J* = 7.0 Hz), 3.47 (1H, q, *J* = 7.1 Hz), 3.39 (1H, d, *J* = 7.0 Hz, OH), 2.20 (3H, m), 2.00−1.80 (2H, m), 1.73 (1H, dt, *J* = 8.0, 7.0 Hz), 1.60−1.40 (3H, m), 1.25 (3H, s), 1.03 (3H, d, *J* = 6.7 Hz), 0.87 (9H, s), 0.12 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR δ 78.7 (s), 78.4 (d), 74.8 (d), 74.5 (d), 50.3 (d), 49.5 (d), 45.9 (d), 38.0 (d), 34.4 (d), 29.5 (q), 28.5 (t), 25.8 (q), 18.5 (q), 18.0 (s), 2.4 (q), −4.4 (q), −4.7 (q).

Compound 13b: mp 130−132 °C (hexanes−EtOAc); $[\alpha]^{22}_D$ +16 (*c* 0.9); MS (FAB) *m*/*z* 439.2667 (M^+ + Na, 12, $C_{21}H_{44}O_4NaSiO_2$ required 439.2676), 309 (31), 269 (19), 177 (100); IR (KBr) ν_{max} 3420 cm^{-1}; ^{1}H NMR δ 4.68 (1H, d, *J* = 11.2 Hz), 3.76 (2H, br dd, *J* = 11.2, 3.2 Hz), 3.44 (1H, td, *J* = 9.4, 5.6 Hz), 2.29 (1H, td, *J* = 12.0, 7.7 Hz), 2.17 (1H, br d, *J* = 9.4 Hz, OH), 1.97 (1H, td, *J* = 12.0, 3.4 Hz), 1.49 (1H, m), 1.26 (3H, s), 1.02 (3H, d, *J* = 6.0 Hz), 0.88 (9H, s), 0.20 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR δ 79.7 (s), 77.5 (d), 77.1 (d), 71.4 (d), 48.9 (d), 48.4 (d), 45.4 (d), 39.0 (t), 31.9 (t), 31.4 (q), 27.4 (t), 25.8 (q), 18.1 (s), 16.7 (q), 2.2 (q), −4.4 (q), −4.7 (q).

Alkene 14. A solution of diol **13b** (25 mg, 0.06 mmol), imidazole (17 mg, 0.25 mmol), chlorodiphenylphosphine (25 μL, 0.13 mmol), and 4-DMAP (1 mg, 0.008 mmol) in toluene (1.5 mL) was heated at a reflux temperature under argon. Iodine (35 mg, 0.14 mmol) was added in portions, and reflux was continued for 30 additional min. After this time, the cold reaction mixture was diluted with EtOAc (50 mL), washed with aqueous 10% $Na_2S_2O_3$ (10 mL) and brine (10 mL), and dried with Na_2SO_4. After solvent removal, the resulting oil was stirred in 0.8 mL of a 3:5:11 H_2O−AcOH−THF mixture for 4 h. The reaction mixture was extracted with EtOAc. The usual workup and chromatography (9:1 hexanes−EtOAc) gave 13 mg (70%) of compound **14**: colorless oil; $[\alpha]_D^{23}$ −58 (*c* 1.8); MS (EI) *m*/*z* 310.2317 (M^+, 1, $C_{18}H_{34}O_2Si$ required 310.2328), 253 (59), 235 (100); IR (NaCl) ν_{max} 3412, 1462, 836 cm^{-1}; ^{1}H NMR δ 5.65 (2 H, m), 3.51 (1H, td, *J* = 9.2, 8.0 Hz), 2.40−2.20 (3H, m), 2.18 (1H, br t, *J* = 9.0 Hz), 1.99 (2H, m), 1.71 (1H, q, *J* = 7.2 Hz), 1.64 (1H, m), 1.54 (1H, ddd, *J* = 12.4, 11.2, 8.0 Hz), 1.16 (3H, s), 0.99 (3H, d, *J* = 6.4 Hz), 0.89 (9H, s), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 132.0 (d), 128.7 (d), 74.5 (s), 78.3

(24) (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241−3243. (b) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087−2089.

