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Full Papers

New Acyclic Sesquiterpenes and Norsesquiterpenes from the Caribbean Gorgonian *Plexaurella grisea*

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The gorgonian *Plexaurella grisea* from Punta Cana, Dominican Republic, contains five new acyclic sesquiterpenes, (3*E*,5*E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene (**3**), (3*Z*,5*E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene (**4**), (3*E*)-6-acetoxy-3,11-dimethyl-7-methylidendodeca-1,3,10-triene (**5**), (3*E*,5*E*)-7-hydroxy-3,7,11-trimethyldodeca-1,3,5,10-tetraene (**6**), and (3*E*,5*E*,9*E*)-8,11-diacetoxy-3,7,11-trimethyldodeca-1,3,5,9-tetraene (**7**), and two new linear norsesquiterpenes, (2*E*,4*E*,7*Z*)-2,6,10-trimethylundeca-2,4,7,9-tetraenal (**8**) and (2*E*,4*E*)-2,6,10-trimethylundeca-2,4,9-trienal (**9**), in addition to the known compounds **1**, **2**, and **10**. The structures of the new compounds **3–9** were elucidated by interpretation of spectroscopic data. In general, the new compounds are mildly cytotoxic against tumor cell lines, and although norsesquiterpene **8** was inactive, norsesquiterpene **9** exhibited the greatest and selective activity against the P-388 tumor cell line.

Since the early years of marine natural products research, marine algae and invertebrates have been the source of an impressive number of novel sesquiterpenes possessing new carbocyclic skeletons and unusual functionalities. Acyclic sesquiterpenoids have been less frequently encountered, being mainly obtained from green algae of the order Caulerpales and sponges. The former ones are characterized for bearing a 1,4-diacetoxybuta-1,3-diene group or a related one, whereas the farnesane derivatives from sponges often display uncommon functionalities such as dichloroimine or isothiocyanate groups.^{1,2}

In a previous paper, Schmitz and co-workers had reported the isolation of the acyclic sesquiterpenoids **1** and **2** from Caribbean specimens of the gorgonian *Plexaurella grisea*.³ To the best of our knowledge this report remains as the only account of acyclic sesquiterpenoids from octocorals.

As a part of our studies of bioactive marine natural products, we obtained specimens of *Plexaurella grisea*

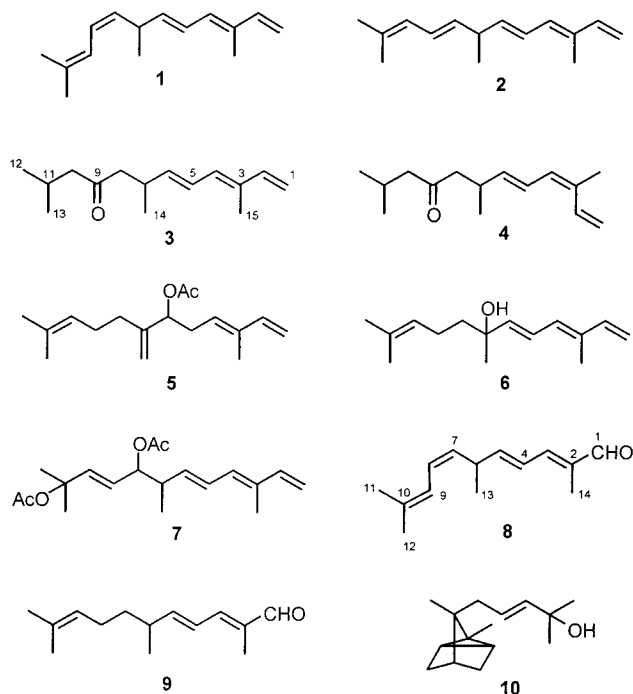
Kunze (Plexauridae) collected at Punta Cana (Dominican Republic). Since the organic extract of this gorgonian exhibited cytotoxicity against the tumor cell lines of mouse lymphoma P-388, human lung carcinoma A-549, and human colon carcinoma HT-29 (IC₅₀ = 2.5 μg/mL), we decided to carry out a chemical study of our specimens in order to identify the bioactive components.

