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Isolactarane and Sterpurane Sesquiterpenoids from the Basidiomycete *Phlebia uda*

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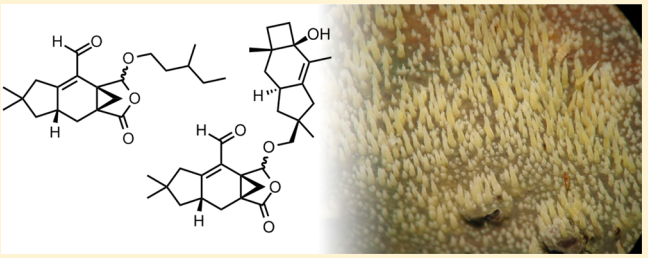
Supporting Information

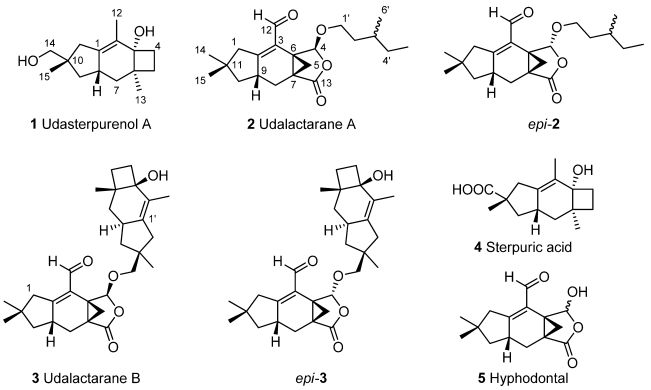
ABSTRACT: Three new sesquiterpenoids, named udasterpurenol A, udalactarane A, and udalactarane B, as well as the known compounds hyphodontal and sterpuric acid have been isolated from the basidiomycete *Phlebia uda*. These compounds represent the first natural products described from this species. The structures were elucidated by NMR spectroscopy and mass spectrometry. Udalactaranes A and B were isolated as mixtures with their respective epimeric acetals. These mixtures inhibited the spore germination of the plant pathogenic fungus *Fusarium graminearum* at 10 and 5 μg/mL, respectively, and were active against Jurkat cells with IC_{50} values of 101 and 42 μM, respectively.



The genus *Phlebia* forms a group of wood-decaying resupinate basidiomycetes to which *Phlebia*-like taxa with teeth, formerly classified in the separate genus *Mycoacia*, were added by Nakasone in 1997.[1] Although basidiomycetes are well known for producing a broad spectrum of natural products,[2] only a few terpenoids[3] and some alkylresorcinol derivatives[4,5] along with odor and aroma constituents[6,7] have been described from this genus. No secondary metabolites have been described from *Phlebia uda* to our knowledge.

We now report isolactaranes and sterpuranes from *P. uda* for the first time, including three new (**1**−**3**) and two known (**4**, **5**) compounds. Isolactarane and sterpurane terpenoids[8] are prominent secondary metabolites of basidiomycetes. The first example of a tetracyclic isolactarane was isolactarorufin isolated from *Lactarius rufus*, the structure of which was reported by Daniewski et al.[9] in 1976 and confirmed one year later by Konitz et al.[10] The first tricyclic isolactarane reported, lacking the lactone moiety, was merulidial isolated from *Merulius tremellosus*.[11,12] The biosynthesis of the isolactaranes from humulene was proposed in the original work of Daniewski et al.,[9] which included sterpurane as an unknown sesquiterpene skeleton not identified in a natural product until 1981, when Ayer et al.[13] described the isolation of the sterpuric acids from *Stereum purpureum*. Sterpurene itself was reported as a naturally occurring hydrocarbon in the same year.[14] It was later proven by Ayer et al.[15] that the biosynthetic pathway to the sterpuranes includes the protoilludane stage.

In screening basidiomycetes for antibiotic activity against *Nematospora coryli*, extracts of the fungus *P. uda* IBWF07065 showed positive results. Refermentation and bioactivity-guided purification yielded compounds **1**−**5**, with compounds **2**, **3**, and **5** exhibiting antibiotic activity, while compounds **1** and **4** were



inactive. All compounds were analyzed with spectroscopic methods, and compounds **1**−**3** were found to be hitherto unknown natural products, while (+)-sterpuric acid (**4**)[13] and (−)-hyphodontal (**5**)[16] had been previously described.

