Ten-Membered Lactones from the Marine-Derived Fungus *Curvularia* sp.

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Investigation of the secondary metabolites of the marine-derived fungus *Curvularia* sp. yielded four new 10-membered lactones (**1**−**4**), along with the known modiolide A (**5**). The structures of **1**−**4** were characterized on the basis of spectroscopic and MS data and resemble known 10-membered lactones, but feature modified oxidation patterns around their macrocycles.

Marine-derived fungi have been proven to be a rich source of chemically diverse natural products with a broad range of biological activities.[1] In our search for new secondary metabolites, we have focused on endophytic and algicolous fungi, which reside inside the tissue of marine algae.[2] In the current study, four new 10-membered lactones (**1**−**4**), besides the known metabolite modiolide A (**5**), were obtained from an isolate of *Curvularia* sp. (strain no. 768), which was associated with a red alga. The structures of the new macrolides **1**−**4** are similar to described 10-membered lactones, e.g., modiolide A (**5**),[3] pyrenolide A,[4] decarestrictines A_1/A_2,[5] stagonolide D,[6] and botryolide A,[7] but differ concerning the oxidation pattern of the macrocycle. Details of the isolation and structure elucidation of these metabolites are presented here.

The fungal strain *Curvularia* sp. (strain no. 768) was isolated from the red alga *Acanthophora spicifera* collected at Fingers Reef, Apra Harbor, Guam. After cultivation on solid biomalt medium containing artificial seawater, the obtained EtOAc crude extract was fractionated via normal-phase VLC and HPLC, giving four new 10-membered lactones (**1**−**4**), along with the known modiolide A (**5**) (Scheme 1).[3]

The elemental composition of **1** was established by HRESIMS as $C_{10}H_{14}O_4$, implying four elements of unsaturation. IR absorption bands at 3411 and 1709 cm^{-1} revealed the presence of a free hydroxy and a carbonyl group, respectively. The ^{13}C NMR spectrum of **1** (Table 1) disclosed an ester carbonyl (δ_C 165.3), two sp^2 methines (δ_C 125.5, and 143.0), four oxymethines (δ_C 56.7, 64.9, 76.1, and 74.7), two methylene groups (δ_C 34.1, and 33.2), and one methyl group (δ_C 21.0). Taking these results together, database and literature searches led to the 10-membered lactones decarestrictines A_1 and A_2,[5,8] which both differ significantly from **1** in their ^{13}C NMR chemical shifts. Therefore, interpretation of the 1D and 2D NMR spectra of **1** was undertaken. In this manner, all protons were assigned to their directly bonded carbon atoms via analysis of the $^1H-^{13}C$ HSQC spectrum, and subsequently the $^1H-^1H$ COSY spectrum provided evidence for connectivities from CH-2 through to CH_3-10 (Figure 1). The geometry of its Δ^2 double bond was assigned as *Z*, on the basis of the $^1H-^1H$ coupling constant $^3J_{H2-H3} = 11.0$ Hz. Furthermore, the ester carbonyl group was found to be linked to C-2, due to the observed HMBC correlation between H-2 and C-1 (Figure 1). The position of the expected free hydroxy group was inferred from the observed $^1H-^1H$ COSY correlation between the hydroxy proton (δ_H 4.12) and H-6 (δ_H 3.20), which was confirmed by HMBC correlations from the hydroxy proton (δ_H 4.12) to C-5, C-6, and C-7 (Figure 1). At this stage of the structural analysis, the two remaining elements of unsaturation had to be taken care of. The ^1H and ^{13}C NMR chemical shifts, as well as the $^1H-^1H$ coupling constants of the adjacent methines CH-4 (δ_C 56.7, δ_H 3.64) and CH-5 (δ_C 64.9, δ_H 2.60), were consistent with a 1,2-disubstituted *trans* epoxide unit ($^3J_{H4-H5} = 2.2$ Hz).[7,9,10] Furthermore, the relatively low field resonance of H-9 (δ_H 4.71) indicated that C-9 is involved in the expected ester-type connection to C-1 according to similar reported 10-membered lactones of fungal origin.[3−7] Thus, compound **1** is a 10-membered macrolide, which resembles decarestrictines A_1 and A_2,[5] but with an altered oxidation pattern. Due to the high flexibility of the 10-membered macrolactone core, interpretation of the observed NOEs did not yield the relative configuration of **1**, and the configuration at C-6 remains unresolved. However, a characteristic Cotton effect attributable to the n−π* transition band of the lactone with a maximum at 208 nm was observed in the CD spectrum of **1** that corresponded well with the obtained Cotton effect of modiolide A (**5**) with a maximum at 216 nm.[11] Comparison of the CD spectrum