Results and Discussion

Specimens of *P. grisea* were collected by hand and immediately frozen. The frozen material was freeze-dried and, subsequently, extracted following the modified Kupchan method.⁴ Column chromatography of the hexane extract followed by HPLC separation of selected fractions allowed isolation of the new sesquiterpenoids (3*E*,5*E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene (**3**, 60.2 mg, 0.016% yield), (3*Z*,5*E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene (**4**, 10.9 mg, 3 × 10⁻³% yield), (3*E*)-6-acetoxy-3,11-dimethyl-7-methylidendodeca-1,3,10-triene (**5**, 9.2 mg, 2 × 10⁻³% yield), (3*E*,5*E*)-7-hydroxy-3,7,11-trimethyldodeca-1,3,5,10-tetraene (**6**, 2.5 mg, 7 × 10⁻⁴% yield), and (3*E*,5*E*,9*E*)-8,11-diacetoxy-3,7,11-trimethyldodeca-1,3,5,9-tetraene (**7**, 4.5

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mg, $1.2 \times 10^{-3}\%$ yield) and the two new norsesquiterpenes (*2E,4E,7Z*)-2,6,10-trimethylundeca-2,4,7,9-tetraenal (**8**, 4.0 mg, $1.2 \times 10^{-3}\%$ yield) and (*2E,4E*)-2,6,10-trimethylundeca-2,4,9-trienal (**9**, 2.0 mg, $5 \times 10^{-4}\%$ yield),⁵ along with an unseparable 85:15 mixture of the known compounds **1** and **2** (1.3 g, 0.34% yield) and the known tricyclic sesquiterpenoid α -photosantalol (**10**, 3.0 mg, $1 \times 10^{-3}\%$ yield). Although the new compounds (**3–9**) isolated from *P. grisea* are optically active, no attempt has been made to determine the absolute configuration. The known compounds were identified by comparison of the spectral data recorded with those reported in the literature (**1,2,3,10**).



Compound **3** was isolated as an optically active colorless oil. The molecular formula $C_{15}H_{24}O$, obtained from the high-resolution mass measurement, required four degrees of unsaturation, one of them attributable to a ketone carbonyl group which gave rise to the ^{13}C NMR signal at δ 209.8 (s) (Table 1) and the IR absorption at 1712 cm^{-1} . The three unsaturations remaining were due to the presence of three double bonds, which gave rise to the ^{13}C NMR signals at δ 141.2 (d), 139.7 (d), 134.1 (s), 131.2 (d), 125.2 (d), and 112.1 (t), indicating that compound **3** possessed an acyclic structure. Furthermore, four signals in the 1H NMR spectrum of **3** (Table 2) at δ 1.83 (3H, d, $J = 1.2$ Hz), 1.04 (3H, d, $J = 6.8$ Hz), 0.90 (3H, d, $J = 6.8$ Hz), and 0.89 (3H, d, $J = 6.8$ Hz) were consistent with a structure of a farnesane sesquiterpenoid for compound **3**.

The location and stereochemistry of the three double bonds and the location of the carbonyl group were established as follows. The olefinic proton signals at δ 6.37 (1H, dd, $J = 17.2, 10.8$ Hz), 5.18 (1H, d, $J = 17.2$ Hz), and 5.01 (1H, d, $J = 10.8$ Hz) were assigned to a monosubstituted double bond that must be located at C-1,C-2 of the farnesane skeleton. A signal at δ 6.00 (1H, d, $J = 11.2$ Hz) exhibited correlations in the COSY spectrum with the vinylic methyl signal at δ 1.83 and with a signal at δ 6.35 (1H, ddd, $J = 15.2, 11.2, 1.2$ Hz), which was additionally coupled with a signal at δ 5.65 (1H, dd, $J = 15.2, 7.6$ Hz). These correlations were consistent with the location at C-3,C-4 and C-5,C-6 of the two remaining double bonds. Furthermore, the chemical shift of the H-2 signal at δ 6.37

