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Colensolide A: a new nitrogenous bromophenol from the New Zealand marine red alga *Osmundaria colensoi*

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ABSTRACT

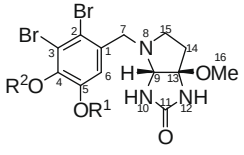
A new nitrogenous bromophenol, colensolide A, is isolated from the New Zealand red alga *Osmundaria colensoi* together with the known bromophenol lanosol and four of its derivatives. In this study, a novel technique is employed to identify potentially new compounds in semi-purified mixtures containing a plethora of structurally similar, known metabolites, using NMR spectroscopy. The structure and relative configuration of colensolide A is determined using standard spectroscopic techniques. Several of the known bromophenols exhibit antibacterial activity and one shows moderate cytotoxicity.

Bromophenols are common marine secondary metabolites, arising largely from the propensity of the phenol moiety to undergo electrophilic bromination.[1] Bromophenols have been isolated from taxonomically diverse marine algae, for example, the brown algae *Fucus vesiculosus*[2] and *Leathesia nana*,[3–5] and the red algae *Lenormandia prolifera*,[6] *Odonthalia corymbifera*,[7] *Polysiphonia lanosa*,[8] and *Rhodomela larix*.[9]

Over the last decade, rapid and efficient dereplication of known secondary metabolites in extracts of marine organisms has become increasingly important. Accordingly, we used extracts of over 30 New Zealand marine algal species to develop a novel 'stacked HSQC mask' dereplication strategy to target successfully sources of potentially new marine natural products in algal extracts. To construct the mask, the HSQC data is exported and added together to generate a digital mask. Through adding the NMR data sets together, the generated mask displays common correlations as strong peaks while the less common correlations are weak. The mask is then subtracted from each individual organism's HSQC spectrum to enhance the unique signals present.

One of the extracts recognized as containing potentially interesting metabolites was obtained from the New Zealand marine red alga *Osmundaria colensoi*. Although the natural product chemistry of *O. colensoi* has not been reported before, a variety of compounds, predominantly bromophenols, have been reported from other species of *Osmundaria* and *Vidalia* (now considered a synonym of *Osmundaria*).[10,11]

O. colensoi was collected using SCUBA from various sites around Northland, New Zealand, over a three year period between December 2003 and November 2006.[12] All of the specimens were frozen immediately after collection. A MeOH extract of approximately 500 g (wet wt) of *O. colensoi* was subjected to two steps of bench-top polymeric reversed-phase chromatography (PSDVB) and four fractions of varying polarity thus obtained were examined by ^{1}H, COSY, HSQC, and HMBC NMR experiments. Analysis of the NMR spectra revealed deshielded aromatic non-protonated carbons and shielded aromatic singlet protons, suggestive of highly-substituted bromophenols often isolated from red algae.[13–16]



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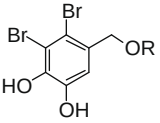

2 R = H
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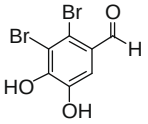

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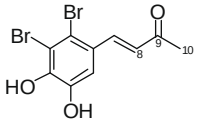

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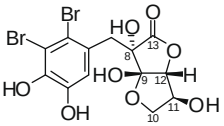

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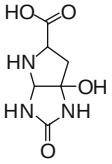

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Further purification of the four semi-purified fractions using reversed-phase (C_{18}) semi-preparative HPLC (MeOH/0.2 M HCOOH) led to the isolation of a new bromophenol, colensolide A (**1**, 3.5 mg),[17] the common bromophenol lanosol (**2**, 46.3 mg), the methyl ether of lanosol (**3**, 1.5 mg), aldehyde (**4**, 1.4 mg), and butenone (**5**, 5.3 mg) derivatives of lanosol and rhodomelol (**6**, 1.8 mg). Only compounds **2** and **3** have been previously reported from species of *Vidalia* and *Osmundaria*, respectively, while **4** has only been reported from other genera of red algae.[18,19] Both **5** and **6** have been reported once each from *P. lanosa* and *Rhodomela confervoides*, respectively.[20,21] The only NMR assignment of rhodomelol (**6**) was reported on semi-synthetic derivatives and therefore a full NMR assignment is reported here in CD_3OD.[22]

