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Drimane Sesquiterpenoids from the Fungus *Aspergillus ustus* Isolated from the Marine Sponge *Suberites domuncula*

ARTICLE *in* JOURNAL OF NATURAL PRODUCTS · SEPTEMBER 2009

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Table 1. ^1H NMR Data (600 MHz, $\text{DMSO}-d_6$) for **1–9**, δ in ppm, J in Hz

position	1	2	3	6	7	8 ^a	9 ^b
1 α	1.97 ^c	1.67 t (12.2)	1.15 t (12.0)	1.85 d (12.9)	1.71 m	1.81 d (13.4)	1.82 d (13.7)
1 β	1.43 m	1.71 ddd (12.2, 5.1, 1.5)	2.12 ddd (12.0, 5.1, 1.5)	1.97 dd (13.6, 4.1)	2.11 m	1.93 dd (13.6, 4.4)	1.95 dd (13.7, 4.0)
2 α	1.50–1.60 ^c			1.61 m	1.61 m	1.56 m	1.60 d (13.6)
2 β	1.50–1.60 ^c	3.70 m	3.66 m	1.48 m	1.44 m	1.46 br d (12.5)	1.46 d (13.6)
3 α	2.91 br d (9.8)	0.94 t (12.2)	1.00 t (11.7)	1.20 m	1.26 m	1.18 td (12.8, 2.5)	1.21 d (12.8)
3 β		1.49 ddd (12.2, 3.6, 1.5)	1.51 ddd (11.7, 3.6, 1.5)	1.35 d (12.0)	1.33 m	1.32 d (12.5)	1.33 d (12.9)
5	2.73 s	2.69 s	2.09 s	2.03 d (4.7)	2.06 m	1.97 d (4.8)	2.00 d (4.7)
6				5.62 br s	5.76 m	5.58 br s	5.58 br s
7	5.59 d (1.3)	5.61 d (1.3)	5.70 br s	5.82 t (1.6)	5.91 br s	5.76 d (1.5)	5.78 d (1.3)
9			2.29 br s				
11a	3.62 d (11.3)	3.64 br d (11.2)	3.75 br d (11.4)				
11b	3.50 d (11.3)	3.53 br d (11.2)	3.61 m				
12	1.95 d (1.3)	1.97 d (1.3)	1.98 br s	4.89 dt (12.6, 1.8)	4.97 br d (12.4)	4.87 dt (12.7, 2.3)	4.87 d (12.7)
				4.80 d (12.6)	4.74 br d (12.4)	4.76 d (12.8)	4.78 d (12.9)
13	1.11 s	1.07 s	1.05 s	0.93 s	1.01 s	0.90 s	0.91 s
14	1.00 s	1.13 s	1.11 s	1.07 s	1.13 s	1.04 s	1.06 s
15	0.98 s	1.02 s	0.85 s	1.07 s	1.20 s	1.04 s	1.05 s
2'				6.43 d (14.5)	6.29 d (15.3)	5.91 d (15.4)	5.93 d (15.1)
3'				7.35 dd (14.5, 11.2)	7.40 dd (15.3, 11.4)	7.20 dd (15.4, 11.2)	7.22 dd (14.8, 11.7)
4'				7.32 dd (14.0, 11.2)	7.18 dd (15.5, 11.4)	6.40 dd (15.5, 11.2)	6.44 dd (15.6, 10.4)
5'				6.39 d (14.0)	6.43 dd (15.5, 7.6)	6.31 dd (15.5, 5.0)	6.30 dd (15.4, 10.6)
6'					9.67 d (7.6)	3.84 br s	3.94 m
7'						3.47 br s	3.55 t (5.83)
8'						1.02 d (6.0)	0.94 d (6.0)
2-OH		4.38 d (4.7)	4.45 d (4.1)				
3-OH	4.37 br s						
6-OH							
9-OH	4.95 s	5.01 s		6.32 br s	5.73 br s	6.29 br s	6.29 br s
11-OH	4.83 br s	4.86 br s	4.67 br s				

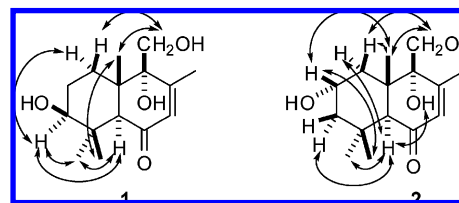
^a NMR data for OH groups of **8**: 5.01 (1H, br s, OH-6'), 4.60 (1H, br s, OH-7'). ^b NMR data for OH groups of **9**: 5.03 (1H, br s, OH-6'), 4.65 (1H, br s, OH-7'). ^c Overlapping signals.

