189. Sarcodictyin A and Sarcodictyin B, Novel Diterpenoidic Alcohols Esterified by (*E*)-*N*(1)-Methylurocanic Acid. Isolation from the Mediterranean Stolonifer *Sarcodictyon roseum*

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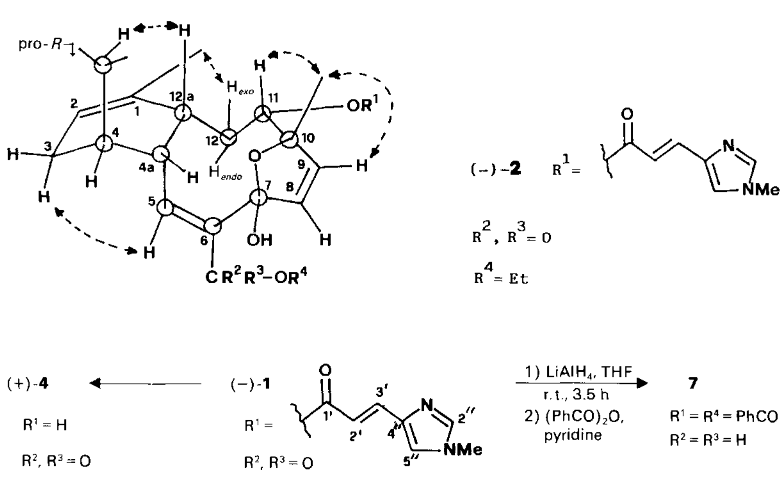
The Mediterranean stolonifer *Sarcodictyon roseum* (= *Rolandia rosea*) (Cnidaria, Anthozoa, Alcyonaria, Stolonifera, Clavulariidae) is shown to contain two novel diterpenoidic alcohols esterified by (*E*)-*N*(1)-methylurocanic acid (= (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylic acid). They are sarcodictyin A (= (–)-(4*R*,4a*R*,7*R*,10*S*,11*S*,12a*R*,1*Z*,5*E*,8*Z*)-7,10-epoxy-3,4,4a,7,10,11,12,12a-octahydro-7-hydroxy-6-(methoxycarbonyl)-1,10-dimethyl-4-(1-methylethyl)benzocyclodecen-11-yl (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylate; (–)-**1**) and sarcodictyin B (the 6-(ethoxycarbonyl analogue; (–)-**2**). The assignment of the structures is mainly based on 1D- and 2D-NMR data, as well as on chemical transformations of (–)-**1**, such as transesterification with MeONa/MeOH giving methyl (*E*)-*N*(1)-methylurocanate (**3**) and the free alcohol (+)-**4** and reduction with $LiAlH_4$ followed by benzoylation giving dibenzoate **7**. Absolute configurations are based on *Horeau*'s method of esterification of (+)-**4**.

1. Introduction. – Cnidaria, chiefly tropical alcyonarians of the orders Alcyonacea, Gorgonacea, and Pennatulacea contain a wide variety of terpenoids [1]. Recently, we have added to the list new interesting sesqui- and diterpenoids isolated from Mediterranean species, the alcyonacean coral *Alcyonium coralloides* [2] and the sea pen *Veretillum cynomorium* [3]. We have also observed that there is a dietary transfer of diterpenoids from this sea pen to its predator, the nudibranch *Armina maculata* [3].

Scheme 1



We have now focussed our attention to Stolonifera, a less common order of alcyonarians, in isolating from the Mediterranean species *Sarcodictyon roseum* a unique meroterpenoid which is optical active due to partial hydrogenation of its quinone moiety [4]. Continuing the study of this animal, we have now isolated novel complex diterpenoidic alcohols esterified by (*E*)-*N*(1)-methylurocanic acid (= (*E*)-3-(1-methyl-1*H*-imidazol-4-yl)acrylic acid). These are sarcodictyin A and B, and we demonstrate in this work that they have the structures (−)-**1** and (−)-**2**, respectively (*Scheme 1*). This is interesting as complex terpenoids have never been isolated before from stolonifers which, from the study of tropical species, are known to contain acetogenins, particularly eicosanoids [5].

2. Results and Discussion. – The compound now isolated from *S. roseum*, sarcodictyin A((−)-**1**), has the highest mass peak at *m/z* 496. High-resolution MS reveals the composition $C_{28}H_{36}N_2O_6$, whilst linked scans [6] show the loss of H_2O, a Me group, and an i-Pr group. That this highest mass peak is the molecular ion is indicated by ^{13}C-NMR spectra which show 28 signals with the multiplicities, revealed by APT experiments [7], reported in *Table 1*. The structure (−)-**1** for sarcodictyin A is also based on its ^{1}H-NMR data (see *Table 2*).