(d), 49.6 (d), 49.3 (d), 43.9 (d), 37.6 (t), 36.5 (t), 28.0 (t), 25.9 (q), 24.7 (q), 18.1 (s), 16.9 (q), −4.4 (q), −4.7 (q).

Dibromide 15. To a solution of alkene **14** (330 mg, 1.07 mmol) in dry toluene (9 mL) was added 3.5 M sodium *tert*-amylate in toluene (3.15 mL, 11 mmol).[24] To this mixture was added a solution of $HCBr_3$ (0.47 mL, 5.4 mmol) in toluene (2.3 mL) dropwise under vigorous stirring. When the reaction was complete, the reaction mixture was allowed to stir for an additional 10 min, and then 50 mL of brine was added. The usual procedure and chromatography (9:1 hexanes−EtOAc) gave 26 mg (8%) of starting material and 360 mg (70%) of compound **15**: mp 118−120 °C (hexanes−EtOAc); $[\alpha]^{21}_D$ +7 (*c* 2.0); IR (KBr) ν_{max} 3420 cm^{-1}; ^1H NMR δ 3.60 (1H, ddd, J = 9.2, 7.8, 6.6 Hz), 2.25 (1H, ddd, J = 11.6, 9.8, 7.8 Hz), 2.10−2.00 (3H, m), 1.95 (1H, td, J = 13.6, 4.8 Hz), 1.80−1.50 (5H, m), 1.38 (3H, s), 1.27 (2H, m), 1.06 (3H, d, J = 6.8 Hz), 0.89 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR δ 73.7 (s), 77.4 (d), 50.5 (d), 45.8 (d), 42.7 (d), 40.7 (t), 37.0 (t), 36.1 (d), 32.6 (d), 27.2 (q), 25.9 (q), 25.8 (s), 24.1 (t), 18.1 (s), 16.0 (q), −4.5 (q), −4.7 (q).

3*β*-*tert*-Butyldimethylsilyloxy-10α-hydroxy-1,5α*H*,-4,6,7*β*H-aromadendrane (16). To a suspension of dry copper(I) cyanide (727 mg, 8.12 mmol) in THF (7.7 mL) was added 1.6 M MeLi in ether (1.5 mL, 16.8 mmol) at −78 °C under argon. The mixture was gradually warmed to 0 °C over 30 min and was stirred at this temperature for an additional 30 min. The mixture was then cooled to −78 °C, and dibromide **15** (268 mg, 0.56 mmol) in THF (11 mL) was added dropwise. The resulting mixture was warmed to room temperature and allowed to stir overnight. The reaction mixture was cooled to 0 °C, and MeI (0.42 mL, 6.75 mmol) was added. After 30 min, the reaction was quenched with a mixture of 18 mL of saturated aqueous NH_4Cl and 2 mL of 34% NH_4OH. The mixture was extracted with ether (3 × 40 mL), washed with NH_4Cl−NH_4OH (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried with Na_2SO_4. Chromatography (9:1 hexanes−EtOAc) afforded 153 mg (80%) of compound **16**: oil; $[\alpha]_D^{23}$ +5 (*c* 2.0); MS (EI) *m*/*z* 352.2809 (M^+, 1, $C_{21}H_{40}O_2Si$ required 352.2798), 334 (6), 295 (14), 277 (34), 203 (100); IR (NaCl) ν_{max} 3411 cm^{-1}; ^1H NMR δ 3.51 (1H, dt, J = 9.9, 6.1 Hz), 2.21 (1H, dt, J = 11.4, 8.2 Hz), 1.99 (1H, ddd, J = 11.7, 7.6, 6.1 Hz), 1.93 (1H, td, J = 12.6, 5.3 Hz), 1.47 (3H, s), 1.03 (3H, s), 0.94 (3H, s), 0.92 (3H, d, J = 6.4 Hz), 0.89 (9H, s), 0.55 (1H, ddd, J = 12.0, 8.2, 4.0 Hz), 0.30 (1H, t, J = 8.2 Hz), 0.06 (3H, s), 0.05 (3H, s); ^{13}C NMR δ 77.8 (d), 74.9 (s), 50.7 (d), 45.2 (d), 39.2 (d), 43.0 (t), 36.8 (t), 29.6 (d), 25.9 (d), 29.0 (q), 27.2 (q), 25.9 (q), 20.1 (s), 21.3 (t), 18.2 (s), 15.9 (q), 15.5 (q), −4.9 (q).

