Isolation and Characterization of New Tetrahydropyranyl Substituted Sesquiterpene and Myrmekiodermin Glycolipid Ether Isolated from the Marine Sponge *Myrmekioderma*

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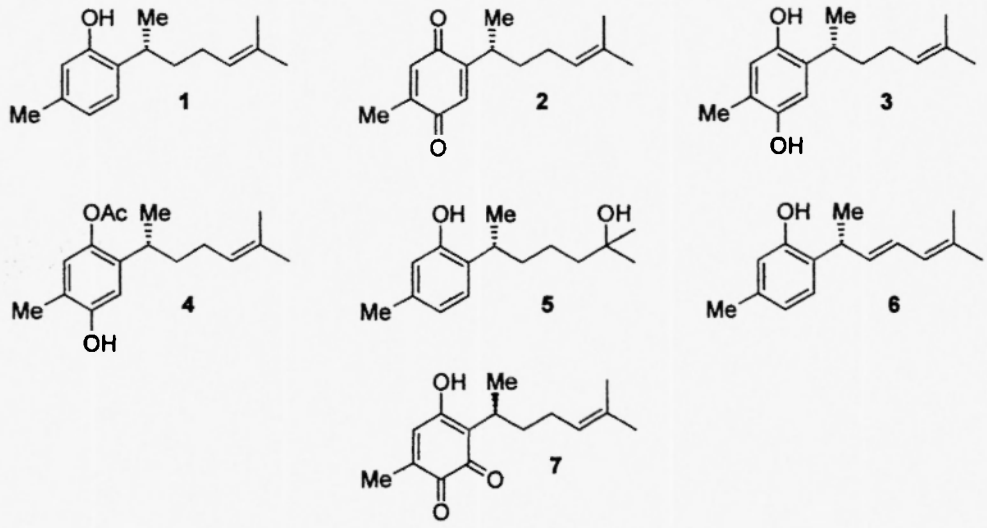
Abstract

New bisabolane sesquiterpene **9** and sesquiterpenes **8** and **10** along with the known (+)-curcuphenol **1** and (+)-dehydrocurcuphenol **6** were isolated from the *n*-hexane extract of the sponge *Myrmekioderma* collected along the Vanuatu coast. Their structure were unambiguously characterized using spectroscopic methods: Two new Myrmekiodermin glycolipid ethers A **11** and B **13** were also isolated from the *n*-BuOH extract and fully identified.

Introduction

A number of bioactive bisabolane sesquiterpenes have been isolated from different marine organisms. (-)-Curcuphenol **1**, (-)-curcuquinone **2** and (-)-curcuhydroquinone **3** were bioactive metabolites isolated from the Caribbean gorgonian *Pseudopterogorgia rigida* showing antibacterial activity against *Staphylococcus aureus* and the marine pathogen *Vibrio auguillarum*.[1] These compounds were also isolated from the gorgonian *Pseudopterogorgia americana* and *Pseudopterogorgia acerosa* along with (-)-curcuhydroquinone-1-monoacetate **4**.[2] Two cytotoxic and antifungal compounds, (+)-curcuphenol **1** and (+)-curcudiol **5**, were isolated from the marine sponge *Didiscus flavus*.[3] Moreover, the sponge *Epipolasis sp.* provided (+)-curcuphenol **1** and dehydrocurcuphenol **6** which have been shown to possess antitumor activity and to inhibit H^+, K^+-ATP-ase.[4] Recently, a novel *o*-quinone **7** was also isolated from *Pseudopterogorgia rigida* (Scheme 1).[5]



Scheme 1

Experimental section

General procedure. NMR spectra were recorded using a JEOL JNM-LA400 at 399.65 MHz for ^{1}H and 100.4 MHz for ^{13}C with $CDCl_3$ as solvent. Chemical shifts are expressed in ppm with TMS as internal standard and coupling constants are given in Hz. HPLC was performed with a Thermo Separation apparatus, an ERC-7515A differential refractometer using a Hibar Licrospher RP-18e Merck (250x10 mm) column.

Animal Material.

Myrmekioderma dendyi (Burton 1959) was collected by scuba along Vanuatu coast (Voulcher: Queensland Museum, South Brisbane, Australia)

Extraction and isolation.

