Chlorosulfolipids and the Corresponding Alcohols from the Octocoral *Dendronephthya griffini*

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Two new polychlorolipids, namely, (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-pentachloropentadec-14-en-4-yl hydrogen sulfate (2) and (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-pentachloropentadec-14-en-4-ol (4), along with a known chlorosulfolipid (1), were isolated from the octocoral *Dendronephthya griffini*. (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*,*E*)-2,3,5,6,7,15-Hexachloropentadec-14-en-4-ol (3) was isolated for the first time from a natural source. The structures of these compounds were elucidated by extensive spectroscopic analysis and by comparison of the NMR data with those of known compound 1. This type of compound was isolated for the first time from the soft corals.

Key words *Dendronephthya griffini*; chlorosulfolipid; octocoral; polychlorolipid

Polychlorosulfolipids were unusual compounds in nature sources and had been isolated from some species of microalgae.[1,2] They were first isolated at the end of the 1960s from freshwater microalgae.[3,4] Another source of polychlorosulfolipids was obtained from harmful microalgae which are accumulated by continuous filter-feeding process of mussels.[5—7] Recently, we have isolated anti-inflammatory steroids from a Formosan octocoral *Dendronephthya griffini*.[8,9] Our continuing chemical investigation on this coral has led to the isolation of three new polychlorolipids, namely, (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-pentachloropentadec-14-en-4-yl hydrogen sulfate (**2**), (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*,*E*)-2,3,5,6,7,15-hexachloropentadec-14-en-4-ol (**3**), and (2*R*,3*S*,-4*R*,5*S*,6*S*,7*R*)- 2,3,5,6,7-pentachloropentadec-14-en-4-ol (**4**), along with a known compound, chlorosulfolipid (**1**). The known compound **1** has been isolated from the digestive glands of Adriatic mussels, *Mytilus galloprovincialis*, and its structure, including absolute configuration, had been determined by extensive NMR analysis and molecular mechanics and dynamics calculations by Fattorusso and colleagues.[5] Soon afterward, a total synthesis was reported by Carreira and colleagues which also confirmed the structure of **1**.[10] Herein, we describe the purification and structure elucidation of new compounds **2**—**4**. Polychlorolipids of this type were isolated for the first time from soft coral.

The negative electrospray ionization-mass spectrometry (ESI-MS) spectrum of **2** exhibited an intense pseudomolecular ion cluster at *m*/*z* 475, 477, 479, 481 (in a ratio *ca.* 3 : 5 : 3 : 1), suggesting the presence of five chlorine atoms in the molecule. The negative HR-ESI-MS spectrum of **2** exhibited a pseudomolecular $[M-H]^-$ peak at *m*/*z* 476.9800 (Calcd for $C_{15}H_{24}{}^{35}Cl_4{}^{37}ClO_4S$, 476.9808), revealing that **2** possessed a molecular formula $C_{15}H_{25}O_4SCl_5$. The ^{13}C-NMR spectrum of **2** (Table 1) displayed fifteen carbon signals and a distortionless enhancement by polarization transfer (DEPT) experiment confirmed the presence of one methyl, six sp^3 methylenes, one sp^2 methylene, six sp^3 methines, and one sp^2 methine. In the IR spectrum of **2**, a strong absorption band at 1259 cm^{-1} indicated the presence of a sulfate.[5] The above data suggested that **2** is an analogue of **1**. The ^{1}H-NMR spectrum of **2** was found to be superimposable with that of **1**,[5,10] except for the signals of three olefinic protons at δ 5.81 (1H, m), 4.99 (1H, br d, J=17.0 Hz), and 4.89 (1H, br d, J=10.0 Hz) (Table 2), indicating that **2** is a 15-dechloro derivative of **1**. The gross structure of **2** was further established by 2D-NMR studies, particularly by correlation spectroscopy (COSY) and heteronuclear multiple bond correlation (HMBC) experiments (Fig. 1). Inspection of the COSY spectrum of **2** led to the establishment of four proton spin systems (H_3-1 to H-2, H-3 to H-4, H-5 to H_2-8, and H_2-13 to H_2-15). In the HMBC spectrum, key correlations from H_3-1 to C-2 and C-3 and from H-3 to C-2, C-4, and C-5 were used to establish the planar structure of **2**. The NMR spectroscopic data of **2** were in full agreement with those of **1** at all chiral carbons (C-2 to C-7), indicating the chiral centers at C-2 to C-7 in **2** should possess the same relative configurations as those in **1**. Also, compound **2** possesses the same sign of specific optical rotation as that of **1** ($[\alpha]_D^{22}$ +30 for **2**; $[\alpha]_D^{22}$ +20 for **1**[5]), and both compounds showed similar key nuclear Overhauser enhancement (NOE) correlations, e.g. the presence of key NOE correlations between H-4 and H-7 and the

