Dendocarbins A−N, New Drimane Sesquiterpenes from the Nudibranch *Dendrodoris carbunculosa*

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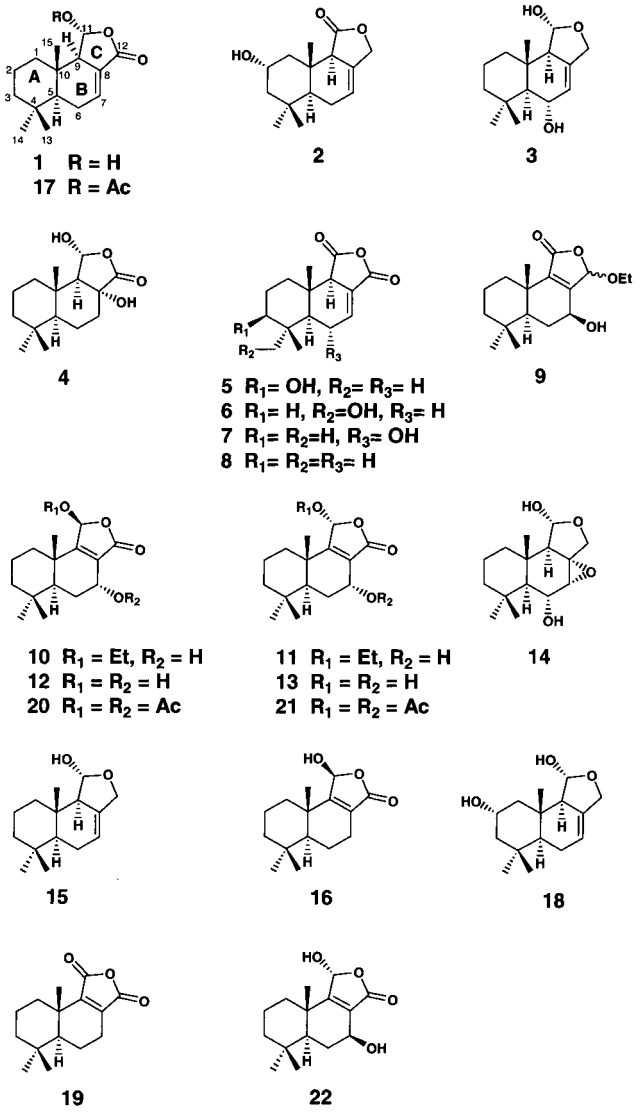
Fourteen new sesquiterpenes of the drimane series dendocarbins A−N (**1**−**14**) were obtained from ethanol extracts of the Japanese nudibranch *Dendrodoris carbunculosa*, together with two known compounds, isodrimeninol (**15**) and 11-epivaldiviolide (**16**). All structures were elucidated mainly from spectral data, and most of these sesquiterpenes were found to exhibit cytotoxicity. In addition, isodrimeninol (**15**), the major sesquiterpene of this animal, was found to have a sharp peppery taste.

Several organic natural products isolated from nudibranchs possess toxic or antifeedant properties,[1] and it is believed that nudibranch molluscs of the genus *Dendrodoris* localize chemicals on the mantle of the body to defend themselves from predators. Most notably polygodial, isolated from *Dendrodoris limbata, D. grondiflola, D. nigra,* and *D. tuberculosa*,[2,3] has been shown to taste like very hot pepper and appears to also have an effect on the taste of insects. Polygodial was, however, first isolated from a number of terrestrial plants,[4] and it was therefore suspected to be a plant defensive strategy. During our studies in a search for bioactive substances from marine and terrestrial natural resources, we have examined the constituents of the Japanese nudibranch *Dendrodoris carbunculosa*. *D. carbunculosa* belongs to a species related to *D. tuberculosa*, differing only in the color of the underside of the mantle. Here we describe isolation and structure elucidation of a series of drimane sesquiterpenoids, including 14 new compounds, dendocarbins A−N (**1**−**14**), from *D. carbunculosa* collected at the south coast of Boso peninsula, Japan. Some of these sesquiterpenes exhibited cytotoxicity against murine leukemia P388 cell lines. The major constituent isodrimeninol (**15**) proved to have a sharp peppery taste.

The animal specimen, *D. carbunculosa* (Kelaart, 1858; family Dendrodoridae), used in this study was exceptionally large; it was 35 cm long in the relaxed condition in a tide pool and could be flattened to a maximum length of 40 cm on the laboratory sink. The wet weight was 2 kg. This species usually lives in tropical areas and is rarely found in Japan.[5] The specimen was extracted with EtOH, and the EtOAc-soluble fraction of the extract was subjected to silica gel column chromatography with a gradient elution of EtOAc in hexane, followed by further purification with reversed-phase HPLC to give 16 sesquiterpenes (**1**−**16**) as colorless oils.

The major sesquiterpene proved to be isodrimeninol (**15**), which was previously isolated from the seeds of *Polygonum hydropiper* (Polygonaceae).[6] Spectral data including optical rotation were identical with those described in the literature, indicating that the same enantiomer of **15** was isolated from *D. carbunculosa* and from *P. hydropiper*. Another known compound obtained from this nudibranch was 11-epivaldiviolide (**16**), which was previously isolated from the sponge *Dysidea fusca*.[7] The remaining 14 sesquiterpenes obtained from this specimen proved to be novel and were named dendocarbins A−N (**1**−**14**).