The sponges were freeze-dried (285 g dry weight) and then extracted with MeOH (3 L). The methanolic extract was decanted off and concentrated in vacuum. The viscous concentrate (80 g) was partitioned between 500 mL of 10% aqueous MeOH and *n*-hexane (3x500 mL). Then the methanolic portion was made 30% aqueous and extracted sequentially with CH_2Cl_2 (3x500 mL) and *n*-BuOH (3x500 mL). Organic layers were concentrated in vacuum to yield 10.1 g of *n*-hexane extract, 12.5 g of CH_2Cl_2 extract and 7.9 g of *n*-BuOH extract.

The *n*-hexane extract (1.1 g) was subjected to bioassay-guided fractionation using column chromatography (15 x 3 cm, silicagel 60) by stepped gradient elution from n-hexane to EtOAc giving nine fractions. Reversed-phase HPLC chromatography of fraction S1, S2 and S3 give (+)-curcuphenol **1** (44 mg, 4% from the *n*-hexane extract), (+)-dehydrocurcuphenol **6** (40 mg, 3.6% from the n-hexane extract) and compounds **8** (96 mg, 8-7% from the *n*-hexane extract), 9 (27 mg, 2.4% from the *n*-hexane extract) and **10** (30 mg, 3.3% from the *n*-hexane extract).

Compound 8. Isolated as a yellow oil by reversed-phase (CH_3CN-H_2O, 80:20, flow rate: 2 mL/min, t_R 10.5 min). $[\alpha]_d^{20}$ (0.1, $CHCl_3$) = + 73. IR (neat) ν_{max} 3378 (br), 2964, 2920, 2876, 1675, 1613, 1506, 1445, 1378, 1291, 1140 cm^{-1}; HREIMS *m/z* 232.1467 $[M]^+$ (calcd for $C_{15}H_{20}O_2$ 232.1463); LREIMS *m/z* 232 (M^+, 40), 217(5), 199(6), 176(13), 161(7), 148(7), 135(82), 121(10), 115(14), 91(24), 83(100), 55(38).

Compound 9. Isolated as an oil by reversed-phase (CH_3CN-H_2O, 90:10, flow rate: 2 mL/min, t_R 12.7 min). IR (neat) ν_{max} 2963, 2931, 2861, 1763, 1609, 1444, 1379, 1212 cm^{-1}; HREIMS *m/z* 220.1834 $[M]^+$ (calcd for $C_{15}H_{24}O$ 220.1827); LREIMS *m/z* 220 (M^+, 31) 205(4), 177(4), 137(100), 135(68), 110(55), 95(45), 82(24).

Compound 10. Isolated as a yellow oil by reversed-phase (CH_3CN-H_2O, 90:10, flow rate: 2 mL/min, t_R 17.4 min). IR (neat) ν_{max} 2962, 2928, 2879, 1617, 1577, 1506, 1443, 1376, 1292, 1225, 1160, 1121, 1036, 974, 805 cm^{-1}; HREIMS *m/z* 46.1631 $[M]^+$ (calcd for $C_{16}H_{22}O_2$ 246.1620); LREIMS *m/z* 246 (M^+, 16) 231(19), 215(10), 199(100), 189(8), 159(5), 135(17), 97(9), 91(8).

Compound 11. HRFABMS Calcd for $C_{35}H_{68}NO_{13}$ *m/z* 710.4691 $[M+H]^+$, found *m/z* 710.4681 (Δ - 1.0 mmu). (+)-LRFABMS using NBA as matrix *m/z* (% relative intensity): 710 $[M+H]^+$ (6), 578 (3), 460 (4), 273 (11), 204 (32).

