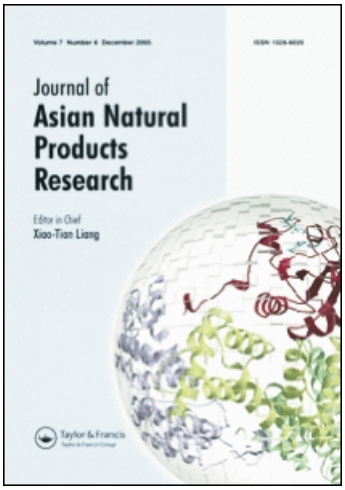


Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

Bromophenols from the brown alga *Leathesia nana*

Xiu-Li Xu[a]; Xiao Fan[b]; Fu-Hang Song[a]; Jie-Lu Zhao[c]; Li-Jun Han[b]; Yong-Chun Yang[c]; Jian-Gong Shi[c]
[a] Graduate School of the Chinese Academy of Sciences, Beijing, China [b] Institute of Oceanology, Chinese Academy of Sciences, Qingdao, China [c] Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

To cite this Article Xu, Xiu-Li , Fan, Xiao , Song, Fu-Hang , Zhao, Jie-Lu , Han, Li-Jun , Yang, Yong-Chun and Shi, Jian-Gong(2004) 'Bromophenols from the brown alga *Leathesia nana*', Journal of Asian Natural Products Research, 6: 3, 217 — 221
To link to this Article: DOI: 10.1080/10286020310001653273
URL: http://dx.doi.org/10.1080/10286020310001653273

Journal of Asian Natural Products Research, September 2004, VOL. 6 (3), pp. 217–221

BROMOPHENOLS FROM THE BROWN ALGA *LEATHESIA NANA*

XIU-LI XU[a,b], XIAO FAN[a], FU-HANG SONG[a,b], JIE-LU ZHAO[c], LI-JUN HAN[a], YONG-CHUN YANG[c] and JIAN-GONG SHI[c,*]

[a]*Institute of Oceanology, Chinese Academy of Sciences, Qingdao 266071, China;* [b]*Graduate School of the Chinese Academy of Sciences, Beijing 100039, China;* [c]*Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*

(Received 3 September 2003; Revised 22 October 2003; In final form 3 November 2003)

Two new bromophenols, (*E*)-3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methylpropenal (**1**) and 3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methyl-1-propanol (**2**), together with 11 known bromophenols (**3**–**13**), were isolated from the ethanolic extract of the brown alga *Leathesia nana* S. et G. Their structures have been elucidated by spectroscopic methods, including IR, MS, HRMS, 1D and 2D NMR techniques.

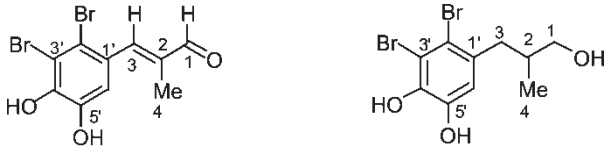
Keywords: Brown alga; Leathesiaceae; *Leathesia nana* S. et G.; Bromophenols

INTRODUCTION

Several bromophenols have been isolated from red alga [1–10], but few from brown alga. *Leathesia nana* S. et G. is a brown alga belonging to the Leathesiaceae family, and is widely distributed in the gulf of the Yellow Sea, China. In our investigation of the chemical constituents of this alga, two new bromophenols, (*E*)-3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methylpropenal (**1**) and 3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methyl-1-propanol (**2**), were obtained (Fig. 1), along with 11 known bromophenols. On the basis of spectral evidence and comparison of their physical and spectral data with those in the literature, the structures of the known bromophenols have been identified as 2,3-dibromo-4,5-dihydroxybenzyl ethyl ether (**3**) [1], 2,3-dibromo-4,5-dihydroxybenzyl methyl ether (**4**) [2,3], 3-bromo-4-(2,3-dibromo-4,5-dihydroxybenzyl)-5-methoxymethylpyrocatechol (**5**) [2,4], 2,3-dibromo-4,5-dihydroxybenzylaldehyde (**6**) [1,3,11], bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**7**) [2,12], 2,2′,3-tribromo-3′,4,4′,5-tetrahydroxy-6′-ethyloxymethyldiphenyl methane (**8**) [5], 2,2′,3,3′-tetrabromo-4,4′,5,5′-tetrahydroxydiphenyl methane (**9**) [10], 3-bromo-4-hydroxybenzoic acid (**10**) [11], 2,3-dibromo-4,5-dihydroxybenzyl alcohol (**11**) [13], 2-bromo-4,5-dihydroxybenzaldehyde (**12**) [12] and 3-bromo-4,5-dihydroxybenzaldehyde

*Corresponding author. E-mail: shijg@imm.ac.cn

ISSN 1028-6020 print/ISSN 1477-2213 online © 2004 Taylor & Francis Ltd
DOI: 10.1080/10286020310001653273



1 **2**

FIGURE 1 Structures of compounds **1** and **2**.

