Longithorols A and B, Novel Prenylated Paracyclophane- and Metacyclophane-Type Hydroquinones from the Tunicate *Aplidium longithorax*

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The tunicate *Aplidium longithorax* collected from Palau contained two novel prenylated paracyclophane- and metacyclophane-type hydroquinones, longithorols A (**1**) and B (**2**), in addition to longithorones A−I. Longithorols A and B were very unstable and were therefore isolated as their more stable pentaacetate forms, **3** and **4**, respectively. The structures of **3** and **4** were determined by spectral data, especially 2D NMR data.

Tunicates have proved to be a rich source of a broad spectrum of natural products with fascinating structures and intriguing biological activities.[1,2] In our continuing search for new and biologically active compounds from marine organisms,[3] we have studied the tunicate *Aplidium longithorax* (Monniot) (family Polyclinidae) and isolated nine unique cyclo-farnesylated quinones, longithorones A−I.[4] Recently, two more members of this class of compounds have been reported from this ascidian.[5] During isolation of longithorone A−I we became aware of the presence of some hydroquinones in the more polar fractions obtained from Si gel chromatography of the CH_2Cl_2-soluble fraction from solvent partitioning. However, isolation and purification of these hydroquinones were hampered because of their rapid decomposition. This problem was solved by acetylating the hydroquinone mixture and chromatographing the resultant esters on a Si gel open column to give pure longithorol A and B pentaacetates **3** and **4**, respectively.[6] We report here the structure elucidation of these two esters.

Longithorol A pentaacetate (**3**) was obtained as an amorphous solid, $[\alpha]_D$ +114.3° (*c* 2.0, MeOH). A matrix-assisted laser desorption ionization−time-of-flight (MALDI−TOF) mass spectrum,[7] which was recorded under the reflector mode and calibrated with internal standard angiotensin, revealed an ion at *m*/*z* 885 corresponding to $[M + Na]^+$. The broad band ^{13}C NMR spectrum of **3** exhibited 52 resolved signals composed of 9 methyls, 11 methylenes, 13 methines, and 19 quaternary carbons according to DEPT and HMQC experiments. The NMR data combined with the mass spectral data supported a molecular formula of $C_{52}H_{62}O_{11}$ for **3**. The IR spectrum of **3** had absorptions at 1764, 1740, and 1714 cm^{-1} consistent with the presence of acetates and an aldehyde group. In support of this, the ^1H and ^{13}C NMR spectra of **3** revealed signals for five acetyl groups (Table 1), a downfield proton singlet at δ 9.69, and a ^{13}C signal at δ 208.9 for an aldehyde.

The NMR data of **3**, which was unambiguously assigned by COSY, RCT−COSY, HMQC, and HMBC experiments, revealed striking similarities to that of longithorone E,[4b] but the former lacked signals for two substituted 1,4-benzoquinones and instead had resonances corresponding to two substituted 1,4-hydroquinones (see signals for H/C-16 to -21 and -16′ to -21′ in Table 1). Also, the methylene group corresponding to C-1 of longithorone E was changed to an acetoxymethine in **3** ($\delta_{H/C}$ 6.61/67.1). Aromatic ring A was assigned para substitution based on the two one-proton singlets at δ 7.06 and 7.24, and aromatic ring B was assigned meta substitution judging from two coupled proton doublets (J = 2.2 Hz) at δ 6.73 and 6.79.