Scheme 1. Compounds **1**−**5** Isolated from *Curvularia* sp. and the Closely Related 10-Membered Lactone Pyrenolide A[4]

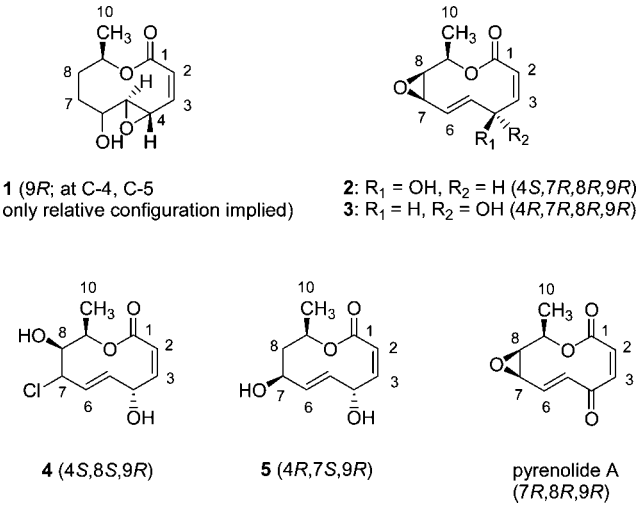

Table 1. ^{13}C NMR Data for **1**−**4** in Acetone-d_6 (δ in ppm)

no.	1	2	3	4
1	165.3, qC	167.5, qC	168.5, qC	168.1, qC
2	125.5, CH	125.5, CH	121.8, CH	121.9, CH
3	143.0, CH	135.2, CH	139.0, CH	138.3, CH
4	56.7, CH	66.8, CH	71.9, CH	71.9, CH
5	64.9, CH	133.0, CH	134.1, CH	130.9, CH
6	76.1, CH	120.5, CH	131.0, CH	129.5, CH
7	34.1, CH_2	56.2, CH	55.8, CH	60.9, CH
8	33.2, CH_2	56.8, CH	56.5, CH	76.0, CH
9	74.7, CH	66.2, CH	68.2, CH	68.0, CH
10	21.0, CH_3	18.6, CH_3	16.0, CH_3	17.4, CH_3

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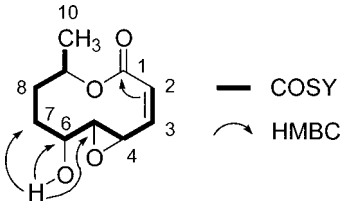

Figure 1. ^{1}H−^{1}H COSY and selected HMBC correlations of **1**.

of **1** with that of the described 10-membered lactone modiolide A (**5**) thus indicated the absolute configuration at the stereogenic center adjacent to the lactone moiety to be 9*R*.[3] Curvulide A is proposed as the trivial name for **1**.

