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Chemical constituents of the soft corals *Sinularia vanderlandi* and *Sinularia gravis* from the coast of Madagascar†

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The crude extracts of the Madagascan soft corals *Sinularia vanderlandi* and *Sinularia gravis* (Alcyoniidae) showed activity against *Plasmodium falciparum* which led us to study their chemical constituents. The new cadinane-type sesquiterpenoid vanderlandin (**1**) has been obtained from *S. vanderlandi* along with 24-methylenecholesterol (**2**). Four new compounds, the spatane-type diterpenoid gravilin (**3**), the monoalkylmonoacylglycerol **4**, the dihomoditerpenoid ketone **5**, and isodecaryiol (**9**), along with the three known compounds (+)-(*S*)-geranyllinalool (**6**), (–)-(*R*)-nephthenol (**7**), and 11,12-epoxysarcophytol A (**8**) have been isolated from the methanol extract of *S. gravis*. The structures were elucidated based on extensive spectroscopic methods, in particular various 2D NMR techniques. The structure of isodecaryiol (**9**) including its absolute configuration could be confirmed by X-ray diffraction.

Introduction

Soft corals of the genus *Sinularia* have been shown to contain intriguing chemical components with various biological activities. Sheu *et al.* isolated the cembrane-type diterpenoids manaarenolide A–I from *Sinularia manaarensis* with some representatives showing moderate cytotoxic activity against Hepa59T/VGH, KB, Hela, and Med cancer cell lines.[1] A series of oxygenated cembranoids, gibberosenes A–G, has been obtained from the Formosan soft coral *Sinularia gibberosa*.[2] The soft corals *Sinularia querciformis*[3,4] and *Sinularia granosa*[3] have also been identified as source of oxygenated cembranoids, some of them with anti-inflammatory activity. A sulfur-containing biscembranoid was obtained from the Formosan soft coral *Sinularia flexibilis*.[5] The cadinane-type sesquiterpenes scabralin A and B from *Sinularia scabra* have been described by Sheu and coworkers.[6] Lin *et al.* isolated asteriscane-type sesquiterpenoids from the soft coral *Sinularia capillosa*.[7] Soft corals from the coast of Madagascar have only rarely been investigated concerning their secondary metabolites.[8–10] This fact and the only very few reports on the chemical constituents of *Sinularia vanderlandi* and *Sinularia gravis* (Alcyoniidae) (see ref. 11–13) prompted us to initiate the present study.

Results and discussion

Sinularia vanderlandi

Samples of *S. vanderlandi* were minced, homogenized, and extracted with methanol. In an anti-malaria assay, the crude methanol extract of *S. vanderlandi* showed an IC_{50} value of 26.88 ± 4.83 μg mL^{-1} for the inhibition of the FCM29 strain of *Plasmodium falciparum* which corresponds to a low activity against this pathogen. After concentration of the crude methanol extract *in vacuo*, the residue was repeatedly extracted with diethyl ether. The diethyl ether extract was then subjected to column chromatography on silica gel using pentane–diethyl ether (4 : 1) as eluent. Further purification by a second column chromatographic step under the same conditions led to the isolation of the new cadinane-type sesquiterpenoid[14–16] vanderlandin (**1**) along with 24-methylenecholesterol (**2**)[17–21] (Fig. 1).

Vanderlandin (**1**) [biogenetic (germacrane) numbering is used according to ref. 16] was isolated as a colorless solid with

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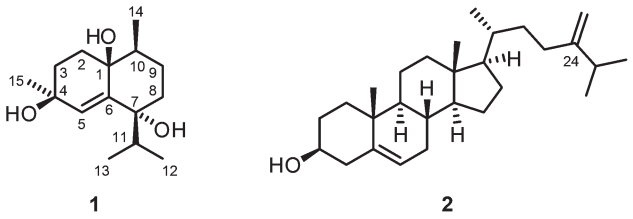
†Electronic supplementary information (ESI) available: Tables S1–S10; Fig. S1–S70 (copies of the ^{1}H, ^{13}C, and 2D NMR spectra for the compounds **1**, **3–5**, and **9**); Fig. S71 (symmetry-independent molecules of compound **9**); details of the antimalarial assay. CCDC 1424360. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob02280k



1 2

Fig. 1 Structures of vanderlandin (**1**) and 24-methylenecholesterol (**2**).

a melting point of 57–58 °C and a specific optical rotation of $[\alpha]_D^{20} = -3.8$ (c 0.1, MeOH). The EI mass spectrum (m/z = 237 $[M - OH]^+$) in combination with the number and intensities of ^1H and ^{13}C NMR signals allowed for the determination of the molecular formula of $C_{15}H_{26}O_3$ which is indicative for three double bond equivalents. A broad IR absorption at ν = 3407 cm^{-1} revealed the presence of hydroxyl groups. The ^1H and ^{13}C NMR spectra in combination with the DEPT spectrum displayed signals for four methyl groups, four methylene groups, and three methine groups (Table S1†). In total, resonances for 15 carbon atoms could be detected in the ^{13}C NMR spectrum including those for three oxygenated quaternary carbon atoms at δ_C = 83.46, 89.10, and 90.27 ppm. One double bond was identified by ^{13}C NMR signals at δ_C = 124.33 and 148.05 ppm and a singlet for a vinylic proton at δ_H = 6.12 ppm. Complete assignment of the proton signals to the corresponding ^{13}C NMR signals was achieved by HSQC and HMBC measurements. A series of HMBC long-range correlations led to the identification of the octahydronaphthalene backbone which is also in agreement with the three double bond equivalents according to the molecular formula. Characteristic HMBC correlations to establish the bicyclic skeleton include the interactions of C-1 with H-2α, H-2β, H-3α, H-3β, H-5, H-9α, and H-9β, of C-4 with H-2α, H-2β, H-3β, and H-5, of C-6 with H-2α, H-2β, H-3α, H-3β, and H-5, and of C-10 with H-2β, H-5, H-8α, H-8β, H-9α, and H-9β (Table S1†). In addition, C-7 correlated with H-5, H-8α, H-8β, H-9α, and H-9β and C-8 exhibited HMBC cross-peaks with H-5, H-9α, H-9β, and H-10. The primary carbon atoms in **1** displayed signals at δ_C = 17.03 ppm for C-12 and C-13, 13.40 ppm for C-14, and 19.84 ppm for C-15, respectively. According to ^1H–^1H COSY measurements, H_3-12 and H_3-13 correlated with H-11 suggesting the presence of an isopropyl group. The location of the isopropyl group at C-7 was determined by HMBC correlations of H-8α, H-8β, H-9α, H-9β, H-11, H_3-12, and H_3-13 with the quaternary carbon C-7 and, in addition, of H-11 with C-5 and C-8. The attachments of the Me groups at C-10 and at C-4 were confirmed by HMBC correlations of H_3-14 with C-9, C-10 and C-1, and of H_3-15 with C-4 and C-3, respectively.

Analysis of proton coupling constants and NOE correlations in combination with MM2 molecular modeling studies led to the assignment of the relative configuration of **1** (Table S1,† Fig. 2). The pseudoaxial β position of the Me group at C-10 in a twist-boat-like B-ring was indicated by a strong NOE interaction of H_3-14 with H-9β but not with H-9α. NOE correlations

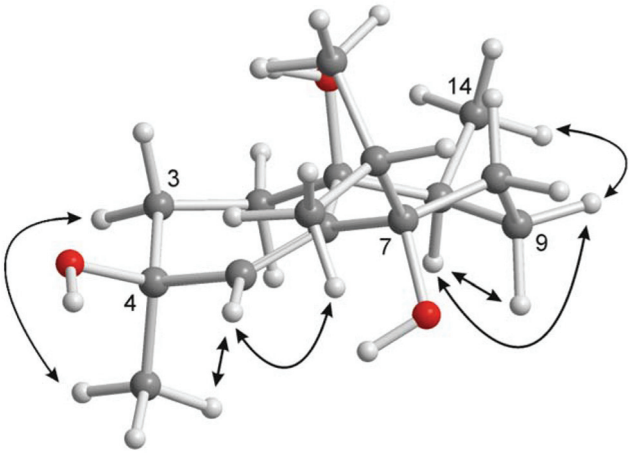


Fig. 2 Characteristic NOE correlations of vanderlandin (**1**) shown at a computer-generated model (MM2 force field).

of similar intensity of H-10 with both H-9α and H-9β suggesting a pseudoequatorial position of H-10 are in support of this assignment. The absence of any NOE correlation of protons of the isopropyl group with H-9α(ax) most likely accounts for a pseudoequatorial position of this group in *cis*-relationship to the Me group at C-10. The *cis*-arrangement of the 1-OH group and the Me group at C-10 was derived from the absence of NOE correlations of H_3-14 with H-2α, H-2β, H-3α, and H-3β. In case of a presumed *trans*-arrangement of the 1-OH group and the Me group at C-10, a much closer proximity of H_3-14 to the protons at C-2 and C-3 would be expected which should give rise to pronounced NOE interactions. The configuration of the Me group at C-4 was derived from a strong NOE correlation of H_3-15 with H-3α(eq) and only a very weak interaction with H-3β(ax). This is in agreement with a pseudoaxial α position of the Me group at C-4 in the preferred half-chair conformation of the cyclohexene ring (Fig. 2). A twist-boat-like conformation with a pseudoaxial Me group at C-4 in β-position, which would equally explain the observed NOESY results, is energetically disfavored according to molecular modeling studies (MM2 force field). Thus, most likely, the Me group at C-4 adopts a *trans*-configuration with respect to the alkyl substituents at C-7 and C-10. Based on these arguments, compound **1** was assigned as (−)-(1*S*/*R*,4*S*/*R*,7*R*/*S*,10*S*/*R*)-cadin-5-ene-1,4,7-triol, a new representative of the cadinane-type bicyclic sesquiterpenes which we have named vanderlandin. Similar di- and trihydroxylated cadinane sesquiterpenes have been isolated for example from *Taiwania cryptomerioides* Hayata,[22,23] the brown alga *Dictyopteris divaricata*,[24] and more recently, from the rhizome of *Acorus calamus* L.[25]

Sinularia gravis

A specimen of the soft coral *S. gravis* collected in the inner reef of Mahambo, Madagascar, was minced and extracted with methanol. The anti-malaria assay of the crude methanol extract of *S. gravis* exhibited an IC_{50} value of 30.81 ± 9.09 μg mL^{-1}

for the inhibition of the FCM29 strain of *Plasmodium falciparum*. The combined methanol extracts were partitioned between water and diethyl ether. After removal of the solvent *in vacuo*, the diethyl ether extract was subjected to column chromatography on silica gel with pentane–diethylether (10 : 1 and 4 : 1) as mobile phase to provide four new compounds, gravilin (**3**), the monoalkylmonoacylglycerol **4**, the ketone **5** (Fig. 3), and isodecaryiol (**9**) (Fig. 5). In addition, the four known compounds 24-methylenecholesterol (**2**) (Fig. 1),[17–21] (+)-(*S*)-geranyllinalool (**6**) (Fig. 3),[26–36] and the cembranoids (−)-(*R*)-nephthenol (**7**)[37–44] and 11,12-epoxysarcophytol A (**8**) (Fig. 5)[2,45–50] were isolated.

