Merosesquiterpenes from Two Sponges of the Genus *Dysidea*

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The chemical study of two sponges of the genus *Dysidea* collected in the Gulf of California has led to the isolation of the new merosesquiterpenes 20-*O*-acetyl-21-hydroxy-*ent*-isozonarol (**2**), 20-*O*-acetylneoavarol (**3**), *ent*-yahazunol (**4**), and dysienone (**5**), together with the known compounds **1** and **6**−**9**. The structures of the new metabolites have been established by spectroscopic techniques. The absolute configuration of compounds **5** and **6** has been investigated by application of a procedure developed by Riguera et al. Compounds **2** and **5** showed cytotoxic activity against three human tumor cell lines.

Since the first isolation of avarol (**1**) and the corresponding quinone, avarone, from the Mediterranean sponge *Dysidea avara*,[1] an array of sesquiterpene-hydroquinones and quinones have been obtained from *Dysidea* species. Like avarol (**1**), most of these metabolites are characterized by possessing a rearranged drimane sesquiterpenoid moiety, including those obtained from *D. avara*,[2−4] *D. cinerea,*[5] and *D. arenaria*[6,7] and those isolated from several unidentified *Dysidea* species collected at the Indian and Pacific oceans.[8−13] A minor number of *Dysidea* merosesquiterpenes possess a drimane sesquiterpenoid residue,[14] while *D. frondosa* has afforded a series of related metabolites possessing an unusual 6,7-bicyclic sesquiterpenoid system.[15] In addition, a variety of biological properties have been described for these sesquiterpene hydroquinones and quinones, including cytotoxic,[3−5,11,12,16] anti-HIV,[5,17] and anti-inflammatory[18] activities, as well as inhibitory activity of protein kinase,[7,10] topoisomerase II,[11] phospholipase A_2,[13] and interleukin-8 receptors.[15]

As a part of our project directed toward the study of new bioactive metabolites from sponges, we obtained specimens of two species of the genus *Dysidea*, collected along the coasts of Sinaloa (Mexico, Gulf of California). The chemical study of these specimens has led to the isolation of the new metabolites 20-*O*-acetyl-21-hydroxy-*ent*-isozonarol (**2**), 20-*O*-acetylneoavarol (**3**), *ent*-yahazunol (**4**), and dysienone (**5**) together with the known compounds avarol (**1**),[1] *ent*-isozonarol (**6**),[19] which is described for the first time from natural sources, neoavarol (**7**),[8] 20-*O*-acetylavarol (**8**),[3] and popolohuanone C (**9**).[10]

Results and Discussion

Freeze-dried specimens of the sponge *Dysidea* sp-1 were extracted with acetone to yield an extract that was subjected to column chromatography eluted with mixtures of hexane/Et_2O of increasing polarity, then $CHCl_3$/MeOH (8:2), and finally MeOH. Further purification of selected fractions yielded the new metabolite **2**, together with an inseparable mixture of compounds **1** and **6**. Freeze-dried specimens of *Dysidea* sp-2 were also extracted with acetone, and the resulting residue was partitioned between H_2O and Et_2O. The organic layer was concentrated under reduced pressure to give an extract that was subjected to column chromatography as described above. Subsequent HPLC separation of selected fractions yielded the new metabolites **2**−**5** together with the known **1** and **7**−**9**.

Compound **2** was obtained as an oil whose molecular formula, $C_{23}H_{32}O_4$, was determined by HRMS. The ^{1}H NMR spectrum exhibited two doublets at δ 6.82 (1H, d, J = 8.7 Hz) and 6.30 (1H, d, J = 8.7 Hz) that together with six signals in the ^{13}C NMR spectrum at δ 152.1 (s), 145.8 (s), 132.7 (s), 119.1 (d), 118.8 (s), and 107.1 (d) indicated the presence of a 1,2,3,4-tetrasubstituted benzene ring. Three of these substituents were identified as oxygenated functions: two hydroxyl groups that gave rise to the IR absorption band at 3432 cm^{-1} and one *O*-acetyl group, as inferred from the NMR signals at δ_H 2.30 (3H, s), δ_C 169.4 (s), and δ_C 21.0 (q). The 15 remaining signals of the ^{13}C NMR spectrum were attributed to a sesquiterpene moiety that had to be linked to the aromatic ring. Furthermore, these 15 signals, as well as those observed in the ^{1}H NMR spectrum corresponding to four methyl groups [δ 1.59 (bs), 0.93 (s), 0.90 (s), and 0.86 (s)], one benzylic methylene [δ 2.76 (1H, dd, J = 14.7 and 8.4 Hz) and 2.70 (1H, dd, J = 14.7 and 4.6 Hz)], and one olefinic proton [δ 5.40 (bs)], were similar to those reported for the drimane moiety of the algal metabolite isozonarol (**10**).[20] Furthermore, all the spectroscopic evidence, including the NOESY data, indicated that compound **2** possessed a sesquiterpenoid residue displaying the same structure and relative configuration as isozonarol (**10**). The analysis of the HMBC spectrum determined that the sesquiterpene residue was linked to the aromatic ring (C-16), with the hydroxyl groups located at the *ortho* positions (C-17 and C-21) and the *O*-acetyl group at the *meta* position (C-20). Especially diagnostic were the correlations between the protons of the benzylic methylene (δ 2.76 and 2.70) and the aromatic ring carbon signals at δ 152.1 and 145.8, attributable to the carbons bearing the hydroxyl groups. Further support for the location of the *O*-acetyl group was obtained by comparison of the chemical shifts of the aromatic hydrogens and carbons of **2** with those calculated for the three possible isomers (*O*-acetyl group at C-17, C-20, or C-21).[21]

At this point we turned to the absolute configuration of the drimane residue present in compound **2**. In addition to compound **2** the two remaining major components of the extract, compounds **1** and **6**, were obtained as an inseparable mixture whose spectroscopic data suggested that these two metabolites had structures and relative configurations identical to avarol (**1**) and isozonarol (**10**), respec-