(**13**) [10]. This paper deals with the isolation and structural elucidation of the two new bromophenols. This is the first time these compounds have been obtained from this brown alga.

RESULTS AND DISCUSSION

Compound **1** was obtained as a red powder, mp 138–140°C. Its IR spectrum shows a strong broad absorption band for hydroxyl groups at 3402 cm^{-1}, conjugated carbonyl at 1647 cm^{-1} and characteristic absorption bands for aromatic rings at 1591, 1509 and 1486 cm^{-1}. The negative FAB mass spectrum of **1** show a dibrominated quasi-molecular ion peak cluster at *m/z* 337.0/335.0/333.0 (1:2:1) and the molecular formula determined as $C_{10}H_8Br_2O_3$ in combination with the NMR data (Table I). The ^1H NMR spectrum of **1** exhibits a diagnostic signal at δ9.66 (1H, s, H-1) for an aldehyde proton, and signals attributed to an olefinic proton at δ7.47 (1H, d, $J = 1.5$ Hz, H-3), an aromatic proton at δ7.30 (1H, s, H-6′) and a methyl at δ1.88 (3H, d, $J = 1.5$, H-4). The ^{13}C NMR spectrum, and DEPT experiments, of **1** reveal ten carbon signals: one methyl, three sp^2 methines (one aldehyde) and six sp^2 quaternary (two oxygenated $\delta > 145$ ppm) carbons (Table I). These data suggest that compound **1** contains two structural units, including a penta-substituted benzene ring and a 2,3-disubstituted propenal moiety, in addition to two bromines, two hydroxyls and one methyl as substituent groups. The connecting position between the two moieties and the location of these substituents have been established by an HMBC experiment in combination with the chemical shifts of the protons and carbons. In the HMBC spectrum (Fig. 2), correlations from H-6′ to C-1′, C-2′, C-4′, C-5′ and C-3 and from H-3 to C-2′ and C-6′

TABLE I ^1H and ^{13}C NMR data of compounds **1** and **2**[a]

	1		*2*	
No.	*δ ^1H (mult. J in Hz)*	*δ ^{13}C (mult.)*	*δ ^1H (mult. J in Hz)*	*δ ^{13}C (mult.)*
1	9.66 (s)	195.5 (d)	(a) 3.45 (dd, 6.0, 10.5) (b) 3.38 (dd, 5.0, 10.5)	66.9 (t)
2		139.6 (s)	1.93 m	37.3 (d)
3	7.47 (d, 1.5)	149.3 (d)	(a) 2.84 (dd, 6.5, 13.5) (b) 2.46 (dd, 8.0, 13.5)	41.4 (t)
4	1.88 (d, 1.5)	10.8 (q)	0.89 (d, 6.5)	21.4 (q)
1′		128.5 (s)		134.0 (s)
2′		117.5 (s)		116.6 (s)
3′		114.4 (s)		113.8 (s)
4′		146.4 (s)		143.5 (s)
5′		145.3 (s)		145.3 (s)
6′	7.30 (s)	116.6 (d)	6.84 (s)	117.6 (s)

[a] NMR data measured in acetone-d_6 at 500 MHz for proton and 125 MHz for carbon. Assignments based on DEPT, $^1H-^1H$ COSY, HMQC and HMBC experiments.

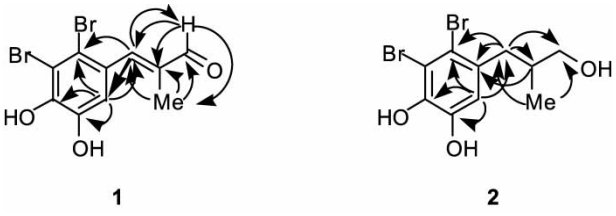


FIGURE 2 Key HMBC correlations of **1** and **2**.

unambiguously reveal the benzene ring moiety as 2′,3′-dibromo-4′,5′-dihydroxyphenyl. Correlations from H-1 to C-2, C-3 and C-4 and from H-4 to C-1, C-2 and C-3 demonstrate that the methyl group is attached at C-2 of the propenal moiety. The connection between the two moieties was unambiguously established by correlations from H-3 to C-2′ and C-6′ and from H-6′ to C-3. To determine the geometric configuration of the propenal moiety, an NOE difference experiment was carried out on **1**. The NOE enhancement of H-3 by irradiating H-1, and in turn the enhancement of H-1 by irradiating H-3, as well as the enhancement of H-4 by irradiating H-6′, unequivocally demonstrates the *E* configuration of the propenal moiety (Fig. 3). Therefore, the structure of **1** is determined as (*E*)-3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methylpropenal.

