Three New Diterpenes from the Marine Soft Coral *Lobophytum crassum*[1]

Gesa F. Matthée, Gabriele M. König,* and Anthony D. Wright

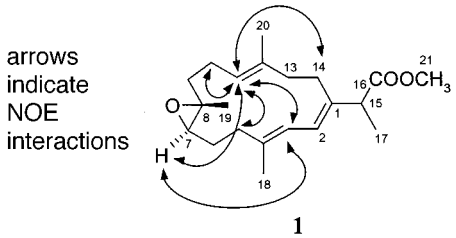
Institute for Pharmaceutical Biology, Technical University of Braunschweig, Mendelssohnstrasse 1, D-38106 Braunschweig, Germany

Received October 8, 1997

Three new terpenoid metabolites (**1**−**3**) were isolated from the CH_2Cl_2 extract of the soft coral *Lobophytum crassum* together with the eudesmane derivative **4** and the known cembrane (2*S*,7*S*,8*S*)-sarcophytoxide (**5**). Compound **1** is a new cembrane-based diterpene with an C7−C8-epoxide and a methyl ester functionality at C-16. (3*E*,5*Z*)- (**2**) and (3*Z*,5*E*)-2-methyl-6-(4a′-methyl-8′-methylene-*trans*-perhydronaphthalen-2′-yl)hepta-3,5-dien-2-ol (**3**) represent two new carbon−carbon double bond isomers of **4**, which has the 3*E*,5*E*-configuration. The structures of **1**−**5** were established by interpretation of their spectroscopic data, mainly 1D and 2D NMR and MS. Biological activity evaluation of compounds **1** and **5** and the crude extracts was carried out using agar diffusion assays toward microbial targets and ELISA assays for investigating the inhibition of HIV-1 reverse transcriptase and $p56^{lck}$ tyrosine kinase.

Soft corals typically contain terpenoid metabolites, mainly sesqui- and diterpenes of the eudesmane and cembranoid type.[2] For several of these natural products biological activities of pharmacological significance are described.[2,3] Terpenes of octocorallian origin were shown to have antiinflammatory, antibacterial, and neuromuscular activities, as summarized by Krebs.[2] Several cembranoids display significant in vitro cytotoxicity toward cultured cancer cell lines;[3] e.g., a highly oxygenated cembrane from *Sinularia* sp., family Alcyoniidae, showed selective cytotoxic effects when tested toward a panel of cell lines.[4] Recently, a cembrane from *Lobophytum cristagalli* (Alcyoniidae) was reported to inhibit Ras farnesyl transferase, a potential therapeutic target for novel anticancer agents.[5] Thus, marine animals of the family Alcyoniidae have proven to be a worthwhile source of natural products for biomedical research.

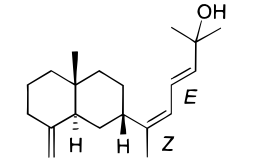
The sample of *Lobophytum crassum* Von Marenzeller 1886 (Alcyoniidae) investigated in the current study was collected from the Great Barrier Reef, Australia. In benchtop assays, both lipophilic (CH_2Cl_2) and hydrophilic ($MeOH/H_2O$) extracts were found to have antimicrobial activity. The current report concentrates on the isolation and structure elucidation of three new natural products that have cembrane (**1**) and eudesmane (**2** and **3**) base structures.



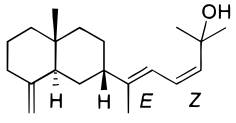
1

Results and Discussion

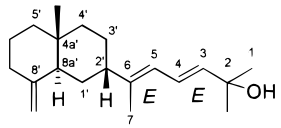
Freeze-dried soft coral material was exhaustively extracted with CH_2Cl_2 followed by MeOH. The MeOH extract was partitioned between water and CH_2Cl_2 and combined with the CH_2Cl_2 extract. These CH_2Cl_2 solubles were fractionated by normal-phase vacuum liquid chromatography (VLC). Chemical screening using ^1H NMR spectroscopy revealed several fractions to contain unsaturated terpenoids. Normal-phase HPLC of those fractions yielded three new compounds **1**−**3** and the known metabolites **4** and **5**.



