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Cytotoxic diterpenoids from two lianas from the Suriname rainforest☆

Eba Adou,[a] Russell B. Williams,[a] Jennifer K. Schilling,[a] Stan Malone,[b] Jan Meyer,[b] Jan H. Wisse,[c] Djon Frederik,[d] Delon Koese,[e] Marga C. M. Werkhoven,[f] Carl E. Snipes,[g] Todd L. Werk[g] and David G. I. Kingston[a,*]

[a]*Department of Chemistry, M/C 0212, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA*
[b]*Conservation International Suriname, Kromme Elleboogstraat No. 20, Paramaribo, Suriname*
[c]*Bedrijf Geneesmiddelen Voorziening Suriname, Commissaris Roblesweg 156, Geyersvlijt, Suriname*
[d]*Akisiamaw Village, Suriname*
[e]*Godo Village, Suriname*
[f]*The National Herbarium of Suriname, PO Box 9212, Paramaribo, Suriname*
[g]*Dow AgroSciences, 9330 Zionsville Rd, Indianapolis, IN 46268, USA*

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Abstract—Bioassay-guided fractionation of the MeOH and EtOAc fractions of extracts of two lianas collected in Suriname has led to the isolation of five new diterpenoids, humirianthone **1**, 1-hydroxy-humirianthone **2**, 15*R*-humirianthol **3**, patagonol **4**, and patagonal **5**, and the five known diterpenoids, humirianthol **7**, annonalide **8**, acrenol **9**, icacinol **10**, and the oxidized annonalide **11**. All 10 diterpenoids showed cytotoxic activity against the A2780 human ovarian cancer cell line, and compounds **1**, **3**, **8**, and **9** also showed activity against phytopathogenic fungi.

1. Introduction

Extracts from two lianas were obtained from Suriname through our International Cooperative Biodiversity Group (ICBG) as part of a continuing investigation of plants from Suriname and Madagascar in an effort to isolate potential anticancer agents. One of the lianas, collected in Godo village, Suriname, under the vernacular name loambitatai, was identified as a *Casimirella* sp. (formerly *Humirianthera* sp.) (Icacinaceae) and tentatively identified as *Casimirella ampla* (Miers) R. A. Howard. A second liana was collected in Akisiamaw village, Suriname, under the vernacular name apukutatai. This collection was sterile and could not be positively identified, but it is most probably also a *Casimirella* species. The tuber of a related species is used as food, while that of *C. ampla* is used as a treatment for snakebites.[2,3] A previous study of this species led to the isolation of three diterpenoids.[2] Our studies have yielded five new and five known cytotoxic diterpenoids. This is the first known investigation of the plant for use as potential anticancer compounds.

2. Results and discussion

The MeOH and EtOAc extracts of the apukutatai liana were partitioned between hexane and 60% aq MeOH, and then partitioned between CH_2Cl_2 and 50% aq MeOH. All the fractions were tested for cytotoxicity, while only the CH_2Cl_2 fraction was active. The active fraction was subjected to reversed-phase C-18 column chromatography, followed by reversed-phase HPLC, to produce the five new diterpenoids **1**–**5**, as well as the five known diterpenoids **7**–**11**.

Compound **1** was isolated as a colorless amorphous solid, and HR-FABMS indicated a molecular formula of $C_{20}H_{24}O_6$ (*m*/*z* 361.1641 $[M+1]^+$). Its ^1H NMR spectrum

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☆ See Ref. 1.
* Corresponding author. Tel.: +1 540 231 6570; fax: +1 540 231 3255; e-mail: dkingston@vt.edu

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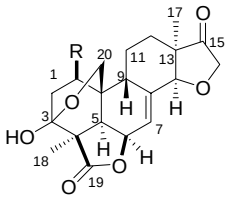
revealed the presence of two methyl groups as singlets at δ 1.00 and δ 1.56 corresponding to the methyl protons on C-17 and C-18, respectively. The spectrum also showed multiplets at δ 1.62, δ 2.22 and 2.25, δ 1.18 and 1.58, and δ 1.32 for C-1, C-2, C-11, and C-12 methylenes, respectively. Also, two doublets of doublets at δ 1.68 (dd, $J = 12.1$, 2.9) and δ 2.34 (dd, $J = 2.6$, 6.9) were observed for the C-9 and C-5 methines, respectively. The spectrum had a pair of doublets at δ 3.68 (d, $J = 3.4$, 5.9) and δ 4.31 (d, $J = 3.4$, 5.9), and also at δ 3.97 (d, $J = 17.2$) and δ 4.53 (d, $J = 17.2$) assigned to the methylene protons on C-20 and C-16, respectively. The spectrum also exhibited a singlet at δ 4.15, a doublet of doublets at δ 4.98 (dd, $J = 2.3$, 4.8), another doublet at δ 6.10 (d, $J = 4.9$), and another singlet at δ 7.02 corresponding to the C-14 and C-6 methines, the C-7 olefinic proton, and the hydroxylic proton on C-3, respectively.