Table 1. *^{13}C-NMR Data (δ_C) and Long-Range C,H Correlations for Sarcodictyin A ((−)-**1**) in C_5D_5N*

C-Atom	δ_C	Correlated protons[a])
C(1)	134.33 (*s*)	Me–C(1), H_α–C(3), H–C(12a)
C(2)	121.78 (*d*)	Me–C(1), H_α–C(3)
C(3)	24.58 (*t*)	
C(4)	42.09 (*d*)	Me(*pro-S*)
C(4a)	34.92 (*d*)	H_α–C(3)
C(5)	143.91 (*d*)	H–C(12a), H–C(4a)
C(6)	135.54 (*s*)	H–C(9), H–C(5), H–C(4a)
C(7)	112.28 (*s*)	H–C(9), H–C(8), H–C(5)
C(8)	134.66 (*d*)	H–C(9), H–C(5)
C(9)	132.97 (*d*)	H–C(11), H–C(8), Me–C(10)
C(10)	89.64 (*s*)	H_{exo}–C(12), Me–C(10), H–C(11), H–C(9), H–C(8)
C(11)	81.77 (*d*)	H_{exo}–C(12), Me–C(10), H–C(12a)
C(12)	32.24 (*t*)	
C(12a)	39.22 (*d*)	H–C(2)
Me_2CH	29.04 (*d*)	Me(*pro-R*)
Me(*pro-S*)	20.38 (*q*)	
Me(*pro-R*)	22.23 (*q*)	
Me–C(1)	22.14 (*q*)	
Me–C(10)	25.88 (*q*)	
C–C(6)	167.95 (*s*)	H–C(5), MeO
MeO	51.75 (*q*)	
C(1′)	167.18 (*s*)	H–C(2′), H–C(3′), H–C(11)
C(2′)	115.31 (*d*)	H–C(3′)
C(3′)	138.04 (*d*)	
C(2″)	140.36 (*d*)	MeN, H–C(5″)
C(4″)	138.32 (*s*)	H–C(2″), H–C(5″), H–C(2′)
C(5″)	124.50 (*d*)	H–C(3′), H–C(2″), MeN
MeN	33.26 (*q*)	H–C(5″)

[a]) These protons are correlated with the C-atoms indicated in the first column.

Table 2. *^{1}H-NMR Data*[a]) *for Sarcodictyin A ((−)-**1**) in C_5D_5N*

H-Atom	(−)-**1**
H–C(2)	5.26 (br. *s*, $J(2,3\beta) \approx 4$, $J(2,3\alpha) \approx J(2,12a) \approx 2.5$, $J(2, Me–C(1)) \approx 1$)
H_α–C(3)	2.38 (br. *d*, $J_{gem} = 18.0$, $J(3\alpha,4) = 6,1$, $J(3\alpha,2) \approx 2.5$, $J(3\alpha,Me–C(1))$ small)
H_β–C(3)	1.94 (br. *d*, $J_{gem} = 18.0$, $J(3\beta,2) \approx 4$, $J(3\beta, Me–C(1))$ small)
H–C(4)	1.17 (*m*, $J(4, Me_2CH) = 10.0$, $J(4,4a) = 2.8$, $J(4,3\alpha) = 6.1$)
H–C(4a)	4.58 (*ddd*, $J(4a,5) = 9.5$, $J(4a,12a) = 4.6$, $J(4a,4) = 2.8$)
H–C(5)	6.97 (*d*, $J(5,4a) = 9.5$)
H–C(8)	7.12 (*d*, $J(8,9) = 5.6$)
H–C(9)	6.28 (*d*, $J(9,8) = 5.6$)
H–C(11)	5.18 (br. *d*, $J(11,12endo) = 7.0$, $J(11,12exo)$ small)
H_{exo}–C(12)	1.98 (br. *d*, $J_{gem} = 15.0$, $J(12exo,12a) = 1.8$, $J(12exo,11)$ small)
H_{endo}–C(12)	1.76 (*ddd*, $J_{gem} = 15.0$, $J(12endo,12a) = 12.2$, $J(12endo,11) = 7.0$)
H–C(12a)	2.95 (br. *d*, $J(12a,12endo) = 12.2$, $J(12a,4a) = 4.6$, $J(12a,12exo) = 1.8$, $J(12a,2) \approx 2.5$, $J(12a,Me–C(1))$ small)
Me_2CH	1.43 (*m*, $J(Me_2CH,4) = 10.0$, $J(Me_2CH, Me(pro\text{-}S)) = J(Me_2CH, Me(pro\text{-}R) = 6.6$)
Me(*pro-S*)	0.91 (*d*, $J(Me(pro\text{-}S), Me_2CH) = 6.6$)
Me(*pro-R*)	0.81 (*d*, $J(Me(pro\text{-}R), Me_2CH) = 6.6$)
Me–C(1)	1.58 (br. *s*, $J(Me–C(1),2) \approx 1$, $J(Me–C(1),12a) \approx J(Me–C(1), 3\beta) \approx J(Me–C(1), 3\alpha)$ small)
Me–C(10)	1.53 (*s*)
MeO	3.65 (*s*)
H–C(2′)	7.14 (*d*, $J(2',3') = 15.5$)
H–C(3′)	8.05 (*d*, $J(3',2') = 15.5$)
H–C(2″)	7.68 (br. *s*, $J(2'',5'')$ small)
H–C(5″)	7.35 (br. *s*, $J(5'',2'')$ small)
Me–N(1″)	3.40 (*s*)

[a]) The pattern reported after the chemical-shift value is for the signal as it appears from the non-decoupled spectrum; most of the coupling constants are derived from double irradiations and are confirmed by COSY experiments. By small, we indicate coupling constants smaller than 0.5 Hz. Approximate values of coupling constants result from difficult evaluations due to the complexity of the spectrum.