The novel spatane diterpenoid gravilin (**3**), the least polar component of the *S. gravis* extract, was isolated as a colorless solid with a specific optical rotation of $[\alpha]_D^{20}$ = +46.0 (*c* 0.8, MeOH) and a melting point of 100–101 °C. The ESI-MS showed peaks at 289 and 306 mass units for $[M + H]^+$ and $[M + NH_4]^+$ ions, respectively. The derived monoisotopic mass of 288 in combination with the number and intensities of ^{1}H and ^{13}C NMR signals led to the molecular formula $C_{20}H_{32}O$. Signals for four methyl groups, seven methylene groups, and six methine groups were identified by ^{1}H NMR, ^{13}C NMR, and DEPT measurements. Complete proton to carbon assignment was achieved by HSQC and HMBC measurements (Table S2†). On interpretation of the NMR data, it soon became clear that the structure resembles that of spatol, a tricyclic diterpene isolated from the brown seaweed *Spatoglossum schmittii*.[51] The spatane backbone was established on the basis of long range HMBC correlations. Characteristic interactions are those of C-4 with H-3α, H-3β, H_2-5, H-6β, H-8, and H-10, of C-8 with H-9 and H-10, of C-9 with H-2α, H-3α, H-3β, and H-10, and of C-10 with H-2β, H-3α, H-3β, H_2-5, H-8, and H-9. In place of the methyl group at C-1 in spatol, a methylene group was identified in **3** by vinylic signals at δ_H = 4.70 (s, H-11a), 4.73 ppm (s, H-11b), and δ_C = 103.76 ppm (C-11). The attachment of the methylene moiety at C-1 was established based on HMBC correlations of H-11a and H-11b with C-9 and C-2. On the other hand, the methylene group at C-13 in spatol was replaced by a methyl group resonating at δ_H = 0.85 ppm (d, *J* = 6.8 Hz, H-14) and δ_C = 17.87 ppm (C-14). Other than in spatol, the position C-5 is not oxygenated exhibiting a multiplet at δ_H = 1.52 ppm. This was assigned based on the HSQC correlation with the ^{13}C NMR signal at δ_C = 42.19 ppm (C-5). The 17,18-epoxide function was identified by the low-field shift of the ^{13}C signals at δ_C = 64.70 and 58.31 ppm, respectively. HMBC correlations of H-15a, H-15b, H-16a, H-16b, H_3-19, and H_3-20 with C-17 and H-16a, H-16b, H-17, H_3-19, and H_3-20 with C-18 have been used to assign the position of the epoxy oxygen atom. In contrast to spatol, no second epoxide function is present. The positions 15 and 16 represent methylene groups with ^{1}H NMR signals at δ_H = 1.49 (m, H-15a), 1.18–1.22 (m, H-15b), 1.63 (m, H-16a), and 1.31–1.37 ppm (m, H-16b) and with ^{13}C NMR signals at δ_C = 32.10 (C-15) and 26.43 ppm (C-16). In agreement with other spatane derivatives,[51–55] a *cis*,*anti*,*cis*-configuration of the tricyclic 5-4-5 ring system was assigned based on NOESY experiments (Table S2,† Fig. 4). The *cis*-fusion of the C-ring was supported by NOESY cross-peaks between H-8 and H_3-12. The *cis*-arrangement of the Me group at C-4 relative to the cyclopentane A-ring was proven by NOE correlations of

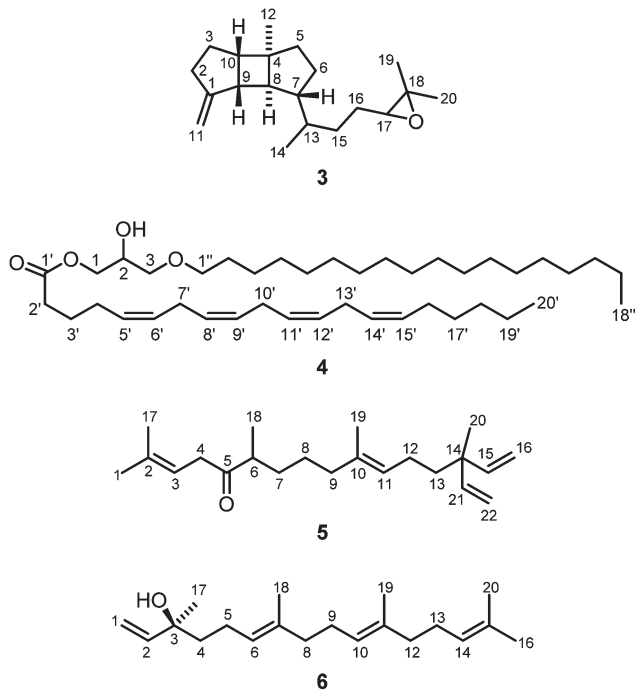


Fig. 3 Structures of gravilin (**3**), monoalkylmonoacylglycerol **4**, ketone **5** and (+)-(*S*)-geranyllinalool (**6**) isolated from *S. gravis*.

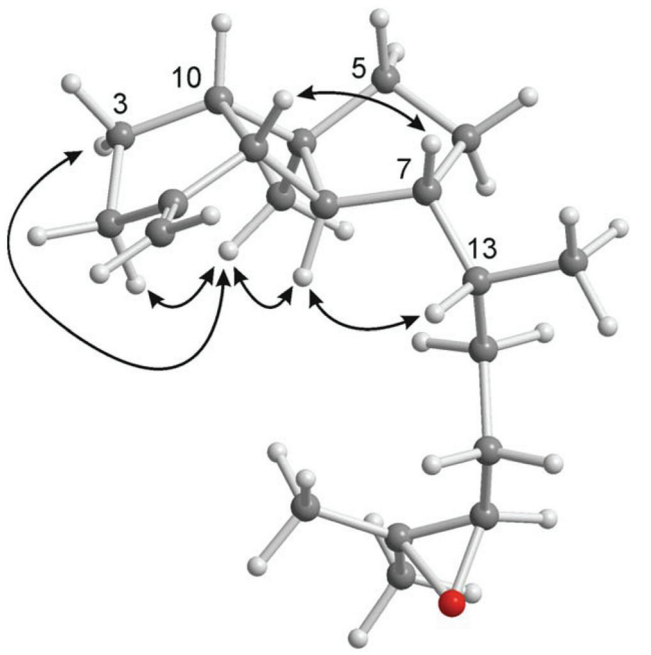


Fig. 4 Characteristic NOE correlations of gravilin (**3**) shown at a computer-generated model (MM2 force field).

H_3-12 with H-2α and H-3α. Therefore, the two cyclopentane moieties must adopt an *anti*-arrangement relative to each other at the central cyclobutane ring. In contrast to the common *trans*-orientation of the side chain at C-7 with respect to H-8 and the Me group at C-4, we found a *cis*-orientation for this substituent. This stereochemical arrangement of the side chain was unambiguously supported by the NOE correlation between H-7 and H-9 and of H-8 with H-13. Only recently, Lin and coworkers isolated the spatane diterpenoid leptoclalin A from *Sinularia leptoclados* with the same spatane backbone and the same relative configuration at C-7.[55] The NMR data of gravilin (**3**) and leptoclalin A are in good agreement with respect to the chemical shifts for the skeletal carbon and proton signals (Table S3†). This is also true for the signals of H-13 and C-13, thus confirming the uncommon α-configuration of the side chain. The related compounds lobophytumin E and F with the same spatane backbone but an opposite relative configuration at C-7 have been isolated from *Lobophytum cristatum*.[54] Their ^{1}H and ^{13}C NMR data are generally also in good agreement with those of **3** but show a significant deviation for the signals of H-13 and C-13 due to the different configuration at C-7 (see NMR data of lobophytumin F in Table S3†). The configurations at C-13 and C-17 of compound **3** remain to be established as well as the absolute configuration. We assume that the spatane skeleton exhibits the same absolute stereochemistry (see Fig. 3) as determined for many other spatane diterpenoids.[51,52,56–59] It is worth noting that gravilin (**3**), leptoclalin A, and lobophytumins E and F are rare examples of spatane diterpenoids isolated from soft corals. Most of the spatanes have been found in brown algae.

Compound **4** (Fig. 3) was isolated as colorless oil. ESI-mass spectrometry performed in positive and negative mode provided peaks for the $[M + H]^+$ ion at m/z = 631.7, $[M + NH_4]^+$ at m/z = 648.7, $[M + Na]^+$ at m/z = 653.8 and $[M + OAc]^-$ at m/z = 689.4. The resulting monoisotopic mass of 630.7 in combination with the number and intensities of ^{1}H and ^{13}C NMR signals suggested a molecular formula of $C_{41}H_{74}O_4$. The ^{1}H NMR, ^{13}C NMR and DEPT spectra displayed signals for two methyl and nine methine groups (Table S4†). The number of 29 methylene groups was deduced from the ^{1}H NMR spectrum taking the molecular mass into account. The low-field shifted ^{13}C NMR signals at δ_C = 65.50, 68.87, 71.37, and 71.78 could be assigned to the oxygenated carbon atoms C-1, C-2, C-3 and C-1″, respectively. In addition, one ^{13}C NMR signal for a carbonyl group was detected at δ_C = 173.68 ppm. These signals were in agreement with a monoalkylmonoacylglycerol structure bearing a free hydroxyl group. The proton signal of the hydroxyl group was identified at δ_H = 2.45 ppm (d, J = 4.5 Hz). In this regard, HMBC correlations allowed for the assignment of the hydroxyl group to position C-2 by strong correlations of the OH proton signal with C-1, C-2, and C-3. Further support was obtained from NOE correlations of OH with H-1a, H-1b, H-2, H-3a, and H-3b. ^{1}H and ^{13}C NMR signals for eight methine groups could be attributed to four double bond systems in a skipped arrangement (C-5′, C-6′, C-8′, C-9′, C-11′, C-12′, C-14′, and C-15′). HMBC correlations (C-1′/H_2-2′, C-2′/H_2-3′, C-3′/H_2-4′, C-4′/H-5′) connected the skipped double bond systems with the carbonyl group at C-1′. Towards the methyl terminus, ^{1}H and ^{13}C NMR signals for four remaining methylene groups could be clearly assigned by sequential HMBC correlations starting from the vinylic position C-15′. The configurations of the double bonds in **4** were determined by NOESY measurements. NOE correlations of H_2-4′ with H_2-7′ and of H_2-13′ with H_2-16′ indicated a *Z*-configuration of the $\Delta^{5'}$- and $\Delta^{14'}$-double bonds. Assuming also a *Z*-configuration of the $\Delta^{8'}$- and $\Delta^{11'}$-double bonds, an arachidonic side chain was suggested as acyl component of the monoalkylmonoacylglycerol which was confirmed by comparison of the ^{1}H and ^{13}C NMR data with literature values.[60] Thus, the fully saturated second side chain must be attached to the glycerol core by an ether linkage. The length of this side chain (C_{18}) was determined taking the intensity of the proton NMR signals and the molecular mass into account. The location of the acyl chain at C-1 of the glycerol moiety was assigned based on HMBC correlations of C-1′ with H-1a and H-1b. Analogously, HMBC correlations of C-1″ with H-3a and H-3b indicated the attachment of the alkyl chain at C-3 of the glycerol unit.