Coupling of H-1/H-2 was evident from the COSY spectrum, and detailed analysis of COSY, RCT−COSY, NOESY, and HMQC data revealed that the remaining isolated spin systems in **3** were the same as in longithorones E−G.[4b] Linkage of the fragments to give structure **3** was achieved by interpretation of HMBC and NOESY data (Table 1) and also by application of biogenetic principles. NOESY correlations between the aldehyde proton at δ 9.69 and H-4β provided evidence for a cis orientation of the aldehyde group and the C-4 methylene group. This NOE also supported the location of the aldehyde group, even though no HMBC correlation was observed for the aldehyde proton. No HMBC correlations were observed to provide direct evidence for connecting C-4′ to C-3′ to close the second macrocyclic ring, but this connection was deduced by a process of elimination and was substantiated by NOESY correlations between H-1′α (δ 2.42) and H-4′a (δ 1.87). The double bonds were assigned as 2*E*, 10*Z*, and 6′*E* according to the chemical shifts for C-13 (δ 16.3), C-15 (δ 27.5), C-14′ (δ 15.4), and also NOE data (Table 1). The orientation of the para-disubstituted hydroquinone ring (A) was assigned as in longithorone E, whose stereochemistry has been determined by X-ray analysis,[4b] because similar NOE cross-peaks were observed in the NOESY spectra of compound **3** and longithorone E:[4b] most importantly H-2/H-18 and H-4β, H-13/H-5, H-21/H-12α. The C-19′ to C-21′ edge of the meta-substituted aromatic ring must be oriented syn to the isopropenyl group at C-10′, as there are clear NOEs between H-21′ and H-15′, H-12′a. The relative configuration of H-2′ could not be determined from NOE data because of overlap of signals (e.g., H-2′ and H-4α; H-14β and H-1′β). The β configuration was assigned to the OAc at C-1 (1*S**) based on a NOESY correlation between H-1 and H-13 (but not between H-1 and H-2 or H-18). Thus, longithorol A pentaacetate was assigned structure **3**, with the configurations at C-2′ and C-10′ and the orientation of ring B left unresolved. Longithorol A is assigned structure **1** with the same stereochemical ambiguities.

Longithorol B pentaacetate (**4**) was obtained as an amorphous powder, $[\alpha]_D$ +20.3° (*c* 1.8, MeOH). The molecular formula deduced from MALDI−TOF MS [*m*/*z* 885 $(M + Na)^+$][7] and NMR data (Table 2) was $C_{52}H_{62}O_{11}$, the same as that of compound **3**, suggesting that these compounds

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Table 1. NMR Data for Compound **3**[a]

position	^{13}C (mult.)[b]	^{1}H (mult., *J* in Hz)[c]	HMBC (C no.)	NOE correlations[d]
1	67.1 (d)	6.61 (d, 10.0)	2, 3, 18, 19, 20	13
2	129.0 (d)	5.18 (d, 10.0)	4, 13	18, 6, 4*β*
(13)	135.5 (s)			
4α	39.9 (t)	2.17 (m)	2, 3, 5	5, 13
4*β*		1.58 (m)	2, 3, 5, 13	2, 13′
5	37.4 (d)	2.26 (m)		6, 13
6	119.2 (d)	4.58 (br s)	3′, 8, 14	2, 4*β*, 5, 8, 9a, 9b, 13
7	137.6 (s)			
8	36.7 (t)	1.70 (m)		6, 10
9a[e]	24.6 (t)	1.40 (m)		6, 21
9b[e]		1.22 (m)		6
10	126.6 (d)	5.03 (m)		8, 15
11	131.5 (s)			
12α	36.8 (t)	3.21 (br d, 17.2)	10, 11, 16, 17	15, 21
12*β*		3.33 (d, 17.2)	10, 11, 15, 16, 17	15
13	16.3 (q)	1.76 (s)	2, 3, 4	1, 4α, 5, 6
14α	39.1 (t)	2.29 (m)		
14*β*		2.05 (m)		13′
15	27.5 (q)	1.83 (s)	10, 11, 12	10, 12α, 12*β*
16	133.7 (s)			
17	148.0 (s)			
18	120.9 (d)	7.24 (s)	1, 16, 17, 20	2
19	132.8 (s)			
20	143.6 (s)			
21	126.3 (d)	7.06 (s)	12, 17, 19, 20	12α, 9a
1′α	31.6 (t)	2.42 (m)	3′, 17′, 18′, 19′	4′a
1′*β*		2.04 (m)		19′
2′	44.4 (d)	2.16 (m)		5′b, 19′
3′	53.1 (s)			
4′a	25.8 (t)	1.87 (m)		6′, 1′α
4′b		1.72 (m)		6′
5′a	19.9 (t)	1.46 (m)		
5′b		0.90 (m)		2′
6′	126.0 (d)	5.00 (br d, 7.2)	4′, 8′, 14′	10′, 8′α, 4′a, 4′b, 5′a, 5′b
7′	133.9 (s)			
8′α	40.7 (t)	2.08 (m)	6′, 7′, 9′, 14′	6′, 10′
8′*β*		2.20 (m)		14′
9′α	31.1 (t)	1.87 (m)		10′, 12′a
9′*β*		1.98 (m)	8′	14′, 12′a, 21′
10′	45.6 (d)	3.39 (d, 10.8)	8′, 9′, 11′, 12′, 16′ 17′, 21′	8′α, 9′α, 15′, 6′, 12′a
11′	149.5 (s)			
12′a	109.8 (t)	4.83 (br s)	10′, 15′	21′, 10′, 9′α, 9′*β*
12′b		4.75 (br s)	10′, 15′	15′
13′	208.7 (d)	9.69 (s)		4*β*, 14*β*, 2′
14′	15.4 (q)	0.96 (s)	6′, 7′, 8′	8′*β*, 9′*β*, 21′
15′	22.4 (q)	1.56 (s)	10′, 11′, 12′	12′b, 21′, 10′
16′	138.4 (s)			
17′	143.0 (s)			
18′	136.6 (s)			
19′	120.8 (d)	6.73 (d, 2.2)	1′, 17′, 20′, 21′	1′*β*, 2′
20′	148.7 (s)			
21′	119.4 (d)	6.79 (d, 2.2)	10′, 17′, 19′, 20′	12′a, 9′*β*, 14′, 15′
acetates[f]				

