89. Verecynarmin A, a Novel Briarane Diterpenoid Isolated from Both the Mediterranean Nudibranch Mollusc *Armina maculata* and its Prey, the Pennatulacean Octocoral *Veretillum cynomorium*

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The briarane diterpenoid verecynarmin A (=(–)-(8a*R*,9*S*,11*S*,12*R*,12a*R*,4*Z*,6*Z*)-11,12-epoxy-8,8a,9,10,11,12,12a,13-octahydro-1,5,8a,12-tetramethylbenzo[4,5]cyclodeca[1,2-*b*]furan-9-yl acetate; (–)-**1**) is shown to be contained in both the Mediterranean nudibranch mollusc *Armina maculata* (RAFINESQUE) and its prey, the pennatulacean octocoral *Veretillum cynomorium* (PALLAS). The structure is mainly solved by 1D-NMR, 2D-NMR, and NOE studies of (–)-**1**. However, the relative configurations at the epoxide and angular methyl centres, as well as the preferred conformation, are established by shift-reagent and NOE studies of diol (–)-**4** obtained by epoxide-ring opening of (–)-**1** with $LiAlH_4$. The absolute configuration is established *via* deacetylation of (–)-**1** followed by *Horeau*'s esterification.

1. Introduction. – Most secondary metabolites of marine molluscs have been isolated from species belonging to the three subclasses Opisthobranchia [1] [2], Pulmonata [1a,b], and Prosobranchia [1a,b]. Opisthobranchia in particular are a rich source of a vast array of secondary metabolites generally of dietary origin [1].

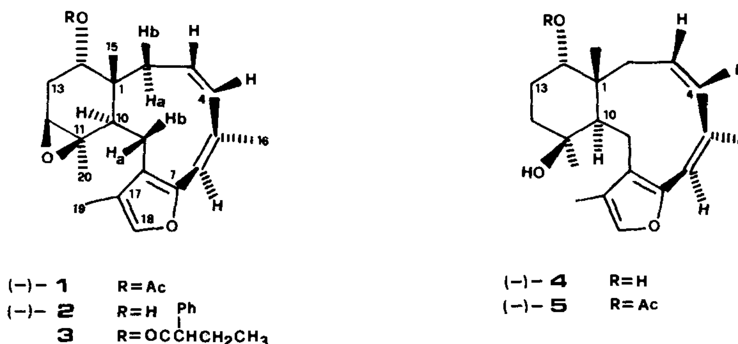
We add here to the studies of Opisthobranchia the case of *Armina maculata* (RAFINESQUE, 1814), a cosmopolitan genus belonging to the little investigated family Arminidae, order Nudibranchia. The only other mollusc of this family for which secondary metabolites have been reported (tripeptide toxins) is *Janolus cristatus* [1c].

A. maculata periodically, though not every year, massively populates the Mediterranean East Pyrenean waters. It is proved here to contain a briarane diterpenoid whose origin is traced to the mollusc's prey, the pennatulacean octocoral *Veretillum cynomorium* (PALLAS). The latter perennially inhabits East Pyrenean waters.

Several briarane diterpenoids have already been isolated from octocorals belonging to the order Pennatulacea such as *Briareum asbestinum* [3a], *Stylatula* sp. [3b,c], *Ptilosarcus gurneyi* [3d], *Scytalium tentaculatum* [3e], *Cavernulina grandiflora* [3f], *Pteroides laboutei* [3g], and *Renilla reniformis* [3h]. Also Gorgonacea have given briarane diterpenoids, such as *Briareum polyanthes* [4a] and *Erythropodium caribeorum* [4b].

The novel briarane diterpenoid described here not only is the first one from molluscs, but it is also the first one from a Mediterranean marine organism.

2. Results and Discussion. – This work started with the collection of the mollusc *Armina maculata* following its massive appearance in August 1984 in French East Pyrenean waters. Organic extracts of the mollusc revealed promising *Ehrlich*-reactive TLC



spots one of which corresponds to verecynarmin A[1] ((–)-**1**) whose structure is strongly supported by its spectral data.

The ^{13}C-NMR spectrum of (–)-**1** *(Table 1)* comprises 22 resonances. At low field there is a *s* for the C=O group of an ester besides signals for 8 olefinic C-atoms. Of these, 4 are *d* (CH=) and the other ones *s*. Moreover, at high field, there are signals for 5 CH_3 groups, 3 CH_2 groups, 1 CH group, and 1 quaternary C-atom. Finally, at medium field, there are 2 CH groups and 1 quaternary C-atom.