Table 1. ^{13}C NMR Data for Compounds **3, 4, 5, 6,** and **7**^{a,b}

C no.	3 δ_C , mult	4 δ_C , mult	5 δ_C , mult	6 δ_C , mult	7 δ_C , mult
1	112.1 t	114.0 t	111.3 t	112.5 t	112.3 t
2	141.2 d	133.3 d	141.2 d	141.2 d	141.2 d
3	134.1 s	132.7 s	136.2* s	135.1* s	134.2 s
4	131.2 d	129.6 d	127.2 d	130.8 d	131.2 d
5	125.2 d	124.0 d	32.2 t	123.7 d	127.5 d
6	139.7 d	138.6 d	76.1 d	141.3 d	135.7 d
7	32.9 d	32.7 d	146.9 s	73.5 s	41.4 d
8	50.2 t	50.3 t	32.1 t	42.4 t	77.2 d
9	209.8 s	209.8 s	26.3 t	23.0 t	124.6 d
10	52.5 t	52.5 t	123.8 d	124.3 d	138.2 d
11	24.4 d	24.5 d	132.0* s	132.1* s	79.8 s
12	22.6 q	22.6 q	25.7 q	25.7 q	26.8 q
13	22.6 q	22.6 q	17.7 q	17.8 q	26.8 q
14	20.2 q	20.2 q	111.5 q	28.4 q	15.8 q
15	12.0 q	19.8 q	11.9 q	12.1 q	12.0 q
OCOCH ₃			170.2 s		169.8 s
OCOCH ₃			21.2 q		21.3 q
OCOCH ₃					170.2 s
OCOCH ₃					22.2 q

^a Assignments aided by APT and HMQC experiments. ^b Values with the same superscript in the same column may be interchanged.

and of the Me-15 carbon signal at δ 12.0 defined the *E* geometry of the C-3,C-4 double bond,^{7,8} whereas the $J_{5,6}$ value of 15.2 Hz was diagnostic of the *E* geometry for the C-5,C-6 unsaturation. Finally, the carbonyl group was located at C-9 upon observation of the correlations in the COSY spectrum between the Me-12 and Me-13 signals at δ 0.90 and 0.89 with the H-11 methine signal at δ 2.11 (1H, m), which was also coupled with the signal at δ 2.25 (2H, d, $J = 6.8$ Hz). This latter signal at δ 2.25 exhibited no further couplings, and it was attributable to a methylene adjacent to the ketone carbonyl group. Therefore the structure (*3E,5E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene was proposed for compound **3**.

The molecular formula $C_{15}H_{24}O$ of compound **4**, obtained from the high-resolution mass measurement, indicated that it was an isomer of the previously discussed sesquiterpene **3**. Furthermore, a comparison of the IR, 1H NMR, and ^{13}C NMR spectra indicated that the structures of both compounds **3** and **4** were closely related, although slight differences were observed in the resonances of the conjugated triene system. In particular, the 1H NMR signal at δ 6.92 (1H, dd, $J = 17.2, 10.8$ Hz) assigned to H-2 and the ^{13}C NMR signals at δ 133.3 (d) and δ 19.8 (q) assigned to C-2 and Me-15, respectively, were consistent with a *Z* geometry in the C-3,C-4 double bond.^{7,8} This difference in the structure of compound **4** upon comparison to that of its isomer **3** was confirmed using NOEDS. In particular, mutual NOE enhancements were observed upon irradiation of H-4 and Me-15 signals. These spectral features required a structure of (*3Z,5E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene for compound **4**.

Compound **5** was isolated as an optically active colorless oil. The molecular formula, $C_{17}H_{26}O_2$, was obtained from the HRMS spectrum. The presence of an acetoxy group was evident from the 1H NMR signal at δ 2.05 (3H, s), the ^{13}C NMR signals at δ 170.2 (s) and 21.2 (q), and the IR absorption at 1740 cm^{-1} . The remaining fifteen ^{13}C NMR signals, eight of them in the olefinic region, were attributed to a tetraolefinic farnesane. The location of the four double bonds as well as the acetoxy group was determined as follows. A signal at δ 5.11 (1H, m), which was correlated in the COSY spectrum with the signals at δ 1.69 (3H, d, $J = 1.2$ Hz) and 1.61 (3H, br s) assigned to two vinylic methyl groups, was consistent with a C-10,C-11 double bond. The