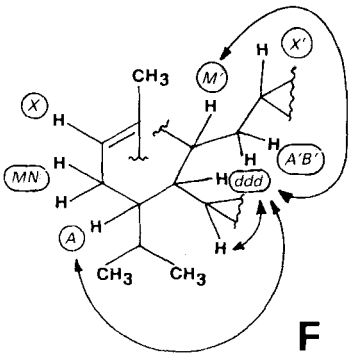
Starting from the low-field side, the ^{13}C-NMR spectrum of (−)-**1** can be described as follows. At 167-168 ppm there are 2 *s* for 2 ester carbonyl groups, in accordance with IR data. Although the region 150–110 ppm shows 4 *s* and 8 *d*, there can only be 5 C=C groups. It will become apparent later that one of the *s* must belong to a tetrahedral C-atom bearing 2 O-atoms [2b] and that one of the *d* must belong to a sp^2 C-atom bound to a N-atom. The region 90–80 ppm, which is typical of tetrahedral C-atoms substituted by 1 O-atom, shows a *d* and a *s*. At 51.75 ppm, there is a *q* for the MeO group of an ester. At 33.26 ppm, there is a *q* suitable for a Me group at a N-atom. Finally, at high field, there are 4 *d*, 2 *t*, and 4 *q* attributable to 4 CH, 2 CH_2, and 4 CH_3 groups, respectively.

The ^{13}C-NMR analysis has thus revealed 35 H-atoms, whereas the MS show 1 H-atom more. This H-atom must be on an O-atom as suggested by the MS observation of the loss of H_2O from the molecular ion. Therefore, accounting for the presence of 2 C=O, 5 C=C, and 1 C=N group, sarcodictyin A must be tretracyclic.

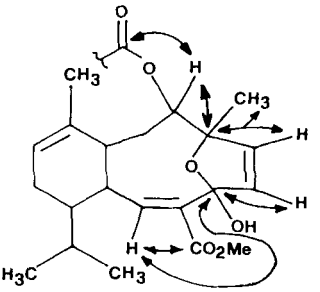
Of the six O-atoms detected by MS, 4 are involved in the 2 ester moieties and 1 in the OH group. The remaining O-atom, in the absence of other indications, has to be part of an ether group, though a simple, linear ether is ruled out by the absence of two isolated C-chain fragments. Therefore, there must be an O-containing heterocycle.

The ^{1}H-NMR spectrum (*Table 2*) reveals 2 *s* for 2 Me groups at heteroatoms, besides 2 *d* and 1 *m* for an i-Pr group, 2 *s* for 2 deshielded Me groups, and a br. *s* and a *d* at 5.26 and 6.97 ppm, respectively, for 2 mutually not coupled olefinic protons. Extensive homonuclear double-resonance experiments (*Table 2*) allow to assign these resonances, while revealing further relationships, thus suggesting the partial structure **F**. This is specifically based, as indicated within circles, on an *AMNX* system (*A* at 1.17 (*m*), *MN* at 2.38 (br. *d*) and 1.94 (br. *d*), and *X* at 5.26 (br. *s*)), an *A′B′M′X′* system[1]) (*A′B′* at 1.98 (br. *d*) and 1.76 (*ddd*), *M′* at 2.95 (br. *d*), *X′* at 5.18 (br. *d*), and a *ddd* at 4.58 ppm for a proton coupled with *M′*, *A*, and, through three bonds, with a further proton, as indicated by the double arrows.

[1]) By the *AMNX* and *A′B′M′X′* systems, we describe here what can be deduced from a simplified analysis of the spectra, as it is feasible at this point of the investigation. Actually, larger portions of the molecule are involved in a more complex spin system; this only becomes evident after these additional experiments are carried out.



F



F'

Though the 1D ^{1}H-NMR spectra also reveal an *AX* system at 6.28 and 7.12 ppm for a C=C bond bearing 2 *cis* H-atoms, any further advancement in the structure elucidation requires 2D-NMR techniques. Thus, ^{13}C,^{1}H correlation experiments [8], adapted to one-bond coupling, allow to assign all H-bearing C-atoms (*Table 1*). Moreover, adaptation of this technique to long-range coupling establishes all the correlations reported in the third row of *Table 1* from which the following conclusions can be made. The C-atoms with signals at 134.33 (*s*) and 39.22 (*d*), being directly correlated, can be joined together to close a six-membered carbocycle as shown in structure **F**[2]). That the six-membered ring must be fused to a ten-membered carbocycle bearing both a Me and a COOMe substituent is suggested by the ^{13}C,^{1}H correlations indicated by the double arrows in the extended partial structure **F'**. In terms of the data in *Table 1*, such arrows mean that C(10) is correlated with H–C(11), and Me–C(10), and H–C(9), whereas C(7) is correlated with H–C(8) and H–C(5) and, finally, *C*–C(6) is correlated with H–C(5).

The above concepts can be further elaborated to assign the *s*'s at 89.64 and 112.28 ppm which are typical of quaternary C-atoms deshielded by 1 or 2 ethereal O-atoms, respectively [2b]. They must be involved in a bridged hemiacetal system as shown in partial structure **F'**. This also accounts for the *AX* system described above in the ^{1}H-NMR, thus rationalizing the 2 *d* at 6.28 and 7.12 ppm which have a typical *J* value (5.6 Hz) for a *cis* C=C bond in a five-membered cycle (*Table 2*).

The remaining ester group accounts for both the deshielded secondary C-atom at 81.77 ppm (*Table 1*) and the proton on it (5.18 ppm (br. *d*); *Table 2*). Correlation of the latter with both the Me-bearing C-atom in α-position at the five-membered heterocycle) and the second unsaturated-ester carbonyl group (*Table 1*) locates the corresponding unsaturated ester moiety as shown in structure **F'**.

