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Antitumour polyether macrolides: Four new halichondrins from the New Zealand deep-water marine sponge *Lissodendoryx* sp.

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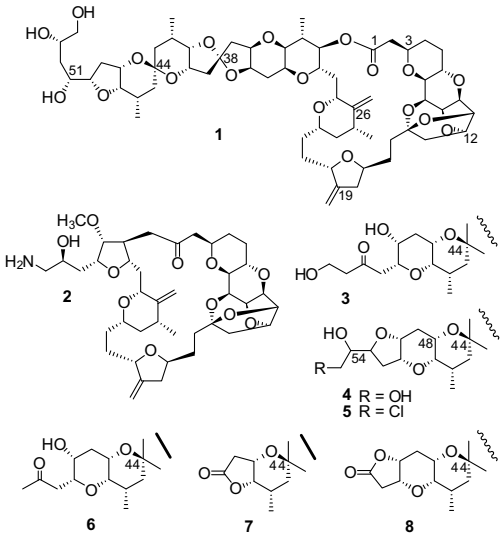
ABSTRACT

The isolation is reported of four new variants of the halichondrin B skeleton, very minor potently bioactive components from the Poecilosclerid sponge *Lissodendoryx* sp. These compounds were isolated in microgram quantities only from a collection of 1 tonne of sponge. The structural elucidations relied heavily on the use of capillary NMR spectroscopy and the application of an HSQC-DEPT overlay technique.

1. Introduction

An ongoing project at the University of Canterbury has been a study of the halichondrin series of compounds (complex polyether macrolides) from the New Zealand bright yellow sponge *Lissodendoryx* sp. (Family Myxillidae, Order Poecilosclerida), collected by dredging from deep-water (>100 m) off the Kaikoura Peninsula.[1,2] These compounds demonstrate potent activity against the P388 murine leukaemia cell line, with IC_{50}s in the sub-nanomolar range. Ten halichondrins, all from the B series, have previously been reported derived from this sponge.[1] These included halichondrin B (**1**)[3] which had achieved promising results in preclinical trials at the NCI (DNIIR) but progressed no further due to uncertainty of supply. Subsequently, a synthetically derived portion of the right hand side of the halichondrin skeleton, eribulin (NSC 707389, E7389) (**2**),[4] has been advanced to phase III clinical trials. Interestingly, eribulin has been found to be consistently more potent than halichondrin B in its interactions with tubulin.[5]

In order to supply halichondrin B (**1**) and isohomohalichondrin B (**3**)[6] for the earlier preclinical trials, 1 tonne of the sponge was collected in 1995.[2] The sponge was freeze-dried and ground, and the halichondrins were extracted with methanol/water and purified by chromatography. Subsequent analysis of the preparative HPLC residues from this large-scale isolation of the known halichondrins indicated the presence of low levels of four new halichondrins. These were separated by further chromatography to give microgram amounts of the new halichondrins **5**–**8**. By necessity the structural assignments relied heavily on 1D and 2D NMR spectra obtained using a capillary NMR probe.



2. Results and discussion

Of these new derivatives, halichondrin B-1140 (**5**) (55 μg) was the least polar (HPLC t_R 5.9 min), and high-resolution LCMS (*m/z*

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Table 1
^{1}H and ^{13}C NMR chemical shift data for halichondrins **5** and **6**[a]