Table 2. ^{13}C NMR Data (δ in ppm, 150 MHz, $\text{DMSO}-d_6$) for **1**, **2**, and **6–9**^a

position	1	2	6	7	8	9
1	30.6	41.0	29.6	30.3	29.3	29.4
2	26.8	62.4	17.4	17.7	17.2	17.5
3	77.5	51.7	44.5	44.8	44.2	44.0
4	38.1	33.4	33.3	33.9	32.9	33.1
5	56.2	54.7	44.2	44.7	43.9	44.0
6	200.5	199.6	66.4	67.3	65.6	65.1
7	128.8	128.1	121.1	123.2	121.1	121.2
8	158.8	157.6	136.9	135.5	136.2	136.4
9	75.6	74.6	73.1	74.6	72.8	72.9
10	45.3	46.2	37.3	37.8	36.9	37.0
11	62.1	61.9	174.4	174.7	174.1	174.3
12	20.0	19.3	68.2	68.9	68.1	68.1
13	29.8	33.8	32.2	32.4	31.9	32.0
14	16.3	22.7	24.4	24.8	24.0	24.1
15	18.7	18.9	18.3	18.4	18.1	18.1
1'			164.8	164.6	165.2	165.3
2'			127.7	129.5	119.7	119.7
3'			142.3	141.2	145.2	145.1
4'			140.3	146.7	126.9	127.1
5'			130.5	137.4	145.9	145.1
6'			166.8	192.8	74.7	74.4
7'					69.4	69.1
8'					19.0	18.1

^a Due to the low amount isolated, no ^{13}C spectrum could be obtained for compound **3**.

determined by a ROESY experiment (Figure 1). The A/B ring *trans*-junction was inferred from ROESY interactions between H-5/H₃-13 and H₃-15/H₃-14. The ROESY correlations of H-3 with H-5, H-1 α , and H₃-13, and of H₂-11 with H₃-15 and H-1 β , suggested an α -oriented H-3 and a β -oriented hydroxymethyl

**Figure 1.** Key ROSEY correlations of **1** and **2**.

group. Accordingly, **1** was identified as 3 β ,9 α ,11-trihydroxy-6-oxodrim-7-ene.

Compound **2**, after purification by HPLC, was obtained as a white powder with the same molecular formula, $\text{C}_{15}\text{H}_{24}\text{O}_4$ (found m/z 291.1560 $[\text{M} + \text{Na}]^+$, calcd 291.1572), as found for **1**. Detailed comparison of ^1H and ^{13}C NMR data of **2** (Tables 1 and 2) with those of **1** showed that the only difference was the position of an OH substituent on ring A. HMBC correlations from H₂-1 to C-3 and C-15 and from H₂-3 to C-13 and C-14 and ^1H – ^1H COSY cross-peaks (H₂-1/H-2, H-2/OH-2, and H-2/H₂-3) confirmed the presence of a 2-OH function. The *trans* A/B ring junction and 9 α -OH orientation were determined by a ROESY experiment (Figure 1), which was in agreement with **1**. The OH group at C-2 was α -oriented from ROESY cross-peaks of H-2 with H₃-15 and H₃-14. Hence, **2** is 2 α ,9 α ,11-trihydroxy-6-oxodrim-7-ene.

Compound **3** was isolated as a white powder, and its molecular formula of $\text{C}_{15}\text{H}_{24}\text{O}_3$ was determined from HRESIMS data (found m/z 253.1800 $[\text{M} + \text{H}]^+$, calcd 253.1804). The ^1H NMR data of **3** were similar to those of **2**, indicating that **3** was an analogue of **2**. The ^1H – ^1H COSY spectrum showed that the methylene protons (H₂-11) correlated with a vicinal proton (δ_{H} 2.29), indicating the

presence of a methine group at C-9 rather than a hydroxylated quaternary carbon as in **1** and **2**. The relative configuration of **3** was determined on the basis of biosynthetic considerations and comparison of NMR data with those of **1**, **2**, and **4**. Therefore, **3** is 2 α ,11-dihydroxy-6-oxodrim-7-ene.