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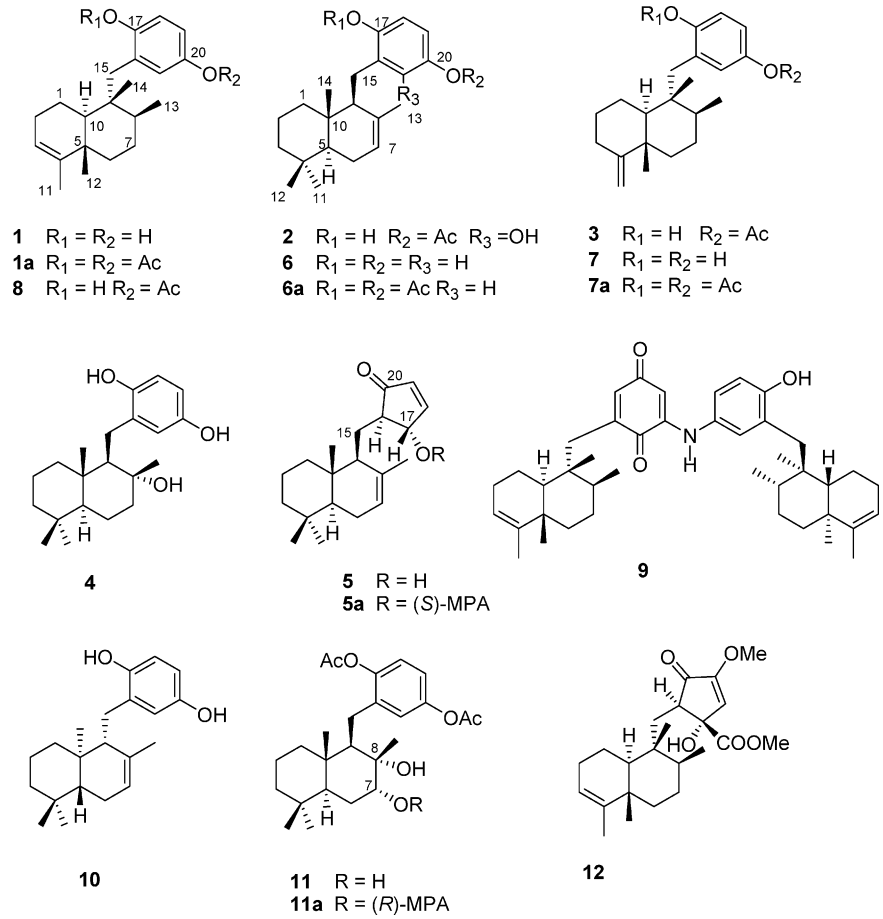
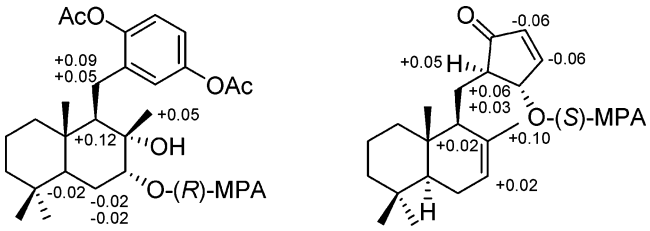
Chart 1



tively. After acetylation, the mixture could be separated by HPLC to yield the diacetyl derivatives **1a** and **6a**. The first one displayed spectroscopic data and optical activity identical to those reported for diacetylavarol (**1a**)[4] ($[\alpha]_D$ +14.0 (*c* 0.1, $CHCl_3$), ref 4 $[\alpha]_D$ +12.5), thus establishing that one of the major metabolites of the sponge was avarol (**1**), whose absolute configuration was established by Minale et al.[1b] Assuming a biogenetic relationship between the rearranged drimane moiety of avarol (**1**) and the drimane residue present in the co-metabolites **2** and **6**, we considered that these latter compounds should possess 5*S*,9*S*,10*S* absolute configuration, that is, opposite to that of the algal isozonarol (**10**). Consequently, the structure 20-*O*-acetyl-21-hydroxy-*ent*-isozonarol was proposed for compound **2**, while compound **6** had to be *ent*-isozonarol. To confirm this proposal, we investigated the absolute configuration of our drimane derivatives via the method developed by Riguera et al. to define the absolute configuration of secondary alcohols.[22] This method implies the chemical derivatization of the alcohol with one of the enantiomers of α-methoxy-α-phenylacetic (MPA) acid and subsequent ^{1}H NMR analysis of the resulting ester at two different temperatures. The drimane derivative **6a** was first transformed into the *cis*-diol **11** by Sharpless asymmetric dihydroxylation.[23] The relative configuration at C-7 and C-8 in compound **11** was deduced from the ^{1}H NMR and NOESY spectra. Thus, the H-7 coupling constant (δ 3.65, d, J = 2.1 Hz), together with the cross-peak in the NOESY spectrum between H-7 and H-6ax (δ 1.55), indicated an equatorial orientation for H-7. The NOESY correlations between Me-13 (δ 1.25) and Me-14 (δ 0.88) and H-6ax (δ 1.55) indicated an axial orientation for Me-13 and therefore a C-8 equatorial hydroxyl. Treatment of **11** with (*R*)-MPA acid led to the ester **11a**, for which ^{1}H NMR spectra at 25 and −50 °C were recorded and analyzed. Negative values of $\Delta\delta^{T1,T2}$ (T1 = 25 °C, T2 = −50 °C) were determined for H-5, H-6ax, and H-6eq, while positive $\Delta\delta^{T1,T2}$ were obtained for H-9, Me-13, and H-15 (Figure 1). Following the model proposed by Riguera et al.,[22] these data indicated an *R* configuration for C-7 and therefore an absolute configuration for the diol derivative as depicted in formula **11**. Thus, both compound **11** and the natural metabolite **6** possess 5*S*,9*S*,10*S* absolute configuration.

Among the sponges of the genus *Dysidea*, the Mediterranean species *D. pallescens* had been the only one to afford a drimane-hydroquinone derivative, the metabolite *ent*-chromazonarol,[14] which was shown to belong to the same enantiomeric series as compound **6.** This is the first description of a *Dysidea* sponge that contains merosesquiterpenes either with a drimane or with a 4,9-friedodrimane residue.

