Dolabellane Diterpenoids from the South Atlantic Gorgonian *Convexella magelhaenica*

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Two new dolabellane diterpenoids (**1** and **2**) were isolated from a small sample of the deep water gorgonian octocoral *Convexella magelhaenica* collected as a nontarget by-catch by dredging (−93 m) in commercial Patagonian scallop fishing grounds in the South Atlantic. The structures of the new compounds, which are major metabolites in the extract, were established by spectroscopic techniques and chemical transformations. Both compounds were cytotoxic against a human pancreatic adenocarcinoma cell line at micromolar concentrations.

Octocorals have been known to produce a wide array of bioactive terpenoids, with novel and fascinating structures.[1] Shallow water samples from coral reefs are the usual targets of natural product chemists mainly due to their abundance and ease of collection.[2] However, in the past few years, deep water species from less biodiverse environments such as temperate and antarctic seas have also yielded some interesting compounds. A particularly relevant result was the isolation of the alcyopterosins, a family of illudalane sesquiterpenoid nitrate esters from the Antarctic soft coral *Alcyonium paessleri*.[3]

As part of a research program on bioactive secondary metabolites from South Atlantic marine invertebrates, a survey was conducted of the associated epibenthos that form the by-catch of commercial Patagonian scallop fisheries.[4] The associated fauna obtained from these fishing operations is a valuable option to provide access to a marine biodiversity that would be very difficult to collect by other means in the South Atlantic, due to a combination of factors such as great depths, rough weather, and low visibility.

From one associated fauna sample, collected using a nonselective dredge (−93 m) in the commercial Patagonian scallop (*Zygochlamys patagonica*) fishing grounds located along the 100 m isobath in the Argentine Sea, a small amount of the gorgonian *Convexella magelhaenica* was obtained. In spite of the small sample available (15 g of freeze-dried tissue), two new bioactive dolabellane diterpenoids (**1** and **2**) were isolated and fully characterized.

Since the first reported isolation in the marine environment from the mollusk *Dolabella californica,*[5] dolabellane diterpenoids have been extensively found in brown algae, mainly from the family Dictyotaceae.[6,7] These algae were often the dietary sources of the compounds that were isolated from mollusks. Dolabellanes have also been found in sponges and octocorals, mainly from the genera *Eunicea*, *Plexaura*, and *Clavularia*.[6,8−12] Although initially the dolabellane skeleton was thought to be exclusively of marine origin, recent findings show that these compounds are also produced by molds and terrestrial plants.[13−15]

C. magelhaenica (Studer, 1879) is a sea whip that belongs to the family Primnoidae and has an amphiamerican subantarctic distribution, with records in southern Chile and Argentina, as well as the Malvinas Islands, Burdwood Bank, and South Orkney Islands.[16] The family Primnoidae is typical of environments of difficult access, with low water temperatures and strong currents, which probably explains the lack of chemical information on these species. In fact, publications up to date report the isolation of only two furanosesquiterpenoids, *trans*-β-farnesene, and polyoxygenated steroids from the Antarctic gorgonian *Dasystenella acanthina.*[17,18] This study reports the presence of secondary metabolites in the primnoid polyp *C. magelhaenica* and represents the first report of these active compounds in the genus *Convexella*, as well as the second report of terpenoids from Primnoidae gorgonians.

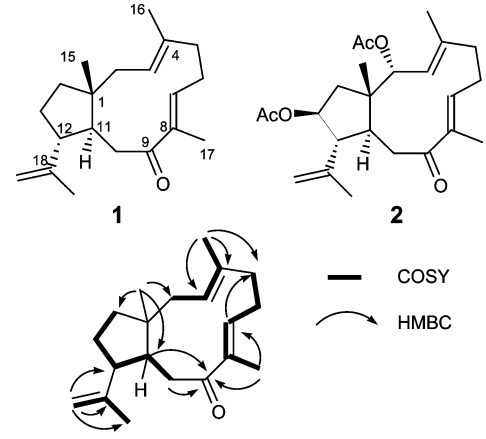

Figure 1. Compounds **1** and **2**. Key COSY and HMBC correlations of **1**.