Compound **6** was obtained as a white powder. Its ^{13}C NMR (Table 2), LRESIMS, and HREIMS data (found m/z 346.1788 [$\text{M} - \text{COOH} + \text{H}$] $^+$, calcd 346.1780) indicated the molecular formula to be $\text{C}_{21}\text{H}_{26}\text{O}_7$. Comparison of its NMR data with those of the known compounds **10**^{4,5} and **5**⁸ revealed that they shared the same drimane sesquiterpene nucleus except for the side chain, where four conjugated olefinic protons were observed instead of the six found in **10**. The ^1H – ^1H COSY correlations between H-2', H-3'/H-4' and H-4'/H-5' in combination with the HMBC correlations from H-2' and H-3' to C-1' and from H-4' and H-5' to C-6' indicated that the side chain of **6** was (2'E,4'E)-5'-carboxypenta-2',4'-dienoyl. The relative configuration of **6** was determined from a ROESY experiment (H-5/H-13 and H-6/H-13) and by comparison of the optical rotation and NMR data with those of **10**.

Compound **7** was isolated as an off-white, amorphous powder. The molecular formula of **7** was established to be $\text{C}_{21}\text{H}_{26}\text{O}_6$ by HREIMS (found m/z 373.1639 [$\text{M} - \text{H}$] $^-$, calcd 373.1652) and from the ^{13}C NMR data (Table 2). Spectroscopic data of **7** were almost the same as those of **6**, except for the presence of a terminal aldehyde group [δ_{H} 9.67 (1H, d, $J = 7.9$ Hz), δ_{C} 192.8] in the side chain of **7** instead of a carboxyl group. This was supported by the ^1H – ^1H COSY experiments (H-2', H-3'/H-4', H-4'/H-5', and H-5'/H-6') and HMBC experiments (correlations from H-3' and H-6' to C-5', from H-4' to C-6'). From a biogenetic point of view, **7** was assumed to be the precursor of **6**, suggesting the relative configuration of **7** is the same as **6**. This assumption was confirmed by comparing their optical rotation and NMR data.

Compound **8** was isolated as a white powder and had the molecular formula $\text{C}_{23}\text{H}_{32}\text{O}_7$ from HRESIMS (found m/z 443.2050 [$\text{M} + \text{Na}$] $^+$, calcd 443.2046). The ^1H and ^{13}C NMR data (Tables 1 and 2) of **8** were comparable to those of **6**, with the exception of the side chain, where the presence of two hydroxylated methines and a methyl group in addition to four olefinic carbons was evident. The ^1H – ^1H COSY correlations of H-5'/H-6', H-6'/H-7', H-7'/H-8', H-6'/OH-6', and H-7'/OH-7' and the HMBC correlations from H-4', H-5', and H-8' to C-6' and from H-6' and H-8' to C-7' indicated the side chain to be (2'E,4'E)-6',7'-dihydroxyocta-2',4'-dienoyl. This moiety was linked to C-6 from the HMBC correlation between H-6 and the carbonyl carbon C-1'. ROESY data indicated the relative configuration of the nucleus was the same as in **6**.

Compound **9** had the same molecular formula, $\text{C}_{23}\text{H}_{32}\text{O}_7$, as **8** from its HRESIMS data (found m/z 443.2050 [$\text{M} + \text{Na}$] $^+$, calcd 443.2046). The NMR (^1H and ^{13}C NMR, ^1H – ^1H COSY, HMQC, HMBC, and ROESY) data revealed that both **8** and **9** possessed the same basic structure. However, the NMR data of the side chain of **8** [δ_{C} 19.0 (C-8'), δ_{H} 3.84 (H-6') and δ_{H} 3.47 (H-7')] suggested the compound to be a *threo*-isomer,^{9,10} whereas those of **9** [δ_{C} 18.1 (C-8'), δ_{H} 3.94 (H-6') and δ_{H} 3.55 (H-7')] hinted at presence of an *erythro*-isomer. Compounds **8** and **9** are therefore stereoisomers that apparently differ in the configuration of carbons 6' and 7' in the side chain.

The crude EtOAc extract of *A. ustus* displayed cytotoxic activity against the murine lymphoma cell line L5178Y at a concentration of 10 $\mu\text{g/mL}$. This prompted us to investigate the various isolated compounds using the same cell line. Compounds **6**, **7**, and **10** exhibited EC_{50} values ranging from 0.6 to 5.3 $\mu\text{g/mL}$, with **7** being the most active congener observed in this study (Table 3). All other compounds were inactive at the range of concentrations analyzed (0.1–10 $\mu\text{g/mL}$). All cytotoxic compounds that were tested featured an olefinic ester side chain comprising two (**6** and **7**) or three conjugated olefinic double bonds (**10**) with a terminal carboxylic, aldehyde, or methyl substituent. Absence of the ester side chain as

