Terpenoids from *Laurencia luzonensis*[1]

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Luzodiol (**4**), a diterpene possessing a new carbon skeleton, and five new sesquiterpenes (**5**−**9**) of the snyderane class have been isolated from the red alga *Laurencia luzonensis* and their structures determined by spectroscopic analysis. The relative stereochemistry of the known luzonensol (**3**) was assigned by its conversion to palisadin B (**10**).

The seasonal red alga *Laurencia luzonensis* is a tropical species that grows abundantly on the coral reefs of Okinawa. Despite extensive chemical research on the genus *Laurencia* since the early 1960s, *L. luzonensis* had not been investigated until our recent reports, in which we described the isolation and structure elucidation of a new diterpene, 3-bromobarekoxide (**1**),[2] the brominated analogue of barekoxide (**2**),[3] and several sesquiterpenoids (e.g., **3**).[4] Debromination of **1** gave rise to a compound identical with barekoxide, enabling us to revise the incorrect stereochemistry initially reported for barekoxide to that shown in **2**. Most of the sesquiterpenes possessed a snyderane skeleton.[5] Our continuing study of *L. luzonensis* has afforded additional new metabolites, luzodiol (**4**), a diterpene based on a new skeleton, and five new snyderane sesquiterpenes (**5**−**9**). In this paper we report the isolation and structure elucidation of these new compounds and also the stereochemistry of luzonensol (**3**), which was previously unknown.

Results and Discussion

Luzodiol (**4**) was obtained as an amorphous solid, $[\alpha]_D$ +13.7°. The molecular formula $C_{20}H_{35}BrO_2$ was deduced from high-resolution mass measurement on $[M - H_2O]^+$ ion peaks at *m/z* 368 and 370 ($C_{20}H_{33}BrO$) coupled to NMR and IR data. A strong IR absorption band at 3434 cm^{-1} and ^{13}C NMR signals at δ 73.4 (C-3) and 72.9 (C-7) indicated that both oxygen atoms were from hydroxyls. The ^1H and ^{13}C NMR data revealed the presence of two double bonds, both a terminal [δ_H 5.92 (dd, J = 17.5, 10.5 Hz), 5.23 (d, J = 10.5 Hz), 5.11 (d, J = 17.5 Hz); δ_C 144.5 (CH), 112.2 (CH_2)] and a trisubstituted olefin [δ_H 5.05 (m); δ_C 131.6 (C), 123.7 (CH)], which thus required **2** to be monocyclic. The NMR data (Table 1) demonstrated the presence of five methyls, six methylenes, two methines, and three quaternary carbons in addition to the four olefinic carbons. Of the five methyl groups, two (δ_H 1.70 s, 1.64 s) were attached to an olefinic carbon, two others (δ_H 1.19 s, 1.30 s) on the oxygenated carbons, and one (δ_H 1.11 s) to a quaternary carbon, implying that **4** is a diterpene. COSY connectivities supported substructures C-1/C-2, C-4/C-6, C-8/C-10, and C-12/C-16, C-17 (Figure 1). These portions could be connected by HMBC data to give a structure consisting of a cyclohexane ring in the center of the geranylgeranyl skeleton. The cyclohexane portion contained the bromine atom and one of the hydroxyls. The relative stereochemistry of the ring portion could be elucidated as shown by NOE analysis (Figure 1). The configuration at C-3 remains to be solved. To the best of our knowledge luzodiol (**4**) possesses a new carbon skeleton.

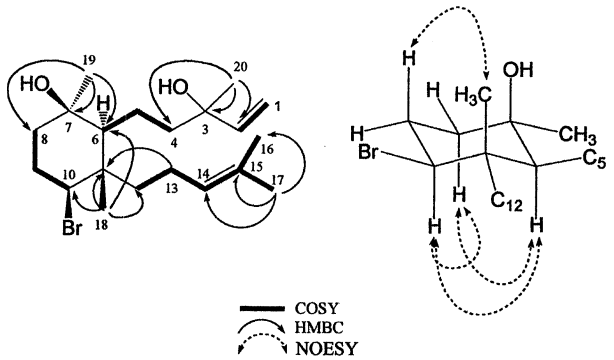

Figure 1. Key COSY, HMBC, and NOESY correlations for **4**.

