174. New Dolabellane Derivatives from the Brown Alga *Dictyota pardalis*

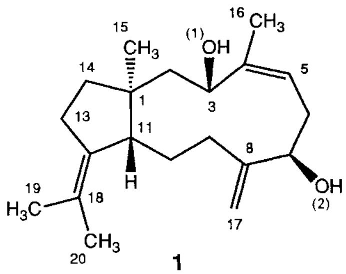
by **Anthony D. Wright**, **Gabriele M. König**, and **Otto Sticher**
Department of Pharmacy, ETH-Zürich, CH-8092 Zürich

and **Paolo Lubini**, **Patrick Hofmann**, and **Max Dobler***
Department of Organic Chemistry, ETH-Zentrum, CH-8092 Zürich

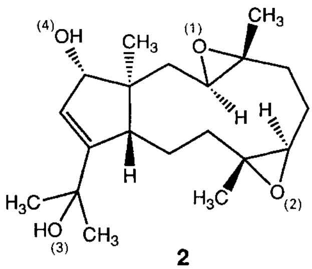
(30.VIII.91)

Reinvestigation of the brown alga *Dictyota pardalis f. pseudohamata* Cribb led to the crystallization of **1** and to the isolation of the two new dolabellane derivatives **2** and **3**. X-Ray analysis of **1** and **2**, together with detailed 1D- and 2D-NMR studies on **2** and **3**, allowed their structures to be elucidated as (1*R**,3*S**,7*S**,11*R**,4*Z*)-dolabella-4,8(17),12(18)-triene-3,7-diol (**1**), (1*R**,3*S**,4*S**,7*S**,8*S**,11*R**,14*R**,12*E*)-3,4:7,8-diepoxydolabell-12-ene-14,18-diol (**2**), and (1*R**,3*S**,4*S**,7*S**,8*S**,11*S**,14*R**)-3,4:7,8-diepoxy-1,4,8,12,12-pentamethylbicyclo[9.3.0]tetradecan-14-ol (**3**).

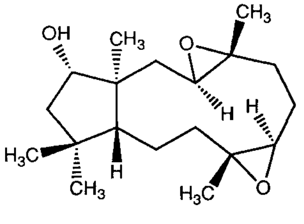
Introduction. – Recently, we reported the isolation and structure elucidation of two new dolabellane derivatives from the brown alga *Dictyota pardalis* [1]. In that report, we were unable to assign the entire configuration of isolate **1** and based part of the configuration of isolate **4** on ^{1}H- and ^{13}C-NMR-data comparisons with previously reported compounds [2] [3]. Prompted by our continuing program of biological testing, we undertook a reinvestigation of *Dictyota pardalis* to obtain further quantities of isolates. As a direct result of this study, we are now able to complete the configurational assignments of **1** and to revise those of **4**. We also report the structures of the two new dolabellane derivatives **2** and **3**.



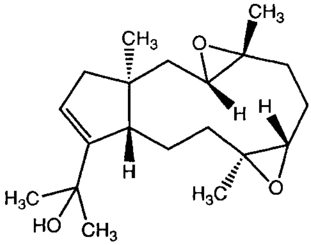
1



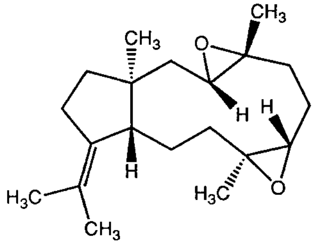
2



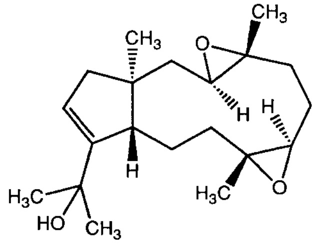
3



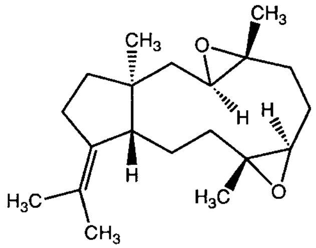
4



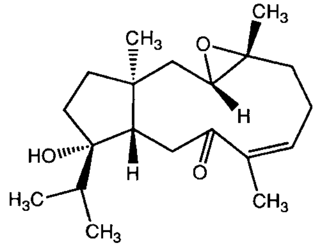
5



6



7



8

Results and Discussion. – *Structure of Compound* **1**. In the course of the current investigation, compound **1** was obtained as a crystalline solid. X-Ray analysis (*Table 1*)

Table 1. *Crystal Data for Compounds* **1** *and* **2**. w = weighted refinement ($1/\sigma^2$).