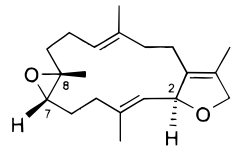
2



3



4



5

The molecular formula of **1**, $C_{21}H_{32}O_3$, was deduced from accurate mass measurement. Significant fragment ions in the mass spectrum were observed at *m*/*z* 300 $[M - CH_3OH]^+$ and 272 $[M - C_2H_4O_2]^+$, indicating the presence of a methyl ester functionality. Proof for a methyl ester within **1** came from ^{13}C NMR resonances at δ 175.3 (s) for the carbonyl carbon, δ 51.8 (q) assigned to the methyl carbon of the ester moiety, and a signal at δ 46.3 (d) attributable to the tertiary carbon atom neighboring the carbonyl group. UV and IR spectra displayed characteristic absorption bands for conjugated carbon−carbon double bonds (λ_{max} 256 nm, log ϵ 4.2) and for a carbonyl (ester) function (λ_{max} 1737 cm^{-1}). The ^{13}C NMR spectrum of **1** also contained three signals for fully substituted olefinic carbon atoms (δ 139.7 (s), 136.6

* To whom correspondence should be addressed. Tel.: +49 531 391 5680. Fax: +49 531 391 8104. E-mail: g.koenig@tu-bs.de. http://www.tu-bs.de/institute/pharm.biol/GAWK.html.

S0163-3864(97)00458-8 CCC: $15.00
Published on Web 02/10/1998

Table 1. ^{1}H NMR (300 MHz, $CDCl_3$) Data for Compounds **1**−**3**

proton	**1**	proton	**2**[a]	**3**
2	6.19 (d, J = 10.9 Hz)	1	1.33 (s)	1.43 (s)
3	5.96 (dq, J = 1.2, 10.9 Hz)	3	5.70 (d, J = 15.1 Hz)	5.49 (d, J = 11.7 Hz)
5	2.25 (m)	4	6.45 (dd, J = 10.9, 15.1 Hz)	6.21 (dd, J = 11.7, 11.7 Hz)
6	1.75 (m)	5	5.74 (d, J = 10.9 Hz)	6.74 (d, J = 11.7 Hz)
7	2.82 (dd, J = 5.3, 5.7 Hz)	7	1.94 (s)	1.74 (s)
9	1.91 (m)	1′	*b*	1.82 (m)
	1.57 (m)			1.60 (m)
10	2.01 (m)	2′	3.17 (m)	2.47 (m)
11	5.06 (brdd, J = 6.4 Hz)	3′	*b*	1.83 (m)
13	2.23 (m)	4′	*b*	1.45 (m)
	1.99 (m)			1.25 (m)
14	2.33 (m)	5′	*b*	1.39 (m)
15	3.20 (q, J = 7.2 Hz)			1.23 (m)
17	1.31 (d, J = 7.2 Hz)	6′	*b*	1.58 (m)
18	1.77 (s)	7′	2.29 (m)	2.28 (m)
19	1.26 (s)		2.00 (m)	1.96 (m)
20	1.58 (s)	8a′	*b*	1.89 (m)
21	3.65 (s)	2-CH_3	1.33 (s)	1.43 (s)
		4a′-CH_3	0.75 (s)	0.78 (s)
		8′-CH_2	4.71 (d, J = 1.5 Hz)	4.70 (d, J = 1.6 Hz)
			4.41 (d, J = 1.5 Hz)	4.43 (d, J = 1.6 Hz)

[a] Assignments based on ^{1}H−^{1}H COSY and comparison with data for **3** and **4**. [b] These protons resonate between δ 1.0 and 1.9. Assignments were not possible as sample decomposed prior to HMQC measurement.