Compound **2** was obtained as a gum, $[\alpha]_D^{20}$ 5 (MeOH, *c* 0.08). Its IR spectrum shows a strong broad absorption band for hydroxyl groups at 3383 cm^{-1} and characteristic absorption bands for aromatic ring at 1576 and 1471 cm^{-1}. Its EIMS spectrum give a dibrominated molecular ion peak cluster at *m/z* 342/340/338 (1:2:1). The molecular formula was thus determined as $C_{10}H_{12}Br_2O_3$ on the basis of HREIMS at *m/z* 337.9158 (calcd. for $C_{10}H_{12}^{79}Br_2O_3$ 337.9153). The ^1H NMR spectrum of **2** shows signals of an aromatic proton singlet at δ6.84 (1H, s, H-6′), two pairs of geminal proton multiplets with ABX coupling patterns at δ3.45 (1H, dd, $J = 6.0$, 10.5 Hz, H-1a) and 3.38 (1H, dd, $J = 5.0$, 10.5 Hz, H-1b); 2.84 (1H, dd, $J = 6.5$, 13.5 Hz, H-3a) and 2.46 (1H, dd, $J = 8.0$, 13.5 Hz, H-3b), a methine proton multiplet at δ 1.93 (1H, m, H-2) and a methyl proton doublet at δ 0.89 (3H, d, $J = 6.5$ Hz, H-4). The ^{13}C NMR and DEPT spectra show ten carbon signals, including one methyl, two methylenes (one oxygenated), two methine (one sp^2) and five sp^2 quaternary (two oxygenated, $\delta > 142$ ppm) carbons. A comparison of the NMR data of **2** with those of **1** indicates that 2-methylpropanol in **2** has replaced 2-methylpropenal in **1**. This was confirmed by $^1H-^1H$ COSY, HMQC and HMBC experiments on **2**. In the $^1H-^1H$ COSY spectrum, cross peaks show that H-2 couples with H_2-1, H_2-3 and H-4, confirming the presence of the 2-methylpropanol moiety. In the HMBC spectrum (Fig. 2), long-range correlations from H_2-3 to C-1, C2, C-4, C-1′, C-2′ and C-6′ confirm that the 2′,3′-dibromo-4′,5′-dihydroxyphenyl moiety is at C-3 of the 2-methylpropanol moiety. Thus, the structure of **2** is 3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methyl-1-propanol. The stereochemistry at the chiral center of **2** has not been determined yet.

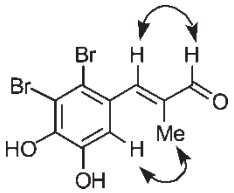


FIGURE 3 Key NOE correlations of **1**.

EXPERIMENTAL

General Experimental Procedures

Melting points were determined on an XT-4 micro melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. IR spectra were recorded as KBr disks on a Nicolet Impact 400 FT-IR spectrophotometer. NMR spectra were obtained at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, on an Inova 500 MHz spectrometer in acetone-d_6 with solvent peaks as references. MS and HRMS data were measured with a Micromass Autospec-Ultima ETOF spectrometer. Column chromatography was performed with silica gel (200–300 mesh), Bio-Beads SX3 (200–400 mesh) and Sephadex LH-20. HPLC was performed using an Alltima C18 preparative column (10 μm, 22 × 250 mm). TLC was carried out with glass precoated silica gel GF254 plates. Spots were visualized under UV light or by spraying with 5% sulfuric acid in EtOH followed by heating.

Plant Material

The brown alga *Leathesia nana* S. et G. was collected at the coast of Weihai, Shandong, China in May 2002 and identified by Dr Kui-Shuang Shao of the Institute of Oceanology, Chinese Academy of Sciences. A voucher specimen has been deposited in the same Institute.