The extract of *C. magelhaeanica* was fractionated by vacuum flash chromatography on silica gel, using a cyclohexane−EtOAc gradient. Selected fractions were purified by reversed-phase HPLC, yielding compounds **1** and **2** (Figure 1). Compound **1** was by far the major product of the extract and had a molecular formula of $C_{20}H_{30}O$ obtained by HRMS (ESI/APCI), indicating six degrees of unsaturation. The ^{13}C NMR spectrum showed signals corresponding to a conjugated ketone (δ_C 207.5) and three double bonds. These data determined a bicyclic skeleton for the compound. A set of 2D NMR spectra led to the complete elucidation of the structure. An isopropenyl group was readily identified by the presence of an sp^2 methylene (δ_H 4.69 s, 2H; δ_C 111.1), which was correlated in the COSY and HMBC spectra with a double-bond methyl and a methine (δ_H 2.16; δ_C 58.4). The ^1H NMR

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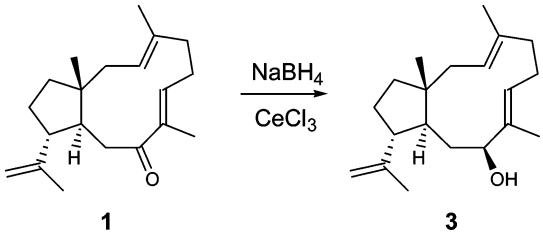

Figure 2. Luche reduction of compound **1**.

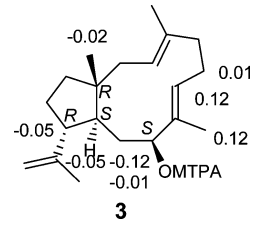

Figure 4. $\Delta\delta$ ($\delta S - \delta R$) values (in ppm) for the MTPA esters of **3**.

spectrum also showed two additional methyls, which were bound to the remaining double bonds, and a singlet methyl (δ_H 1.03) bound to the only quaternary sp^3 carbon of the molecule, which had to be located at the bridgehead. The HSQC spectrum showed that there were only two aliphatic methines in the molecule, the above-mentioned at δ_C 58.4 and another (δ_H 1.69; δ_C 46.1) that was correlated by HMBC to the bridgehead methyl at δ_H 1.03 and was located at the ring juncture. The correlations observed in the COSY and HMBC spectra allowed the closure of a five-membered ring in which the isopropenyl group was vicinal to the ring juncture methine, a typical feature in a dolabellane skeleton. The singlet methyl at δ_H 1.03 showed an additional HMBC correlation to a methylene at δ_C 42.4, which in turn correlated to one of the trisubstituted double bonds that belonged to the remaining ring. From the ring juncture methine at δ_H 1.69, COSY correlations were observed to a pair of deshielded methylene protons at δ_H 2.98 (dd, $J = 13.3$, 3 Hz) and 2.02 (dd, $J = 13.3$, 9 Hz). The large geminal coupling, together with HMBC correlations, indicated that this methylene was vicinal to the conjugated carbonyl group. The vinylic methyl at δ_H 1.65 showed an HMBC cross-peak with the carbonyl, confirming that the corresponding quaternary sp^2 carbon was vicinal to the ketone. A pair of coupled methylenes connected the two double bonds through COSY correlations to both vinylic protons and enabled the closure of an 11-membered ring typical of the dolabellane skeleton. The relative configuration of **1** was analyzed by ROESY correlations, which established a *trans* relationship for the ring juncture and a *cis* relationship for the isopropenyl group at C-12 and the bridgehead methine (H-11). Further examination of the ROESY spectrum revealed cross-peaks of Me-16 with H-2 (δ 2.33), H-3, and H-7, Me-17 with H-6 (δ 2.44), and H-7 with H-10 (δ 2.98), all of which, together with the ^{13}C chemical shifts of Me-16 and Me-17, indicated that the double bonds had an *E* configuration, confirming the structure of a dolabella-3*E*,7*E*,18-trien-9-one.

