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TERPENOIDS FROM THE DORID NUDIBRANCH *CADLINA LUTEOMARGINATA*

JOCELYNE HELLOU and RAYMOND J. ANDERSEN*
Departments of Chemistry and Oceanography, University of British Columbia, Vancouver, B.C., Canada, V6T 2W5

and

JANICE E. THOMPSON
Scripps Institution of Oceanography, University of California, San Diego, La Jolla, CA 92093, U.S.A.

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Abstract—Methanol extracts of intact specimens of *Cadlina luteomarginata*, collected in Howe Sound and Barkley Sound, British Columbia, have been shown to contain sesquiterpenoids and a degraded terpenoid. Albicanol (**2**) and its acetate **1** possess the drimane skeleton. Furodysin (**4**), furodysinin (**5**) and microcionin-2 (**6**) are furanosesquiterpenoids of sponge origin. Luteone (**8**), the degraded terpenoid, represents a new carbon skeleton.

Dorid nudibranchs are delicate, shell-less and often strikingly colored molluscs that would seem to be ill-equipped to ward off predators. In spite of their apparent vulnerability, few animals have been recorded as predators of nudibranchs.[1] It has been suggested that utilization of various combinations of behaviour, coloration, chemical secretions, spicules, and nematocyst storage effectively thwarts nudibranch predators.[2] The chemical secretions may be either concentrated sulfuric acid[3] or organic metabolites.[1b]

A large number of fascinating metabolites, many of which are toxic or antibacterial, have been isolated from soft bodied molluscs belonging to the class gastropoda.[4] The dorid nudibranchs, however, have received relatively little chemical attention. Burreson *et al.* showed that the tropical dorid *Phyllidia varicosa* secretes 9-isocyanopupukeanane, which is a fish and crustacean toxin.[5] *Hypselodoris godeffroyana* and *Chromodoris maridadilus*, two Hawaiian dorids, ingest and store the sponge metabolites nakafuran-8 and nakafuran-9. Both compounds effectively repel frequently encountered reef fishes in laboratory bioassays.[6] Marsilin and idiadione, two furanoterpenoids, have been reported by Faulkner *et al.* from extracts of the California dorids *Chromodoris marislae*[7] and *Cadlina luteomarginata*[8] respectively. The same group has reported a series of nine chlorinated acetylenes from *Dialula sandiegensis*.[9] Castiello *et al.* have recently identified a series of long chain acetylenes in extracts of the Mediterranean dorid *Peltodoris atromaculata*.[10] Doridosine, a pharmacologically active purine derivative, has been isolated by Fuhrman *et al.* from the digestive glands of the California dorid *Anisodoris nobilis*.[11] Our group has shown that extracts of *Archidoris ohdneri* contain a series of farnesic acid glycerides[12] and that extracts of *Adalaria* sp. contain steroidal peroxides.[13]

We have undertaken an investigation of the extracts of *Cadlina luteomarginata* (McFarland, 1966) as part of an ongoing program to study the chemical secretions of soft bodied molluscs from British Columbia waters. Our initial attraction to *C. luteomarginata* was prompted by the pleasant fruity odor of freshly collected specimens.† In this paper we report the isolation of five sesquiterpenoids and a twenty three carbon degraded terpenoid from *C. luteomarginata*, as well as some observations on the relationship between diet and the occurrence of the metabolites.

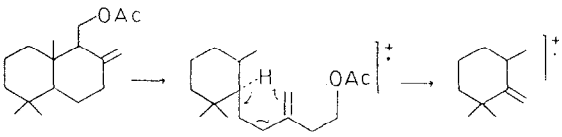
RESULTS AND DISCUSSION

C. luteomarginata was collected by hand using SCUBA (−5 to −18 m) in Howe Sound and Barkley Sound, British Columbia. Freshly collected specimens were immersed whole in methanol and left at room temperature for 72 hr at which time the extraction solvent was decanted and evaporated *in vacuo*. The residue was partitioned between water and chloroform resulting in a fragrant oily organic extract (1.1 g/200 nudibranchs). Fractionation of the organic extract by silica gel column chromatography and subsequent silica gel preparative thin layer chromatography (ptlc) produced a series of pure sesquiterpenoids and a fraction containing impure luteone.