Extraction and Isolation

Air-dried alga *L. nana* (8.25 kg) was powdered and extracted with 95% EtOH at room temperature (3 × 72 h). After removing the solvent under reduced pressure at $<40°C$, a dark residue (710 g) was obtained, which was then suspended in water and partitioned with EtOAc. The EtOAc-soluble fraction (125 g) was chromatographed over silica gel, eluting with a gradient of increasing Me_2CO (0–100%) in light petroleum. The fraction eluted by 30% Me_2CO in light petroleum was decolorized by column chromatography over Bio-Beads SX3, using $CHCl_3$–EtOAc, (1:2) and then rechromatographed over Sephadex LH-20 using light petroleum–$CHCl_3$–MeOH (5:5:1) to afford two subfractions. The first fraction was further separated by reversed-phase preparative HPLC using MeOH–H_2O–AcOH (70:30:0.1) as mobile phase to yield compounds **1** (9 mg), **2** (27 mg), **3** (15 mg), **4** (17 mg), **5** (35 mg) and **6** (87 mg). Separation of the second fraction by reversed-phase preparative HPLC, using MeOH–H_2O–AcOH (75:25:0.1) as mobile phase, yielded compounds **7** (62 mg), **8** (146 mg), **9** (27 mg), **10** (249 mg), **11** (46 mg), **12** (52 mg) and **13** (75 mg).

(E)-3-(2,3-Dibromo-4,5-dihydroxyphenyl)-2-methylpropenal (1)

A red powder, mp 138–140°C; IR (KBr) ν_{max} (cm^{-1}): 3402, 2922, 2723, 1647, 1591, 1509, 1486, 1398, 1346, 1294, 1201, 1173, 1007, 860; ^{1}H (CD_3COCD_3, 500 MHz) and ^{13}C NMR (CD_3COCD_3, 125 MHz) see Table I; FABMS *m/z* 337.0/335.0/333.0 $[M - H]^-$ (47/100/44%).

3-(2,3-Dibromo-4,5-dihydroxyphenyl)-2-methyl-1-propanol (2)

A gum; $[\alpha]_D^{20} + 5$ (MeOH, *c* 0.41); IR (KBr) ν_{max} (cm^{-1}): 3383, 2924, 2871, 1699, 1576, 1471, 1404, 1273, 1184, 1026, 980, 856; ^{1}H (CD_3COCD_3, 500 MHz) and ^{13}C NMR (CD_3COCD_3, 125 MHz) see Table I; EIMS *m/z* 342.4/340.4/338.4 $[M]^+$ (19/35/21%),

283.2/281.2/279.2 (42/89/41), 262.3/260.3/258.3 (18/33/15), 203.2/201.2 (96/100), 149.2 (36), 123.2 (52); HREIMS *m/z* 337.9158 (calcd. for $C_{10}H_{12}^{79}Br_2O_3$, 337.9153).

Acknowledgements

The authors are grateful to Professor Ablez Zeper for mass spectra measurements. This work was supported by a grant from the National High Technology Development Project (863 Project) (No. 2001AA620403).

References

[1] Lundgren, L., Olsson, K. and Theander, O. (1979), *Acta Chem. Scand. B.* **33**, 105–108.
[2] Minoru, S., Nobuhiko, K. and Etsuro, K. (1980), *Bull. Chem. Soc. Jpn.* **53**, 2099–2100.
[3] Weinstein, B., Rold, T.L., Harrell, C.E. and Burns, M.W. (1975), *Phytochemistry* **14**, 2667–2670.
[4] Kurata, K. and Amiya, T. (1977), *Chem. Lett.* **12**, 1435–1438.
[5] Fan, X., Xu, N.J. and Shi, J.G. (2003), *J. Nat. Prod.* **3**, 455–458.
[6] Kurata, K., Taniguchii, K., Takashima, K., Hayashi, I. and Suzuki, M. (1997), *Phytochemistry* **45**, 485–487.
[7] Wiemer, D.F., Idler, D.D. and Fenical, W. (1991), *Experientia* **47**, 851–853.
[8] Kurihara, H., Mitani, T., Kawabata, J. and Takahashi, K. (1999), *Fish. Sci.* **65**, 300–303.
[9] Olsen, C.M., Meussen-Elholm, E.T.M., Holme, J.A. and Hongslo, J.K. (2002), *Toxicol. Lett.* **129**, 55–63.
[10] Kurata, K. and Amiya, T. (1980), *Bull. Chem. Soc. Jpn.* **53**, 2020–2022.
[11] Jürgen, B., Susanne, L.F., Andrea, M. and Wolfgang, S. (1998), *Synthesis*, 1047–1051.
[12] Katsui, N., Suzuki, Y., Kitamura, S. and Irie, T. (1967), *Tetrahedron* **23**, 1185–1188.
[13] Kurihara, H., Mitani, T., Kawabata, J. and Takahashi, K. (1999), *J. Nat. Prod.* **62**, 882–884.