(s), 135.3 (s)), and three for CH olefinic carbon atoms (δ 126.1 (d), 122.9 (d), 121.0 (d)). From these and the ^{1}H NMR data (see Table 1) it was evident that **1** had three trisubstituted carbon−carbon double bonds and a carbonyl group as the only multiple bonds; the molecule was bicyclic. Further functionality was deduced from ^{13}C NMR signals at δ 60.0 (d) and 61.3 (s) originating from oxygenated carbons, possibly an epoxy function. Further, the ^{1}H and ^{13}C NMR spectra of **1** contained distinctive resonances for four methyl groups (δ 1.26 (s), 1.31 (d, J = 7.2 Hz), 1.58 (s), 1.77 (s), 18.1 (q), 16.8 (q), 17.1 (q), 17.2 (q)), a methine group (δ 3.20, H-15 (q, J = 7.2 Hz)) neighboring the methyl doublet with resonance at δ 1.31, and one proton (δ 2.82, H-7 (dd, J = 5.3, 5.7 Hz)) assigned to the epoxide moiety. The downfield shift of the resonance for H-15 (δ 3.20) is consistent with it being allylic and adjacent to an ester group.

A ^{1}H−^{13}C 2D NMR shift correlated measurement (HMQC)[6] of **1** led to the correlation of all proton resonances with the resonances of their directly bonded carbon atoms and enabled two major molecular fragments to be deduced from an ^{1}H−^{1}H COSY spectrum of **1**. The ^{1}H−^{1}H COSY spectrum revealed couplings from H_2-13 (δ 1.99, 2.23 (m)) to H_2-14 (δ 2.33 (m)), from H_2-14 to H-2 (δ 6.19 (d, J = 10.9 Hz)), from H-2 to H-15 (δ 3.20 (d, J = 7.2 Hz) and to H-3 (δ 5.96 (dq, J = 10.9, 1.2 Hz), from H-15 to H_3-17 (δ 1.31 (d, J = 7.2 Hz)), from H-3 to H_3-18 (δ 1.77 (s)) and to H_2-5 (δ 2.25 (m)), from H_2-5 to H_2-6 (δ 1.75 (m)), and from H_2-6 to H-7 (δ 2.82 (dd, J = 5.3, 5.7 Hz)), giving the first major fragment of the molecule, from C-13 to C-7. The second molecular fragment was deduced from cross-peaks in the ^{1}H−^{1}H COSY spectrum between H_2-9 (δ 1.57, 1.91 (m)) and H_2-10 (δ 2.01 (m)), H_2-10 and H-11 (δ 5.06 (brdd, J = 6.4 Hz)), and H-11 and H_3-20 (δ 1.58 (s)). Thus, the C-9−C-12 part of the molecule including the C-20 methyl group was established. ^{1}H−^{13}C long-range NMR (HMBC)[6] measurements revealed couplings between C-8 (δ 60.0) and H_3-19 and H_2-9, between C-7 (δ 61.3) and H_3-19 (δ 1.26 (s)), and between C-9 (δ 36.9) and H_3-19, thus proving the connectivity of the two fragments deduced above to C-7 and C-8 of the epoxide ring and the position of the C-19 methyl group at C-8. Cross peaks between C-12 (δ 135.3) and H_2-13, C-13 (δ 38.2) and H_3-20, and C-12 and H_2-14 indicated the second ring closure to be between C-12 and C-13. Couplings between C-1 (δ 139.7) and H-15 and H_3-17 and between C-16 (δ 175.3) and H-15, H_3-17, and H_3-21 confirmed the substructure of the methyl ester side chain of the molecule. The *E*-configuration of the $\Delta^{1,2}$, $\Delta^{3,4}$, and $\Delta^{11,12}$ double bonds of **1** was established by comparison of its ^{13}C NMR data with reported data[7] and confirmed by NOE measurements.[8] NOE difference measurements also allowed the relative configuration of **1** at C-7 and C-8 to be proposed. Thus, low power irradiation at δ 5.06 (H-11) led to the enhancement of signals for H-3, H_2-5, H-7, H_2-10, and H_2-14. Enhancement of the signals for H-3 and H_2-5 was observed following low-power irradiation at δ 2.82 (H-7). Inspection of a Dreiding model of **1** indicated that these NOE interactions were only possible if the relative configuration at the epoxide moiety was trans (Figure 1). Determination of the absolute stereochemistry at C-7, C-8, and C-15 was not possible on the basis of the reported data.

