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Journal of Asian Natural Products Research

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/ganp20>

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Available online: 19 Oct 2011

To cite this article: Sylvain Valère Tanemossu Sob, Hippolyte Kamdem Wabo, Chun-Ping Tang, Pierre Tane, Bonaventure Tchaleu Ngadjui & Yang Ye (2011): Phenol esters and other constituents from the stem barks of *Stereospermum acuminatissimum*, *Journal of Asian Natural Products Research*, 13:12, 1128-1134

To link to this article: <http://dx.doi.org/10.1080/10286020.2011.619182>

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Phenol esters and other constituents from the stem barks of *Stereospermum acuminatissimum*

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(Received 10 June 2011; final version received 28 August 2011)

A new ester, 2-(4'-hydroxyphenyl)ethyl dotriacontanoate (**1**), and a new inseparable mixture of octacosan-1,28-dioldiferulate and triacontan-1,30-dioldiferulate (**2**) were isolated from the stem barks of *Stereospermum acuminatissimum*, along with 24 known compounds including 4 triterpenoids, 11 anthraquinones, 2 lignans, 3 phenylpropanoids, 2 4-hydroxyphenethyl esters, 1 methoxyphenol, and 1 iridoid. The structures of the new metabolites were determined with the help of spectroscopic data including extensive 2D NMR spectroscopy. The known compounds were identified by comparison of their physical and spectroscopic data with those reported in the literature. The compounds were tested against *Candida albicans* ATCC 24433, *C. albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258, and *Candida parapsilosis* ATCC 22019. Some of them were moderately active.

Keywords: *Stereospermum acuminatissimum*; Bignoniaceae; phenol esters; antifungal activity

1. Introduction

Stereospermum acuminatissimum K. Schum. (Bignoniaceae) is a tall tree with pink or pale purple flowers found in the forest of west tropical Africa or planted for ornamental purposes [1]. The leaves and barks are used in Cameroonian traditional medicine for antimalarial and anti-inflammatory purposes. To the best of our knowledge, no phytochemical study is reported on this plant. Previous studies of species of *Stereospermum* genus have led to the isolation of lignans, phenolic and iridoid glycosides [2,3], quinones [4–8], and hydroxyphenylethyl esters [8]. As part of our continuing search of new biologically active substances from Cameroonian

medicinal species [9,10], we have carried out the chemical investigation of the title plant and now report on the constituents of the stem barks.

The air-dried and powdered stem barks of *S. acuminatissimum* (3 kg) were macerated with CH₂Cl₂–MeOH (1:1) (3 × 72 h) and the solvent removed under reduced pressure to afford a crude extract. The CH₂Cl₂–MeOH (1:1) extract was subjected to sequential liquid–liquid partition with petroleum ether (PE), CHCl₃, EtOAc, and *n*-BuOH. The CHCl₃ fraction was separated by chromatography on silica gel and Sephadex LH-20, affording the new compound 2-(4'-hydroxyphenyl)ethyl dotriacontanoate (**1**) and the new mixture

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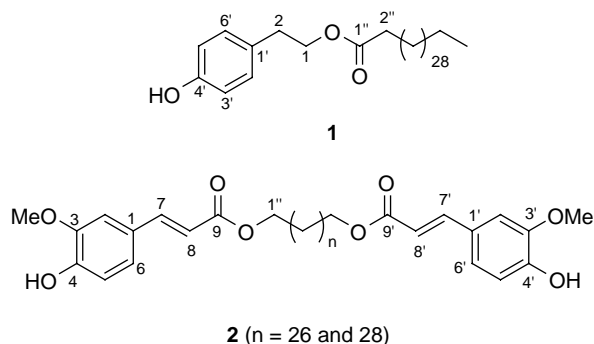


Figure 1. Structures of compounds **1** and **2**.