Table 1. ^{13}C-NMR Spectroscopic Data for Compounds **2**—**4**

Position	**2**[a]	**3**[b]	**4**[c]
1	19.4 (CH_3)	19.1 (CH_3)	19.1 (CH_3)
2	57.3 (CH)	56.1 (CH)	56.1 (CH)
3	69.1 (CH)	66.4 (CH)	66.5 (CH)
4	75.6 (CH)	72.0 (CH)	72.0 (CH)
5	68.1 (CH)	67.6 (CH)	67.7 (CH)
6	69.3 (CH)	67.5 (CH)	67.5 (CH)
7	63.4 (CH)	61.2 (CH)	61.2 (CH)
8	38.0 (CH_2)	36.4 (CH_2)	36.5 (CH_2)
9	26.8 (CH_2)	26.2 (CH_2)	26.2 (CH_2)
10	29.4 (CH_2)	28.6 (CH_2)	28.7 (CH_2)
11	29.4 (CH_2)	28.6 (CH_2)	28.8 (CH_2)
12	29.2 (CH_2)	28.7 (CH_2)	28.8 (CH_2)
13	34.5 (CH_2)	30.7 (CH_2)	33.7 (CH_2)
14	140.0 (CH)	133.8 (CH)	138.9 (CH)
15	114.7 (CH_2)	116.9 (CH)	114.4 (CH_2)

a) Recorded at 125 MHz in acetone-d_6 at 25 °C. *b*) Recorded at 75 MHz in $CDCl_3$ at 25 °C. *c*) Recorded at 125 MHz in $CDCl_3$ at 25 °.

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Table 2. ^{1}H-NMR Spectroscopic Data for Compounds **2**—**4**

Position	**2**[a]	**3**[b]	**4**[c]
1	1.61 d (7.5)	1.61 d (6.9)	1.61 d (6.9)
2	5.09 qd (7.5, 1.5)	4.67 qd (6.9, 3.0)	4.67 qd (6.9, 3.0)
3	4.43 dd (10.0, 1.5)	4.32 dd (9.6, 3.0)	4.32 dd (9.6, 3.0)
4	4.71 dd (10.0, 1.0)	4.02 dd (11.4, 9.6)	4.02 dd (11.5, 10.0)
5	4.79 d (10.0, 1.0)	4.86 dd (8.7, 1.5)	4.86 dd (8.7, 1.5)
6	4.73 dd (10.0, 2.0)	4.27 dd (8.7, 2.7)	4.27 dd (8.7, 2.7)
7	5.15 ddd (8.5, 4.0, 2.0)	4.19 ddd (8.1, 5.1, 2.7)	4.19 ddd (8.1, 5.1, 2.7)
8	1.90 m	1.96 m	1.96 m
	1.85 m	1.88 m	1.88 m
9	1.56 m	1.40 m	1.40 m
	1.42 m		
10	1.29—1.43 m	1.30—1.44 m	1.30—1.44 m
11	1.29—1.43 m	1.30—1.44 m	1.30—1.44 m
12	1.29—1.43 m	1.30—1.44 m	1.30—1.44 m
13	2.09 m	2.05 dt (6.6, 6.0)	2.05 dt (6.6, 6.0)
14	5.81 m	5.88 dt (13.2, 6.6)	5.80 m
15	4.99 br d (17.0)	5.95 d (13.2)	5.00 dd (17.0, 1.0)
	4.89 br d (10.0)		4.94 dd (10.0, 1.0)
OH		2.35 d (11.4)	2.32 d (11.5)