Position	Halichondrin B-1140 (**5**)		Halichondrin B-1092 (**6**)	
	C[b]	H	C[c]	H
1	[d]		[d]	
2	40.3	2.35, 2.58	40.4	2.34, 2.59
3	73.6	3.87	73.6	3.87
4	30.7	1.36, 1.74	30.6	1.36, 1.74
5	29.9	1.37, 2.08	30.0	1.37, 2.08
6	68.2	4.32	68.2	4.32
7	77.6	2.93	77.6	2.93
8	74.3	4.32	74.3	4.31
9	73.8	4.05	73.8	4.04
10	76.5	4.18	76.5	4.18
11	82.1	4.58	82.2	4.58
12	81.2	4.67	81.1	4.66
13	48.3	1.94, 2.13	48.3	1.94, 2.15
14	[d]		[d]	
15	34.4	1.62, 2.15	34.4	1.61, 2.18
16	28.1	1.40, 2.17	28.0	1.42, 2.15
17	75.3	4.09	75.3	4.09
18	38.7	2.25, 2.79	38.7	2.25, 2.78
19	[d]		[d]	
19=CH_2	[d]	4.91, 4.98	[d]	4.91, 4.98
20	75.3	4.36	75.3	4.36
21	29.4	1.42, 1.89	29.4	1.39, 1.86
22	32.0	1.60, 1.60	32.0	1.60, 1.60
23	74.8	3.53	74.8	3.53
24	43.2	1.05, 1.68	43.3	1.04, 1.70
25	35.9	2.20	35.9	2.21
25–Me	18.0	1.06	17.9	1.06
26	151.7		[d]	
26=CH_2	[d]	4.75, 4.80	[d]	4.76, 4.80
27	73.6	3.53	73.6	3.53
28	36.9	1.92, 2.00	36.8	1.92, 2.01
29	71.3	4.18	71.2	4.19
30	76.9	4.64	76.9	4.64
31	36.3	2.04	36.5	2.02
31–Me	15.0	0.98	15.0	0.99
32	77.5	3.17	77.4	3.17
33	66.4	3.79	66.3	3.80
34	29.1	1.79, 2.13	29.0	1.80, 2.13
35	75.3	4.09	75.3	4.09
36	76.3	4.10	76.2	4.09
37	43.5	1.91, 2.35	43.5	1.90, 2.33
38	[d]		[d]	
39	42.6	2.19, 2.19	42.6	2.21, 2.21
40	70.8	3.92	71.1	3.91
41	79.5	3.58	79.1	3.61
42	25.7	2.32	25.7	2.28
42–Me	17.6	0.92	17.5	0.93
43	36.9	1.33, 1.45	36.9	1.33, 1.52
44	[d]		[d]	
45	36.9	1.44, 1.44	37.1	1.43, 1.48
46	28.7	2.18	28.6	2.15
46–Me	17.1	0.90	16.8	0.89
47	72.8	3.06	76.0	3.22
48	63.6	3.53	66.4	3.72
49	31.4	1.79, 2.19	34.4	1.83, 2.10
50	74.7	3.90	66.4	3.49
51	76.4	4.06	76.3	3.77
52	37.9	2.02, 2.02	45.7	2.59, 2.72
53	77.3	4.38	[d]	
54	72.6	3.66	31.1	2.18
55	45.9	3.55, 3.55		

[a] Values in ppm relative to $CHCl_3$ (δ 7.25) and $CDCl_3$ (δ 77.0).
[b] Values obtained from HSQC-DEPT and ClGAR spectra.
[c] Values obtained from HSQC-DEPT spectrum.
[d] Values not detected.

1179.5001 [M+K]$^+$, Δ = −6.1 mmu), in combination with NMR data (Table 1), gave the molecular formula $C_{61}H_{85}ClO_{18}$ (19 double bond equivalents). A preliminary inspection of the ^{1}H NMR spectrum of **5** (Fig. 1, Supplementary data) showed this was very similar to the spectrum of homohalichondrin B (**4**)[3] ($C_{61}H_{86}O_{19}$), but with an increase of 18 Da suggesting the replacement of a hydroxyl group in