Compound **3** was isolated as an oil of molecular formula $C_{23}H_{32}O_3$ as measured by HRMS. The NMR spectra indi-



11a **5a**

Figure 1. $\Delta\delta^{T1,T2}$ (T1 = 25 °C, T2 = −50 °C) observed for the (*R*)-MPA ester **11a** and the (*S*)-MPA ester **5a**.

cated that compound **3** possessed a monoacetylated hydroquinone ring linked to a sesquiterpene residue. However, this latter moiety gave rise to NMR signals significantly different from those described for compound **2**. In particular, the signals at δ 2.68 (1H, d, J = 14.4 Hz) and 2.52 (1H, d, J = 14.4 Hz) indicated that the benzylic methylene in **3** was linked to a fully substituted carbon. These data, together with the presence of two methyl singlets (δ 1.06 and 0.86), one methyl doublet (δ 0.99), and the signals of an exocyclic methylene (δ 4.43 and 4.39), matched with a $\Delta^{4(11)}$ rearranged drimane structure for the sesquiterpene moiety of **3**. In fact, all the spectroscopic data were found to be almost identical to those reported for neoavarol (isoavarol) (**7**),[8] indicating that compound **3** was a monoacetyl derivative of **7**. The distinction between the two possible isomeric structures in favor of the compound bearing the *O*-acetyl group at C-20 was based on the cross-peaks observed in the HMBC spectrum, in particular those between the benzylic methylene protons and the hydroxylated aromatic carbon (δ 152.3). Finally, on the basis of biogenetic grounds compound **3** likely belongs to the same enantiomeric series as its co-metabolites avarol (**1**) and neoavarol (**7**). Compound **3** is thus 20-*O*-acetylneoavarol.

Compound **4** was isolated as an oil whose molecular formula, $C_{21}H_{32}O_3$, was determined by HRMS. The NMR spectra of compound **4** were similar to those of diacetyl-*ent*-isozonarol (**6a**), except for the absence of the aromatic acetyl resonances and the olefinic C-7, C-8 resonances. The ^{13}C NMR spectrum of **4** showed a signal at δ 76.1 (s) consistent with the presence of a tertiary hydroxyl group at C-8. The NOESY spectrum showed correlations between Me-13 (δ 1.31) and Me-14 (δ 0.93) and between the methine protons H-5 (δ 0.95) and H-9 (δ 1.62). These data were in agreement with a *trans*-fused decalin system with H-5, H-9, Me-13, and Me-14 axially oriented. Thus, the structure and relative configuration of compound **4** was identical to that of yahazunol, a metabolite isolated from the brown seaweed *Dictyopteris undulata* and more recently synthesized.[24] However, the sponge-derived metabolite showed a specific rotation opposite in sign to that of yahazunol, and therefore it was characterized as *ent*-yahazunol (**4**).

Following the isolation of *ent*-chromazonarol from *D. pallescens*,[14] the presence of the drimane derivatives **2** and **6** in *Dysidea* sp-1 and **2** and **4** in *Dysidea* sp-2 gives further evidence that the alga *Dictyopteris undulata* and *Dysidea* sponges possess related biosynthetic pathways that lead to separate series of enantiomeric terpenoids.

Compound **5** was isolated as an oil whose molecular formula, $C_{20}H_{30}O_2$, was established by HRMS. The NMR spectra suggested that compound **5** was a merosesquiterpene related to those described above. Analysis of the upfield region of the NMR data showed that compound **5** contained a drimane sesquiterpenoid moiety identical to that of compounds **2** and **6**. However, the ^{13}C NMR spectrum of **5** displayed only five additional signals, three of which were attributable to an α,β-unsaturated ketone moiety, at δ 207.8 (C=O), 134.3 (C-α), and 160.4 (C-β). The δ 78.4 resonance was assigned to a methine linked to a hydroxyl group that gave rise to the IR absorption band at 3419 cm^{-1}. The remaining signal at δ 55.6, which was correlated in the HSQC with a proton at δ 2.41 (1H, ddd, J = 9.2, 6.3, and 2.5 Hz), was attributed to a methine linked to the ketone carbonyl group. In the COSY spectrum the methine proton at δ 2.41 correlated with a proton at δ 4.67, which in turn correlated with the olefinic proton at δ 7.45 (1H, dd, J = 5.8 and 2.1 Hz). The data were consistent with the presence of a γ-hydroxycyclopentenone subunit that had to be linked through C-δ to the sesquiterpene residue. Further confirmation was obtained from the HMBC spectrum, since both the carbonyl and the hydroxylated methine carbons correlated with the C-15 protons. The relative configuration at C-16 and C-17 was deduced from the $^3J_{16,17}$ coupling constant of 2.5 Hz, typical of *trans*-oriented protons and significantly different from *cis* protons (5−6 Hz).[25] The absolute configuration was determined by application of the procedure of Riguera, which is particularly useful when small amounts of the natural compound is available.[22] Thus, the ester **5a** was obtained upon treatment of **5** with (*S*)-α-methoxy-α-phenylacetic (MPA) acid. After recording the ^{1}H NMR spectra of **5a** at 25 and −50 °C, negative values of $\Delta^{T1,T2}$ were obtained for H-18 and H-19, while positive values were found for H-7, H-9, Me-13, H-15, and H-16 (Figure 1). These data were consistent with an *S* absolute configuration at C-17 and therefore *R* for C-16, and with structure **5** for dysienone.

The five-carbon unit present in dysienone is unusual among the merosesquiterpenes of sponges. A literature survey revealed that Faulkner described, from a sponge of the genus *Dactylospongia*, the isolation of four diastereomeric compounds possessing a rearranged drimane moiety linked to a cyclopentenone unit, exemplified by dactylospongenone A (**12**).[26] This cyclopentenone moiety, additionally functionalized with one *O*-methyl group at the α position and with one hydroxyl and one methoxycarbonyl groups at C-γ, was proposed to arise through the contraction of a 2-hydroxy-5-methoxy-1,4-benzoquinone ring. More recently, a sponge of the genus *Dysidea* has afforded the dysidenones,[13] which differ from the metabolites of *Dactylospongia* in the sesquiterpene portion. Dysienone (**5**), in addition to a different carbon framework for the sesquiterpene moiety, contains a cyclopentenone ring that lacks the *O*-methyl group at C-α and the methoxycarbonyl group at C-γ. It could therefore be proposed that this ring arises from a 2-hydroxy-1,4-benzoquinone ring through ring contraction and subsequent decarboxylation. If so, the quinone derivative of compound **2** could be a plausible biosynthetic precursor of dysienone. However, in the absence of further evidence, an alternative biosynthetic origin for the cyclopentenone ring of dysienone (**5**) cannot be ruled out.