		1	**2**			**1**	**2**
Formula		$C_{20}H_{32}O_2$	$C_{20}H_{32}O_4$	Reflections	unique	3389	2471
Space group		$P2_1$	$P2_12_12_1$		used ($I > 3\,\sigma(I)$)	2986	–
Crystal system		monoclinic	orthorhombic		used ($I > 2.5\,\sigma(I)$)	–	1051
a	[Å]	8.989(4)	8.122(4)	R factor		0.057	0.060
b	[Å]	13.971(5)	14.022(5)	R_w		0.054	0.052
c	[Å]	15.45(1)	17.439(1)				
β	[°]	104.36(4)	–				
V	[Å^3]	1879.9	1985.9				
Z		4	4				
d_x	[g cm^{-3}]	1.08	1.134				
Θ_{max}	[°]	25	27				

showed that **1** is (1*R**,3*S**,7*S**,11*R**,4*Z*)-dolabella-4,8(17),12(18)-triene-3,7-diol, confirming our original structural assignments and also providing the hitherto unknown configuration at C(3). From the X-ray crystallographic data, it is evident that the asymmetric unit for **1** consists of two molecules **I** and **II** with almost identical conformations. *Fig. 1* depicts the structure of **I** and *Table 2* lists the bond lengths for **I** and **II**. A least-squares fit of **I** and **II** shows a rms deviation of 0.046 Å, with a maximum deviation of 0.2 Å for the $CH_3(20)$ group. The two molecules are connected by two intermolecular H-bonds between the OH groups and are related by a non-crystallographic dyad axis

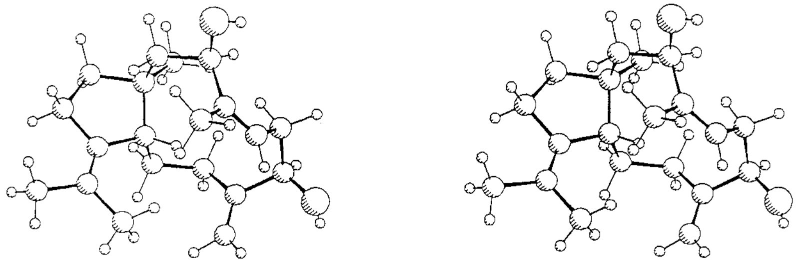


Fig. 1. *Stereoscopic view of molecule* **1** (**I**). The configuration shown is (1*S*,3*R*,7*R*,11*S*,4*Z*).

Table 2. *Bond Lengths in Å* (standard deviations) *for Compounds* **1** *and* **2**