Table 3. Cytotoxicity Assay for Isolated Compounds^a

compound tested	EC_{50} ($\mu\text{g/mL}$)		
	L5178Y	PC 12	HeLa
6	5.3	>10	>10
7	0.6	7.2	5.9
10	1.9	>10	7.5
kahalalide F (positive control)	6.3	n.d. ^b	n.d. ^b

^a Compounds **1**–**5**, **8**, and **9** were inactive at the range of concentration analyzed (0.1–10 $\mu\text{g/mL}$). ^b n.d., not determined.

observed for **5** resulted in a loss of cytotoxic activity. The isomeric compounds **8** and **9**, which were likewise inactive compared to **6**, **7**, and **10**, also feature an olefinic ester side chain. The side chain of **8/9**, however, carries two vicinal OH functions, which nullified the bioactivity. When tested against PC12 or HeLa cells, compounds **6**, **7**, and **10** were far less active than observed for the lymphoma cell line L5178Y (Table 3). The EC_{50} value of the most active congener (**7**) dropped 10-fold from 0.6 $\mu\text{g/mL}$ to 5.9 $\mu\text{g/mL}$ against HeLa cells, whereas the EC_{50} value against PC12 cells was 7.2 $\mu\text{g/mL}$. Similar trends were observed for **6** and **10**, suggesting a cell line specificity. Further studies that should also include other lymphoma cell lines are needed to corroborate this hypothesis.

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer-241 MC polarimeter. ^1H and ^{13}C NMR spectra were recorded on Bruker ARX 500 or AVANCE DMX 600 NMR spectrometers. ESIMS data were recorded on a Finnigan LCQ Deca mass spectrometer and HRESIMS spectra on a Micromass Qtof-mass spectrometer. Solvents were distilled before use, and spectral grade solvents were used for spectroscopic measurements. HPLC analyses were performed using a HPLC (Dionex P580) system coupled to a photodiode array detector (UVD340S). Routine detection was at 235, 254, 280, and 340 nm. The separation column (125 \times 4 mm, L \times i.d.) was prefilled with Eurospher-10 C₁₈ (Knauer, Germany), and a linear gradient of 0.02% H_3PO_4 in H_2O and MeOH was used.

Fungal Material. The fungus *Aspergillus ustus*, internal strain 8009, was isolated from the marine sponge *Suberites domunculus*, which had been collected from the Adriatic Sea and then grown in an aquarium until fungi were isolated from sponge segments as previously described.⁶ It was identified according to both morphological and molecular attributes.⁶

Cultivation and Extraction. For production of secondary metabolites, the fungus was cultivated at 22 $^{\circ}\text{C}$ for 21 days on both biomalt agar¹¹ and barley-spelt solid media.⁶ For initial analysis of the natural products, the cultures were lyophilized and extracted with ethyl acetate, and the dried residues were defatted by petroleum extraction.

Isolation. The EtOAc extract (3.6 g) was fractionated by vacuum-liquid chromatography (VLC) on silica gel using CH_2Cl_2 –MeOH gradient elution to yield 10 fractions. Fraction 2 (913 mg) was separated by Sephadex LH-20 eluting with CH_2Cl_2 –MeOH (1:1) and further by flash silica gel column chromatography (hexane–acetone, 5:1) to give **7** (9.3 mg) and **10** (10.0 mg). Fraction 6 (262 mg) was purified by Sephadex LH-20 (CH_2Cl_2 –MeOH, 1:1) and further by semipreparative HPLC (MeOH– H_2O , 50:50) to give **8** (9.6 mg) and **9** (5.8 mg). Fraction 7 (377 mg) was fractionated by Sephadex LH-20 (MeOH) and further purified by semipreparative HPLC (MeOH– H_2O , 30:70) to yield **1** (2.0 mg), **2** (4.1 mg), **3** (0.9 mg), **4** (1.5 mg), and **5** (1.9 mg). Fraction 8 (366 mg) was purified by Sephadex LH-20 (MeOH) and further by silica gel column chromatography (CH_2Cl_2 –MeOH, 95:5) to give **6** (10.4 mg).

Compound 1 (3 β ,9 α ,11-trihydroxy-6-oxodrim-7-ene): white, amorphous powder; $[\alpha]_{\text{D}}^{20}$ –55 (c 0.1, MeOH); UV λ_{max} (MeOH) 238 nm; ^1H and ^{13}C NMR see Tables 1 and 2; LRESIMS m/z 313 [$\text{M} + \text{HCOOH} - \text{H}$] $^-$, 581 [$2\text{M} + \text{HCOOH} - \text{H}$] $^-$; HRESIMS m/z 269.1750 [$\text{M} + \text{H}$] $^+$ (calcd for $\text{C}_{15}\text{H}_{25}\text{O}_4$ 269.1753).