Albicanyl acetate (**1**), isolated as a colorless oil (yield 0.5% of crude extract) which shows $[\alpha]_D = +24°$ (*c* 0.5, $CHCl_3$), is the major component of *C. luteomarginata* extracts from both Howe Sound and Barkley Sound. The high resolution mass spectrum (HRMS) of **1** indicated a molecular formula of $C_{17}H_{28}O_2$ (M^+ 264.2088, calc. 264.2082) and it showed a base peak at *m/z* 204 suggesting a loss of acetic acid. A CO stretch at 1740 cm^{-1} in the IR spectrum and a three proton singlet in the ^1H NMR spectrum at 2.01 ppm confirmed the presence of an acetate ester in **1**. Three additional Me singlets in the ^1H NMR at 0.76, 0.81 and 0.88 ppm and two one proton doublets at 4.51 and 4.85 ppm (J = 1 Hz) led to the hypothesis that **1** was a bicyclic sesquiterpenoid containing one exocyclic double bond and an acetate functionality. A pair of deshielded protons at 4.18 (dd, J = 9, 11 Hz) and 4.34 (dd, J = 4, 11 Hz) ppm implied that the acetate functionality was attached to a primary carbon which

†"Many nudibranchs, but especially the dorids, have a penetrating fruity odor that is pleasant when mild but nauseating when concentrated. Undoubtedly, this odor is one of the reasons why nudibranchs seem to be let strictly alone by predatory animals". E. F. Ricketts and J. Calvin in *Between Pacific Tides*.[14]

was in turn bonded to a carbon bearing only one proton. All the obvious structural features could be accounted for if **1** were a $\Delta^{8,12}$ drimane sesquiterpenoid containing an acetoxy functionality at C-11. The mass spectrum shows a strong ion at *m/z* 137 (Scheme 1) supporting this structure.



Scheme 1.

Hydrolysis of acetate **1** (MeOH, K_2CO_3, RT) gave a high yield of albicanol (**2**), which was identical by IR and ^{1}H NMR comparison to authentic albicanol isolated from the liverwort *Diplophyllum albicans*,[14] verifying the proposed structure. Albicanol also occurs as a constituent of *C. luteomarginata* extracts (0.05% of crude). Since albicanol (**2**) is not produced when acetate **1** is resubjected to the extraction procedure it cannot be an isolation artifact.

There is no literature value for the optical rotation of authentic albicanol. In order to determine if the nudibranch contained the same optical antipode as the liverwort, we reduced (H_2, PtO_2, HOAc) the *Cadlina* derived material to (+) drimanol (**3**) ($[\alpha]_D = +15°$, *c* 0.4, $CHCl_3$).[15] Careful ^{1}H NMR analysis showed that the proton on C-8 in **3** was equatorial,[16] confirming that the reduction had occurred from the α face of albicanol. We can conclude from the results of the reduction that nudibranch derived albicanol and albicanyl acetate must have the (5*S*), (9*S*), (10*R*) absolute configuration which is identical to that of the liverwort derived albicanol.

The nonpolar fractions of extracts from *Cadlina* collected at several sites in Barkley Sound contained varying amounts of three furanosesquiterpenoids. Extracts of all collections except one contained a mixture of furodysin (**4**) and furodysinin (**5**) while the exceptional collection contained only microcionin-2 (**6**).

Scheme 2.

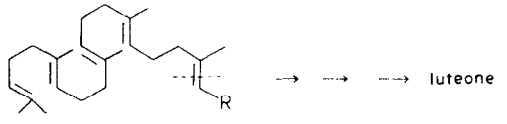
Multiple development ptlc (hexane) on 50 cm plates allowed the isolation of pure furodysinin (**5**) and a fraction containing a mixture of furodysin (**4**) and **5**. The HRMS of pure **5** showed a parent ion corresponding to a molecular formula of $C_{15}H_{20}O$ (M^+ 216.1512, calc. 216.1509) and a base peak at *m/z* 122 resulting from an extremely facile retro Diels–Alder cleavage (Scheme 2). A ^{1}H NMR spectrum of this material showed three methyl singlets at 1.17, 1.18 and 1.64 ppm, an olefinic proton at 5.57 ppm and two furan protons at 6.08 and 7.08 ppm. Consideration of the spectral data indicated that the pure sesquiterpenoid had either structure **4** or **5**. Comparison of the ^{1}H NMR with an authentic spectrum of furodysinin (**5**)[17] showed them to be identical. A mass spectrum of the mixture of isomers showed major peaks at *m/z* 216 and 122 and visual inspection of the ^{1}H NMR of the mixture revealed that it contained signals appropriate for both furodysinin (**5**) and furodysin (**4**). We have thus tentatively concluded that the second component of the mixture is furodysin (**4**).