1 R = H
2 R = OH

The ^{13}C NMR spectrum of compound **1** showed the presence of 20 carbons. It had one carbonyl resonance at δ 216.2 assigned as C-15 and one lactone resonance at δ 179.2 assigned as C-19. The carbon resonances at δ 119.2 and δ 144.3 corresponding to C-7 and C-8, respectively, indicated the presence of one double bond. The DEPT spectrum revealed that its carbon skeleton was composed of two methyls, six methylenes, five methines, and seven quaternary carbons. The final structure was elucidated using COSY, HMQC, HMBC, and NOESY correlation spectra. The structure was confirmed by comparing its ^{13}C NMR and 2D NMR data with the published data of the known compound **7**.[2] Both compounds had essentially identical spectra for the A and B rings, and differed significantly only in the resonances of the atoms of the tetrahydrofuran ring D. As indicated above, the resonances of **1**, with a carbonyl resonance at C-15, were consistent with the assigned structure.

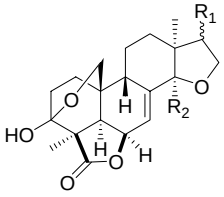
Compound **2** was also a colorless amorphous solid, and HR-FABMS indicated a molecular formula of $C_{20}H_{24}O_7$ (*m/z* 377.1624 $[M+1]^+$). Its ^{1}H NMR spectrum was very similar to that of **1** (Table 1), differing primarily in the resonances for C-1. In compound **1**, the two C-1 protons appeared as two multiplets at δ 1.62 and 1.68, but in **2** the single C-1 proton appeared as a doublet of doublets at δ 4.25. This and other associated changes, including a singlet at δ 6.90 and a doublet at δ 6.87 (d, $J = 4.0$) for hydroxylic protons on C-3 and C-1, indicated that **2** was a 1-hydroxy derivative of **1**. The final structure was confirmed using COSY, HMQC, HMBC, and NOESY correlation spectra. The stereochemistry of the C-1 hydroxyl group was assigned as β based on a NOESY correlation.

Compound **3**, also a colorless amorphous solid, was isolated along with the known compound **7**.[2] It had the same molecular formula as **7** ($C_{20}H_{26}O_6$), and its ^{1}H NMR spectrum (Table 1) was very similar to that of **7**, differing significantly only in the resonances for the

Table 1. ^{1}H and ^{13}C NMR data for compounds **1**–**3** in C_5H_5N

Position	Humirianthone (**1**)		1-Hydroxy-humirianthone (**2**)		15*R*-Humirianthol (**3**)	
	δ H	δ C	δ H	δ C	δ H	δ C
1	1.62 m, 1.68 m	29.2	4.25 dd (1.9, 3.9)	66.6	1.64, 1.71 m	28.5
2	2.22 m, 2.25 m	28.5	2.99 dd (4, 4)	41.5	2. 22 m, 2.25 m	28.2
3		97.2		97.9		97.2
4		50.8		51.2		50.9
5	2.34 dd (2.6, 6.9)	45.1	2.70 dd (2.6, 7)	43.8	2.34 dd (2.9, 12.2)	45.3
6	4.98 dd (2.3, 4.8)	72.5	5.13 dd (2.3, 4.8)	71.8	4.96 dd (4.8, 6.8)	72.6
7	6.10 d (4.9)	119.2	6.16 d (4.6)	119.5	5.96 d (4.8)	116.9
8		144.3		145.1		147.1
9	1.68 dd (12.1, 2.9)	37.1	2.41 dd (2.6, 7)	36.6	1.78 dd (12.2, 2.9)	37.7
10		30.7		30.1		30.8
11	1.18 m, 1.58 m	25.5	1.18 m, 1.58 m	25.7	1.18 m, 1.61 m	25.9
12	1.32 m	29.7	1.32 m	30.2	1.21 m	29.4
13		50.1		50.7		47.2
14	4.15 s	87.8	4.19	87.8	3.9 s	88.1
15		216.2		216.7	4.05 t (8.1), 4.23 t (8.1)	79.4
16	3.97 d (17.2)	70.7	3.96 d (16.95)	72.3	3.68 dd (1.9, 8.9)	72.7
	4.53 d (17.2)		4.47 d (16.95)		4.33 dd (1.9, 8.9)	
17	1.00	14.8	1.03	15.5	1.04 s	19.3
18	1.56	19.2	1.60	19.9	1.55 s	19.4
19		179.2		179.4		179.5
20	3.68 dd (3.4, 5.9)	72.1	4.33 dd (3.4, 5.9)	67.2	3.68 dd (1.9, 8.9)	71.9
	4.31 dd (3.4, 5.9)		4.64 dd (3.4, 8.9)		4.33 dd (1.9, 8.9)	
1-OH			6.90 s, 6.87 d (4.0)			
3-OH	7.02 s		6.90		6.83 s	
15-OH					6.82 d (4)	

