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New Non-Contiguous Polypropionates from Marine Molluscs: A Comment on their Natural Product Status

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Abstract—The structure of the rearranged polypropionate ester siserrone A (**8**), isolated from *Siphonaria serrata*, was investigated by standard spectroscopic methods and the relative stereochemistry determined by ROESY spectroscopy and chemical degradation studies. Base-catalysed rearrangement of denticulatin A (**13**) yields the polypropionate ester (**16**) while careful work-up of *S. baconi* yields the siphonarins, but not the baconipyrones, as earlier reported. The natural product status of polypropionate ester metabolites is discussed.

Gastropod molluscs are a source of novel secondary metabolites shown to be biosynthesised from propionate units.[1–3] Examples of these metabolites, which possess a non-contiguous polypropionate backbone, include the baconipyrones A–D (**1**–**4**) from the pulmonate *Siphonaria zelandica*,[4] the ester **5** from *S. australis*,[5] and dolabriferol (**6**) from the anaspidean mollusc *Dolabrifera dolabrifera*.[6] All of these 'metabolites' have been hypothesised to arise from a hemiketal precursor by ring-opening and rearrangement. In this paper we report the structure of a new polypropionate ester, siserrone A (**8**), from *S. serrata* which may derive from dihydrosiphonarin A (**7**)[7] and also provide experimental evidence for polypropionate rearrangements under mild base-catalysed conditions.

A preliminary investigation of an acetone extract of an endemic South African siphonariid, *S. serrata*, revealed a mixture of the known polypropionate compounds, **7** and dihydrosiphonarin B (**9**),[7] and a minor γ-pyrone containing polypropionate metabolite, **8**. To obtain more of **8** for structural studies a second collection of *S. serrata* from the same collection site was made. Surprisingly, exhaustive semi-preparative HPLC of an acetone extract of the latter collection of siphonariids yielded only **8** and did not contain any discernable quantities of **7** or **9**.

The molecular formula of **8** was established as $C_{28}H_{44}O_8$ from HREIMS data (*m*/*z* 508.3040 Δmmu+0.7) while the IR spectrum revealed absorbances consistent with hydroxyl (ν_{max} 3390 cm^{-1}) and carbonyl functionalities (ν_{max} 1720 cm^{-1}). Similarities between the NMR data of **7** and **8** enabled the assignment of five deshielded ^{13}C NMR signals (179.2, 160.7, 160.5, 120.3 and 119.1 ppm) and three olefinic ^{1}H NMR methyl singlets (δ 1.99, 1.88 and 2.18) to a trimethylated γ-pyrone ring in the latter compound. The ^{13}C NMR and HMQC spectra of **8** also supported the presence of a ketone and an ester carbonyl (209.9 and 175.1 ppm) and an acetal quaternary carbon (99.5 ppm). These data accounted for six of the seven degrees of unsaturation implied by the molecular formula and required siserrone A to be bicyclic. The COSY spectrum of **8** confirmed the presence of four isolated spin systems (H-1 to H-21, H-8 to H-22, H-23 to H-24 and H-14 to H-25).

The HMBC data of **8** facilitated the linkage of these separate spin systems via the intervening quaternary carbon atoms. Three bond HMBC correlations from H-6 and the methylene protons (2H-8) to the acetal carbon (C-7) effectively connected the first two spin systems. In the absence of evidence to the contrary, we propose that the oxymethine carbon C-3 (74.5 ppm) is linked through an oxygen atom to C-7 to form a tetrahydropyran ring. The chemical shift of the deshielded H-5 proton signal (δ 5.18) placed the ester functionality at C-5, an observation supported by a three bond HMBC correlation between H-5 and the ester carbonyl (C-9). Two and three bond HMBC correlations from H-10 and H-11 to C-9, respectively, linked the third spin system (H-23 to H-24) to the first two. Further HMBC correlations from H-14 to C-13, C-15 and C-16 and from the methyl protons (3H-25) to C-13 and C-15 identified the $CH–CH_3$ unit (C-14–C-25) as the fourth substituent of the γ-pyrone