The sample contained one further cembranoid diterpene (**5**), whose molecular formula was deduced to be $C_{20}H_{30}O_2$. Comparison of its ^{1}H and ^{13}C NMR spectroscopic data and optical rotation with published data proved **5** to be (2*S*,7*S*,8*S*)-sarcophytoxide.[9]

Three further natural products in *L. crassum* could be identified as eudesmane derivatives. Compound **4** analyzed for $C_{20}H_{32}O$ by mass spectrometry. Absorption bands in the UV and IR spectra of **4** were characteristic of conjugated double bonds and hydroxyl functionality (λ_{max} 241 nm, log ϵ 4.5; λ_{max} 3360, 1645, 1375, 1145 cm^{-1}). Comparison of its ^{1}H and ^{13}C NMR spectroscopic data and optical rotation with literature values led to the identification of **4** as (3*E*,5*E*)-2-methyl-6-(4a′-methyl-8′-methylene-*trans*-perhydronaphthalen-2′-yl)hepta-3,5-dien-2-ol.[10]

The molecular formulas of **2** and **3**, $C_{20}H_{32}O$, were both established from accurate mass measurements.

Table 2. ^{13}C NMR (75.5 MHz, $CDCl_3$) Data[a] for Compounds **1**−**3**

carbon	**1**	carbon	**2**[b]	**3**
1	139.7 s	1	29.9 q	31.4 q
2	122.9 d	2	71.0 s	71.8 s
3	121.0 d	3	139.3 d	135.8 d
4	136.6 s	4	125.1 d	125.2 d
5	35.9 t	5	122.6 d	120.2 d
6	25.7 t	6	145.0 s	142.0 s
7	61.3 d	7	24.8 q	16.0 q
8	60.0 s	1′	28.9 t[c]	26.1 t
9	36.9 t	2′	40.7 d	40.7 d
10	22.3 t	3′	23.5 t[c]	23.4 t
11	126.1 d	4′	37.2 t[c]	36.9 t
12	135.3 s	4a′	35.5 s	36.4 s
13	38.2 t	5′	42.6 t	42.3 t
14	29.0 t	6′	24.7 t[c]	23.5 t
15	46.3 d	7′	38.3 t[c]	37.1 t
16	175.3 s	8′	150.0 s	151.2 s
17	16.8 q	8a′	45.3 d	44.3 d
18	17.2 q	2-CH_3	29.9 q	31.4 q
19	18.1 q	4a′-CH_3	15.9 q	16.0 q
20	17.1 q	8′-CH_2	105.5 t	105.1 t
21	51.8 q			

[a] Multiplicity by DEPT, s = C, d = CH, t = CH_2, q = CH_3. [b] Assignments based on $^1H-^1H$ COSY and comparison with data for **3** and **4.** [c] Assignments are tentative as sample decomposed prior to HMQC measurement.