tetrahydrofuran ring. Both compounds also had similar ^{13}C NMR spectra, but showed a clear difference in the chemical shifts of C-13–C-17. Thus, the chemical shifts for C-13–C-17 were at δ 50.0, 86.5, 78.8, 76.4, and 15.6 for compound **7**, and δ 47.2, 88.1, 79.4, 72.7, and 19.3 for **3**. These minor differences are only explicable if the compounds differ in stereochemistry at C-15. Since the absolute configuration at carbon C-15 for the known compound **7** was previously determined as *S*,[2] compound **3** must have the *R* configuration at C-15.



3 R_1 = β-OH ; R_2 =H
7 R_1 = α–OH ; R_2 =H
10 R_1 = α–OH ; R_2 =OH

Compound **4** was isolated as a colorless amorphous solid, with the molecular formula of $C_{20}H_{30}O_3$ (*m*/*z* 301.2157 $[M-OH]^+$), as determined by HR-FABMS. Its ^1H NMR spectrum indicated the presence of three methyl groups; two of these, with resonances at δ 0.77 and 1.10, were attached to quaternary carbons, while one (δ 0.85, d, J = 6.4 Hz) was attached to a methine. Resonances at δ 4.01, 4.03 (m), and δ 4.80 (m) appeared to be due to two oxygenated methylenes. Two vinylic proton resonances were also observed. One was at δ 5.55 (m) and the other at δ 7.33 (m), suggesting the presence of an α,β-unsaturated carbonyl. The ^{13}C NMR and DEPT spectra indicated that compound **4** contained three methyl groups, eight methylene groups (including two CH_2O groups at δ 62.8 and 72.1), four methines (including two vinylic groups at δ 122.4 and 147.2), and five quaternary carbons (two vinylic quaternary carbons at δ 135.0 and 148.6, and one lactone at δ 176.9). An examination of the literature indicated that **4** was an analog of patagonic acid (**6**). The ^{13}C NMR data for **4** were thus very similar to those for **6**, differing significantly only at positions C-3 and C-18.[4] These differences could be accounted for by the change from the C-18 COOH group of **6** to the CH_2OH group of **4**. The structure was confirmed as the allylic alcohol analog **4** by its HMQC, HMBC, and COSY correlations, and its relative configuration was confirmed by NOESY correlations (Fig. 1).

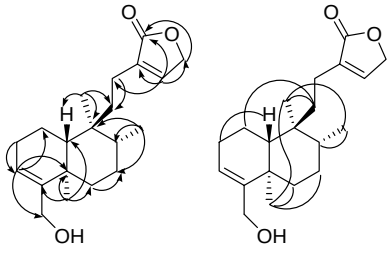
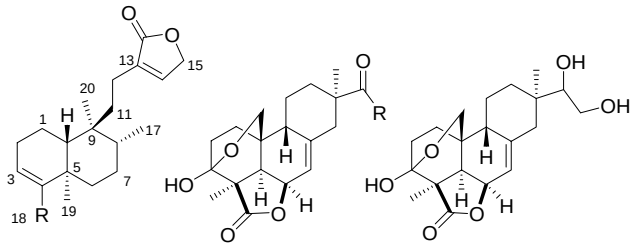


Figure 1. HMBC (left) and NOESY (right) correlations for **4**.