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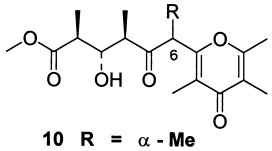
Table 1. Proton and ^{13}C NMR data for siserrone A (**8**)

Position	δ^1H[a] (multiplicity)[b]	$\delta^{13}C$[c]	HMBC to C	ROESY to H
1	0.89 (*m*)	9.4	2, 3	4
2	1.38 (*m*), 1.63 (*m*)	25.4	3	–
3	3.49 (*m*)	74.5	–	5
4	1.63 (*m*)	33.6	3, 5	–
5	5.18 (*dd*, 11.2, 4.9)	76.5	9, 20, 21	3, 6, 20
6	1.95 (*dq*, 4.9, 6.9)	38.3	4, 5, 7	5
7	–	99.5	–	–
8	1.55 (*m*)	31.9	7, 22	–
9	–	175.1	–	–
10	2.65 (*m*)	41.2	9, 23	11
11	3.59 (*m*)	77.0	9	10
12	2.73 (*m*)	48.4	11	14
13	–	209.9	–	–
14	4.00 (*q*, 6.9)	51.1	13, 15, 16, 25	12, 26
15	–	160.7[d]	–	–
16	–	120.3	–	–
17	–	179.2	–	–
18	–	119.1	–	–
19	–	160.5[d]	–	–
20	0.76 (*d*, 6.9)	8.6	3, 4, 5	3, 5
21	0.75 (*d*, 6.2)	13.0	5, 6, 7	4
22	0.89 (*m*)	6.4	5, 7, 8	–
23	1.27 (*d*, 7.2)	15.1	9, 10, 11	11
24	0.89 (*d*, 7.0)	14.0	11, 12, 13	–
25	1.32 (*d*, 6.9)	12.8	13, 14, 15	–
26	1.99 (*s*)	9.8	15, 16, 17	14
27	1.88 (*s*)	9.9	17, 18, 19	–
28	2.18 (*s*)	17.4	18, 19	–

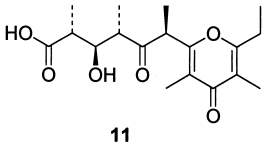
[a] 400 MHz; solution in $CDCl_3$ referenced to $CDCl_3$ at $^1H=\delta$ 7.25.
[b] Coupling constants in Hz.
[c] Inverse detection at 400 MHz (HMQC); solution in $CDCl_3$ referenced at $^{13}C=\delta$ 77.0.
[d] Assignments may be interchanged.

ring and also linked this disubstituted ethyl unit to the ketone carbonyl (C-13). Finally, an HMBC correlation from the three overlapping methyl resonances (3H-1, 3H-22 and 3H-24) to C-13 was attributed to the three bond connectivity between the latter methyl proton signal and this carbon atom, thereby completing the structure elucidation of **8**. To account for the eight oxygen atoms implied by the molecular formula of siserrone A, the oxymethine carbon (C-11) must bear an hydroxyl substituent. The NMR data for **8** are presented in Table 1.

A ROESY NMR experiment was used to explore the relative stereochemistry of the cyclic hemiketal in **8**. The strong NOE connectivity observed between H-3 (δ 3.49) and H-5 (δ 5.18) tentatively placed these two protons in axial positions and suggested that the tetrahydropyran ring adopts a thermodynamically preferred chair conformation with the C-3 and C-5 substituents in equatorial positions. ROESY correlation between H-5 and H-6 (δ 1.96) implied that the latter proton was equatorial thus requiring the C-21 methyl group to be axial. The large $J_{4,5}$ coupling constant (11.2 Hz) was indicative of a *trans* diaxial relationship between H-4 and H-5 while the smaller $J_{5,6}$ coupling constant (4.9 Hz) supported a *gauche* arrangement between H-5 and H-6.[9] The coupling constant for an equatorial methyl group, on a tetrahydropyran ring, is generally $\geq$7 Hz[7,8] and the observed $J_{4,20}$ coupling constant of 6.9 Hz for the C-20 methyl group tentatively placed this group in an equatorial position. The stereochemistry at C-7 in **8** could not be conclusively established from either NOE data or recourse to molecular modeling studies of the hemiketal ring in both C-7 epimers of this compound and subsequent comparison of the observed $J_{5,6}$ coupling constant with those calculated using the Karplus/Altona equation.