[a] Spectra were recorded in CD_2Cl_2. [b] ^{13}C NMR at 125 MHz, referenced to CD_2Cl_2 (δ 53.8), multiplicities inferred from a DEPT experiment. [c] ^{1}H NMR at 500 MHz, referenced to residual solvent CD_2Cl_2 (δ 5.32). [d] NOE interactions between the protons at the same carbon are not reported. [e] The letters a and b designate different protons when the relative stereochemistry could not be assigned. [f] Signals for the acetate carbonyls and methyls, not assigned: δ_H 2.07 (s), 2.25 (s), 2.28 (s), 2.34 (s), 2.45 (s); δ_C 170.2 (s), 169.6 (s), 169.5 (s), 169.3 (s), 169.0 (s), 21.3 (q), 21.2 (q), 20.99 (q), 21.01 (q), 20.9 (q).

are stereoisomers. The IR spectrum of **4** was essentially the same as that of **3**. The NMR data (Table 2) of **4** matched closely the data for **3** with slight differences in the chemical shifts of ^{1}H and ^{13}C signals surrounding the cyclohexene ring.

Interpretation of the COSY, RCT−COSY, HMQC, and HMBC spectra of **4** established that the gross structure of compound **4** was identical to that of **3**. HMBC correlations between C-3′ and H-13′ and H-4′b confirmed the connection between C-3′ and C-4′ and between C-3′ and C-13′, though these correlations were not observed in the HMBC spectrum of **3**. NOE data indicated that the para-disubstituted hydroquinone ring was oriented as in **3** and that the OAc group at C-1 was *β* (1*S**) (Table 1). Unequivocal NOE correlations were observed between H-13′ and H-4*β* just as for **3**, and hence the aldehyde group and the C-4 methylene group are assigned a cis configuration. Overlap of crucial signals (H-4α/H-14*β*; H-1′a/H-2′) precluded definitive assignment of the H-2′/CHO relative configuration on the basis of NOESY data. The cis arrangement of C-13 and C-1 was confirmed by NOE data (H-13/H-1). The C-19′ to C-21′ edge of aromatic ring B was assigned a syn relationship with the C-10′ isopropenyl group (NOE correlations between H-21′ and H-15′, H-12a′). Because the ^{13}C NMR chemical shifts of the carbons of the cyclohexene ring are virtually identical in the spectra of **4** and lon-

Table 2. NMR Data for Compound **4**[a]