Compound 2 (2 α ,9 α ,11-trihydroxy-6-oxodrim-7-ene): white, amorphous powder; $[\alpha]_{\text{D}}^{20}$ –58 (c 0.1, MeOH); UV λ_{max} (MeOH) 236 nm; ^1H and ^{13}C NMR see Tables 1 and 2; LRESIMS m/z 267 [$\text{M} - \text{H}$] $^-$, 313 [$\text{M} + \text{HCOOH} - \text{H}$] $^-$, 581 [$2\text{M} + \text{HCOOH} - \text{H}$] $^-$; HRESIMS m/z 291.1560 [$\text{M} + \text{Na}$] $^+$ (calcd for $\text{C}_{15}\text{H}_{24}\text{O}_4\text{Na}$ 291.1572).

Compound 3 (2 α ,11-dihydroxy-6-oxodrim-7-ene): white, amorphous powder; $[\alpha]_D^{20}$ -14 (c 0.03, MeOH); UV λ_{\max} (MeOH) 242 nm; ^1H NMR see Table 1; LRESIMS m/z 549 $[\text{M} + \text{HCOOH} - \text{H}]^-$; HRESIMS m/z 253.1800 $[\text{M} + \text{H}]^+$ (calcd for $\text{C}_{15}\text{H}_{25}\text{O}_3$ 253.1804).

Compound 6 [mono(6-strobilactone-B) ester of (E,E)-2,4-hexadienedioic acid]: white, amorphous powder; $[\alpha]_D^{20}$ -157 (c 0.1, MeOH); UV λ_{\max} (MeOH) 265 nm; ^1H and ^{13}C NMR see Tables 1 and 2; LRESIMS m/z 389 $[\text{M} - \text{H}]^-$, 779 $[\text{2M} - \text{H}]^-$; HREIMS m/z 346.1788 $[\text{M} - \text{COOH} + \text{H}]^+$ (calcd for $\text{C}_{20}\text{H}_{26}\text{O}_5$ 346.1780).

Compound 7 [(6-strobilactone-B) ester of (E,E)-6-oxo-2,4-hexadienoic acid]: white, amorphous powder; $[\alpha]_D^{20}$ -164 (c 0.1, MeOH); UV λ_{\max} (MeOH) 272 nm; ^1H and ^{13}C NMR see Tables 1 and 2; LRESIMS m/z 419 $[\text{M} + \text{HCOOH} - \text{H}]^-$; HREIMS m/z 373.1639 $[\text{M} - \text{H}]^-$ (calcd for $\text{C}_{21}\text{H}_{25}\text{O}_6$ 373.1652).

Compound 8 [(6-strobilactone-B) ester of (E,E)-6,7-dihydroxy-2,4-octadienoic acid]: white, amorphous powder; $[\alpha]_D^{20}$ -156 (c 0.1, MeOH); UV λ_{\max} (MeOH) 209, 261 nm; ^1H and ^{13}C NMR see Tables 1 and 2; LRESIMS m/z 465 $[\text{M} + \text{HCOOH} - \text{H}]^-$, 885 $[\text{2M} + \text{HCOOH} - \text{H}]^-$; HRESIMS m/z 443.2050 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{23}\text{H}_{32}\text{O}_7\text{Na}$ 443.2046).

Compound 9 [(6-strobilactone-B) ester of (E,E)-6,7-dihydroxy-2,4-octadienoic acid]: white, amorphous powder; $[\alpha]_D^{20}$ +1.6 (c 0.1, MeOH); UV λ_{\max} (MeOH) 206, 263 nm; ^1H and ^{13}C NMR see Tables 1 and 2; LRESIMS m/z 465 $[\text{M} + \text{HCOOH} - \text{H}]^-$, 885 $[\text{2M} + \text{HCOOH} - \text{H}]^-$; HRESIMS m/z 443.2050 $[\text{M} + \text{Na}]^+$ (calcd for $\text{C}_{23}\text{H}_{32}\text{O}_7\text{Na}$ 443.2046).

Cell Proliferation Assays. Cytotoxicity was tested against L5178Y, HeLa, and PC12 cells using the MTT assay as described previously.^{6,12}

Acknowledgment. Financial support by the BMBF to P.P. and B.S. and of MOST to W.L. is gratefully acknowledged. H.L. wishes to thank the Alfried Krupp von Bohlen und Halbach Foundation for a scholarship.

Supporting Information Available: This material is available free of charge via the Internet at <http://pubs.acs.org>.

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NP900220R