The determination of the absolute configuration of **1** (either 1*R*,11*S*,12*R* or 1*S*,11*R*,12*S*) was important, as both optical antipodes of dolabellanes had been previously isolated from marine organisms. In order to determine the correct configuration, chemical modifications of the compound had to be performed. The carbonyl group of **1** was reduced with $NaBH_4$−$CeCl_3$ to obtain a secondary alcohol, which could be analyzed by the modified Mosher's method.[19] The reduction proceeded with complete chemo- and stereoselectivity, resulting in only one of the possible diasteromeric alcohols (**3**) and no reduction of the conjugated double bond (Figure 2). Compound **3** was completely characterized by 2D NMR, and the stereochemical relationship of the new hydroxy group at C-9 to the ring system was determined on the basis of NOESY correlations observed for H-9 to H-11 and one of the H-10 protons, while the other H-10 proton correlated to Me-15 (Figure 3). Additional NOESY correlations of H-9 with H-7 and Me-20 were useful in order to determine the relative configuration of C-9. All of these data placed the C-9 hydroxy on the same face as Me-15 and require the absolute configuration of **3** to be either 1*R*,9*S*,11*S*,12*R* or 1*S*,9*R*,11*R*,12*S*. MTPA esters of **3** were prepared, and the $\Delta\delta$ values observed in the ^1H NMR spectra were measured.[20] COSY spectra of both MTPA esters were necessary in order to identify the C-10 and C-11 protons in the corresponding compounds. The $\Delta\delta$ ($\delta S - \delta R$) were negative for both C-10 protons, H-11, H-12, and Me-15. At the same time, Me-17, H-7, and H-6 showed positive $\Delta\delta$ ($\delta S - \delta R$) values (Figure 4). All these data were consistent with a 9*S* configuration and confirmed that the absolute configuration of **3** was indeed 1*R*,9*S*,11*S*,12*R*. Compound **1** was thus determined as the new diterpenoid (1*R*,3*E*,7*E*,11*S*,12*R*)-dolabella-3,7,18-trien-9-one.

A molecular formula $C_{24}H_{34}O_5$ was obtained by HRMS (ESI/APCI) for compound **2**, indicating the presence of eight degrees of unsaturation. The ^{13}C NMR spectrum showed three carbonyls at 204.7, 170.8, and 170.3 ppm, which were assigned to an unsaturated ketone and two esters. In the same spectrum, six vinyl resonances were observable (two methines, a methylene, and three quaternary carbons), which accounted for three unsaturations. Both ester carbonyls were readily assigned as acetates after inspection of the ^1H NMR spectrum, which also showed three double-bond methyls, an additional singlet methyl, and an isopropenyl group, closely resembling compound **1**. In the HMBC spectrum, one of

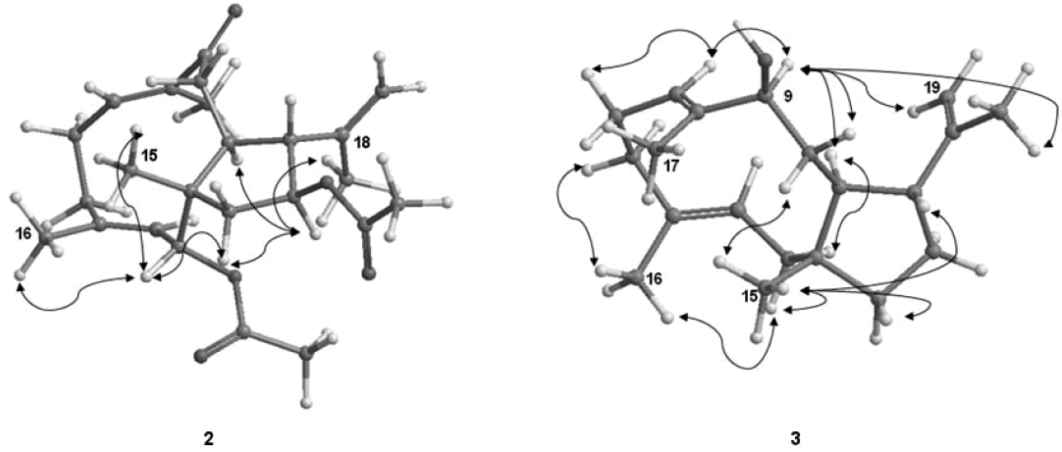

Figure 3. Key NOESY correlations of **2** and **3**.