position	^{13}C (mult.)[b]	^{1}H (mult., *J* in Hz)[c]	HMBC (C no.)	NOE correlations[d]
1	67.2 (d)	6.65 (d, 10.1)	2, 3, 18, 19, 20	13
2	129.6 (d)	5.21 (d, 10.1)	4, 13	4*β*, 6, 18
3	135.1 (s)			
4α	40.4 (t)	2.50 (m)	2, 3, 5, 6	5, 13
4*β*		1.86 (m)	5, 6, 13	2, 6, 13′
5	38.4 (d)	2.18 (m)	4, 6, 3′	4α, 13, 1′α
6	119.6 (d)	4.50 (br s)	5, 8, 14, 3′	2, 4*β*, 5, 9a, 9b
7	137.2 (s)			
8a[e]	37.3 (t)	1.68 (m)		
8b[e]		1.58 (m)		
9a	24.7 (t)	1.32 (m)	10	6, 21
9b		1.16 (m)	10	6, 10
10	126.5 (d)	5.01 (m)		9b, 15
11	131.4 (s)			
12*β*	36.8 (t)	3.34 (d, 17.2)	10, 11, 15, 16, 17, 21	15
12α		3.23 (br d, 17.2)	10, 11, 16, 17, 21	15, 21
13	16.2 (q)	1.95 (s)	2, 3, 4	1, 4α, 5
14*β*	37.8 (t)	2.50 (m)		13′
14α		1.90 (m)	6, 7, 8, 1′, 3′	
15	27.5 (q)	1.82 (s)	10, 11, 12	10, 12α, 12*β*
16	133.7 (s)			
17	148.0 (s)			
18	120.8 (d)	7.27 (s)	1, 16, 17, 20	2
19	132.7 (s)			
20	143.6 (s)			
21	126.2 (d)	7.09 (s)	12, 17, 19. 20	12α, 9α
1′a	32.6 (t)	2.36 (m)	2′, 17′, 19′	5, 5′b, 19′
1′b		2.01 (m)	2′	19′
2′	39.4 (d)	2.36 (m)	5, 7	4′b, 13′
3′	52.9 (s)			
4′a	30.6 (t)	2.19 (m)		6′, 13′
4′b		1.35 (m)	3′	2′, 6′
5′a	20.9 (t)	1.53 (m)		6′, 14′
5′b		1.05 (m)		1′a, 14′
6′	126.4 (d)	4.92 (br d, 7.9)	4′, 8′, 14′	4′a, 4′b, 5′a, 8′b
7′	133.9 (s)			
8′a	40.6 (t)	2.23 (m)	10′	14′
8′b		2.07 (m)	9′, 14′	6′, 10′
9′a	31.3 (t)	1.96 (m)		12′a, 14′, 21′
9′b		1.90 (m)		10′
10′	45.8 (d)	3.33 (d, 10.1)	9′, 11′, 12′, 15′, 16′, 17′, 21′	8′b, 9′b, 12′a, 15′
11′	149.3 (s)			
12′a	110.0 (t)	4.86 (br s)	10′, 15′	9′a, 10′, 21′
12′b		4.79 (br s)	10′, 15′	15′
13′	205.9 (d)	9.50 (s)	3′	4*β*, 14*β*, 2′, 4′a
14′	15.2 (q)	0.91 (s)	6′, 7′, 8′	5′a, 5′b, 8′a, 9′a, 21′
15′	22.5 (q)	1.56 (s)	10′, 11′, 12′	10′, 12′b, 21′
16′	138.1 (s)			
17′	142.8 (s)			
18′	136.1 (s)			
19′	120.8 (d)	6.88 (d, 2.9)	1′, 17′, 20′, 21′	1′a, 1′b
20′	148.9 (s)			
21′	119.4 (d)	6.82 (d, 2.9)	10′, 17′, 19′, 20′	9′a, 12′a, 14′, 15′
acetates[f]				