Udasterpurenol A (**1**) had an elemental composition of $C_{15}H_{24}O_2$ according to high-resolution MS. The NMR spectra (Table 1) indicated a structure very similar to that of **4**, with a hydroxylated methylene group (δ_H 3.19 and 3.17, δ_C 69.8) instead of the carboxylic acid being the only difference. The relative stereoconfiguration was determined by NOESY (Figure 1) and was found to be the same as in the closely related (+)-sterpuric acid (**4**).[13] Like **4** and the parent hydrocarbon,[17] udasterpurenol A (**1**) is dextrorotatory.

High-resolution MS of udalactarane A (**2**) gave an elemental composition of $C_{21}H_{30}O_4$. The NMR spectra (Table 1) showed

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Table 1. ^{1}H (400 MHz) and ^{13}C NMR (101 MHz) Data of Compounds 1−3

	udasterpurenol A (**1**)[a]			udalactaran A (**2**)[b]		*epi*-udalactaran A (*epi*-**2**)[b]		udalactaran B (**3**)[b]		*epi*-udalactaran B (*epi*-**3**)[b]	
position	δ_C	δ_H (J in Hz)	position	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)
			1	44.3, CH_2	2.73, dd (19.4, 1.4) 2.60, m	43.5, CH_2	2.67, m	44.3, CH_2	2.73, dd (19.5, 1.4) 2.59, m	43.6, CH_2	2.66, m
			2	166.3, qC		164.3, qC		166.2, qC		164.3, qC	
			3	128.5, qC		128.8, qC		128.4, qC		128.9, qC	
			4	104.5, CH	5.75, s	103.8, CH	5.69, s	104.5, CH	5.76, s	103.5, CH	5.69, s
			5	18.0, CH_2	1.84, d (5.6) 1.42, d (5.6)	20.6, CH_2	1.30, 1.27, m	18.1, CH_2	1.83, d (5.5) 1.44, d (5.5)	20.6, CH_2	1.31, 1.28, m
			6	30.5, qC		28.4, qC		30.6, qC		29.2, qC	
			7	32.7, qC		29.3, qC		32.7, qC		32.1, qC	
			8	22.3, CH_2	2.59, 1.41, m	21.3, CH_2	2.57, 1.54, m	22.3, CH_2	2.57, 1.39, m	21.5, CH_2	2.57, 1.53, m
			9	39.3, CH	2.58, m	39.4, CH	2.56, m	39.3, CH	2.60, m	39.3, CH	2.56, m
			10	45.6, CH_2	1.87, 1.29, m	45.4, CH_2	1.88, 1.72, m	45.7, CH_2	1.87, ddd (8.6, 7.0, 1.2) 1.26, m	45.2, CH_2	1.88, 1.35, m
			11	38.7, qC		38.7, qC		38.7, qC		38.8, qC	
			12	189.5, CH	9.92, s	189.3, CH	9.83, s	189.4, CH	9.91, s	189.4, CH	9.82, s
			13	175.0, qC		176.2, qC		175.1, qC		176.2, qC[c]	
			14	29.4, CH_3	1.14, s	29.5, CH_3	1.15, s	29.4, CH_3	1.14, s	29.4, CH_3	1.14, s
			15	28.3, CH_3	1.04, s	28.6, CH_3	1.05, s	28.2, CH_3	1.04, s	28.6, CH_3	1.06, s
1	138.1, qC		1′	69.9, CH_2	3.87 m	69.0, CH_2	3.81, m 3.54, dt (9.4, 7.3)	140.3, qC		139.4, qC	
2	127.8, qC		2′	36.1, CH_2	1.73, 1.53, m	35.9, CH_2	1.55, 1.29 m	126.7, qC		126.7, qC	
3	71.7, qC		3′	31.5, CH	1.52, m	31.4, CH	1.32, m	73.5, qC		73.4, qC	
4	33.5, CH_2	2.06, q (10.8) 1.78, ddd (10.8, 8.7, 2.1)	4′	29.6, CH_2	1.40, 1.22, m	29.7, CH_2	1.25, 1.13, m	34.4, CH_2	2.13, 2.00, m	34.5, CH_2	2.15, 1.98, m
5	21.6, CH_2	1.44, 1.10, m	5′	11.4, CH_3	0.88, t (7.4)	11.4, CH_3	0.84, t (7.3)	22.0, CH_2	1.53, 1.22, m	22.1, CH_2	1.50, 1.20, m
6	43.3, qC		6′	19.2, CH_3	0.89, d (6.9)	19.1, CH_3	0.83, d (6.3)	43.9, qC		43.9, qC	
7	35.4, CH_2	1.48, m 0.75, dd (12.8, 11.3)	7′					35.3, CH_2	1.55, m 0.85, dd (13.2, 11.2)	35.3, CH_2	1.55, m 0.79, dd (13.2, 11.2)
8	36.2, CH	2.50, m	8′					36.6, CH	2.56, m	36.5, CH	2.52, m
9	42.8, CH_2	1.45, 1.10, m	9′					43.5, CH_2	1.65, 1.25, m	43.6, CH_2	1.53, 1.07, m
10	42.0, qC		10′					41.2, qC		41.1, qC	
11	39.4 CH_2	2.21, br d (17.0) 1.85 dq (17.0, 1.4)	11′					40.3, CH_2	2.45, br d (17.2) 2.04, m	40.4, CH_2	2.18, br d (17.3) 1.95, br d (17.3)
12	13.1, CH_3	1.52, m	12′					13.0, CH_3	1.64, m	12.9, CH_3	1.61, m
13	23.9, CH_3	1.09, s	13′					23.6, CH_3	1.20, s	23.6, CH_3	1.19, s
14	69.8, CH_2	3.19, d (9.0) 3.17, d (9.0)	14′					79.8, CH_2	3.62, s	78.7, CH_2	3.60, d (8.6) 3.32, d (8.6)
15	24.9, CH_3	0.98, s	15′					25.4, CH_3	1.13, s	25.3, CH_3	0.99, s
OH-1		4.46, br s									
OH-14		4.6, br s									