The molecular formula of colensolide A (**1**), isolated as a yellow oil, was established as $C_{13}H_{15}N_3O_4Br_2$ from HRESIMS data (435.9496 $[M+H]^+$, Δ 1.5 ppm). The ^{13}C NMR spectrum revealed 13 distinct resonances while the multiplicity-edited HSQC spectrum in CD_3OD accounted for 11 of the 15 protons thus suggesting the presence of four exchangeable protons, which were partially confirmed by the observation of 13 of the 15 expected protons when the ^1H NMR spectrum was acquired in DMSO-d_6. Identifiable features in the CD_3OD NMR spectra included one carbonyl resonance (δ_C 163.9), two strongly deshielded aromatic resonances (δ_C 145.2 and 146.5), three non-protonated aromatic resonances (δ_C 114.4, 116.2 and 130.9), one protonated aromatic resonance (δ_C 116.4, δ_H 6.98), a strongly deshielded methine (δ_C 77.7, δ_H 4.74), two slightly deshielded methylenes [(δ_C 55.1, δ_H 3.86 and 3.68) and (δ_C 49.0, δ_H 2.79 and 2.67)], an aliphatic methylene (δ_C 38.6, δ_H 2.12 and 2.00) and, finally, an oxymethyl group (δ_C 51.0, δ_H 3.28).

Strong HMBCs from both proton resonances of a deshielded diastereotopic methylene (C-7: δ_C 55.1, δ_H 3.86 and 3.68) to two aromatic non-protonated carbons (C-1: δ_C 130.9, C-2: δ_C 116.2) and the aromatic methine (C-6: δ_C 116.4, δ_H 6.98) indicated direct connectivity to an aromatic ring. The relatively shielded chemical shift of C-2 suggests bromine attachment at this carbon, indicating direct attachment of C-7 to the aromatic ring through C-1. HMBCs from H-6 to C-1, C-2 and a further three aromatic non-protonated carbons (C-3: δ_C 114.4, C-4: δ_C 146.5 and C-5: δ_C 145.2) established a 2,3-dibromo-4,5-dihydroxybenzyl substructure. The strongly deshielded chemical shifts of C-4 and C-5 are consistent with oxygen attachment at both these carbons. Once more, the shielded chemical shift of C-3 suggested bromine attachment, in accordance with the requirements of the molecular formula. Finally, the ^{13}C chemical shifts of the aromatic functionality in **1** compared favorably with the analogous compounds **2**–**6**,[9,18,20,21,23] and helped confirm the substitution pattern around the aromatic ring. In total, these observations accounted for four of the seven double-bond equivalents required by the molecular formula.

COSY correlations from the proton resonances of a slightly deshielded methylene (C-14: δ_C 38.6, δ_H 2.12 and 2.00) to those of a more strongly deshielded methylene (C-15: δ_C 49.0, δ_H 2.79 and 2.67) indicated an isolated spin system. One-bond carbon–proton coupling constants, which range from 110 to 320 Hz, are dependent on a variety of factors, including increasing with angular distortion and substitution of electron-withdrawing groups.[24] This precedence suggested the attachment of nitrogen, an electronegative atom, to C-15, resulting in the high $^1J_{CH}$ values (H-15a: 143 Hz, H-15b: 133 Hz; aminomethane: 133 Hz)[25] and the deshielded chemical shift (Fig. 1). This was confirmed by the observation of a downfield shift of the carbon and proton resonances and significant increases in the $^1J_{CH}$ values when colensolide A (**1**) was acidified with TFA (H-15a: 151 Hz, H-15b: 148 Hz; methylammonium ion: 145 Hz).[25,26]

The deshielded nature of the carbon and proton resonances of the C-7 methylene and the relatively large $^1J_{CH}$ values of H-7a and H-7b (136 and 135 Hz, respectively) again were similarly