The remaining C-atoms bear no correlation with any one proton of fragment **F'** and must, therefore, belong to the unsaturated-ester side-chain[3]). In fact, from the data in *Tables 1* and *2* it is seen that corresponding ester carbonyl group must be conjugated to an (*E*)-olefinic group (according to the high *J* values), and that this side chain must bear an aromatic group (from the H–C(3'),C(5") and C(4"),H–C(2') correlations). This accommodates the 2 N-atoms one of which must bear a Me group. This is also in accordance with the loss of a fragment of *m/z* 152 (unsaturated-acid moiety) from the molecular ion. However, though it is now clear that the ester fragment contains a five-membered aromatic ring with 2 heterocyclic N-atoms, it remains to clarify, whether it is an imidazole or a pyrazole ring.

Base hydrolysis of (–)-**1** followed by acidification at pH 5 and methylation with CH_2N_2 leads to the methyl ester **3** of the acid moiety (*Scheme 2*) whereas neither the intact terpenoidic moiety nor any fragment from it can be recovered from the reaction mixture.

However, transesterification of (–)-**1** with MeONa/MeOH leads to the esterified terpenoidic moiety (+)-**4** (*Scheme 1*) besides methyl urocanate **3** (*Scheme 2*). The struc-

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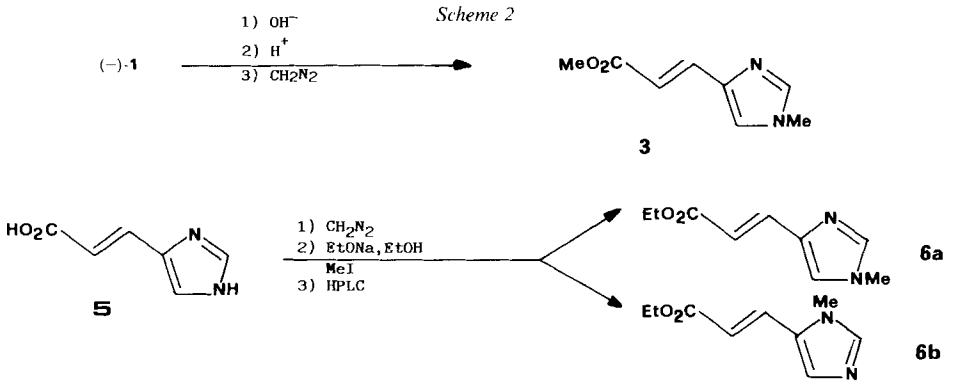
[2]) The 1D ^{1}H-NMR data in *Table 2*, revealing small coupling constants of H–C(12a) with both Me–C(1) and H–C(2), support this conclusion. However, such small coupling constants could only be reliably noticed with the 2D experience at hand.

[3]) Suspicions about this structural feature first arose from the results of COSY experiments [9] which showed that H–C(2") is correlated with both H–C(3') and Me–N(1"), while H–C(5") is correlated with both H–C(2') and Me–N(1").

Scheme 2



ture of **3** is secured by the synthesis, from commercial (*E*)-urocanic acid (**5**), of both methyl-substituted urocanates **6a** and **6b** which can be separated by HPLC (*Scheme 2*). The structural assignment of the two esters as regards the position of the Me group is based on NOE data, as reported in the *Exper. Part.*

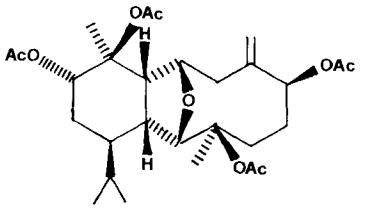
The configuration at the C(5)=C(6) bond of (−)-**1** can be indirectly derived from the ^{1}H-NMR coupling patterns. However, it is also directly proved by the reduction of (−)-**1** with $LiAlH_4$ giving **7**, after esterification with benzoic anhydride/pyridine[4]). The structure of **7** rests on NOE studies the results of which are represented by dotted double arrows (*Scheme 1*). Thus, there is a sizable NOE effect at $PhCOOH_2C$–C(6) on irradiation at the double-bond proton in *cis*-position. Concomitantly, there is also a NOE effect on H_α–C(3) which supports the configuration at the ring junction and the pseudoaxial position of the i-Pr group. This is confirmed by NOE experiments with (−)-**1** which show a positive effect between Me_2CH and H–C(12a) (*Exper. Part*). With (−)-**1**, there are also differential, positive NOE effects on Me–C(1) (on irradiation at either H–C(2) or H_{exo}–C(12)) and on Me–C(10) (on irradiation at either H–C(11) or H–C(9)) which further support the structural conclusions from the ^{13}C,^{1}H experiments.

Structure (−)-**1** must also represent the absolute configuration. In fact, terpenoid (+)-**4**, though labile, could be subjected, immediately as produced, to esterification according to *Horeau*'s methods, giving α-phenylbutyric acid with negative optical rotation.

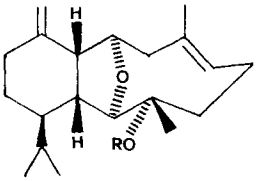
A minor metabolite extracted form *S. roseum*, sarcodictyin B ((−)-**2**), is the 6-ethoxycarbonyl analogue of sarcodictyin A ((−)-**1**). Its structure is supported by both spectral data (*Exper. Part*) and the fact that, on treatment with MeONa/MeOH, (−)-**2** gives the same products as in the case of (−)-**1**. Therefore, structure (−)-**2** represents also the absolute configuration.