Table 1. *^{13}C-NMR Data for Verecynarmin A* ((–)-**1**), *14-O-Deacetylverecynarmin A* ((–)-**2**), *and Compounds (–)-***4** *and (–)-***5**[a])[1])

C-Atom	(–)-**1**[b])	(–)-**2**	(–)-**4**	(–)-**5**[c])
C(1)	39.20 (*s*)	39.96 (*s*)	41.79 (*s*)	40.95 (*s*)
C(2)	39.78 (*t*)	40.23 (*t*)	40.96 (*t*)	40.28 (*t*)
C(3)	128.89 (*d*)	129.61 (*d*)	130.64 (*d*)	129.95 (*d*)
C(4)	133.88 (*d*)	133.75 (*d*)	133.23 (*d*)	133.33 (*d*)
C(5)	138.51 (*s*)	138.64 (*s*)	139.36 (*s*)	139.26 (*s*)
C(6)	120.51 (*d*)	120.47 (*d*)	120.16 (*d*)	120.22 (*d*)
C(7)	148.64 (*s*)	148.86 (*s*)	148.98 (*s*)	148.77 (*s*)
C(8)	124.35 (*s*)	124.48 (*s*)	125.31 (*s*)	125.22 (*s*)
C(9)	24.44 (*t*)	24.44 (*t*)	21.62 (*t*)	21.64 (*t*)
C(10)	39.16 (*d*)	38.76 (*d*)	46.63 (*d*)	47.26 (*d*)
C(11)	62.95 (*s*)	63.22 (*s*)	72.59 (*s*)	72.40 (*d*)
C(12)	59.81 (*d*)	60.08 (*d*)	34.71 (*t*)	35.48 (*t*)
C(13)	27.02 (*t*)	30.38 (*t*)	25.17 (*t*)	22.29 (*t*)
C(14)	77.47 (*d*)	75.26 (*d*)	76.53 (*d*)	78.87 (*d*)
C(15)	17.01 (*q*)	17.44 (*q*)	19.04 (*q*)	18.70 (*q*)
C(16)	24.37 (*q*)	24.91 (*q*)	25.00 (*q*)	24.58 (*q*)
C(17)	121.60 (*s*)	121.66 (*s*)	121.51 (*s*)	121.44 (*s*)
C(18)	138.05 (*d*)	137.89 (*d*)	137.61 (*d*)	137.78 (*d*)
C(19)	8.79 (*q*)	8.89 (*q*)	9.21 (*q*)	9.13 (*q*)
C(20)	23.04 (*q*)	23.23 (*q*)	31.00 (*q*)	30.85 (*q*)

[a]) Concentrations and solvents as in *Table 2* and in the *Exper. Part*. The assignment of non-tertiary and tertiary C-atoms are based on one-bond (compounds (–)-**1** and (–)-**4**) and long-range (compound (–)-**1**) ^{13}C,^{1}H shift correlation experiments [7], respectively.

[b]) CH_3*C*O at 169.54 (*s*) and *C*H_3CO at 20.60 (*q*).

[c]) CH_3*C*O at 169.50 (*s*) and *C*H_3CO at 20.77 (*q*).

[1]) Except for retrieval purposes (see the systematic names in the *Exper. Part*), for the sake of convenience, we use the numbering of the hypothetical briaran skeleton [3d] according to which the name of verecynarmin A ((–)-**1**) is (–)-(1*R*,10*R*,11*R*,12*S*,14*S*,3*Z*,5*Z*)-11,12-epoxybriara-3,5,7,17-tetraen-14-yl acetate.

Table 2. *^{1}H-NMR Data for Verecynarmin A* ((–)-**1**[a])[1])

H-Atom	(–)-**1**
H_a–C(2)	2.47 (br. *dd*, J_{gem} = 12.5, *J* (2a,3) = 10.9, *J* (2a,15) small)
H_b–C(2)	1.42 (*ddd*, J_{gem} = 12.5, *J* (2b,3) = 5.5, *J* (2b,4) = 0.7)
H–C(3)	5.50 (*dddd*, *J* (3,4) = 11.2, *J* (3,2a) = 10.9, *J* (3,2b) = 5.5, *J* (3,6) = 0.5)
H–C(4)	5.78 (br. *d*, *J* (4,3) = 11.2, *J* (4,6) = 1.5, *J* (4,16) = 1.3, *J* (4,2b) = 0.7)
H–C(6)	6.41 (*m*, *J* (6,16) = 1.3, *J* (6,3) = 0.5, *J* (6,9b) = 1.3, *J* (6,4) = 1.5, *J* (6,18) small)
H_b–C(9)	2.97 (br. *d*, J_{gem} = 15.6, *J* (9b,6) = 1.3, *J* (9b,10) small)
H_a–C(9)	2.65 (*dd*, J_{gem} = 15.6, *J* (9a,10) = 8.8)
H–C(10)	2.43 (br. *d*, *J* (10,9a) = 8.8, *J* (10,9b) small)
H–C(12)	2.63 (br. *d*, *J* (12,13α) = 5.7, *J* (12,14) = 1.3, *J* (12,13β) = 0.6)
H_α–C(13)	1.86 (*ddd*, J_{gem} = 16.5, *J* (13α,14) = 2.8, *J* (13α,12) = 5.7)
H_β–C(13)	2.00 (*ddd*, J_{gem} = 16.5, *J* (13β,12) = 0.6, *J* (13β,14) = 2.8)
H–C(14)	4.60 (*ddd*, *J* (14,13α) = *J* (14,13β) = 2.8, *J* (14,12) = 1.3)
CH_3(15)	0.88 (br. *s*, *J* (15,2a) small)
CH_3(16)	1.82 (*dd*, *J* (16,6) = *J* (16,4) = 1.3)
H–C(18)	6.97 (br. *q*, *J* (18,19) = 1.3, *J* (18,6) small)
CH_3(19)	1.86 (*d*, *J* (19,18) = 1.3)
CH_3(20)	1.02 (*s*)
CH_3CO	1.71 (*s*)

[a]) 0.012 g in 0.45 ml of C_6D_6.