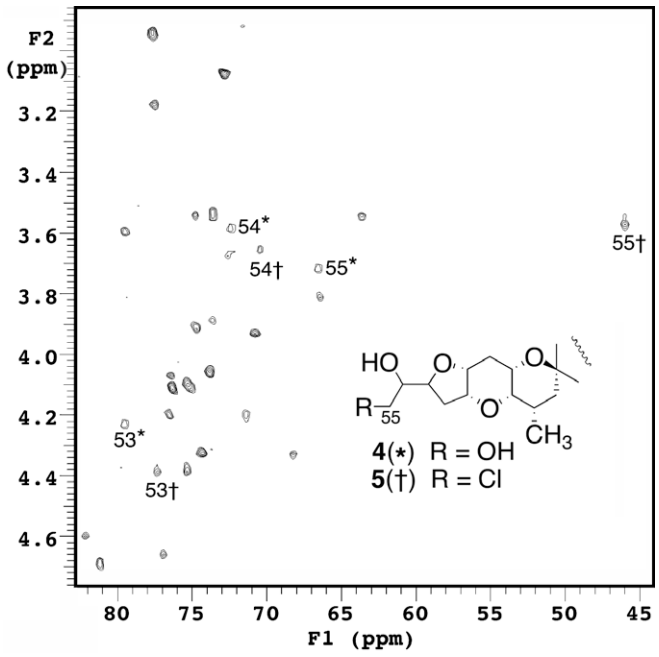

Figure 1. The mid-field region of the HSQC-DEPT NMR spectra of homohalichondrin B (**4**) and halichondrin B-1140 (**5**). All correlations are identical for both molecules, except for those marked with * which appear in the spectrum of **4**, but not in that of **5**, and those marked † which appear in the spectrum of **5**, but not in that of **4**.

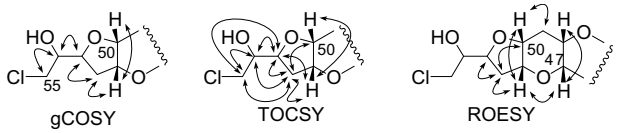

Figure 2. gCOSY and TOCSY correlations for the C50–C55 region and selected ROESY correlations for the C47–C55 region of compound **5**.

homohalichondrin B (**4**) with chlorine. The ^{1}H and ^{13}C NMR spectra of homohalichondrin B (**4**) had both been fully assigned. Comparison, therefore, of the HSQC-DEPT spectra offers a higher resolution and two-dimensional approach to establishing the similarity and the points of difference between **4** and **5**. This assumption was verified by overlaying the HSQC-DEPT spectra of **4** and **5** (Fig. 1), and observing that they were identical except for the loss of correlations for C53, C54 and C55 from the spectrum of homohalichondrin B (**4**), being replaced by correlations (δ_H/δ_C) at 4.38/77.3 (CH), 3.66/72.6 (CH) and 3.55/45.9 (CH_2) in the HSQC-DEPT spectrum of **5**. These changes were consistent with the replacement of the 55-OH group in **4** with a Cl atom in **5**. The connectivity of the left hand end of the molecule was confirmed by gCOSY and TOCSY data, and ROESY correlations confirmed the relative stereochemistries, which were consistent with those observed for homohalichondrin B (**4**) (Fig. 2). An attempt to determine the stereochemistries at positions C53 and C54 from coupling constants derived from cross sections in the TOCSY experiment failed due to insufficient resolution. This is the first chloro-halichondrin to be reported.

Halichondrin B-1092 (**6**) (88 μg) was the second least polar (HPLC t_R 5.7 min) of the four new halichondrin derivatives, and high-resolution LCMS (*m/z* 1115.5530 [M+Na]$^+$, Δ = −2.5 mmu), in combination with NMR data (Table 1), gave the molecular formula $C_{60}H_{84}O_{18}$ (19 double bond equivalents). A preliminary inspection of the ^{1}H NMR spectrum of **6** (Fig. 2, Supplementary data) showed this to be very similar to the spectrum of isohomohalichondrin B (**3**) ($C_{61}H_{86}O_{19}$), with a decrease of 30 Da suggesting

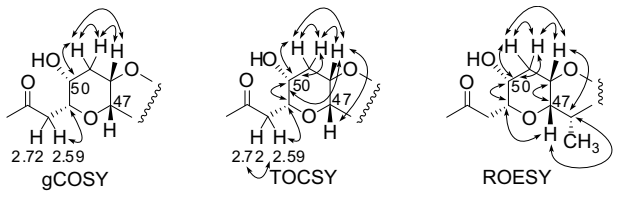

Figure 3. gCOSY and TOCSY correlations for the C47–C54 region and selected ROESY correlations for the C46–C54 region of compound **6**.