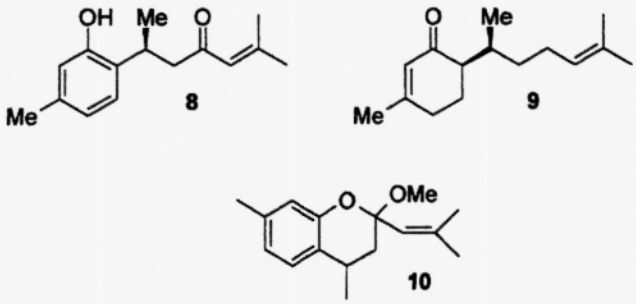
Compound 12. HRFABMS Calcd for $C_{49}H_{82}NO_{20}$ *m/z* 1004.5430 $[M+H]^+$, found *m/z* 1004.5444 (Δ + 1.4 mmu); (+)-LRFABMS using NBA as matrix *m/z* (% relative intensity): 1004 $[M+H]^+$ (15), 330 (100), 288 (8), 259 (51), 228 (8), 210 (31), 199 (29), 168 (50), 157 (86), 150 (55), 139 (80), 126 (22), 97 (81). ^{1}H-NMR δ 5.74 (1H, d, *J* = 5.7 Hz, NH), 5.21 (1H, dd, *J* = 8.8 and 5.6 Hz, H-3'), 5.18 (1H, dd, *J* = 9.4 and 7.9 Hz, H-3"), 5.06 (1H, t, *J* = 9.9 Hz, H-4"), 4.94 (1H, td, *J* = 9.1 and 5.2 Hz, H-4'), 4.87 (1H, dd, *J* = 8.9 and 7.1 Hz, H-2'), 4.80 (1H, d, *J* = 8.5Hz, H-1"), 4.56 (1H, d, *J* = 7.1 Hz, H-1'), 4.24 (1H, dd, *J* = 12.3 and 4.9 Hz, H-6"), 4.13 (1H, dd, *J* = 12.3 and 3.1 Hz, H-6"), 4.08 (1H, m, H-5'), 4.05 (2H, t, *J* = 6.7 Hz, H-21), 3.91 (1H, m, H-1), 3.86 (1H, m, H-2"), 3.83 (1H, m, H-2), 3.67 (1H, m, H-5"), 3.65 (1H, m, H-1), 3.50 (2H, m, H-3), 3.41 (2H, m, H-4), 3.39 (1H, m, H-5'), 2.09, 2.06, 2.05, 2.04, 2.03, 2.02 and 2.01 (21H, s, 7 x AcO), 1.95 (3H, s, AcNH), 1.63 (2H, m, H-20), 1.55 (2H, m, H-5), 1.37-1.20 (27H, H6 to H19), 0.83 (3H, t, *J* = 6.5 Hz, H-22). ^{13}C-NMR δ 171.24 (s, Ac-21), 170.89 (s, Ac-3"), 170.67 (s, Ac-6"), 170.24 (s, Ac-4'), 170.00 (s, Ac-2"), 169.89 (s, Ac-3'), 169.54 (s, Ac-2'), 169.38 (s, Ac-4"), 100.95 (d, C-1"), 100.92 (d, C-1'), 77.69 (d, C-2), 72.90 (d, C-3"), 71.95 (d, C-5"), 71.86 (t, C-4), 71.58 (d, C-3'), 71.39 (t, C-3), 71.12 (d, C-2'), 69.00 (s, C-4'), 69.00 (t, C-1), 68.59 (d, C-4"), 64.67 (d, C-21), 62.16 (t, C-

5'), 62.15 (t, C-6"), 54.79 (d, C-2"), 37.13, 30.05 to 29.27, 27.12 and 27.06 (t, C-6 to C-18), 32.78 (d), 28.62 (t, C-19), 26.22 (t, C-5), 25.93 (t, C-20), 23.26 (q, AcNH), 21.02-20.26 (q, 7 x AcO), 19.70 (q, C-22).

Compound 13. HRFABMS Calcd for $C_{34H66}NO_{13}$ *m/z* 696.4534 $[M+H]^+$, found *m/z* 696.4530 (Δ - 0.4 mmu). (+)-LRFABMS using NBA as matrix *m/z* (% relative intensity): 696 $[M+H]^+$ (5), 564 (2), 460 (3), 375 (8), 204 (86), 186 (12).

Results and Discussion

In our continuing research for bioactive substances from marine organisms, we have investigated marine sponge *Myrmekioderma* extracts collected along Vanuatu coast. Methanolic extract obtained from 285 g of *Myrmekioderma* was partitioned between *n*-hexane, CH_2Cl_2 and *n*-butanol. *n*-Hexane layer, which showed antibacterial activity, was purified by repeated chromatography on silicagel and reversed-phase HPLC to yield (+)-curcuphenol **1** (44 mg), (+)-dehydrocurcuphenol 6 (40 mg) and compounds 8 (96 mg), 9 (27 mg) and **10** (30 mg).