The ^{1}H-NMR spectrum of (–)-**1** *(Table 2)* reveals, in the low-field region, the signals for a disubstituted olefin fragment (5.50, 5.78 ppm) and for 2 trisubstituted olefin fragments (6.41, 6.97 ppm). Hence, the 4th olefinic fragment, detectable by ^{13}C-NMR spectroscopy *(Table 1)* and not yet assigned, has to be attributed to a tetrasubstituted olefinic group.

The NMR resonances of one of the above trisubstituted olefin groups (δ_H 6.97 ppm; δ_C 8.79, 121.60, 138,05 ppm) and of the tetrasubstituted olefin group (δ_C 124.35, 148.64 ppm) are typical of a α,β,β'-trialkyl-substituted furan [5] which is also consistent with both a marked *Ehrlich* reactivity and the MS spectrum. This shows the highest-mass signal at *m/z* 356 which must be taken as the molecular ion of composition $C_{22}H_{28}O_4$ to account for the above NMR spectra. Loss of fragments of mass 60 (AcOH) and 76 (AcOH + O) from $M^{+\cdot}$ is in accordance with NMR indications as to the presence of both an AcO group (δ_C 169.54, 20.60 ppm; δ_H 1.71 ppm) and a trisubstituted epoxide group (δ_C 62.95 (*s*), 59.81 (*d*) ppm [5b]; δ_H 2.63 ppm), implying that verecynarmin A has two carbocycles besides the furan and epoxide rings.

The ^{1}H-NMR spectrum of (–)-**1** *(Table 2)* also reveals couplings for the fragment C(15)–C(1)–C(2)–C(3)–C(4)–C(5)[C(16)]–C(6)–C(7)–C(8)[C(17)–C(18)–C(19)]C(9)–C(10). In particular, a small coupling between CH_3(15) and H_a–C(2) *(Table 2)*, as for an antiperiplanar relationship, prompts us to connect C(15) to C(2) *via* the quaternary C(1). Moreover, H–C(4) is related by *cis* coupling to H–C(3) which has a large coupling, for a nearly antiperiplanar relationship, with H_a–C(2), other than a smaller coupling with H_b–C(2). Another relevant observation is that both H–C(3) and H–C(4) are coupled with H–C(6). Finally, CH_3(16) is coupled with both H–C(4) and H–C(6), the latter being also long-range-coupled with both H–C(18) (^5J) and H_b–C(9) (homoallylic). At this point, being aware of the furan ring, C(6) and C(9) can be joined *via* the C(7)=C(8) fragment.

Long-range ^{13}C,[1]H shift correlations [6] with (–)-**1**, optimised for *J*(C,H) = 8 Hz, show that CH_3(15) and H–C(10) are correlated to, respectively, C(10) and C(15). This forces us to join C(1) with C(10), thus forming a ten-membered ring.

These observations imply that the other carbocycle must be six-membered, and the fragment C(12)–C(13)–C(14) is clearly evidenced by a small coupling between H–C(12) and H_β–C(13), suitable for a dihedral angle close to 90°, as in structure (–)-**1**. Moreover, the AcO group must be located at C(14) in order to account for the relatively low-field NMR resonances (δ_H 4.60 ppm; δ_C 77.47 ppm) of the H–C(14) group. Moreover, H–C(14) must occupy a pseudoequatorial position owing to small couplings with 2 H–C(13). Such a conclusion is further supported by strong, differential NOE effects (14 and 10%) at H–C(14), on irradiation at either CH_3(15) or H_b–C(2), respectively[2]). Moreover, owing to a W relationship between H–C(14) and H–C(12),

the latter must occupy a pseudoequatorial position to have both protons approximately in the same plane, as in structure (−)-**1**.

The oxirane ring must involve C(12) owing to typical values (δ_H 2.63, δ_C 59.81 ppm) for H−C(12). The other C-atom must be C(11) which accounts for both trisubstitution and biogenetic rules. The fragment can thus be closed to form a six-membered carbocycle as in structure (−)-**1**.

The (*Z*)-configuration at the olefinic bonds rests on the typical coupling constant $J(3,4)$ = 11.2 Hz for the 3,4-double bond and on the typically deshielded signal for C(16) (δ_C 24.37 ppm) for the 5,6-double bond.

All these conclusions are fully supported by further long-range ^{13}C,^{1}H shift-correlation [6] and differential NOE experiments (*Exper. Part*).

The UV absorption of (−)-**1** at relatively short wavelength (λ_{max} 273 nm) is in accordance with conjugation of C(5)=C(6) with only the furan fragment. This, and the NOE data discussed above, fully support the preferential conformation of the 'eastern' hemisphere of verecynarmin A as in structure (−)-**1**.

However, the spectral data for verecynarmin A do not allow us to assign the configuration at the oxirane centre. To clarify this point, verecynarmin A (−)-**1** was reduced with $LiAlH_4$ into the diol (−)-**4**.