Table 1. NMR Data for Compound **4** ($CDCl_3$)

C no.	δ_C	δ_H (mult, J in Hz)	HMBC (H→C)
1	112.2 (CH_2)	5.11 (d, 17.5)	C-3
		5.23 (d, 10.5)	C-3
2	144.5 (CH)	5.92 (dd, 17.5, 10.5)	C-20
3	73.4 (C)		
4	44.9 (CH_2)	1.53 (m)	C-20
5	21.5 (CH_2)	1.41 (m)	C-11
6	48.8 (CH)	1.21 (m)	C-18
7	72.9 (C)		
8	41.9 (CH_2)	1.66 (m)	C-19
9	29.9 (CH_2)	2.04 (m)	C-11
		2.41 (dq, 13.5, 3.5)	C-11
10	63.3 (CH)	4.16 (dd, 12.5, 4.0)	C-18
11	43.0 (C)		
12	39.1 (CH_2)	1.33 (m)	C-18
13	21.0 (CH_2)	1.55 (m)	C-11
14	123.7 (CH)	5.05 (m)	C-16, C-17
15	131.6 (C)		
16	25.7 (CH_3)	1.70 (s)	C-14, C-15, C-17
17	17.8 (CH_3)	1.64 (s)	C-14, C-15, C-16
18	18.4 (CH_3)	1.11 (s)	C-6, C-10, C-11, C-12
19	30.8 (CH_3)	1.19 (s)	C-6, C-7, C-8
20	27.9 (CH_3)	1.30 (s)	C-2, C-3, C-4

Luzonenone (**5**), $C_{15}H_{22}Br_2O_2$, was isolated as a colorless oil. The ^{13}C NMR spectrum revealed the presence of an α,β-unsaturated ketone (δ_C 200.5, 156.9, 117.2). The rest of the molecule consisted of four methyls, four methylenes, two methines, and two quaternary carbons, as shown by the NMR data (Table 2). The absence of any other sp^2 carbon signals and the required degrees of unsaturation suggested that the molecule contained two rings. Comparison of the NMR data of **5** with those of the palisadins (e.g., **10**)[4,6] suggested that it had the same six-membered ring portion.

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Chart 1

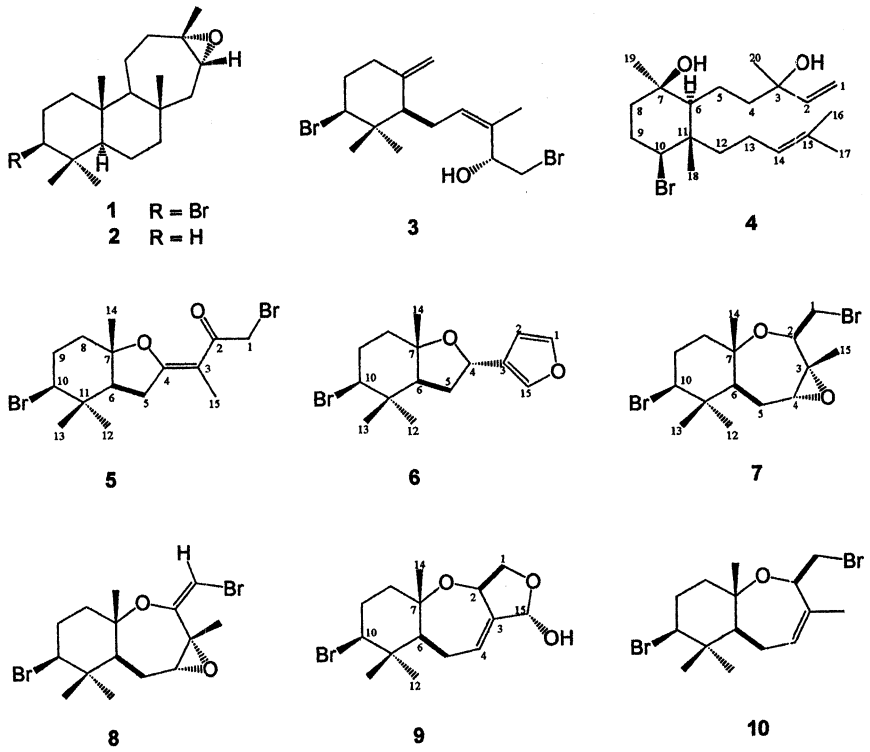

Table 2. NMR Data for Compounds **5** and **6** ($CDCl_3$)