Scheme 2

Compound 8 was obtained as a pale yellow oil. The IR spectrum exhibits characteristic bands for hydroxyl group (3378 cm^{-1}), conjugated carbonyl (1675 cm^{-1}) and aryl moities (1613 cm^{-1}). LREIMS showed the molecular ion at *m/z* 232 (HREIMS *m/z* 232.1467 $C_{15}H_{20}O_2$) requiring six insaturations. ^{1}H NMR spectrum contained a set of three coupled aromatic resonances at 6.98 (H-5, d, J = 7.8 Hz), 6.69 (H-2, br. s) and 6.65 (H-4, d, J = 7.7 Hz) ppm. Chemical shifts and coupling constants along with the ^{13}C NMR data (153.63, 117.71, 136.86, 121.47, 126.45 and 130.01 ppm) for these signals are consistent with a 1,3,4-trisubstituted ring (Table 1).

^{1}H NMR spectra also showed the presence of one olefinic broad singlet proton at 6.02 ppm, one methylene at 2.79-2.82 ppm, one methine at 3.58 ppm and four methyls at 2.19, 2.08, 1.86 and 1.24 (d, J = 6.7 Hz) ppm. Detailed bond connectivities and assignment of all the NMR signals were obtained from COSY, HMQC and HMBC data establishing unambiguously the structure of 8. Absolute stereochemistry of **8** was assigned by comparison with the known (+)-turmeronol B.[6]

Table 1. ^{1}H NMR and ^{13}C NMR data for **8**, **9** and **10**

	8		**9**			**10**	
	δH, m, *J* (Hz)[a]	δC[a]	δH, m, *J* (Hz)[b]	δC[a]	δC[b]	δH, m, *J* (Hz)[a]	δC[a]
1	-	153.63	-	201.04	204.07	-	151.43
2	6.69, s	117.71	5.82, s	127.12	127.35	6.68, s	117.39
3	-	136.86	-	161.04	165.43	-	136.95
4	6.65, d, 7.7	121.47	2.38, dd, 7.2, 4.4	30.86	31.73	6.75, d, 7.8	121.68
5	6.98, d, 7.8	126.45	1.94, m 1.76, m	22.33	23.66	7.12, d, 7.8	126.47
6	-	130.01	2.20, dd, 12.0, 4.5	49.81	51.05	-	124.83
7	3.58, m	27.72	2.27, m	30.24	31.51	3.11, m	24.86
8	2.82, dd, 16.9, 7.0 2.79, dd, 16.9, 6.7	52.99	1.30, m	34.65	35.66	2.12, dd, 13.7, 6.8 1.58, t, 13.5	40.55
9	-	202.31	1.99, m	25.96	26.96	-	99.82
10	6.02, s	123.51	5.11, t, 7.2	124.47	125.61	5.31, s	124.96
11	-	157.21	-	131.34	132.36	-	137.83
12	1.86, s	27.36	1.67, s	25.64	25.92	1.79, s	26.65
13	2.08, s	20.97	1.60, s	17.58	17.76	1.82, s	18.32
14	1.24, d, 6.7	20.78	0.79, d, 6.7	15.55	16.14	1.29, d, 6.8	19.26
15	2.19, s	20.91	1.96, s	24.04	24.23	2.28, s	20.93
OMe	-	-	-	-	-	3.19, s	49.61

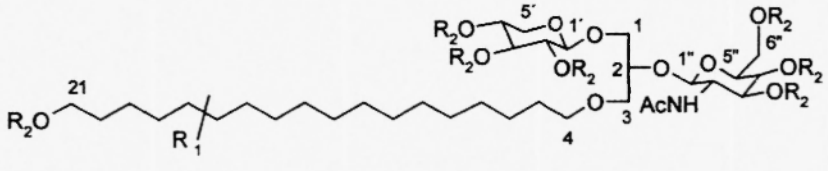
[a] NMR spectra recorded in $CDCl_3$. [b] NMR spectra recorded in CD_3OD.