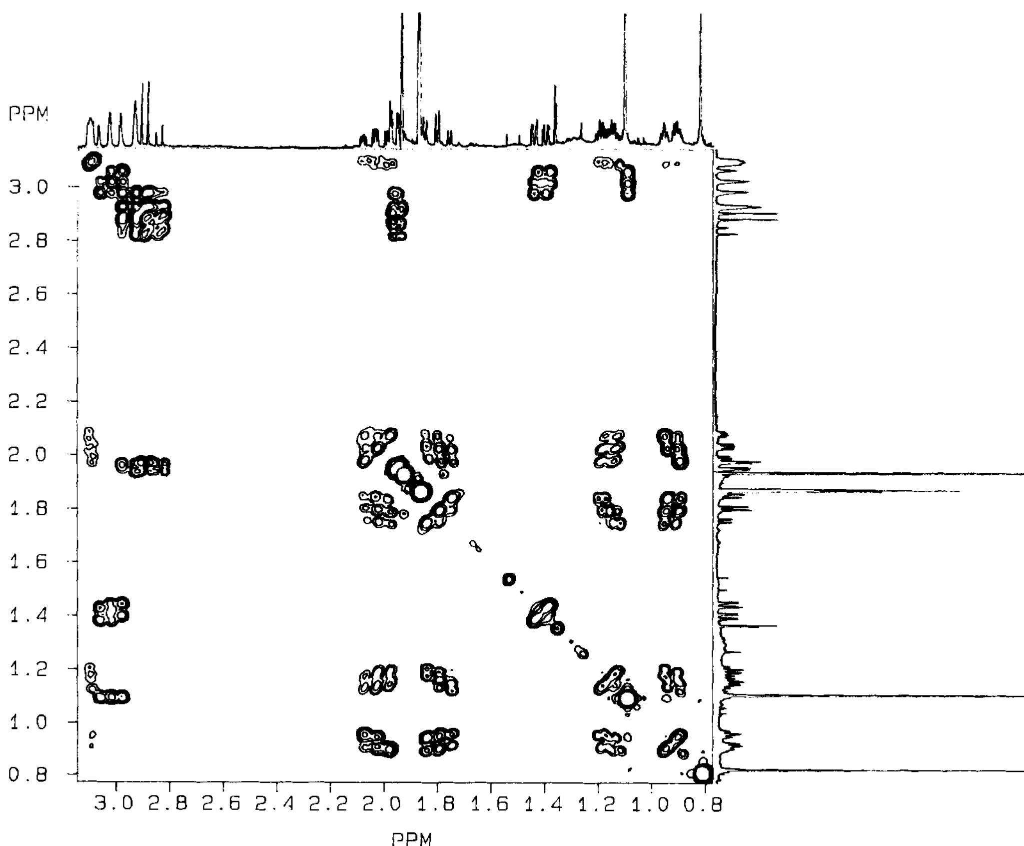


Figure. *High-field region of COSY plot of (−)-4*. After *Fourier* transformation, the absolute-value spectra was folded and represented as a contour plot.

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[2]) Owing to a relatively low-field resonance (δ_H 2.47 ppm), H_a−C(2) must be spatially close to the AcO group, which is consistent with the pseudoaxial position for the latter.

In the ^{1}H-NMR spectrum of (−)-**4**, H−C(14) has only small couplings with both protons at C(13). This suggests the equatorial position for H−C(14). Moreover, H_α−C(12) is a strongly coupled to H_β−C(13) as for an antiperiplanar relationship (see *Exper. Part*). Both these facts, which can be directly appreciated from the COSY plot [7] in the *Figure*, can only be accommodated by a preferential chair conformation of the six-membered carbocycle in (−)-**4**.

Other mutually consistent facets are to be mentioned. Thus, CH_3(15) is appreciably deshielded by the OH group at C(11) whilst CH_3(20) is shielded by the furan fragment. These is also a +13% differential NOE effect at H_β−C(13) on irradiation at CH_3(15), whilst there is no appreciable NOE effect between CH_3(15) and CH_3(20). Also, on irradiation at CH_3(20), there is a +1.5% differential NOE effect at CH_3(19).

Finally, acetylation of diol (−)-**4** gives (−)-**5** which interacts with the shift-reagent [Eu(fod)$_3$] (*Exper. Part*) preferentially by the ester group rather than the OH group. This further proves that the OH group occupies the sterically crowded axial position at C(11). In conclusion, all observations suggest the configuration at the epoxide centre as shown in both (−)-**4** and (−)-**5** and thus also in (−)-**1**[3]).

Verecynarmin A ((−)-**1**) can be easily hydrolyzed to give alcohol (−)-**2** whose reaction with (±)-α-phenylbutyric anhydride, according to *Horeau*'s procedure [8], proceeded sluggishly though with high optical yield, giving highly optically enriched levorotatory α-butyric acid. On the reasonable assumption that C(1), with its environment, is bulkier than CH_2(13), the absolute configuration of verecynarmin A is thus represented by structure (−)-**1**.

As briarane diterpenoids are typical of Anthozoa of the orders Pennatulacea [3] and Gorgonacea [4], and since *Armina maculata*, from which our briarane diterpenoid has been isolated, is known to feed on the pennatulacean anthozoan *Veretillum cynomorium* [9], the latter was worthy of examination, particularly as during the period of the collection, the two animals had the same habitat. In fact, verecynarmin A proves now to be contained also in the anthozoan. Therefore, following our introductory discussion, this diterpenoid is most likely a dietary product of the mollusc.