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Results and Discussion

A molecular formula of $C_{15}H_{22}O_3$ was suggested for dendocarbin A (**1**) on the basis of its HRFABMS data (*m/z* 251.1641, M + H, Δ −0.6 mmu). The presence of OH and C=O groups was indicated by IR absorption bands at 3440 and 1740 cm^{-1}, respectively. The ^1H NMR spectrum of **1** showed signals due to three tertiary methyls [δ 0.98 (C-13), 1.02 (C-14), and 0.93 (C-15)] and an olefinic proton [δ 6.90 (H-7)]. The UV absorption of **1** (λ_{max} at 220 nm) along with the ^{13}C NMR chemical shifts [δ_C 137.8 (C-7), 130.6 (C-8), and 171.1 (C-12)] implied the presence of a conjugated ester or lactone group. On the basis of these spectral data as well as analyses of its $^1H-^1H$ COSY, HMQC, and HMBC spectra, compound **1** was suggested to be a drimane sesquiterpene with a γ-lactone moiety at the C-ring. In the ^1H and ^{13}C NMR spectra of dendocarbin A (**1**), however, signals for H-11 and C-11 were not observed, either in CD_3OD or in C_6D_6 solution. This phenomenon may be ascribed to some chemical exchange or conformational equilibrium at the hemiacetal functionality at C-11. Thus, an acetate (**17**) was prepared from **1** by treatment with acetic anhydride in pyridine. The ^1H NMR of the acetate (**17**) displayed a clear signal corresponding to a dioxygenated methine proton [δ_H 6.50, d, J = 6.0 Hz (H-11)] together with a singlet due to an acetyl methyl group (δ_H 2.21). The $^1H-^1H$ COSY spectrum of **17** further confirmed the assignment of the H-11 signal, which revealed a cross-peak with a vicinal methine proton at δ_H 2.86 (H-9). The difference NOE experiment of the acetate (**17**) showed correlations between H-11 and H_3-15 (δ 0.96); irradiation of H-11 caused 6.3% enhancement of H_3-15, while irradiation of H_3-15 yielded 14% NOE in the H-11 signal. These findings suggest a β-configuration for H-11 in **17**. From these results, the structure of dendocarbin A was concluded as **1**, corresponding to a 12-oxo derivative of isodrimeninol (**15**), but the configuration at C-11 of **1** was not defined since it is still unknown that the configuration of C-11 of **1** is the same as that of **17**.

The molecular formula of dendocarbin B (**2**), $C_{15}H_{22}O_3$, was deduced to be the same as that of **1** from the HRFABMS data (*m/z* 251.1627, M + H, Δ −2.0 mmu). The ^1H and ^{13}C NMR data of **2** revealed that compound **2** had a trisubstituted double bond [δ_H 5.02 (H-7); δ_C 120.3 (C-7) and 149.9 (C-8)] and an oxymethylene group [δ_H 4.03 (2H, m) (H-12); δ_C 69.0 (C-12)]. The oxymethylene was assigned to the allylic position at C-12 from HMBC correlations to C-8 and $^1H-^1H$ COSY cross-peaks with H-7. The ^1H and ^{13}C NMR spectra of **2** showed signals of an oxygenated methine (δ_H 3.57 and δ_C 63.6), which were assigned to C-2/H-2 from the $^1H-^1H$ COSY (H_2-1/H-2 and H-2/H_2-3) and HMBC (H_2-1/C-2 and H_2-3/C-2) correlations. Dendocarbin B (**2**) was therefore suggested to have a 2-hydroxidrimane skeleton with a $\Delta^{7,8}$-double bond, and the remaining carbonyl group had to be located at C-11, thus constructing a γ-lactone ring at the C-ring moiety. The hydroxyl group on C-2 was shown to have an α-equatorial orientation, since NOEs were observed from H-2 to H_3-15 (8%) and from H_3-15 to H-2 (1.1%). From these observations, the structure of dendocarbin B was concluded to be **2**. A drimane sesquiterpene possessing a 2α-hydroxyl group (2α-hydroxyisodrimeninol, **18**) has been isolated from the fungus *Pestalotiopsis* sp.,[8] which corresponded to a 11-dihydro derivative of dendocarbin B (**2**).

Dendocarbin C (**3**) was suggested to have the molecular formula $C_{15}H_{24}O_3$ from FABMS data (*m/z* 235.1701, M − H_2O + H, Δ +0.3 mmu), having an additional oxygen atom on **15**. The ^1H, ^{13}C, and 2D NMR spectra of **3** revealed that the only structural difference from **15** was the presence of a methine group (δ_H 4.04 and δ_C 68.6) in **3** bearing a secondary hydroxyl. The $^1H-^1H$ COSY spectrum showed a cross-peak between the methine proton at H-5 (δ_H 0.91, d, J = 9.5 Hz) and the oxygenated methine (δ_H 4.04). Thus, this oxygenated methine was identified as H-6/C-6. H-6 was implied to have the β-axial orientation from the coupling constant between H-5 and H-6 (9.5 Hz). On the hemiacetal carbon at C-11, the hydroxyl group was oriented α, as suggested by the 4% NOE observed from H_3-15 to H-11. This stereochemistry was coincident with that of isodrimeninol (**15**). Thus, dendocarbin C (**3**) was revealed to be 6α-hydroxyisodrimeninol.

The molecular formula $C_{15}H_{24}O_4$ was suggested for dendocarbin D (**4**) by the HRFABMS [*m/z* 269.1743 (M + $H)^+$, Δ −0.9 mmu]. The ^1H and ^{13}C NMR spectra of **4** were similar to those of 11-epivaldiviolide (**16**), but signals due to an oxygenated quaternary carbon (δ_C 76.0) and an sp^3 methine (δ_H 1.99; δ_C 65.0) were observed instead of the signals of one tetrasubstituted olefin [δ_C 127.9 (C-8) and 138.9 (C-9)] observed in the ^{13}C NMR of **16**. On the basis of the HMBC spectrum of **4**, the oxygenated quaternary carbon and the sp^3 methine were assigned to C-8 and C-9, respectively, from the long-range correlations between the methine proton at δ_H 1.99 (H-9) and the carbons resonating at δ_C 41.1 (C-1), 76.0 (C-8), 37.2 (C-10), 100.0 (C-11), 174.0 (C-12), and 16.4 (C-15), thus suggesting that a tertiary hydroxyl group was located on C-8. Difference NOE experiments revealed substantial NOE correlations between H-11 and CH_3-15, indicating that H-11 was β and, in addition, H-9 had to be α. The hydroxyl group on C-8 also had to be α (viz., cis at B/C ring juncture) from the manual model considerations. From these results, the structure of dendocarbin D was concluded to be **4**.