Bond	**1** Molecule **I**	**1** Molecule **II**	**2**	Bond	**1** Molecule **I**	**1** Molecule **II**	**2**
C(1)–C(2)	1.543(6)	1.535(7)	1.55(1)	C(8)–O(2)			1.459(9)
C(1)–C(11)	1.581(7)	1.562(7)	1.57(1)	C(9)–C(10)	1.544(7)	1.520(8)	1.548(9)
C(1)–C(14)	1.562(9)	1.542(9)	1.58(1)	C(10)–C(11)	1.546(6)	1.552(7)	1.563(9)
C(1)–C(15)	1.533(8)	1.547(9)	1.53(1)	C(11)–C(12)	1.514(7)	1.542(8)	1.52(1)
C(2)–C(3)	1.529(7)	1.533(7)	1.50(1)	C(12)–C(13)	1.509(9)	1.517(9)	1.32(1)
C(3)–C(4)	1.531(7)	1.519(7)	1.47(1)	C(12)–C(18)	1.321(9)	1.297(9)	1.53(1)
C(3)–O(1)	1.439(5)	1.427(5)	1.43(1)	C(13)–C(14)	1.535(9)	1.520(9)	1.50(1)
C(3)–H(31)			0.97(5)	C(13)–H(131)			0.95(7)
C(4)–C(5)	1.339(6)	1.330(7)	1.52(1)	C(14)–O(4)			1.43(1)
C(4)–C(16)	1.494(6)	1.517(8)	1.50(1)	C(17)–H(171)	1.07(5)	1.09(5)	
C(4)–O(1)			1.47(1)	C(17)–H(172)	1.03(5)	1.18(6)	
C(5)–C(6)	1.499(6)	1.482(7)	1.55(1)	C(18)–C(19)	1.518(8)	1.512(9)	1.56(1)
C(5)–H(51)	1.06(4)	0.77(4)		C(18)–C(20)	1.498(9)	1.53(1)	1.54(1)
C(6)–C(7)	1.525(6)	1.530(6)	1.51(1)	C(18)–O(3)			1.411(9)
C(7)–C(8)	1.521(8)	1.517(7)	1.47(1)	O(1)–H(1)	0.75(5)	0.80(5)	
C(7)–O(2)	1.421(7)	1.442(7)	1.47(1)	O(2)–H(2)	0.91(5)	0.72(5)	
C(7)–H(71)			1.04(7)	O(3)–H(3)			1.00
C(8)–C(9)	1.532(8)	1.517(8)	1.52(1)	O(4)–H(4)			1.00
C(8)–C(17)	1.308(9)	1.327(8)	1.49(1)				

approximately perpendicular to the plane of the four O-atoms. *Fig. 2* shows the spacing in the crystallographic unit cell. The dimers are connected *via* two further H-bonds, and as a consequence, infinite chains along the *a* axis are formed. The H-bond geometry for **1** is given in *Table 3*. The H-atoms of the OH-groups seem to occur in two alternative orientations. *Table 3* and *Fig. 2* show the data corresponding to the orientation with higher peaks in a difference *Fourier* series and giving better geometry.

As a direct result of finding **1** crystalline, we were encouraged to investigate a further fraction (original VLC fraction 9 [1]) that had also started to crystallize. HPLC separation of this fraction, employing normal-phase silica gel and AcOEt/hexane 3:2 as eluent, afforded the two pure compounds **2** and **3**.

Structure of Compound **2**. Compound **2**, a white crystalline solid of the molecular formula $C_{20}H_{32}O_4$, was quickly recognized, from its ^1H- and ^{13}C-NMR data (*Table 4*), as a 14-hydroxy derivative of **4** [1]. However, it was not possible to assign the configuration at

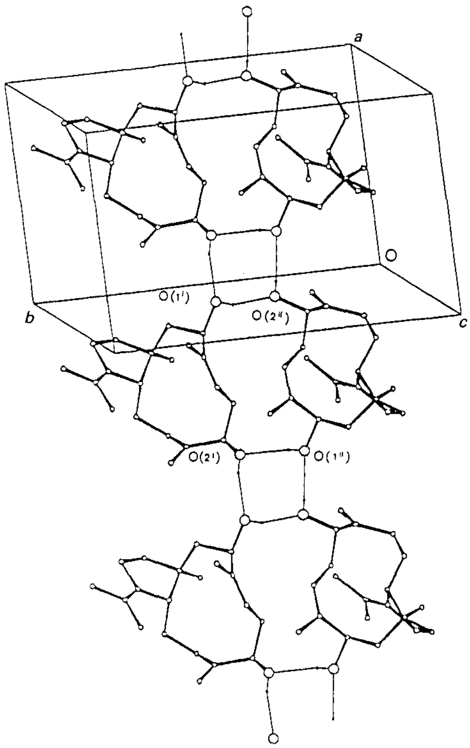


Fig. 2. *Packing of molecules on the unit cell for* **1**. Infinite chains along tha *a* axis are formed through H-bonds connecting the OH-groups.

Table 3. *Intermolecular H-Bond Geometry for* **1**. Distances in Å and angles in degrees.