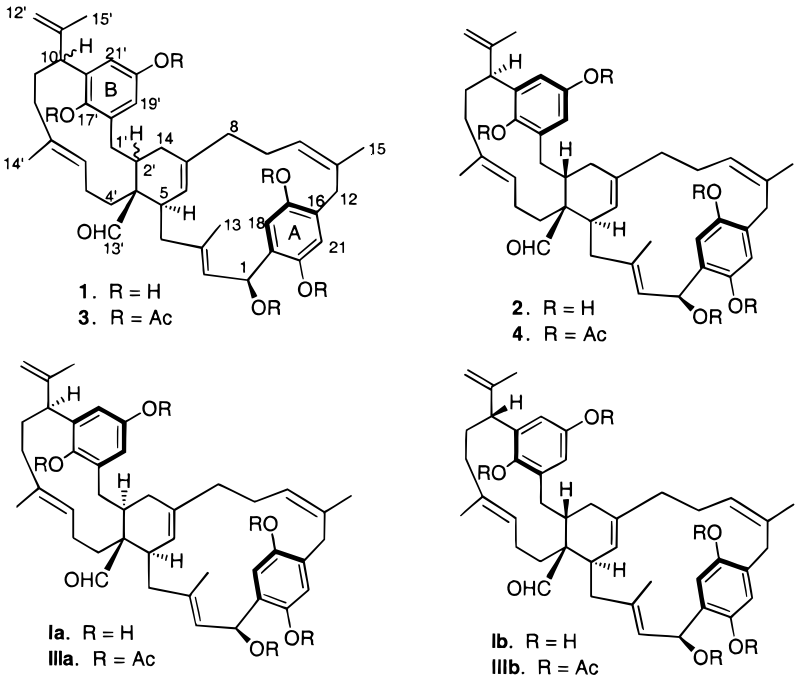
[a] Spectra were recorded in CD_2Cl_2. [b] ^{13}C NMR at 125 MHz, referenced to CD_2Cl_2 (δ 53.8), multiplicities inferred from a DEPT experiment. [c] ^{1}H NMR at 500 MHz, referenced to residual solvent CD_2Cl_2 (δ 5.32). [d] NOE interactions between the protons at the same carbon are not reported. [e] The letters a and b designate different protons when the relative stereochemistry could not be assigned. [f] Signals for the acetate carbonyls and methyls, not assigned: δ_H 2.11 (s), 2.26 (s), 2.28 (s), 2.388 (s), 2.394 (s); δ_C 170.2 (s), 169.6 (s), 169.19 (s), 169.16 (s), 168.9 (s), 21.0 (q, 3C), 21.2 (q), 21.3 (q).

githorone E (configurations established by X-ray), we favor a cis H-2′/C-13′ arrangement for **4** (and **2**) to give the overall relative stereochemistry shown.

We propose that **1** and **3** differ from **2** and **4** either by an inversion of configuration at C-2′ resulting in stereostructure **Ia/IIIa** or by inversion of configuration at C-10′ and also flipping of ring B to keep the isopropenyl group and C-21′ syn to each other giving stereostructure **Ib/IIIb** (Chart 1). We favor stereostructure **Ia/IIIa** because the ^{13}C NMR shifts of C-2′, C-4′, and C-13′ for **3** differ from their counterparts in **4** by +5, −4.8, and +2.8 ppm, respectively, whereas the remainder of the carbon shifts are nearly identical in the two isomers.[8] If the ^{13}C NMR shift differences indeed reflect a cis/trans ring-fusion difference between **4** and **3**, then the ring fusion stereochemical assignments for longithorones F, G, H, and I[4b] are also thrown into doubt. The different ring fusion stereochemistries could arise by Diels−Alder reactions, with precursor α,*β*-unsaturated aldehydes[4] having different double-bond geometries.

A variety of prenylated hydroquinones and quinones have now been isolated from tunicates of the genus *Aplidium*.[4,5,9−12] Of these, members of the longithorone series are the most complex because they possess unique

Chart 1



carbocyclic skeletons derived by cyclization of farnesyl hydroquinone to yield [9] and [10]metacyclophane and [12]-paracyclophane structures.[4,5] Longithorols A (**1**) and B (**2**) represent the first examples of hydroquinones in this structure class.

Experimental Section

General Experimental Procedures. All solvents were redistilled. Merck Si gel 60 (230−240 mesh) was used for vacuum flash chromatography. HPLC was conducted using a UV detector and a Spherex 5 C_{18} column. IR spectra were obtained on a Bio-Rad 3240-SPC FT instrument. NMR experiments were conducted with a Varian VXR-500 instrument equipped with a 3-mm $^1H/^{13}C$ switchable gradient microprobe (MDG-500-3) and a pulsed-field gradient driver; signals are reported in parts per million (δ), referenced to the solvent used. MALDI−TOF MS were recorded using a 2,5-dihydroxybenzoic acid matrix under the reflector mode on a PerSeptive Biosystems Voyages Elite instrument and were calibrated with internal standard angiotensin (1296.685 Da). Specific rotations were measured on a Rudolph Autopol III polarimeter (*c* g/100 mL) at 589 nm.

Animal Material. The tunicate *Aplidium longithorax* (Monniot) was collected in Palau and identified by Dr. F. Monniot, Museum National d'Histoire Naturelle, Paris, France. A voucher specimen (1-PA-94) has been deposited in the University of Oklahoma.