The epimeric compounds **2** and **3** were isolated as a 4:3 mixture (**2** and **3**, respectively), which could not be separated using normal-phase or reversed-phase HPLC techniques. From the ^{1}H NMR spectrum it became apparent that **2** and **3** are of diastereomeric nature. Considerations that the mixture is composed of two conformers could be excluded due to the applied high- and low-temperature ^{1}H NMR experiments (up to +55 °C and −35 °C, respectively), which did not give rise to any changes of the respective proton resonance signals. The structural elucidation of both compounds from the mixture was possible because of the well-separated resonance signals observed in the ^{1}H and ^{13}C NMR spectra (see Supporting Information). The molecular formula of **2** and **3** was determined by high-resolution EIMS as $C_{10}H_{12}O_4$, suggesting an additional olefinic double bond in comparison to compound **1**, which was supported by their ^{1}H and ^{13}C NMR data (Tables 1, 2). After assignment of all protons to their directly attached carbon atoms via 2D HSQC, the spin systems of **2** and **3** from CH-2 to CH_3-10 could be deduced from the ^{1}H−^{1}H COSY spectrum. HMBC correlations from both H-2 and H-9 to C-1 clearly delineated the gross structures of **2** and **3** as 10-membered lactones with a modified oxidation pattern compared to **1** (Scheme 1). In the case of **2** and **3**, the free hydroxy group was linked to C-4, and the 1,2-disubstituted epoxide moiety appeared to be located at C-7 and C-8, this time consistent with a *cis* configuration ($^3J_{H7-H8}$ = 4.4 and 4.0 Hz, respectively).[4−7] The geometry of the additional Δ^5 double bond in **2** and **3** has been established from the ^{1}H−^{1}H coupling constants as 5*E* ($^3J_{H5-H6}$ = 15.8 and 17.2 Hz, respectively). Compounds **2** and **3** are thus diastereomers of 7,8-epoxy-4-hydroxy-2*Z*,5*E*-decadien-9-olide, and curvulides B_1 and B_2 are proposed as trivial names, respectively.

The relative configuration at C-7, C-8, and C-9 of both **2** and **3** was proposed to be identical to that of the closely related lactone pyrenolide A,[4] on the basis of comparisons of the respective ^{1}H−^{1}H coupling constants (**2**: $^3J_{H6-H7}$ = 4.0 Hz, $^3J_{H7-H8}$ = 4.4 Hz, $^3J_{H8-H9}$ = 1.1 Hz; **3**: $^3J_{H6-H7}$ = 4.7 Hz, $^3J_{H7-H8}$ = 4.0 Hz, $^3J_{H8-H9}$ = 4.0 Hz; pyrenolide A: $^3J_{H6-H7}$ = 6.0 Hz, $^3J_{H7-H8}$ = 4.5 Hz, $^3J_{H8-H9}$ = 2.0 Hz) (Figure S1, Supporting Information). An observed strong positive Cotton effect at 217 nm in the CD spectrum of the mixture suggested the (9*R*) absolute configuration of **2** and **3**, and hence the (7*R*,8*R*) absolute configuration of both compounds **2** and **3**. Owing to the remarkable changes in the ^{1}H−^{1}H coupling constants of H-4, we assume that the only difference between **2** and **3** is the different orientation of the hydroxy group at C-4. The $^3J_{H4-H5}$ coupling constant of 7.3 Hz and the ^{13}C NMR shifts for C-3 (δ_C 139.0) and C-4 (δ_C 71.9) of **3** agree with the respective values found for the closely related lactone modiolide A (**5**) ($^3J_{H4-H5}$ = 7.3 Hz; C-3, δ_C 138.7; C-4, δ_C 73.0), in contrast to the observed small $^3J_{H4-H5}$ coupling constant of 2.9 Hz found for **2** and the differing ^{13}C NMR shifts for the corresponding positions (C-3, δ_C 135.2; C-4, δ_C 66.8).[3] Taking these results and a similar conformation of **2**, **3**, and modiolide A (**5**) into account, the hydroxy group at C-4 in **3** is most likely α-orientated and in **2** β-orientated; thus the proposed absolute configuration for **2** is 4*S*,7*R*,8*R*,9*R* and for **3** 4*R*,7*R*,8*R*,9*R* (Figure S1, Supporting Information).

The planar structure of compound **4** was elucidated on the basis of MS and NMR data analysis. Interpretation of the LRESIMS spectrum revealed the presence of one chlorine atom, due to the observed characteristic isotope patterns in a ratio of 3:1 [*m*/*z* 250, 252 in a ratio of 3:1 $(M + NH_4)^+$; 291, 293 in a ratio of 3:1 $(M + CH_3COO)^-$], and the elemental composition of **4** was established to be $C_{10}H_{13}ClO_4$ on the basis of HREIMS measurements. We consider the chlorination at position C-7 to be the result of a nucleophilic substitution at the epoxide of **3** during extract workup with the solvent dichloromethane. The absolute configuration at C-9 was assigned as *R*, inferred from the CD spectrum. Taking the discussed mechanism of reaction into account, the absolute configuration at C-4 and C-8 is most likely identical to that found in **3**, but remains unresolved at position C-7, because it is not possible to predict the mode of the nucleophilic attack, i.e., S_N1 or S_N2.[12] Therefore, the absolute configuration of **4** is best described as (4*S*,8*S*,9*R*).