[a] CD_3CN. [b] $CDCl_3$. [c] Indirectly detected.

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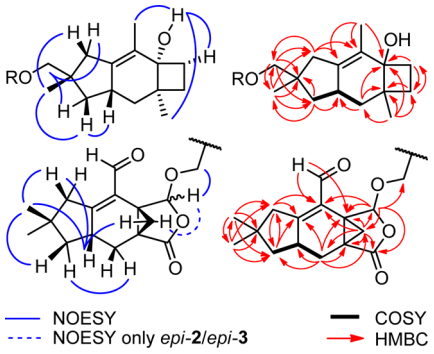

Figure 1. Relevant 2D NMR data for **1**–**3**.

the presence of two structurally related isomeric components. NMR data also revealed the isolactaran-type sesquiterpenoid skeleton of hyphodontal (**5**)[16] with the exocyclic acetal oxygen atom carrying a 3-methylpentyl residue. The relative configuration of the isolactarane skeleton was the same as in hyphodontal (**5**) as determined by NOESY (Figure 1). The minor component in the mixture was accordingly identified as a diastereomer of **2** (dr 1.6:1). While hyphodontal exhibited fast epimerization at the acetalic center, resulting in line broadening, no equilibrium was detected in the NMR spectra between the two components. The isomers were the two epimeric acetals as was apparent in the NOESY spectrum from the NOE contacts between H-4 and H_a-5, the relative intensity of which was decreased about 10-fold in *epi*-udalactarane A (*epi*-**2**). To study the possibility of an epimerization during the purification procedure, the isolation of **2** and *epi*-**2** was repeated under acid-free conditions, giving the same diastereomeric ratio (1.6:1) in the resulting mixture. The mechanism for the formation of two epimers remains unknown.

Udalactarane B (**3**) had an elemental composition of $C_{30}H_{40}O_5$ by high-resolution MS. Again, the compound was found as a mixture of two closely related isomers. The analysis of the NMR spectra (Table 1) led to the conclusion that the same isolactarane scaffold as found in **2** and *epi*-**2** was present here. In this case however, the acetal appeared to be connected to a second, structurally different sesquiterpenoid unit. NMR data (HMBC, NOESY) indicated that a methylene group (δ_C 79.8) was bound to the acetalic oxygen atom, which corresponded to C-14 in udasterpurenol A (**1**). Thus, udalactarane B (**3**) was a disesquiterpene[18] consisting of an isolactarane and a sterpurene part. For naming, the isolactarane part was given higher priority because it had more oxygen atoms and more rings. As found for udalactarane A (**2**), udalactarane B (**3**) was a mixture with its 4-epimer *epi*-udalactarane B (*epi*-**3**) in a diastereomeric ratio of 3:1. Again, no chemical exchange could be detected in NOESY.