In view of the spectroscopic data, compound **4** was assigned as 2-hydroxy-3-(octadecyloxy)propyl (5*Z*,8*Z*,11*Z*,14*Z*)-icosa-5,8,11,14-tetraenoate or 1-*O*-arachidonoyl-3-*O*-stearylglycerol with an unknown configuration at the stereogenic center C-2 (Fig. 3). This monoalkylmonoacylglycerol isolated from *S. gravis* from Madagascar has been reported for the first time. The respective 1-alkyl-2-acyl-*sn*-glycerol isomer with the arachidonoyl chain attached to the central position of the glycerol moiety, thus having a primary hydroxyl group, has been identified by Myher and Kuksis during their GC analysis of mixtures of diradylglycerols obtained from the corresponding glycerophospholipids.[61,62] The monoalkylmonoacylglycerol **4** may be derived from monoalkyldiacylglycerol precursors by hydrolytic processes. The latter are well-documented components of soft coral lipids, in particular also in *Sinularia* species.[63,64]

Compound **5** (Fig. 3) was isolated from the pentane–diethyl ether (4 : 1) fraction of *S. gravis* as a colorless solid. The ^{1}H NMR, ^{13}C NMR, and DEPT spectra displayed signals for five methyl groups, eight methylene groups, five methine groups, and four quaternary carbon atoms (Table S5†). Assignment of all ^{13}C NMR signals to the respective ^{1}H NMR signals could be achieved by an HSQC measurement. The ^{13}C NMR spectrum displayed one signal for a carbonyl group at δ_C = 213.13 ppm (C-5). Signals for eight vinylic protons and eight vinylic carbon atoms could be identified in the ^{1}H and ^{13}C NMR spectra and assigned to two trisubstituted double bonds and two equivalent monosubstituted terminal double bonds. The connectivity of all groups, and thus the constitution of compound **5**, could be unambiguously established by analysis of the HMBC spectrum. For example, the attachment of the methyl groups at C-2, C-6, C-10, and C-14 was suggested by HMBC correlations of C-2 with H_3-1 and H_3-17, of C-6 with H_3-18, of C-10 with H_3-19, and of C-14 with H_3-20. This assignment was supported by the corresponding HMBC cross-peaks of the ^{13}C signals for the methyl groups with adjacent protons,

namely of C-1 with H-3 and H_3-17, C-17 with H_3-1 and H-3, C-18 with H-6, H-7a, and H-7b, C-19 with H_2-9 and H-11, and C-20 with H-15/H-21. The location of the carbonyl group at C-5 was assigned based on the HMBC correlations of H_2-4, H-6, and H-7b with C-5. A strong NOE correlation of H_3-19 with H_2-12 confirmed the *E*-configuration of the Δ^{10}-double bond. The analytical data allowed to identify compound **5** as (*E*)-2,6,10,14-tetramethyl-14-vinylhexadeca-2,10,15-trien-5-one (Fig. 3) which has not been described before. It exhibits a geranylgeranyl backbone with two additional carbon atoms in form of a vinyl group attached to the branching position of the terminal isoprene unit. A similar branching motif has been reported for a series of botryococcenes.[65–68] The compound is also reminiscent of geranylgeranylacetone (GGA) which is applied as drug for the treatment of gastric ulcers.[69] GGA and its derivatives have also been investigated for the treatment of neurodegenerative diseases including paralysis.[70]

Compound **6** was isolated from the pentane–diethyl ether (10 : 1) fraction of *S. gravis* as colorless oil with a specific optical rotation of $[\alpha]_D^{20}$ = +23.8 (*c* 0.07, MeOH). The CD spectrum (MeOH) of **6** showed molar circular dichroism values of $\Delta\varepsilon$ = +1.94 (202 nm) and +0.12 (247 nm). Based on the data obtained from ^{1}H NMR, COSY, HSQC, HMBC, and NOESY experiments and by comparison of the ^{13}C NMR chemical shifts with those reported in the literature[71] (Table S6†) the structure of **6** was unambiguously elucidated as (+)-(3*S*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-1,6,10,14-tetraen-3-ol [(+)-(*S*)-geranyllinalool] (Fig. 3). The absolute configuration had been determined earlier by Svatoš and coworkers *via* total synthesis of both enantiomers.[32] Geranyllinalool has been isolated before from various plants such as from the oleoresin of the Norwegian spruce *Picea abies*[27,31] and from South African *Helichrysum* species.[28,29] It has been identified as component of various essential oils, for example from pequi fruits collected from the Brazilian Cerrado ecosystem,[36] and as ingredient of many fragrances.[35] Thus, it plays a decisive role in the fragrance of jasmine.[26,30,34] Whilst the laevorotatory (*R*)-enantiomer has been described frequently, the dextrorotatory (*S*)-enantiomer is rare. It has been found in jasmine oil[26] and in the freshwater aquatic plant *Potamogeton pectinatus*.[33] In the course of the present study, (+)-(*S*)-geranyllinalool (**6**) was isolated for the first time from a soft coral (*S. gravis*).

Compound **7** was also isolated from the pentane–diethyl ether (10 : 1) fraction of *S. gravis* as colorless oil with a specific optical rotation of $[\alpha]_D^{20}$ = −35.9 (*c* 1.0, MeOH) and molar circular dichroism values of $\Delta\varepsilon$ = −7.78 (207 nm) and +0.94 (240 nm). Analysis of the 1D and 2D NMR data and the mass spectra led to the structure of (−)-(*R*)-nephthenol (**7**) (Fig. 5). Comparison of the analytical data including ^{1}H and ^{13}C NMR and EI-MS with those reported for a synthetic sample by Pfander *et al.*[39] proved the identity of the compound also with respect to the absolute configuration which had been determined before by chemical degradation.[72] In addition, there is a full agreement of the ^{13}C NMR data of (−)-(*R*)-nephthenol (**7**) from *S. gravis* with those from a sample isolated from the soft coral *Litophyton arboreum*[42] (Table S7†). (−)-(*R*)-Nephthenol (**7**) has been isolated first from *Nephthea* sp.[37] and later also from *Lithophyton arboreum*,[42,43] *Lobophytum pauciflorum*,[43] *Sarcophyton decaryi*,[38,44] and *Sinularia erecta*.[40] It is noteworthy that (+)-(*S*)-nephthenol has also been isolated from natural sources, namely a Caribbean gorgonian octocoral *Eunicea* species.[41] Herein we describe the first isolation of (−)-(*R*)-nephthenol (**7**) from *S. gravis*.

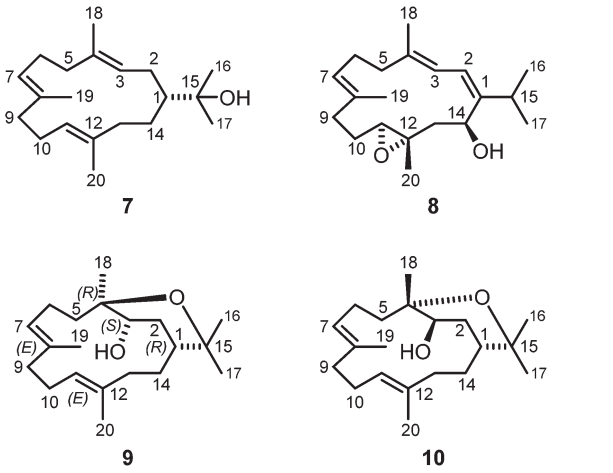


Fig. 5 Structures of (−)-(*R*)-nephthenol (**7**), 11,12-epoxysarcophytol A (**8**) and isodecaryiol (**9**) isolated from *S. gravis* and decaryiol (**10**).

Compound **8** was obtained from the pentane–diethyl ether (4 : 1) fraction of *S. gravis* as yellow solid with a melting point of 68–70 °C and a specific optical rotation of $[\alpha]_D^{20}$ = +220 (*c* 0.1, MeOH). Based on the spectroscopic data (IR, EI-MS, ^{1}H NMR, ^{13}C NMR, DEPT, COSY, NOESY, HSQC, and HMBC), compound **8** could be unambiguously identified as 11,12-epoxysarcophytol A (Fig. 5). The ^{1}H NMR and ^{13}C NMR data of compound **8** isolated from *S. gravis* were in full agreement with those of 11,12-epoxysarcophytol A obtained from *Sinularia gibberosa* (Table S8†).[2] The optical rotation value of **8** with $[\alpha]_D^{20}$ = +220 (*c* 0.1, MeOH) is consistent with that reported by Bowden *et al.*[45] with $[\alpha]_D$ = +229 (*c* 0.95) and also with that of the synthetic product described by Li and coworkers[50] with $[\alpha]_D^{20}$ = +218 (*c* 0.35, $CHCl_3$). The total synthesis of 11,12-epoxysarcophytol A (**8**) by Li *et al.* allowed to elucidate its absolute configuration as depicted in Fig. 5.[50] 11,12-Epoxysarcophytol A (**8**) has been isolated from several soft coral species, first from *Lobophytum* sp.[45] and subsequently also from *Sarcophyton trocheliophorum*,[46] *Cladiella kashmani*,[47] *Sinularia gibberosa*,[2] *Sarcophyton* sp.,[48] and *Sarcophyton ehrenbergi*.[49] This is the first report on the isolation of 11,12-epoxysarcophytol A (**8**) from the soft coral *S. gravis*.

In addition to **8**, the chromatographic separation of the pentane–diethyl ether (4 : 1) fraction of *S. gravis* afforded also compound **9** as colorless crystals with a melting point of 94.0–94.5 °C and a specific optical rotation of $[\alpha]_D^{20}$ = +14.0 (*c* 0.1, MeOH). EI- and ESI-MS displayed peaks at *m*/*z* = 306 $[M]^+$ and *m*/*z* = 307 $[M + H]^+$, respectively. In combination with the number and intensities of the ^{1}H and ^{13}C NMR signals a

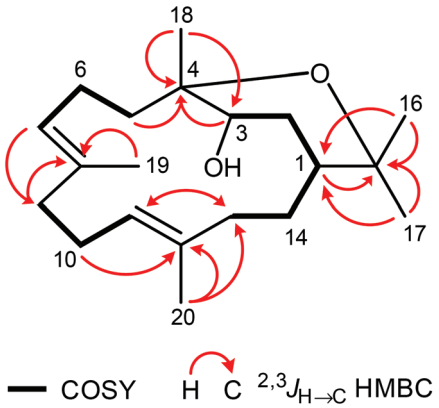


Fig. 6 Characteristic COSY and HMBC correlations of **9**.

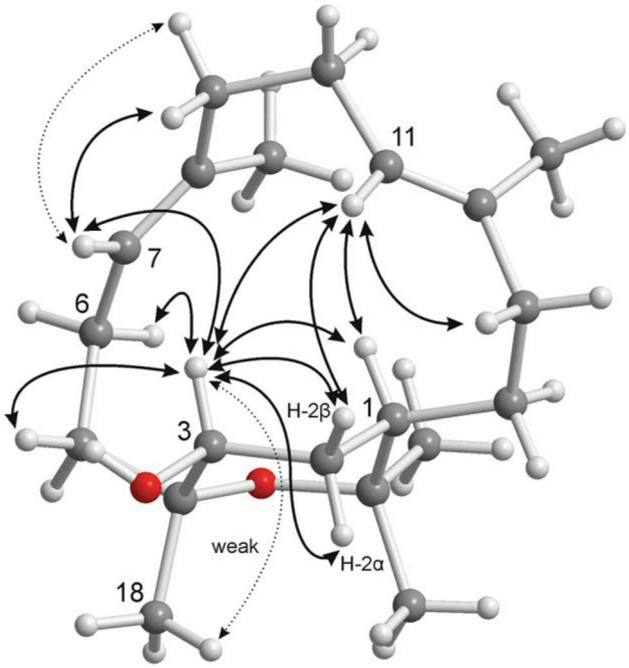


Fig. 7 Characteristic NOE correlations of **9** (structure from X-ray analysis).