The new metabolites **2**−**5** were tested in bioassays directed to detect in vitro activity against the human tumor cell lines MDA-MB-231 (mammary gland adenocarcinoma), A-549 (lung carcinoma), and HT-29 (colon adenocarcinoma). The measured parameters were GI_{50} (concentration that causes 50% growth inhibition), TGI (concentration that causes total growth inhibition), and LC_{50} (concentration that causes 50% cell killing: cytotoxic effect). The individual cell line identifiers are given along with the corresponding GI_{50}, TGI, and LC_{50} values (μM) for each compound tested. 20-*O*-Acetyl-21-hydroxy-*ent*-isozonarol (**2**): MDA-MB-231 (10.5, 11.0, 11.8), A-549 (10.5, 11.0, 11.8), HT-29 (11.3, 12.6, 14.0). 20-*O*-Acetylneoavarol (**3**): MDA-MB-231 (21.0), A-549 (25.5). *ent*-Yahazunol (**4**): MDA-MB-231 (27.7), A-549 (17.4). Dysienone (**5**): MDA-MB-231 (15.2, 16.5, 17.9), A-549 (12.9, 13.6, 14.2), HT-29 (13.6, 14.2, 15.2). The most active compounds were **2** and **5**, showing a cytotoxic effect on the three tested lines (LC_{50} = 14.2−17.9 μM).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 241 polarimeter, and IR spectra were recorded on a Perkin-Elmer FT-IR System Spectrum BX spectrophotometer. ^{1}H and ^{13}C NMR spectra

were recorded on a Varian INOVA 400 or on a Varian INOVA 600 spectrometer using $CDCl_3$ as solvent. Proton chemical shifts were referenced to the residual $CHCl_3$ signal at δ 7.26, and ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at δ 77.0. NOESY experiments, COSY, HSQC, and HMBC were performed using standard Varian pulse sequences. Low-resolution mass spectra were recorded on a Finnigan Voyager GC8000^{top} spectrometer. High-resolution mass spectra (HRMS) were obtained on a Autospec-Q spectrometer. Column chromatography was carried out on Merck silica gel 60 (70−230 mesh). HPLC separations were performed on a LaChrom-Hitachi apparatus equipped with LiChrospher Si-60 (Merck) columns in normal-phase mode and LiChrosorb RP-18 (Merck) columns in reversed-phase mode using a RI-71 differential refractometer. All solvents were spectral grade or were distilled prior to use.

Collection and Identification. Specimens of *Dysidea* sp-1 and *Dysidea* sp-2 were collected by hand using scuba in the Gulf of California and immediately frozen. *Dysidea* sp-1 is an undescribed soft sponge spreading on mangrove roots, with multiple flattened lobate projections, which frequent anastomoses. The sponge can cover extensions up to 15 cm in diameter and 1.8 cm high, with lobes up to 1 cm in length. The texture is soft and flexible, and the sponge is easily compressible. The color is light brown to light gray. It has a coarsely conulose surface, with conules 4−7 mm high, ending in pointed tips, each of which is elevated by a singular primary tip; sometimes the primary fibers bifurcate in the tip of a same conule. The surface of the sponge is very characteristic because the primary fibers that run along the subsurface are externally visible and give an irregular weblike appearance to the surface. The dermal membrane is not charged with detritus. Oscules are 1.5−2 mm in diameter, some with slightly elevated rims. The skeleton is a loose irregular network of fibers formed mainly by primary fibers with little secondary connections. Primary fibers are from 50 to 100 μm in diameter (70 μm average), and they are always cored with debris and sand grains. Very little clear spongin remains in the fibers. The secondary fibers are 20−40 μm in diameter (30 μm average), and they are mostly free of debris. Debris occurs only at the point of connection with the primary fibers. The specimens were collected in La Reforma (Mexico, Pacific Ocean; 24°54′51″ N; 108°02′33″ W), and they have been deposited in the Sponge Collection in the UNAM with the code LEB-ICML-UNAM-188. *Dysidea* sp-2 is also an undescribed species collected in Topolobampo Bay (Mexico, Pacific Ocean; 25°36′25″ N; 109°04′33″ W). It is an encrusting to massive sponge from which rounded lobes protrude, most of them with a central oscule. The color varies from light gray to almost white, and the individuals can cover up to 12 cm in diameter, but are most commonly around 7−11 cm long and wide and 3−5 cm high. The sponge has a very characteristic lobate appearance, with simple lobes, although two or more lobes can frequently fuse. The lobes vary in diameter from 0.3 cm in the simple form to 1.5 cm when fused and can be up to 0.8 mm high. The surface is evenly covered with rounded conules, giving the surface a granular appearance. Oscules are usually circular, 1.5−3.5 mm in diameter, scattered over the top of the lobes and flush with the surface. The skeleton is arranged following a rectangular plan, typical of the genus *Dysidea*. The primary fibers are simple, and they are spaced approximately 50−200 μm apart. They vary from 150 to 200 μm in diameter, and they are completely cored with sand grains. Secondary fibers are 40−100 μm in diameter and also incorporate debris, although the spongin is always visible around the material depending on the nature and extent of the debris. A voucher has been deposited in the Sponge Collection in the UNAM with the code 716-LEB-ICML-UNAM. Both species are going to be formally described in a specialized journal. Underwater photographs and voucher samples are available from J.L.C.

Extraction and Isolation. Freeze-dried specimens of the sponge *Dysidea* sp-1 (16.2 g) were extracted with 1.25 L of acetone at room temperature. After filtration of the solvent, the solution was evaporated under reduced pressure to obtain a brown oil (512 mg), which was chromatographed on a SiO_2 column using solvents of increasing polarities from hexane to Et_2O, then $CHCl_3$/MeOH (8:2), and finally MeOH. The fraction eluted with hexane/Et_2O (7:3) was further purified by filtration on a RP-18 cartridge eluting with MeOH/H_2O (97:3) to obtain a mixture of compounds **1** and **6** (73.5 mg, 0.44% dry wt) inseparable by HPLC. This mixture was treated with Ac_2O/Py and subjected to normal-phase HPLC to yield the diacetyl derivatives **1a** (31.4 mg) and **6a** (41.3 mg). The fraction of the general chromatography eluted with hexane/Et_2O (1:1) was filtered through an RP-18 cartridge eluting with MeOH/H_2O (93:7) to obtain compound **2** (40.9 mg, 0.25% dry wt).