Table 1. NMR Spectroscopic Data (500 MHz for ^{1}H; 125 MHz for ^{13}C; $CDCl_3$) for Compounds **1**−**3**

	1		**2**		**3**	
position	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)	δ_C, mult.	δ_H (J in Hz)
1	45.2, C		47.2, C		44.2, C	
2	42.4, CH_2	2.24, m	79.3, CH	5.23, d (7.0)	40.3, CH_2	2.09, dd (14.4, 8.6)
		1.75, br d (12.1)				1.80, dd (14.4, 5.6)
3	124.8, CH	5.25, dd (12.1, 2.5)	123.6, CH	4.92, br d (7.0)	123.9, CH	4.92, m
4	135.6, C		136.7, C		133.9, C	
5	39.3, CH_2	2.36, m	38.9, CH_2	2.26, m	38.8, CH_2	2.17, m
		2.26, m				2.13, m
6	24.0, CH_2	2.44, m	24.3, CH_2	2.50, m	24.2, CH_2	2.24, m
		2.24, m		2.30, m		2.19, m
7	141.2, CH	6.02, br d (6.8)	143.0, CH	6.10, ddd (10.0, 4.0, 1.0)	125.3, CH	5.15, t (6.8)
8	134.8, C		136.4, C		138.6, C	
9	207.5, C		204.7, C		76.7, CH	3.89, dd (11.3, 2.4)
10	45.4, CH_2	2.98, dd (13.3, 3.1)	41.6, CH_2	3.12 ddd, (9.0, 7.0, 7.0)	39.6, CH_2	1.76, dd (12.6, 11.3)
		2.02, dd (13.3, 9.0)		2.19, m		1.24, ddd (12.6, 9.7, 2.4)
11	46.1, CH	1.69, ddd (9.7, 9.7, 2.8)	39.7, CH	2.20, m	43.1, CH	1.29, dd (9.7, 9.7)
12	58.3, CH	2.16, m	61.5, CH	2.37, dd (10.0, 10.0)	57.8, CH	2.33, ddd (9.7, 9.7, 7.0)
13	30.6, CH_2	1.60, m	74.0, CH	5.11, ddd (10.0, 10.7, 0.7)	28.5, CH_2	1.62, m
		1.45, m				1.48, m
14	43.3, CH_2	1.61, m	44.5, CH_2	2.10, dd (13.0, 7.0)	41.2, CH_2	1.61, m
		1.45, m		1.44, dd (13.0, 10.0)		1.38, m
15	23.7, CH_3	1.03, s	23.4, CH_3	1.09, s	23.5, CH_3	0.91, s
16	15.3, CH_3	1.57, br s	17.1, CH_3	1.73, br s	15.7, CH_3	1.53, br s
17	12.2, CH_3	1.66, br s	12.2, CH_3	1.75, br s	12.9, CH_3	1.58, br s
18	146.5, C		142.5, C		147.8, C	
19	111.2, CH_2	4.70, br s	114.8, CH_2	4.89, m	111.2, CH_2	4.86, d (2.3)
				4.87, br s		4.71, m
20	20.3, CH_3	1.62, br s	18.6, CH_3	1.72, br s	18.6, CH_3	1.72, br s
AcO-2			170.3, C			
			21.2, CH_3	2.17, s		
AcO-13			170.8, C			
			21.0, CH_3	1.99, s		

the acetate carbonyls was correlated to a methine at δ 5.10. This signal in turn showed a cross-peak in the COSY spectrum with a signal at δ 2.36, which was identified as H-12 due to its HMBC correlations to the isopropenyl group, thus placing one of the acetates at C-13. The other acetate was correlated by HMBC to an oxidized methine (δ_C: 79.3; δ_H: 5.21), which was identified as C-2 by the HMBC correlations to Me-15, C-1, C-3, C-4, and C-11. The stereochemical relationships of the substituents were obtained from a NOESY experiment. A correlation between Me-15 and H-2 indicated a *trans* relationship between Me-15 and the C-2 acetate. Me-15 also correlated to H-12, indicating a *trans* relationship with the isopropenyl group, and to one of the C-14 protons (δ 1.44), while the geminal C-14 proton (δ 2.09) in turn correlated to H-13 (δ 5.10). These correlations indicated that both Me-15 and the acetate at C-13 were located on the same face of the five-membered ring. An additional NOESY correlation between H-13 and H-11 confirmed this relative configuration (Figure 3). Finally, the NOESY correlations of the double-bond methyls, together with their ^{13}C chemical shifts, established *E* geometries for the double bonds. Assuming the same configurations of C-1, C-11, and C-12 as in **1**, compound **2** was identified as the new dollabellane (1*S*,2*R*,3*E*,7*E*, 11*S*,12*R*,13*S*)-2,13-diacetoxydolabella-3,7,18-trien-9-one.