The absolute configuration of verecynarmin A ((−)-**1**) at C(1), C(10), and C(14) is the same as for all other investigated briaranes[4]) [3a] [4a,b]. In contrast, the configurations at C(11) and C(12) of (−)-**1** are opposite to those reported for all other relevant natural briaranes [3a,b,d,e,g,h] [4a,b]. This is allowed in the hypothetical scheme for the biogenesis of briaranes [10] starting from the cyclization C(1)−C(14) of geranylgeraniol and followed by a further cyclization C(2)−C(7), perhaps of cembrene. However, no likely precursor of verecynarmin A has yet been found in the animals studied here. In this connection, it must be remembered that the only known source of cembranoids from Mediterranean marine organisms is the alcyonacean *Alcyonium* (= *Parerythropodium*) *coralloides* [5b].

We thank Mr. *Nicola Demattè* for isolating verecynarmin A, Dr. *J.M. Amoroux* for the taxonomic determinations, the *Laboratoire Arago* for laboratory facilities, and the *Provincia Autonoma di Trento*, the *C.N.R.*, and *M.P.I.* (Progetti di Interesse Nazionale), Roma, for financial support.

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[3]) These conclusions are also indirectly supported by comparison of the ^{1}H-NMR chemical shift of H−C(10) for (−)-**1** with those for semisynthetic 11,12-epoxybriaranes obtained as 2:1 mixtures of the 11β,12β- and 11α,12α-isomers on epoxidation with a peracid of natural 11,12-unsaturated briaranes [3c]. Thus, δ(H−C(10)) is much the same for (−)-**1** and the β-isomer, whilst there is a 0.5 ppm difference with the α-isomer [3c].

[4]) Unfortunately, the sign of optical rotation for such briaranes have not been reported.

Experimental Part

1. *General.* All evaporations were carried out at reduced pressure. Column chromatography: *Merck Kieselgel 60* 63–200 µm. Flash chromatography: *Merck RP-18 LiChroprep* 40–65 µm. HPLC: *Merck-LiChrosorb Si-60* (7 µm). Reverse-phase HPLC: *Merck-LiChrosorb RP18* (7 µm). All HPLC columns were 25 × 1 cm with solvent flux 5 ml/min; monitoring by UV at 270 nm. Polarimetric data: *JASCO-DP-181* polarimeter. UV (λ_{max} in nm, ε in $mol^{-1}lcm^{-1}$) and IR ($\tilde{\nu}_{max}$ in cm^{-1}): *Perkin-Elmer-Lambda-3* and *Pye-Unicam-SP3-200* spectrometers, respectively. NMR: *Varian-XL-300* (^{13}C (75.43 MHz), ^{1}H (300 MHz)): probe temp. 22°; δ (ppm) relative to internal Me_4Si (= 0 ppm) and J in Hz. All couplings in ^{1}H-NMR spectra were deduced from double irradiations and those > 0.5 Hz were confirmed by COSY [7] experiments. The notation 'small' indicates couplings < 0.5 Hz. Multiplicities in ^{13}C-NMR spectra were derived from DEPT experiments [12] with 0.0036 s delay between each pulse. $^{13}C,^{1}H$-NMR-shift-correlation experiments [6] were carried out with spectral width 12132 Hz (2048 points) along the ^{13}C domain and 2045 Hz (128 time increments) along the ^{1}H domain. For each FID, 1024 transients were recorded. The data matrix was zero filled to 4096 × 512 and pseudo-echo processing was used in both time dimensions. For one-bond experiments, $\Delta_1 = 0.00357$ and $\Delta_2 = 0.0238$ s. For long-range experiments, $\Delta_1 = 0.0625$ and $\Delta_2 = 0.0417$ s. For COSY experiments [7], a $\pi/4$ mixing pulse was used. The data matrix of 1024 points × 512 time increments was zero filled to 2048 × 2048 and pseudo-echo processing was used in both time dimensions. NOE experiments were carried out on N_2-flushed (0.5 h) samples with optimization of the decoupler power. MS (EI; m/z (%)): home-built spectrometer based on the *ELFS-4-162-8-Extranuclear* quadrupole [11].

2. *Isolations. A. maculata* was collected in July-August 1984 in the French East Pyrenean Mediterranean waters (between Cap Bear and La Cerbere at 1–3 miles from the coast by dredging at depths of 60–70 m). The animals, closely packed, were stored in 95% EtOH in a 5-l glass jar. Homogenization, filtration, and EtOH evaporation led to both an aq. residue (1 l) and a residue of the extracted animals (170 g after oven drying). The aq. phase was extracted with petroleum ether, and the org. phase was evaporated to leave 13.2 g of a dark oily residue. A portion of the latter (6.5 g) was subjected to flash chromatography on 400 g of stationary phase (gradient elution petroleum ether/Et_2O). A mixture containing verecynarmin A ((–)-**1**) was eluted with petroleum ether/Et_2O 65:35 and subjected to HPLC with hexane/(i-Pr)$_2$O 3:2 to get (–)-**1** mixed with two minor, unidentified products. This mixture was subjected to reverse-phase HPLC with MeOH/H_2O 3:1 giving pure (–)-**1** (0.016 g, 0.02% on dry animal residue), t_R 10 min. This represents a lower limit for the yield for two reasons. First, the animal proved so rich of fats that a much better extraction procedure would have been lyophilization followed by defatting. Moreover, (–)-**1** as well its derivatives reported in this work, are unstable in $CHCl_3$ and, though less so, even in benzene. For example, even during an overnight COSY experiment with (–)-**1** in C_6D_6, there was detectable decomposition which could be accounted for, however.