Table 2. ^1H NMR Data for Compounds **3**, **4**, **5**, **6**, and **7**^{a,b}

C no.	3 δ_{H} , mult, J (Hz)	4 δ_{H} , mult, J (Hz)	5 δ_{H} , mult, J (Hz)	6 δ_{H} , mult, J (Hz)	7 δ_{H} , mult, J (Hz)
1	5.01 d (10.8); 5.18 d (17.2)	5.12 dt (10.8,1.6); 5.22 dd (17.2,1.2)	4.96 d (10.8); 5.11 d (17.6)	5.04 d (10.8); 5.21 d (17.2)	5.02 d (10.4); 5.19 d (17.2)
2	6.37 dd (17.2,10.8)	6.92 dd (17.2,10.8)	6.35 dd (17.6,10.8)	6.41 ddd (17.2,10.8,0.8)	6.39 ddd (17.2,10.4,0.8)
3					
4	6.00 d (11.2)	5.92 d (11.2)	5.40 dd (7.6,6.8)	6.08 d (11.2)	6.04 d (11.2)
5	6.35 ddd (15.2,11.2,1.2)	6.49 ddd (15.2,11.2,1.2)	2.52 m	6.58 dd (15.2,11.2)	6.37 ddd (15.0,11.2,1.2)
6	5.65 dd (15.2,7.6)	5.58 dd (15.2,7.6)	5.24 t (6.4)	5.81 d (15.2)	5.65 dd (15.0,7.8)
7	2.83 m	2.81 m			2.60 m
8	2.35 dd (16.0,7.2); 2.45 dd (16.0,6.8)	2.34 dd (16.0,7.2); 2.44 dd (16.0,6.8)	2.06 m	1.61 m	5.16 ddd (7.2,6.0,1.2)
9			2.15 m	2.04 m	5.52 dd (16.0,16.0,7.2)
10	2.25 d (6.8)	2.25 d (6.8)	5.11 m	5.13 m	5.90 dd (16.0,1.2)
11	2.11 m	2.13 m			
12	0.89* d (6.8)	0.90 d (6.4)	1.69 d (1.2)	1.68 d (0.8)	1.48* s
13	0.90* d (6.8)	0.90 d (6.4)	1.61 br s	1.56 s	1.49* s
14	1.04 d (6.8)	1.04 d (6.8)	4.93 d (1.2); 5.04 t (0.8)	1.32 s	1.04 d (6.8)
15	1.83 d (1.2)	1.86 s	1.75 d (1.2)	1.88 d (1.2)	1.85 d (1.2)
OCOCH ₃			2.05 s		2.07 s
OCOCH ₃					1.96 s
OH				3.49 br s	

^a Assignments aided by COSY experiments. ^b Values with the same superscript in the same column may be interchanged.

signal at δ 5.11 was additionally coupled with an allylic methylene signal at δ 2.15 (2H, m), which was also coupled with another allylic methylene signal at δ 2.06 (2H, m). Since this latter signal at δ 2.06 was correlated with the olefinic methylene signals at δ 5.04 (1H, d, $J = 0.8$ Hz) and 4.93 (1H, d, $J = 1.2$ Hz), a second double bond was located at C-7,C-14. The olefinic proton signals at δ 6.35 (1H, dd, $J = 17.6, 10.8$ Hz), 5.11 (1H, d, $J = 17.6$ Hz), and 4.96 (1H, d, $J = 10.8$ Hz) were assigned to a C-1,C-2 double bond. The remaining olefinic proton signal at δ 5.40 (1H, dd, $J = 7.6, 6.8$ Hz) exhibited a cross-peak in the COSY spectrum with the vinylic methyl signal at δ 1.75 (3H, d, $J = 1.2$ Hz), indicating the presence of a trisubstituted double bond which must be located at C-3,C-4, whose geometry was proposed as *E* upon observation of the Me-15 carbon signal at δ 11.9 and the H-2 signal at δ 6.35.^{7,8} Finally, the location at C-6 of the acetoxy group was defined by the correlations observed between the signal at δ 5.24 (1H, t, $J = 6.4$ Hz) assigned to the proton geminal to the acetoxy group and the allylic methylene at δ 2.52 (2H, m), which was additionally correlated with the H-4 proton signal at δ 5.40. The structure (3*E*)-6-acetoxy-3,11-dimethyl-7-methylidendodeca-1,3,10-triene was proposed for compound **5**.

Compound **6** was obtained as a colorless oil.⁹ The low-resolution mass spectrum exhibited the molecular ion peak at m/z 220. This datum together with the presence of fifteen carbon signals in the ^{13}C NMR spectrum, eight of them in the olefinic region, and the general resemblance of the ^1H NMR spectrum with those of the rest of the members of this series suggested that compound **6** was a tetraolefinic sesquiterpenoid of molecular formula $\text{C}_{15}\text{H}_{24}\text{O}$. Furthermore, the IR absorption at 3430 cm^{-1} and the ^{13}C NMR singlet at δ 73.5 indicated that compound **6** was a tertiary alcohol. A detailed analysis of the ^1H and ^{13}C NMR spectra, and in particular of the COSY spectrum, allowed us to propose for sesquiterpene **6** a conjugated 1,3,5-triene system as in compound **3** and an isolated C-10,C-11 double bond as in compound **5**. Finally, the H-10 proton signal at δ 5.13 (1H, m) showed a cross-peak in the COSY spectrum with an allylic methylene signal at δ 2.04 (2H, m) that, in addition, was correlated with an aliphatic methylene signal at δ 1.61 (2H, m), which did not present any additional correlation. This rationale was consistent with the C-7

position of the hydroxyl group and the structure of (3*E*,5*E*)-7-hydroxy-3,7,11-trimethyldodeca-1,3,5,10-tetraene for compound **6**.