The ^1H and ^{13}C NMR spectra of dendocarbins E (**5**), F (**6**), G (**7**), and H (**8**) were similar to each other. From the EI and/or FAB mass spectral data, the molecular formulas of dendocarbins E−G (**5**−**7**) were all deduced to be $C_{15}H_{20}O_4$, while that of dendocarbin H (**8**) was $C_{15}H_{20}O_3$. Detailed analysis of the $^1H-^1H$ COSY, HMQC, and HMBC spectra of dendocarbin E (**5**) indicated the presence of an acid anhydride moiety at the C-ring [UV (end absorption); HMBC correlation: H-9/C-11 and H-9/C-8]. The presence of a secondary hydroxyl group at C-3 (δ_H 3.28; δ_C 79.3) was suggested from the $^1H-^1H$ COSY cross-peak between this methine (H-3) and methylene protons at C-2 [δ_H 1.71 (2H, m)] as well as the HMBC correlations from this methine proton (H-3) to C-1 (δ_C 39.7), C-2 (δ_C 28.0), C-4 (δ_C 39.8), C-13 (δ_C 28.7), and C-14 (δ_C 16.0). The stereochemistry of H-3 was assigned to be axial on the basis of $^1H-^1H$ coupling constants ($J_{2\beta,3}$ = 9.6 and $J_{2\alpha,3}$ = 6.0 Hz). Thus, the structure of dendocarbin E was elucidated as **5**. The ^1H NMR spectrum of dendocarbin F (**6**) showed only two signals for tertiary methyl groups, although all drimane sesquiterpenes described above had three tertiary methyl groups. In the ^1H and ^{13}C NMR spectra of **6**, signals due to an isolated hydroxymethylene moiety were observed [δ_H 3.05 and 3.38 (each 1H, d, J = 11.5 Hz; H_2-14); δ_C 71.5 (C-14)], and this hydroxymethylene group was placed on C-14 (α methyl carbon at C-4 of drimane nucleus) from its HMBC connectivities observed from H_2-14 to C-3 (δ_C 36.4) and from H_3-13 (δ_H 0.92) to C-14 along with the NOE correlations (6.0% from H_3-13 to H_3-15 and 8.2% from H_3-15 to H_3-13). Consequently, the structure of dendocarbin F was concluded to be **6**. Dendocarbin G (**7**), having the same molecular formula as **5** and **6**, was inferred to be isomeric with these two compounds with respect to the

position of the hydroxyl group. The ^{1}H and ^{13}C NMR spectra of **7** showed signals for an oxygenated methine at δ_H 4.39 (1H, br d, J = 10.5 Hz) and δ_C 69.0, which was assignable to the C-6 position from the ^{1}H−^{1}H COSY correlations observed from H-6 to H-5 (δ_H 1.33) together with the HMBC connectivity observed between H-5 and C-6. The ^{1}H−^{1}H coupling constant ($J_{5,6}$ = 10.5 Hz) indicated the configuration of H-6 to be β-axial, and this assignment was further supported by difference NOE correlations observed between H-6 and H_3-15 (5.2% from H-6 to H_3-15 and 3.4% from H_3-15 to H-6). The structure of dendocarbin G was therefore represented as **7**. Dendocarbin H (**8**), having one less oxygen atom than **5**, **6**, or **7** (vide supra), had no signals for an oxygenated methine or methylene carbon in the ^{1}H and ^{13}C NMR spectra. Aside from this fact, the spectral data of **8**, including the ^{1}H−^{1}H COSY, HMQC, and HMBC spectra, were similar to those of compounds **5**−**7**, thus suggesting that dendocarbin H (**8**) corresponded to the dehydroxy derivative of compounds **5**−**7**. The structure of dendocarbin H (**8**) was closely related to winterin (**19**), which was isolated from the stem bark of *Drimys winteri*.[9]

The molecular formulas of dendocarbins I (**9**), J (**10**), and K (**11**) were all determined to be $C_{17}H_{26}O_4$ by HRFABMS data, and these three compounds were shown to possess an ethoxy group from their ^{1}H and ^{13}C NMR spectra [e.g., for **9**, δ_H 3.25 and 3.39 (each 1H, m; OC*H*$_2$CH$_3$), and 1.09 (3H, t, J = 7.0 Hz; OCH$_2$C*H*$_3$); δ_C 65.0 (OC*H*$_2$CH$_3$) and 15.7 (OCH$_2$C*H*$_3$)]. The ^{1}H and ^{13}C NMR spectra of dendocarbin I (**9**) revealed the presence of three tertiary methyls [δ_H 0.69, 0.72, and 1.10 (each 3H singlet)], an oxymethine (δ_H 3.98 and δ_C 73.2), and an acetal methine (δ_H 5.68 and δ_C 94.8). Detailed analysis of the ^{1}H−^{1}H COSY, HMQC, and HMBC spectra of **9** showed the location of the oxymethine group at C-7 (^{1}H−^{1}H COSY, H-5/H-6β and H$_2$-6/H-7; HMBC, H_3-15/C-5, H-5/C-6, H-6α/C-5, H-6α/C-10, and H-6α/C-7). The presence of a tetrasubstituted olefin was suggested at the C-8−C-9 position, which was conjugated with an ester (or lactone) carbonyl group (UV, end absorption; HMBC, H_3-15/C-9, H-6α/C-8, and H-7/C-8), and the ^{13}C chemical shift data implied that C-8 (δ_C 156.7) and C-9 (δ_C 140.5) were at β- and α-positions to the carbonyl group, respectively, thus placing the carbonyl at the C-11 position. Thus, the ethoxy group had to be located on C-12. The H-7 methine proton was shown to be α-axial from the ^{1}H−^{1}H coupling constants ($J_{6\beta,7}$ = 9.8 and $J_{6\alpha,7}$ = 6.7 Hz), whereas the configuration of H-12 remained unassigned since no NOE data were obtained.

The ^{1}H and ^{13}C NMR spectral data of dendocarbins J (**10**) and K (**11**) were similar to each other, except for the chemical shifts of the 15-CH$_3$ group (**10**, δ_H 0.99 and δ_C 18.0; **11**, δ_H 0.64 and δ_C 20.0). Interpretation of ^{1}H and ^{13}C NMR spectra of **10** and **11** as well as their 2D NMR data suggested that **10** and **11** were 7-hydroxy derivatives of 11-epivaldiviolide (**16**), in which the hydroxyl group on C-11 was replaced by an ethoxy group. The structural difference between **10** and **11** was the configuration of the ethoxy group at C-11 (**10**, α-H and β-OEt; **11**, β-H and α-OEt), since the difference NOE correlations were observed between H_3-15 and H-11 for **11** (2.7% from H-11 to H_3-15 and 4.5% from H_3-15 to H-11), while the signal of H-11 of **10** showed substantial NOE (7%) on irradiation of methylene protons on C-1 [δ_H 1.50 (2H, m)]. Both **10** and **11** were shown to contain a C-7 α-axial hydroxyl group since an equatorial configuration for H-7 was indicated from the ^{1}H−^{1}H coupling constants [H-7, δ_H 4.27 (1H, br d, J = 4.6 Hz) for **10**; δ_H 4.29 (1H, br d, J = 4.9 Hz) for **11**].