a) Recorded at 500 MHz in acetone-d_6 at 25 °C. *b*) Recorded at 300 MHz in $CDCl_3$ at 25 °C. *c*) Recorded at 500 MHz in $CDCl_3$ at 25 °C.

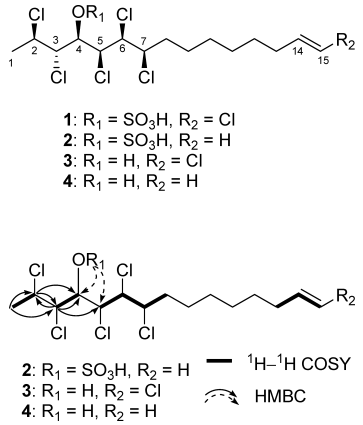

Fig. 1. Selected COSY and HMBC Correlations for **2** (Solid Arrows), **3** (Solid and Dashed Arrows), and **4** (Solid and Dashed Arrows)

absence between H-2 and H-5 in both compounds. Thus, the structure of **2** was established as (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-pentachloropentadec-14-en-4-yl hydrogen sulfate.

The negative ESI-MS spectrum of **3** displayed a pseudomolecular ion cluster $[M-H]^-$ at *m*/*z* 429, 431, 433, 435, 437 (in a ratio *ca.* 4 : 7 : 6 : 3 : 1), and the positive electron impact-mass spectrum (EI-MS) showed a $[M-HCl]^+$ peak at *m*/*z* 394, 396, 398, 400 (in a ratio *ca.* 3 : 5 : 3 : 1), appropriate for the presence of six chlorine atoms in its formula. Its positive HR-EI-MS exhibited a pseudomolecular $[M-HCl]^+$ peak at *m*/*z* 394.0189 (Calcd for $C_{15}H_{23}{}^{35}Cl_5O$, 394.0192) and negative HR-ESI-MS at *m*/*z* 430.9839 $[M-H]^-$ (Calcd for $C_{15}H_{23}{}^{35}Cl_5{}^{37}ClO$, 430.9851) and *m*/*z* 466.9590 $[M+Cl]^-$ (Calcd for $C_{15}H_{24}{}^{35}Cl_6{}^{37}ClO$, 466.9617). The above data suggested that **3** had a molecular formula $C_{15}H_{24}Cl_6O$. The ^{13}C-NMR spectrum of **3** (Table 1) displayed fifteen carbon signals, including one methyl, six sp^3 methylenes, six sp^3 methines, and two sp^2 methines. The ^{1}H-NMR spectrum of **3** showed an one-proton doublet at δ 2.35 which did not show any correlation in the ^{1}H-detected multiple quantum coherence connectivity (HMQC) spectrum and also its IR spectrum showed an absorption band at 3534 cm^{-1}, suggesting the presence of a hydroxy group. In its ^{13}C-NMR spectrum (Table 1), resonances for an *E* geometry 1-chloro, 2-alkyl double bond at δ 133.8 (CH) and 116.9 (CH) were also observed.[5] The remaining five chlorine atoms were suggested to attach at C-2, C-3, C-5, C-6, and C-7, similar to **1** and **2**. Hence, it was proposed that **3** should be a desulfated derivative of **1**. To confirm the above proposed structure, 2D-NMR experiments and chemical transformation from **1** to **3** were used. Proton–proton connectivity from the COSY experiment of **3** established fragments (C-1 to C-7 and C-13 to C-15) similar to those of **1** (Fig. 1). However, the hydroxy proton showed HMBC correlations from this proton to C-4 and C-5, revealing that the hydroxy group should be located at C-4. Furthermore, acid hydrolysis of **1** using 1 N HCl–MeOH (1 : 1) afforded its corresponding alcohol, of which the spectroscopic data were consistent with those of **3**. According to the *J*-based configuration analysis made for known compound **1**,[5] a molecular model for its desulfated derivative **3** was proposed, as shown in Fig. 2. The crucial NOE correlations for the hydroxyl proton (2.35) with both H-2 and H-6 in **3** and the $^3J_{H,H}$ coupling constants (Fig. 2) were helpful for confirmation that **3** has the same relative configurations as **1**. The above data, together with the same positive sign of specific optical rotation of **3** ($[\alpha]_D^{22}$ +18) as that of **1** ($[\alpha]_D^{25}$ +20),[5] demonstrated that the absolute configurations at all chiral centers in **3** were identical with those in **1**. Consequently, the structure of **3** was established as (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*,*E*)-2,3,5,6,7,15-hexachloropentadec-14-en-4-ol. It was found that **3** has been prepared from hydrolysis of **1**[5] and by a total synthesis of racemic **3**,[10] however, the former report provided only selected ^{1}H-NMR spectroscopic data in CD_3OD and no specific optical rotation was reported, and the latter provided detailed ^{1}H- and ^{13}C-NMR data of a racemic mixture which were found to be in full agreement with those of our present study. Compound **3** was isolated for the first time from a natural source.