The ^{13}C NMR spectrum of compound **7** exhibited nineteen signals, four of them at δ 170.2 (s), 169.8 (s), 22.2 (q), and 21.3 (q) attributable to the presence of two acetoxy groups in the molecule.⁹ These data together with the mass spectrum fragmentation were consistent with a farnesane diacetate of molecular formula $\text{C}_{19}\text{H}_{28}\text{O}_4$. The ^1H and ^{13}C NMR signals indicated the presence in compound **7** of a conjugated 1,3,5-triene moiety like that present in compounds **3** and **6** previously discussed. A signal at δ 2.60 (1H, m) was assigned to the allylic methine proton H-7 adjacent to the conjugated double bond system. This signal showed, in addition to the couplings with the H-6 and Me-14 signals, a cross-peak in the COSY spectrum with a signal at δ 5.16 (1H, ddd, $J = 7.2, 6.0, 1.2$ Hz), which was correlated in the HMQC spectrum with the signal at δ 77.2 (d), indicating the presence of a secondary acetoxy group at C-8. The H-8 signal at δ 5.16 was correlated with an olefinic proton signal at δ 5.52 (1H, dd, $J = 16.0, 7.2$ Hz), which, together with the signal at δ 5.90 (1H, dd, $J = 16.0, 1.2$ Hz), were due to an *E* double bond at C-9,C-10. Finally, the second acetoxy group must be attached to C-11, whose ^{13}C NMR signal appeared at δ 79.8 (s). This rationale defined the structure of (3*E*,5*E*,9*E*)-8,11-diacetoxy-3,7,11-trimethyldodeca-1,3,5,9-tetraene for compound **7**.

Compound **8** was isolated as an optically active colorless oil. The molecular formula, $\text{C}_{14}\text{H}_{20}\text{O}$, was obtained from the HRMS spectrum and implied five degrees of unsaturation. The IR absorptions at 1688 and 1634 cm^{-1} indicated the presence of a carbonyl group and double bonds in the structure of **8**. In particular, the doublet in the ^{13}C NMR spectrum at δ 195.1 (Table 3), together with eight signals in the olefinic carbon region, defined the presence of an aldehyde carbonyl and four double bonds, respectively, which accounted for the five unsaturations of the molecule. These data together with the presence in the ^1H NMR spectrum (Table 3) of four methyl signals at δ 1.83 (3H, s), 1.83 (3H, d, $J = 1.2$ Hz), 1.77 (3H, s), and 1.18 (3H, d, $J = 6.8$ Hz) indicated that compound **8** was an acyclic linear norsesquiterpene containing an aldehyde group and four double bonds.

An olefinic signal at δ 6.06 (1H, dq, $J = 11.6, 1.2$ Hz)

Table 3. NMR Data for Compounds **8** and **9**^{a,b}

C no.	8 ^c		9	
	δ_C , mult	δ_H , mult, J (Hz)	δ_C , mult	δ_H , mult, J (Hz)
1	195.1 d	9.41 s	195.1 d	9.42 s
2	136.5* s		138.4 s	
3	149.3 d	6.82 d (11.2)	151.4* d	6.83 d (11.2)
4	123.8 d	6.50 ddd (15.2, 11.2, 1.2)	124.1 [†] d	6.48 ddd (14.8, 11.2, 0.8)
5	148.9 d	6.18 dd (15.2, 6.4)	149.5* d	6.12 dd (14.8, 8.0)
6	35.6 d	3.53 m	36.6 d	2.35 m
7	130.6 d	5.16 br t (10.0)	37.2 t	1.41 m
8	124.8 d	6.22 dd (12.0, 11.6)	25.8 t	1.98 m
9	119.8 d	6.06 dq (11.6, 1.2)	124.2 [†] d	5.09 m
10	137.1* s		131.8 s	
11	18.2 q	1.77 s	25.7 q	1.69* d (1.2)
12	26.4 q	1.83 s	14.1 q	1.59* s
13	20.5 q	1.18 d (6.8)	20.0 q	1.08 d (6.8)
14	9.5 q	1.83 d (1.2)	13.0 q	1.84 d (1.2)