Dendocarbins L (**12**) and M (**13**) were isolated as a mixture in a ratio of 2:5, and the ^{1}H and ^{13}C NMR spectra revealed that this mixture consisted of two epimers that corresponded to **10** and **11** except for the absence of the ethoxy group replaced by a hydroxyl group on C-11, respectively. This was consistent with the FABMS data of this mixture (**12** and **13**), which afforded a molecular ion peak at m/z 267 $(M + H)^+$, indicating the molecular formula $C_{15}H_{22}O_4$. Difference NOE experiments revealed an α-H configuration at C-11 for **12** (3.3% NOE observed from H$_2$-1 to H-11) and a β-H configuration for **13** (1.1% NOE observed from H-11 to H_3-15). The signals due to H-7 of **12** and **13** were both observed as broad singlets, whereas acetylation of the mixture of **12** and **13** afforded a mixture of diacetates (**20** and **21**, respectively), whose ^{1}H NMR spectrum showed a double doublet signal assignable to H-7 [δ_H 5.61 (1H, dd, J = 2.8 and 1.8 Hz) and δ_H 5.69 (1H, dd, J = 4.0 and 2.5 Hz), respectively], and these coupling constant data suggested the configuration of H-7 to be equatorial. Dendocarbin M (**13**) is thus a C-7 epimer of fuegin (**22**), which was isolated from *Drimys winteri*.[10]

The ^{1}H and ^{13}C NMR data of dendocarbin N (**14**) showed the signals due to a hemiacetal [δ_H 4.96 (1H, br s; H-11) and δ_C 99.2 (C-11)], an oxymethylene [δ_H 3.49 and 4.18 (each 1H, d, J = 10 Hz; H$_2$-12) and δ_C 68.2 (C-12)], and a secondary hydroxyl group [δ_H 3.73 (1H, m; H-6) and δ_C 69.0 (C-6)]; these data resembled those of dendocarbin C (**3**). The spectral data of **14**, however, showed no signals assignable to an olefinic bond, but instead signals for an oxymethine [δ_H 2.96 (1H, d, J = 3.3 Hz; H-7) and δ_C 69.0 (C-7)] and an oxygenated quaternary carbon [δ_C 68.2 (C-8)] were observed. The chemical shifts of these signals implied the presence of an epoxide group, located at C-7−C-8 [^{1}H−^{1}H COSY, H-6/H-7; HMBC, H-7/C-6]. The presence of a secondary hydroxyl group on C-6 was suggested by the ^{1}H−H COSY spectrum (H-5/H-6 and H-6/H-7), and the coupling constant between H-5 and H-6 (10 Hz) indicated the configuration of H-6 to be β-axial. The stereochemistry of the 7,8-epoxide was inferred to be α from NOE data [2.2% from H-7 to H-12 (δ_H 3.49) and 4.0% inversely]. The observed NOE between H-11 and H_3-15 (4.4% from H-11 to H_3-15 and 3.5% inversely) indicated a β-H configuration at C-11. Thus, the structure of dendocarbin N was concluded as **14**, which corresponded to α-epoxide of the $\Delta^{7,8}$-double bond of dendocarbin C (**3**).

All sesquiterpene compounds we have isolated here possess the drimane skeleton. The ethoxy groups found in dendocarbins I (**9**), J (**10**), and K (**11**) were most likely introduced during extraction with EtOH. The cytotoxic activity of these sesquiterpenes against murine leukemia P388 cells were examined, and the IC_{50} values against adriamycin (ADR)- and vincristine (VCR)-resistant P388 cells (P388/ADR and P388/VCR, respectively) as well as those against sensitive P388 strain (P388/S) are presented in Table 1. Although these sesquiterpene derivatives had no reversal effect of multidrug resistance,[11] compounds **10** and **16** exhibited moderate cytotoxicity against both sensitive and resistant cell strains. This animal was described to have a bitter and sharp peppery taste.[12] The major sesquiterpene isolated, isodrimeninol (**15**), was found to have a sharp peppery taste.

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a JASCO J-20. UV spectra were obtained on a Hitachi U-3400 spectrometer. IR spectra were measured as KBr disks on a Hitachi 260-10 infrared spectrophotometer. NMR spectra were recorded on JEOL JNM GSX-A400, A500,

Table 1. Cytotoxic Activity (IC_{50} Values, μg/mL) of the Sesquiterpenes Isolated from *D. carbunculosa*[a]

compound	P388/S	P388/VCR(−)	P388/VCR(+)	P388/ADR(−)	P388/ADR(+)
1	>25	>25	>25	>25	>25
2	11.5	10.2	9	7	10.5
3	>25	> 25	>25	>25	>25
4	15	16	14	16	16
5	>25	22.5	>25	19	>25
6	>25	> 25	>25	>25	22
7	>25	> 25	>25	>25	>25
8	10.8	10.1	8	10.1	10.5
9	10	10.2	10.2	8	10
10	17	4	4	11	8
11	10.5	10.5	9	9	10.5
12/**13**[b]	>25	>25	>25	>25	> 25
14	>25	>25	>25	>25	>25
15	13	22	>25	18	18
16	3.2	2.5	2.5	2.5	2.5
17	10.2	10.2	9	8	10.1

[a] P388/ADR and P388/VCR are adriamycin- and vincristine-resistant P388 cell lines, respectively, while P388/S is a sensitive P388 cell line. Tests toward P388/ADR and P388/VCR cell lines were carried out in the absence (−) and presence (+) of 0.1 μg/mL of ADR and 0.004 μg/mL of VCR, respectively, which did not affect the growth of the cells, respectively. These tests were performed according to literature procedures.[13] [b] A 2:5 mixture of **12** and **13**.

and ecp600 spectrometers. High-resolution fast atom bombardment (HRFAB) mass spectra were acquired on a JMS HX-110 mass spectrometer and electron ionization (EI) mass spectra on a AUTO MS-20 mass spectrometer. GC−MS spectra were obtained on a Hewlett-Packard 5890 Series II gas chromatograph with a 5971A mass selective detector.

Animal Material. A specimen of *Dendrodoris carbunculosa* was collected in Amatsu-kominato, Boso Peninsula, central Japan (35 07N, 140 11E), on November 23rd, 1999. It was found near the surface on the concrete wall at a fishing port.