Extracts of one collection of *C. luteomarginata* from Barkley Sound contained a single furanosesquiterpenoid in the non-polar fractions. It could easily be purified to a colorless oil which had a molecular formula $C_{15}H_{22}O$ (M^+ 218.1612, calc. 218.1665). The ^{1}H NMR spectrum of this sesquiterpenoid showed three protons at 6.13, 7.08 and 7.21 ppm characteristic of a β substituted furan, two Me singlets at 1.08 and 1.62 ppm, a Me doublet at 0.99 ppm and an olefinic proton at 5.36 ppm. Comparison of the spectral data of this molecule to the data for known porifera sesquiterpenoids revealed that they were identical to those reported for microcionin-2 (**6**),[18] previously isolated from *Microciona toxystila*.

The metabolite responsible for the fragrance of British Columbia *C. luteomarginata* specimens is present in extremely minute quantities. We were unable to chromatographically separate it from a persistent phthalate ester contamination. Purification was ultimately achieved by preparation of a crystalline 2,4-dinitrophenylhydrazone (DNPH) derivative (MeOH, m.p. 84–86°). A HRMS of the derivative showed that it had a molecular formula of $C_{29}H_{40}N_4O_5$ (M^+ 524.3000, calc. 524.2988) indicating that the underivatized metabolite, which we have named luteone, had a molecular formula of $C_{23}H_{36}O_2$.

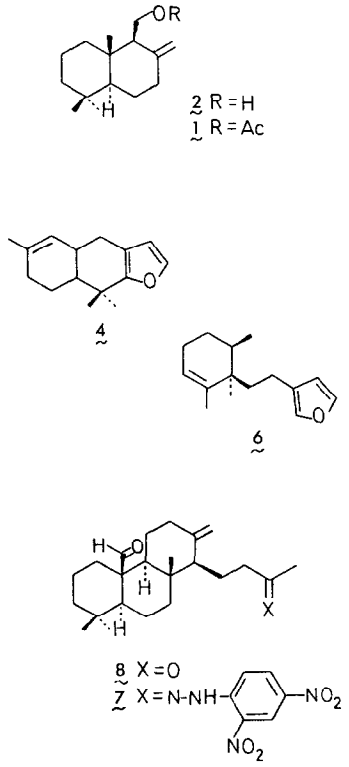
The ^{1}H NMR spectrum of the luteone DNPH derivative (**7**) showed three shielded Me singlets at 0.64, 0.76 and 0.78 ppm, a deshielded Me singlet at 2.07 ppm, two exocyclic methylene protons at 4.56 and 4.89 ppm and an aldehyde proton at 10.12 ppm in addition to the dinitrophenyl resonances. Consideration of the mass spectrum and ^{1}H NMR spectrum of the DNPH derivative suggested that the parent molecule was terpenoid and that it contained a sterically hindered alkehyde, a methyl ketone, one olefin and three rings. The limited supply of luteone prevented further chemical studies. Single crystal X-ray analysis of the DNPH derivative **7** demonstrated that luteone had the tricyclic structure **8**.[19]

Albicanol (**2**) and its acetate (**1**) are of chemical interest because they represent examples of marine derived drimanes that do not have either a phenyl or quinone substituent attached to C-11. Luteone (**8**) appears to be a degraded terpenoid in which the ring system is formed by a straightforward cyclization (Scheme 3). It is interesting to note that luteone is the first example of a degraded terpenoid containing twenty three carbon atoms; twenty one carbon degraded sesterterpenoids are well known sponge metabolites.[20]



Scheme 3.

There are numerous examples of molluscan metabolites having their biosynthetic origin in dietary organisms.[5,6,8,10] Preliminary examination of formalin-fixed gut contents from seventeen individuals of *C. luteomarginata* collected at both study sites indicated that the diets of these dorids is comprised solely of demosponges with siliceous skeletons.[21] Sponge species



consumed were determined by an examination of the spicule types present in the stomachs of an additional 84 individuals.[22] Diets differed between sites both in terms of sponge species and relative proportions consumed (Table 1). A total of seven sponge species were consumed by *C. luteomarginata* at both sites; *Myxilla incrustans* is the major dietary sponge in Howe Sound individuals, while *Hymedesmia* sp. is dominant in he Barkley Sound individuals.