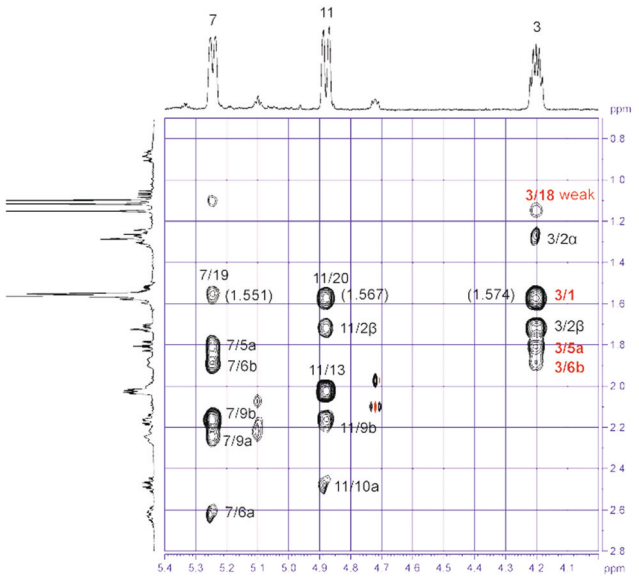


Fig. 8 Expansion of the NOESY spectrum of isodecaryiol (**9**).

molecular formula of $C_{20}H_{34}O_2$ was concluded. Extensive 1D and 2D NMR experiments, in particular COSY, HSQC, and HMBC measurements (Fig. 6), led to a structure with the same framework as decaryiol (**10**),[38,40,73–78] a cembranoid which has been isolated first from *Sarcophyton decaryi* by Kashman and coworkers.[38] In particular, the ^{13}C NMR shifts were almost identical (Table S9†). The ^{1}H NMR data were also similar but differed in certain aspects (Table S10†). For example, H-1 in compound **9** gives a triplet of triplets (J = 11.6, 1.9 Hz; theoretically, the triplets are doublets of doublets with identical coupling constants) with one large coupling constant to vicinal protons instead of a doublet of doublets of triplets (J = 11.5, 3.0, 2.0 Hz) with one large and two small coupling constants in compound **10**. Slightly different coupling constants were also observed for H-5b and H-6b. In addition, the chemical shifts of H-6b, H-9a, H-9b, and H-10b differ significantly. Most striking, however, was the fact that the value for the optical rotation of +14.0 (c 0.1, MeOH) and the melting point of 94.0–94.5 °C of **9** were not in agreement with those reported for decaryiol (**10**) (m.p. 126–128.5 °C,[38] 123–125 °C;[74] $[\alpha]_D^{24}$ = +69 (c 1.3, $CHCl_3$),[38] $[\alpha]_D$ = +65 (c 1.1),[73] $[\alpha]_D^{25}$ = +72 ($CHCl_3$),[74] $[\alpha]_D^{23}$ = +67.4 (c 1.0, $CHCl_3$)[75]). A detailed analysis of the ^{1}H NMR coupling constants and NOE correlations revealed a different relative stereochemistry of **9** as compared to **10**. The proton at C-3 of compound **9** [δ_H = 4.20 (dt, J = 11.7, 5.9 Hz)] (just as the corresponding proton of **10**) adopts an axial position in the pyran ring according to the large coupling constant of 11.7 Hz with the vicinal axial proton H-2α and a small coupling constant of J = 5.9 Hz with the equatorial proton H-2β. In contrast to **10**, H-1 in **9** [δ_H = 1.58 (tt, J = 11.6, 1.9 Hz)] also occupies an axial position as indicated by two large axial–axial coupling constants with the adjacent protons H-2α and H-14b. This accounts for a *cis*-relationship between H-1 and H-3 in the pyran ring and consequently also between the hydroxyl group at C-3 and the macrocyclic substituent at C-1. Strong NOE correlations between H-1 and H-3 confirm this assignment (Fig. 7 and 8). The relative configuration at C-4 was assigned based on the NOESY spectrum. NOE correlations from H-3 to H-6b and H-5a suggest a *cis*-arrangement of H-3 and the macrocyclic side chain at C-4. In support of this, the NOE interaction between H-3 and H_3-18 is only weak. Consequently, compound **9** has the opposite configuration at the stereogenic centers C-3 and C-4 relative to C-1 as compared to decaryiol (**10**). Therefore, we propose for compound **9** the name isodecaryiol.

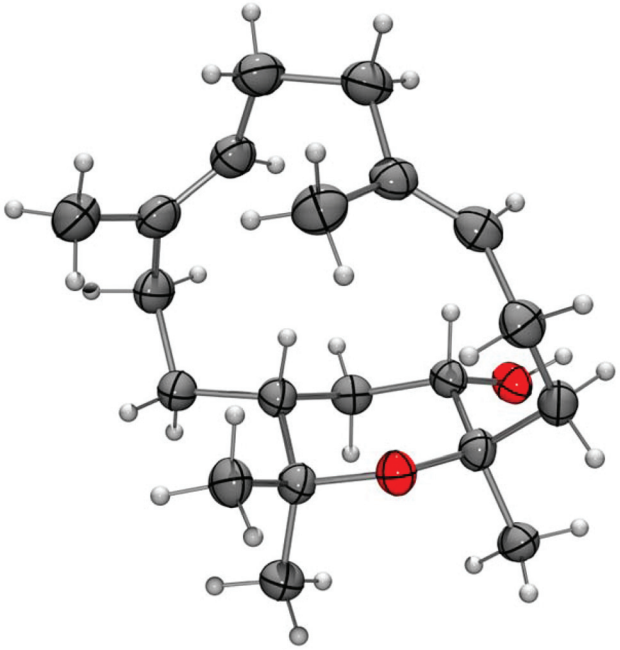


Fig. 9 Molecular structure of isodecaryiol (**9**) in the crystal (thermal ellipsoids at 50% probability level).

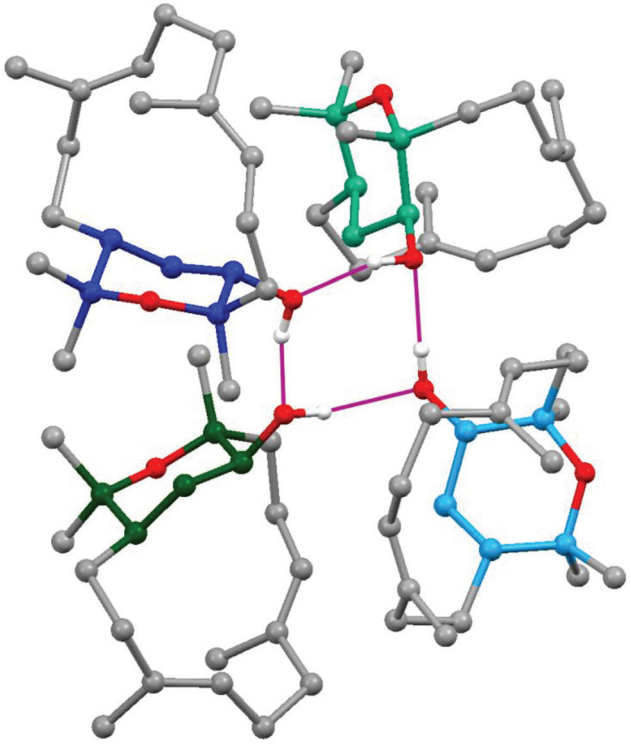


Fig. 10 View of the cyclic tetrameric arrangement of isodecaryiol (**9**) in the crystal *via* hydrogen bond assembly (only the protons of the hydroxyl groups are shown; all other hydrogen atoms are omitted for clarity).

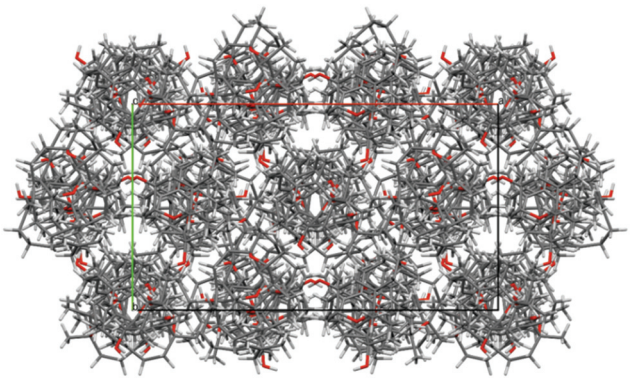


Fig. 11 Fragment of the crystal packing of isodecaryiol (**9**) viewed along the *c*-axis.

The stereochemistry of isodecaryiol (**9**) has been unequivocally confirmed by an X-ray crystal structure determination (Fig. 9). The unit cell of the crystal has an extremely high number of 12 symmetry-independent molecules (Z' = 12; see Fig. S71†) which represents a rare case.[79] The chirality of the natural product contributes to this high Z' value.[79] The individual molecules have minor conformational differences in the 14-membered ring system and *via* hydrogen bonds they form tetramers with a cyclic arrangement (Fig. 10). The packing of the molecules in the unit cell is shown in Fig. 11. The absolute configuration of isodecaryiol (**9**) was determined by the anomal dispersion (Flack parameter:[80] χ = 0.08(4)). The symmetry-independent molecules have an identical relative and absolute stereochemistry (1*R*,3*S*,4*R*). The *R*-configuration at C-1 is in agreement with the original assignment for decaryiol (**10**) by the group of Kashman which was based on chemical correlation with (−)-(*R*)-nephthenol.[38] The *S*-configuration at C-3 and the *R*-configuration at C-4 of **9** confirm our assignment based on ^{1}H coupling constants and NOE correlations (see above). 3,4-Epoxynephthenol has been suggested as biogenetic precursor of decaryiol (**10**).[38,73] Price *et al.* observed that 3,4-epoxynephthenol, isolated from the eggs of *Lobophytum microbulatum*, is readily transformed to decaryiol (**10**) under acidic conditions or during prolonged chromatography on silica gel.[73] Considering the absolute configuration, (1*R*,3*R*,4*R*)-3,4-epoxynephthenol should be the biogenetic precursor which is transformed into decaryiol (**10**) by nucleophilic opening of the epoxide ring. Accordingly, isodecaryiol (**9**) would derive from (1*R*,3*S*,4*S*)-3,4-epoxynephthenol having the opposite orientation of the oxirane ring. The isolation of decaryiol (**10**) has been reported several times from various soft corals (*Sarcophyton decaryi*,[38] *Lobophytum microlobulatum*,[73] *Sclerophytum* sp.,[74] *Sinularia erecta*,[40,76] *Nephthea* sp.,[75,78] and *Lobophytum* sp.[77]). Decaryiol (**10**) inhibits the growth of human cancer cell lines HM02 selectively during the G2/M phase.[75] Isodecaryiol (**9**) constitutes a new representative of cembranoid diterpenes. Most likely, the compound isolated from *Nephthea* sp., which Wright and coworkers described as decaryiol (**10**),[78]

was in fact isodecaryiol (**9**). The optical rotation value of $[\alpha]_D^{20}$ = +27.2 (*c* 0.01) reported by Wright *et al.*[78] is more close to the value of $[\alpha]_D^{20}$ = +14.0 (*c* 0.1, MeOH) we found for isodecaryiol (**9**) rather than to the values commonly reported in the literature for decaryiol (**10**), which are in the range of $[\alpha]_D$ = +65 to +72 (see above). In addition, the chemical shifts for H-6b, H-9a, and H-9b in the ^{1}H NMR spectrum (Table S10†) as well as the NOE interactions described by Wright *et al.*[78] fit better to the structure of isodecaryiol (**9**). However, these authors mentioned an agreement of the ^{1}H NMR data of their natural product with those data reported by Kashman *et al.* for decaryiol (**10**),[38] but they gave a configuration at C-3 (orientation of the hydroxyl group) which is different from decaryiol (**10**).[78]

Conclusions

Previously, the Madagascan soft corals *Sinularia vanderlandi* and *Sinularia gravis* were investigated only very scarcely. From the crude extracts of these species, we have isolated five new natural products: vanderlandin (**1**), gravilin (**3**), the monoalkylmonoacylglycerol **4**, the dihomoditerpenoid ketone **5**, and isodecaryiol (**9**). The absolute configuration of isodecaryiol (**9**) has been unequivocally confirmed by an X-ray crystal structure determination. Moreover, for the first time (+)-(*S*)-geranyllinalool (**6**) has been isolated from a soft coral. Vanderlandin (**1**), gravilin (**3**), and isodecaryiol (**9**) represent interesting and challenging targets for total synthesis. A detailed study of the biological activities of the new natural products (**1**, **3–5**, and **9**) still remains.