Extraction and Purification. The sea slug (2 kg, wet weight) was soaked in EtOH to give 167 g of an extract after evaporation of the solvent. The extract was partitioned between EtOAc (350 mL × 3) and H_2O, and the aqueous phase was further extracted with 1-butanol (300 mL × 3). The EtOAc-soluble material (469 mg) was subjected to silica gel column chromatography (PSQ 100B, Fuji silysia, 1.5 × 26 cm) and eluted with EtOAc/hexane (1:6 to 3:1). The first five fractions were purified separately with HPLC (Develosil ODS-UG5, Nomura Chemical, 10 × 250 mm; flow rate, 2 mL/min; detection, UV at 220 nm and RI; eluent, vide infra) to yield 16 components. The first fraction (35 mg; eluent, 80% MeOH in water) afforded dendocarbin I (**9**, 0.1 mg, t_R 18.2 min) together with isodrimeninol (**15**, 13.6 mg, t_R 23.6 min) and 11-epivaldiviolide (**16**, 1.3 mg, t_R 16.4 min). From the second fraction (36 mg; eluent, 73% MeOH in water), dendocarbin A (**1**, 3.3 mg, t_R 21.4 min), dendocarbin J (**10**, 1.1 mg, t_R 28.0 min), and dendocarbin K (**11**, 0.7 mg, t_R 20.4 min) were obtained, while the third fraction (39 mg; eluent, 68% MeOH) provided dendocarbin B (**2**, 4.1 mg, t_R 12.8 min), dendocarbin D (**4**, 0.4 mg, t_R 21.6 min), and a 2:5 mixture of dendocarbins L (**12**) and M (**13**) (2.8 mg, t_R 15.5 min). The fourth fraction (32 mg; eluent, 67% MeOH) gave dendocarbins C (**3**, 1.4 mg, t_R 16.7 min), H (**8**, 0.7 mg, t_R 40.6 min), and N (**14**, 0.6 mg, t_R 13.0 min), whereas the final, fifth fraction (26 mg; eluent, 58% MeOH) afforded dendocarbins E (**5**, 1.0 mg, t_R 9.8 min), F (**6**, 0.8 mg, t_R 12.6 min), and G (**7**, 1.3 mg, t_R 22.2 min).

Dendocarbin A (1): colorless oil; $[\alpha]_D^{25}$ −10° (*c* 0.14, $CHCl_3$); IR (KBr) λ_{max} 3440, 1740, and 1640 cm^{-1}; UV (MeOH) λ_{max} 220 (ϵ 10 000) nm; ^1H NMR (CD_3OD) δ_H 1.33 and 1.85 (each 1H, m; H_2-1), 1.53 and 1.66 (each 1H, m; H_2-2), 1.29 and 1.52 (each 1H, m; H_2-3), 1.39 (1H, m; H-5), 2.18 and 2.47 (each 1H, m; H_2-6), 6.90 (1H, br s; H-7), 2.57 (1H, br s; H-9), 0.98 (3H, s; H_3-13), 1.02 (3H, s; H_3-14), and 0.93 (3H, s; H_3-15); FABMS *m/z* 501 $(2M + H)^+$, 273 $(M + Na)^+$, 251 $(M + H)^+$, and 233 $(M - H_2O + H)^+$; HRFABMS *m/z* 251.1641 [calcd for $C_{15}H_{23}O_3$, (M + H) 251.1647].

Acetylation of 1. A solution of dendocarbin A (**1**, 0.5 mg) in acetic anhydride (0.2 mL) was added to pyridine (0.1 mL). The reaction mixture was stirred at room temperature for 16.5 h, and evaporation of an excess of the reagents gave an oily product, **17** (ca. 1 mg): $[\alpha]_D^{25}$ −48° (*c* 0.05, $CHCl_3$); IR (KBr) λ_{max} 1770 and 1690 cm^{-1}; UV (MeOH) λ_{max} 220 (ϵ 7000) nm; ^1H NMR (CD_3OD) δ_H 1.54 (1H, m; H-5), 2.26 and 2.56 (each 1H, m; H_2-6), 6.98 (1H, dd, *J* = 7.0 and 3.5 Hz; H-7), 2.86 (1H, m; H-9), 6.50 (1H, d, *J* = 6.0 Hz; H-11), 1.04 (3H, s; H_3-13), 1.01 (3H, s; H_3-14), 0.96 (3H, s; H_3-15), and 2.21 (3H, s; C*H*$_3$-CO); FABMS *m/z* 293 $(M + H)^+$; HRFABMS *m/z* 293.1737 [calcd for $C_{17}H_{25}O_4$, (M + H) 293.1753].

Dendocarbin B (2): colorless oil; $[\alpha]_D^{25}$ −88° (*c* 0.03, $CHCl_3$); IR (KBr) λ_{max} 3460 and 1650 cm^{-1}; UV (MeOH) λ_{max} 220 (ϵ 10 000) nm; ^1H NMR (C_6D_6) δ_H 0.97 and 2.90 (each 1H, m; H_2-1), 3.57 (1H, m; H-2), 1.04 and 1.62 (each 1H, m; H_2-3), 0.82 (1H, dd, *J* = 11.8 and 5.4 Hz; H-5), 1.50 and 1.72 (each 1H, m; H_2-6), 5.02 (1H, br s; H-7), 2.20 (1H, br s; H-9), 4.03 (2H, m; H_2-12), 0.68 (3H, s; H_3-13), 0.66 (3H, s; H_3-14), and 0.77 (3H, s; H_3-15); FABMS *m/z* 501 $(2M + H)^+$, 251 $(M + H)^+$, and 233 $(M - H_2O + H)^+$; HRFABMS *m/z* 251.1627 [calcd for $C_{15}H_{23}O_3$, (M + H) 251.1647].

Dendocarbin C (3): colorless oil; $[\alpha]_D^{25}$ +26° (*c* 0.06, $CHCl_3$); IR (KBr) λ_{max} 3430 and 1690 cm^{-1}; ^1H NMR (C_6D_6) δ_H 1.30 and 1.40 (each 1H, m; H_2-1), 1.13 (2H, m; H_2-2), 1.50 (2H, m; H_2-3), 0.91 (1H, d, *J* = 9.5 Hz; H-5), 4.04 (1H, br d, *J* = 9.5 Hz; H-6), 5.16 (1H, br s; H-7), 2.17 (1H, br s; H-9), 5.03 (1H, d, *J* = 3.0 Hz; H-11), 4.03 and 4.44 (each 1H, d, *J* = 11.5 Hz; H_2-12), 1.20 (3H, s; H_3-13), 0.94 (3H, s; H_3-14), and 0.69 (3H, s; H_3-15); FABMS *m/z* 235 $(M - H_2O + H)^+$ and 217 $(M - 2H_2O + H)^+$; HRFABMS *m/z* 235.1701 [calcd for $C_{15}H_{23}O_3$, (M − H_2O + H) 235.1698].