Compound **9** was isolated as a clear oil. LREIMS spectrum showed a molecular ion at *m/z* 220 whose molecular formula $C_{15}H_{24}O$ (three insaturations) was deduced on the basis of its HREIMS peak (*m/z* 220.1834, M^+). The most relevant resonances observed in ^{1}H NMR (CD_3OD) were two protons at 5.82 (H-10, s) and 5.11 (H-4, t, J = 7.2 Hz) ppm corresponding to two isolated olefins, two methines protons at 2.27 (H-7, m) and 1.30 (H-8, m), and four methyls at 1.96, 1.67, 1.60 and 0.79 (d, J – 6.7 Hz) ppm. ^{13}C NMR spectrum displayed one α, β unsaturated ketone at 204.07 ppm, four olefinic carbons (165.43, 132.36, 127.35 and 125.61 ppm), two methine signals at 51.05 and 31.51 ppm, four methylenes (35.66, 31.73, 26.96 and 23.66 ppm) and four methyls at 25.92, 24.23, 17.76 and 16.14 ppm. However, compound **9** contains a $(CH_3)_2CHCH_2$- moiety and a trisubstituted olefin with one methyl substituent. Detailed analysis of one- and two-dimensional NMR spectra indicates that **9** has a 7,8-dihydro-α-bisabolene structure with a ketone group in C-1.[10]

Compound **10** had a molecular formula of $C_{16}H_{22}O_2$ (four insaturations) determinated by HREIMS (m/z 246.1631, calcd 246.1620). ^{13}C NMR spectrum showed the presence of 16 signals: six aromatic carbons characteristic of a 1,3,4-trisubstituted ring (151.43, 136.95, 126.47, 124.83, 121.68 and 117.39 ppm), two olefinic carbons (137.83 and 124.96 ppm), a quaternary carbon at 99.82 ppm, one methoxy group at 49.61 ppm, one methine at 24.86 ppm, one methylene at 40.55 ppm, and four methyls group (26.65, 20.93, 19.26 and 18.32 ppm). The most important signals observed in ^1H NMR were aromatic protons at δ 7.12 (H-5, d, J = 7.8 Hz), 6.68 (H-2, s) and 6.75 (H-4, d, J = 7.8 Hz) ppm, olefinic proton at δ 5.31 (H-10, s) ppm and a methoxy group at 3.19 ppm. A combination of HMQC, COSY and HMBC data showed that the quaternary carbon at 99.82 ppm (C-9) was connected to the methine at 5.31 ppm (H-10) and the methylene at 1.58-2.12 ppm (H-8). HMBC correlation between methoxy group at 3.19 ppm and a carbon signal at 99.82 ppm (C-9), downfield deplacement of this carbon, and absence of an hydroxyl band in the IR spectrum confirm the presence of an additional ring in structure **5**. Thus, the molecular formula requirement (six insaturations) is satisfied.

Antibacterial and antifungal activity tests on pure substance showed that the main active component was (+)-curcuphenol **1**. This compound showed antibacterial activity against *Escherichia coli* CIP 54127 (IC_{50} = 12.5 μg/mL), *Staphylococcus aureus* CIP 53154 (IC_{50} = 12.5 μg/mL), *Enterococcus hirae* CIP 5855 (IC_{50} = 12.5 μg/mL) and *Candida albicans* CIP 118079 (IC_{50} = 25 μg/mL). (+)-Dehydrocurcuphenol **6** displayed activity against *Saccharomyces cerevisiae* ATCC 28383 with IC_{50} = 17.5 μg/mL.[10] Nevertheless, no significant activities have been encountered for compounds **8**, **9** and **10**.

Two new Myrmekiodermin glycolipid ethers A **11** and B **13** were also isolated from *n*-BuOH fraction (Scheme 3).[11-14] Thus, Myrmekiodermin A **11** was purified by reversed-phase HPLC (MeOH: H_2O 90: 10). It is noteworthy that to our knowledge, it was the first time that unusual hydroxylation at the terminal position of the saturated long chain was encountered.[15] Molecular formula of **11** ($C_{35}H_{67}NO_{13}$) was established by HRFABMS of its molecular ion at *m/z* 710.4681.



11 $R_1 = CH_3$ $R_2 = H$

12 $R_1 = CH_3$ $R_2 = Ac$

13 $R_1 = H$ $R_2 = H$

Scheme 3

^{13}C/DEPT-NMR showed the presence of 35 signals. A carbonyl group at 173.71 ppm, two methines at 104.91 and 102.51 ppm, six methylenes at 72.75, 72.51, 70.18, 66.66, 62.99 and 62.68

ppm, eight methine at 78.99, 77.91, 77.29, 75.84, 74.64, 71.95, 71.10 and 57.72 ppm methylenes between 33.65 and 26.94 ppm, and two methyls at 23.26 and 20.17 ppm (Table 2).