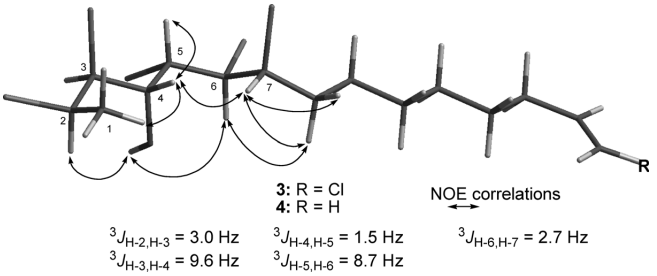

Fig. 2. Key NOE Correlations, $^3J_{H,H}$ Values, and Computer-Generated Perspective Model Using MM2 Force Field Calculations for **3** and **4**

The negative ESI-MS spectrum of **4** displayed a pseudomolecular ion cluster $[M-H]^-$ at *m*/*z* 395, 397, 399, 401 (in a ratio *ca.* 3 : 5 : 3 : 1), revealing that it possessed five chlorine atoms in the formula. Its negative HR-ESI-MS exhibited a pseudomolecular $[M-H]^-$ peak at *m*/*z* 397.0242 (Calcd for $C_{15}H_{24}{}^{35}Cl_4{}^{37}ClO$, 397.0240), revealing that it had a molecular formula $C_{15}H_{25}Cl_5O$. From the ^{1}H-NMR spectrum, it became apparent that **4** is an analogue of **1**—**3**. In the same manner, a hydroxy group in **4** was deduced by the proton doublet at δ 2.32 without any correlations in the HMQC spectrum and the presence of an IR absorption band at

3530 cm^{-1}. Three olefinic protons resonating at δ 5.80 (1H, m), 5.00 (1H, dd, J=17.0, 1.0 Hz), and 4.94 (1H, dd, J=10.0, 1.0 Hz) suggested the presence of a monosubstituted double bond (Table 2), like that in **2**. The above data coupled with a comparison of NMR spectroscopic data of **4** with those of **1**—**3** disclosed **4** to be a desulfated derivative of **2**. Inspection of the COSY and HMBC spectra of **4** (Fig. 1) allowed the confirmation of its planar structure. Except for the difference of olefinic moiety, compounds **3** and **4** shared the same NOE correlations (Fig. 2). In addition, compound **2** was also hydrolyzed using 1 N HCl–MeOH (1 : 1) to afford **4**, demonstrating that both compounds possessed the same absolute configurations at all chiral centers. Accordingly, the structure of **4** was determined as (2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-pentachloropentadec-14-en-4-ol. In order to rule out the possibility of the isolates **3** and **4** as artifacts, a CH_2Cl_2–EtOAc–MeOH solution of sulfate **1** or **2** was kept at room temperature with silica gel for 2 d. It was found that under this condition the corresponding alcohols **3** and **4** were not yielded.