the loss of CH_2O from **3**. Overlaying the HSQC-DEPT spectrum of **6** with that of isohomohalichondrin B (**3**) confirmed that the two compounds had identical ^1H and ^{13}C chemical shifts for all protonated carbons up to position C50, with only a slight change for the shifts at position C51 (data in Table 1). The loss of correlations corresponding to C52, C54 and C55 for isohomohalichondrin B (**3**) and their replacement by correlations (δ_H/δ_C) at 2.59,2.72/45.7 (CH_2) and 2.18/31.1 (CH_3) in the HSQC-DEPT spectrum of **6** could be accounted for by a loss of the C55 CH_2OH group from isohomohalichondrin B (**3**). The connectivity of this portion of the molecule was confirmed from gCOSY and TOCSY data, and the relative stereochemistries were confirmed to be the same as those observed for isohomohalichondrin B from ROESY correlations (Fig. 3).

Halichondrin B-1020 (**7**) (50 μg) was the second most polar (HPLC t_R 5.3 min) of the four new halichondrin derivatives. High-resolution LCMS (*m/z* 1038.5372 $[M+NH_4]^+$, $\Delta = -5.4$ mmu), in combination with NMR data (Table 2, and Fig. 3, Supplementary data), gave the molecular formula $C_{56}H_{76}O_{17}$ (19 double bond equivalents). This is 90 Da less than that observed for halichondrin B (**1**), corresponding to the replacement of the terminal chain from carbon 50 in halichondrin B (**1**) with a carbonyl moiety, thus converting the terminal ring to a γ-lactone. The NMR assignments (Table 2) were confirmed by gCOSY, TOCSY, ROESY and HSQC-DEPT 2D experiments, in addition to comparisons with the known NMR chemical shifts for halichondrin B (**1**). The observed ^1H NMR chemical shifts for compound **7** showed excellent agreement with those of halichondrin B up to C45. The connectivity of the remainder of the molecule was established from gCOSY and TOCSY data (Fig. 4). The presence of a large $^2J_{HH}$ value of 17 Hz for the methylene protons at C49 (δ 2.50, 2.66) was consistent with the presence of a carbonyl group at C50.[8] H47 (δ 4.21) and H48 (δ 4.26) were determined to be *cis* from the small 2 Hz coupling constant observed for H48, and the relative stereochemistry of these protons was established from observed ROESY correlations between H46 (δ 2.43) and both H47 and H48 (Fig. 4). These stereochemistries were consistent with those observed for halichondrin B (**1**).

Halichondrin B-1076 (**8**) (110 μg) was the most polar (HPLC t_R 5.1 min) of the five new halichondrin derivatives, and high-resolution LCMS (*m/z* 1099.5171 $[M+Na]^+$, $\Delta = -7.1$ mmu), in combination with NMR data (Table 2, and Fig. 4, Supplementary data), gave the molecular formula $C_{59}H_{80}O_{18}$ (20 double bond equivalents). This is 46 Da less than the mass observed for homohalichondrin B (**4**), corresponding to the replacement of the terminal chain from carbon 53 in homohalichondrin B with a carbonyl group, thus converting the terminal ring to a γ-lactone. Overlaying the HSQC-DEPT spectrum of **8** with that of homohalichondrin B (**4**) showed that the two compounds had identical ^1H and ^{13}C chemical shifts (data in Table 2) for all protonated carbons up to position C46, with only a slight change for the shifts at position C47. The ^{13}C NMR chemical shift for C47 (δ 73.2) was confirmed from a CIGAR experiment,[9] leading to confirmation of the ^1H NMR chemical shift (δ 3.13) from the HSQC-DEPT spectrum. This left three methines and two methylenes unassigned from the HSQC-DEPT spectrum of **8**. The connectivity of this portion of the molecule was established from gCOSY and TOCSY data (Fig. 5). As observed for C49 in halichondrin B-1020 (**7**), a large $^2J_{HH}$ value of 17 Hz for the methylene protons at C52 (δ 2.56, 2.65) was consistent with the presence of a carbonyl group at C53.