Similar significant fragment ions in the mass spectrum (*m*/*z* 288 [M^+], 273, 270, 255, 189, 161, 147), comparable absorption bands in the UV (λ_{max} = 241 (**2**) and 243 nm (**3**)) and IR (ν 3400 (**2**) and 3415 (**3**), 2925, 1455, 1375 cm^{-1}) spectra, and similar shifts in the ^1H and ^{13}C NMR spectra (Tables 1 and 2) indicated **2** and **3** to be stereoisomers. Further examination of their spectroscopic data also indicated them to be isomers of **4**. All three compounds differed only with respect to the $\Delta^{3,4}$ and $\Delta^{5,6}$ double bond configurations as evidenced by the signals in the region δ 5.4−6.8 of their ^1H NMR spectra. For each compound the geometry of the $\Delta^{3,4}$ double bond was established by interpretation of the $^3J_{3,4}$ coupling constants and at the $\Delta^{5,6}$ double bond from the ^{13}C NMR shift of the C-7 methyl group.[11] Thus, it was concluded that compound **2**, with $^3J_{3,4}$ = 15.1 Hz and C-7 resonating at δ 24.8, was the 3*E*,5*Z*-isomer and compound **3**, displaying $^3J_{3,4}$ = 11.7 Hz and C-7 resonating at δ 16.0, had the 3*Z*,5*Z*-configuration, with the known compound **4** of 3*E*,5*E*-configuration having $^3J_{3,4}$ = 15.3 Hz and C-7 resonating at δ 16.7.

Compounds **2**−**4** were extremely unstable, probably due to the facile loss of water and subsequent polymerization as has already been described for compound **4**.[10]

Biological Activity. CH_2Cl_2 and MeOH extracts of *L. crassum* were found to inhibit the growth of *Escherichia coli* and *Bacillus megaterius* in an agar diffusion assay.[12] After isolation, (2*S*,7*S*,8*S*)-sarcophytoxide (**5**) inhibited the growth of the microalgae *Chlorella fusca* (50 μg/3 mm) and of the fungus *Ustilago violacea* (50 μg/3 mm), and compound **1** inhibited the growth of *Ustilago violacea* (50 μg/1 mm). Compounds **2**−**4** decomposed prior to further biological evaluation. In enzyme inhibition assays neither extracts nor pure compounds were found to be active against ^{p56}lck tyrosine kinase or against HIV-1 reverse transcriptase.

Compound **1** and (2*S*,7*S*,8*S*)-sarcophytoxide (**5**) show weak antifungal activity toward only one, *Ustilago violacea*, of three tested fungal species. Antialgal activity in the agar plate diffusion assay can be observed for (2*S*,7*S*,8*S*)-sarcophytoxide (**5**) but not for the cembranoid **1**. Literature data describe ecologically relevant antialgal activity for compound **4**,[13] a sarcophytoxide-derivative, whose absolute stereochemistry is not clearly described, and other structurally related cembranes.[14] From these data a high degree of algal growth inhibition of cembranes seems to depend on the presence of a five-membered dihydrofuran moiety and an epoxide group in the molecule, as seen in **5**. The lack of activity of compound **1**, which bears only an epoxide functionality, is thus consistent with the above suggested structure−activity relationships for antialgal activity of cembranes.

Cembranes represent a large group of natural products with many structural variations, including further cyclizations and a multitude of functionalizations, e.g., lactones, epoxides, furans, esters, ethers, hydroxyl, aldehyde, and carboxylic moieties. Surprisingly, only a few cembranoid diterpenes exist with a methyl ester function, examples being sarcodictyin derivatives from *Sarcodictyon roseum*, a Mediterranean stolonifer, a briarane-type compound from *Stylatula* sp., (Pennatulaceae),[15] and a cembrane, closely related to compound **1**, from *Sinularia mayi*, an Okinawan soft coral.[7]

Experimental Section

General Experimental Procedures. For details see ref 16.

Animal Material. The soft coral samples were collected at low tide from a large rock on Magnetic Island. The soft coral was identified as *L. crassum* Von Marenzeller 1886 (Alcyoniidae) by Dr. Phil Alderslade, Museum and Art Galleries of the Northern Territory, Darwin, Australia, where a voucher specimen has been deposited, voucher no. NTM C 12523.

