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Lanostane-type triterpenes from the fungal endophyte *Scleroderma* UFSMSc1 (Persoon) Fries

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ABSTRACT

Two lanostane triterpenoids (sclerodols A and B) were isolated from the culture of the *Eucalyptus grandis* derived from the endophyte *Scleroderma* UFSM Sc1(Persoon) Fries together with three known compounds: one related triterpenoid lanosta-8,23-dien-3β,25-diol, the disaccharide α,β-trehalose, and the sugar alcohol mannitol. Their structures were elucidated on the basis of 2D NMR, HRME, and single-crystal X-ray diffraction data. The methanol crude extract and the isolated lanostane triterpenoids showed promising anticandidal activities.

Pathogen resistance to current antibiotics has become a serious health problem, especially in sick people with low immunity. In an attempt to minimize these problems, several research groups around the world have been concerned with the research of new antimicrobial agents. In this context, natural products obtained from various sources, such as plants, microorganisms and marine sources are both a fundamental source of new chemical diversity and an integral component of today's pharmaceutical compendium.[1] *Candida* species are capable of a wide spectrum of infections (candidiasis) in human host, being a risk factor in cancer, AIDS, transplant and ICU patient population. According to the literature,[2] approximately 95% of all evasive *Candida* infections are caused by five species: *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei*. With the exception of *C. glabrata*, all species have been tested in this work against the crude extract and isolated lanostenoids from the cultivated fungal endophyte *Scleroderma* UFSMSc1.

The ectomycorrhiza *Scleroderma* UFSMSc1 (Persoon) Fries is an endophytic fungus, that is, parasitic on the exotic species *Eucalyptus grandis* or occurs as saprophytic soil or decaying wood.[3] The increasing need to overcome the resistance of clinically important microorganisms to existing antibiotics is a major concern worldwide. Consequently, there has been much interest in finding new antibiotics to effectively treat antibiotic-resistant microorganisms. In this context, our research group has been searching for new natural sources of substances with antimicrobial potential. With this aim, the culture of the endophyte *Scleroderma* UFSMSc1 (Persoon) Fries, derived from *E. grandis* was analyzed. Bioassay guided isolation led to the isolation and identification of two new lanostane triterpenoid, named sclerodol A (**1**) and B (**2**), together with one known related lanostane triterpenoid (**3**)[4] (Fig. 1), the disaccharide α,β-trehalose, and the sugar alcohol mannitol. Lanostanes are a relevant group of tetracyclic triterpenoids derived from lanosterol that possess important biological and pharmacologic properties, such as potential anticancer,[5–8] antimicrobial,[9,10] anti-inflammatory,[11] and antiviral activities.[12,13] Astrakurkurol and astrakurkurone, two lanostane-type triterpenes isolated from the Mushroom *Astraeus hygrometricus*,[14] and 31-hydroxycarboxyacetylquercinic acid, a lanostenoid hydroxy acid isolated from *Daedalea dickinsii*,[9] showed excellent in vitro anticandidal activities. Furthermore, the carbohydrates trehalose (**4**) and mannitol (**5**) were also isolated. Possibly mannitol serves as a reserve nutrient,[15] whereas trehalose serves as a thermoprotectant and precursor of critical cell wall metabolites.[16]

*Sclerodol A (**1**).* Colorless solid; mp 169.0–170.3 °C, $[\alpha]_D^{25}$ +41.4 (c 0.021, CH_2Cl_2); UV ($CHCl_3$): λ_{max}/nm 230; IR (KBr) ν_{max}/cm^{-1} 3396, 2963, 2963, 1641, 1456, 1372, 1060, 1038, 972; HRESIMS(+) *m*/*z*,

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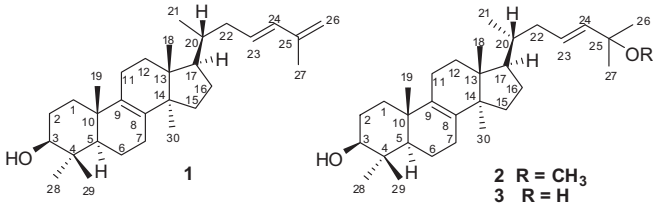

Figure 1. Structures of lanostane-type triterpenes compounds **1**–**3** isolated of from the fungal endophyte *Scleroderma* UFSMSc1.

Anal. Calcd for $C_{30}H_{48}O$ [M+H]$^+$: 425.3778. Found: 425.3801; NMR data (see Table 1).

Sclerodol B (***2***). Colorless solid; mp 166.0–167.4 °C; $[\alpha]_D^{25}$ +29.8 (c 0.09, CH_2Cl_2); UV ($CHCl_3$): λ_{max}/nm 223; IR (KBr) ν_{max}/cm^{-1} 3460, 2954, 1739, 1666, 1452, 1214, 1034, 751; HRESIMS(+) *m*/*z*, Anal. Calcd for $C_{30}H_{48}O$ [M+H−MeOH]$^+$: *m*/*z* 425.3778. Found: 425.3766; NMR data (see Table 1).