Experimental

General methods

Thin layer chromatography was performed on aluminum plates from Merck (60 F_{254}) coated with silica gel. For visualization, the plates were analyzed under UV light or treated with a solution of 0.5 g vanillin dissolved in 100 mL of 80/20 (v/v) sulfuric acid/ethanol and subsequently heated. Column chromatography was performed using silica gel from Acros Organics (0.035–0.070 mm). Melting points were measured on a Gallenkamp MPD 350 melting point apparatus. Optical rotations were determined on a Perkin Elmer 341 polarimeter at a wavelength of 589 nm (sodium D line) using a 1.0-decimeter cell with a total volume of 1.0 mL. CD spectra were measured on a JASCO J-815 CD spectrometer. UV spectra were recorded on a Perkin Elmer Lambda 25 UV-Vis spectrometer. Fluorescence spectra were measured on a Varian Cary Eclipse fluorescence spectrometer. IR spectra were recorded on a Thermo Nicolet Avatar 360 FT-IR spectrometer using the ATR technique (attenuated total reflectance). NMR spectra were recorded on a Bruker AVANCE III 600 spectrometer. The chemical shifts δ are reported in ppm using the solvent signal as internal standard (^{1}H: δ_H 7.250 ppm $CHCl_3$; ^{13}C: δ_C 77.00 ppm $CDCl_3$). The following abbreviations have been used: s: singlet, d: doublet, t: triplet, q: quartet, quint: quintet, sept: septet, m: multiplet, and br: broad. Assignment of the ^{1}H NMR and ^{13}C NMR signals was achieved using the 2D NMR methods COSY, HSQC, HMBC, and NOESY. The mass spectra were measured by GC-MS coupling with an Agilent Technologies 6890 N GC system equipped with a 5973 Mass Selective Detector (electron impact, 70 eV). ESI-MS were recorded on a Bruker-Esquire mass spectrometer with an ion trap detector; positive and negative ions were detected. X-ray single crystal structure analysis: X-ray diffraction data were collected on a Bruker AXS Kappa APEX Duo diffractometer with microfocus tube, Cu K_α radiation (λ = 1.54184 Å). Programs used: data collection APEX2,[81] data reduction SAINT,[82] absorption correction SADABS version 2.10,[83] structure solution SIR2002,[84] structure refinement by full-matrix least-squares against F^2 using SHELXL.[85] Hydrogen atoms were placed into calculated positions and refined as riding atoms at carbon atoms. The hydrogen atoms of hydroxyl groups were refined using AFIX 148 constraints. The figures were generated using the programs ORTEP-III,[86] POV-Ray 3.7, and Mercury 3.1.[87]

Natural sources. The soft corals *S. vanderlandi* and *S. gravis* were collected in March 2006 by hand using scuba in a depth of 5–6 m at the inner reef of Mahambo, located in the Tamatave province at the east coast of Madagascar. The species were assigned by Dr. Shirley Parker-Nance (Nelson Mandela Metropolitan University, Port Elizabeth, and South African Institute for Aquatic Biodiversity (SAIAB), Grahamstown, South Africa). Voucher specimens of the two soft corals investigated in this study have been deposited at the SAIAB (collection numbers: 201728 for *S. gravis* and 201733 for *S. vanderlandi*).

Extraction and isolation. After collection, the sample of *S. vanderlandi* (280 g wet weight) was minced, then homogenized, and extracted with methanol. The combined extracts were concentrated *in vacuo* and the residue (8 g) was extracted with diethyl ether. The diethyl ether extract (1.26 g) was subjected to column chromatography on silica gel using pentane–diethyl ether mixtures of increasing polarity as mobile phase. The fraction (184 mg) eluting with pentane–diethyl ether (4 : 1) was further purified by column chromatography with pentane–diethyl ether (4 : 1) to yield 4.8 mg of compound **1** and 77.2 mg of 24-methylenecholesterol (**2**).

A specimen of the soft coral *S. gravis* (595 g wet weight) was minced and extracted with methanol. After removal of the solvent under reduced pressure, the residue (25 g) was suspended in water and extracted with diethyl ether. The diethyl ether extract was dried with anhydrous Na_2SO_4 and, after removal of the solvent *in vacuo*, the residue (7.8 g) was subjected to column chromatography on silica gel and eluted with pentane–diethyl ether mixtures (10 : 1 and 4 : 1) to give two fractions. Fraction 1 (1 g) was further separated by column chromatography on silica gel with pentane–diethyl ether (10 : 1) to afford three subfractions (1-1, 1-2, and 1-3). Subfraction 1-1 (17 mg) was submitted to repeated column chromatography on silica gel with pentane–dichloromethane (9 : 1) to give 3 mg of compound **3**. Subfraction 1-2 afforded 51 mg of (+)-(*S*)-geranyllinalool (**6**). Subfraction 1-3 (65 mg) was further

purified by column chromatography on silica gel with pentane–diethyl ether (10 : 1) to give 43 mg of (−)-(*R*)-nephthenol (**7**). Fraction 2 (1.24 g) was separated by column chromatography on silica gel using pentane–diethyl ether (4 : 1) as mobile phase to give four subfractions (2-1, 2-2, 2-3 and 2-4). Subfraction 2-1 (46 mg) was submitted to repeated column chromatography on silica gel with pentane–diethyl ether (17 : 3) to give 22 mg of the monoalkylmonoacylglycerol **4**. Purification of subfraction 2-2 (58 mg) by silica gel column chromatography eluting with pentane–diethyl ether (17 : 3) followed by a second column chromatography with dichloromethane afforded 3 mg of (*E*)-2,6,10,14-tetramethyl-14-vinylhexadeca-2,10,15-trien-5-one (**5**). Subfraction 2-3 (538 mg) was subsequently subjected to column chromatography on silica gel with pentane–diethyl ether (4 : 1) to give three subfractions (2-3-1, 2-3-2 and 2-3-3). Subfraction 2-3-1 (194 mg) and fraction 2-4 (84 mg) afforded 278 mg of 24-methylenecholesterol (**2**). Subfraction 2-3-2 was purified by silica gel column chromatography with dichloromethane to give 2 mg of 11,12-epoxysarcophytol A (**8**). Finally, 10 mg of isodecaryiol (**9**) were isolated after purification by column chromatography of subfraction 2-3-3 with pentane–diethyl ether (4 : 1).

Antimalaria assay. The antiplasmodial activity against the FCM29 strain of *Plasmodium falciparum* was determined by using the microfluorimetric assay previously reported (see ESI†).[88–90] Results are given as IC_{50} values in μg mL^{-1}. Quinine (IC_{50} = 3.5 μg mL^{-1}) was used for positive and the solvent (methanol) for negative control.

Molecular modeling. Energy minimization of the conformations for vanderlandin (**1**) (Fig. 2) and gravilin (**3**) (Fig. 4) was achieved by repeated molecular dynamics calculations using the MM2 force field implemented in the Chem3D software (Version 15.0.0.106).

*Vanderlandin (**1**).* Colorless solid; m.p. 57–58 °C. $[\alpha]_D^{20}$ = −3.8 (*c* 0.1, MeOH). UV (MeOH): λ = 206, 283 (sh) nm. Fluorescence (MeOH): λ_{ex} = 206 nm, λ_{em} = 303, 363 nm. IR (ATR): ν = 3407 (br), 2925, 2854, 1726, 1712, 1457, 1374, 1173, 1074, 1001, 892, 721 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.97 (3H, d, *J* = 7.2 Hz, H_3-12/H_3-13), 0.99 (3H, d, *J* = 6.8 Hz, H_3-12/H_3-13), 1.06 (3H, d, *J* = 7.2 Hz, H_3-14), 1.41 (1H, dddd, *J* = 14.1, 5.0, 3.7, 2.9 Hz, H-9β), 1.50 (1H, ddd, *J* = 14.1, 11.9, 5.7 Hz, H-9α), 1.54 (3H, s, H_3-15), 1.70 (1H, dddd, *J* = 14.5, 5.3, 3.8, 0.6 Hz, H-8β), 1.78 (1H, dt, *J* = 13.4, 8.0 Hz, H-3α), 1.85 (1H, ddd, *J* = 13.7, 8.8, 3.7 Hz, H-2α), 1.88 (1H, sept, *J* = 6.9 Hz, H-11), 1.89 (1H, ddd, *J* = 14.7, 11.9, 4.9 Hz, H-8α), 1.90–1.96 (1H, m, H-10), 1.97 (1H, ddd, *J* = 13.7, 8.9, 7.6 Hz, H-2β), 2.07 (1H, ddd, *J* = 13.4, 7.5, 3.7 Hz, H-3β), 6.12 (1H, s, H-5), 7.38 (1H, s, OH). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 13.40 (C-14), 17.03 (C-12, C-13), 19.84 (C-15), 27.91 (C-9), 30.61 (C-8), 34.46 (C-3), 34.57 (C-2), 35.52 (C-11), 38.50 (C-10), 83.46 (C-7), 89.10 (C-1), 90.27 (C-4), 124.33 (C-5), 148.05 (C-6). MS (EI, 70 eV): *m*/*z* (%) = 237 $[M - OH]^+$ (4), 201 (3), 191 (6), 173 (8), 163 (20), 145 (49), 135 (24), 121 (37), 107 (21), 95 (24), 81 (20), 71 (29), 55 (39), 43 (100).

*24-Methylenecholesterol (**2**).* Colorless solid; m.p. 129–130 °C. $[\alpha]_D^{20}$ = −28.3 (*c* 0.1, MeOH). CD (MeOH): $\Delta\varepsilon$ (λ) +1.55 (202 nm), −0.43 (250 nm). UV (MeOH): λ = 202 nm. Fluorescence (MeOH): λ_{ex} = 202 nm, λ_{em} = 298 nm. IR (ATR): ν = 3416 (br), 2958, 2936, 2868, 2851, 1641, 1458, 1378, 1051, 958, 886 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.67 (3H, s, H_3-18), 0.90–0.94 (1H, m, H-9), 0.94 (3H, d, *J* = 6.4 Hz, H_3-21), 0.96–1.01 (1H, m, H-14), 1.00 (3H, s, H_3-19), 1.01 (3H, d, *J* = 6.8 Hz, H_3-26 or H_3-27), 1.02 (3H, d, *J* = 6.8 Hz, H_3-26 or H_3-27), 1.03–1.10 (2H, m, H-1b, H-15b), 1.10–1.19 (3H, m, H-12b, H-17, H-22b), 1.25–1.30 (1H, m, H-16b), 1.40–1.47 (3H, m, H-8, H-11b, H-20), 1.47–1.60 (5H, m, H-2b, H-7b, H-11a, H-15a, H-22a), 1.80–1.90 (4H, m, H-1a, H-2a, H-16a, H-23b), 1.94–2.03 (2H, m, H-7a, H-12a), 2.05–2.11 (1H, m, H-23a), 2.19–2.26 (2H, m, H-4b, H-25), 2.29 (1H, ddd, *J* = 12.8, 4.9, 1.9 Hz, H-4a), 3.48–3.55 (1H, m, H-3), 4.64 (1H, br d, *J* = 1.5 Hz, H-28a), 4.70 (1H, br s, H-28b), 5.33–5.36 (1H, m, H-6). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 11.85 (CH_3), 18.70 (CH_3), 19.39 (CH_3), 21.07 (CH_2), 21.86 (CH_3), 21.99 (CH_3), 24.28 (CH_2), 28.21 (CH_2), 30.96 (CH_2), 31.66 (CH_2), 31.89 (CH_2), 31.89 (CH), 33.79 (CH), 34.67 (CH_2), 35.75 (CH), 36.49 (C), 37.24 (CH_2), 39.77 (CH_2), 42.30 (CH_2), 42.35 (C), 50.11 (CH), 55.97 (CH), 56.75 (CH), 71.80 (CH), 105.91 (CH_2), 121.70 (CH), 140.75 (C), 156.90 (C). MS (EI, 70 eV): *m*/*z* (%) = 398 $[M^+]$ (8), 383 (12), 365 (10), 314 (100), 299 (34), 271 (55), 253 (13), 229 (26), 213 (25), 159 (29), 145 (35), 133 (30), 119 (28), 105 (48), 91 (46), 69 (80), 55 (99), 41 (63). ESI-MS (+10 V): *m*/*z* = 416 $[M + NH_4]^+$, 819 $[2M + Na]^+$.