Extraction and Isolation. Frozen soft coral tissue was freeze-dried (150 g) and extracted with CH_2Cl_2 (3 × 0.6 L), followed by MeOH (3 × 0.6 L), to give 7.3 g of brown oil (CH_2Cl_2 extract) and 15.0 g of green gum (MeOH extract). The MeOH extract was partitioned between H_2O (0.2 L) and CH_2Cl_2 (3 × 0.2 L), and the CH_2Cl_2 phase was combined with the CH_2Cl_2 extract to yield the CH_2Cl_2 solubles (8.2 g, 5.5%). This material was fractionated by normal-phase VLC (gradient elution hexane/EtOAc/MeOH) to yield 13 fractions each of 80 mL. Three VLC fractions were further investigated and purified by normal-phase HPLC. Fraction 7 (EtOAc/hexane 3%) gave compounds **1** (10 mg) and **3** (15 mg). Purification of fraction 8 (EtOAc/hexane 8%) gave compounds **2** (10 mg) and **4** (>100 mg). Fraction 9 was purified (EtOAc/hexane 9%) to give (2*S*,7*S*,8*S*)-sarcophytoxide (**5**) (350 mg).

Compound 1: obtained as a clear oil (10 mg, 0.007%); $[\alpha]_D$ +56° (*c* 0.008, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 256 nm (4.2); IR (film) λ_{max} 2925, 1735, 1450, 1435, 1240, 1195, 1170, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) see Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) see Table 2; EIMS *m*/*z* 332 [M^+] (12), 300 (4), 272 (4), 245 (12), 121 (100); HREIMS *m*/*z* 332.2365 (calcd for $C_{21}H_{32}O_3$, 332.2352).

Compound 2 [(3*E*,5*Z*)-2-methyl-6-(4a′-methyl-8′-methylene-*trans*-perhydronaphthalen-2′-yl)hepta-3,5-dien-2-ol]: isolated as a clear oil (10 mg, 0.007%); $[\alpha]_D$ +51° (*c* 0.00041, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 241 nm (4.5); IR (film) ν_{max} 3400, 2925, 1455, 1375, 1235

cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) see Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) see Table 2; EIMS *m/z* 288 [M^+] (45), 273 (5), 270 (17), 255 (16), 189 (92), 162 (100), 161 (26), 147 (70), 123 (68); HREIMS *m/z* 288.245 (calcd for $C_{20}H_{32}O$, 288.2453).

Compound 3 [(3*Z*,5*E*)-2-methyl-6-(4a′-methyl-8′-methylene-*trans*-perhydronaphthalen-2′-yl)hepta-3,5-dien-2-ol]: isolated as a clear oil (15 mg, 0.01%); $[\alpha]_D$ +70° (*c* 0.0014, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 243 nm (4.1); IR (film) ν_{max} 3415, 2925, 1645, 1440, 1375, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) see Table 1; ^{13}C NMR (75.5 MHz, $CDCl_3$) see Table 2; EIMS *m/z* 288 [M^+] (12), 273 (3), 270 (17), 255 (9), 189 (18), 173 (8), 161 (19), 147 (17), 125 (100); HREIMS *m/z* 288.2448 (calcd for $C_{20}H_{32}O$, 288.2453).

Compound 4 [(3*E*,5*E*)-2-methyl-6-(4a′-methyl-8′-methylene-*trans*-perhydronaphthalen-2′-yl)hepta-3,5-dien-2-ol]: obtained as a clear oil (>100 mg, 0.07%); $[\alpha]_D$ +102° (*c* 0.009, $CHCl_3$); all other data as previously published.[10]

(2*S*,7*S*,8*S*)-(+)-Sarcophytoxide (5): obtained as white needles (350 mg, 0.23%); mp 83 °C (lit.[17] mp 79−81 °C); $[\alpha]_D$ −172° (*c* 0.003, $CHCl_3$) (lit.[17] $[\alpha]_D$ −191° (*c* 0.4, $CHCl_3$)); all other data as previously published.[9]