Extraction and Isolation. Freshly thawed specimens of *A. longithorax* (7.9 kg wet wt; 218 g dry wt after extraction) were extracted with MeOH (3 × 10 L), and then with MeOH−CH_2Cl_2 (1:1, 3 × 8 L). All extracts were combined and the solvents evaporated. The residue was dissolved in 10% aqueous MeOH (3 L), and the solution extracted with hexane (3 × 3 L) to yield, after evaporation of solvent, 5 g of hexane extract. The aqueous MeOH solution was diluted with H_2O (ca. 860 mL) to 30% H_2O in MeOH and extracted with CH_2Cl_2 (3 × 1.8 L), to give 10 g of CH_2Cl_2 extract. A portion of this CH_2Cl_2 extract (ca. 3.5 g) was subjected to chromatography over Si gel using increasing amounts of EtOAc in hexane as eluent (40−80% EtOAc in hexane). In all, 24 fractions were collected. The less polar fractions therefrom contained the dimeric prenylated quinones that have been reported previously.[4] The 50% EtOAc in hexane eluate contained longithorols A (**1**) and B (**2**), but we were unable to obtain pure longithorols A and B because they decomposed rapidly. Therefore, the fractions containing longithorols were pooled and subjected to acetylation as described below.

Longithorol A Pentaacetate (3) and Longithorol B Pentaacetate (4). A solution of longithorol-containing residue (210 mg), Ac_2O (1.5 mL), and pyridine (1.5 mL) was kept overnight at room temperature, then the mixture was diluted with iced H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was separated, washed with H_2O, and dried over Na_2SO_4. After evaporation of $CHCl_3$, the residue was chromatographed on Si gel using a step-gradient elution of hexane with increasing amounts of EtOAc (10−60% EtOAc in hexane) to give compounds **3** (30.2 mg) and **4** (21.6 mg).

Longithorol A pentaacetate (3): amorphous solid, $[\alpha]_D$ +114.3° (*c* 2.0, MeOH); IR (film) ν_{max} 1764 (vs), 1740, 1714, 1368, 1232, 1193, 1164, 1011 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; MALDI−TOF MS *m/z* 885 $[M + Na]^+$.

Longithorol B pentaacetate (4): amorphous solid, $[\alpha]_D$ +20.3° (*c* 1.8, MeOH); IR (film) ν_{max} 1766, 1743, 1717, 1370, 1235, 1198, 1164, 1013 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; MALDI−TOF MS *m/z* 885 $[M + Na]^+$.

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(6) Special care (no acidic solutions, keeping the sample in a freezer, low temperature evaporation) had to be taken during the isolation, especially before acetylation. Both longithorols A and B were either easily decomposed into intractable residues or air oxidized to give the corresponding 17′,20′-quinone that was evidenced from ^{1}H NMR data, although the oxidized compounds were not completely characterized. For instance, prominent ^{1}H NMR (CD_2Cl_2) signals could be assigned as follows in the spectrum of the acetylation mixture to 17′,20′-quinone longithorol A diacetate: δ 6.60 (1H, d, J = 9.3 Hz, H-1), 5.17 (1H, d, J = 9.3 Hz, H-2), 4.56 (1H, s, H-6), 5.01 (1H, m, H-10), 3.20 (1H, br d, J = 17 Hz, H-12), 3.32 (1H, d, J = 17 Hz, H-12), 1.77 (3H, s, H-13), 1.82 (3H, s, H-15), 7.24 (1H, s, H-18), 7.05 (1H, s, H-21), 2.76 (1H, dd, J = 13.5, 11.5 Hz, H-1′), 2.05 (1H, m, H-1′), 5.32 (1H, m, H-6′), 3.11 (1H, t, J = 8.2 Hz, H-10′), 4.69 (1H, s, H-12′), 4.59 (1H,s, H-12′), 9.56 (1H, s, H-13′), 1.26 (3H, s, H-14′), 1.65 (3H, s, H-15′), 6.61 (2H, s, H-19′, and −21′), 2.01, 2.27, and 2.34 (all s, 3H each, acetyl methyls).
(7) Neither FABMS nor EIMS of **3** and **4** gave informative ions.
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