Freeze-dried specimens of the sponge *Dysidea* sp-2 (257 g) were extracted with 2.25 L of acetone/MeOH (1:1) at room temperature. After filtration, the solution was evaporated under reduced pressure to obtain a residue that was partitioned between H_2O and Et_2O. The organic layer was taken to dryness to give a brown oil (5.4 g), which was chromatographed on a SiO_2 column using solvents of increasing polarities from hexane to Et_2O, then $CHCl_3$/MeOH (8:2), and finally MeOH. The fraction eluted with hexane/Et_2O (8:2) was subjected to reversed-phase HPLC eluted with MeOH/H_2O (85:15) to obtain an inseparable mixture of compounds **1** and **7** (26.4 mg), compound **3** (4.0 mg, 1.6×10^{-3} % dry wt), and compound **8** (24 mg, 9.3×10^{-3} % dry wt). The mixture of compounds **1** and **7** was acetylated with Ac_2O/Py and separated by normal-phase HPLC eluted with hexane/Et_2O (95:5) to yield the diacetyl derivatives **7a** (8.0 mg) and **1a** (17.0 mg). The fraction of the general chromatography eluted with hexane/Et_2O (7:3) was chromatographed on a SiO_2 column to yield a mixture of compounds **1** and **7** (1.2 g, 0.55% dry wt) as well as a mixture of compounds that was subjected to reversed-phase HPLC eluting with MeOH/H_2O (83:17) to yield compounds **2** (19.1 mg, 7.4×10^{-3} % dry wt) and **9** (2.8 mg, 1.1×10^{-3} % dry wt). The fraction of the general chromatography eluted with hexane/Et_2O (3:7) was subjected to reversed-phase HPLC eluted with MeOH/H_2O (83:17) to obtain further amounts of compound **2** (3.5 mg) together with compounds **4** (2.4 mg, 1.0×10^{-3} % dry wt) and **5** (2.2 mg, 8.5×10^{-4} % dry wt).

20-*O*-Acetyl-21-hydroxy-*ent*-isozonarol (2): yellowish oil; $[\alpha]^{25}_D$ −36.3° (*c* 0.09, $CHCl_3$); IR (film) ν_{max} 3432, 2924, 1746, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.82 (1H, d, J = 8.7 Hz, H-19), 6.30 (1H, d, J = 8.7 Hz, H-18), 5.40 (1H, bs, H-7), 5.36 (1H, s, OH), 4.81 (1H, bs, OH), 2.76 (1H, dd, J = 14.7 and 8.4 Hz, H-15a), 2.70 (1H, dd, J = 14.7 and 4.6 Hz, H-15b), 2.62 (1H, m, H-9), 2.30 (3H, s, OCOC*H*$_3$), 1.96 (1H, m, H-6α), 1.91 (1H, m, H-1*β*), 1.86 (1H, m, H-6*β*), 1.59 (3H, bs, H-13), 1.51 (1H, m, H-2*β*), 1.38 (2H, m, H-2α and H-3*β*), 1.25 (1H, m, H-5) 1.15 (1H, m, H-3α), 1.13 (1H, m, H-1α), 0.93 (3H, s, H-14), 0.90 (3H, s, H-12), 0.86 (3H, s, H-11); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 169.4 (C, O*C*OCH$_3$), 152.1 (C, C-17), 145.8 (C, C-21), 135.8 (C, C-8), 132.7 (C, C-20), 122.6 (CH, C-7), 119.1 (CH, C-19), 118.8 (C, C-16), 107.1 (CH, C-18), 51.9 (CH,C-9), 50.3 (CH, C-5) 42.2 (CH_2, C-3), 39.1 (CH_2, C-1), 37.4 (C, C-10), 33.4 (CH_3, C-11), 33.1 (C, C-4), 23.7 (CH_2, C-6), 22.1 (CH_3, C-13), 22.1 (CH_2, C-15), 21.9 (CH_3, C-12), 21.0 (CH_3, OCO*C*H$_3$), 19.0 (CH_2, C-2), 13.6 (CH_3, C-14); EIMS *m/z* 372 $[M]^+$(4), 330 (39), 191 (95), 139 (87), 109 (100); HRCIMS(+) *m/z* 372.2291 (calcd for $C_{23}H_{32}O_4$, 372.2300).

20-*O*-Acetylneoavarol (3): yellowish oil; $[\alpha]^{25}_D$ −31.9° (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 3437, 2927, 1760, 1633 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.79 (1H, dd, J = 8.5 and 2.8 Hz, H-19), 6.73 (1H, d, J = 2.8 Hz, H-21), 6.68 (1H, d, J = 8.5 Hz, H-18), 4.75 (1H, bs, OH), 4.43 (1H, t, J = 1.8 Hz, H-11a), 4.39 (1H, t, J = 1.5 Hz, H-11b), 2.68 (1H, d, J = 14.4 Hz, H-15a), 2.52 (1H, d, J = 14.4 Hz, H-15b), 2.33 (1H, m, H-3*β*), 2.26 (3H, s, OCOC*H*$_3$), 2.09 (1H, m, H-3α), 2.00 (1H, m, H-1α), 1.88 (1H, m, H-2*β*), 1.55 (1H, m, H-1*β*), 1.50 (1H, m, H-6*β*), 1.42 (1H, m, H-7), 1.38 (1H, m, H-8), 1.30 (2H, m, H-2α and H-6α), 1.06 (3H, s, H-12), 0.99 (3H, d, J = 6.2 Hz, H-13), 0.97 (1H, dd, J = 12.3 and 2.3 Hz, H-10), 0.86 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9 (C, O*C*OCH$_3$), 159.9 (C, C-4), 152.3 (C, C-17), 143.6 (C, C-20), 126.3 (C, C-16), 125.4 (CH, C-21), 120.0 (CH, C-19), 115.8 (CH, C-18), 102.9 (CH_2, C-11), 48.2 (CH, C-10), 42.1 (C, C-9), 40.2 (C, C-5), 37.5 (CH_2, C-15), 36.5 (CH_2, C-6),

36.3 (CH, C-8), 33.0 (CH_2, C-3), 28.1 (CH_2, C-2), 27.7 (CH_2, C-7), 23.2 (CH_2, C-1), 21.1 (CH_3, OCO*C*H_3), 20.6 (CH_3, C-12), 17.6 (CH_3, C-13), 17.5 (CH_3, C-14); EIMS *m/z* 356 $[M]^+$ (3), 314 (8), 191 (88), 123 (94), 94 (100); HRCIMS (+) *m/z* 356.2337 (calcd for $C_{23}H_{32}O_3$, 356.2351).