of octacosan-1,28-dioldiferulate and triacontan-1,30-dioldiferulate (**2**) (Figure 1) together with the known compounds ursolic acid (**3**) [11], pomolic acid (**4**) [11], quinovic acid (**5**) [11], oleanolic acid (**6**) [11], (+)-cycloolivil (**7**) [2], paulownin (**8**) [12], methyl *trans*-ferulate (**9**) [13,14], coniferaldehyde (**10**) [15], (*E*)-methyl 3-(4'-hydroxyphenyl)acrylate (**11**) [14], 2-(4'-hydroxyphenyl)ethyl undecanoate (**12**) [8], 2-(4'-hydroxyphenyl)ethyl nonacosanoate (**13**) [8], 2-methoxy-4-[3'-(3'',4'',5''-trimethoxyphenyl)allyloxymethyl]phenol (**14**) [8], pinnatal (**15**) [5], stereochenol B (**16**) [7], sterekunthal B (**17**) [5], sterequinone B (**18**) [4], sterequinone F (**19**) [8], sterequinone H (**20**) [8], sterequinone A (**21**) [4], sterequinone E (**22**) [4], zenkequinone B (**23**) [6], zenkequinone A (**24**) [6], sterequinone C (**25**) [4], and norviburtinal (**26**) [8].

2. Results and discussion

Compound **1** was obtained as a white powder. It reacted positively to the FeCl_3 reagent suggesting the presence of a phenolic hydroxyl group. The molecular formula $\text{C}_{40}\text{H}_{72}\text{O}_5$ was deduced from the EI-MS at m/z 601 $[\text{M} + \text{H}]^+$. This molecular formula was confirmed by the HR-EI-MS at m/z 600.5447 $[\text{M}]^+$. The IR spectrum showed strong absorption bands due to hydroxyl (3301 cm^{-1}) and ester carbonyl (1728 cm^{-1}) groups, and also of

an aromatic ring (1519 cm^{-1}). The ^1H NMR spectrum exhibited two doublets of *ortho*-coupled aromatic protons at δ_{H} 7.08 (2H, $J = 8.4\text{ Hz}$, H-2') and 6.76 (2H, $J = 8.4\text{ Hz}$, H-3'), suggesting the presence of a 1,4-disubstituted aromatic ring. This spectrum also showed two triplets of two protons each at δ_{H} 4.23 ($J = 7.1\text{ Hz}$, H-1) and 2.85 ($J = 7.1\text{ Hz}$, H-2) of an oxymethylene and a benzylic methylene, respectively. These data suggested the presence of a 4-hydroxyphenylethyl group, which was substantiated by a fragment at m/z 121 in its EI-MS [8]. The ^1H NMR spectrum further displayed a three-proton triplet at δ_{H} 0.89 ($J = 6.8\text{ Hz}$), which was characteristic of a terminal methyl group of an aliphatic chain [5]. The triplet at δ_{H} 2.27 (2H, $J = 7.6\text{ Hz}$, H-2'') was assignable to a methylene adjacent to a carbonyl group. A broad singlet at δ_{H} 1.25 integrating for 56 protons accounted for the presence of an aliphatic chain comprising 28 methylenes. The ^{13}C NMR spectrum showed signals of one ester carbonyl (δ_{C} 173.9), one oxygenated aromatic carbon (δ_{C} 154.2), two aromatic methines (δ_{C} 130.0 and 115.3), one oxymethylene (δ_{C} 64.9), and one aliphatic methyl group (δ_{C} 14.1). In the HMBC spectrum (Figure 2), pertinent correlations were observed between H-3'' and C-1'', between H-2'' and C-1'', as well as between H-1 and C-1'', H-2 and C-2'. Further correlations were observed

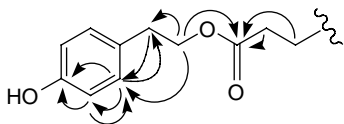


Figure 2. Selected HMBC correlations for compound **1**.

between H-2' and C-2, C-3' and C-4', and between H-3' and C-4' and C-2'. Compound **1** was thus characterized as 2-(4'-hydroxyphenyl)ethyl dotriacontanoate. Two phenylethyl esters were previously isolated from *Stereospermum personatum* [8].