H-Bond	*d*(O–O)	*d*(O–H)	Angle (O–H–O)	Symmetry operation
$O(1^{I})–H(2^{I})–O(2^{I})$	2.70	1.84	155.2	$x + 1, y, z$
$O(1^{I})–H(1^{I})–O(2^{II})$	2.80	2.07	165.1	–
$O(2^{I})–H(1^{II})–O(1^{II})$	2.79	1.99	169.0	–
$O(2^{II})–H(2^{II})–O(1^{II})$	2.73	2.04	162.3	$x + 1, y, z$

C(14) from these data. Previous investigations of dolabellanes containing the 3,4-epoxy function [1–3] also failed to address their configurations spectroscopically. On the basis of these configurational uncertainties, a single-crystal X-ray crystallographic analysis of **2** was undertaken.

Fig. 3 shows a stereoscopic view of a single molecule of **2** with the relative configurations found from the single-crystal X-ray structure determination. The bond lengths for **2** are listed in *Table 2*. In the direction of the *a*- and *b*-axis, individual molecules are connected by H-bonds, formed by epoxide and OH lone pairs and by the two OH H-atoms. (These interactions may account for the unusual chemical shifts observed for C(14) and C(18) (85.2 (*d*) and 71.7 (*s*) ppm, resp.).) The geometry of the

Table 4. *^{1}H-NMR Data* (300 MHz, CDCl$_3$) *for* **2** *and ^{13}C-NMR Data* (75.5 MHz, CDCl$_3$) *for* **2**, **3**, *and* **6**[a]). δ in ppm, *J* in Hz.

2			**2**	**3**	**6**[a])
		C(1)	46.2 (*s*)	49.8 (*s*)	43.7 (*s*)
CH$_2$(2)	1.20 (*dd*, *J* = 11.3, 13.4), 1.71 (*dd*, *J* = 3.0, 13.4)	C(2)	40.0 (*t*)	40.6 (*t*)	40.7 (*t*)
H–C(3)	3.10 (*dd*, *J* = 3.0, 11.3)	C(3)	63.2 (*d*)	61.8 (*d*)	63.0 (*d*)
		C(4)	61.3 (*s*)	61.3 (*s*)	61.5 (*s*)
CH$_2$(5)	1.36 (*m*), 2.24 (*m*)	C(5)	37.6 (*t*)	37.4 (*t*)	37.4 (*t*)
CH$_2$(6)	1.67 (*m*), 1.98 (*m*)	C(6)	23.5 (*t*)	23.6 (*t*)	23.5 (*t*)
H–C(7)	2.83 (*d*, *J* = 8.6)	C(7)	64.9 (*d*)	64.8 (*d*)	64.9 (*d*)
		C(8)	61.5 (*s*)	61.8 (*s*)	61.7 (*s*)
CH$_2$(9)	1.33 (*m*), 2.03 (*m*)	C(9)	36.2 (*t*)	37.6 (*t*)	36.0 (*t*)
CH$_2$(10)	1.51 (*m*), 2.26 (*m*)	C(10)	29.0 (*t*)	27.1 (*t*)	25.4 (*t*)
H–C(11)	2.60 (br. *d*, *J* = 11.7)	C(11)	47.1 (*d*)	50.4 (*d*)	46.9 (*d*)
		C(12)	161.7 (*s*)	35.0 (*s*)	150.2 (*s*)
H–C(13)	5.62 (*dd*, *J* = 0.8, 3.0)	C(13)	124.7 (*d*)	42.2 (*t*)	125.7 (*d*)
H–C(14)	3.90 (*d*, *J* = 3.0)	C(14)	85.2 (*d*)	71.5 (*d*)	48.1 (*t*)
CH$_3$(15)	1.31 (*s*)	C(15)	16.7 (*q*)	17.5 (*q*)	22.5 (*q*)
CH$_3$(16)	1.27 (*s*)	C(16)	16.5 (*q*)	16.2 (*q*)	16.5 (*q*)
CH$_3$(17)	1.47 (*s*)	C(17)	16.7 (*q*)	17.1 (*q*)	16.8 (*q*)
		C(18)	71.7 (*s*)		82.7 (*s*)
CH$_3$(19)	1.51 (*s*)	C(19)	34.1 (*q*)	22.3 (*q*)	26.8 (*q*)
CH$_3$(20)	1.39 (*s*)	C(20)	33.7 (*q*)	24.7 (*q*)	26.7 (*q*)

[a]) Revised structure of **4**.