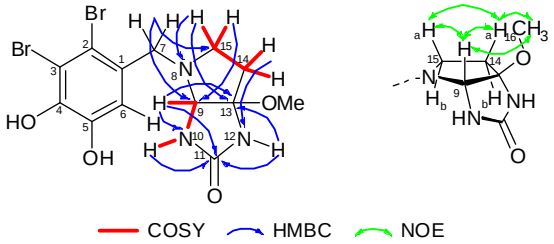

Figure 1. Key COSY and HMBCs and NOE enhancements observed for colensolide A (**1**).

indicative of nitrogen attachment at this position. Once more, the NMR spectrum of the acidified derivative of **1** showed a downfield shift of the carbon and proton resonances and a significant increase in the $^1J_{CH}$ value (H_2-7: 147 Hz). HMBCs from H-15a to a nitrogen (N-8: δ_N −319.3),[27] from H-15b to C-7, and from both proton resonances of CH_2-7 to C-15 indicated that C-7 and C-15 were connected through the same nitrogen. Selective excitation of the methylene protons H-7a and H-7b showed NOE enhancements to H-15a and H-15b, confirming this connectivity.

HMBCs from both proton resonances of CH_2-7 to a strongly deshielded methine (C-9: δ_C 77.7, δ_H 4.74) completed the substitution around the tertiary amine. This was confirmed by a significant increase in the $^1J_{CH}$ value for C-9 in the NMR spectrum of the acidified derivative of **1** (164 Hz increased to 175 Hz), and HMBCs from H-9 to C-7, N-8 and C-15. The strongly deshielded nature of C-9 along with the very large $^1J_{CH}$ value indicated connectivity to another heteroatom. A HMBC from H-9 to a second nitrogen (N-10: δ_N −291.1), along with a COSY correlation between H-9 and H-10 when the spectrum was recorded in DMSO-d_6, supported this aminal assignment. HMBCs from both proton resonances of CH_2-15 to a strongly deshielded non-protonated carbon (C-13: δ_C 99.7) positioned this carbon next to the C-14 methylene. A HMBC from the oxymethyl (C-16: δ_C 51.0, δ_H 3.28) to C-13 and HMBCs from both proton resonances of CH_2-14 to a third nitrogen (N-12: δ_N −280.5) accounted for the strongly deshielded nature of the hemi-aminal ether carbon, C-13.

A further HMBC from H-9 to a shielded carbonyl (C-11: δ_C 163.9) suggested an amide moiety through N-10. The ^{15}N HSQC spectra recorded in DMSO-d_6 showed that both N-10 and N-12 were secondary amides [(N-10: δ_N −290.6, δ_H 7.12) and (N-12: δ_N −279.6, δ_H 7.32)]. HMBCs observed from H-10 to C-9 and C-11 and from H-12 to C-11 and C-13 suggested a urea moiety connecting N-10 and N-12 through the C-11 carbonyl. This assignment was supported by the observed chemical shifts of both N-10 and N-12 being consistent with amides, which generally occur in the range -210 to -300 ppm; urea occurs at -302.8 ppm.[28] A HMBC between H-9 and C-13 completed the connectivity of these two centers and created the bicyclic substructure containing an imidazolone moiety. Finally, the ^1H chemical shifts of the bicyclic substructure in **1** compared favorably with the analogous synthetic compound **9**, reported in 2006.[29]

All detected carbon and nitrogen resonances were now accounted for. The observed chemical shift of N-8 δ_N −319.3) is consistent with an alkylamine which generally occur in the range of −310 to −380 ppm,[28] while the acidified counterpart (δ_H −298.9) is consistent with an ammonium ion (−290 to −360 ppm).[30] The presence of the benzene ring and the bicyclic system accounted for six double-bond equivalents and the seventh was accounted for by the presence of the carbonyl carbon of the imidazolone moiety. The final two unaccounted protons from the molecular formula were satisfied by assigning positions C-4 and C-5 as hydroxyl groups, identifying the ring as an orthohydroquinone.