The structure of modiolide A (**5**) was identified by comparing its NMR data and specific rotation with published values.[3] The recorded CD spectrum of **5** displayed a positive Cotton effect at 216 nm attributable to the n−π* transition band of the lactone and was helpful to deduce the absolute configuration of **1**−**4** at the lactone-bearing stereogenic center C-9.[11]

Ten-membered lactones, similar to **1**−**4**, were shown to be polyketides[13,14] and have been described with diverse oxidation patterns on the macrocycle, e.g., aspinolides,[14] diplodialides,[15] cephalosporolides,[16] and multiplolides,[17] as well as the above-mentioned modiolides,[3] pyrenolides,[4] decarestrictines,[5] stagonolides,[6] and botryolides.[7] Owing to the conformational flexibility of the 10-membered ring of **1**−**4**, the relative configuration of these structures is not accessible via interpretation of NOEs. Therefore, the stereochemical assignments of the new lactones **1**−**4** were proposed on the basis of ^{1}H NMR *J* values and CD data in comparison to structurally closely related macrolides. The appearance of diastereomeric mixtures such as **2** and **3** has already been reported for mixtures of the related 9-decenolides decarestrictines A_1/A_2 and C_1/C_2, which also differ among each other concerning the orientation of hydroxy substituents.[5]

Compounds **2/3**, **4**, and **5** were evaluated in antibacterial (*Escherichia coli*, *Bacillus megaterium*), antifungal (*Mycotypha microspora*, *Eurotium rubrum*, and *Microbotryum violaceum*), and antialgal (*Chlorella fusca*) assays at the 50 μg/disk level, but did not show any activities.[18] However, stagonolide was reported to be highly phytotoxic,[6] and decarestrictines A−D were patented for their cholesterol biosynthesis inhibitory properties.[5,19]

Experimental Section

General Experimental Procedures. Optical rotation was measured on a JASCO DIP 140 polarimeter. UV and IR spectra were obtained employing Perkin-Elmer Lambda 40 and Perkin-Elmer Spectrum BX instruments, respectively. CD spectra were recorded in CH_3CN at room temperature with a JASCO J-810-150S spectropolarimeter; the path length was d = 0.1 cm. ^{1}H, ^{13}C, COSY, NOESY, HSQC, and HMBC NMR spectra were recorded in acetone-d_6 (**1**−**4**) or methanol-d_4 (**5**) using a Bruker Avance 300 DPX spectrometer operating at 300 MHz for proton and at 75 MHz for ^{13}C. Spectra were referenced to the residual solvent signal of acetone-d_6 and methanol-d_4 with resonances at $\delta_{H/C}$ 2.04/29.8 and 3.35/49.0, respectively. LRESIMS measurements were performed employing an API 2000, triple quadrupole LC/MS/MS, Applied Biosystems/MDS Sciex, and ESI source. HREIMS was recorded on a Finnigan MAT 95 spectrometer, and HRESIMS on a Bruker Daltonik micrOTOF-Q time-of-flight mass spectrometer with ESI source. Preparative HPLC was carried out using a Waters 515 HPLC pump and a Knauer K-2300 differential refractometer as detector.