^a Assignments aided by COSY and APT experiments. ^b Values with the same superscript in the same column may be interchanged. ^c Assignments aided by an HMQC experiment.

exhibited couplings in the COSY spectrum with two vinylic methyl signals at δ 1.83 and 1.77, and with another olefinic proton signal at δ 6.22 (1H, dd, $J = 12.0, 11.6$ Hz), which was additionally correlated with a signal at δ 5.16 (1H, br t, $J = 10.0$ Hz). This latter signal at δ 5.16 was also correlated to a methine proton signal at δ 3.53 (1H, m), which exhibited a cross-peak with the methyl signal at δ 1.18. These data defined a 1,5-dimethylhexa-2,4-dienyl subunit with *Z* geometry in the structure of **8**. Furthermore, the signal at δ 3.53 was additionally correlated with a signal at δ 6.18 (1H, dd, $J = 15.2, 6.4$ Hz), which together with the signal at δ 6.50 (1H, ddd, $J = 15.2, 11.2, 1.2$ Hz) were due to the protons of an *E* disubstituted double bond.

Finally, the signal at δ 6.50 was additionally coupled with the remaining olefinic proton signal at δ 6.82 (1H, d, $J = 11.2$ Hz) corresponding to a trisubstituted double bond bearing a methyl group and conjugated to the aldehyde carbonyl. The stereochemistry of this double bond was defined upon observation of the vinylic methyl signal at δ 9.5 (q) and of the NOE enhancement produced on the aldehyde proton signal upon irradiation of the olefinic proton signal at δ 6.82. These data defined the structure (2*E*,4*E*,7*Z*)-2,6,10-trimethylundeca-2,4,7,9-tetraenal for compound **8**.

Compound **9** was the minor component isolated from *P. grisea*. Its molecular formula, $C_{14}H_{22}O$, was obtained from the HRMS measurement. This datum together with a general inspection of the ¹H and ¹³C NMR spectra indicated that compound **9** was a norsesquiterpene aldehyde closely related to compound **8** previously discussed. However, the ¹³C NMR spectrum exhibited only six double bond carbon signals at δ 151.4 (d), 149.5 (d), 138.4 (s), 131.8 (s), 124.2 (d), and 124.1 (d) attributable to two trisubstituted and one disubstituted double bonds, which gave rise to the ¹H NMR signals at δ 6.83 (1H, d, $J = 11.2$ Hz), 6.48 (1H, ddd, $J = 14.8, 11.2, 0.8$ Hz), 6.12 (1H, d, $J = 14.8, 8.0$ Hz), and 5.09 (1H, m). Following a COSY-based rationale similar to that followed above, it was deduced that compound **9** was the aldehyde that would arise by C-7, C-8 reduction of norsesquiterpene **8** and that its structure was (2*E*,4*E*)-2,6,10-trimethylundeca-2,4,9-trienal (**9**).

A survey of marine natural products literature reveals that the data concerning the pharmacological potential of acyclic sesquiterpenoids are, in general, scarce. A single example of mild antitumor activity¹⁰ and three other accounts of antimicrobial activity have been reported.^{11–13} We have tested five⁹ of the new compounds (**3**, **4**, **5**, **8**, and

9) against the tumor cell lines of mouse lymphoma P-388, human lung carcinoma A-549, human colon carcinoma HT-29, and human melanoma MEL-28 to detect *in vitro* cytotoxicity. With the exception of compound **8**, which was inactive ($IC_{50} > 10 \mu\text{g/mL}$), the other new sesquiterpenes and norsesquiterpene tested exhibited a mild cytotoxicity with IC_{50} values between 2.5 and 5 $\mu\text{g/mL}$. Among the results obtained, the norsesquiterpene **9** exhibited the greatest and selective activity against P-388 line with $IC_{50} = 0.5 \mu\text{g/mL}$.

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Mattson Genesis Series FT-IR spectrophotometer, and UV spectra were recorded on a Philips PU 8710 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ¹H NMR and ¹³C NMR were recorded on a Varian 400 at 399.952 and 100.577 MHz, respectively, using CDCl₃ as solvent. The resonance of residual CHCl₃ at δ_H 7.26 and the central peak of CDCl₃ at δ_C 77.0 were used as internal references for ¹H NMR and ¹³C NMR, respectively. Mass spectra were measured on a Finnigan Voyager GC 8000^{top} or on a VG Autospec spectrometer. In high-performance liquid chromatography (HPLC) separations, Li-Chrosorb Si-60 was used in normal phase mode using a differential refractometer. All solvents were distilled from glass prior to use.