Table 1
^{15}N (60 MHz), ^{13}C (150 MHz) and ^{1}H (600 MHz) NMR data for colensolide A (**1**) and the TFA acidified derivative of **1**

Pos	**1**, CD_3OD						**1**, DMSO-d_6			Acidified **1**, CD_3OD		
	δ_C or δ_N	δ_H	J (mult, Hz)	$^1J_{CH}$ (Hz)	COSY	HMBC	δ_C or δ_N	δ_H	$^1J_{CH}$ (Hz)	δ_C or δ_N	δ_H	$^1J_{CH}$ (Hz)
1	130.9						129.7			122.5		
2	116.2						114.1			118.7		
3	114.4						113.3			115.2		
4	146.5						145.1			148.1		
5	145.2						143.4			147.1		
6	116.4	6.98	s	161	7a,7b	1,2,3,4,5,7	115.4	6.98	162	118.6	7.07	162
7a	55.1	3.86	d (14.2), 1H	136	6,7b	1,2,3,5,6,9,15	53.5	3.72	135	56.7	4.50	146
7b		3.68	d (14.4), 1H	135	6,7a	1,2,6,9,15		3.52	136			
8	−319.3						−319.6			−298.9		
9	77.7	4.74	s	164		8,10,11,13,14,15	75.8	4.54	162	81.4	5.39	175
10	−291.1						−290.6	7.12	94	[a]		
11	163.9						160.6			161.4		
12	−280.5						−279.6	7.32	94	−280.4		
13	99.7						97.5			97.4		
14a	38.6	2.12	ddd (12.2,10.1,6.8), 1H	130	14b,15a,15b	8,12,13,15	37.3	1.99	132	67.7	2.45	133
14b		2.00	ddd (12.2,5.2,2.1), 1H	131	14a,15a,15b	8,9,12,13		1.93	135		2.36	137
15a	49.0	2.79	ddd (9.1,6.6,2.2), 1H	143	14a,14b,15b	8,9,13,14	48.6	2.66	145	50.9	3.48	151
15b		2.67	td (9.8,5.1), 1H	133	14a,14b,15a	7,9,13,14		2.51	135		3.40	148
16	51.0	3.28	s	141		13	49.9	3.14	142	51.3	3.32	143

[a] Not observed.

The relative configuration of colensolide A (**1**) was assigned on the basis of observed NOE enhancements. Selective excitation of the methine proton H-9 showed NOE enhancements to H-14a, H-15a, and H_3-16. Selective excitation of H-14a showed NOE enhancements to its geminal partner H-14b, H-9, H-15a, and H_3-16, while selective excitation of H-14b showed NOE enhancements to its geminal partner H-14a and H-15b. This series of NOE enhancements determined the cis-fused bicyclic ring system with H-9, H-14a, H-15a, and H_3-16 on the same face of the five-membered ring (Fig. 1).

Selective excitation of the methyl protons H_3-16 showed expected NOE enhancements to H-9 and H-14a, and interestingly, weakly to H-14b. This is not unreasonable due to the free rotation of the C-13-OMe bond and the relative angles of the two methylene protons in the five-membered ring. Optical rotation measurements were negligible {$[\alpha]_D^{25}$ −2 to −6 (*c* 0.35, MeOH)}, which may imply a racemic mixture of two enantiomers. NMR data for **1** is presented in both CD_3OD and DMSO-d_6 (Table 1).

The exchangeable phenolic protons of colensolide A (**1**) were not observed when the ^1H NMR spectrum was acquired in DMSO-d_6. Accordingly, a two step methylation was accomplished to confirm the proposed structure. Treatment of **1** with $TMSCHN_2$ resulted in a regiospecific mono-methylation to form 5-*O*-methylcolensolide A (**7**).[31] Further methylation was achieved when **7** was treated with MeI to form 4,5-di-*O*-methylcolensolide A (**8**),[32] confirming the orthohydroquinone substructure of **1**.