Strictly speaking, sarcodictyin A ((−)-**1**) and B ((−)-**2**) have the same carbon skeleton as eunicellin ((−)-**8**), isolated from the gorgonian *Eunicella stricta* [10], as cladiellin (**9a**) and acetoxycladiellin (**9b**), isolated from the alcyonacean *Cladiella* sp. (no chiroptical data reported [11]), and as products isolated from the gorgonian *Muricella* sp. [11b] and from an unknown alcyonacean collected at Majuro Atoll [11c]. Moreover, 14-membered

[4]) As reported in the *Exper. Part*, **7** is obtained in extremely poor yield. The main product (or products) contains an α-substituted furan ring, though its detailed nature is not yet clear. Work is in progress to clarify this and other interesting transformations of the sarcodictyins.



(–)–8



9a R = H
b R = Ac

cembranoid intermediates may well be biogenetic precursors of all these compounds [12]. However, the different position and the different nature (hemiacetal *vs.* ether) of the O-bridge in the sarcodictyins confers them distinct chemical properties to warrant establishing a distinct series.

It is known that many bacteria possess L-histidine ammonia lyase (histidase) which brings about the transformation of histidine into urocanic acid [13]. Such a process occurs, for example, with preserved fish, and urocanic acid has been proposed as a spoilage index [13]. It is also known that urocanic acid is an inhibitor of histidine decarboxylase [14] and that it has specific toxicity towards certain neoplastic cells [15]. Moreover, being subjected to a (*E*/*Z*) photoisomerization [16], urocanic acid may find use to protect the human epidermis from solar radiations [17].

In sarcodictyin A and B, urocanic acid blocks the OH–C(11) function, thus stabilizing an otherwise very labile diterpenoidic alcohol while making the compounds soluble in body fluids. Although the cladiellins are known to exert a most potent antiinflammatory activity [18], it is not yet known whether the urocanic-acid moiety serves to further strengthen some bioactivity of the sarcodictyins.

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Experimental Part

1. *General.* All evaporations were carried out at reduced pressure at r.t. TLC: *Merck Kieselgel 60 PF_{254}* plates. UV and IR spectra: *Perkin-Elmer Lambda-3* (λ_{max} in nm, ε in $dm^3\ mol^{-1}\ cm^{-1}$) and *Pye-Unicam SP3–100* ($\tilde{\nu}_{max}$ in cm^{-1}) spectrophotometers, resp. Polarimetric data: *JASCO-DIP-181* digital polarimeter. ^1H- and ^{13}C-NMR spectra: *Varian XL300* (300 or 75.43 MHz, resp.); δ (ppm) relative to internal Me_4Si (= 0 ppm) and J in Hz; the notation small indicates $J < 0.5$ Hz; J's are derived from homonuclear decoupling; multiplicities in the ^{13}C-NMR by APT [7] or DEPT [19] techniques; all chemical-shift assignments are supported by $^{13}C,^1H$-NMR shift correlation experiments (HETCOR) [8] which were carried out with spectral width 11 891 Hz (2048 points) along the ^{13}C domain and 2330 Hz (128 time increments) along the ^1H domain; for one-bond experiments, for each FID, 256 transients were recorded with $\Delta_1 = 0.0036$ and $\Delta_2 = 0.024$ s; for long-range experiments, for each FID, 768 transients were recorded with $\Delta_1 = 0.042$ and $\Delta_2 = 0.028$ s; the COSY experiment was carried out by acquiring 512 FID (16 transients each) with spectral width 2400 Hz; the data matrix thus obtained was zero filled and pseudo-echo processed. Mass spectra: high-resolution and linked scan (B/E) studies [6], *VGZAB2F* spectrometer; low resolution, home-built quadrupole mass spectrometer based on the *ELFS-4-162-8 Extranuclear* quadrupole [20].

2. *Isolations. S. roseum* (= *Rolandia rosea* (PHILIPPI) was collected by scuba diving 100 meters off Cap Bear, East Pyrenean, at depths of 25–35 m in August 1986, on the skeleton of gorgonians. The animal and the underlying dead gorgonian skeleton were accurately freed from the closely living gorgonian, cut in small pieces, and closely packed, together with the gorgonian skeleton, in a 4-l vessel which was filled with 95% EtOH. After 1 month, the solvent was decanted, and the residual animals were extracted 3 times with abundant, fresh 95% EtOH. The combined extracts were evaporated, H_2O was added and the mixture extracted with AcOEt. The org. phase was evaporated, and the residue was subjected to reverse-phase flash chromatography on a 6×10 cm frit filter filled with *Serva Polyamide-6* (100–300 μm) with a H_2O/CH_3CN gradient. The first fractions were evaporated, and the residue was subjected to HPLC on a 25×1 cm *Merck-LiChrosorb-CN* (7 μm) column with a 5 ml/min flux of hexane/EtOH/(i-Pr)NH_2 80:18:2. Sarcodictyin B ((−)-**2**; 0.052 g) and A ((−)-**1**; 0.115 g) were thus eluted at t_R 10.3 and 11.2 min, resp.