3*β*,10α-Dihydroxy-1,5α*H*,4,6,7*β*H-aromadendrane (17). To a solution of compound **16** (370 mg, 1.05 mmol) in THF (60 mL) was added 45% aqueous HF (4 mL), and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with EtOAc (75 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried, and concentrated under reduced pressure. Chromatography of the residue with 2:8 hexanes−EtOAc gave 237 mg (95%) of compound **17**: mp 234−236 °C (hexanes−EtOAc); $[\alpha]^{24}_D$ −25 (*c* 0.8); MS (EI) *m*/*z* 238.1935 (M^+, 3, $C_{15}H_{26}O_2$ required 238.1933), 220 (27), 205 (17), 202 (21), 177 (26), 147 (83), 122 (100); IR (KBr) ν_{max} 3290 cm^{-1}; ^1H NMR δ 3.60 (1H, m), 2.22 (1H, br q, J = 12.1 Hz), 2.12 (1H, m), 1.94 (1H, td, J = 12.7, 4.8 Hz), 1.80−1.50 (4H, m), 1.47 (3H, s), 1.12 (1H, m), 1.04 (3H, s), 0.99 (3H, d, J = 6.0 Hz), 0.95 (3H, s), 0.57 (1H, ddd, J = 12.2, 8.2, 4.1 Hz), 0.31 (1H, t, J = 8.2 Hz); ^{13}C NMR δ 77.5 (d), 74.8 (s), 50.7 (d), 45.3 (d), 42.8 (d), 39.9 (d), 36.6 (t), 29.6 (d), 26.0 (d), 29.0 (q), 27.1 (q), 21.2 (t), 20.1 (s), 15.8 (q), 15.5 (q).

10α-Hydroxy-3α-(*o*-nitrophenylselenenyl)-1,5α*H*,4,6,7*β*H-aromadendrane (18). To a solution of diol **17** (80 mg, 0.34 mmol) and *o*-nitrophenylselenocyanate (540 mg, 2.38 mmol) in pyridine (0.45 mL) was added via syringe *n*-Bu_3P (0.77 mL, 3.09 mmol) under argon. After 24 h, the reaction mixture was diluted with ether (50 mL), washed with 2 M HCl (2 × 10 mL) and brine (15 mL), and dried with Na_2SO_4. After filtration and evaporation of the solvent under reduced pressure, the residue was chromatographed (8:2 hexanes−EtOAc) to give 124 mg (84%) of compound **18**: yellow oil; $[\alpha]^{24}_D$ −52 (*c* 2.0); IR ν_{max} (NaCl) 3300, 1508, 1337 cm^{-1}; ^1H NMR δ 8.21 (1H, d, J = 8.0 Hz), 7.66 (1H, d, J = 8.0 Hz), 7.47 (1H, t, J = 8.0 Hz), 7.27 (1H, t, J = 8.0 Hz), 3.97 (1H, t, J = 5.5 Hz), 2.57 (1H, dt, J = 10.5, 7.6 Hz), 2.38 (1H, ddd, J = 13.3, 10.5, 6.3 Hz), 2.11 (2H, m), 1.92 (1H, td, J = 13.3, 4.8 Hz), 1.80 (1H, t, J = 8.4 Hz), 1.74 (1H, m), 1.61 (1H, br d, J = 13.3 Hz), 1.42 (3H, s), 1.17 (1H, m), 1.11 (3H, d, J = 6.8 Hz), 1.05 (3H, s), 1.00 (3H, s), 0.56 (1H, ddd, J = 4.2, 8.8, 11.9 Hz), 0.24 (1H, t, J = 8.8 Hz); ^{13}C NMR δ 147.5 (s), 133.5 (d), 133.2 (s), 129.9 (d), 126.4 (d), 125.2 (d), 74.7 (s), 48.1 (d), 48.0 (d), 46.7 (d), 41.6 (d), 42.9 (t), 35.9 (t), 29.7 (d), 26.0 (d), 29.1 (q), 27.3 (q), 20.2 (s), 21.1 (t), 16.4 (q), 15.5 (q).