*Gravilin (**3**).* Colorless solid; m.p. 100–101 °C. $[\alpha]_D^{20}$ = +46.0 (*c* 0.8, MeOH). UV (MeOH): λ = 206, 300 (sh) nm. Fluorescence (MeOH): λ_{ex} = 206 nm, λ_{em} = 286 nm. IR (ATR): ν = 2923, 2855, 1739, 1659, 1457, 1377, 1121, 1085, 961, 879 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.85 (3H, d, *J* = 6.8 Hz, H_3-14), 0.97 (3H, s, H_3-12), 1.10–1.15 (1H, m, H-13), 1.18–1.22 (1H, m, H-15b), 1.24 (3H, s, H_3-20), 1.29 (3H, s, H_3-19), 1.31–1.37 (1H, m, H-16b), 1.49 (1H, m, H-15a),[a] 1.51 (1H, m, H-6α),[a] 1.52 (2H, m, H_2-5),[a] 1.54 (1H, m, H-8),[a] 1.58 (1H, m, H-3β),[a] 1.62 (1H, m, H-7),[a] 1.63 (1H, m, H-16a),[a] 1.80 (1H, dd, *J* = 13.3, 7.9 Hz, H-3α), 1.86–1.92 (1H, m, H-6β), 2.28 (1H, dd, *J* = 15.1, 7.9 Hz, H-2β), 2.32 (1H, t, *J* = 7.5 Hz, H-10), 2.42 (1H, dd, *J* = 6.9, 3.9 Hz, H-9), 2.48–2.56 (1H, m, H-2α), 2.66 (1H, t, *J* = 6.4 Hz, H-17), 4.70 (1H, s, H-11a), 4.73 (1H, s, H-11b) [[a]Chemical shift derived from the HSQC spectrum]. ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 17.87 (C-14), 18.69 (C-20), 21.55 (C-12), 24.91 (C-19), 26.43 (C-16), 27.22 (C-3), 29.93 (C-6), 32.10 (C-15), 33.75 (C-2), 36.38 (C-13), 42.19 (C-5), 43.14 (C-4), 45.77 (C-10), 48.04 (C-9), 55.22 (C-7), 55.29 (C-8), 58.31 (C-18), 64.70 (C-17), 103.76 (C-11), 157.33 (C-1). MS (EI, 70 eV): *m*/*z* (%) = 288 $[M^+]$ (0.1), 255 (1), 207 (5), 189 (16), 161 (15), 147 (10), 135 (8), 121 (58), 107 (25), 91 (27), 81 (100), 67 (12), 59 (16), 41 (33). ESI-MS (+10 V): *m*/*z* = 289 $[M + H]^+$, 306 $[M + NH_4]^+$.

*1-O-Arachidonoyl-3-O-stearylglycerol (**4**).* Colorless oil. UV (MeOH): λ = 205, 276 (sh) nm. Fluorescence (MeOH): λ_{ex} = 205 nm, λ_{em} = 285 nm. IR (ATR): ν = 3455 (br), 3011, 2922, 2853, 1740, 1650, 1464, 1392, 1236, 1173, 1119, 720 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.87 (3H, t, *J* = 7.2 Hz, H_3-18″), 0.88 (3H, t, *J* = 6.8 Hz, H_3-20′), 1.24 (24H, br s, H_2-5″–H_2-16″), 1.26–1.32 (10H, m, H_2-18′, H_2-19′, H_2-3″, H_2-4″, H_2-17″), 1.32–1.37 (2H, m, H_2-17′), 1.53–1.58 (2H, m, H_2-2″), 1.71 (2H,

quint, J = 7.5 Hz, H_2-3′), 2.04 (2H, q, J = 7.2 Hz, H_2-16′), 2.11 (2H, q, J = 7.3 Hz, H_2-4′), 2.35 (2H, t, J = 7.5 Hz, H_2-2′), 2.45 (1H, d, J = 4.5 Hz, OH), 2.80 (4H, q, J = 5.6 Hz, H_2-7′, H_2-13′), 2.83 (2H, t, J = 6.0 Hz, H_2-10′), 3.41 (1H, dd, J = 9.8, 6.4 Hz, H-3b), 3.42–3.46 (2H, m, H_2-1″), 3.48 (1H, dd, J = 9.8, 4.5 Hz, H-3a), 3.96–4.01 (1H, m, H-2), 4.11 (1H, dd, J = 11.7, 6.4 Hz, H-1b), 4.16 (1H, dd, J = 11.7, 4.1 Hz, H-1a), 5.29–5.42 (8H, m, H-5′, H-6′, H-8′, H-9′, H-11′, H-12′, H-14′, H-15′). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 14.07 (C-20′), 14.11 (C-18″), 22.57 (C-19′), 22.69 (C-17″), 24.75 (C-3′), 25.61–25.63 (C-7′, C-10′, C-13′), 26.08 (C-3″), 26.53 (C-4′), 27.22 (C-16′), 29.32 (C-17′), 29.47 (C-4″), 29.58–29.66 (C-2″, C-5″–C-15″), 31.52 (C-18′), 31.92 (C-16″), 33.53 (C-2′), 65.50 (C-1), 68.87 (C-2), 71.37 (C-3), 71.78 (C-1″), 127.53 (C-14′), 127.86, 128.13, 128.25, 128.86, 128.93 (C-6′, C-8′, C-9′, C-11′, C-12′), 128.59 (C-5′), 130.50 (C-15′), 173.68 (C-1′). ESI-MS (+10 V): m/z = 648.7 $[M + NH_4]^+$. ESI-MS (+25 V): m/z = 631.7 $[M + H]^+$, 648.8 $[M + NH_4]^+$. ESI-MS (+75 V): m/z = 653.8 $[M + Na]^+$. ESI-MS (−50 V): m/z = 689.4 $[M + OAc]^-$.

*(E)-2,6,10,14-Tetramethyl-14-vinylhexadeca-2,10,15-trien-5-one (**5**).* Colorless solid. UV (MeOH): λ = 207, 218, 284 (sh) nm. Fluorescence (MeOH): λ_{ex} = 218 nm, λ_{em} = 308 nm. IR (ATR): ν = 3490 (br), 2967, 2927, 2858, 2056, 1710, 1652, 1454, 1375, 1110, 996, 918 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.05 (3H, d, J = 6.8 Hz, H_3-18), 1.27 (3H, s, H_3-20), 1.27–1.30 (1H, m, H-7b), 1.30–1.34 (2H, m, H_2-8), 1.56 (3H, s, H_3-19), 1.57–1.61 (3H, m, H-7a, H_2-13), 1.61 (3H, s, H_3-17), 1.74 (3H, s, H_3-1), 1.93 (2H, t, J = 7.1 Hz, H_2-9), 2.02–2.07 (2H, m, H_2-12), 2.48–2.58 (1H, m, H-6), 3.12 (2H, d, J = 6.8 Hz, H_2-4), 5.05 (2H, d, J = 10.9 Hz, H-16b, H-22b), 5.07–5.14 (1H, m, H-11), 5.20 (2H, d, J = 17.3 Hz, H-16a, H-22a), 5.30 (1H, br t, J = 7.2 Hz, H-3), 5.90 (2H, dd, J = 17.3, 10.9 Hz, H-15, H-21). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 15.84 (C-19), 16.44 (C-18), 18.07 (C-17), 22.65 (C-12), 25.45 (C-8), 25.72 (C-1), 27.88 (C-20), 32.52 (C-7), 39.55 (C-9), 41.00 (C-4), 42.05 (C-13), 45.64 (C-6), 73.45 (C-14), 111.70 (C-16, C-22), 116.09 (C-3), 124.45 (C-11), 135.23, 135.39 (C-2, C-10), 145.00 (C-15, C-21), 213.13 (C-5). MS (EI, 70 eV): m/z (%) = 288 (2), 219 (5), 201 (4), 151 (21), 139 (19), 121 (33), 109 (34), 93 (93), 81 (100), 69 (83), 55 (71), 41 (90).

*(+)-(S)-Geranyllinalool (**6**).* Colorless oil. $[\alpha]_D^{20}$ = +23.8 (c 0.07, MeOH); lit.: $[\alpha]_D^{20}$ = +18.2 (c 0.06, $CHCl_3$),[32] $[\alpha]_D$ = +14.5.[26] CD (MeOH): $\Delta\varepsilon$ (λ) +1.94 (202 nm), +0.12 (247 nm). UV (MeOH): λ = 211, 280 (sh) nm. Fluorescence (MeOH): λ_{ex} = 211 nm, λ_{em} = 305 nm. IR (ATR): ν = 3414 (br), 2965, 2924, 2855, 1724, 1447, 1376, 1109, 995, 919 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.27 (3H, s, H_3-17), 1.54–1.58 (2H, m, H_2-4), 1.58 (3H, s, H_3-19), 1.59 (6H, s, H_3-18, H_3-20), 1.67 (3H, q, J = 1.3 Hz, H_3-16), 1.94–1.99 (4H, m, H_2-8, H_2-12), 1.99–2.03 (2H, m, H_2-5), 2.02–2.08 (4H, m, H_2-9, H_2-13), 5.05 (1H, dd, J = 10.5, 1.1 Hz, H-1b), 5.07–5.11 (2H, m, H-10, H-14), 5.13 (1H, tq, J = 7.2, 1.4 Hz, H-6), 5.21 (1H, dd, J = 17.3, 1.1 Hz, H-1a), 5.91 (1H, dd, J = 17.3, 10.9 Hz, H-2). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 16.00 (C-19), 16.03 (C-18), 17.69 (C-20), 22.71 (C-5), 25.69 (C-16), 26.55 (C-9), 26.75 (C-13), 27.90 (C-17), 39.69 (C-8), 39.71 (C-12), 42.06 (C-4), 73.49 (C-3), 111.67 (C-1), 124.09 (C-10), 124.19 (C-6), 124.38 (C-14), 131.27 (C-15), 135.05 (C-11), 135.61 (C-7), 145.05 (C-2). MS (EI, 70 eV): m/z (%) = 290 $[M]^+$ (0.4), 272 (1), 257 (1), 229 (1), 203 (4), 189 (4), 161 (8), 147 (7), 135 (10), 121 (12), 107 (28), 93 (40), 81 (44), 69 (100), 55 (20), 41 (51). ESI-MS (+10 V): m/z = 291 $[M + H]^+$, 308 $[M + NH_4]^+$.