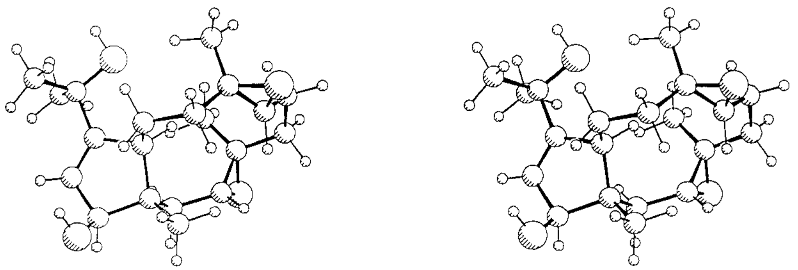


Fig. 3. *Stereoscopic view of molecule* **2**. The configuration shown is (1*S*,3*R*,4*R*,7*R*,8*R*,11*S*,14*S*,12*E*).

H-bonds is given in *Table 5*. Thus, the crystal is built from layers of molecules which extend in the *ab* plane. There are no connections in the *c*-direction, and because of the 2_1 screw axis, only alternating layers have the same orientation. *Fig. 4* shows one of these layers viewed along the *c*-axis. Of the four molecules in the unit cell, only two are shown, the other two lie above them and form part of the next layer. These two come

Table 5. *Intermolecular H-Bond Geometry for* **2**. Distances in Å and angles in degrees.

H-Bond	*d*(O–O)	*d*(O–H)	Angle (O–H–O)	Symmetry operation
$O(1^{I})–H(4^{II})–O(4^{II})$	2.81	1.90	150.4	$-x, -0.5+y, -1.5-z$
$O(4^{I})–H(3^{III})–O(3^{III})$	2.81	1.92	148.9	$x+1, y, z$

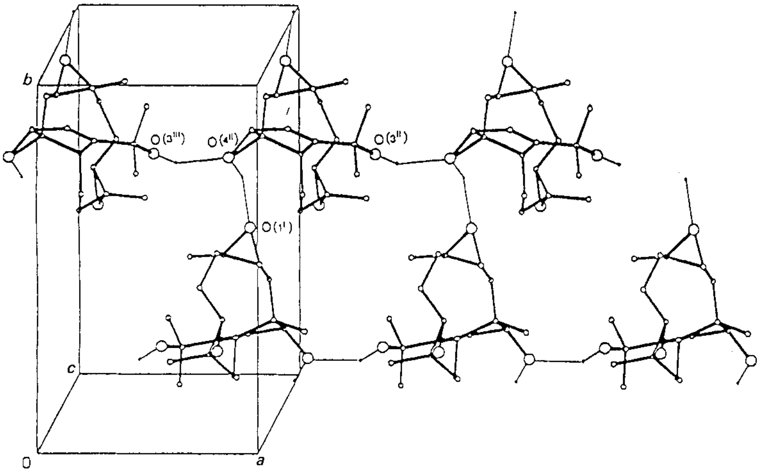


Fig. 4. *Layer of molecules of* **2**, *connected* via *H-bridge bonds, viewed along the* c-*axis*

from the other molecules *via* 2_1 screw axis in the *a* or *c* direction. Compound **2** is thus (1*R**,3*S**,4*S**,7*S**,8*S**,11*R**,14*R**,12*E*)-3,4:7,8-diepoxydolabell-12-ene-14,18-diol.

Clearly, from the results of this X-ray analysis of **2**, *the structures of compounds* **4** [1] *and* **5** [3] *should be revised to* **6** *and* **7**, *respectively*. It should be noted that the configuration originally proposed for the 3,4-epoxy function in **4** was based on ^{13}C-NMR data comparisons with those for **8** [2], whose configuration at these centres was based upon the theoretical stereochemical outcome of an epoxidation.