Furodysin (**4**), furodysinin (**5**), and microcionin-2 (**6**) were all originally iolated from sponges.[14,15] They were present in *Cadlina* extracts from some collecting sites but absent from others. Chemical analysis of gut contents showed that they were always present in the gut when they were found in the skin extracts.[23] It appears certain that these furanosesquiterpenoids are of sponge origin.

The origin of albicanyl acetate (**1**), albicanol (**2**) and luteone (**8**) is less clear. These three metabolites were found at all collecting sites. Chemical analysis of gut contents failed to conclusively show their presence in the diet.[23] We believe it is likely, however, that they are of dietary origin since extracts of *C. luteomarginata* from California never contain drimanes or luteone.[24]

A standard goldfish bioassay[24] was utilized to test the anti-feedant properties of the *C. luteomarginata* terpenoids. Albicanyl acetate (**1**) and furodysinin (**5**) show activity at 5 and 10 μg/mg respectively while all the other metabolites are inactive (Table 2). It is interesting to note that albicanyl acetate is both the major metabolite in skin extracts and the most potent anti-feedant. We estimate that acetate **1** is present at a concentration of 1 to 10 μg/mg in the dorsum of the nudibranch, a concentration which may possibly be sufficient to deter potential fish predators.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Nicolet-Oxford H-270 and Varian XL-100 spectrometers. TMS was used as an internal standard. Low resolution mass spectra were recorded on an AEI MS902 spectrometer and high resolution mass spectra were recorded on an AEI MS50 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 70B spectrometer and optical rotations were measured on a Perkin-Elmer 141 polarimeter using a 1 dm cell. Melting points were obtained on a Fisher-Johns apparatus and values are uncorrected. Merck silica gel 60 PF-254 was used for ptlc and Merck silica gel 60 (70–230 mesh) was used for columns.

Extraction and purification. Specimens ranging in size between 2 and 6 cm were collected by SCUBA from rocky sites characterized by strong currents located within both Howe Sound and Barkley Sound, British Columbia. Immediately after collection, the nudibranchs were placed in a glass jar containing MeOH (125 ml/100 nudibranchs). After soaking the animals for 3 days, the supernatant was filtered through Whatman #1 filter paper and

Table 1. Results of gutcontent analysis

	Number of Individuals		
	Barkley Sound	Howe Sound	Total
Sponges Consumed			
Myxilla incrustans	9	19	28
Hymedesmia	13	4	17
Zygherpe hyaloderma	4	0	4
Suberites sp.	0	3	3
Higginsia sp.	1	2	3
Mycale hispida	0	1	1
Lissodendoryx firma	0	1	1
Gut empty	7	20	27

Table 2. Standard goldfish[a] antifeedant bioassay results[24]

Compound \ Concentration	5 µg/mg	10 µg/mg	50 µg/mg	100 µg/mg
Albicanol (2)	*[b]	+	+	*
Albicanylacetate (1)[c]	+/-	-	-	*
Luteone (8)	*	+	*	*
Furodysinin (5)	*	+/-	*	-

a) *Carassius auratus*

b) * not tested
- pellet rejected (not eaten)
+/- pellet partially eaten
+ pellet eaten

c) We estimate that albicanyl acetate is present in the dorsum of *C. luteomarginata* at a concentration of 1 to 10 µg/mg.

evaporated *in vacuo* to about one third the original volume. The concentrated extract was partitioned between chloroform and brine. The organic phase was dried over Na_2SO_4, fitered and evaporated to give a sweet smelling oily residue. Repetition of the extraction procedure four times resulted in a yield of 1.03 gm of crude material from ≈ 200 nudibranchs.

The crude extract was chromatographed on a silica gel column (45 × 3 cm, $CHCl_3$ eluent) to remove steroids and polar material from the sesquiterpenoids. Silica gel ptlc ($CHCl_3$ eluent) of the terpenoid fraction gave bands containing: (1) furanosesquiterpenoids R_f 0.6 → 0.8: 2) albicanyl acetate R_f 0.4 → 0.6: 3) albicanol and luteone R_f 0.2 → 0.4.