3. *Sarcodictyin A* (= *(−)-(4R,4aR,7R,10S,11S,12aR,1Z,5E,8Z)-7,10-Epoxy-3,4,4a,7,10,11,12,12a-octahydro-7-hydroxy-6-(methoxycarbonyl)-1,10-dimethyl-4-(1-methylethyl)benzocyclodecen-11-yl (E)-3-(1-Methyl-1H-imidazol-4yl)acrylate*[5]); (−)-**1**. Colourless microcrystalline powder. M.p. 219–222° (from MeOH). $[\alpha]^{20} = -15.2°$ (589), −16.3° (577), −21.4° (546), −71.3° (435) (*c* = 1.12, EtOH). UV (ETOH): 290 (20000), 202 (17000). IR (KBr): 3400*s* (OH), 1710*s* (C=O), 1700*s* (C=O), 1640*s*, 1270*s*, 1170*s*, 1050*s*. Differential NOE effects (C_5D_5N; irradiated proton (δ)→% NOE effect on the observed proton(s) (δ)): terpenoidic portion: 0.81→10% on 1.94 and 11% on 1.43; 0.91→11% on 4.58 and 7% on 1.43; 1.17→3% on 1.97 and 6% on 4.58; 1.53→12% on 6.28 and 7% on 5.18; 1.58→15% on 5.26 and 5% on 1.98; 2.38→11% on 6.97, 4.7% on 5.26, and 12% on 1.94; 2.95→5% on 5.18, 8% on 4.58, and 6% on 1.43; 4.58→4% on both 1.17 and 2.95, and 8% on 5.18; 5.18→5% on both 4.58 and 2.95, and 2% on 1.53; 6.97→7.5% on 2.38, and 2% on 1.17; urocanate portion: 3.40→19% on 7.68 and 13% on 7.35; 7.35→13% on 8.05 and 4% on 3.40; 7.68→3% on 3.40. MS: 496 (51, $M^{+\cdot}$), 344 (51, $M^{+\cdot}$ −152), 285 (37), 283 (58), 269 (75), 251 (47), 245 (37), 231 (41), 204 (35). HR-MS: 496.2672 ● 0.01 ($C_{28}H_{36}N_2O_6$, calc. 496.2573), 344.2002 ± 0.01 ($C_{21}H_{28}O_4$, calc. 344.1987). Linked scans (B/E [6]): working on $M^{+\cdot}$, peaks were observed at *m/z* 478 ($-H_2O$), 464 (−MeOH), and 453 ($-C_3H_7$), whereas working on *m/z* 344, peaks were observed at *m/z* 326 ($-H_2O$), 312 (−MeOH), 301 ($-C_3H_7$).

4. *Hydrolysis of (−)-***1**. A soln. of (−)-**1** (0.005 g, 0.01 mmol) in 2 ml of 4% KOH in MeOH was heated at reflux for 40 min. The mixture was buffered with AcOH and evaporated, CH_2N_2 was added in excess, the resulting mixture evaporated, and the residue subjected to prep. TLC with AcOEt/i-$PrNH_2$ 98:2. *Methyl N(1)-methylurocanate* (= *methyl (E)-3-(1-methyl-1H-imidazol-4-yl)acrylate*; **3**; 0.001 g, 65%) was obtained from the band at R_f 0.2.

5. *Transesterification of (−)-***1**. A soln. of (−)-**1** (0.015 g, 0.03 mmol) in 2.8 ml of 1M MeONa in MeOH was stirred at r.t. for 3 h. The mixture was subjected to flash chromatography on *Merck Kieselgel 60* with Et_2O to remove MeONa, thus making the eluate neutral. After evaporation, the residue was subjected to prep. TLC with AcOEt/i-$PrNH_2$ 95:5 to obtain (+)-**4** (0.005 g, 48%) and **3** (0.004 g, 89%) at R_f 0.7 and 0.3, resp.

(+)-Methyl (4R,4aR,7R,10S,11S,12aR,1Z,5E,8Z)-7,10-Epoxy-3,4,4a,7,10,11,12,12a-octahydro-7,11-dihydroxy-1,10-dimethyl-4-(1-methylethyl)benzocyclodecene-6-carboxylate ((+)-**4**): ^{1}H-NMR (CD_3OD): 6.58 (*d*, *J*(5,4a) = 9.5, H−C(5)); 6.41 (*d*, *J*(8,9) = 5.6, H−C(8)); 5.99 (*d*, *J*(9,8) = 5.6, H−C(9)); 5.31 (br. *s*, (H−C(2)); 4.36 (*ddd*, *J*(4a,5) = 9.5, *J*(4a,12a) ≈ 5, *J*(4a,4) ≈ 3, H−C(4a)); 3.56 (br. *d*, *J*(11,12*endo*) ≈ 7, *J*(11,12*exo*) small, H−C(11)); 3.32 (*s*, MeO); 2.44 (br. *s*, partially superimposed, H−C(12a)); 2.40 (br. *d*, partially superimposed, H_α−C(3)); 2.08 (br. *d*, *J*(3β,3α) ≈ 18, H_β−C(3)); 1.73 (br. *d*, *J*(12*exo*,12*endo*) ≈ 15, *J*(12*exo*,12a) = 2, H_{exo}−C(12)); 1.60 (br. *s*, Me−C(1)); 1.55 (*m*, Me_2CH); 1.51 (*s*, Me−C(10)); 1.34 (*ddd*, *J*(12*endo*,12*exo*) ≈ 15, *J*(12*endo*,12a) ≈ 12, *J*(12*endo*,11) ≈ 7.0, H_{endo}−C(12)); 1.24 (*m*, H−C(4)); 0.96 (*d*, *J*(Me(*pro-S*), Me_2CH) = *J*(Me(*pro-R*), Me_2CH) ≈ 7.0, Me_2CH).