***ent*-Yahazunol (4):** yellowish oil; $[\alpha]^{25}_D$ +11.8° (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 3402, 2868, 1654, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.70 (1H, d, J = 8.4 Hz, H-18), 6.61 (1H, d, J = 3.1 Hz, H-21), 6.56 (1H, dd, J = 8.4 and 3.1 Hz, H-19), 2.86 (1H, dd, J = 15.2 and 2.3 Hz, H-15a), 2.37 (1H, dd, J = 15.2 and 6.0 Hz, H-15b), 1.89 (1H, ddd, J = 12.2, 3.3, and 3.3 Hz, H-7β), 1.77 (1H, m, H-1β), 1.69 (1H, m, H-6α), 1.62 (1H, dd, J = 6.0 and 2.3 Hz, H-9), 1.58 (2H, m, H-2β and H-7α), 1.40 (1H, m, H-2α), 1.34 (1H, m, H-3β), 1.31 (3H, s, H-13), 1.29 (1H, m, H-6β), 1.05 (1H, ddd, J = 13.7, 13.3, and 3.8 Hz, H-3α), 0.95 (1H, m, H-5), 0.93 (3H, s, H-14), 0.83 (3H, s, H-11), 0.80 (3H, s, H-12), 0.79 (1H, m, H-1α); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 149.3 (C, C-20), 147.9 (C, C-17), 130.2 (C, C-16), 118.2 (CH, C-21), 117.2 (CH, C-18), 114.0 (CH, C-19), 76.1 (C, C-8), 60.6 (CH, C-9), 55.7 (CH, C-5), 43.9 (CH_2, C-7), 41.5 (CH_2, C-3), 40.3 (CH_2, C-1), 39.8 (C, C-10), 33.3 (CH_3, C-11) 33.1 (C, C-4), 27.4 (CH_2, C-15), 24.7 (CH_3, C-13), 21.4 (CH_3, C-12), 20.4 (CH_2, C-6), 18.2 (CH_2, C-2), 15.4 (CH_3, C-14); EIMS *m/z* 314 $[M - H_2O]^+$ (29), 191 (100), 161 (41), 123 (80), 95 (46); HRCIMS (+) *m/z* 332.2351 (calcd for $C_{21}H_{32}O_3$, 332.2351).

Dysienone (5): yellowish oil; $[\alpha]^{25}_D$ −12.5° (*c* 0.07, $CHCl_3$); IR (film) ν_{max} 3419, 2925, 1700 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.45 (1H, dd, J = 5.8 and 2.1 Hz, H-18), 6.16 (1H, dd J = 5.8 and 1.1 Hz, H-19), 5.44 (1H, bs, H-7), 4.67 (1H, bs, H-17), 2.41 (1H, ddd, J = 9.2, 6.3, and 2.5 Hz, H-16), 2.39 (bs, H-9), 1.99 (1H, m, H-6α), 1.88 (1H, m, H-6β), 1.82 (1H, ddd, J = 14.6, 9.2, and 2.9 Hz, H-15a), 1.75 (1H, m, H-1β), 1.74 (3H, bs, H-13), 1.50 (2H, m, H-2β and H-15b), 1.44 (1H, m, H-2α), 1.39 (1H, m, H-3β), 1.30 (1H, dd, J = 12.2 and 4.9 Hz, H-5), 1.20 (1H, m, H-3α), 1.18 (1H, m, H-1α), 0.88 (3H, s, H-12), 0.86 (3H, s, H-11), 0.78 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 207.8 (C, C-20), 160.4 (CH, C-18), 134.4 (C, C-8), 134.3 (CH, C-19), 123.3 (CH, C-7), 78.4 (CH, C-17), 55.6 (CH, C-16), 50.8 (CH, C-9), 49.9 (CH, C-5), 42.1 (CH_2, C-3), 39.2 (CH_2, C-1), 37.5 (C, C-10), 33.1 (CH_3, C-11), 33.0 (C, C-4) 26.7 (CH_2, C-15), 23.9 (CH_2, C-6), 22.9 (CH_3, C-13), 21.9 (CH_3, C-12), 18.8 (CH_2, C-2), 13.4 (CH_3, C-14); EIMS *m/z* 302 $[M]^+$ (3), 204 (32), 191 (31), 161 (35), 109 (100); HRCIMS (+) 302.2233 (calcd for $C_{20}H_{30}O_2$, 302.2245).

17,20-Di-*O*-acetyl-*ent*-isozonarol (6a): yellowish oil; $[\alpha]^{25}_D$ −16.3° (*c* 0.1, $CHCl_3$); IR (film) ν_{max} 2926, 1765, 1207, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.07 (1H, d, J = 2.6 Hz, H-21), 7.00 (1H, d, J = 8.7 Hz, H-18), 6.92 (1H, dd, J = 8.7 and 2.6 Hz, H-19), 5.40 (1H, bs, H-7), 2.59 (1H, dd, J = 15.6 and 2.4 Hz, H-15a), 2.45 (1H, dd, J = 15.6 and 9.3 Hz, H-15b), 2.32 (3H, s, OCOCH_3), 2.30 (1H, m, H-9), 2.29 (3H, s, OCOCH_3), 2.00 (1H, m, H-6α), 1.89 (1H, m, H-6β), 1.82 (1H, m, H-1β), 1.54 (1H, m, H-2β), 1.44 (1H, m, H-2α), 1.41 (1H, m, H-3β), 1.41 (3H, bs, H-13) 1.28 (1H, dd, J = 12.0 and 4.9 Hz, H-5), 1.19 (1H, ddd, J = 13.6, 13.6, and 3.9 Hz, H-3α), 1.04 (1H, ddd, J = 13.0, 13.0, and 3.7 Hz, H-1α), 0.90 (3H, s, H-12), 0.88 (3H, s, H-11), 0.86 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3 (C, O*C*OCH$_3$), 169.2 (C, O*C*OCH$_3$), 148.2 (C, C-17), 146.0 (C, C-20), 137.1 (C, C-16), 134.7 (C, C-8), 123.0 (CH, C-18), 122.8 (CH, C-7), 122.3 (CH, C-21), 119.4 (CH, C-19), 54.0 (CH, C-9), 50.2 (CH, C-5), 42.2 (CH_2, C-3), 39.7 (CH_2, C-1), 36.8 (C, C-10), 33.2 (CH_3, C-11), 33.0 (C, C-4), 26.6 (CH_2, C-15), 23.7 (CH_2, C-6), 22.4 (CH_3, C-13), 21.9 (CH_3, C-12), 21.1 (CH_3, OCO*C*H$_3$), 20.9 (CH_3, OCO*C*H$_3$), 18.8 (CH_2, C-2), 13.9 (CH_3, C-14); EIMS *m/z* 398 $[M]^+$ (2), 231 (37), 191 (73), 190 (89), 109 (100); HRCIMS (+) *m/z* 399.2519 $[M + H]^+$ (calcd for $C_{25}H_{35}O_4$, 399.2535).