Based on these spectral data, **4** was identified as the new compound neocleroda-3,13-diene-15,16-olide-18-ol, and in keeping with previous nomenclature the trivial name patagonol is proposed.

Compound **5** was isolated as a colorless oil, and the molecular formula $C_{20}H_{28}O_3$ (*m*/*z* 317.2113 $[M+H]^+$) was assigned by HR-FABMS. A comparison of the MS and ^1H and ^{13}C NMR data of **5** to those of **4** indicated that the compounds were very similar, and that the allylic alcohol group found in **4** had been oxidized to an aldehyde (δ 9.31, s; δ 194.2). Since only a limited amount of compound **5** was available, its structure was confirmed by semisynthesis from compound **4**. Oxidation of **4** using Dess-Martin periodinane gave **5**, and the ^1H and ^{13}C NMR spectra of the synthetic product matched those of the isolated compound exactly. The structure of **5** was also confirmed using HMQC, HMBC, and COSY correlations. Thus, compound **5** was determined to be the new compound neocleroda-3,13-diene-15,16-olide-18-al, and the trivial name patagonal is proposed.

Compounds **7**, **8**, **9**, **10**, and **11**, obtained as colorless amorphous solids, were identified as humirianthol (**7**), annonalide (**8**), acrenol (**9**), icacinol (**10**), and the annonalide oxidation product **11**. Compound **11** was previously produced by the oxidation of annonalide, but is isolated here for the first time as a natural product.[5] Compounds **7**, **8**, and **9** were previously isolated from *Humirianthera ampla*, but their biological activities were not reported.[2] The ^1H and ^{13}C NMR spectra and low-resolution mass of the known compounds agreed with the previously reported data. Their structures were also confirmed with 2D NMR (HMQC, HMBC, COSY, and NOESY).



4 R = CH_2OH
5 R = CHO
6 R = CO_2H

8 R = CH_2OH
11 R = OH

9

Compounds **1**, **4**, **5**, **7**, and **8** were also isolated from the Suriname collection of loambitatai, identified most probably as *C. ampla*.

Compounds **1**, **3**, **7**, **8**, **9**, and **10** exhibited cytotoxic activity against the A2780 human ovarian cancer cell line, with IC_{50} values of 6.1, 2.2, 3.0, 3.9, 1.8, and 1.7 μM, respectively. Compounds **2**, **4**, **5**, and **11** were weakly active, with IC_{50} values of 43, 47, 33, and 40 μM, respectively. Compounds **7** and **8** were submitted to the NCI for testing in the 60 cell-line screen. With the exception of **1**, the other compounds were not isolated in sufficiently large quantities for testing. Only after **7**

and **8** were tested was a large enough quantity of **1** isolated. The total growth inhibition (TGI) values for compound **7** (humirianthol) in the 60 cell lines ranged from >100 to 2.5 μM, and the values for compound **8** (annonalide) were between >100 and 4.8 μM. These values were not sufficiently potent or selective to warrant further investigation.

Compounds **1**, **3**, **8**, and **9** were tested for activity against the phytopathogenic fungi *Leptosphaeria nodurum*, *Phytophthora infestans*, *Pyricularia oryzae*, *Septoria tritici*, *Ustilago maydis*, and *Saccharomyces cerevisiae* (Table 3). All four compounds showed moderate to good activity against *P. infestans*, with compound **1** being the most potent. None of the compounds showed significant activity against the other organisms.

3. Experimental section

3.1. General procedures

Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. IR and UV spectra were measured on MIDAC M-series FTIR and Shimadzu UV-1201 spectrophotometers, respectively. The NMR spectra were obtained either on a JEOL Eclipse 500 spectrometer or a Varian Inova 400 spectrometer. The mass spectra were obtained on a JEOL JMS-HX-110 instrument. A flash chromatograph from Biotage Inc. was used for flash chromatography. HPLC was performed on a Shimadzu LC-10AT instrument using a Varian Dynamax C-18 column (250 × 10 mm). C-18 SPE columns were obtained from Supelco.