Dendocarbin D (4): colorless oil; $[\alpha]_D^{25}$ +15° (*c* 0.02, $CHCl_3$); IR (KBr) ν_{max} 3460 and 1750 cm^{-1}; ^1H NMR (C_6D_6) δ_H 2.20 (2H, br d, *J* = 12.8 Hz; H_2-1), 0.99 and 1.03 (each 1H, m; H_2-2), 1.20 and 1.25 (each 1H, m; H_2-3), 0.88 (1H, m; H-5), 1.15 and 1.25 (each 1H, m; H-6), 1.70 (2H, m; H-7), 1.99 (1H, br s; H-9), 5.19 (1H, br s; H-11), 0.71 (3H, s; H_3-13), 0.56 (3H, s; H_3-14), and 0.69 (3H, s; H_3-15); FABMS *m/z* 537 $(2M + H)^+$, 291 $(M + Na)^+$, 269 $(M + H)^+$, 251 $(M - H_2O + H)^+$, and 233 $(M - 2H_2O + H)^+$; HRFABMS *m/z* 269.1743 [calcd for $C_{15}H_{25}O_4$, (M + H) 269.1752].

Dendocarbin E (5): colorless oil; $[\alpha]_D^{25}$ −42° (*c* 0.05, $CHCl_3$); IR (KBr) ν_{max} 3450 and 1700 cm^{-1}; UV (MeOH) end absorption; ^1H NMR (CD_3OD) δ_H 1.57 and 2.04 (each 1H, m; H_2-1), 1.71 (2H, m; H_2-2), 3.28 (1H, dd, *J* = 9.6 and 6.0 Hz; H-3), 1.32 (1H, dd, *J* = 7.5 and 4.5 Hz; H-5), 2.27 (2H, m; H_2-6), 7.01 (1H, d, *J* = 5.5 Hz; H-7), 3.13 (1H, br s; H-9), 1.05 (3H, s; H_3-13), 0.94 (3H, s; H_3-14), and 0.96 (3H, s; H_3-15); EIMS *m/z* 264 $(M)^+$, 246 $(M - H_2O)^+$ and 231 $(M - H_2O - CH_3)^+$; GC−MS *m/z* 264 $(M)^+$, 246 $(M - H_2O)^+$ and 218 $(M - H_2O - CO)^+$.[14]

Dendocarbin F (6): colorless oil; $[\alpha]_D^{25}$ −65° (*c* 0.06, $CHCl_3$); IR (KBr) ν_{max} 3450, 1700, and 1650 cm^{-1}; UV (MeOH) end absorption; ^1H NMR (CD_3OD) δ_H 1.39 (1H, dd, *J* = 13.3 and 3.8 Hz; H-1), 2.01 (1H, m; H-1), 1.35 and 1.56 (each 1H, m; H_2-2), 1.33 and 1.58 (each 1H, m; H_2-3), 1.68 (1H, dd, *J* = 11.8 and 4.3 Hz; H-5), 2.15 and 2.28 (each 1H, m; H_2-6), 6.98 (1H, br d, *J* = 6.5 Hz; H-7), 3.18 (1H, br s; H-9), 3.05 and 3.38 (each 1H, d, *J* = 11.5 Hz; H_2-14), 0.92 (3H, s; H_3-13), and 1.01 (3H, s; H_3-15); GC−MS *m/z* 264 $(M)^+$ and 231 $(M - H_2O - CH_3)^+$.[14]

Dendocarbin G (7): colorless oil; $[\alpha]_D^{25}$ −31° (*c* 0.07, $CHCl_3$); IR (KBr) ν_{max} 3440 and 1690 cm^{-1}; UV (MeOH) end absorption; ^1H NMR (CD_3OD) δ_H 1.46 (1H, m; H-1), 1.90 (1H, br d, *J* = 14.0 Hz; H-1), 1.48 and 1.61 (each 1H, m; H_2-2), 1.35 and 1.51 (each 1H, m; H_2-3), 1.33 (1H, m; H-5), 4.39 (1H, br d *J* = 10.5 Hz; H-6), 6.75 (1H, s; H-7), 3.17 (1H, br s; H-9), 1.20 (3H, s; H_3-13), 1.14 (3H, s; H_3-14), and 1.02 (3H, s; H_3-15); EIMS *m/z* 264 (M^+), 249 $(M - CH_3)^+$, and 231 $(M - CH_3 - H_2O)^+$; GC−MS *m/z* 264 (M^+), 249 $(M - CH_3)^+$, and 231 $(M - CH_3 - H_2O)^+$.[14]

Dendocarbin H (8): colorless oil; $[\alpha]_D^{25}$ −55° (*c* 0.04, $CHCl_3$); IR (KBr) ν_{max} 1770 and 1650 cm^{-1}; UV (MeOH) end absorption; ^1H NMR (C_6D_6) δ_H 1.22 and 2.01 (each 1H, m; H_2-