Isolation and Taxonomy of the Fungal Strain. The red algae *Acanthophora spicifera* was collected in 2−4 m depth by snorkelling at Fingers Reef, Apra Harbor, Guam. After surface sterilization of the algae with 70% EtOH, algal samples were rinsed with sterile H_2O and pressed onto biomalt agar plates to detect the presence of any fungal spores on the surface of algae. Sterilized algae were then cut into pieces

Table 2. ^{1}H NMR Data for **1**−**4** in Acetone-d_6 (δ in ppm, mult., J in Hz)

no.	1	2	3	4
2	5.90 (dd, 1.8, 11.0, 1H)	5.87 (d, 12.0, 1H)[a,b]	5.79 (dd, 1.4, 12.4, 1H)	5.80 (dd, 1.1, 12.4, 1H)[a,b]
3	6.52 (dd, 1.5, 11.0, 1H)	6.01 (dd, 5.9, 12.0, 1H)[a]	5.84 (dd, 2.2, 12.4, 1H)	5.86 (dd, 2.2, 12.4, 1H)[a]
4	3.64 (m, 1H)	4.71 (m, 1H)	4.80 (br t, 6.2, 1H)	4.82 (br t, 7.0, 1H)
5	2.60 (dd, 2.2, 8.4, 1H)	5.95 (dd, 2.9, 15.8, 1H)[a,b]	5.69 (dd, 7.3, 17.2, 1H)	5.86 (ddd, 1.8, 8.0, 15.8, 1H)[a,b]
6	3.20 (m, 1H)	5.86 (dd, 4.0, 15.8, 1H)[a,b]	5.51 (dd, 4.7, 17.2, 1H)	6.25 (dd, 3.3, 15.8, 1H)
7	1.67 (m, 1H)[a] 2.03 (m, 1H)	3.57 (m, 1H)	3.71 (br t, 4.5, 1H)	4.75 (m, 1H)
8	1.67 (m, 1H)[a] 1.94 (m, 1H)	2.98 (dd, 1.1, 4.4, 1H)	3.19 (t, 4.0, 1H)	3.82 (br t, 5.8, 1H)
9	4.71 (m, 1H)	5.38 (dq, 1.1, 7.0, 1H)	5.21 (dq, 4.0, 7.0, 1H)	5.56 (br q, 6.6, 1H)
10	1.25 (d, 6.2, 3H)	1.42 (d, 7.0, 3H)	1.31 (d, 7.0, 3H)	1.23 (d, 6.6, 3H)
OH	4.12 (d, 3.0, 1H)	4.25 (d, 5.5, 1H)	4.51 (d, 5.5, 1H)	4.47 (d, 5.8, 1H)
OH				5.03 (d, 6.8, 1H)

[a] Overlapping signals. [b] ^{1}H−^{1}H coupling constants J were partly determined from HSQC and HMBC.

and placed on agar plates containing isolation medium: 15 g/L agar, artificial seawater, benzyl penicillin (250 mg/L), and streptomycin sulfate (250 mg/L). Fungal colonies growing out of the algal tissue were transferred to medium for sporulation (15 g/L agar, 20 g/L biomalt extract, artificial seawater). The fungal strain was identified as *Curvularia* sp. by the Centraalbureau voor Schimmelcultures, Utrecht, The Netherlands.

Cultivation. The fungal strain (strain number 768, culture collection of Institute for Pharmaceutical Biology, University of Bonn, Germany) was cultivated at room temperature for seven weeks in 38 Fernbach flasks (250 mL each). The solid biomalt medium contained 20 g/L of Biomalt (Villa Natura Gesundheitsprodukte GmbH, Germany), 15 g/L agar (Fluka Chemie AG), and artificial seawater [(g/L): KBr (0.1), NaCl (23.48), $MgCl_2$ $6H_2O$ (10.61), $CaCl_2$ $2H_2O$ (1.47), KCl (0.66), $SrCl_2$ $6H_2O$ (0.04), Na_2SO_4 (3.92), $NaHCO_3$ (0.19), H_3BO_3 (0.03)].