The fact that both compounds are very abundant metabolites in the extract suggests that they may play some ecological role, such as chemical defense, antifeedant, or antifouling effects. Since there are no reports on specific predators of this species, the possible role of compounds **1** and **2** as a stage in the food chain cannot be addressed for the moment. The effect of compounds **1** and **2** on cell growth was assayed on log phase unsynchronized monolayers of two different cell lines: LM3 (murine lung adenocarcinoma cells) and PANC 1 (human ductal pancreatic carcinoma). Both compounds showed selective cytotoxicity toward the pancreatic carcinoma cell line, with compound **1** being the most active. The observed IC_{50} values in the experiments with PANC 1 were 2.5 μM for compound **1** and 17.8 μM for **2**. On the other hand, both compounds were less active toward the murine LM3 cell line, with IC_{50} values of 39.8 μM for **1** and 398.1 μM for **2**.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 343 polarimeter. UV spectra were obtained on a Hewlett-Packard 8453 spectrophotometer, and IR spectra were recorded on a Nicolet Magna 550 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance-2 (500 MHz) spectrometer, using $CDCl_3$ as solvent. Proton chemical shifts were referenced to the residual signal of $CHCl_3$ at δ 7.26 ppm, and ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at 77.0 ppm. All 2D NMR experiments (COSY, HSQC, DEPT-HSQC, HMBC, ROESY, NOESY) were performed using standard pulse sequences. ESI/APCI HRMS experiments were recorded at the UCR Mass Spectrometry Facility, California, on a Micromass Ultima Global QTOF high-resolution mass spectrometer. Vacuum flash chromatography was carried out on TLC grade silica gel (Aldrich Chemical Co). HPLC separations were performed using a Thermo Separations Spectra Series P100 pump, a Thermo Separations Refractomonitor IV RI detector, a Thermo Separations SpectraSeries UV 100 UV detector, HPLC grade solvents, and a YMC RP-18 (5 μm, 10 mm × 250 mm) column. UV detection was performed at 220 nm. TLC was carried out on Merck silica gel 60 F_{254} plates. All other solvents were distilled prior to use.

Biological Material. The pink gorgonian *Convexella magelhaenica* (40 g) was collected by trawling at a depth of 93 m in a Patagonian scallop fishery with coordinates 38°20,31′ S, 55°40,35′ W. The biological material was kept frozen at −20 °C. A voucher specimen was classified by one of us (C.D.P.) and is kept at the cnidarian collection of the Anthozoan Research Group (GPA) at the Academic Center of Vitoria, University of Pernambuco (Brazil), with the number GPA 156.

Extraction and Isolation. Frozen gorgonian tissue was freeze-dried to yield 15 g of dry sample, which was ground and extracted twice with 200 mL of CH_2Cl_2. The solvent was evaporated at low pressure to yield 250 mg of an extract, which by TLC inspection contained two main components, that were detectable by UV light at 254 nm. The extract was subjected to vacuum flash chromatography on silica gel (cyclohexane−EtOAc−MeOH gradient). The fractions that contained

the main components were pooled (60 mg), and the compounds were purified by reversed-phase HPLC using MeOH−H_2O (9:1) as eluent and a flow rate of 2 mL/min to yield compounds **1** (15 mg) and **2** (1 mg).

(1*R*,3*E*,7*E*,11*S*,12*R*)-Dolabella-3,7,18-trien-9-one (1): colorless oil; $[\alpha]^{25}_D$ −23.42 (*c* 7.50, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 248 (3.01) nm; IR (film) ν_{max} 2937, 2864, 1677, 1446, 888 cm^{-1}; ^1H and ^{13}C NMR: see Table 1; ESI-MS *m*/*z* $[M + H]^+$ 287.2370 (calcd for $C_{20}H_{31}O$, 287.2375).