Animal Material. Specimens of *P. grisea* were collected by hand using apneal diving in a lagoon zone near Punta Cana (Dominican Republic) and immediately frozen.

Extraction and Isolation Procedures. The frozen tissue was lyophilized, and the freeze-dried material was extracted with MeOH. The MeOH solution was concentrated to leave an oily residue (23.0 g), which was dissolved in MeOH (500 mL) and subsequently extracted using a modified Kupchan partition⁴ as follows. The H₂O content (% v/v) of the MeOH extract was adjusted prior to sequential partitioning against hexane (10% v/v) and CHCl₃ (40% v/v). The hexane-soluble material (9.38 g) was chromatographed on a SiO₂ column using solvents of increasing polarity from hexane to hexane/Et₂O (3:7) and finally with CHCl₃/MeOH (8:2). Fractions eluted with hexane yielded a 85:15 mixture of compounds (3*E*,5*E*,8*Z*)-3,7,11-trimethyldodeca-1,3,5,8,10-pentaene (**1**) and (3*E*,5*E*,8*E*)-3,7,11-trimethyldodeca-1,3,5,8,10-pentaene (**2**) (1.3 g, 0.34% yield). Fractions of the general chromatography eluted with hexane/Et₂O (80:20) were further chromatographed on a SiO₂ column eluting with hexane and hexane/Et₂O (93:7). Selected fractions were subjected to normal phase HPLC separations eluting with hexane or hexane/EtOAc mixtures (from 99.5:0.5 to 97.5:2.5) to obtain (3*E*,5*E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene (**3**, 60.2 mg, 0.016% yield), (3*Z*,5*E*)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene (**4**, 10.9 mg, 3 $\times 10^{-3}$ % yield), (3*E*)-6-acetoxy-3,11-dimethyl-7-methylidendodeca-1,3,10-triene (**5**, 9.2 mg, 2 $\times 10^{-3}$ % yield), (2*E*,4*E*,7*Z*)-2,6,10-trimethylundeca-2,4,7,9-tetraenal (**8**, 4.0 mg, 1.2 $\times 10^{-3}$ % yield), and (2*E*,4*E*)-2,6,10-trimethylundeca-2,4,9-trienal (**9**, 2.0 mg, 5 $\times 10^{-4}$ % yield). Fractions from the general chromatography eluted with hexane/Et₂O (70:30) were further separated by normal phase HPLC eluting with hexane/EtOAc mixtures (from 93:7 to 90:10) to obtain (3*E*,5*E*)-7-hydroxy-3,7,11-trimethyldodeca-1,3,5,10-tetraene (**6**, 2.5 mg, 7 $\times 10^{-4}$ % yield), (3*E*,5*E*,9*E*)-8,11-diacetoxy-3,7,11-trimethyldodeca-1,3,5,9-tetraene (**7**, 4.5 mg, 1.2 $\times 10^{-3}$ % yield), and (α)-photosantalol A (**10**, 3.0 mg, 1 $\times 10^{-3}$ % yield).

(3*E*,5*E*)-3,7,11-Trimethyl-9-oxododeca-1,3,5-triene (3): colorless oil; $[\alpha]_D^{25} +38.4^\circ$ (*c* 0.87, CHCl₃); UV (hexane) λ_{max} (ϵ) 280 (19500), 269 (24600), 259 (18800) nm; IR (dry film) ν_{max} 3090 (olefinic C–H), 1712 (C=O), 1617 (C=C); ¹H NMR, see Table 2; ¹³C NMR, see Table 1; HREIMS *m/z* 220.1846 (calcd for C₁₅H₂₄O, 220.1827).

(3*Z*,5*E*)-3,7,11-Trimethyl-9-oxododeca-1,3,5-triene (4): colorless oil; $[\alpha]_D^{25} +18.1^\circ$ (*c* 0.27, CHCl₃); UV (hexane) λ_{max}

(ϵ) 280 (16300), 270 (21200), 260 (16400) nm; IR (dry film) ν_{\max} 3088 (olefinic C–H), 1712 (C=O), 1622 (C=C); ^1H NMR, see Table 2; ^{13}C NMR, see Table 1; HREIMS m/z 220.1729 (calcd for $\text{C}_{15}\text{H}_{24}\text{O}$, 220.1827).