Synthesis of Compound 11. A solution of **1a** (16.7 mg, 0.042 mmol) in 1 mL of *t*-BuOH/H_2O (1:1) was treated with 190 mg of AD-mixβ and 10 mg of methanesulfonamide. After stirring overnight at room temperature, the reaction was quenched with an excess of anhydrous sodium sulfite and stirred for a further 45 min. Water (3 mL) was added to the reaction mixture and extracted with 4 mL of EtOAc. The organic layer was taken to dryness under reduced pressure and the residue purified on HPLC (hexane/EtOAc, 55:45) to afford 5 mg of compound **11** (0.012 mmol, 28.6% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.08 (1H, d, J = 2.7 Hz, H-21), 6.98 (1H, d, J = 8.7 Hz, H-18), 6.91 (1H, dd, J = 8.7 and 2.7 Hz, H-19), 3.65 (1H, d, J = 2.1, H-7), 2.67 (1H, dd, J = 15.0 and 6.0 Hz, H-15), 2.59 (1H, dd, J = 15.0 and 4.9 Hz, H-15), 2.34 (3H, s, OCOCH_3), 2.29 (3H, s, OCOCH_3), 1.96 (1H, t, J = 5.5, H-9), 1.85 (1H, m, H-6α), 1.61 (1H, m, H-1β), 1.58 (1H, m, H-2β), 1.55 (1H, m, H-6β), 1.52 (1H, m, H-5), 1.40 (1H, m, H-2α), 1.37 (1H, m, H-3β), 1.25 (3H, s, H-13), 1.17 (1H, ddd, J = 14.1, 13.3, and 5.1 Hz, H-3α), 0.88 (3H, s, H-14), 0.87 (3H, s, H-11), 0.84 (1H, m, H-1α), 0.80 (3H, s, H-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6 (C, O*C*OCH$_3$), 169.4 (C, O*C*OCH$_3$), 148.2 (C, C-20), 145.7 (C, C-17), 137.5 (C, C-16), 123.4 (CH, C-21), 123.1 (CH, C-18), 119.6 (CH, C-19), 74.6 (CH, C-7), 74.6 (C, C-8), 55.5 (CH, C-9), 46.3 (CH, C-5), 41.7 (CH_2, C-3), 39.8 (CH_2, C-1), 38.8 (C, C-10), 33.1 (CH_3, C-11), 32.8 (C, C-4), 25.8 (CH_2, C-6), 24.1 (CH_2, C-15), 23.4 (CH_3, C-13), 21.5 (CH_3, C-12), 21.2 (CH_3, OCO*C*H$_3$), 21.1 (CH_3, OCO*C*H$_3$), 18.5 (CH_2, C-2), 14.8 (CH_3, C-14).

Synthesis of the (*R*)-MPA Ester 11a. A solution of compound **11** (1.5 mg, 3.5×10^{-3} mmol) in 0.5 mL of CH_2Cl_2 was treated with CH_2Cl_2 solutions of *N*,*N*-dicyclohexylcarbodiimide (9.0 mg, 4.4×10^{-2} mmol in 0.5 mL), *N*,*N*-(dimethylamino)pyridine (2.0 mg, 1.8×10^{-2} mmol in 0.5 mL), and (*R*)-α-methoxy-α-phenylacetic acid (3.0 mg, 1.8×10^{-2} mmol in 0.5 mL) and stirred at room temperature for 20 h. Evaporation of the solvent under reduced pressure yielded a residue that was purified on HPLC (hexane/EtOAc, 55:45) to obtain 1.0 mg (1.7×10^{-3} mmol, 48.6% yield) of (*R*)-MPA ester **11a**: ^1H NMR ($CDCl_3$, 600 MHz, 25 °C; selected data, assignments aided by a COSY experiment) δ 4.76 (1H, dd, J = 3.5 and 2.1 Hz, H-7), 2.68 (1H, dd, J = 15.1 and 4.9 Hz, H-15a), 2.50 (1H, dd, J = 15.1 and 5.7 Hz, H-15b), 1.90 (1H, ddd, J = 14.9, 3.3, and 2.6 Hz, H-6α), 1.69 (1H, t, J = 5.3 Hz, H-9), 1.52 (1H, m, H-6β), 1.18 (3H, s, H-13), 1.10 (1H, dd, J = 13.2 and 2.0 Hz, H-5); ^1H NMR ($CDCl_3$, 600 MHz, −50 °C; selected data, assignments aided by a COSY experiment) δ 4.76 (1H, bs, H-7), 2.59 (1H, dd, J = 14.9 and 4.9 Hz, H-15a), 2.45 (1H, dd, J = 14.9 and 4.8 Hz, H-15b), 1.92 (1H, bd, J = 15.4 Hz, H-6α), 1.57 (1H, m, H-9), 1.54 (1H, m, H-6β) 1.13 (3H, s, H-13), 1.13 (1H, m, H-5).

Synthesis of the (*S*)-MPA Ester 5a. Compound **5** (1.1 mg, 3.7×10^{-3} mmol) was dissolved in 0.5 mL of CH_2Cl_2 and treated with CH_2Cl_2 solutions of *N*,*N*-dicyclohexylcarbodiimide (9.5 mg, 4.6×10^{-2} mmol in 0.5 mL), *N*,*N*-(dimethylamino)-pyridine (3.0 mg, 2.5×10^{-2} mmol in 0.5 mL), and (*S*)-α-methoxy-α-phenylacetic acid (4.0 mg, 2.4×10^{-2} mmol in 0.5 mL) as described above (rt, 16 h). Evaporation of the solvent under reduced pressure yielded a residue that was purified on HPLC (hexane/EtOAc, 8:2) to obtain 0.55 mg (1.2×10^{-3} mmol, 32.4% yield) of (*S*)-MPA ester **5a**: ^1H NMR ($CDCl_3$, 600 MHz, 25 °C; selected data, assignments aided by a COSY experiment) δ 7.45 (1H, dd, J = 5.8 and 2.4 Hz, H-18), 6.25 (1H, dd, J = 5.8 and 1.2 Hz, H-19), 5.61 (1H, dd, J = 3.5 and 2.3 Hz, H-17), 5.31 (bs, H-7), 2.28 (1H, ddd, J = 9.9, 5.9, and 2.1 Hz, H-16), 2.10 (1H, bs, H-9), 1.68 (1H, m, H-15a), 1.41 (1H, m, H-15b), 1.35 (3H, bs, H-13); ^1H NMR ($CDCl_3$, 600 MHz, −50 °C; selected data, assignments aided by a COSY experiment) δ 7.51 (1H, dd, J = 5.7 and 2.0 Hz, H-18), 6.31 (1H, bd, J = 5.7 Hz, H-19), 5.64 (1H, bs, H-17), 5.29 (1H, bs, H-7), 2.23 (1H, m, H-16), 2.08 (1H, bs, H-9), 1.62 (1H, m, H-15a), 1.38 (1H, m, H-15b), 1.25 (3H, bs, H-13).