*(−)-(R)-Nephthenol (**7**).* Colorless oil. $[\alpha]_D^{20}$ = −35.9 (c 1.0, MeOH) (lit.: $[\alpha]_D^{20}$ = −39.6 (c 1.11, $CHCl_3$),[39] $[\alpha]_D^{23}$ = −35 (c 1.0, $CHCl_3$)[42]). CD (MeOH): $\Delta\varepsilon$ (λ) −7.78 (207 nm), +0.94 (240 nm). UV (MeOH): λ = 205, 284 (sh) nm. Fluorescence (MeOH): λ_{ex} = 205 nm, λ_{em} = 288 nm. IR (ATR): ν = 3414 (br), 2924, 2855, 1740, 1725, 1665, 1473, 1440, 1379, 1130, 973, 932, 883, 837 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.15 (1H, s, OH), 1.19 (6H, s, H_3-16, H_3-17), 1.25–1.28 (1H, m, H-14b), 1.29–1.35 (1H, m, H-1), 1.55 (3H, s, H_3-20), 1.55–1.57 (6H, m, H_3-18, H_3-19), 1.61–1.67 (1H, m, H-14a), 1.85–1.92 (1H, m, H-2b), 1.97–2.04 (2H, m, H-9b, H-13b), 2.05–2.16 (8H, m, H-2a, H_2-5, H-6b, H-9a, H_2-10, H-13a), 2.16–2.24 (1H, m, H-6a), 4.93 (1H, br t, J = 6.0 Hz, H-7), 4.99 (1H, br t, J = 6.4 Hz, H-11), 5.08–5.12 (1H, m, H-3). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 15.30 (C-19), 15.56 (C-18, C-20), 24.00 (C-10), 24.65 (C-6), 27.50 (C-17), 27.65 (C-16), 28.27 (C-14), 28.44 (C-2), 37.70 (C-13), 38.82 (C-5), 39.40 (C-9), 48.45 (C-1), 73.97 (C-15), 124.98 (C-11), 125.76 (C-7), 125.94 (C-3), 133.06 (C-8), 133.37 (C-4), 134.04 (C-12). MS (EI, 70 eV): m/z (%) = 290 $[M]^+$ (1), 272 (26), 257 (15), 229 (14), 202 (12), 189 (19), 175 (12), 161 (25), 147 (26), 136 (37), 121 (74), 107 (78), 93 (99), 81 (84), 67 (96), 59 (100), 41 (69). ESI-MS (+10 V): m/z = 291 $[M + H]^+$, 308 $[M + NH_4]^+$.

*11,12-Epoxysarcophytol A (**8**).* Yellow solid; m.p. 68–70 °C (lit.: m.p. 75–76 °C).[45] $[\alpha]_D^{20}$ = +220 (c 0.1, MeOH) (lit.: $[\alpha]_D$ = +229 (c 0.95),[45] $[\alpha]_D^{20}$ = +218 (c 0.35, $CHCl_3$),[50] $[\alpha]_D^{21}$ = +203.3 (c 0.33, $CHCl_3$)[47]). UV (MeOH): λ = 217 nm. Fluorescence (MeOH): λ_{ex} = 217 nm, λ_{em} = 293 nm. IR (ATR): ν = 3425 (br), 2961, 2922, 2869, 1724, 1641, 1473, 1453, 1378, 1112, 995, 917, 871, 683 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.06 (3H, d, J = 6.8 Hz, H_3-16), 1.08 (3H, d, J = 6.8 Hz, H_3-17), 1.29 (3H, s, H_3-20), 1.45–1.52 (1H, m, H-10b), 1.58 (3H, d, J = 0.8 Hz, H_3-19), 1.73 (3H, d, J = 0.8 Hz, H_3-18), 1.82–1.89 (1H, m, H-10a), 1.97 (1H, dd, J = 15.4, 4.5 Hz, H-13a), 2.04–2.09 (1H, m, H-9b), 2.10 (1H, dd, J = 15.4, 7.5 Hz, H-13b), 2.13–2.19 (1H, m, H-5b), 2.21 (1H, br s, OH), 2.22–2.28 (4H, m, H-5a, H-6a, H-6b, H-9a), 2.66 (1H, sept, J = 6.8 Hz, H-15), 3.18 (1H, t, J = 6.4 Hz, H-11), 4.72 (1H, br t, J = 6.0 Hz, H-14), 5.10 (1H, br t, J = 6.4 Hz, H-7), 5.75 (1H, br dd, J = 10.5, 1.7 Hz, H-3), 5.98 (1H, d, J = 10.9 Hz, H-2). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 15.02 (C-19), 17.26 (C-18), 19.44 (C-20), 23.79 (C-17), 24.12 (C-10), 24.22 (C-16), 25.96 (C-6), 27.63 (C-15), 36.45 (C-9), 38.33 (C-5), 42.15 (C-13), 58.60 (C-11), 59.98 (C-12), 65.76 (C-14), 118.32 (C-2), 119.52 (C-3), 126.90 (C-7), 133.64 (C-8), 136.78 (C-4), 148.45 (C-1).

*Isodecaryiol (**9**).* Colorless crystals, m.p. 94.0–94.5 °C. $[\alpha]_D^{20}$ = +14.0 (c 0.1, MeOH). UV (MeOH): λ = 206, 250 (sh) nm. Fluorescence (MeOH): λ_{ex} = 206 nm, λ_{em} = 301 nm. IR (ATR): ν = 3336 (br), 2972, 2914, 2856, 1474, 1428, 1378, 1281, 1246, 1195, 1178, 1142, 1119, 1067, 1017, 981, 968, 937, 920, 894, 849, 829, 804, 744 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89 (1H, ddt, J = 13.3, 11.6, 3.6 Hz, H-14b), 1.10 (3H, s, H_3-16), 1.12 (3H, s, H_3-17), 1.15 (3H, s, H_3-18), 1.23–1.32 (1H, m, H-2α), 1.27 (1H, OH, br s), 1.28–1.34 (1H, m, H-14a), 1.53 (1H, ddd, J = 14.4, 6.0, 3.3 Hz, H-5b), 1.55 (3H, s, H_3-20), 1.56 (3H, s, H_3-

19), 1.58 (1H, tt, J = 11.6, 1.9 Hz, H-1), 1.72 (1H, ddd, J = 12.5, 5.4, 2.0 Hz, H-2β), 1.81 (1H, ddd, J = 14.5, 11.2, 3.3 Hz, H-5a), 1.88 (1H, dddd, J = 15.4, 7.6, 3.9, 1.9 Hz, H-6b), 1.99–2.03 (1H, m, H-10b), 2.03 (2H, br dd, J = 8.9, 3.7 Hz, H-13a, H-13b), 2.16 (1H, ddd, J = 14.0, 11.7, 3.8 Hz, H-9b), 2.22–2.29 (1H, m, H-9a), 2.48 (1H, dtd, J = 15.0, 11.4, 3.6 Hz, H-10a), 2.62 (1H, dddd, J = 15.2, 11.4, 9.9, 3.6 Hz, H-6a), 4.20 (1H, dt, J = 11.7, 5.9 Hz, H-3), 4.88 (1H, br d, J = 11.6 Hz, H-11), 5.24 (1H, br d, J = 9.4 Hz, H-7). ^{13}C NMR and DEPT (150 MHz, $CDCl_3$): δ = 14.82 (C-19), 15.20 (C-20), 22.25 (C-17), 23.76 (C-6), 24.22 (C-18), 25.19 (C-14), 25.27 (C-10), 28.93 (C-2), 29.61 (C-16), 36.42 (C-13), 38.06 (C-5), 39.30 (C-9), 39.97 (C-1), 70.40 (C-3), 75.26 (C-15), 76.79 (C-4), 127.70 (C-7), 128.08 (C-11), 132.59 (C-8), 133.02 (C-12). MS (EI, 70 eV): m/z (%) = 306 $[M]^+$ (4), 288 (10), 273 (3), 263 (4), 205 (3), 192 (4), 175 (5), 161 (7), 151 (13), 136 (24), 123 (20), 107 (30), 95 (32), 81 (55), 69 (74), 55 (430), 43 (100). ESI-MS (+10 V): m/z = 307 $[M + H]^+$.

Crystal data for ***9***. $C_{20}H_{34}O_2$, M = 306.47 g mol^{-1}, crystal size: 0.27 × 0.25 × 0.22 mm^3, monoclinic, space group $C2$, a = 24.3170(11) Å, b = 13.7760(6) Å, c = 67.036(3) Å, β = 91.6033 (13)°, V = 22 447.5(17) Å^3, Z = 48, Z' = 12, ρ_{calcd} = 1.088 g cm^{-3}, μ = 0.519 mm^{-1}, T = 100(2) K, λ = 1.54178 Å, θ range = 1.98–67.68°, reflections collected 182 016 (R_{int} = 0.0214), 2461 refined parameters, R_1 = 0.0347, wR_2 = 0.1178 [$I > 2\ \sigma(I)$]; maximal residual electron density: 0.42 e Å^{-3}; Flack parameter: χ = 0.08 (4). The thermal displacement parameters of the independent molecules A and E (Fig. S71†) are indicative of a disorder, which was impossible to resolve as the whole molecule should be disordered. The disorder resulted in an alert B in the Hirshfeld test. CCDC-1424360 contains the supplementary crystallographic data for this structure.

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Notes and references

1 J.-H. Su, A. F. Ahmed, P.-J. Sung, C.-H. Chao, Y.-H. Kuo and J.-H. Sheu, *J. Nat. Prod.*, 2006, **69**, 1134–1139.
2 A. F. Ahmed, Z.-H. Wen, J.-H. Su, Y.-T. Hsieh, Y.-C. Wu, W.-P. Hu and J.-H. Sheu, *J. Nat. Prod.*, 2008, **71**, 179–185.
3 Y. Lu, C.-Y. Huang, Y.-F. Lin, Z.-H. Wen, J.-H. Su, Y.-H. Kuo, M. Y. Chiang and J.-H. Sheu, *J. Nat. Prod.*, 2008, **71**, 1754–1759.
4 Y.-Y. Lin, Y.-H. Jean, H.-P. Lee, W.-F. Chen, Y.-M. Sun, J.-H. Su, Y. Lu, S.-Y. Huang, H.-C. Hung, P.-J. Sung, J.-H. Sheu and Z.-H. Wen, *PLoS One*, 2013, **8**, e62926.
5 B.-W. Chen, C.-H. Chao, J.-H. Su, C.-Y. Huang, C.-F. Dai, Z.-H. Wen and J.-H. Sheu, *Tetrahedron Lett.*, 2010, **51**, 5764–5766.
6 J.-H. Su, C.-Y. Huang, P.-J. Li, Y. Lu, Z.-H. Wen, Y.-H. Kao and J.-H. Sheu, *Arch. Pharmacal Res.*, 2012, **35**, 779–784.
7 D. Chen, W. Chen, D. Liu, L. van Ofwegen, P. Proksch and W. Lin, *J. Nat. Prod.*, 2013, **76**, 1753–1763.
8 J. J. Poza, R. Fernández, F. Reyes, J. Rodríguez and C. Jiménez, *J. Org. Chem.*, 2008, **73**, 7978–7984.
9 A. Longeon, M.-L. Bourguet-Kondracki and M. Guyot, *Tetrahedron Lett.*, 2002, **43**, 5937–5939.
10 Y. Hou and L. Harinantenaina, *Curr. Med. Chem.*, 2010, **17**, 1191–1219.
11 V. Anjaneyulu, P. V. S. Rao and P. Radhika, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1999, **38**, 357–360.
12 V. Anjaneyulu, P. V. S. Rao, P. Radhika, H. Laatsch and L. N. Misra, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2000, **39**, 121–124.
13 P. Radhika, M. Cabeza, E. Bratoeff and G. García, *Steroids*, 2004, **69**, 439–444.
14 G. Rücker, *Angew. Chem., Int. Ed. Engl.*, 1973, **85**, 895–907.
15 M. Bordoloi, V. S. Shukla, S. C. Nath and R. P. Sharma, *Phytochemistry*, 1989, **28**, 2007–2037.
16 *Dictionary of Marine Natural Products with CD-ROM*, ed. J. W. Blunt and M. H. G. Munro, Taylor & Francis, Boca Raton, FL, USA, 2008.
17 G. W. Patterson, *Lipids*, 1971, **6**, 120–127.
18 G. W. Patterson, *Comp. Biochem. Physiol.*, 1968, **24**, 501–505.
19 K. Iguchi, S. Saitoh and Y. Yamada, *Chem. Pharm. Bull.*, 1989, **37**, 2553–2554.
20 W. Lu, C. Zhang, L. Zeng and J. Su, *Steroids*, 2004, **69**, 803–808.
21 M. P. Rahelivao, M. Gruner, H. Andriamanantoanina, B. Andriamihaja, I. Bauer and H.-J. Knölker, *Mar. Drugs*, 2015, **13**, 4197–4216.
22 Y. T. Lin, Y. S. Cheng and Y. H. Kuo, *J. Chin. Chem. Soc.*, 1970, **17**, 111–113.
23 Y. H. Kuo, Y. S. Cheng, S. T. Kao and Y. T. Lin, *J. Chin. Chem. Soc.*, 1973, **20**, 83–86.
24 F. Song, X. Fan, X. Xu, J. Zhao, Y. Yang and J. Shi, *J. Nat. Prod.*, 2004, **67**, 1644–1649.
25 W. Dong, D. Yang and R. Lu, *Planta Med.*, 2010, **76**, 454–457.
26 E. Demole and E. Lederer, *Bull. Soc. Chim. Fr.*, 1958, 1128–1137.
27 B. Kimland and T. Norin, *Acta Chem. Scand.*, 1967, **21**, 825–826.