Udalactarane A and *epi*-udalactarane A (**2** and *epi*-**2**, ratio 1.6:1), udalactarane B and *epi*-udalactarane B (**3** and *epi*-**3**, ratio 3:1), and hyphodontal (**5**) inhibited spore germination of various organisms (Table 2). The known hyphodontal (**5**) showed growth-inhibiting activity in the agar diffusion assay and cytotoxicity as previously described,[16] while udasterpurenol A (**1**), **2** and *epi*-**2** (ratio 1.6:1), **3** and *epi*-**3** (ratio 3:1), and sterpuric acid (**4**) were not active in the agar diffusion assay (up to 50 μg/mL). The growth of Jurkat cells was inhibited by **2** and *epi*-**2** (ratio 1.6:1; IC_{50} 35 μg/mL, 101 μM), **3** and *epi*-**3** (ratio 3:1; IC_{50} 20 μg/mL, 42 μM), and sterpuric acid (**4**; IC_{50} 40 μg/mL, 160 μM), whereas udasterpurenol A (**1**) was not active (up to 50 μg/mL). The aforementioned compounds showed no activity against HepG2 cells (up to 50 μg/mL).

Table 2. Inhibition of Spore Germination between 75% and 100% by Udalactarane A and *epi*-Udalactarane A (2 and *epi*-2, ratio 1.6:1), Udalactarane B and *epi*-Udalactarane B (3 and *epi*-3, ratio 3:1), and Hyphodontal (5); Positive Control: 50 μg/mL Ciclopirox

organism	**2** and *epi*-**2** (μg/mL)	**3** and *epi*-**3** (μg/mL)	hyphodontal (**5**, μg/mL)
Fusarium graminearum	10	5	10
Magnaporthe grisea	10	>100	10
Phytophthora infestans	100	10	25
Botrytis cinerea	>100	>100	50

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were determined with a Dr. Tottoli apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 578 and 546 nm and extrapolated to 589 nm using Drude's equation.[19] UV and IR spectra were measured with a Perkin-Elmer Lambda-16 spectrophotometer and a Bruker IFS48 FTIR spectrometer, respectively. NMR spectra were recorded on a Bruker Avance-II 400 spectrometer with a 5 mm BBO probehead. The chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H 7.26 ppm, δ_C 77.16 ppm; CD_3CN: δH 1.94 ppm, δC 1.32 ppm; DMSO-d_6: δ_H 2.50 ppm, δ_C 39.52 ppm).[20] HRESIMS data were recorded on an Agilent 6224 TOF LC/MS or on a Waters Q-TOF-Ultima 3 equipped with a LockSpray interface with trialkylamines as external reference. HPLC-MS analyses were performed on a Hewlett-Packard Series 1100 LC-MSD instrument using positive and negative APCI ionization.

Producing Organism. The basidiomycete IBWF07065 was obtained from the culture collection of the Institute of Biotechnology and Drug Research (IBWF e.V.), Kaiserslautern, Germany. The ITS sequence of the species shows high similarity to *Phlebia uda* (99.6% in 517 bp, GenBank accession no. AB084621) and to *Mycoacia uda* (98.9% in 573 bp, GenBank accession no. AY787676), which is used as a synonym for *P. uda*.[1] The fungus is maintained in YMG media (yeast extract 4 g/L, malt extract 10 g/L, glucose 4 g/L; the pH value was adjusted to 5.5 before autoclaving; for solid media 2% agar was added).