Previous study on antiproliferative activity of the known compound **1** showed that this compound did not significantly inhibit the growth of a limited panel of cancer cell lines,[5] thus, the isolates **1**—**4** were investigated on the inhibition of lipopolysaccharide (LPS)-induced pro-inflammatory nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) proteins expression in RAW264.7 macrophage cells by Western blot analysis. The result reveals that all isolates were unable to reduce the levels of iNOS and COX-2.

Interestingly, known compound **1** was isolated from two different organisms, mussel and soft coral, living in two entirely different habitats. Thus, it is likely that these compounds are from dietary sources.

Experimental

General Experimental Procedures Optical rotations were measured on a JASCO P-1020 polarimeter. IR spectra were recorded on JASCO FT/IR-4100 Fourier transform infrared spectrophotometer. The NMR spectra were recorded on Varian Mercury-Plus 300 FT-NMR (or Varian Unity INOVA 500 FT-NMR) instrument at 300 MHz (or 500 MHz) for ^{1}H (referenced to TMS, 0 ppm and δ_H 2,05 for CD_3COCD_3) and 75 MHz (or 125 MHz) for ^{13}C (referenced to δ_C 77.0 ppm for $CDCl_3$ and 29.8 ppm for CD_3COCD_3). Positive LR- and HR-EI-MS were obtained on a Bruker APEX II mass spectrometer. Negative LR- and HR-ESI-MS analyses were recorded using an API 4000 tandem mass spectrometer and VARIAN 901-MS, respectively. Silica gel (Merck, 230—400 mesh) and C18 reversed phase silica gel (Silicycle, 230—400 mesh) were used for column chromatography. Precoated silica gel plates (Merck Kieselgel 60 F_{254} 0.2 mm) were used for analytical thin-layer chromatography (TLC). High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC-10AT apparatus equipped with a Shimadzu SPD-10A UV detector. The column used in HPLC separation was Purospher STAR RP-18e (reverse-phase column, 250 mm×10 mm, 5 μm).

Animal Material The octocoral *D. griffini* was collected unexpectedly by a bottom trawl net at depths ranged from 200 to 100 m during an ecological investigation at Taiwan Straight in December 2004. The location was about 60 km west of Singda Harbor, Kaohsiung County, Taiwan. A voucher specimen was deposited in the Department of Marine Biotechnology and Resources, National Sun Yat-sen University (specimen no. 041206A).

Extraction and Isolation The octocoral (15 kg fresh weight) was collected and freeze-dried. The freeze-dried material was minced and extracted exhaustively with EtOH (3×10 l). The organic extract was concentrated to an aqueous suspension and was further partitioned between EtOAc and water. The EtOAc extract (100 g) was fractionated by open column chromatography on silica gel using *n*-hexane–EtOAc and EtOAc–MeOH mixtures of increasing polarity to yield 19 fractions. Fraction 12, eluting with *n*-hexane–EtOAc (1 : 5), was further separated by C18 column chromatography with gradient elution (MeOH–H_2O, 1 : 1 to 9 : 1) and followed by silica gel column chormatography (CH_2Cl_2–*n*-hexane, 15 : 95) to yield **4** (4.3 mg) and **3** (3.0 mg). Fraction 15, eluting with EtOAc–MeOH (1 : 1), was fractionated by C18 column chromatography with gradient elution (MeOH–H_2O, 1 : 1 to 9 : 1) to obtain a subfraction containing a mixture of **1** and **2**. This mixture was subsequently chromatographied on a C18 column using gradient elution from 40 to 50% CH_3CN in 100 mM $NaClO_4$ (aq.) to afford subfractions 15A1 and 15A2, which contained impure **1** and **2**, respectively. Finally, compounds **1** (4.8 mg) and **2** (1.5 mg) were obtained from subfractions 15A1 and 15A2, respectively, by C18-HPLC chromatography using eluent of 45% CH_3CN in H_2O.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-Pentachloropentadec-14-en-4-yl Hydrogen Sulfate (**2**): Colorless gum; $[\alpha]_D^{22}$ +30 (c=0.19, MeOH); IR (KBr) ν_{max} 3000—3500, 1259, 1038, 1007, and 853 cm^{-1}; ^{13}C- and ^{1}H-NMR data, see Tables 1 and 2; ESI-MS (negative ion mode) *m/z* 475, 477, 479, 481 $[M-H]^-$; HR-ESI-MS (negative ion mode) *m/z* 476.9800 $[M-H]^-$ (Calcd for $C_{15}H_{24}{}^{35}Cl_4{}^{37}ClO_4S$, 476.9808).