	11			**13**	
	δ_H, m, *J* (Hz)	**δ_C, m**	**HMBC**	**δ_H, m, *J* (Hz)**	**δ_C, m**
1	3.85, dd, 10.6, 5.2 3.66, dd, 10.6, 5.3	70.18, t	C-2, 3, 1'	3.87, dd, 10.5, 5.1 3.67, dd, 10.5, 5.2	70.21, t
2	3.91, quint	78.99, d	C-1, 3, 1"	3.37, m	79.02, d
3	3.58, dd, 10.7, 5.7 3.52, dd, 10.7, 5.2	71.51, t	C-1, 2, 4	3.39, dd, 12.5, 5.1 3.47, dd, 12.4, 5.2	71.55, t
4	3.42, m	72.75, t	C-3, 5, 6	3.34, m	72.78, t
5	1.55, m	30.82, t	C-4, 6	1.48, m	30.77, t
6	1.25, m	27.26, t		1.24, m	27.28, t
7-18	1.17-1.21, m	27.05		1.22-1.27, m	27.05, m
19	1.25, m	26.94, t	C-20, 18	1.29, m	26.95, t
20	1.52, m	33.65, t	C-21, 19	1.52, m	33.69, t
21	3.48, m	62.99, t	C-20	3.63, m	63.03, t
22	0.81, d, 6.3	20.17, q		-	-
1'	4.24, d, 7.4	104.91, d	C-1, 2', 5'	4.33, m	104.98, d
2'	3.14, dd, 8.9, 7.4	74.64, d	C-1', 3'	2.92, m	74.70, d
3'	3.28, t, 8.9	77.29, d	C-2', 4'	3.54, t, 8.6	77.34, d
4'	3.46, m	71.10, d	C-3', 5'	3.66, m	71.16, d
5'	3.82, dd, 11.5, 6.5 3.16, t, 11.5	66.66, t	C-1', 3', 4'	3.71, dd, 10.6, 5.5 3.61, t, 10.6	66.70, t
1"	4.55, d, 8.5	102.51, d	C-2	4.99, d, 9.0	102.55, d
2"	3.54, dd, 10.2, 8.5	57.72, d	C-1", 3", CO	3.82, dd, 9.0, 7.2	57.79, d
3"	3.45, dd, 10.2, 8.7	75.84, d	C-2", 4"	3.97, dd, 9.0, 7.1	75.92, d
4"	3.27, t, 8.7	71.95, d	C-3", 5"	2.61, m	72.04, d
5"	3.22, m	77.91, d	C-3", 4"6"	3.66, m	77.98, d
6"	3.86, m 3.64, dd, 12.5, 5.5	62.68, t	C-5"	3.63, m 3.42, dd, 10.1, 4.7	62.74, t
OH	4.23	-	-	4.33, m	-
NHCOCH3	-	173.71, s	-	-	173.76, s
NHCO*CH3*	1.93, s	23.16, q	CO	1.93, s	23.1, q

Table 2. ^{1}H NMR and ^{13}C NMR data for **11** and **13**

^{1}H-NMR displayed two CH doublets at 4.55 (J = 8.5 Hz) and 4.24 (J = 7.4 Hz) ppm corresponding to two anomeric protons in β position, six methylenes and eight methines between 3.90 and 3.10 ppm, signals for a long aliphatic hydrocarbon chain at 1.55-1.25 ppm and two methyls at 1.93 (s) and 0.81 (d, J = 6.3 Hz). Structure of **11** was determined by a detailed analysis of one- and two-dimensional NMR spectra. Combination of HMQC, COSY and HMBC indicates the presence of four independent spin systems which could be ascribed to the four substructures: one N-acetyl-glucosamine, one xylose, one glycerol, and a long saturated chain with two terminal oxymethylene groups and a methyl doublet. The expected structure was confirmed by NMR analysis of compound **12** obtained by acetylation of the OH group of compound **11**. Nevertheless, the exact position of the methyl group on the long aliphatic hydrocarbon chain has not been clearly determined.

Myrmekiodermin glycolipid ether B **13** has molecular formula of $C_{34}H_{66}NO_{13}$ determined by HREIMS (m/z 694.4530, calcd 696.4534). ^{13}C NMR spectrum showed the presence of 23 different signals. This compound presents a similar structure to that of compound **11** differing only by the absence of a methyl group on the long saturated chain.

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