	5			**6**		
C no.	δ_C	δ_H (mult, *J* in Hz)	HMBC (H→C)	δ_C	δ_H (mult, *J* in Hz)	HMBC (H→C)
1	32.0 (CH_2)	3.89 (d, 11.0)	C-3	143.5 (CH)	7.39 (br t, 1.5)	C-2, C-3, C-15
		3.96 (d, 11.0)	C-3			
2	200.5 (C)			108.4 (CH)	6.32 (dd, 1.5, 0.9)	C-1, C-3, C-4, C-15
3	117.2 (C)			128.7 (C)		
4	156.9 (C)			70.4 (CH)	5.10 (dd, 9.4, 2.7)	C-2, C-3, C-5, C-7
5	42.5 (CH_2)	2.67 (dd, 17.5, 10.5)	C-3, C-4, C-6, C-7	32.7 (CH_2)	1.80 (ddd, 9.5, 7.0, 2.5)	C-4, C-6
		2.79 (dd, 17.5, 4.0)	C-3, C-4, C-6, C-7		2.30 (m)	C-4, C-6
6	48.9 (CH)	2.03 (dd, 10.0, 4.0)	C-5, C-7, C-11	55.1 (CH)	1.70 (dd, 13.5, 7.0)	C-5, C-7, C-10, C-11
7	83.9 (C)			78.1 (C)		
8	41.9 (CH_2)	1.98 (m)	C-7, C-9, C-10	39.5 (CH_2)	1.60 (dq, 12.5, 4.5)	C-9, C-10, C-14
		2.09 (m)	C-7, C-9, C-10		1.90 (td, 13.0, 3.5)	C-9, C-10, C-14
9	32.2 (CH_2)	1.85 (m)	C-7, C-8, C-10	32.6 (CH_2)	2.10 (dq, 12.5, 4.0)	C-8, C-10
		2.25 (m)	C-7, C-8, C-10		2.35 (m)	C-8, C-10
10	64.7 (CH)	3.98 (dd, 12.5, 4.0)	C-9, C-11, C12, C-13	65.5 (CH)	3.95 (dd, 12.5, 4.5)	C-9, C-11, C-12, C-13
11	40.6 (C)			38.7 (C)		
12	29.9 (CH_3)	1.14 (s)	C-6, C-10, C-11, C-13	30.3 (CH_3)	1.01 (s)	C-6, C-10, C-11, C-13
13	17.2 (CH_3)	0.98 (s)	C-6, C-10, C-11, C-12	17.0 (CH_3)	0.99 (s)	C-6, C-10, C-11, C-12
14	20.4 (CH_3)	1.39 (s)	C-6, C-7, C-8	20.3 (CH_3)	1.21 (s)	C-6, C-7, C-8
15	13.8 (CH_3)	1.85 (s)	C-2, C-3, C-4	138.9 (CH)	7.36 (dd, 1.5, 0.9)	C-1, C-3

The other ring was shown to be a five-membered cyclic ether fused onto the six-membered ring, as revealed by HMBC data. The HMBC data also established the connectivity of the α,β-unsaturated ketone moiety with a vinyl methyl (δ_H 1.85, δ_C 13.8) and a bromomethyl group (δ_H 3.96, 3.89; δ_C 32.0). The relative stereochemistry of the ring portion was the same as that of **10**, as shown by NOE measurements (H-6/H-10, H-13/H-14). A *Z* configuration was assigned to the double bond by the observation of a higher field ^{13}C chemical shift (δ 13.8) for the vinyl methyl (C-15) and also by NOE observation between H-5 and H-15.