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*,*E*)-2,3,5,6,7,15-Hexachloropentadec-14-en-4-ol (**3**): Colorless gum; $[\alpha]_D^{22}$ +18 (c=0.19, MeOH); IR (KBr) ν_{max} 3534, 2930, 2857, 1456, 1382, 1264, 1089, 934, 805, 774 cm^{-1}; ^{13}C- and ^{1}H-NMR data, see Tables 1 and 2; ESI-MS (negative ion mode) *m/z* 429, 431, 433, 435, 437 $[M-H]^-$; HR-EI-MS *m/z* 394.0189 $[M-HCl]^+$ (Calcd for $C_{15}H_{23}{}^{35}Cl_5O$, 394.0192); HR-ESI-MS (negative ion mode) *m/z* 430.9839 $[M-H]^-$ (Calcd for $C_{15}H_{23}{}^{35}Cl_5{}^{37}ClO$, 430.9851), *m/z* 466.9590 $[M+Cl]^-$ (Calcd for $C_{15}H_{24}{}^{35}Cl_6{}^{37}ClO$, 466.9617).

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-Pentachloropentadec-14-en-4-ol (**4**): Colorless gum; $[\alpha]_D^{22}$ +22 (c=0.34, MeOH); IR (KBr) ν_{max} 3530, 2928, 2856, 1456, 1382, 1267, 1089, 1011, 912 cm^{-1}; ^{13}C- and ^{1}H-NMR data, see Tables 1 and 2; ESI-MS (negative ion mode) *m/z* 395, 397, 399, 401 $[M-H]^-$; HR-EI-MS *m/z* 360.0573 $[M-HCl]^+$ (Calcd for $C_{15}H_{24}{}^{35}Cl_4O$, 360.0581); HR-ESI-MS (negative ion mode) *m/z* 397.0242 $[M-H]^-$ (Calcd for $C_{15}H_{24}{}^{35}Cl_4{}^{37}ClO$, 397.0240), *m/z* 432.9997 $[M+Cl]^-$ (Calcd for $C_{15}H_{25}{}^{35}Cl_7{}^{37}ClO$, 433.0001).

Hydrolysis of 1 and 2 Compound **1** (1 mg) was hydrolyzed at 80 °C for 4 h in a mixture of MeOH (1 ml) and 1 N HCl (1 ml). After cooling, the mixture was concentrated under reduced pressure and then extracted with EtOAc (3×2 ml). The combined extracts were evaporated in vacuum to give a residue, which was chromatographied with a short silica gel column using CH_2Cl_2–*n*-hexane (15 : 95) as eluent to obtain the corresponding alcohol **3** (0.8 mg). The same procedure was applied to **2** (0.7 mg) for preparing alcohol **4** (0.5 mg). The ^{1}H-NMR spectrum and specific optical rotations of the hydrolysis products from **1** and **2** were in agreement with those isolated from natural sources, compounds **3** and **4**, respectively.

***In Vitro* Anti-inflammatory Assay** Assay was performed as in our previous report.[11]

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