Structure of Compound **3**. Compound **3**, a nor-diterpene of the molecular formula $C_{19}H_{32}O$, has no signals for either sp- or sp^2-hybridized C-atoms in its ^{13}C-NMR spectrum; the molecule is thus tetracyclic. Comparison of the ^{1}H- and ^{13}C-NMR data of **3** with those of **2** (*Table 4* and *Exper. Part*) reveals that these two molecules are structurally identical in the C(1) to C(11) region. With the 11-membered ring and its associated functionalities established, this leaves two tertiary Me groups, a CH_2 group, a CH bearing an OH group, and a quarternary C-atom to account for. From the ^{1}H,^{1}H COSY spectrum of **3**, it is evident that the CH_2 protons couple to O*H*–CH, and that these three protons form a discrete spin system. These data imply the residual fragment to be either $CH_2CH(OH)C(CH_3)_2$ or $(OH)CHCH_2C(CH_3)_2$. As C*H* only couples to the adjacent CH_2 group, one of these groups must be connected to C(1), leaving the $(CH_3)_2C$ moiety to be bound to C(11). This gives rise to two possible structures for **3**. In an attempt to unambiguously position the OH group at either C(13) or C(14), a shift-reagent study as well as an NOE investigation of **3** were undertaken. The results of both studies clearly indicate the OH group to reside at C(14) and to be in α position (NOE interaction between H_β–C(2) (δ 1.20 (*m*)) and H–C(14)). Thus, **3** is (1*R**,3*S**,4*S**,7*S**,8*S**,11*S**,14*R**)-3,4:7,8-diepoxy-1,4,8,12,12-pentamethylbicyclo-[9.3.0]tetradecan-14-ol.

Experimental Part

1. *X-Ray Analyses.* Cell parameters and space group for both structures were obtained from precession photographs and from diffractometer measurements (least-squares fit of 22 reflections in the range $6 < \Theta < 10°$). The intensities of the reflections were measured at r.t. on a four-circle *Enraf Nonius CAD4* diffractometer with a graphite monochromator: $\lambda(\mathrm{Mo}K_\alpha) = 0.71069$ Å. During the measurement of both **1** and **2**, two reflections were taken for intensity control every 10000 s; these showed no significant variation of the intensities. Three reflections were used for orientation control every 200 reflections. The intensities were corrected for *Lorentz* and polarisation effects, but not for absorption. The structures were solved by direct methods with SHELXS-86 [4], and refined with SHELX-76 [5] using $\sigma(F)^{-2}$ weights. Heavy atoms (C, O) were refined anisotropically. The positions of the H-atoms (with exception of the olefinic and epoxide H's) attached to C-atoms were calculated and refined using constraints: H-atoms fixed at a distance of 1.08 Å, displacement parameters restricted to 120% of $(U_{11} + U_{22} + U_{33})/3$ of the corresponding C-atom. The positions of the OH, olefinic, and epoxide H-atoms were determined from difference *Fourier* maps. They were refined with isotropic temperature factors; in the second structure, the two OH H-atoms were fixed at a distance of 1.0 Å. Crystal for **1** and **2** are given in *Table 1*. Full lists of coordinates and isotropic displacement parameters as well as all H-positions are available from the authors and have been deposited with the *Cambridge Crystallographic Data Center.*

2. *General.* Experimental procedures are given in [1] and [6].

3. *Plant Material and Isolation from* Dictyota pardalis f. pseudohamata (A7749). See [1].

4. *(1R*,3S*,7S*,11R*,4Z)-Dolabella-4,8(17),12(18)-triene-3,7-diol* (= *(1R*,3S*,7S*,11R*,4Z)-12-Isopropylidene-1,4-dimethyl-8-methylidenebicyclo[9.3.0]tetradec-4-ene-3,7-diol*; **1**) was recrystallized from MeOH. All physical and spectroscopic data as previously reported [1].