Luzofuran (**6**) was isolated as an oil, $[\alpha]_D$ +5.1°, and had the formula $C_{15}H_{21}BrO_2$ as shown by its low-resolution EIMS and NMR data (Table 2). The ^1H (δ_H 7.39 brt, 7.36 dd, 6.32 dd) and ^{13}C NMR [δ_C 143.5 (CH), 138.9 (CH), 128.7 (C), 108.4 (CH)] data clearly indicated the presence of a 3-substituted furan ring. Spectroscopic data indicated that the remaining portion of the molecule was similar to that of **5**. The absence of any hydroxyl or carbonyl absorption bands in the IR spectrum suggested that the other oxygen atom was incorporated in an ether moiety. The ^{13}C NMR signals at δ_C 78.1 (C) and 70.4 (CH) and HMBC analysis revealed that the ethereal linkage was between C-4 and C-7, forming a tetrahydrofuran ring fused onto the six-membered ring, as in **5**. The connectivity of the furan to C-4 was shown by HMBC correlations, e.g., H-2/C-4, H-4/C-2. The configuration at C-4 was deduced from NOE correlations observed between H-4 and H-14. Luzofuran is the first furan-containing compound among the snyderane class sesquiterpenes from *Laurencia*.

Compound **7**, a colorless oil, exhibited no molecular ion in its EIMS. A high-resolution measurement of an ion at *m/z* 315 ($M^+ - Br$) suggested the formula $C_{15}H_{24}BrO_2$. The molecular formula of **7** was determined as $C_{15}H_{24}Br_2O_2$ from

Table 3. NMR Data for Compounds **7** and **8** ($CDCl_3$)

	7			**8**		
C no.	δ_C	δ_H (mult, *J* in Hz)	HMBC (H→C)	δ_C	δ_H (mult, *J* in Hz)	HMBC (H→C)
1	32.9 (CH_2)	3.29 (dd, 10.5, 9.0)	C-2	99.0 (CH)	6.09 (s)	C-2, C-3
		3.57 (dd, 10.5, 4.0)	C-2			
2	72.7 (CH)	4.01 (dd, 9.5, 4.5)	C-1, C-7	153.3 (C)		
3	63.9 (C)			60.4 (C)		
4	64.1 (CH)	2.99 (dd, 3.0, 1.5)	C-5	63.7 (CH)	3.17 (d, 5.0)	C-5, C-6
5	25.4 (CH_2)	2.12 (m)	C-4, C-6	25.9 (CH_2)	2.05 (m)	C-4, C-6
		2.23 (m)	C-4, C-6		2.47 (m)	C-4, C-6
6	44.4 (CH)	1.55 (m)	C-5, C-11, C-7	49.0 (CH)	1.93 (m)	C-7, C-8
7	78.9 (C)			82.1 (C)		
8	38.3 (CH_2)	1.55 (m)	C-7, C-9	41.8 (CH_2)	1.90 (m)	C-6, C-7, C-10
		1.65 (m)	C-7, C-9		2.07 (m)	C-6, C-7, C-10
9	32.7 (CH_2)	2.05 (m)	C-8, C-10	31.8 (CH_2)	2.01 (m)	C-7, C-8, C-10
		2.25 (m)	C-8, C-10		2.21 (m)	C-7, C-8, C-10
10	65.8 (CH)	3.93 (dd, 13.0, 4.5)	C-9, C-11	66.4 (CH)	4.05 (dd, 12.5, 4.0)	C-9, C-11
11	40.4 (C)			40.1 (C)		
12	30.5 (CH_3)	1.14 (s)	C-6, C-10, C-11, C-13	30.2 (CH_3)	1.18 (s)	C-6, C-10, C-11, C-13
13	18.2 (CH_3)	0.92 (s)	C-6, C-10, C-11, C-12	17.4 (CH_3)	0.96 (s)	C-6, C-10, C-11, C-12
14	22.3 (CH_3)	1.25 (s)	C-6, C-7, C-8	21.4 (CH_3)	1.23 (s)	C-6, C-7, C-8
15	19.2 (CH_3)	1.31 (s)	C-2, C-3, C-4	18.7 (CH_3)	1.50 (s)	C-2, C-3, C-4