Albicanyl acetate (**1**). Repeated PTLC [(a) CH_2Cl_2/hexane (2:1) R_f 0.3; (b) $CHCl_3$/EtOAc (20:1) R_f 0.48] of crude fraction 2 produced pure albicanyl acetate as a clear oil: (5 mg, yield 0.5% of crude); $[\alpha]_D = +24°$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$) 2920, 2860, 1740, 1460, 1440, 1400, 1380, 1240, 1040 and 900 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.76, (s, 3H), 0.81 (s, 3H), 0.88 (s, 3H), 2.01 (s, 3H), 2.41 (ddd, 1H-7e, J = 13, 4.5, 3 Hz), 4.18 (dd, 1H-11, J = 9, 11 Hz), 4.34 (dd, 1H-11', J = 4, 11 Hz), 4.51 (d, 1H-12, J = 1 Hz), 4.85 (d, 1H-12, J = 1 Hz); MS (*m/z* relative intensity 264(3), 249(3), 222(3), 221(3), 204(100), 189(33), 137(78), 123(33), 109(22), 95(30).

Hydrolysis of albicanyl acetate. 12 mg of **1** and 20 mg K_2CO_3 were added to 1 ml MeOH and the mixture was stirred overnight. The mixture was filtered through glass wool, partitioned between water and ether and the organic residue was purified via PTLC (CH_2Cl_2 eluent) to give **2** (9 mg, 88% yield) which was identical to albicanol isolated from the crude extracts (see below).

Albicanol (**2**). Repeated PTLC [(a) $CHCl_3$/EtOAc (8:1) R_f = 0.46, (b) $CHCl_3$/EtOAc (20:1) R_f = 0.31] of crude fraction 3 gave **2**: yield 0.05% of crude extract; m.p. 68–69° (hexane); $[\alpha]_D = +13$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$) 3350, 2920, 2850, 1640, 1390, 1370, 1030 and 890 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.72 (s, 3H), 0.81 (s, 3H), 0.88 (s, 3H), 2.02 (m, 2H), 2.41 (ddd, 1H-7e, J = 13, 4, 2 Hz), 3.76 (t, 1H, J = 11 Hz), 3.84 (dd, 1H, J = 11, 4 Hz), 4.65 (d, 1H, J = 1.5 Hz), 4.93 (d, 1H, J = 1.5 Hz): MS (*m/z*, relative intensity) 222(38), 207(13), 204(17), 189(14), 137(100), 123(33), 109(28), 95(25).

An 80 MHz ^1H NMR ($CDCl_3$) of albicanol was obtained for comparison purposes. The ^1H NMR chemical shifts and the IR absorption frequencies were identical to those for authentic albicanol.[16]

Reduction of albicanol (**2**). **2** (9 mg) was dissolved in 1 ml AcOH and PtO_2 (5 mg) was added to the soln. The mixture was stirred overnight under H_2 (1 atm press), filtered, and partitioned between water and $CHCl_3$. The organic solvent was evaporated to give **3** (6 mg, 68% yield, m.p. 100° (hexane)). Drimanol showed: $[\alpha]_D = +15°$ (*c* 0.5 $CHCl_3$): IR ($CHCl_3$) 3620, 2470, 2950, 2890, 2870, 1470, 1400, 1380, 1140, 1100, 1030, 998 and 980 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.82 (s, 3H), 0.85 (s, 6H), 0.96 (d, 3H, J = 7.5 Hz), 2.15 (m, 1H), 3.59 (t, 1H, J = 10.5 Hz), 3.86 (dd, 1H, J = 10.5, 4.5 Hz): MS (*m/z*, relative intensity) 224(34), 209(24), 206(5), 191(3), 123(100), 109(22), 95(32).

Furodysin (**4**) *and furodysinin* (**5**). Multiple development ptlc (hexane, 3 × 50 cm) of crude fraction 1 gave **5** (m.p. 75°, Hexane, yield = 0.1% of crude extract) and a fraction containing a mixture of **5** and **4**.