Table 2
^1H and ^{13}C NMR chemical shift data for halichondrins **7** and **8**[a]

Position	Halichondrin B-1020 (**7**)		Halichondrin B-1076 (**8**)	
	C[b]	H	C[c]	H
1	[d]		[d]	
2	40.4	2.35, 2.59	40.3	2.32, 2.57
3	73.7	3.88	73.7	3.87
4	30.6	1.38, 1.75	30.6	1.37, 1.73
5	30.0	1.37, 2.09	29.9	1.37, 2.07
6	68.3	4.33	68.2	4.30
7	77.7	2.94	77.7	2.92
8	74.3	4.32	74.4	4.30
9	73.8	4.05	73.8	4.03
10	76.5	4.19	76.5	4.17
11	82.1	4.59	82.2	4.57
12	81.1	4.68	81.1	4.66
13	48.3	1.94, 2.16	48.3	1.93, 2.14
14	[d]		[d]	
15	34.4	1.62, 2.16	34.4	1.61, 2.15
16	28.2	1.43, 2.17	28.1	1.41, 2.15
17	75.2	4.10	75.2	4.09
18	38.6	2.27, 2.79	38.6	2.26, 2.78
19	[d]		[d]	
19=CH_2	[d]	4.91, 4.99	[d]	4.90, 4.97
20	75.3	4.37	75.3	4.37
21	29.6	1.40, 1.88	29.5	1.39, 1.88
22	32.0	1.61, 1.61	31.9	1.59, 1.59
23	74.8	3.54	74.7	3.52
24	43.4	1.04, 1.70	43.3	1.04, 1.67
25	36.0	2.20	35.9	2.19
25–Me	18.0	1.07	17.9	1.05
26	[d]		151.7	
26=CH_2	[d]	4.76, 4.81	[d]	4.74, 4.79
27	73.5	3.53	73.6	3.50
28	36.9	1.94, 2.02	36.8	1.92, 2.02
29	71.2	4.21	71.3	4.19
30	76.9	4.65	77.0	4.65
31	36.5	2.04	36.3	2.01
31–Me	15.0	1.00	15.0	0.97
32	77.5	3.19	77.4	3.15
33	66.3	3.81	66.3	3.78
34	29.1	1.80, 2.13	29.1	1.77, 2.14
35	75.2	4.10	75.2	4.09
36	76.2	4.10	76.3	4.10
37	43.4	1.92, 2.36	43.4	1.88, 2.34
38	[d]		[d]	
39	42.7	2.22, 2.22	42.6	2.18, 2.18
40	71.7	3.98	70.9	3.89
41	79.1	3.63	79.3	3.57
42	25.4	2.23	25.6	2.26
42–Me	17.5	0.94	17.5	0.90
43	36.2	1.35, 1.47	36.6	1.32–1.40
44	[d]		[d]	
45	36.1	1.37, 1.58	36.6	1.32–1.40
46	25.5	2.43	28.6	2.17
46–Me	17.2	1.06	16.9	0.88
47	81.0	4.21	73.2	3.13
48	68.8	4.26	62.7	3.59
49	38.6	2.50, 2.66	29.9	1.91, 2.37
50	[d]		75.2	4.31
51			72.8	4.18
52			38.6	2.56, 2.65
53			[d]	

[a] Values in ppm relative to $CHCl_3$ (δ 7.25) and $CDCl_3$ (δ 77.0).
[b] Values obtained from HSQC-DEPT spectrum.
[c] Values obtained from HSQC-DEPT and CIGAR spectra.
[d] Values not detected.

The biological activities of the halichondrin compounds **1,3–8** in an in vitro P388 murine leukaemia cell line assay[7] are given in Table 3. All compounds were found to have comparable potency in this assay. These results are consistent with previous results showing that

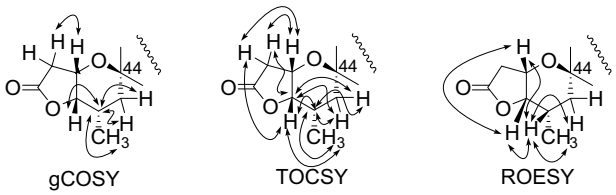

Figure 4. gCOSY and TOCSY correlations and selected ROESY correlations for the C44–C50 region of compound **7**.