(3E)-6-Acetoxy-3,11-dimethyl-7-methylidendodeca-1,3,10-triene (5): colorless oil; $[\alpha]_{\text{D}}^{25} + 8.8^\circ$ (c 0.4, CHCl_3); UV (MeOH) λ_{\max} (ϵ) 228 (14800) nm; IR (dry film) ν_{\max} 3089 (olefinic C–H), 1740 (C=O), 1648 (C=C), 1237 [C(=O)–O] cm^{-1} ; ^1H NMR, see Table 2; ^{13}C NMR, see Table 1; HREIMS m/z 262.1937 (calcd for $\text{C}_{17}\text{H}_{26}\text{O}_2$, 262.1933).

(3E,5E)-7-Hydroxy-3,7,11-trimethyldodeca-1,3,5,10-tetraene (6): colorless oil; $[\alpha]_{\text{D}}^{25} - 1.1^\circ$ (c 0.18, CHCl_3); IR (dry film) ν_{\max} 3430 (O–H), 1634 (C=C); ^1H NMR, see Table 2; ^{13}C NMR, see Table 1; EIMS m/z 220 [M] $^+$ (5), 205 (5), 203 (6), 187 (10), 175 (16), 121 (77), 119 (50), 109 (46), 107 (49), 105 (53), 93 (100).

(3E,5E,9E)-8,11-Diacetoxy-3,7,11-trimethyldodeca-1,3,5,9-tetraene (7): colorless oil; $[\alpha]_{\text{D}}^{25} - 2.1^\circ$ (c 0.28, CHCl_3); IR (dry film) ν_{\max} 1726 (C=O), 1651 (C=C), 1248 [C(=O)–O] cm^{-1} ; ^1H NMR, see Table 2; ^{13}C NMR, see Table 1; EIMS m/z 260 [M – HOAc] $^+$ (26), 200 (50), 185 (73), 121 (95), 119 (92), 109 (94), 107 (90), 105 (93), 93 (96), 91 (100).

(2E,4E,7Z)-2,6,10-Trimethylundeca-2,4,7,9-tetraenal (8): colorless oil; $[\alpha]_{\text{D}}^{25} + 294.0^\circ$ (c 0.16, CHCl_3); UV (MeOH) λ_{\max} (ϵ) 239 (15200), 281 (19200) nm; IR (dry film) ν_{\max} 1688 (C=O), 1634 (C=C) cm^{-1} ; ^1H NMR and ^{13}C NMR, see Table 3; HREIMS m/z 203.1493 (M – 1) $^+$ (calcd for $\text{C}_{14}\text{H}_{19}\text{O}$, 203.1436).

(2E,4E)-2,6,10-Trimethylundeca-2,4,9-trienal (9): colorless oil; $[\alpha]_{\text{D}}^{25} + 40.0^\circ$ (c 0.05, CHCl_3); UV (MeOH) λ_{\max} (ϵ) 238 (10500) nm; IR (dry film) ν_{\max} 1687 (C=O), 1634 (C=C) cm^{-1} ; ^1H NMR and ^{13}C NMR, see Table 3; HREIMS m/z 206.1643 (calcd for $\text{C}_{14}\text{H}_{22}\text{O}$, 206.1671).

Cytotoxicity Assays. Compounds **3**, **4**, **5**, **8**, and **9** were tested against the tumor cell lines P-388 (mouse lymphoma), A-549 (human lung carcinoma), HT-29 (human colon carcinoma), and MEL-28 (human melanoma). The individual cell line identifiers are given along with the corresponding IC_{50} values ($\mu\text{g/mL}$) for each compound tested. (3E,5E)-3,7,11-trimethyl-9-oxododeca-1,3,5-triene (**3**): P-388 (2.5), A-549 (5), HT-29 (5), MEL-28 (5); (3Z,5E)-3,7,11-trimethyl-9-oxododeca-

1,3,5-triene (**4**): P-388 (2.5), A-549 (2.5), HT-29 (2.5), MEL-28 (2.5); (3E)-6-acetoxy-3,11-dimethyl-7-methylidendodeca-1,3,10-triene (**5**): P-388 (2.5), A-549 (5), HT-29 (5), MEL-28 (5); (2E,4E,7Z)-2,6,10-trimethylundeca-2,4,7,9-tetraenal (**8**): P-388 (>10), A-549 (>10), HT-29 (>10), MEL-28 (>10); (2E,4E)-2,6,10-trimethylundeca-2,4,9-trienal (**9**): P-388 (0.5), A-549 (2.5), HT-29 (2.5), MEL-28 (2.5).

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