28 F. Bohlmann and A. Suwita, *Phytochemistry*, 1979, **18**, 2046–2049.
29 F. Bohlmann, C. Zdero, W.-R. Abraham, A. Suwita and M. Grenz, *Phytochemistry*, 1980, **19**, 873–879.
30 M. Verzele, G. Maes, A. Vuye, M. Godefroot, M. van Alboom, J. Vervisch and P. Sandra, *J. Chromatogr., A*, 1981, **205**, 367–386.
31 V. I. Roshchin, R. A. Baranova and V. A. Solov'ev, *Chem. Nat. Compd.*, 1986, **22**, 156–163.
32 A. Svatoš, K. Urbanová and I. Valterová, *Collect. Czech. Chem. Commun.*, 2002, **67**, 83–90.
33 P. Waridel, J.-L. Wolfender, J.-B. Lachavanne and K. Hostettmann, *Phytochemistry*, 2003, **64**, 1309–1317.
34 L. Jirovetz, G. Buchbauer, T. Schweiger, Z. Denkova, A. Slavchev, A. Stoyanova, E. Schmidt and M. Geissler, *Nat. Prod. Commun.*, 2007, **2**, 407–412.
35 A. Lapczynski, S. P. Bhatia, C. S. Letizia and A. M. Api, *Food Chem. Toxicol.*, 2008, **46**, S176–S178.
36 K. C. Geőcze, L. C. A. Barbosa, P. H. Fidêncio, F. O. Silvério, C. F. Lima, M. C. A. Barbosa and F. M. D. Ismail, *Food Res. Int.*, 2013, **54**, 1–8.
37 F. J. Schmitz, D. J. Vanderah and L. S. Ciereszko, *J. Chem. Soc., Chem. Commun.*, 1974, 407–408.
38 S. Carmely, A. Groweiss and Y. Kashman, *J. Org. Chem.*, 1981, **46**, 4279–4284.
39 R. Schwabe, I. Farkas and H. Pfander, *Helv. Chim. Acta*, 1988, **71**, 292–297.
40 A. Rudi, T. Lev-Ari Dayan, M. Aknin, E. M. Gaydou and Y. Kashman, *J. Nat. Prod.*, 1998, **61**, 872–875.
41 Y.-P. Shi, A. D. Rodríguez and O. L. Padilla, *J. Nat. Prod.*, 2001, **64**, 1439–1443.
42 K. H. Shaker, M. Müller, M. A. Ghani, H.-M. Dahse and K. Seifert, *Chem. Biodiversity*, 2010, **7**, 2007–2015.
43 Y. Kashman, M. Bodner, Y. Loya and Y. Benayahu, *Isr. J. Chem.*, 1977, **16**, 1–3.
44 A. Groweiss, Y. Kashman, D. J. Vanderah, B. Tursch, P. Cornet, J. C. Braekman and D. Daloze, *Bull. Soc. Chim. Belg.*, 1978, **87**, 277–283.
45 B. F. Bowden, J. C. Coll and D. M. Tapiolas, *Aust. J. Chem.*, 1983, **36**, 2289–2295.
46 G. J. Greenland and B. F. Bowden, *Aust. J. Chem.*, 1994, **47**, 2013–2021.
47 C. A. Gray, M. T. Davies-Coleman and M. H. Schleyer, *J. Nat. Prod.*, 2000, **63**, 1551–1553.
48 F. Cao, J. Zhou, K.-X. Xu, M.-Q. Zhang and C.-Y. Wang, *Nat. Prod. Commun.*, 2013, **8**, 1675–1678.
49 C. Bhujanga Rao, D. C. Babu, T. V. Bharadwaj, D. Srikanth, K. S. Vardhan, T. V. Raju, R. A. Bunce and Y. Venkateswarlu, *Nat. Prod. Res.*, 2014, **29**, 70–76.
50 J. Lan, Z. Liu, H. Yuan, L. Peng, W.-D. Z. Li, Y. Li, Y. Li and A. S. C. Chan, *Tetrahedron Lett.*, 2000, **41**, 2181–2184.
51 W. H. Gerwick, W. Fenical, D. Van Engen and J. Clardy, *J. Am. Chem. Soc.*, 1980, **102**, 7991–7993.
52 W. H. Gerwick and W. Fenical, *J. Org. Chem.*, 1983, **48**, 3325–3329.
53 Y. Venkateswarlu and M. A. F. Biabani, *Phytochemistry*, 1995, **40**, 331–333.
54 L. Li, L. Sheng, C.-Y. Wang, Y.-B. Zhou, H. Huang, X.-B. Li, J. Li, E. Mollo, M. Gavagnin and Y.-W. Guo, *J. Nat. Prod.*, 2011, **74**, 2089–2094.
55 T.-C. Tsai, Y.-J. Wu, J.-H. Su, W.-T. Lin and Y.-S. Lin, *Mar. Drugs*, 2013, **11**, 114–123.
56 W. H. Gerwick, W. Fenical and M. U. S. Sultanbawa, *J. Org. Chem.*, 1981, **46**, 2233–2241.
57 R. G. Salomon, B. Basu, S. Roy and N. D. Sachinvala, *J. Am. Chem. Soc.*, 1991, **113**, 3096–3106.
58 S. D. Rosa, C. Iodice, M. Khalaghdoust, S. Oryan and A. Rustaiyan, *Phytochemistry*, 1999, **51**, 1009–1012.
59 H. Yamase, K. Umemoto, T. Ooi and T. Kusumi, *Chem. Pharm. Bull.*, 1999, **47**, 813–818.
60 G. A. Frangulyan, A. V. Komkov, E. P. Prokof'ev, V. M. Belotserkovets, E. É. Lavut and V. I. Panov, *Chem. Nat. Compd.*, 1987, **23**, 168–173.
61 J. J. Myher and A. Kuksis, *Can. J. Biochem. Cell Biol.*, 1984, **62**, 352–362.
62 J. J. Myher and A. Kuksis, *J. Chromatogr., A*, 1989, **471**, 187–204.
63 A. B. Imbs, H. V. Luu and L. Q. Pham, *Chem. Nat. Compd.*, 2007, **43**, 610–611.
64 A. B. Imbs, *Russ. J. Mar. Biol.*, 2013, **39**, 153–168.
65 J. R. Maxwell, A. G. Douglas, G. Eglinton and A. McCormick, *Phytochemistry*, 1968, **7**, 2157–2171.
66 R. E. Cox, A. L. Burlingame, D. M. Wilson, G. Eglinton and J. R. Maxwell, *J. Chem. Soc., Chem. Commun.*, 1973, 284–285.
67 P. Metzger and E. Casadevall, *Tetrahedron Lett.*, 1983, **24**, 4013–4016.
68 P. Metzger, E. Casadevall, M. J. Pouet and Y. Pouet, *Phytochemistry*, 1985, **24**, 2995–3002.
69 S. Endo, N. Hiramatsu, K. Hayakawa, M. Okamura, A. Kasai, Y. Tagawa, N. Sawada, J. Yao and M. Kitamura, *Mol. Pharmacol.*, 2007, **72**, 1337–1348.
70 H. Serizawa, A. B. Argade, A. Datwani, N. Spencer, Y. Pan and F. Ermini, *WO* 2014163643, 2014.
71 M.-C. Blanc, P. Bradesi and J. Casanova, *Magn. Reson. Chem.*, 2005, **43**, 176–179.
72 B. Tursch, J. C. Braekman and D. Daloze, *Bull. Soc. Chim. Belg.*, 1975, **84**, 767–774.
73 J. C. Coll, B. F. Bowden, G. M. König, R. Braslau and I. R. Price, *Bull. Soc. Chim. Belg.*, 1986, **95**, 815–834.
74 D. V. Rao, T. S. Rao and C. B. Rao, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1990, **29**, 683–684.
75 H. Gross, S. Kehraus, M. Nett, G. M. König, W. Beil and A. D. Wright, *Org. Biomol. Chem.*, 2003, **1**, 944–949.
76 A. Rudi, G. Shmul, Y. Benayahu and Y. Kashman, *Tetrahedron Lett.*, 2006, **47**, 2937–2939.
77 E. Fattorusso, A. Romano, O. Taglialatela-Scafati, C. Irace, C. Maffettone, G. Bavestrello and C. Cerrano, *Tetrahedron*, 2009, **65**, 2898–2904.
78 H. I. Januar, E. Chasanah, C. A. Motti, D. M. Tapiolas, C. H. Liptrot and A. D. Wright, *Mar. Drugs*, 2010, **8**, 2142–2152.

79 K. M. Steed and J. W. Steed, *Chem. Rev.*, 2015, **115**, 2895–2933.
80 H. D. Flack, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 1983, **39**, 876–881.
81 Bruker, *APEX2 Software Suite for Crystallographic Programs*, Bruker AXS Inc., Madison, WI, USA, 2009.
82 Bruker, *Area Detector Control and Integration Software. Version 5.1. In: SMART and SAINT*, Bruker Analytical X-ray Instruments Inc., Madison, WI, USA, 1996.
83 G. M. Sheldrick, *SADABS. Program for Absorption Correction. Version 2.10*, University of Göttingen, Germany, 1996.
84 M. C. Burla, M. Camalli, B. Carrozzini, G. L. Cascarano, C. Giacovazzo, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 2003, **36**, 1103.
85 G. Sheldrick, *Acta Crystallogr., Sect. A: Fundam. Crystallogr.*, 2008, **64**, 112–122.
86 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565–565.
87 C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Crystallogr.*, 2006, **39**, 453–457.
88 W. Trager and J. B. Jensen, *Science*, 1976, **193**, 673–675.
89 W. Trager and J. B. Jensen, *J. Parasitol.*, 2005, **91**, 484–486.
90 Y. Corbett, L. Herrera, J. Gonzalez, L. Cubilla, T. L. Capson, P. D. Coley, T. A. Kursar, L. I. Romero and E. Ortega-Barria, *Am. J. Trop. Med. Hyg.*, 2004, **70**, 119–124.