3.2. Cytotoxicity assays

The A2780 human ovarian cancer cell line cytotoxicity assay was performed at Virginia Polytechnic Institute and State University, as previously reported.[6]

3.3. Fungicidal assays

Cultures of test organisms were maintained on various agar formulations, such as potato dextrose agar or broth; rye seed or rice polish agar depending on the test organism. Assays for growth inhibition of test organisms were conducted using liquid minimal media:

Inoculum was harvested and prepared concurrent with assay plate preparation. Conidia were harvested by flooding a culture plate with assay medium and scraping with a sterile cell lifter. The conidial suspension was then filtered through two layers of sterile cheesecloth and sterile glass wool to remove hyphal fragments that may be present. The conidial suspensions were then adjusted to 3×10^5 conidia/mL for PHYTIN, PYRIOR, LEPTNO, and SEPTTR using a hemocytometer. Conidia concentrations for USTIMA and SACCCE were determined by measuring the optical density at 450 nm using a spectrophotometer and were adjusted to 0.075–0.100 OD_{450}.

Compounds were tested for inhibition of fungal growth (% INH) in 96-well polystyrene microtiter plates. The test compounds were diluted to desired concentrations in DMSO so that all wells received 2.5 μl DMSO. Plates were inoculated by adding 200 μl of the conidial suspension. The incubation times were 1 day for SACCCE

Table 2. ^1H and ^{13}C NMR data for compounds **4** and **5**

Position	Patagonol (**4**)[a]		Patagonal (**5**)[b]	
	δ H	δ C	δ H	δ C
1	1.45[c], 1.71[c]	19.3	1.42[c], 1.74 dd (12.8, 6.7)	17.5
2	2.14 m	27.5	2.38 m, 2.48 m	28.6
3	5.55 m	122.4	6.59 dd (4.4, 2.8)	152.4
4		148.6		151.7
5		38.9		37.6
6	1.35 ddd (12.8, 12.8, 3.9) 1.77 ddd (12.8, 3.1, 3.1)	37.4	1.11 ddd (12.7, 12.7, 4.5) 2.65 ddd (13.3, 3.2, 3.2)	35.2
7	1.43[c] 1.53[c]	28.4	1.45[c] 1.53[c]	27.1
8	1.55[c]	37.6	1.54[c]	36.3
9		39.8		38.7
10	1.44[c]	47.7	1.34 d (11.7)	46.7
11	1.51[c], 1.64 dd (12.7, 4.9)	37.3	1.50[c], 1.66 ddd (13.7, 13.7, 4.7)	36.0
12	2.07 m, 2.19 m	19.9	2.05 m, 2.22 m	19.0
13		135.0		134.9
14	7.33 m	147.2	7.10 dd (3.0, 1.6)	143.5
15	4.80 m	72.1	4.78 dd (3.6, 1.7)	70.2
16		176.9		174.4
17	0.85 d (6.4)	16.3	0.83 d (6.2)	15.9
18	4.01 m, 4.03 m	62.8	9.31 s	194.2
19	1.10 s	21.7	1.16 s	20.1
20	0.77 s	18.6	0.77 s	18.3

[a] Spectra collected in CD_3OD.
[b] Spectra collected in $CDCl_3$.
[c] Resonances were in overlapping regions.

Table 3. In vitro IC_{50} (lowest concentration in μg/mL inhibiting growth by 50% or more) for compounds **1**, **3**, **8**, and **9** against plant pathogens

Fungus	9	3	1	8
LEPTNO	>25	>25	>25	>25
PHYTIN	25	25	0.93	25
PYRIOR	>25	>25	>25	>25
SACCCE	>25	>25	>25	>25
SEPTTR	>25	>25	>25	>25
USTIMA	>25	>25	>25	>25

LEPTNO, *L. nodurum*; PHYTIN, *P. infestans*; PYRIOR, *P. oryzae*; SACCCE, *S. cerevisiae*; SEPTTR, *S. tritici*; USTIMA, *U. maydis*.

and USTIMA, 2 days for LEPTNO, SEPTTR, and PYRIOR, and 3 days for PHYTIN. All plates were evaluated for percent inhibition of fungal growth using a nephlometer (Nephelostar Galaxy, BMG Labtechnologies, Offenburg, Germany).