Table 2. ^{13}C NMR Data of Compounds **1**−**16** and **18**[a]

position (solvent)	**1** (CD_3OD)	**2** (C_6D_6)	**3** (C_6D_6)	**4** (C_6D_6)	**5** (CD_3OD)	**6** (CD_3OD)	**7** (CD_3OD)	**8** (C_6D_6)	**9** (C_6D_6)	**10** (C_6D_6)	**11** (C_6D_6)	**12** (C_6D_6)	**13** (C_6D_6)	**14** (C_6D_6)	**15** ($CDCl_3$)	**16** ($CDCl_3$)	**18**[b] ($CDCl_3$)
1	41.3	47.8	36.2	41.1	39.7	41.3	41.8	40.1	34.5	34.8	34.5	34.5	34.4		39.8	35.3	48.6
2	20.1	63.6	19.0	18.0	28.0	19.0	19.5		18.3	18.7	18.5	18.4	18.4		18.5	18.2	64.5
3	44.1	51.1	43.7	41.6	79.3	36.4	44.9	42.2	41.4	41.9	41.5	41.3	41.5		42.4	41.6	51.1
4	34.6	34.2	33.4	32.6	39.8	38.6	34.4	33.0	32.8	33.1	32.6	33.1	33.1	32.9	32.9	33.2	34.5
5	51.4	48.7	58.6	51.2	49.8	43.0	56.4	48.6	50.2	46.5	45.5	46.0	46.0	51.4	49.8	51.5	49.1
6	26.6	23.2	68.6	18.0	24.7	24.6	69.0		25.9	28.0	27.9	28.0	28.0	69.0	23.6	17.8	23.5
7	137.8	120.3	120.5	32.0	140.2	140.5	143.5	142.1	73.2	60.6	59.9	65.1	60.3	61.2	117.1	21.1	136.2
8	130.6	149.9		76.0	131.2	124.4			156.7	128.0	129.4	130.1	129.9	68.2	136.4	127.9	117.1
9	60.4	53.3	61.5	65.0	59.0	59.1	59.1	57.8	140.5	168.2	168.5			60.0	61.5	138.9	61.1
10	36.2	35.5	39.9	37.2	36.4	36.5	39.4	36.0	35.6	37.2	37.8	37.3	37.6	37.0	33.4	36.7	35.0
11			99.4	100.0	175.8					102.4	101.0	97.9	97.9	99.2	99.4	96.8	99.0
12	171.1	69.0	68.6	174.0					94.8	170.7	170.1	171.5	171.7	68.2	68.9	167.8	68.6
13	34.4	32.9	36.9	33.4	28.7	18.4	37.2	33.1	33.1	33.4	32.9	32.9	33.2	35.7	33.1	33.3	33.1
14	22.6	22.2	22.4	21.8	16.0	71.5	22.9	22.5	21.4	21.6	21.3	21.5	21.5	22.4	21.5	21.5	22.4
15	15.6	14.7	15.2	16.4	15.9	16.5	16.9	15.8	19.7	18.0	20.0	21.4	21.4	15.8	14.0	19.6	14.9
OCH_2CH_3									65.0	66.0	65.5						
OCH_2CH_3									15.7	15.3	15.1						

[a] Blank positions are those not observed. [b] Reference 8.

1), 1.01 and 1.36 (each 1H, m; H_2-2), 1.24 (2H, m; H_2-3), 0.85 (1H, m; H-5), 1.65 and 1.70 (each 1H, m; H_2-6), 7.06 (1H, br s; H-7), 3.27 (1H, br s; H-9), 0.67 (3H, s; H_3-13), 0.64 (3H, s; H_3-14), and 0.96 (3H, s; H_3-15); FABMS *m/z* 249 $(M + H)^+$, 221 $(M - CO + H)^+$, and 203 $(M - CO - H_2O + H)^+$; HRFABMS *m/z* 249.1480 [calcd for $C_{15}H_{21}O_3$, (M + H) 249.1491].

Dendocarbin I (9): colorless oil; $[\alpha]_D^{25}$ −47° (*c* 0.02, $CHCl_3$); IR (KBr) ν_{max} 3460 and 1690 cm^{-1}; UV (MeOH) end absorption; ^1H NMR (C_6D_6) δ_H 1.05 and 2.73 (each 1H, m; H_2-1), 1.33 and 1.36 (each 1H, m; H_2-2), 0.95 and 1.21 (each 1H, m; H_2-3), 0.92 (1H, m; H-5), 1.41 (1H, m; H-6α) and 2.00 (1H, dd, *J* = 12.2 and 6.7 Hz; H-6α), 3.98 (1H, dd, *J* = 9.8 and 6.7 Hz; H-7), 5.68 (1H, s; H-12), 0.72 (3H, s; H_3-13), 0.69 (3H, s; H_3-14), 1.10 (3H, s; H_3-15), 3.25 and 3.39 (each 1H, m; OCH_2CH_3), and 1.09 (3H, t, *J* = 7.0 Hz; OCH_2CH_3); FABMS *m/z* 589 $(2M + H)^+$, 295 $(M + H)^+$, and 277 $(M - H_2O + H)^+$; HRFABMS *m/z* 295.1906 [calcd for $C_{17}H_{27}O_4$, (M + H) 295.1910].

Dendocarbin J (10): colorless oil; $[\alpha]_D^{25}$ +17° (*c* 0.06, $CHCl_3$); IR (KBr) ν_{max} 3460, 1750, and 1650 cm^{-1}; UV (MeOH) end absorption; ^1H NMR (C_6D_6) δ_H 1.50 (2H, m; H_2-1), 1.25 and 1.27 (each 1H, m; H_2-2), 1.27 (2H, m; H_2-3), 1.36 (1H, m; H-5), 1.36 and 1.67 (each 1H, m; H_2-6), 4.27 (1H, br d, *J* = 4.6 Hz; H-7), 5.34 (1H, s; H-11), 0.83 (3H, s; H_3-13), 0.69 (3H, s; H_3-14), 0.99 (3H, s; H_3-15), 3.20 and 3.60 (each 1H, m; OCH_2-CH_3), and 0.94 (3H, t, *J* = 7.0 Hz; OCH_2CH_3); FABMS *m/z* 589 $(2M + H)^+$, 295 $(M + H)^+$, and 277 $(M - H_2O + H)^+$; HRFABMS *m/z* 295. 1898 [calcd for $C_{17}H_{27}O_4$, (M + H) 295.1909].

Dendocarbin K (11): colorless oil; $[\alpha]_D^{25}$ −57° (*c* 0.04, $CHCl_3$); IR (KBr) ν_{max} 3420, 1750, and 1650 cm^{-1}; UV (MeOH) λ_{max} 216 (ε 9000) nm; ^1H NMR (C_6D_6) δ_H 1.48 (2H, m; H_2-1), 1.31 (2H, m; H_2-2), 1.02 (1H, dd, *J* = 13.0 and 4.2 Hz; H-3), 1.24 (1H, m; H-3), 1.57 (1H, dd, *J* = 13.0 and 2.0 Hz; H-5), 1.22 (1H, m; H-6), 1.70 (1H, br d, *J* = 14.3 Hz; H-6), 4.29 (1H, br d, *J* = 4.9 Hz; H-7), 5.37 (1H, d, *J* = 1.5 Hz; H-11), 0.83 (3H, s; H_3-13), 0.67 (3H, s; H_3-14), 0.64 (3H, s; H_3-15), 3.27 and 3.61 (each 1H, m; OCH_2CH_3), and 0.96 (3H, t, *J* = 7.0 Hz; OCH_2CH_3); FABMS *m/z* 589 $(2M + H)^+$, 295 $(M + H)^+$, and 277 $(M - H_2O + H)^+$; HRFABMS *m/z* 295. 1917 [calcd for $C_{17}H_{27}O_4$, (M + H) 295.1909].