Fermentation and Isolation. *P. uda* IBWF07065 was grown in YMG medium in a 20 L fermenter (Biolafitte) at 22–24 °C with agitation (120 rpm) and aeration (3 L/min). The fermentation was stopped after seven days, when the glucose in the medium was depleted and the antifungal activity against *Nematospora coryli* had reached a maximum. The mycelium was separated from the culture fluid by filtration, and the filtrate was extracted twice with an equal volume of ethyl acetate. After evaporation of the solvent the crude extract (2.9 g) was applied onto a silica gel column (90 g, Merck 60, 0.063–0.2 mm). Elution with cyclohexane–ethyl acetate (9:1) yielded 87 mg of fraction A, with cyclohexane–ethyl acetate (3:1) 129 mg of fraction B, and with cyclohexane–ethyl acetate (1:1) 667 mg of fraction C. Subsequent preparative HPLC (Macherey-Nagel, Nucleosil C_{18}, 7 μm, column 21 × 250 mm) of fraction A yielded 4 mg of udalactarane B and *epi*-udalactarane B (**3** and *epi*-**3**, ratio 3:1, MeCN–H_2O gradient, 50% MeCN to 100% MeCN in 33 min, 15 mL/min, t_R 16.5 min), that of fraction B yielded 2.8 mg of udalactarane A and *epi*-udalactarane A (**2** and *epi*-**2**, ratio 1.6:1, MeCN–H_2O gradient, 25% MeCN to 100% MeCN in 50 min, 15 mL/min, t_R 21.5 min), and that of fraction C (MeCN–H_2O gradient, 45% MeCN to 65% MeCN in 13 min, 15 mL/min) yielded 89 mg of hyphodontal (**5**, t_R 9.5 min), 23.5 mg of sterpuric acid (**4**, t_R 11 min), and 20 mg of an udasterpurenol A (**1**)-enriched intermediate. A 14 mg amount of udasterpurenol A (**1**, t_R 7 min) was obtained by isocratic HPLC using

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RP8 (Agilent, Zorbax Eclipse XDB 8, 5 μm, column 9.4 × 250 mm, eluent 45% MeCN–0.1% HCOOH in H_2O).

Udasterpurenol A (1): amber oil; $[\alpha]^{24}_{546}$ +35.6, $[\alpha]^{24}_{578}$ +31.3, $[\alpha]^{24}_{D}$ +30.1 (*c* 0.82, DMSO); no UV absorption above 200 nm; IR (KBr) ν_{max} 3400, 2934, 1632, 1375, 1039 cm^{-1}; APCIMS *m*/*z* 219.2 $[M - OH]^+$ (100), 201.2 $[M - H_2O - OH]^+$ (41); HRESIMS *m*/*z* 300.1944 (calcd for $[C_{15}H_{24}O_2+CH_3CN+Na]^+$, 300.1939).

Udalactarane A (2), *epi*-udalactarane A (*epi*-2): yellow oil; $[\alpha]^{28}_{546}$ −67.2, $[\alpha]^{28}_{578}$ −53.3, $[\alpha]^{28}_{D}$ −49.7 (*c* 0.19, $CDCl_3$); UV (MeCN) λ_{max} (log ε) 259 (3.97) nm; IR (KBr) ν_{max} 3432, 2957, 1773, 1677, 1461, 945 cm^{-1}; APCIMS *m*/*z* 347.2 $[M + H]^+$ (100); HRESIMS *m*/*z* 347.2213 (calcd for $[C_{21}H_{30}O_4+H]^+$, 347.2217).

Udalactarane B (3), *epi*-udalactarane B (*epi*-3): yellowish foam; no significant optical rotation was detected; UV (MeCN) λ_{max} (log ε) 259 (3.94) nm; IR (KBr) ν_{max} 3438, 2952, 1772, 1676, 1458, 945 cm^{-1}; APCIMS (neg.) *m*/*z* 479.2 $[M - H]^-$ (100); HRESIMS *m*/*z* 503.2766 (calcd for $[C_{30}H_{40}O_5+Na]^+$, 503.2768).

Sterpuric acid (4): colorless oil; $[\alpha]^{24}_{546}$ +99.2, $[\alpha]^{28}_{578}$ +87.2, $[\alpha]^{28}_{D}$ +83.6 (*c* 0.31, DMSO); NMR data were in accordance with the literature.[13]

Hyphodontal (5): yellow solid; mp 173–175 °C; $[\alpha]^{29}_{546}$ −83.6, $[\alpha]^{29}_{578}$ −101.3, $[\alpha]^{29}_{D}$ −78.7 (*c* 0.37, CD_3CN); NMR data were in accordance with the literature.[16]

Biological Assays and ITS. The antimicrobial activity[21] and the cytotoxicity[22] were assayed as described in the literature. The spore germination was tested with *M. grisea* as described before[23] and was adapted for the spore germination assay with *Phytophthora infestans*, *Botrytis cinerea*, and *Fusarium graminearum*. The ITS sequence was generated by using methods described before.[24]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR spectra for compounds **1**–**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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