Veretyllum cynomorium was collected together with the mollusc. The extraction and purification procedure were the same as above for the mollusc (even in this case lyophilization would be the method of choice as the animal is extremely rich of H_2O) obtaining pure (–)-**1** (0.016 g, 0.004% on dry animal residue).

3. *Verecynarmin A*[1]) (= *(–)-(8a*R*,9*S*,11*S*,12*R*,12a*R*,4*Z*,6*Z*)-11,12-Epoxy-8,8a,9,10,11,12,12a,13-octahydro-1,5,8a,12-tetramethylbenzo[4,5]cyclodeca[1,2-*b*]furan-9-yl Acetate*; (–)-**1**). Colourless foam. M.p. 127–135°. $[\alpha]^{20} = -255.7°$ (589), –272.6° (577), –320.8° (546), –682.7° (435), –1500.9° (365; c = 1.13, EtOH). UV (EtOH): 201 (11100), 220 (6200), 273 (10000). IR (metastable liquid film): 1735 (C=O); 1245, 941 (ν_s and ν_{as} of the epoxide). Positive differential NOE effects (irradiated H → % increment (relaxed H)): H_b–C(2)→28 (H_a–C(2)), 8 (H–C(3)), 10 (H–C(14)); H–C(3)→4 (H_b–C(2)), 6 (H_b–C(9)), 0.5 (CH_3(15)); H–C(4)→7 (H–C(3)), 3 (H_b–C(9)); H_b–C(9)→5 (H–C(3)), 3 (H–C(4)), 20 (H_a–C(9)), 3.5 (H–C(10)), 1.5 (CH_3(15)); CH_3(15)→4 (H–C(3)), 8 (H_b–C(9)), 4 (H_β–C(13)), 10 (H–C(14)); CH_3(20)→3 (H–C(10)), 12 (H–C(12)). Long-range $^{13}C,^{1}H$ shift-correlation data: H_a–C(2)→C(15); H_b–C(2)→C(3); H_a–C(9)→C(7); H_b–C(9)→C(8), C(11); H–C(10)→C(8), C(9), C(15); H–C(12)→C(11), C(20); H–C(14)→C(12); H–C(15)→C(1), C(10), C(14); H–C(19)→C(8), C(18); H–C(20)→C(11), C(12); CH_3CO→CO. MS: 356 (12, $M^{+\cdot}$), 296 (28, $M^{+\cdot}$ – AcOH), 281 (17, 296 – Me), 280 (5, 296 – 0), 173 (79), 161 (72), 159 (86), 145 (100).

4. *14-*O*-Deacetylverecynarmin A* (= *(–)-(8a*R*,9*S*,11*S*,12*R*,12a*R*,4*Z*,6*Z*)-11,12-Epoxy-8,8a,9,10,11,12,12a,13-octahydro-1,5,8a,12-tetramethylbenzo[4,5]cyclodeca[1,2-*b*]furan-9-ol*; (–)-**2**). Compound (–)-**1** (0.014 g, 0.039 mmol) was heated at reflux in 3 ml of 3% KOH/MeOH for 40 min. The mixture was neutralized with AcOH, evaporated to 0.5 ml, and subjected to flash chromatography to give 0.010 g (82%) of (–)-**2**. Colourless oil. $[\alpha]^{20} = -262.7°$ (589), –277.3° (577), –325.5° (546), –676.0° (435), –1340.6° (365; c = 0.96, EtOH). UV (EtOH): 220 (7300), 272 (9300). ^{1}H-NMR (0.010 g in 0.45 ml of C_6D_6): 2.91 (br. *dd*, J_{gem} = 11.2, J (2a,3) = 11.2, J (2a,15) small, H_a–C(2)); 1.38 (br. *dd*, J_{gem} = 11.2, J (2b,3) = 5.3, J (2b,4) small, H_b–C(2)); 5.62

(*dddd*, J(3,4) = 10.8, J(3,2a) = 11.2, J(3,2b) = 5.3, J(3,6) = 0.8, H–C(3)); 5.84 (br. *d*, J(4,3) = 10.8, J(4,6) = 1.5, J(4,16) = 1.4, J(4,2b) small, H–C(4)); 6.45 (*m*, J(6,16) = 1.4, J(6,3) = 0.8, J(6,4) = 1.5, J(6,9b) and J(6,18) small, H–C(6)); 3.06 (br. *d*, J_{gem} = 15.8, J(9b,6) and J(9b,10) small, H_b–C(9)); 2.68 (*dd*, J_{gem} = 15.8, J(9a,10) = 8.8, H_a–C(9)); 2.51 (br. *d*, J(10,9a) = 8.8, J(10,9b) small, H–C(10)); 2.69 (br. *d*, J(12,13β) small, J(12,14) = 0.9, J(12,13α) = 6.0, H_α–C(12)); 1.42 (*ddd*, J_{gem} = 15.9, J(13α,14) = 2.7, J(13α,12) = 6.0, H_α–C(13)); 1.99 (br. *dd*, J_{gem} = 15.9, J(13β,12) small, J(13β,14) = 2.9, H_β–C(13)); 2.87 (*ddd*, J(14,13α) = 2.7, J(14,13β) = 2.9, J(14,12) = 0.9, H–C(14)); 0.90 (br. *s*, J(15,2a) small, CH_3(15)); 1.88 (*dd*, J(16,6) = J(16,4) = 1.4, CH_3(16)); 6.98 (br. *q*, J(18,19) = 1.4, J(18,6) small, H–C(18)); 1.89 (*d*, J(19,18) = 1.4, CH_3(19)); 1.07 (*s*, CH_3(20)). MS: 314 (64, $M^{+\cdot}$), 299 (3, $M^{+\cdot} - CH_3$), 296 (5, $M^{+\cdot} - H_2O$), 199 (13), 197 (12), 174 (23), 173 (38), 161 (32), 159 (90), 146 (28), 145 (55), 43 (100).