Extraction and Isolation. Cultivation medium (9.5 L) and mycelia were extracted with EtOAc (3 × 5 L) after being homogenized using an Ultra Turrax. The EtOAc crude extract (3.55 g, reddish, oily) was fractionated via normal-phase VLC (silica gel 60, 0.063−0.200 mm, Merck, Darmstadt, Germany) with a CH_2Cl_2−EtOAc−MeOH gradient in 10 steps to yield 10 fractions. Fraction 4 was separated by normal-phase HPLC (column: Knauer, Eurospher-100-Si, 5 μm, 250 × 8 mm; petroleum ether/acetone, 80:20; 2 mL/min) to obtain pure compound **4** (4.9 mg) and a mixture of **1**, **2**, and **3**. Required purification was performed via normal-phase HPLC (column: Knauer, Eurospher-100-Si, 5 μm, 250 × 4 mm; petroleum ether/acetone, 91:9; 1 mL/min) to yield pure compound **1** (1.9 mg) and a mixture of **2** and **3** (9.3 mg), which could not be separated by HPLC techniques. VLC fraction 6 was separated by normal-phase HPLC (column: Knauer, Eurospher-100-Si, 5 μm, 250 × 8 mm; petroleum ether/acetone, 75:25; 2 mL/min) to afford pure compound **5** (24.3 mg).

Curvulide A (1): colorless, amorphous solid (1.9 mg, 0.05%), $[\alpha]_D^{23}$ +133 (*c* 0.08, MeOH); UV λ_{max} (MeOH)/nm 205 (ε 5450); CD (*c* 5.0 × 10^{-3} mol/L, CH_3CN)/nm $\Delta\varepsilon$ = 208 (+7.83); IR (ATR) ν_{max} 3411 (br), 2936, 1709 cm^{-1}; ^{1}H and ^{13}C NMR data (see Tables 1 and 2); LRESIMS *m/z* 181 $(M - H_2O + H)^+$, 199 $(M + H)^+$, 216 $(M + NH_4)^+$; HRESIMS calcd for $C_{10}H_{14}NaO_4$ $(M + Na)^+$ *m/z* 221.0790, found *m/z* 221.0784.

Curvulides B_1/B_2 (2/3): mixture in a ratio of 4:3 (**2** and **3**, respectively); colorless, amorphous solid (9.3 mg, 0.26%), $[\alpha]_D^{22}$ −29 (*c* 0.15, acetone); UV λ_{max} (EtOH)/nm 204 (ε 6183); CD (*c* 2.5 × 10^{-3} mol/L, CH_3CN)/nm $\Delta\varepsilon$ = 217 (+4.65), IR (ATR) ν_{max} 3417 (br), 2983, 1722 cm^{-1}; ^{1}H and ^{13}C NMR data (see Tables 1 and 2); LRESIMS *m/z* 179 $(M - H_2O + H)^+$, 197 $(M + H)^+$, 214 $(M + NH_4)^+$; HREIMS calcd for $C_{10}H_{11}O_3$ $(M - OH)^+$ *m/z* 179.0708, found *m/z* 179.0707.

Compound 4: colorless, amorphous solid (4.9 mg, 0.14%), $[\alpha]_D^{20}$ +12 (*c* 0.2, acetone); UV λ_{max} (MeOH)/nm 206 (ε 3936); CD (*c* 2.2 × 10^{-3} mol/L, CH_3CN)/nm $\Delta\varepsilon$ = 218 (+2.86); IR (ATR) ν_{max} 3358 (br), 2932, 1699 cm^{-1}; ^{1}H and ^{13}C NMR data (see Tables 1 and 2); LRESIMS *m/z* 250, 252 in the ratio 3:1 $(M + NH_4)^+$, 291, 293 in the ratio 3:1 $(M + CH_3COO)^-$; HREIMS calcd for $C_{10}H_{13}ClO_4$ (M^+) *m/z* 232.0502, found *m/z* 232.0505.

Modiolide A (5): colorless, amorphous solid (24.3 mg, 0.68%), NMR and MS data as well as the specific rotation ($[\alpha]_D^{20}$ +38 (*c* 0.5, MeOH); lit. $[\alpha]_D^{18}$ +42 (*c* 0.25, MeOH)) matches the previously published data;[3] CD (*c* 2.5 × 10^{-3} mol/L, CH_3CN)/nm $\Delta\varepsilon$ = 216 (+3.71).

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Supporting Information Available: NMR and CD spectra of **1**−**5** and Figure S1, showing selected $^3J_{H-H}$ values of **2** and **3**. This information is available free of charge via the Internet at http://pubs.acs.org.

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