10 R = α - Me
12 R = β - Me



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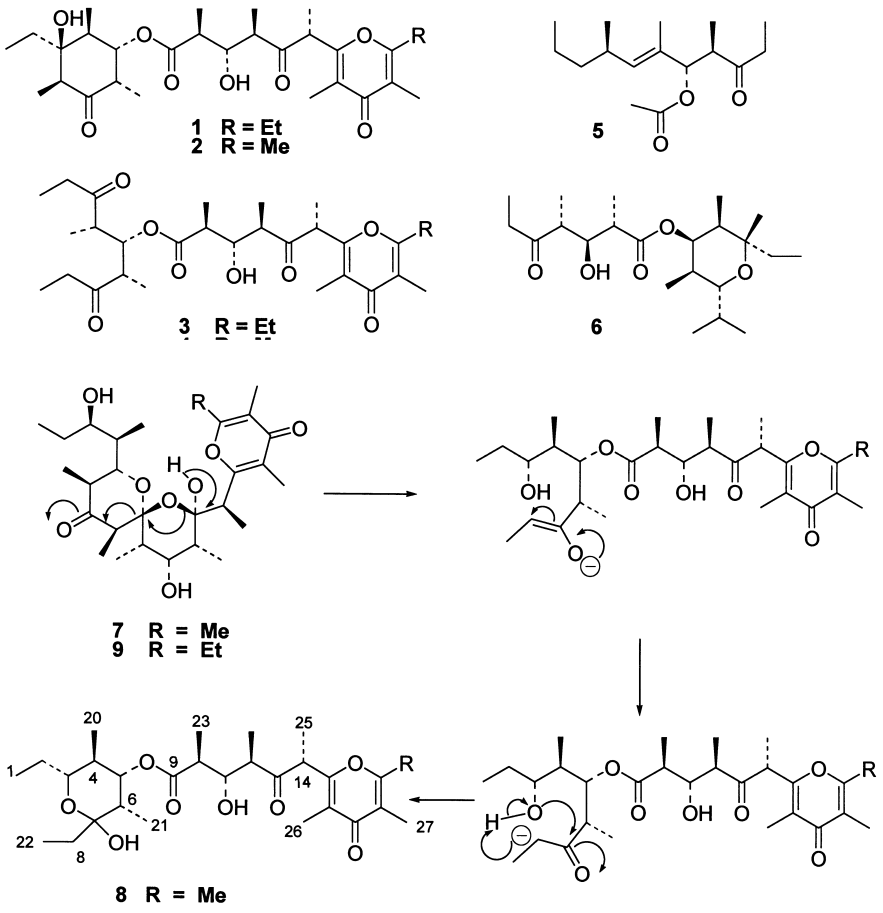
Unfortunately, **8** was unstable and degraded prior to the determination of the optical rotation. A TLC and NMR examination of an EtOAc solution of the degradation products revealed a complex mixture of both polar and non-polar compounds. Removal of the EtOAc under reduced pressure followed by partitioning of the resultant residue between hexane and acetonitrile separated the degradation products, with the latter partition fraction yielding a 4:1 mixture of two diastereomeric acids. The acidic mixture was esterified with ethereal diazomethane and the methyl esters separated by HPLC (EtOAc/hexane 4:1). The ^1H and ^{13}C NMR data of the major methyl ester (**10**) was consistent with those of the saponified ethyl homologue (**11**) prepared by Paterson et al.,[10] and tentatively suggested that these two compounds have the same relative stereochemistry at the four acyclic chiral centres. Compound **8**, and hence **10**, may be derived from **7** (Scheme 1) and the stereochemistry of **10** is thus antipodal to that of **11**.[1]

A comparison of the ^{13}C NMR data of **10**, **11** and the minor methyl ester **12**, revealed that the greatest difference in ^{13}C chemical shift occurred at C-6 ($\Delta\delta_{C\text{-}6}$=3.3 ppm) in the latter compound, possibly reflecting epimerization of this carbon atom through facile, resonance stabilized, keto–enol tautomerism. The co-occurrence of **7** and **8**, in the first collection of *S. serrata*, supports the position of **7** as a possible precursor of **8** as outlined in Scheme 1. However, the status of siserrone A as a natural product is tenuous and it is possible that the formation of **8** from **7** may occur during isolation.