the NMR signals at δ_H 3.93 (dd, J = 13.0, 4.5 Hz, H-10), 3.57 (dd, J = 10.5, 4.0 Hz, H-1), and 3.29 (dd, J = 10.5, 9.0 Hz, H-1), consistent with the presence of two bromine atoms as in **10** [δ_H 3.91 (dd, J = 13.0, 4.5 Hz, H-10), 3.68 (dd, J = 10.5, 4.0 Hz, H-1), and 3.36 (dd, J = 10.5, 8.5 Hz, H-1)]. The formula requires three degrees of unsaturation, which together with the absence of sp^2 carbon signals in the ^{13}C NMR spectrum (Table 3) revealed the tricyclic nature of **7**. One of the rings was shown to be an epoxide from the characteristic NMR signals [δ_C 63.9 (C), 64.1 (CH); δ_H 2.99 dd]. The rest of the molecule was closely related to that of **10**, as revealed from NMR analysis including COSY and HMBC; thus **7** was determined to be 3,4-epoxypalisadin B (**7**). The configurations for the six-membered ring portion and for C-3 and C-4 were established from NOE correlations (H-6/H-10, H-13/H-14, H-4/H-15), while that of C-2 was assumed to be the same as that of **10**.

Compound **8** was obtained as an oil, $[\alpha]_D$ −58.8°. The EIMS showed a molecular ion cluster at *m/z* 392, 394, and 396, indicating the presence of two bromine atoms and thus a formula $C_{15}H_{22}Br_2O_2$, which requires four sites of unsaturation. The NMR data (Table 3) were similar to those of **7** except for the double-bond signals (δ_H 6.09 s; δ_C 99.0, 153.3) assigned to the C_1/C_2 residue. 2D NMR analysis confirmed the structure of **8** as 1,2-dehydro-3,4-epoxypalisadin B. The configuration of the double bond was assumed to be *E* by the absence of a NOE between H-1 and H-15. The stereochemistries at all the chiral centers were the same as those of **7** from NOESY analysis. Although 3,4-epoxypalisadin A has been reported,[7] epoxy derivatives of palisadin B have never been described.

Compound **9** was isolated as a colorless oil, $[\alpha]_D$ +20.2°. The molecular formula $C_{15}H_{23}BrO_3$ was deduced from EIMS (M^+ at *m/z* 330, 332) and NMR data. The presence of a double bond (δ_C 138.9, 131.3) and the four sites of unsaturation required by the formula suggested that **9** was tricyclic. An IR absorption band at 3334 cm^{-1} indicated the presence of a hydroxyl group. Comparison of the NMR data with those of palisadin A[4] revealed their close structural similarity. 2D NMR analysis confirmed its gross structure as 15-hydroxypalisadin A (**9**). The carbon resonance [δ_C 107.1 (CH)] at C-15, shifted to lower field from δ_C 70.9 (CH_2) in palisadin A, is consistent with a value expected for a hemiacetal carbon. The configuration of C-15 was determined from the NOE correlations (H-15/H-1β, H-1α/H-2, H-2/H-6). These NOE data also confirmed that the stereochemistry of the remaining portion was the same as palisadin A.

To determine the stereochemistry of luzonensol (**3**) unresolved in our earlier report,[4] **3** was converted to palisadin B (**10**) by treatment with mercuric trifluoroacetate followed by reduction with sodium borohydride. The product obtained was shown to be identical in all respects, including the optical rotation, with a sample of palisadin B isolated from the alga, thus establishing the relative stereochemistry of **3** as the same as **10**.

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Jasco FT IR-300 spectrometer and optical rotations on a Jasco DIP-1000 digital polarimeter. NMR spectra were recorded on a JEOL 500 MHz FT NMR spectrometer with TMS as internal standard. EIMS were measured on a Hitachi M-2500 instrument and HRCIMS on a JEOL JMS-700 machine. The columns used for HPLC were normal-phase LiChrosorb Si60 (7 μm) and reversed-phase μ-Bondapack C18 (Waters).