6. *Reduction of (−)-***1** *and Benzoylation*. To 2.0 ml of a THF soln. of 0.020 g (0.04 mmol) of (−)-**1** was added $LiAlH_4$ in a 1.5 fold molar excess. The mixture was stirred at r.t. for 3.5 h, then quenched with H_2O, extracted with AcOEt, and the extract evaporated. To the residue (0.02 g), pyridine and benzoic anhydride were added and stirred at r.t. for 24 h. After addition of H_2O and stirring for 1 h, aq. NaOH soln. was added, the mixture extracted with AcOEt, the org. phase evaporated, and the residue subjected to prep. TLC with Et_2O/petroleum ether 95:5. The band at R_f 0.93 was extracted and resubjected to prep. TLC with Et_2O/petroleum ether 6:4 to give *11-(benzoyloxy)-7,10-epoxy-3,4,4a,7,10,11,12,12a-octahydro-7-hydroxy-1,10-dimethyl-4-(1-methylethyl)benzocyclodecene-6-methyl benzoate* (**7**; 0.001 g, 4.5%) from the band at R_f 0.7. ^{1}H-NMR (C_6D_6): 8.03 (*m*, 4H), 7.58 (*m*, 2H), 7.45 (*m*, 4H, together 2 Ph); 6.28, 6.27 (*AB*, J_{AB} = 5.5, H−C(9), H−C(8)); 5.76 (*d*, *J*(5,4a) = 9.4, H−C(5)); 5.26 (br. *s*,

[5]) The diesters (−)-**1** and (−)-**2** are numbered like the corresponding hydroxy-monoester (+)-**4**.

H–C(2)); 4.98 (br. *d*, *J*(11,12*endo*) = 7.1, H–C(11)); 4.91, 4.85 (*AB*, J_{AB} = 12.0, CH_2–C(6)); 4.09 (*m*, H–C(4a)); 2.82 (br. *s*, H–C(12a)); 2.30 (*m*, H_α–C(3)); 2.03 (*m*, H_{exo}–C(12)); 1.72 (br. *d*, H_β–C(3)); 1.53 (*s*, Me–C(10)); 1.50 (br. *s*, Me–C(1)); 1.03 (*q*, *J* (Me(*pro-S*), Me_2CH) = 6.5, Me(*pro-S*)); 0.95 (*d*, *J* (Me(*pro-R*), Me_2CH) = 6.4, Me(*pro-R*)); 1.3–1.6 (remains, partially submerged by the Me signals); on irradiation at 5.76, differential NOE effects at 4.91 and 4.85 (6%) and at 2.30 (5%).

7. *Sarcodictyn B* (= *(–)-(4*R,*4a*R,*7*R,*10*S,*11*S,*12a*R,*1*Z,*5*E,*8Z)-7,10-Epoxy-6-(ethoxycarbonyl)-3,4,4a,7,10,11,12,12a-octahydro-7-hydroxy-1,10-dimethyl-4-(1-methylethyl)benzocyclodecen-11-yl (*E*)-3-(1-Methyl-1*H*-imidazol-4-yl)acrylate*[5]); (–)-**2**). $[\alpha]_D^{20}$ = –4.36° (*c* = 0.27, EtOH). ^{1}H-NMR (C_5D_5N; correlations derived from COSY, in brackets, represented by C-numbering or the appropriate group representation): 5.28 (br. *s*, [2→12a; 2→3β; 2→Me–C(1)], H–C(2)); 2.41 (br. *d*, [3α→3β; 3α→Me–C(1); 3α→4], H_α–C(3)); 1.96 (superimposed with H_{exo}–C(12), [3β→3α; 3β→Me–C(1); 3β→2], H_β–C(3)); 4.57 (*m*, *J*(4a,5) = 9.7, [4a→12a; 4a→4], H–C(4a)); 1.18 (*m*, [4→3α; 4→4a; 4→Me_2CH], H–C(4)); 6.98 (*d*, *J* (5,4a) = 9.7, H–C(5)); 7.13 (*d*, *J*(8,9) = 5,9, H–C(8)); 6.30 (*d*, *J* (9,8) = 5,9 H–C(9)); 5.18 (br. *d*, *J*(11,12*endo*) = 7.0, *J* (11,12*exo*) = small, H–C(11)); 1.99 (superimposed to H_β–C(3), [12*exo*→12*endo*; 12*exo*→11], H_{exo}–C(12)); 1.77 (*ddd*, J_{gem} = 15.0, *J*(12*endo*, 12a) = 12.0, *J*(12*endo*, 11) = 7.0, H_{endo}–C(12)); 2.96 (br. *d*, [12a→2; 12a→4a; 12a→12*exo*; 12a→12*endo*; 12a→Me–C(1)], H–C(12a)); 1.44 (*m*, *J*(Me_2CH, Me(pro-*S*)) = 6.6, *J*(Me_2CH, Me(pro-*R*) = 6.5, [Me_2CH→4], Me_2CH); 0.92 (*d*, *J* (Me(pro-*S*), Me_2CH) = 6.6, Me(pro-*S*)); 0.81 (*d*, *J* (Me(pro-*R*)), Me_2CH) = 6.5, Me(pro-*R*)); 1.58 (br., *s*, [C–C(1)→3β; C–C(1)→3α; C–C(1)→12a; C–C(1)→2], Me–C(1)); 1.55 (*s*, Me–C(10)); 4.20, 4.12, 1.13 (*ABX*$_3$, J_{AB} = 12.0, $J_{AX} = J_{BX}$ = 7.0, CH_3CH_2O); 7.13 (*dd*, *J* (2′,3′) = 15.5, *J*(2′,5′) = 0.3, H–C(2′)); 8.05 (br. *d*, *J*(3′,2′) = 15.5, [3′→2″], H–C(3′)); 7.70 (br. *s*, *J*(2″,5″) = 1.2, [2″→2′; 2″→MeN], H–C(2″)); 7.37 (br. *s*, *J*(5″,2″) = 1.2 [5″→MeN], H–C(5″)); 3.41 (*s*, [MeN→2″; MeN→5″], MeN). ^{13}C-NMR (C_5D_5N; assignments from HETCOR [8]; multiplicities from DEPT [19]): 134.24 (*s*, C(1)); 121.58 (*d*, C(2)); 24.44 (*t*, C(3)); 41.97 (*d*, C(4)); 34.75 (*d*, C(4a)); 143.29 (*d*, C(5)); 167.47 (*s*, *C*–C(6)); 135.81 (*s*, C(6)); 112.19 (*s*, C(7)); 134.70 (*d*, C(8)); 132.68 (*d*, C(9)); 89.44 (*s*, C(10)); 81.65 (*d*, C(11)); 32.12 (*t*, C(12)); 39.11 (*d*, C(12a)); 28.88 (*d*, Me_2CH); 20.24 (*q*, Me(pro-*S*)); 22.00 (*q*, Me(pro-*R*)); 21.95 (*q*, *Me*–C(1)); 25.75 (*q*, *Me*–C(10)); 167.02 (*s*, C(1′)); 115.26 (*d*, C(2′)); 137.89 (*d*, C(3′)); 140.05 (*d*, C(2″)); 138.39 (*s*, C(4″)); 124.07 (*d*, C(5″)); 32.85 (*q*, MeN); 13.99 (*q*, CH_3CH_2O); 60.49 (*t*, CH_3CH_2O).