The unusual non-contiguous polypropionate backbone of siserrone A is structurally related to the baconipyrones A–D, previously reported by Manker et al. from a Victorian collection of *S. baconi* (=*S. zelandica*[11]) together with siphonarin A[4]; our own work has previously revealed both the siphonarins and baconipyrones from *S. zelandica*, the common siphonariid of S.E. Queensland.[12] The baconipyrones are proposed to be rearrangement products generated from a siphonarin precursor.[4] However it is equally plausible that the baconipyrones are generated as artifacts during extraction of the limpets and metabolite isolation. A sample of *S. baconi* from Sorrento, Victoria was collected and carefully extracted. TLC and NMR examination did not reveal the presence of any baconipyrones thus casting suspicion on the natural product status of these polypropionate ester compounds.

We then found that polypropionate esters could be obtained by mild chemical treatment of contiguous polypropionates.



Scheme 1. Possible mechanism for the formation of siserrone A from dihydrosiphonarin A (adapted from Faulkner et al.[4]).

As part of a study to derivatise denticulatin A (**13**) we reacted this metabolite with the Sharpless AD-mix dihydroxylation reagents, but obtained instead the polypropionate funiculatin A (**14**).[13] We therefore speculated that the K_2CO_3 component present in the reagent had triggered rearrangement. When denticulatin A was stirred with K_2CO_3 alone for 24 h, several polypropionate products were isolated by HPLC, including the carboxylic acid (**15**) and the ester (**16**). The structure of **15** was easily assigned by comparison of its spectral data with those of the denticulatins.[14] The ester product **16** was unstable, decomposing within 4 h in chloroform solution at room temperature to acid **15**; nonetheless the former product was characterised by its ^1H and ^{13}C NMR spectra and by mass spectrometric analysis. The low resolution EIMS suggested that **16** was a structural isomer of denticulatin A. A small peak at *m/z* 378, consistent with $C_{23}H_{38}O_4$, was assigned to (M^+-H_2O) while a peak at *m/z* 57 suggested an ethyl ketone. Unfortunately no high resolution measurements could be made because of the instability of this compound.

The ^1H and ^{13}C NMR data for **16** are shown in Table 2. Detection of some carbon signals, e.g. C-3, was complicated

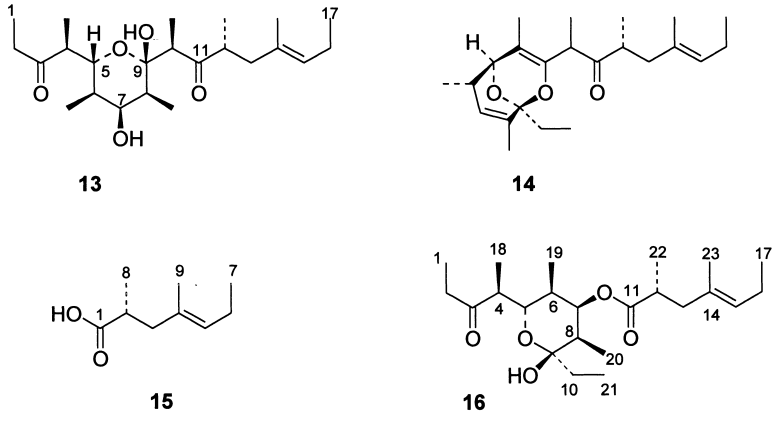


Table 2. Proton and ^{13}C NMR data for the polypropionate ester (**16**)