Plant Material. The alga *Laurencia luzonensis* Masuda (Rhodomelaceae) was collected on the reef of Kudaka Island, Okinawa, in September 2000. After washing with tap water it was allowed to dry in the air for 2 days to give a partially dry material (1.1 kg).

Extraction and Isolation. After a triple extraction with 95% ethanol (3 L), the combined extracts were concentrated and the resulting residue was partitioned between EtOAc and H_2O to give an oil (4.2 g). The oil was separated on silica gel by eluting with a stepped gradient consisting of hexane, CH_2Cl_2, EtOAc, and MeOH to give 20 fractions. The second fraction was further separated on silica using the same solvent system to give eight subfractions. Subfraction **4** (248 mg) was purified by HPLC (Si60, hexane/EtOAc, 10:1) to give compounds **5** (1.7 mg), **7** (4.2 mg), and **8** (2.4 mg). Fraction 12 (140 mg) was repeatedly separated using HPLC (Si60, hexane/EtOAc, 9:1) to afford compound **6** (3.5 mg). Compound **9** (4.8 mg) was obtained by similar separation of fraction 13 (130 mg) by HPLC (Si60, hexane/EtOAc, 7:1). Fraction 16 (700 mg) was subjected to another silica gel separation (hexane/EtOAc, 2:1) followed by HPLC purification (RP-18, MeOH/H_2O, 5:1) to afford compound **4** (2.5 mg).

Luzodiol (4): white amorphous solid, $[\alpha]^{23}_D$ +13.7° (*c* 0.12, $CHCl_3$); IR (film) ν_{max} 3434, 1457 cm^{-1}; ^1H and ^{13}C NMR data (see Table 1); EIMS (70 eV) *m/z* 370 (16), 368 (15, $M^+ - H_2O$), 288 (43), 271 (76), 205 (19), 189 (31), 177 (15), 162 (29), 147 (30), 135 (29), 122 (35), 109 (60), 95 (58), 81 (75), 71 (65), 69 (100), 55 (42), 43 (80); HRCIMS *m/z* 369.1817 [calcd for

$C_{20}H_{34}{}^{79}BrO$ ($M^+ + H - H_2O$), 369.1793], 371.1758 (calcd for $C_{20}H_{34}{}^{81}BrO$, 371.1773).

Luzonenone (5): colorless oil, $[\alpha]^{27}_D$ −67.2° (*c* 0.08, $CHCl_3$); IR (film) ν_{max} 2926, 1659, 1601, 1462, 1385, 1344, 1132, 1099 cm^{-1}; ^1H and ^{13}C NMR data (see Table 2); EIMS (70 eV) *m/z* 396 (2), 394 (4), 392 (2, M^+), 355 (4), 353 (8), 351 (4), 315 (37), 313 (38), 273 (12), 271 (11), 218 (25), 216 (27), 179 (98), 177 (100), 137 (27), 135 (32), 123 (44), 121 (63), 71 (81), 69 (60), 43 (59).

Luzofuran (6): colorless oil, $[\alpha]^{30}_D$ +5.10° (*c* 0.18, $CHCl_3$); IR (film) ν_{max} 2952, 1455, 1380, 1155, 1022, 873, 784 cm^{-1}; ^1H and ^{13}C NMR data (see Table 2); EIMS (70 eV) *m/z* 315 (27), 313 (28, $M^+ + 1$), 300 (38), 298 (40), 219 (32), 217 (32), 137 (100), 81 (57), 68 (50).