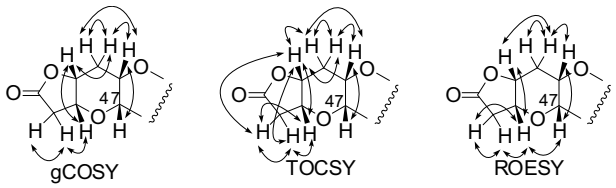

Figure 5. gCOSY and TOCSY correlations for the C47–C54 region and selected ROESY correlations for the C46–C54 region of compound **8**.

the biological activity of the halichondrin B compounds derives principally from the region of the molecule up to C30 (the right hand half).[1,2] The estimated sample masses of the new halichondrins (**5**–**8**) are also shown in Table 3. These masses were calculated by an NMR method, involving the calibration of the intensity of the residual $CHCl_3$ solvent signal as described in Section 4.

3. Conclusion

The structures of four new halichondrins (**5**–**8**) have been determined. All of these compounds are similar to known B series halichondrins, with differences occurring only beyond carbon 48. As biological activity has been shown to be derived from the region of the molecule between carbons 1 and 30, halichondrins **5**–**8** all retained good activity in the P388 assay as expected. Structural analysis of these compounds was markedly assisted by the overlaying of HSQC-DEPT spectra of the compounds with those of related, known halichondrins. This comparison technique effectively showed the identity of the related ^{13}C and ^{1}H chemical shifts for most of the protonated carbons in the compounds being compared. The tedious task of individually assigning all protons and carbons from a range of 1D and 2D NMR spectra for each new compound, and the subsequent visual comparison of numeric data, was be avoided. This approach should be of value in similar situations involving data comparisons for large molecules. This report has also demonstrated the value of using a capillary NMR probe capable of providing high quality 1D and 2D NMR data for microgram quantities of moderately large molecules.

4. Experimental

All NMR spectra were recorded at 23 °C on a Varian INOVA 500 MHz spectrometer fitted with a 500 MHz Protasis Capillary NMR probe, using $CDCl_3$ with 0.1% C_5D_5N as the solvent. Typically, all of the available sample (50–110 μg) was dissolved in 7 μL of solvent for injection into the capillary probe. High-resolution liquid chromatography mass spectra (HRLCMS) were recorded on a Waters 2790 HPLC system equipped with a Waters 996 photodiode array detector (PDA) coupled to a Micromass LCT spectrometer using a probe voltage of 3200 V, an operating temperature of 150 °C and a source temperature of 80 °C. The carrier solvent was 50:50 ACN/H_2O at 20 μL/min (for direct inject mode). Typically, 10 μL of a 10 μg/mL solution was injected. Leucine enkephalin was used as the internal standard.

Table 3
Estimated sample masses and in vitro cytotoxicities of selected halichondrins

Compound	Sample mass (μg)	P388 IC_{50} (ng/mL)
Halichondrin B (**1**)		0.78
Isohomohalichondrin B (**3**)		0.18
Homohalichondrin B (**4**)		0.22
Halichondrin B-1140 (**5**)	55	2.0
Halichondrin B-1092 (**6**)	88	0.76
Halichondrin B-1020 (**7**)	50	1.1
Halichondrin B-1076 (**8**)	110	1.1

The *Lissodendoryx* sp. sponge (1 tonne; collected under licence from the Department of Conservation following a field survey that established stock of ~300 tonne in the area) was collected by trawling at depths of ~100 m off the Kaikoura coast of New Zealand in 1995 in order to supply halichondrin B (**1**, ~200 mg) and isohomohalichondrin B (**3**, ~300 mg) for further trials.[2] The sponge was frozen immediately after collection, freeze-dried, and ground to a powder. The powder was extracted with water and methanol (to give a final water/methanol ratio of 1:4) in batches (10.5 kg), followed by petroleum ether and ethyl acetate partitions, giving a crude extract (106 g). This extract was subjected to ODS-silica column chromatography, eluting with increasing concentrations of methanol in water followed by CH_2Cl_2, yielding an oil (5.8 g) that was then further purified by Sephadex LH-20 column chromatography, eluting with CH_2Cl_2, again yielding an oil (4.6 g). This oil was purified via preparative HPLC on ODS-silica (CH_3CN/H_2O, 7:3 or 9:1).