Position	δ^1H[a] (multiplicity)[b]	$\delta^{13}C$[c]	DQFCOSY to H	HMBC to C[d]
1	1.05 (*t*, 7.5)	7.0	2	2
2	2.50 (*dq*, 7.2, 14.5)	32.8	1	1
	2.62 (*dq*, 7.2, 14.5)		1	–
3	–	[e]	–	–
4	2.55 (*dq*, 6.9, 3.1)	48.0	5, 18	–
5	4.18 (*dd* 3.1, 10.6)	69.3	4, 6	–
6	1.81 (*ddq*, 10.6, 6.9, 2.8)	36.1	5, 7, 19	–
7	5.28 (*dd*, 2.8, 2.8)	76.3	6, 8	5, 9
8	1.89 (*dq* 7.1, 2.8)	39.3	7, 20	–
9	–	99.2	–	–
10	1.51 (*dq*, 7.4, 14.5)	31.4	21	9, 21
	1.60 (*m*)		21	9, 21
11	–	175.3	–	–
12	2.72 (*ddq*, 6.6, 7.0, 8.4)	37.8	13, 22	11, 13, 22
13	2.04 (*dd*, 8.4, 14.2)	43.5	12	12, 15, 22, 23
	2.42 (*dd*, 6.6, 14.2)		12	11, 12, 15, 22, 23
14	–	131.0	–	–
15	5.19 (*t*, 6.4)	129.8	16, 23	13, 16, 17, 23
16	1.98 (*m*, 7.6)	21.1	15, 17	15, 17
17	0.92 (*t*, 7.6)	14.1	16	15, 16
18	1.08 (*d*, 6.9)	16.1	–	4, 5
19	0.79 (*d*, 6.9)	16.2	6	5, 6, 7
20	0.91 (*d*, 7.1)	15.2	8	7, 8, 9
21	0.82 (*t*, 7.4)	7.0	10	9, 10
22	1.17 (*d*, 7.0)	17.9	12	11, 12, 13
23	1.61 (br *s*)	15.5	15	13, 15

[a] 500 MHz; solution in $CDCl_3$ referenced to $CDCl_3$ at $^1H=\delta$ 7.24.
[b] Coupling constants in Hz.
[c] Inverse detection at 500 MHz (HMQC); solution in $CDCl_3$ referenced at $^{13}C=\delta$ 77.0.
[d] Inverse detection at 500 MHz; correlations observed when ^1J $^{13}C-^1H=135$ Hz and long range J $^{13}C-^1H=4$ Hz.
[e] Not detected.

by the ease with which this compound decomposed during the acquisition of NMR data. Three triplet signals at δ 0.82, 0.92 and 1.05, indicating three ethyl signals, together with an ester at 175.3 ppm confirmed a rearrangement product. In addition an acetal signal was observed at 99.2 ppm. The fragments C-1 to C-6 and C-12 to C-17 were deduced by DQFCOSY, HMQC and HMBC data and by comparison with the spectroscopic data for the denticulatins;[14] the chemical shift of H7 (δ 5.28 compared to δ 4.39 in denticulatin A) clearly suggested the ester moiety was attached to this position. The spectroscopic data for the tetrahydropyranyl ring fragment were again assigned by analysis of 2D spectra, in particular the COSY correlations from H-5 through to H-8 and associated methyls, and match closely the equivalent data for dolabriferol **4**.[6] A vicinal coupling of 10.6 Hz suggested that H-5 and H-6 were both axial, hence the 2.8 Hz coupling between H-6 and H-7 was consistent with H-7 being equatorial. The H-7 to H-8 coupling of 2.8 Hz did not distinguish whether H-8 was axial or equatorial because of the adjacent axial ester substituent. However, the H-8 axial orientation could be deduced from the H-8 to H-20 coupling of 7.1 Hz, consistent with an equatorial Me-20.[8] The stereochemistry at C-6 to C-8 was thus identical to that in denticulatin A. The ester **16** was formed under reversible conditions, hence the hemiacetal hydroxyl was placed in the energetically-preferred axial position where it is likely to be strongly hydrogen-bonded to the ester carbonyl. The stereochemistry at C-4 and C-12 was inferred from that of denticulatin A. The instability of **16** prevented attempts to acquire NOESY or NOE data in support of the proposed stereochemistry. In conclusion, we propose that this rearrangement of denticulatin A is initiated by base catalysed opening of the hemiacetal ring, followed by intramolecular attack of the 7-hydroxyl on C-11, resulting in retro-aldol cleavage of the C-10/11 bond to form ester **16**.