(1*S*,2*R*,3*E*,7*E*,11*S*,12*R*,13*S*)-2,13-Diacetoxydolabella-3,7,18-trien-9-one (2): colorless oil, UV (EtOH) λ_{max} (log ε) 249 (4.12) nm; IR (film) ν_{max} 2935, 2870, 1721, 1687, 1440, 890 cm^{-1}; ^1H and ^{13}C NMR see Table 1; ESI-MS *m*/*z* $[M + Na]^+$ 425.2298 (calcd for $C_{24}H_{34}NaO_5$, 425.2304).

Luche Reduction of Compound 1. To a solution of compound **1** (10.7 mg; 0.0374 mmol) and 13.3 mg of $CeCl_3$ (0.0357 mmol) in 1 mL of MeOH at 0 °C was added 4 mg of $NaBH_4$ (0.102 mmol). The solution was stirred for 1 h, diluted with EtOAc, and washed with H_2O. The organic layer was taken to dryness and purified by preparative TLC (cyclohexane−EtOAc (85:15)) to yield 4.7 mg (44%) of compound **3**.

(1*R*,3*E*,7*E*,9*S*,11*S*,12*R*)-Dolabella-3,7,18-trien-9-ol (3): colorless oil; UV (EtOH) λ_{max} (log ε) 234 (2.95) nm; IR (film) ν_{max} 3550, 2937, 2864, 1650, 1350, 890 cm^{-1}; ^1H and ^{13}C NMR see Table 1; ESI-MS *m*/*z* $[M + Na]^+$ 311.2340 (calcd for $C_{20}H_{32}NaO$, 311.2345).

Preparation of MTPA Esters of Compound 3. To a solution of compound **3** (1.9 mg, 6.6 μmol) in dry pyridine (0.5 mL) was added (*R*)-MTPA-Cl (20 μL, 0.1 mmol). After 30 min at room temperature, the resultant mixture was diluted with EtOAc, extracted three times with 2 M HCl, and then washed with H_2O several times. The organic layer was taken to dryness, and the crude product was purified by TLC using cyclohexane−CH_2Cl_2 (7:3) to yield 0.9 mg of the (*S*)-MTPA ester of **3**. Treatment of **3** (1.8 mg) with (*S*)-MTPA-Cl in a similar way yielded the corresponding (*R*)-MTPA ester of **3** (0.6 mg).

(*S*)-MTPA Ester of 3: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48−7.37 (5H, aromatic H), 5.30 (1H, t, J = 7.6 Hz, H-7), 5.09 (1H, dd, J = 12.0, 2.3 Hz, H-9), 4.94 (1H, dd, J = 8.7, 5.0 Hz, H-3), 4.83 (1H, br s, H-19), 4.78 (1H, br s, H-19), 3.51 (3H, s, O-Me), 2.28 (1H, m, H-12), 2.22 (2H, m, H-6), 1.87 (1H, dd, J = 12.0, 12.0 Hz, H-10), 1.76 (3H, s, Me-20), 1.62 (3H, s, Me-17), 1.54 (3H, s, Me-16), 1.32 (1H, m, H-11), 1.26 (1H, m, H-10), 0.88 (3H, s, Me-15).

(R)-MTPA Ester of 3: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.48−7.37 (5H, aromatic H), 5.17 (1H, t, J = 7.6 Hz, H-7), 5.02 (1H, dd, J = 12.0, 2.3 Hz, H-9), 4.90 (1H, dd, J = 8.7, 5.0 Hz, H-3), 4.85 (1H, br s, H-19), 4.76 (1H, br s, H-19), 3.55 (3H, s, O-Me), 2.33 (1H, m, H-12), 2.21 (2H, m, H-6), 1.88 (1H, dd, J = 12.0, 12.0 Hz, H-10), 1.77 (3H, s, Me-20), 1.53 (3H, s, Me-16), 1.49 (3H, s, Me-17), 1.38 (1H, m, H-10), 1.37 (1H, m, H-11), 0.90 (3H, s, Me-15).

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Supporting Information Available: A full set of 1D and 2D NMR spectra of compounds **1**−**3**. ^1H NMR and COSY spectra of MTPA esters of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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