3.4. Plant material

A liana was collected in Akisiamaw village, Suriname, under the vernacular name apukutatai as collection number CI-944MeMiI10986 in June 2000. A second liana was collected in Godo village, Suriname, under the vernacular name loambitatai, and was identified as a *Casimirella* sp. (formerly *Humirianthera* sp.) (Icacinaceae), and tentatively identified as *C. ampla* (Miers) R.A. Howard. It was given the code CI-2996MeKd11888 and herbarium number CI-1114. The liana had a height of 4 m and a diameter of 2 cm, and was collected near a riverbank on sandy loam. MeOH and EtOAc extracts of dried plant material were prepared at BGVS and shipped to VPISU for bioassay and isolation chemistry. Extracts of CI-944MeMiI10986 were designated BGVS 940412 and extracts of CI-2996MeKd11888 were designated BGVS 220013.

3.5. Extraction and isolation

The MeOH and EtOAc extracts of BGVS 940412 (4 g) were partitioned between hexane and 60% aqueous MeOH, and then followed by partition between CH_2Cl_2 and 50% aqueous MeOH. BGVS 220013 (0.3 g) was treated similarly. All the fractions were evaporated to dryness and tested for their biological activity, and only the CH_2Cl_2 fraction was active. The active fraction was subjected to reversed-phase C-18 column chromatography (MeOH/H_2O, 1/1), followed by reversed-phase HPLC using the same solvent system as mobile phase to produce the three new diterpenoids **1** (15 mg),**2** (1.7 mg), and **3** (1.5 mg), as well as the five known diterpenoids **7** (20 mg), **8** (10 mg), **9** (1.1 mg), **10** (1.2 mg), and **11** (0.8 mg) as colorless amorphous solids. The new compounds **4** and **5** were isolated from the CH_2Cl_2 fraction after partition on a C-18 SPE column. The column was washed with 50% aq MeOH, and the fraction containing **4** and **5** was collected using 100% MeOH. The 100% MeOH fraction was purified by RP-HPLC with 70% aq MeCN to give **4** (5 mg) and **5** (0.9 mg).

3.6. Compound 1

Colorless amorphous solid; $[\alpha]_D^{20}$ −119° (*c* 0.1, $CHCl_3$/MeOH 1/1); IR ν_{max} cm^{-1} 3496 br, 2922, 1761, 1663 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HR-FABMS *m/z* 361.1641 $[M+H]^+$ (calcd for $C_{20}H_{25}O_6$, 361.1651).

3.7. Compound 2

Colorless amorphous solid; $[\alpha]_D^{20}$ −27° (*c* 0.05, $CHCl_3$/MeOH 1/1); IR ν_{max} 3496 br, 1761, 1663 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HR-FABMS *m/z* 377.1624 $[M+H]^+$ (calcd for $C_{20}H_{25}O_7$, 377.1600).

3.8. Compound 3

Colorless amorphous solid; $[\alpha]_D^{20}$ −91° (*c* 0.06, $CHCl_3$/MeOH 1/1); IR ν_{max} cm^{-1} 3550 br, 2940, 1761 cm^{-1}; ^1H and ^{13}C NMR, see Table 1; HR-FABMS *m/z* 363.1824 $[M+H]^+$ (calcd for $C_{20}H_{27}O_6$, 363.1808).

3.9. Patogonol (4)

Colorless amorphous solid; $[\alpha]_D^{26}$ −43° (*c* 0.12, MeOH); UV (EtOH) λ_{max} ($\log\varepsilon$) 216 (3.56) nm; IR ν_{max} 3400 br, 1752 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; HR-FABMS *m/z* 301.2157 $[M-OH]^+$ (calcd for $C_{20}H_{29}O_2$, 301.2168).

3.10. Patogonal (5)

Colorless oil; $[\alpha]_D^{20}$ −41° (*c* 0.087, $CHCl_3$); UV (EtOH) λ_{max} ($\log\varepsilon$) 217 (3.90) nm; IR ν_{max} 1753, 1686 cm^{-1}; ^1H and ^{13}C NMR, see Table 2; HR-FABMS *m/z* 317.2113 $[M + H]^+$ (calcd for $C_{20}H_{29}O_3$, 317.2117).

3.11. Oxidation of patogonol (4)

Compound **4** (2.1 mg) was dissolved in 0.3 mL MeCN and stirred with 3.1 mg (1.1 equiv) of Dess-Martin periodinane for 30 min. The product **5** (1.8 mg) was collected using the SPE method used above. The isolated compound had identical ^1H and ^{13}C NMR spectra to those of the natural product.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2005.07.026.

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