Dendocarbins L (12) and M (13) (a 2:5 mixture): colorless oil; $[\alpha]_D^{25}$ +10° (*c* 0.14, $CHCl_3$); IR (KBr) λ_{max} 3420, 1750, and 1690 cm^{-1}; UV (MeOH) λ_{max} 210 (ε 13 000) nm; FABMS *m/z* 267 $(M + H)^+$; HRFABMS *m/z* 267.1574 [calcd for $C_{15}H_{23}O_4$, (M + H) 267.1596]. For **12**: ^1H NMR (C_6D_6) δ_H 1.67 (2H, m; H_2-1), 1.46 (2H, m; H_2-2), 1.21 (2H, m; H_2-3), 1.45 (1H, m; H-5), 1.59 (1H, m; H-6), 2.00 (1H, dd, *J* = 13.5 and 7.0 Hz; H-6), 4.31 (1H, br s; H-7), 5.73 (1H, s; H-11), 0.71 (3H, s; H_3-13), 0.68 (3H, s; H_3-14), and 0.71 (3H, s; H_3-15). For **13**: ^1H NMR (C_6D_6) δ_H 1.67 (2H, m; H_2-1), 1.46 (2H, m; H_2-2), 1.31 (2H, m; H_2-3), 1.45 (1H, m; H-5), 1.42 (1H, m; H-6), 1.75 (1H, d, *J* = 12.4 Hz; H-6), 4.40 (1H, s; H-7), 5.83 (1H, s; H-11), 0.93 (3H, s; H_3-13), 0.68 (3H, s; H_3-14), and 0.71 (3H, s; H_3-15).

Acetylation of 12 and 13. A solution of a 2:5 mixture of **12** and **13** (0.6 mg) in acetic anhydride (0.2 mL) was added to pyridine (0.1 mL). The reaction mixture was stirred at room temperature for 17 h, and evaporation of an excess of the reagent gave an oily product, a mixture of **20** and **21**. For **20**: ^1H NMR (CD_3OD) δ_H 5.61 (1H, dd, *J* = 2.8 and 1.8 Hz; H-7) and 7.02 (1H, d, *J* = 2.0 Hz; H-11). For **21**: ^1H NMR (CD_3OD) δ_H 5.69 (1H, dd, *J* = 4.0 and 2.5 Hz; H-7) and 7.08 (1H, s; H-11).

Dendocarbin N (14): colorless oil; $[\alpha]_D^{25}$ −40° (*c* 0.03, $CHCl_3$); IR (KBr) ν_{max} 3450 and 2930 cm^{-1}; ^1H NMR (C_6D_6) δ_H 0.67 (1H, d, *J* = 10.0 Hz; H-5), 3.73 (1H, m; H-6), 1.01 (1H, br d, *J* = 9.1 Hz; OH-6), 2.96 (1H, d, *J* = 3.3 Hz; H-7), 1.79 (1H, br s; H-9), 4.96 (1H, br s; H-11), 1.78 (1H, br s; OH-11), 3.49 and 4.18 (each 1H, d, *J* = 10 Hz; H_2-12), 1.11 (3H, s; H_3-13), 0.93 (3H, s; H_3-14), and 0.59 (3H, s; H_3-15); EIMS *m/z* 250 $(M - H_2O)^+$, 222 $(M - CO - H_2O)^+$, 204 $(M - CO - 2H_2O)^+$, and 189 $(M - CO - CH_3 - 2H_2O)^+$; HREIMS *m/z* 250.1574 [calcd for $C_{15}H_{22}O_3$, $(M - H_2O)$ 250.1569] and *m/z* 232.1452 [calcd for $C_{15}H_{20}O_2$, $(M - 2H_2O)$ 232.1464].

Isodrimeninol (15): colorless oil; $[\alpha]_D^{25}$ −12° (*c* 0.68, $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 1.24 (1H, m; H-1), 1.74 (1H, dd, *J* = 13.2 and 2.0 Hz; H-1), 1.44 and 1.55 (each 1H, m; H_2-2), 1.20 and 1.44 (each 1H, m; H_2-3), 1.27 (1H, m; H-5), 1.87 (1H, m; H-6), 2.09 (1H, br s; H-6), 5.48 (1H, s; H-7), 2.15 (1H, m; H-9), 5.24 (1H, d, *J* = 3.7 Hz; H-11), 3.20 (1H, br s; OH-11), 4.14 and 4.44 (each 1H, d, *J* = 11.5 Hz; H_2-12), 0.85 (3H, s; H_3-13), 0.89 (3H, s; H_3-14), and 0.78 (3H, s; H_3-15); EIMS *m/z* 236 (M^+), 221 $(M - CH_3)^+$, and 207 $(M - 2CH_3 + H)^+$; FABMS *m/z* 219 $(M - H_2O + H)^+$. These spectral data were identical with those reported in the literature.[6]

11-Epivaldiviolide (16): colorless oil; $[\alpha]_D^{25}$ +11° (*c* 0.07, $CHCl_3$); ^1H NMR ($CDCl_3$) δ_H 1.32 and 1.88 (each 1H, m; H_2-1), 1.60 (2H, m; H_2-2), 1.20 and 1.50 (each 1H, m; H_2-3), 1.08 (1H, m; H-5), 1.80 (2H, m; H_2-6), 2.13 and 2.38 (each 1H, m; H_2-7), 6.03 (1H, s; H-11), 0.90 (3H, s; H_3-13), 0.89 (3H, s; H_3-14), and 1.23 (3H, s; H_3-15); EIMS *m/z* 250 (M^+), 232 $(M - H_2O)^+$, and 217 $(M - H_2O - CH_3)^+$; FABMS *m/z* 501 $(2M + H)^+$, 251 $(M + H)^+$, and 233 $(M - H_2O + H)^+$. These spectral data were identical with those reported in the literature.[7]

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References and Notes

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