10α-Hydroxy-1,5α*H*,4,6,7*β*H-2-aromadendrene (19). To a solution containing compound **18** (114 mg, 0.26 mmol) in 7 mL of THF cooled to 0 °C was added 30% H_2O_2 (0.21 mL, 2.1 mmol). The mixture was stirred at room temperature for 1 h, diluted with EtOAc (60 mL), and washed with 8% aqueous $Na_2S_2O_3$ (15 mL) and brine (50 mL). The usual procedure and chromatography (9:1 hexanes−EtOAc) yielded 48 mg (84%) of compound **19**: mp 68−69 °C (hexanes−EtOAc); $[\alpha]^{24}_D$ −260 (*c* 0.3); MS (EI) *m*/*z* 220.1829 (M^+, 4, $C_{15}H_{24}O$ required 220.1827), 202 (7), 177 (12), 140 (29), 119 (28), 107 (21), 80 (100); IR (KBr) ν_{max} 3390 cm^{-1}; ^1H NMR (250 MHz) δ 5.78 (1H, dt, J = 6.0, 1.6 Hz), 5.74 (dt, J = 6.0, 2.4 Hz), 2.94 (1H, br d, J = 9.6 Hz), 2.54 (1H, m), 1.93 (1H, td, J = 13.2, 4.8 Hz), 1.79−1.66 (3H, m), 1.35 (3H, s), 1.27 (1H, m), 1.05 (3H, s), 1.04 (3H, d, J = 6.0 Hz), 0.97 (3H, s), 0.56 (1H, ddd, J = 12.2, 9.2, 4.2 Hz), 0.38 (1H, dd, J = 9.2, 6.4 Hz); ^{13}C NMR δ 138.1 (d), 130.6 (d), 75.5 (s), 56.1 (d), 50.5 (d), 42.9 (d), 42.7 (t), 29.3 (d), 26.2 (d), 29.0 (q), 27.3 (q), 21.2 (t), 19.6 (s), 19.7 (q), 15.6 (q).

Plagiochiline N (3). A solution of alkene **19** (30 mg, 0.14 mmol) in 5 mL of dry dichloromethane was treated with ozone as described in the synthesis of compound **12**. The resulting solution was treated with dimethyl sulfide (0.85 mL) and stirred for 36 h at room temperature, and the solvent was removed under reduced pressure. The resulting oil was dissolved in benzene (5.7 mL), and TsOH was added (18 mg, 2.1 mmol); the mixture was heated at a reflux temperature for 1 h. The mixture was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), dried, and concentrated. Column chromatography (pentane) afforded 7 mg (23%) of plagiochiline N (**3**): oil; $[\alpha]^{20}_D$ +43 (*c* 0.2) (lit.[9] +46.1 (*c* 2.08)); MS (EI) *m*/*z* 216.1522 (M^+, 100, $C_{15}H_{20}O$ required 216.1514), 201 (21), 173 (62); IR (NaCl) ν_{max} 2930, 1695, 1631, 1200 cm^{-1}; ^1H NMR δ 6.44 (1H, s), 6.08 (1H, br s), 5.51 (1H, br dd, J = 8.9, 2.5 Hz), 2.97 (1H, d, J = 10.2 Hz), 2.25 (1H, m), 2.15 (1H, m), 1.75 (3H, s), 1.55 (3H, s), 1.19 (1H, m), 1.10 (3H, s), 0.97 (3H, s), 0.70 (1H, dd, J = 10.6, 9.4 Hz); ^{13}C NMR δ 138.4 (d), 133.8 (d), 132.0 (s), 127.2 (d), 117.7 (s), 111.9 (s), 34.8 (d), 34.4 (d), 30.5 (d), 28.3 (q), 24.1 (t), 22.7 (q), 20.2 (s), 16.5 (q, two signals).

Acknowledgment. Financial support from Dirección General de Investigación Científica y Técnica (PB 94-0985) is gratefully acknowledged. L.L. is especially thankful to Conselleria de Cultura, Educació i Ciència (Generalitat Valenciana) for a grant. We thank Professor Y. Asakawa and Dr. F. Nagashima from Tokushima Bunri University for providing us with copies of NMR spectra of natural plagiochiline N.

Supporting Information Available: Copies of ^1H NMR spectra of **3** and **7**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO010567D