5. Horeau's *Procedure with* (–)-**2**. To alcohol (–)-**2** (0.012 g, 0.038 mmol) in 1.5 ml of dry pyridine was added (±)-α-phenylbutyric anhydride (0.074 g), and the mixture was stirred for 10 h at r.t. Then, 1 ml of H_2O was added and stirred for 40 min. After addition of 10 ml of C_6H_6, the mixture was titrated with 0.05M NaOH (→alkaline) extracted, in the order, with C_6H_6 and $CHCl_3$. The aq. residue was acidified and extracted with C_6H_6. The org. phase was concentrated to 2 ml, and αD was –0.070° in a 10-cm optical path cell. Esterification yield 26%; optical yield 89%. The combined $C_6H_6/CHCl_3$ extracts were evaporated to dryness. The residue in C_6D_6 showed clear ^{1}H-NMR signals for only the prevailing diastereoisomeric (*S*)-*α-phenylbutyrate* **3** of 14-*O*-deacetylverecynarmin A as follows: 7.00 (H–C(18)); 6.48 (H–C(6)); 5.77 (H–C(4)); 5.46 (H–C(3)); 4.50 (H–C(14)); 3.02 (H_b–C(9)); 2.64 (H_a–C(9)); 2.53 (H–C(12)); 2.48 (H_a–C(2)); 2.45 (H–C(10)); 1.88 (H_β–C(13)); 1.87 (CH_3(19)); 1.80 (H_α–C(13)); 1.76 (CH_3(16)); 1.45 (H_b–C(2)); 1.09 (CH_3 (20)); 0.83 (CH_3(15)); 7.32, 7.11, 7.05 (arom. H; 3.4, 1.75, 0.89 (phenylbutyrate).

6. *(–)-(8a*R*,9*S*,12*S*,12a*R*,4*Z*,6*Z*)-8,8a,9,10,11,12,12a,13-Octahydro-1,5,8a,12-tetramethylbenzo[4,5]cyclodeca[1,2-*b*]furan-9,12-diol* ((–)-**4**). To (–)-**1** (0.011 g, 0.032 mmol) in 3 ml of dry THF was added $LiAlH_4$ (0.006 g, 0.16 mmol), and the mixture was stirred at 0° for 2 h. Then, 2 drops of H_2O were added, and the mixture was directly subjected to flash chromatography and further purified by HPLC ((i-Pr)$_2$O): (–)-**4** (0.004 g, 40%), t_R 7.5 min. Colourless oil. $[\alpha]^{20}$ = –200.9° (589), –209.1° (577), –247.0° (546), –525.2° (435), –1190.1° (365; *c* = 0.27, EtOH). UV (EtOH): 202 (8100), 220 (4900), 269 (6500). ^{1}H-NMR (0.004 g in 0.45 ml of C_6D_6): 3.02 (br. *dd*, J_{gem} = 12.9, J(2a,3) = 11.5, J(2a,15) = 0,7, J(2a,4) small, H_a–C(2)); 1.42 (*ddd*, J_{gem} = 12.9, J(2b,3) = 4.9, J(2b,4) = 1.1, H_b–C(2)); 5.74 (br. *ddd*, J(3,4) = 10.5, J 3,2a) = 11.5, J(3,2b) = 4.9, J(3,6) small, H–C(3)); 5.86 (br. *d*, J(4,3) = 10.5, J(4,6) = 1.6, J(4,16) = 1.3, J(4,2b) = 1.1, J(4,2a) small, H–C(4)); 6.41 (*m*, J(6,16) = 1.3, J(6,9b) = J(6,4) = 1.6, J(6,3) and J(6,18) small, H–C(6)); 2.93 (*ddd*, J_{gem} = 16.1, J(9b,6) = 1,6, J(9b,10) = 1.5, H_b–C(9)); 2.88 (*dd*, J_{gem} = 16.1, J(9a,10) = 7.2, H_a–C(9)); 1.96 (*dd*, J(10,9a) = 7.2, J(10,9b) = 1.5, H–C(10)); 1.80 (*ddd*, J_{gem} = J(12α,13β) = 13.8, J(12α,13α) = 3.6, H_α–C(12)); 0.93 (br. *ddd*, J_{gem} = 13.8, J(12β,13α) = J(12β,13β) = 3.6, J(12β,14) small, H_β–C(12)); 1.17 (*dddd*, J_{gem} = 13.8, J(13α,12β) = J(13α,12α) = 3.6, J(13α,14) = 3.4, H_α–C(13)); 2.03 (*dddd*, J_{gem} = J(13β,12α) = 13.8, J(13β,12β) = 3.6, J(13β,14) = 2.1, H_β–C(13)); 3.10 (br. *dd*, J(14,13α) = 3.4, J(14,13β) = 2.1, J(14,12β) small, H–C(14)); 1.10 (*d*, J(15,2a) = 0.7, CH_3(15)); 1.87 (*dd*, J(16,6) = J(16,4) = 1.3, CH_3(16)); 7.01 (br. *q*, J(18,19) = 1.2, J(18,6) small, H–C(18)); 1.93 (*d*, J(19,18) = 1.2, CH_3(19)); 0.82 (*s*, CH_3(20)). Positive differential NOE effects (irradiated proton→% increment, (relaxed protons)): CH_3(15)→5 (H–C(3)), 5 (H_b–C(9)), 12 (H_β–C(13)), 8 (H–C(14)); CH_3(20)→2 (H_a–C(9)), 9 (H–C(10)), 8 (H_α–C(12)), 1.5 (CH_3(19)). MS: 316 (99, $M^{+\cdot}$), 298 (66, $M^{+\cdot} - H_2O$), 283 (7, $M^{+\cdot} - H_2O - CH_3$), 280 (20, $M^{+\cdot} - 2\ H_2O$), 265 (38, $M^{+\cdot} - 2\ H_2O - CH_3$), 199 (100), 173 (58), 159 (57), 145 (35), 43 (29).