Acknowledgment. We thank Dr. Phil Alderslade, Museum and Art Galleries of the Northern Territory, Darwin, Australia, for taxonomic classification of the soft coral, Dr. Victor Vray and his group, GBF, Braunschweig, for recording all NMR spectra, Dr. Ruprecht Christ, GBF, Braunschweig, and Dr. Hans-Martin Schiebel, Department of Chemistry, Technical University of Braunschweig, for making mass spectral measurements. Financial Support of the Deutsche Forschungsgemeinschaft (Ko 902/2-2) is gratefully acknowledged.

References and Notes

(1) Presented at the 9. Frühjahrstagung der DPhG für den wissenschaftlichen Nachwuchs, Würzburg, Germany, March 13−16, 1997, Poster P50.
(2) Krebs, H. Chr. *Prog. Chem. Org. Nat. Prod.* **1986**, *49*, 152−363.
(3) Rodriguez, A. D.; Piña, I. C.; Barnes, C. L. *J. Org. Chem.* **1995**, *60*, 8096−8100.
(4) König, G. M.; Wright, A. D.; Sticher, O.; Angerhofer, C. K.; Pezzuto, J. M. *Planta Med.* **1994**, *60*, 532−537.
(5) Coval, S. J.; Patton, R. W.; Petrin, J. M.; James, L.; Rothofsky, M. L.; Lin, S. L.; Patel, M.; Reed, J. K.; McPhail, A. T.; Bishop, W. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 909−912.
(6) König, G. M.; Wright, A. D. *Phytochem. Anal.* **1997**, *8*, 167−172 and references therein.
(7) Kusumi, T.; Yamada, K.; Ishitsuka, M. O.; Fujita, Y.; Kakisawa, H. *Chem. Lett.* **1990**, 1315−1318.
(8) Neuhaus, D.; Williamson, M. P. *The nuclear Overhauser effect in structural and conformational analysis*; VCH: New York, Weinheim, Cambridge, 1989; and references therein.
(9) Bowden, B. F.; Coll, J. C.; Heaton, A.; König, G.; Bruck, M. A.; Cramer, R. E.; Klein, D. M.; Scheuer, P. J. *J. Nat. Prod.* **1987**, *50*, 650−659.
(10) Bowden, B. F.; Coll, J. C.; Liyanage, N.; Mitchell, S. J.; Stokie, G. J.; Van Altena, I. A. *Aust. J. Chem.* **1978**, *31*, 163−170.
(11) Couperus, P. A.; Clague, A. D. H.; van Dongen, J. P. C. M. *Org. Magn. Reson.* **1976**, *8*, 426−431.
(12) Schulz, B.; Sucker, J.; Aust, H. J.; Krohn, K.; Ludewig, K.; Jones, P. G.; Döring, D. *Mycol. Res.* **1995**, *99*, 1007−1015.
(13) Coll, J. C.; Bowden, B. F.; König, G. M.; Braslau, R.; Price, I. R. *Bull. Soc. Chim. Belg.* **1986**, *95*, 815−834.
(14) Coll, J. C.; Price, I. R.; König, G. M.; Bowden, B. F. *Mar. Biol.* **1987**, *96*, 129−135.
(15) Wahlberg, I.; Eklund, A.-M. *Prog. Chem. Org. Nat. Prod.* **1992**, *60*, 1−141.
(16) Wright, A. D.; König, G. M.; Angerhofer, C. K.; Greenidge, P.; Linden, A.; Desqueyroux-Faundez, R. *J. Nat. Prod.* **1996**, *59*, 710−716.
(17) Bowden, B. F.; Coll, J. C.; Hicks, W.; Kazlauskas, R.; Mitchell, S. J. *Aust. J. Chem.* **1978**, *31*, 2707−2712.

NP970458N