3,4-Epoxypalisadin B (7): colorless oil, $[\alpha]^{27}_D$ +37.5° (*c* 0.18, $CHCl_3$); IR (film) ν_{max} 2974, 2951, 1464, 1150, 1132, 1086 cm^{-1}; ^1H and ^{13}C NMR data (see Table 3); EIMS (70 eV) *m/z* 317 (8), 315 (8, $M^+ - Br$), 247 (14), 245 (14), 203 (19), 201 (19), 189 (24), 187 (24), 165 (50), 123 (100), 121 (91), 107 (36), 81 (26), 71 (40), 69 (38); HREIMS *m/z* 315.0954 (calcd for $C_{15}H_{24}{}^{79}BrO_2$ 315. 0957); HRCIMS *m/z* 397.0256 (calcd for $C_{15}H_{25}{}^{79}Br^{81}BrO_2$, 397.0201).

1,2-Dehydro-3,4-epoxypalisadin B (8): colorless oil, $[\alpha]^{27}_D$ −58.8° (*c* 0.10, $CHCl_3$); ^1H and ^{13}C NMR data (see Table 3); EIMS (70 eV) *m/z* 396 (12), 394 (22), 392 (12, M^+), 381 (7), 379 (16), 377 (8), 315 (14), 313 (14), 217 (16), 215 (18), 178 (31), 176 (24), 149 (20), 147 (15), 135 (100), 121 (37), 107 (27), 69 (21).

15-Hydroxypalisadin A (9): colorless oil, $[\alpha]^{29}_D$ +20.2° (*c* 0.19, $CHCl_3$); IR (film) ν_{max} 3334, 2948, 1463, 1384, 1338, 1151, 1099, 1047, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.06 (brs, H-4), 5.78 (s, H-15), 4.93 (brs, H-2), 4.42 (t, 8.5 Hz, H-1), 3.90 (dd, 13.0, 4.5 Hz, H-10), 3.74 (dd, 9.0, 4.5 Hz, H-1), 2.37 (m, H-5), 2.25 (m, H-9), 2.10 (dq, 13.0, 4.0 Hz, H-9), 2.03 (dd, 8.5, 4.0 Hz, H-5), 2.01 (dd, 8.5, 4.0 Hz, H-6), 1.75 (dt, 13.0, 4.0 Hz, H-8), 1.60 (m, H-8), 1.25 (s, H-14), 1.14 (s, H-12), 0.92 (s, H-13); ^{13}C NMR ($CDCl_3$) δ 138.9 (C, C-3), 131.3 (CH, C-4), 107.1 (CH, C-15), 78.2 (C, C-7), 72.7 (CH_2, C-1), 67.7 (CH, C-2), 65.8 (CH, C-10), 51.0 (CH, C-6), 40.8 (C, C-11), 37.5 (CH_2, C-8), 32.5 (CH_2, C-9), 30.7 (CH_3, C-12), 26.6 (CH_2, C-5), 21.6 (CH_3, C-14), 17.9 (CH_3, C-13); EIMS (70 eV) *m/z* 332 (5), 330 (5, M^+), 315 (33), 313 (35), 301 (17), 299 (16), 250 (21), 234 (26), 233 (47), 232 (24), 174 (34), 149 (75), 135 (53), 121 (56), 107 (100).

Conversion of Luzonensol (3) to Palisadin B (10). To a solution of $Hg(CF_3CO_2)_2$ (2.27 mg) in 1:1 THF/water (5 mL) was added a solution of **3** (2.0 mg) in THF (0.5 mL), and the mixture was stirred at room temperature until the yellow color of the solution disappeared (17 min). To this mixture was successively added a solution (5 mL) of 3 N NaOH and a solution (5 mL) of 0.5 M $NaBH_4$ in 3 N NaOH. The reaction mixture was kept stirring (30 min) to precipitate mercury. After adding water (2 mL) the mixture was filtered. The solution was concentrated, in vacuo, and the resulting residue extracted with $CHCl_3$ (10 mL). The organic layer was washed with saturated sodium chloride solution, dried over $MgSO_4$, and concentrated to give a crude product, which was then purified by HPLC (normal phase, 30:1 hexane/EtOAc) to afford 1.3 mg (65%) of a colorless oil. The oil, $[\alpha]_D{}^{29}$ +14.2° ($CHCl_3$), was shown to be identical with palisadin B (**10**) in $[\alpha]_D$ and ^1H and ^{13}C NMR data.

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References and Notes

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