8. *Transesterification of (–)-***2**. Starting from 0.020 g (0.04 mmol) of (–)-**2** and operating as above for (–)-**1**, (+)-**4** (0.008 g, 54%) and **3** (0.005 g, 83%) were obtained.

9. *Esterification of (+)-***4** *According to* Horeau. To (+)-**4** (0.010 g, 0.029 mmol) in 1 ml of dry pyridine was added (±)-α-phenylbutyric anhydride (0.023 g, 0.072 mmol), and the mixture was stirred for 5 h at r.t. Then, H_2O (0.3 ml) was added, the mixture stirred for 1.5 h, titrated with 0.1M NaOH, and extracted with Et_2O. The aq. residue was acidified and extracted with Et_2O and the org. phase evaporated. The resulting α-phenylbutyric acid in 2 ml of C_6H_6 had α_D = –0.022° (10-cm optical path cell). Esterification yield (from ^{1}H-NMR [3]) 57%; optical yield 16.1%.

10. *Esterification and Methylation of Urocanic Acid* (**5**). Methyl urocanate (obtained from CH_2N_2 treatment of urocanic acid (**5**; *Aldrich*; 0.414 g, 3 mmol)) and MeI (2.33 µl, 3.7 mmol) were dissolved in 20 ml of 0.19M EtONa in EtOH and heated at reflux for 2 h. The mixture was then evaporated and extracted with AcOEt. The org. phase was evaporated and the residue subjected to HPLC on *Merck LiChrosorb-CN* with hexane/EtOH/i-$PrNH_2$ 80:18:2 to give ethyl urocanate (0.025 g, 6%), *ethyl (E)-3-(1-methyl-1*H*-imidazol-5-yl)acrylate* (**6b**; 0.12 g, 24%), and *ethyl (E)-3-(1-methyl-1*H*-imidazol-4-yl)acrylate* (**6a**; 0.33 g, 66%) at t_R 5.5, 6.2, and 6.9 min, resp.

6b: ^{1}H-NMR ($CDCl_3$): 8.07 (br. *s*, H–C(2″)); 7.51 (br. *s*, H–C(4″)); 7.48 (*d*, *J*(3′,2′) = 16.0, H–C(3′)); 6.32 (*d*, *J*(2′,3′) = 16.0, H–C(2′)); 4.25 (*q*, *J* = 7.0, CH_3CH_2O); 3.81 (*s*, MeN); 1.34 (*t*, *J* = 7.0, CH_3CH_2O); differential positive NOE effects (irradiated proton (δ)→resulting effect on): 3.81→H–C(3′) (1.4%); 8.07→MeN (0.8%).

6a: ^{1}H-NMR ($CDCl_3$): 7.52 (*d*, *J*(3′,2′) = 16.0, H–C(3′)); 7.48 (br. *s*, H–C(2″)); 7.07 (br. *s*, H–C(5″)); 6.53 (*d*, *J*(2′,3′) = 16.0, H–C(2′)); 4.22 (*q*, *J* = 7.0, CH_3CH_2O); 3.70 (*s*, MeN); 1.31 (*t*, *J* = 7.0, CH_3CH_2O); differential positive NOE effects (irradiated proton (δ)→resulting effect on): 7.07→H–C(3′) (3.6%) and MeN (1.8%); 3.70→H–C(5″) (12%) and H–C(2″) (4%).

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