5. *(1R*,3S*,4S*,7S*,8S*,11R*,14R*,12E)-3,4:7,8-Diepoxydolabell-12-ene-14,18-diol* (= *(1R*,4S*,5S*,8S*,9S*,11R*,12R*,13E)-4,5:8,9-Diepoxy-14-(1-hydroxy-1-methylethyl)-4,8,11-trimethylbicyclo[9.3.0]tetradec-13-en-12-ol* **2**): 3.3 mg (0.06%). Recrystallized from MeOH. M.p. 204°. $[\alpha]_D^{25} = +13.0$ ($c = 0.09$, $CHCl_3$). IR (film): 3420 (OH), 2940 (CH), 1700 (C=C), 1455*w*. EI-MS: 318 (9, $[M - H_2O]^+$), 300 (5, $[M - 2H_2O]^+$), 275 (64), 257 (14), 207 (31), 189 (37), 163 (38), 149 (80), 121 (48), 43 (100).

6. *(1R*,3S*,4S*,7S*,8S*,11S*,14R*)-3,4:7,8-Diepoxy-1,4,8,12,12-pentamethylbicyclo[9.3.0]tetradecan-14-ol* (**3**): 2.4 mg (0.04%). $[\alpha]_D^{25} = +40.8$ ($c = 0.12$, $CHCl_3$). IR (film): 3420 (OH), 2915 (CH), 1700*w*, 1455*w*, 1385*w*, 1240 ($(CH_3)_2C$). ^{1}H-NMR (300 MHz, $CDCl_3$): 1.05 (*s*, Me–C(1)); 1.14 (*s*, Me–C(18), *cis* to C(13)); 1.18 (*s*, Me–C(18), *trans* to C(13)); 1.20 (*m*, 1 H–C(2)); 1.21 (*s*, Me–C(14)); 1.31 (*m*, 1 H–C(5)); 1.35 (*m*, 1 H–C(9)); 1.45 (*s*, Me–C(8)); 1.58 (*m*, 1 H–C(10)); 1.66 (*m*, 1 H–C(6)); 1.67 (*m*, 1 H–C(13)); 1.83 (*m*, 1 H–C(10)); 1.85 (*m*, 1 H–C(2)); 1.89 (*m*, 1 H–C(13)); 2.03 (*m*, 1 H–C(6)); 2.08 (*m*, 1 H–C(9)); 2.26 (*m*, 1 H–C(5)); 2.53 (*d*, $J = 8.6$, 1 H–C(11)); 2.69 (*d*, $J = 9.5$, 1 H–C(7)); 2.96 (*dd*, $J = 2.1$, 10.8, 1 H–C(3)); 3.78 (*dd*, $J = 3.5$, 12.1, 1 H–C(14)). EI-MS: 293 (1, $[M - Me]^+$), 275 (1, $[M - Me - H_2O]^+$), 225 (3), 207 (15), 149 (35), 137 (10), 121 (22), 43 (100). HR-EI-MS: 293.2112 ($C_{18}H_{29}O_3$, calc. 293.2117).

We thank Dr. *Ian R. Price*, Department of Botany and Mr. *Rocky de Nys*, Department of Chemistry and Biochemistry, James Cook University, Townsville, Q4811, Australia, for performing taxonomic identification of all algal materials and for providing us with the freeze-dried plant materials, and Mr. *O. Greter* and Dr. *W. Amrein*, ETH Chemistry Department Mass Spectral Service, for recording all mass spectra and making accurate mass measurements as required.

REFERENCES

[1] A. D. Wright, G. M. König, O. Sticher, *Tetrahedron* **1990,** *46,* 3851.

[2] C. Bheemasankara Rao, K. C. Pullaiah, R. K. Surapaneni, B. W. Sullivan, K. F. Albizati, D. J. Faulkner, He Cun-heng, J. Clardy, *J. Org. Chem.* **1986,** *51,* 2736.

[3] A. D. Wright, J. C. Coll, I. R. Price, *J. Nat. Prod.* **1990,** *53,* 845.

[4] G. M. Sheldrick, 'SHELX-86, Crystallographic Computing 3', Eds. G. M. Sheldrick, C. Krueger, and R. Goddard, Oxford University Press, Oxford, 1985.

[5] G. M. Sheldrick, 'SHELX-76, System of Computing Programs', University of Cambridge, Cambridge, England.

[6] A. D. Wright, G. M. König, O. Sticher, R. de Nys, *Tetrahedron* **1991,** *47,* 5717.