Our data, together with those of the Paterson group,[10,15] show that polypropionate metabolites undergo facile rearrangement under mild conditions. The natural product status of polypropionate esters isolated from siphonariids should therefore be viewed with suspicion.

Experimental

The ^1H and ^{13}C NMR spectra were recorded on Bruker 400 and 500 MHz AMX NMR spectrometers using $CDCl_3$ as the solvent, referenced at δ 7.24/77.0 ppm for $^1H/^{13}C$. 2D Spectra were acquired using a 1 K by 256 complex data matrix which was zero filled once in both dimensions using a $\pi/2$ shifted sine bell squared window function before transformation. The HMBC and phase sensitive HMQC spectra were acquired with 64 transients using a 1 K×256 complex data matrix which was zero filled once in each dimension and a shifted sine-squared bell window function was applied in both dimensions before Fourier transformation. The evolution delay was set for ^nJCH of 8 Hz (HMBC) and ^1JCH of 135 Hz (HMQC). The DQFCOSY spectra were acquired with 16 or 24 transients per increment. A mixing time of 800 ms was used in the ROESY experiments. The high resolution mass spectrum of **8** was obtained by Dr P. Boshoff of the Mass Spectrometry Unit at the Cape Technikon, Cape Town, and HPLC

separations of this compound and its degradation products were achieved using a Whatman Magnum 9 Partisil column. The IR data for this compound were obtained on a Perkin–Elmer 180 spectrometer. HPLC separation of **16** was achieved using a Waters C_{18} semipreparative column.

Collection and extraction of *Siphonaria serrata*

Concentration under reduced pressure of the acetone extract of 270 specimens of *S. serrata*, collected from the Cape Recife area of South Africa in April 1996, followed by partitioning between ethyl acetate and water, gave a crude ethyl acetate partition fraction which was chromatographed on silica (EtOAc/hexane). Further normal phase chromatography (2:5 EtOAc/hexane) of the EtOAc silica chromatography fraction, yielded **8** as a pale yellow oil (0.4 mg/animal); IR (film) 3390, 2980, 1720, 1450, 1380, 1180; ^{1}H and ^{13}C NMR data see Table 1; HREIMS obsd. 508.3040, $C_{28}H_{44}O_8$ requires 508.3033.

Methylation of the degradation products of 8

The degradation products of **8** (28 mg) were partitioned between hexane and CH_3CN. The CH_3CN partition fraction was washed several times with hexane and the solvent removed under vacuum to yield a mixture of diastereomeric acids (23 mg). A solution of this acidic mixture (23 mg) in methanol (1 mL) was cooled (−10°C) and treated with an excess of ethereal diazomethane solution, allowed to stand (8 min. −10°C) and warmed to room temperature. Removal of the solvent under vacuum followed by normal phase HPLC (hexane/EtOAc 1:4) yielded the diastereomers **10** and **12** as pale yellow oils.

Diastereomer 10. (8.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3H, $J_{4,13}$=6.8 Hz, 3H-13), 1.28 (d, 3H, $J_{2,12}$=7.2 Hz, 3H-12), 1.36 (d, 3H, $J_{6,14}$=7.0 Hz, 3H-14), 1.93 (s, 3H, 3H-16), 2.05 (s, 3H, 3H-15), 2.21 (s, 3H, 3H-17); 2.66 (dq, 1H, $J_{2,3}$=3.0 Hz, $J_{2,12}$=7.2 Hz, H-2), 2.76 (dq, 1H, $J_{3,4}$=9.1 Hz, $J_{4,13}$=6.8 Hz, H-4), 3.28 (s, 1H, OH), 3.60 (dd, 1H, $J_{2,3}$=3.0 Hz, $J_{3,4}$=9.1 Hz, H-3), 3.67 (s, 3H, OMe), 4.02 (q, 1H, $J_{6,14}$=7.0 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) 9.9 (q, C-15), 10.0 (q, C-16), 12.8 (q, C-14), 14.1 (q, C-13), 15.0 (q, C-12), 17.5 (q, C-17), 41.0 (d, C-2), 48.2 (d, C-4), 51.2 (d, C-6), 52.0 (q, OMe), 77.4 (d, C-3), 119.3 (s, C-10), 120.4 (s, C-8), 160.5 (s, C-11), 160.6 (s, C-7), 175.8 (s, C-1), 179.4 (s, C-9), 210.0 (s, C-5) ppm.