7. *(–)-(8a*R*,9*S*,12*S*,12a*R*,4*Z*,6*Z*)-12-Hydroxy-8,8a,9,10,11,12,12a,13-octahydro-1,5,8a,12-tetramethylbenzo[4,5]cyclodeca[1,2-*b*]furan-9-yl Acetate* ((–)-**5**). A soln. of (–)-**4** (0.003 g, 0.011 mmol) in 2 ml of Ac_2O and 2 drops of pyridine was stirred at r.t. for 6 h. The mixture was directly subjected to flash chromatography and then further purified by reverse-phase HPLC with MeOH/H_2O 4:1 obtaining (–)-**5** (0.003 g, 76%) at t_R 7.0 min. Colourless oil. ^{1}H-NMR (0.003 g in 0.45 ml of C_6D_6): 2.70 (br. *dd*, J_{gem} = 12.9, J(2a,3) = 11.5, J(2a,15) and J(2a,4) small, H_a–C(2)); 1.50 (*ddd*, J_{gem} = 12.9, J(2b,3) = 4.9, J(2b,4) = 1.0, H_b–C(2)); 5.62 (*ddd*, J(3,4) = 11.0, J(3,2a) = 11.5, J(3,2b) = 4.9, H–C(3)); 5.80 (br. *d*, J(4,3) = 11.0, J(4,16) = 1.3, J(4,2b) = 1.0, J(4,2a) and J(4,6) small, H–C(4)); 6.40 (br. *q*, J(6,16) = 1.3, J(6,9b), J(6,4) and J(6,18) small, H–C(6)); 2.86 (*m*, superimposed, H_b–C(9)); 2.86 (*m*, superimposed, H_a–C(9)); 1.91 (*dd*, J(10,9a) = 6.0, J(10,9b) = 2.2, H–C(10)); 1.67 (*ddd*, J_{gem} = J(12α,13β) = 13.7, J(12α,13α) = 3.8, H_α–C(12)); 0.94 (br. *ddd*, J_{gem} = 13.7, J(12β,13α) = J(12β,13β) = 3.8, J(12β,14) small, H_β–C(12)); 1.57 (*dddd*, J_{gem} = 13.7, J(13α,12β) = J(13α,12α) = 3.8, J(13α,14) = 2.4, H_α–C(13)); 2.02 (*dddd*, J_{gem} = J(13β, 12α) = 13.7, J(13β,12β) = 3.8, J(13β,14) = 2.2, H_β–C(13)); 4.88 (br. *dd*, J(14,13α) = 2.4, J(14,13β) = 2.2, J(14,12β) small, H–C(14)); 1.11 (br. *s*, J(15,2a) small, CH_3(15)); 1.81 (*dd*, J(16,6) = J(16,4) = 1.3, CH_3(16)); 6.99 (br. *q*, J(18,19) = 1.3, J(18,6) small, H–C(18)); 1.90 (*d*,

$J(19,18) = 1.3$, $CH_3(19)$); 0.78 (*s*, $CH_3(20)$); 1.71 (*s*, CH_3CO). ^{1}H-NMR([Eu(fod)$_3$]/substrate 2:7 molar ratio; $\Delta\delta$): 0.96 (H–C(14)); 0.82 (CH_3CO); 0.58 (H_α–C(13)); 0.46 (H_a–C(2)); 0.38 (H_b–C(2)); 0.33 (H_α–C(12)); 0.28 (H–C(10)); 0.25 (H_β–C(13)); 0.20 (H_β–C(12)); 0.14 ($CH_3(15)$); 0.12 ($CH_3(20)$); 0.13 ($CH_3(16)$); < 0.1 for the remaining H. MS: 358 (20, $M^{+\cdot}$), 340 (15, $M^{+\cdot} - H_2O$), 298 (18, $M^{+\cdot}$ – AcOH), 280 (35, 298 – H_2O), 265 (98, 280 – CH_3), 199 (90), 159 (100), 145 (55).

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