Cytotoxicity Assays. Compounds **2**, **3**, **4**, and **5** were tested against the human tumor cell lines MDA-MB-231 (mammary gland adenocarcinoma), A-549 (lung carcinoma), and HT-29 (colon adenocarcinoma). Cytotoxicity assays were performed by PharmaMar. A colorimetric type of assay using sulforhodamine B (SRB) reaction has been adapted for a quantitative measurement of cell growth and viability following the method described in the literature.[27]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **2**−**5**. This information is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Minale, L.; Riccio, R.; Sodano G. *Tetrahedron Lett.* **1974**, *38*, 3401−3404. (b) De Rosa, S.; Minale, L.; Riccio, R.; Sodano, G. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1408−1414.
(2) Cimino, G.; De Rosa, S.; De Stefano, S.; Cariello, L.; Zanetti, L. *Experientia* **1982**, *38*, 896.
(3) Crispino, A.; De Giulio, A.; De Rosa, S.; Strazzullo, G. *J. Nat. Prod.* **1989**, *52*, 646−648.
(4) De Giulio, A.; De Rosa, S.; Di Vicenzo, G.; Strazzullo, G. *Tetrahedron* **1990**, *46,* 7971−7976.
(5) Hirsch, S.; Rudi, A.; Kashman, Y.; Loya, Y. *J. Nat. Prod.* **1991**, *54*, 92−97.
(6) Schmitz, F. J.; Lakshmi, V.; Powell, D. R.; van der Helm, D. *J. Org. Chem.* **1984**, *49*, 241−244.
(7) Yoo, H.-D.; Leung, D.; Sanghara, J.; Daley, D.; van Soest, R.; Andersen R. J. *Pharm. Biol.* **2003**, *41*, 223−225.
(8) Iguchi, K.; Sahashi, A.; Kohno, J.; Yamada, Y. *Chem. Pharm. Bull.* **1990**, *38*, 1121−1123.
(9) Rodríguez, A. D.; Yoshida, W. Y.; Scheuer, P. J. *Tetrahedron* **1990**, *46*, 8025−8030.
(10) Alvi, K. A.; Diaz, M. C.; Crews, P.; Slate, D. L.; Lee, R. H.; Moretti, R. *J. Org. Chem.* **1992**, *57*, 6604−6607.
(11) Carney, J. R.; Scheuer, P. J. *Tetrahedron Lett.* **1993**, *34*, 3727−3730.
(12) de Guzman, F. S.; Copp, B. R.; Mayne, C. L.; Concepcion, G. P.; Mangalindan, G. C.; Barrows, L. R.; Ireland, C. M. *J. Org. Chem.* **1998**, *63*, 8042−8044.
(13) Giannini, C.; Debitus, C.; Lucas, R.; Ubeda, A.; Payá, M.; Hooper, J. N. A.; D'Auria, M. V. *J. Nat. Prod.* **2001**, *64*, 612−615.
(14) Cimino G.; De Stefano, S.; Minale, L. *Experientia* **1975**, *31*, 1117−1118.
(15) Patil, A. D.; Freyer, A. J., Killmer, L.; Offen, P.; Carte, B.; Jurewicz, A. J.; Johnson, R. K. *Tetrahedron* **1997**, *53*, 5047−5060.
(16) (a) Müller, W. E. G.; Zahn, R. K.; Gasic, M. J.; Dogovic N.; Maidhof, A.; Becker, C.; Diehl-Seifert B.; Eich, E. *Comp. Biochem. Physiol.* **1985**, *80c*, 47−52. (b) Müller, W. E. G.; Maidhof, A.; Zahn, R. K.; Schröder, H. C.; Gasic, M. J.; Heidemann, D.; Bernd, A.; Kurelec, B.; Eich, E.; Seibert, G. *Cancer Res.* **1985**, *45*, 4822−4826.
(17) Sarin, P. S.; Sun, D.; Thornton, A.; Müller, W. E. G. *J. Natl. Cancer Inst.* **1987**, *78*, 663−666.
(18) Ferrándiz, M. L.; Sanz, M. J.; Bustos, G.; Payá, M.; Alcaraz, M. J.; De Rosa, S. *Eur. J. Pharmacol.* **1994**, *253*, 75−82.
(19) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Chahboun, R.; Galera P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2325−2328.
(20) (a) Fenical. W.; Sims, J. J.; Squatrito, D.; Wing, R. M.; Radlick, P. *J. Org. Chem.* **1973**, *38*, 2383−2386. (b) Schröder, J.; Magg, C.; Seifert, K. *Tetrahedron Lett.* **2000**, *41*, 5469−5473.
(21) Crews, P.; Rodríguez, J.; Jaspars, M. *Organic Structure Analysis*; Oxford University Press: Oxford, 1998; pp 87−90.
(22) (a) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Am. Chem. Soc.* **1998**, *120*, 877−882. (b) Seco, J. M.; Quiñoá, E.; Riguera, R. *Tetrahedron Asymmetry* **2001**, *12*, 2915−2925.
(23) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S., Kwong, H.-L., Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771.
(24) (a) Ochi, M.; Kotsuki, H.; Muraoka, K.; Tokoroyama, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 629−630. (b) Laube, T.; Schröder, J.; Stehle, R.; Seifert, K. *Tetrahedron* **2002**, *58*, 4299−4309.
(25) (a) Che, Y.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2002**, *65*, 399−402. (b) Iijima, T.; Yaoita, Y.; Kikuchi, M. *Chem. Pharm. Bull.* **2003**, *51*, 894−896. (c) Watanabe, K.; Sekine, M.; Iguchi, K. *Chem. Pharm. Bull.* **2003**, *51*, 909−913.
(26) Kushlan, D. M.; Faulkner, D. J.; Parkanyi, L.; Clardy, J. *Tetrahedron* **1989**, *45*, 3307−3312.
(27) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107−1112.

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