Furodysinin (**5**) showed: IR ($CHCl_3$) 2960, 2910, 2870, 1460, 1210, 1080 and 1070 cm^{-1}; ^1H NMR (CCl_4, 270 MHz) δ 1.17 (s, 6H), 1.64 (s, 3H), 2.25 (dd, 1H, J = 17.5, 12.5 Hz), 2.69 (m, 2H), 5.57 (m, 1H), 6.08 (d, 1H, J = 2 Hz), 7.08 (bs, 1H); MS (*m/z*, relative intensity) 216(20), 201(8), 122(100). An 80 MHz ^1H NMR (CCl_4) was run for comparison purposes. Comparison of IR and ^1H NMR spectra of our material with those of authentic furodysinin[16] showed them to be identical.

The fraction containing a mixture of **4** and **5** showed: IR ($CHCl_3$) 2960, 2920, 2870, 1460, 1080 and 1070 cm^{-1}; ^1H NMR (CCl_4, 270 MHz) furodysin (*), furodysinin (**) δ 0.90 (d, 3H), 1.05 (s, 3H), 1.17 (s, 6H)**, 1.23 (s, 6H)*, 1.64 (s, 3H)**, 1.69 (s, 3H)*, 5.57 (m), 5.91 (s, 1H), 5.93 (bs, 1H)*, 6.08 (bs, 1H)**, 6.98 (bs, 1H)*, 7.08 (bs, 1H)**; MS (*m/z* relative intensity) 216(25), 201(14), 122(100). An 80 MHz ^1H NMR ($CDCl_3$) was also obtained to allow comparison with spectra of authentic samples.

Microcionin-2 (**6**). Ptlc (hexane) of crude fraction 1 from a July collection of Cadlina from Barkley Sound gave pure microcionin-2: yield 0.3% of crude extract; IR ($CHCl_3$) 2940, 2860, 1460, 1380, 1165, 1030 and 880 cm^{-1}. ^1H NMR (CCl_4, 270 MHz) δ 0.99 (d, 3H, J = 7 Hz), 1.06 (s, 3H), 1.62 (s, 3H), 1.96 (bs, 2H), 2.32 (m, 2H), 5.36 (bs, 1H), 6.13 (bs, 1H), 7.08 (bs, 1H), 7.21 (bs, 1H); MS (*m/z* relative intensity) 218(30), 203(14), 137(4), 123(100), 95(38), 81(44).

2-4-Dinitrophenylhydrazone derivative of luteone. All chromatographic attempts to isolate the odoriferous constituent, luteone, from crude fraction 3 failed to yield a pure substance. Therefore, 12 mg of crude fraction 3 was dissolved in 1 ml MeOH and to this soln was added 10 mg of 2,4-dinitrophenylhydrazone in 1 ml MeOH containing two drops of conc HCl. The mixture was stirred for 1 hr at which time crystals had formed in the flask. The crystals were collected by filtration and subjected to ptlc (CH_2Cl_2) and crystallization from MeOH (m.p. 84–86°, yield

3 mg). Luteone DNPH showed: IR ($CHCl_3$, 3310, 2920, 2850, 1700, 1670, 1510, 1340 and 1320 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.64 (s, 3H), 0.76 (s, 3H), 0.78 (s, 3H), 2.07 (s, 3H), 4.56 (bs, 1H), 4.89 (bs, 1H), 7.96 (d, 1H, J = 10 Hz), 8.32 (dd, 1H, J = 2.5, 10 Hz), 9.15 (d, 1H, J = 2.5 Hz), 10.12 (s, 1H); MS (*m/z*, relative intensity) 524(9), 495(12), 449(15), 327(28), 326(32), 161(80), 135(68), 123(52), 121(76), 109(95), 107(76), 95(100), 93(76), 81(95), 55(80). Weak signals are also present in the ^1H NMR for the syn isomer of the phenylhydrazone.

Gut analyses. Since solvent extraction generally makes gut analysis difficult, 17 individuals from Barkley Sound and 8 individuals from Howe Sound were anaesthetized in 0.1% 2-phenoxyethanol before fixation in 5% buffered formaldehyde soln. The gut contents were removed and examined at 400× with a compound microscope. Since all full guts (n = 7) were filled primarily with indigestible sponge spicules, we assumed these animals were feeding solely on siliceous sponges as reported by Bloom;[20] solvent-extracted nudibranchs could then be used for sponge spicule-based gut analyses. Consequently, the gut contents of 84 solvent-extracted individuals from both sites were digested in household bleach and examined to determine the spicule types present and thus the sponge species consumed. Sponges were identified according to literature procedures.[21]

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