Compounds **1**–**6** and **8** were evaluated for cytotoxicity against the human leukemia cell line HL-60 to 10 μM and for antibacterial activity against the MC^{2}155 strain of *Mycobacterium smegmatis* to 100 μM. Lanosol butenone (**5**) exhibited moderate activity against human leukemia cells (IC_{50} 8.0 μM)[33] while lanosol methyl ether (**3**), lanosol butenone (**5**) and rhodomelol (**6**) all exhibited antibacterial activity (IC_{50} 7.8, 26.2, and 28.1 μM, respectively).[34]

The presence of nitrogen-containing side chains in bromophenols is not unprecedented, with ten nitrogenous bromophenols unrelated to **1** reported recently from an extract of the red alga *Rhodomela confervoides*.[35–37] The nitrogen-containing moiety of colensolide A (**1**) may have its biosynthetic origins from oxygenated histidine. Agon et al. were able to prepare **9** via a singlet oxygen-mediated photo-oxidation of histidine.[29] Decarboxylation of the bicyclic product prepared by Agon et al. would afford the desired bicyclic moiety observed in colensolide A (**1**). The biosynthetic incorporation of the bromophenol ring could occur before or after the histidine oxidation. An alternative biogenesis could involve oxidation and cyclization of histamine, removing the need for decarboxylation.

Acknowledgments

Financial assistance from the Cancer Society of New Zealand is gratefully acknowledged. The alga was identified by Joe Zuccarello, School of Biological Sciences, Victoria University of Wellington. Cytotoxicity assays were performed by Ariane Chan while antibacterial assays were performed by Chris Miller.

Supplementary data

Supplementary data (1D and 2D NMR spectra for compounds **1** to **8**) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.118.

References and notes

1. Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335–346.
2. Pedersén, M.; Fries, L. *Z. Pflanzenphysiol.* **1974**, *74*, 272–274.
3. Xu, X.; Song, F.; Wang, S.; Li, S.; Xiao, F.; Zhao, J.; Yang, Y.; Shang, S.; Yang, L.; Shi, J. *J. Nat. Prod.* **2004**, *67*, 1661–1666.
4. Xu, X. L.; Fan, X.; Song, F. H.; Zhao, J. L.; Han, L. J.; Shi, J. G. *Chin. Chem. Lett.* **2004**, *15*, 661–663.
5. Xu, X.-L.; Fan, X.; Song, F.-H.; Zhao, J.-L.; Han, L.-J.; Yang, Y.-C.; Shi, J.-G. *J. Asian Nat. Prod. Res.* **2004**, *6*, 217–221.
6. Saenger, P.; Pedersén, M.; Rowan, K. S. *Phytochemistry* **1976**, *15*, 1957–1958.
7. Weinstein, B.; Rold, T. L.; Harrell, C. E., Jr.; Burns, M. W., III; Waaland, J. R. *Phytochemistry* **1975**, *14*, 2667–2670.
8. McLachlan, J.; Craigie, J. S. *J. Phycol.* **1966**, *2*, 133–135.
9. Katsui, N.; Suzuki, Y.; Kitamura, S.; Irie, T. *Tetrahedron* **1967**, *23*, 1185–1188.
10. Adams, N. M. *Seaweeds of New Zealand. An Illustrated Guide*; Canterbury University Press: Christchurch, 1994. p 334.
11. Guiry, M.D.; Guiry, G.M. *AlgaeBase*; World-wide electronic publication: National University of Ireland, Galway, 2008, http://www.algaebase.org (accessed Nov 18, 2007).
12. Voucher sample PTN2_80A, stored at Victoria University of Wellington, Wellington, New Zealand.
13. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1–49.
14. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2005**, *22*, 15–61.
15. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26–78.
16. Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2007**, *24*, 31–86.