Diastereomer 12. (2.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 3H, $J_{2,12}$=7.0 Hz, 3H-12), 1.13 (d, 3H, $J_{4,13}$=7.0 Hz, 3H-13), 1.34 (d, 3H, $J_{6,14}$=7.0 Hz, 3H-14), 1.93 (s, 3H, 3H-16), 2.03 (s, 3H, 3H-15), 2.23 (s, 3H, 3H-17); 2.61 (dq, 1H, $J_{2,3}$=5.0 Hz, $J_{2,12}$=7.0 Hz, H-2), 2.83 (dq, 1H, $J_{3,4}$=7.1 Hz, $J_{4,13}$=7.0 Hz, H-4), 3.10 (s, 1H, OH), 3.65 (s, 3H, OMe), 3.68 (dd, 1H, $J_{2,3}$=5.0 Hz, $J_{3,4}$=7.1 Hz, H-3), 4.03 (q, 1H, $J_{6,14}$=7.0 Hz, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) 9.9 (q, C-15), 10.0 (q, C-16), 13.2 (q, C-14), 14.6 (q, C-12), 15.0 (q, C-13), 17.5 (q, C-17), 42.1 (d, C-2), 47.2 (d, C-4), 47.9 (d, C-6), 51.8 (q, OMe), 76.0 (d, C-3), 119.2 (s, C-10), 120.3 (s, C-8), 159.9 (s, C-11), 160.7 (s, C-7), 175.2 (s, C-1), 179.2 (s, C-9), 210.4 (s, C-5) ppm.

Collection and extraction of *S. zelandica*

Isolation of siphonarins A and B and of baconipyrone C from 330 specimens of *S. zelandica* collected from the intertidal region at Caloundra, Queensland, was accomplished according to literature procedures.[4,7] A collection of 100 specimens of *S. zelandica* from Sorrento, Victoria, was worked up in identical fashion and gave the siphonarins A and B, but no baconipyrones were present in the extract.

Isolation of rearrangement products 15 and 16

Denticulatin A (10 mg) in dichloromethane (10 mL) was stirred vigorously with aqueous K_2CO_3 at room temperature for 24 h. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2×10 mL), then the combined organic layers dried over Na_2SO_4 and evaporated to dryness. Purification of the residue by reverse-phase HPLC (80% methanol/H_2O) gave the acid **15** and the ester **16** (<1 mg of each). The rearranged product **16** was not stable, decomposing to **15** after about 4 h in *d*-chloroform; to obtain sufficient for 2D NMR studies, the products from several reactions were pooled.

Acid 15. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, 3H, $J_{6,7}$=7.6 Hz, 3H-7), 1.15 (d, 3H, $J_{2,8}$=7.0 Hz, 3H-8), 1.58 (br s, 3H-9), 2.00 (m, 2H, $J_{6,7=}$7.6 Hz, 2H-6), 2.15 (dd, 1H, $J_{2,3}$=8.4 Hz, $J_{3,3}$=14.2 Hz, H-3), 2.43 (dd, 1H, $J_{2,3}$=6.6 Hz, $J_{3,3}$=14.2 Hz, H-3), 2.62 (ddq, 1H, $J_{2,3}$=6.6 Hz, $J_{2,3}$=8.4 Hz, $J_{2,8}$=7.0 Hz), 5.20 (t, 1H, $J_{5,6}$=6.9 Hz, H-5); ^{13}C NMR (125 MHz, $CDCl_3$) 14.2 (t, C-7), 15.4 (q, C-9), 16.3 (q, C-8), 21.2 (t, C-6), 37.6 (d, C-2), 43.5 (t, C-3), 129.4 (d, C-5), 131.0 (s, C-4), 181.4 (s, C-1) ppm.

Ester 16. EIMS 378 (8%, M^+-H_20), 296 (7%), 223 (38%), 167 (45%), 137 (100%), 109 (90%), 83 (50%), 69 (42%) and 57 (78%); ^{1}H and ^{13}C NMR see Table 2.

Acknowledgements

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