Compound **2** was obtained as a white powder. It was isolated as an inseparable mixture of phenylalkanoids of *trans*-ferulic acid and long-chain alcohols as shown in the ^1H and ^{13}C NMR spectra. The IR spectrum showed absorption bands typical of hydroxyl (3432 cm^{-1}), conjugated ester carbonyl groups (1704 and 1668 cm^{-1}), and aromatic ring (1592 cm^{-1}). The ^1H NMR spectrum exhibited one singlet of methoxyl groups at δ_{H} 3.92. This spectrum also showed two doublets at δ_{H} 6.29 ($J = 15.6\text{ Hz}$, H-8/H-8') and 7.60 ($J = 15.6\text{ Hz}$, H-7/H-7'), typical of deshielded *trans* olefinic protons of an α,β -unsaturated carbonyl group [16] and signals of an ABX system of aromatic protons at δ_{H} 6.91 (d, $J = 8.1\text{ Hz}$, H-5/H-5'), 7.03 (br s, H-2/H-2'), and 7.07 (br d, $J = 8.4\text{ Hz}$, H-6/H-6'). The ^{13}C NMR spectrum showed signals of substituted aromatic carbons at δ_{C} 127.0 (C-1/C-1'), 146.7 (C-3/C-3'), and 147.8 (C-4/C-4'). These data suggested the presence of a *trans*-ferulate system. The broad singlet at δ_{H} 1.28 and the multiplet at δ_{H} 1.66 in the ^1H NMR spectrum and signals at δ_{C} 29.3 and 29.7 in the ^{13}C NMR spectrum were indicative of long-chain aliphatic alcohol moieties [17]. The number of carbons of the long-chain alcohol was determined by the HR-ESI-MS, which exhibited molecular formulas $\text{C}_{48}\text{H}_{74}\text{O}_8$ and $\text{C}_{50}\text{H}_{78}\text{O}_8$. Compound **2** was thus assigned as a

mixture of octacosan-1,28-dioldiferulate and triacontan-1,30-dioldiferulate. The relative ratio in the ESI-MS of $\text{C}_{50}\text{H}_{78}\text{O}_8$ and $\text{C}_{48}\text{H}_{74}\text{O}_8$ was 1.26; the relative amount of these two compounds was obtained as 48:38.

In addition to the above new esters, 24 known compounds (**3–26**) were also isolated. Their structures were established by comparison of NMR spectral data with those in the literature.

Candida albicans is the causative fungus of many superficial infections and over 90% of the systemic or deep yeast of infections, particularly in immunocompromised patients. It colonizes the wound site in burn patients, causing mortality in 73% of bone marrow recipients [18,19]; there is evidence of invasive candidal infections in patients with hematological malignancies due to intensive myelosuppressive chemotherapy [18]. In addition, a number of non-*albicans* *Candida* strains are currently emerging [18,20]. This prompted us to evaluate the antifungal activity of some of the isolated compounds against five *Candida* strains, *C. albicans* ATCC 24433, *C. albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258, and *Candida parapsilosis* ATCC 22019. Some of them showed only moderate activity (Table 1). Compound **11** was more active against *C. krusei* ATCC 6258 [minimum inhibitory concentration (MIC) = $25\text{ }\mu\text{g/ml}$] than the reference compound fluconazole (MIC = $50\text{ }\mu\text{g/ml}$). The most sensitive strains were *C. krusei* ATCC 6258, *C. albicans* ATCC 90028, and *C. glabrata* ATCC 90030.

3. Experimental

3.1 General experimental procedures

IR spectra were recorded on a Nicolet Magna FT-IR 750 spectrophotometer using KBr disks. UV spectra were recorded on a Shimadzu UV-2550 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz,

Table 1. Antifungal activities (MIC in $\mu\text{g/ml}$) of some compounds isolated from the stem barks of *S. acuminatissimum*.

Yeasts	Test substances																		RA1	RA2	
	1	2	3	4	6	7	9	10	11	13	15	16	19	20	21	22	23	25			
<i>C. albicans</i> ATCC 24433	50	50	50	100	100	50	50	50	50	150	100	100	50	50	100	50	50	100	50	0.195	0.195
<i>C. albicans</i> ATCC 90028	50	50	50	50	50	50	50	100	50	50	50	100	50	100	50	50	50	50	50	0.195	0.097
<i>C. glabrata</i> ATCC 90030	100	50	100	50	50	50	100	100	50	50	100	100	50	100	100	50	100	50	100	0.195	25
<i>C. krusei</i> ATCC 6258	50	50	50	50	50	50	50	50	25	50	50	50	50	50	50	50	50	50	50	1.562	50
<i>C. parapsilosis</i> ATCC 22019	100	100	100	50	50	50	100	100	100	100	100	50	100	100	100	50	100	100	100	1.562	3.125

Note: RA1, reference antibiotic 1 (Amphotericin B); RA2, reference antibiotic 2 (Fluconazole).