(3S,5R*,10S*,13R*,14R*,17R*,20R*)-lanosta-8,23-diene-3β,25-diol* (***3***). Colorless solid; mp 189–190 °C; $[\alpha]_D^{25}$ +38.8 (c 0.026, MeOH); UV (DMSO-d_6): λ_{max}/nm 233; IR (KBr) ν_{max}/cm^{-1} 2962, 2836, 1448, 1370, 1065, 1034, 978; HRESIMS(+) *m*/*z*, Anal. Calcd for $C_{30}H_{48}O$ [M+H−H_2O]$^+$: 425.3778. Found: 425. 3766; ^{13}C NMR data (see Table 1).

Crystallographic data of **2** and **3** have been solved and refined using the Bruker SHELXTL Software Package, [SHELXTL Version 2008/4, Bruker AXS Inc., Madison, WI, USA, 2008], and deposited at the Cambridge Crystallographic Data Centre, under CCDC deposition numbers CCDC 873084 and CCDC 1015524. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 IEZ.[18]

The minimal inhibitory concentration (MIC) was determined on 96-well culture plates by a micro dilution method using a microorganism suspension at a density of 10^5 CFU mL^{-1} with Sabouraud Broth incubated for 48 h at 25 °C for yeasts. Cultures that did not present growth were used to inoculate plates of solid medium (Muller Hinton Agar and Sabouraud Agar) in order to determine the minimal lethal concentration (MLC). Proper blanks were assayed simultaneously and samples were tested in triplicate. The reference antifungal used was nistatin (Sigma). Technical data have been described previously.[19]

The crude methanol extract (2 g) of *Scleroderma* UFSMSc1 mycelia suspension was chromatographed on a silica gel open column eluted with *n*-hexane-EtOAc and EtOAc–MeOH gradient to afford compounds **1**–**5**.

Table 1
^{1}H- (400 MHz) and ^{13}C (100 MHz) NMR assignment for compounds **1**–**3**[a]

Compound	**1**		**2**		**3**	
Position	δ_H (*J* in Hz)[b]	δ_C[b]	δ_H (*J* in Hz)[b]	δ_C[b]	δ_H (*J* in Hz)[c]	δ_C[c]
1a	1.26, m	35.6	1.27, m	35.6	1.12, m	35.1
1b	1.76, m		1.76, m		1.65, m	
2a	1.72, m		1.60, m	27.9	1.32, m	27.9
2b	1.74, m	27.9	1.68, m		1.91, m	
3	3.24, dd (12.0, 4.6)	78.9	3.24, dd (11.6, 4.8)	79.0	3.04, m	76.8
4		38.9	–	38.9	–	38.4
5	1.16, m	50.4	1.09, dd (13.6, 5.2)	50.2	1.49, m	49.4
6	2.03,1.06, m	21.0	2.04, m	21.0	1.99, m	20.3
7	1.80,2.10, m	26.5	2.07, m	26.5	2.01, m	25.9
8	–	134.5	–	134.5	–	134.3
9	–	134.4	–	134.4	–	133.5
10	–	37.1	–	37.1	–	36.5
11a	1.60, m	18.3	1.53, m	18.3	1.63, m	18.3
11b	1.71, m		1.72, m		1.64, m	
12a	1.22, m	30.9	1.21, m	31.0	1.64, m	30.3
12b	1.74, m		1.71, m		1.69, m	
13	–	44.6	–	44.6	–	43.9
14	–	49.9	–	50.5	–	49.3
15a	1.80, m		1.21, m	30.9	1.63, m	30.4
15b	2.25, m	30.9	1.71 m		1.69, m	
16a	1.40, m		1.37, m	28.1	1.48, m	27.4
16b	2.06, m	28.2	1.97, m		1.48, m	
17	1.56, m	50.5	1.52, m	50.2	0.98, m	50.0
18	0.71, s	15.8	0.73, s	15.8	0.67, s	15.5
19	0.98, s	18.7	1.00, s	18.7	0.93, s	18.8
20	1.54, m	37.1	1.51, m	36.7	1.65, m	36.0
21	0.90, d (5.9)	18.8	0.92, d (6.8)	19.2	0.87, d (5.9)	17.7
22a	1.69, m	39.7	2.21, m	39.4	1.73, m	38.4
22b	2.03, m		1.81, m		2.08, m	
23	5.64, ddd (15.2, 8.3, 6.7)	129.5	5.55, ddd (16.0, 8.2, 5.0)	128.7	5.48, d (7.1)	123.0
24	6.14, *d* (15.6)	134.1	5.44, d (16.0)	136.7	5.50, s	140.6
25	–	142.3	–	74.9	–	68.7
26	4.85, sl	113.9	1.27, s	26.2	1.16, d	30.0
27	1.84, s	19.1	1.27, s	25.8	1.16, d	30.1
28	1.00, s	28.0	1.02, s	28.0	0.91, s	27.4
29	0.81, s	15.4	0.83, s	15.4	0.72, s	15.6
30	0.88, s	24.3	0.89, s	24.2	0.84, s	23.8
O-Me	–		3.17, s	49.9	–	–
3-OH					4.15, d (4.0)	
25-OH					4.22, s	

[a] Assignments aided by COSY, DEPT 135, HMQC and HMBC experiments.
[b] NMR spectra were recorded in: $CDCl_3$ at 25 °C.
[c] NMR spectra were recorded in: DMSO-d_6 at 25 °C.