17. Colensolide A (**1**), yellow oil; $[\alpha]_D^{25}$ −2 to −6 (*c* 0.35, MeOH); UV (MeOH) λ_{max} 293 nm; HRESIMS, obsd. *m*/*z* 417.9386:419.9374:421.9368 (1:2:1) $[M-H_2O+H]^+$, $C_{13}H_{14}N_3O_3Br_2^+$ requires 417.9396:419.9377:421.9358, Δ 2.6 ppm, obsd. *m*/*z* 435.9496:437.9468:439.9474 (1:2:1) $[M+H]^+$, $C_{13}H_{16}N_3O_4Br_2^+$ requires 435.9502:437.9482:439.9464, Δ 1.5 ppm.
18. Retz de Carvalho, L.; Guimaraes, S. M. P. d. B.; Roque, N. F. *Rev. Bras. Bot.* **2006**, *29*, 453–459.
19. Yoo, H.-D.; Ketchum, S. O.; France, D.; Bair, K.; Gerwick, W. H. *J. Nat. Prod.* **2002**, *65*, 51–53.
20. Zhao, J.; Fan, X.; Wang, S.; Li, S.; Shang, S.; Yang, Y.; Xu, N.; Lu, Y.; Shi, J. *J. Nat. Prod.* **2004**, *67*, 1032–1035.
21. Glombitza, K. W.; Sukopp, I.; Wiedenfeld, H. *Planta Med.* **1985**, *51*, 437–440.
22. Rhodomelol (**6**), brown oil; ^{13}C NMR (150 MHz, CD_3OD): 176.5 (C-13), 145.7 (C-5), 144.9 (C-4), 128.2 (C-1), 119.2 (C-6), 117.9 (C-2), 113.6 (C-3), 109.0 (C-9), 88.2 (C-12), 79.4 (C-8), 76.6 (C-10), 75.5 (C-11), 41.7 (C-7); ^1H NMR (600 MHz, CD_3OD): 7.03 (s, H-6), 4.59 (s, H-12), 4.41 (dd, *J* = 5.6, 3.4 Hz, H-11), 4.24 (dd, *J* = 9.8, 5.9 Hz, H-10b), 4.09 (dd, *J* = 9.7, 3.1 Hz, H-10a), 3.37 (d, *J* = 14.9 Hz, H-7a), 3.11 (d, *J* = 14.7 Hz, H-7b).
23. Craigie, J. S.; Gruenig, D. E. *Science* **1967**, *157*, 1058–1059.
24. Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*, 6th ed.; John Wiley & Sons: New York, 1998. p 233.
25. Nelson, J. H. *Nuclear Magnetic Resonance Spectroscopy*; Pearson Education: New Jersey, 2003. p 140.
26. To a sample of **1** (1.7 mg, 3.9 μmol) in CD_3OD (250 μL) in a 3 mm NMR tube, TFA (0.5 μL, 6.7 μmol) was added to yield acidified colensolide A (1.7 mg).
27. Indirectly-detected ^{15}N shifts were referenced to the unified TMS scale with a Ξ ratio of 10.136767.
28. Marek, R.; Lycka, A.; Kolehmainen, E.; Sievanen, E.; Tousek, J. *Curr. Org. Chem.* **2007**, *11*, 1154–1205.
29. Agon, V. V.; Bubb, W. A.; Wright, A.; Hawkins, C. L.; Davies, M. J. *Free Radical Biol. Med.* **2006**, *40*, 698–710.
30. Nelson, J. H. *Nuclear Magnetic Resonance Spectroscopy*; Pearson Education: New Jersey, 2003. p 69.
31. To a sample of **1** (1.1 mg, 2.5 μmol) in 500 μL of dry CH_3CN, 2.0 M $TMSCHN_2$ in diethyl ether (50 μL, 100 μmol) was added. The reaction was left to stir under argon at rt for 45 min and then quenched with 2% AcOH (2 mL) and left overnight.
32. To a sample of **7** (0.7 mg, 1.6 μmol) in 500 μL of dry CH_3CN with K_2CO_3 (2.1 mg, 15.2 μmol), MeI (10 μL, 160.6 μmol) was added. The reaction was left to stir under argon at rt for 24 h and then quenched with H_2O (2 mL).
33. Chan, A. Victoria University of Wellington, New Zealand, Unpublished work, 2008.
34. Miller, C. Victoria University of Wellington, New Zealand, Unpublished work, 2008.
35. Ma, M.; Zhao, J.; Wang, S.; Li, S.; Yang, Y.; Shi, J.; Fan, X.; He, L. *J. Nat. Prod.* **2007**, *70*, 337–341.
36. Ma, M.; Zhao, J.; Wang, S.; Li, S.; Yang, Y.; Shi, J.; Fan, X.; He, L. *J. Nat. Prod.* **2006**, *69*, 206–210.
37. Zhao, J.; Ma, M.; Wang, S.; Li, S.; Cao, P.; Yang, Y.; Yang, L.; Shi, J.; Xu, N.; Fan, X.; He, L. *J. Nat. Prod.* **2005**, *68*, 691–694.