respectively, in CDCl_3 . The chemical shift (δ) values are given in ppm with TMS as an internal standard, and coupling constants (J) are in Hz. EI-MS and HR-EI-MS were recorded on a Finnigan MAT-95 mass spectrometer. ESI-MS and HR-ESI-MS were recorded on a Micromass LC-MS-MS mass spectrometer. Silica gel was used for flash chromatography and was produced by Qingdao Marine Chemical Industrials (Qingdao, China). Preparative HPLC was carried out on a Varian SD1 instrument with a 320 single wave detector. Chromatographic separation was carried out on two C18 columns (220×25 mm, $10 \mu\text{m}$, Merck, Darmstadt, Germany; 220×50 mm, $10 \mu\text{m}$, Merck), using a gradient solvent system of $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ containing 0.1% HCO_2Cl , at a flow rate of 15 and 60 ml/min, respectively. Sephadex LH-20 (Pharmacia Biotech AB, Uppsala, Sweden) was also used as a column packing material. TLC was carried out on precoated silica gel GF₂₅₄ plates (Yantai Chemical Industrials, Yantai, China), and the TLC spots were viewed at 254 nm and visualized by 5% sulfuric acid in alcohol containing 10 mg/ml vanillin.

3.2 Plant material

The stem bark of *S. acuminatissimum* was collected in February 2008 at Mount Eloumden, Yaounde, Center Region of Cameroon. The plant was identified by Mr Nana Victor, Botanist, at the Cameroon National Herbarium, Yaoundé, where a voucher specimen (No. 43622/HNC) has been deposited.

3.3 Extraction and isolation

Air-dried and finely powdered stem bark of *S. acuminatissimum* (3 kg) was extracted by percolation at room temperature with a mixture of $\text{CH}_2\text{Cl}_2-\text{MeOH}$ (1:1). The crude extract (220 g) was dissolved in the mixture $\text{H}_2\text{O}-\text{MeOH}$

(70:30) and sequentially partitioned with PE, CHCl_3 , EtOAc, and *n*-BuOH. Evaporation of the solvent from the PE, CHCl_3 , EtOAc, and *n*-BuOH solutions yielded 13, 17, 38.50, and 138 g of respective extracts. The CHCl_3 extract was subjected to dry flash column chromatography (CC) on silica gel (200–300 mesh, 7×80 cm, 340 g) eluting with gradients of CH_2Cl_2 –acetone and acetone–MeOH. Twenty-three fractions of 250 ml each were collected, combined on the basis of their TLC profiles, and concentrated to dryness to give six major fractions A–F: A (500 mg, CH_2Cl_2), B (120 mg, CH_2Cl_2), C (420 mg, CH_2Cl_2 –acetone 1:0, 95:5), D (1.48 g, CH_2Cl_2 –acetone 95:5, 9:1), E (1.30 g, CH_2Cl_2 –acetone 9:1, 85:15, 8:2, 7:3, 1:1), and F (1.26 g, CH_2Cl_2 –acetone 1:1, 0:1; acetone–MeOH 9:1, 0:1). Fraction A, eluted on a silica gel (200–300 mesh, 3×45 cm, 280 g) CC with a step gradient of PE–EtOAc (5 ml/min), afforded compounds **1** (40 mg), **19** (23 mg), **2** (34 mg), **25** (14 mg), and **3** (26 mg). Fraction B was subjected to the same procedure to give compounds **9** (12 mg) and **15** (6.7 mg). Fraction C was further purified by repeated silica gel CC with a gradient of PE–EtOAc, followed by gel permeation through Sephadex LH-20 (60×4.5 cm, 120 g; Pharmacia) eluting with $\text{CHCl}_3-\text{MeOH}$ (1:1; 100 ml) to yield compounds **13** (7 mg), **17** (5 mg), **26** (3 mg), and **10** (4.5 mg). Sub-fractions eluted with the mixture of PE–EtOAc (7:3) were further purified by HPLC (flow rate 10 ml/min, wavelength 220 nm) with a gradient of $\text{CH}_3\text{CN}-\text{H}_2\text{O}$, to afford compounds **11** (10 mg), **18** (7.9 mg), **20** (13 mg), and **24** (8.2 mg). Fraction D was repeatedly chromatographed over silica gel with the mixture CH_2Cl_2 –acetone in increasing polarity, to give compounds **4** (39 mg), **5** (3 mg), **12** (9 mg), **16** (6 mg), **6** (28 mg), **7** (7.8 mg), **22** (4 mg), **14** (2.8 mg), **21** (11.5 mg), **23** (9.4 mg), and **8** (4 mg).