During the final HPLC purification of isohomohalichondrin B (**3**), 12 bottles (each 2.5 L) of side cut residues were accumulated. The residues from each of these bottles were dried down individually, weighed, and analysed by ^{1}H NMR and analytical HPLC on ODS-silica (CH_3CN/H_2O, 7:3 and 9:1). Signals in the ^{1}H NMR spectra characteristic of the halichondrins (e.g., those between δ 4.7 and 5 ppm corresponding to the 19=CH_2 and 26=CH_2 exocyclic methylenes) were observed in the extracts of all twelve bottles. In the HPLC chromatograms, halichondrin-like peaks, which exhibit end absorption only, were also seen.

The dried residues were combined (~300 mg), and processed on an LH-20 column (250 g, 57 × 4.3 cm, eluting with CH_2Cl_2) to give 60 fractions. Fractions containing halichondrins were identified via DIOL TLC (4% MeOH/CH_2Cl_2), analytical HPLC on ODS-silica and ^{1}H NMR analysis. These fractions were processed on a semi-preparative ODS-silica HPLC column, eluting with 50% CH_3CN/H_2O. Fractions containing halichondrins were identified as described above, and processed by analytical HPLC on ODS-silica (CH_3CN/H_2O, 7:3) to give four pure fractions (halichondrin B-1140 (**5**), t_R 5.9 min, 55 μg; halichondrin B-1092 (**6**), t_R 5.7 min, 88 μg; halichondrin B-1020 (**7**), t_R 5.3 min, 50 μg; halichondrin B-1076 (**8**), t_R 5.1 min, 110 μg) that were characterised by HRLCMS and a full range of NMR spectra run on a capillary NMR probe.

The quantity of each compound was estimated by a ^{1}H NMR spectroscopic method in which each sample was dissolved in 7 μL of $CDCl_3$ with 0.1% C_5D_5N and injected into a capillary probe (cell size ~ 6 μL). Sample masses were then estimated using the formula:

$$(MW/\#H) \times (\text{total integral for } \#H)/(\text{integral for } CHCl_3) \times CF$$

where MW is the molecular weight of the compound, #H is the number of protons in the selected resonances used for integration, 'total integral for #H' is the sum of the integrals for the selected resonances, and CF is the calibration factor that had previously been determined from a standard solution containing quinine (5 mg/mL) in the same $CDCl_3$ solvent. #H was typically ~10, with resonances selected on the basis of their resolution from other resonances and from the solvent peak. Acquisition parameters were maintained constant for all of these determinations.

*Halichondrin B-1140 (**5**).* White solid (estimated 55 μg), UV (CH_3CN/H_2O, 7:1) end absorption only; P388 IC_{50} 2.0 ng/mL; NMR data in Table 1; HRLCMS *m/z* 1179.5001 $[M+K]^+$ (calcd for $C_{61}H_{85}O_{18}ClK$, 1179.5062).

*Halichondrin B-1092 (**6**).* White solid (estimated 88 μg), UV (CH_3CN/H_2O, 7:1) end absorption only; P388 IC_{50} 0.76 ng/mL; NMR data in Table 1; HRLCMS *m/z* 1115.5530 $[M+Na]^+$ (calcd for $C_{60}H_{84}O_{18}Na$, 1115.5555).

*Halichondrin B-1020 (**7**).* White solid (estimated 50 μg), UV (CH_3CN/H_2O, 7:1) end absorption only; P388 IC_{50} 1.1 ng/mL; NMR data in Table 2; HRLCMS *m/z* 1038.5372 $[M+NH_4]^+$ (calcd for $C_{56}H_{80}O_{17}N$, 1038.5426).

*Halichondrin B-1076 (**8**).* White solid (estimated 110 μg), UV (CH_3CN/H_2O, 7:1) end absorption only; P388 IC_{50} 1.1 ng/mL; NMR data in Table 2; HRLCMS *m/z* 1099.5171 $[M+Na]^+$ (calcd for $C_{59}H_{80}O_{18}Na$, 1099.5242).

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Supplementary data

^1H NMR spectra of halichondrins **5**–**8** are given in Figures 1–4, respectively. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2008.10.093.

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