3.3.1 2-(4'-Hydroxyphenyl)ethyl dotriacontanoate (1)

A white powder, UV (CHCl₃) λ_{max} (log ε): 282 (3.00), 276 (3.07) nm; IR (KBr) ν_{max}: 3301, 2918, 2848, 1728, 1519, 1473, 1463, 1184, 827, 719 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ_H: 7.08 (2H, d, *J* = 8.4 Hz, H-2'), 6.76 (2H, d, *J* = 8.4 Hz, H-3'), 4.23 (2H, t, *J* = 7.1 Hz, H-1), 2.85 (2H, t, *J* = 7.1 Hz, H-2), 2.27 (2H, t, *J* = 7.6 Hz, H-2''), 1.59 (2H, m, H-3'''), 1.25 (56H, brs, H-4'' to H-31''), 0.89 (3H, t, *J* = 6.8 Hz, H-32''); ¹³C NMR (75 MHz, CDCl₃) δ_C: 173.9 (C-1''), 154.2 (C-4'), 130.0 (C-6' and C-2'), 115.3 (C-5' and C-3'), 64.9 (C-1), 34.2 (C-2), 31.9 (C-2''), 29.7 and 22.7 (C-3'' and C31''), 14.1 (C-32''); EI-MS (70 eV) *m/z* (rel. int.): 601 [M + H]⁺ (3), 452 (24), 435 (9), 121 (41), 120 (100); HR-EI-MS *m/z* 600.5447 [M]⁺ (calcd for C₄₀H₇₂O₃, 600.5481).

3.3.2 Octacosan-1,28-dioldiferulate and triacontan-1,30-dioldiferulate (2)

A white powder, UV (CHCl₃) λ_{max} (log ε): 257 (4.01) nm; IR (KBr) ν_{max}: 3432, 2917, 2850, 1704, 1668, 1592, 1471, 1274, 1163, 717 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ_H: 1.28 (–[CH₂]_{*n*}–, brs), 1.66 (OCH₂CH₂, m), 3.92 (s, OMe groups), 4.18 (t, *J* = 6.6 Hz, OCH₂), 5.84 (s, OH), 6.29 (d, *J* = 15.6 Hz, H-8/H-8'), 6.91 (d, *J* = 8.1 Hz, H-5/H-5'), 7.03 (2H, brs, H-2/H-2'), 7.07 (br d, *J* = 8.4 Hz, H-6/H-6'), 7.60 (d, *J* = 15.6 Hz, H-7/H-7'); ¹³C NMR (75 MHz, CDCl₃) δ_C: 29.3 and 29.7 (–[CH₂]_{*n*}–), 55.9 (OMe), 64.6 (CH₂O), 109.2 (C-2/C-2'), 114.7 (C-5/C-5'), 115.7 (C-8/C-8'), 123.0 (C-6/C-6'), 127.0 (C-1/C-1'), 144.6 (C-7/C-7'), 146.7 (C-3/C-3'), 147.8 (C-4/C-4'), 167.4 (C-9/C-9'); ESI-MS *m/z* (rel. int.): 806 (48), 805 (94), 791 (24), 778 (38), 777 (100), 749 (18), 629 (8), 601 (1), 452 (4), 194 (24), 177 (75), 137 (19), 121 (22), 120 (44). HR-ESI-MS: *m/z* 778.5350 [M]⁺ (calcd for C₄₈H₇₄O₈, 778.5384) and 806.5663 (calcd for C₅₀H₇₈O₈, 806.5697).

3.4 Bioassays

The antifungal assays were carried out as previously described [21]. Sabouraud Dextrose Agar was used for the activation of micro-organisms and Sabouraud Dextrose Broth (Conda, Madrid, Spain) for antifungal assays. Stock solutions of the compounds in DMSO were diluted to give serial twofold dilutions that were added to each medium resulting in concentrations ranging from 1.56 to 200 μg/ml. The final concentration of DMSO in the assay did not exceed 1%. The antimicrobial agents amphotericin B (at the concentrations ranging between 0.0488 and 6.25 μg/ml) and fluconazole (at the concentrations ranging between 0.0488 and 6.25 μg/ml for *C. albicans* ATCC 24433, *C. albicans* ATCC 90028, and *C. parapsilosis* ATCC 22019 and between 0.781 and 100 μg/ml for *C. glabrata* ATCC 90030 and *C. krusei* ATCC 6258) served as positive controls. The plates were incubated for 48 h at 35°C. Tests were carried out in triplicate. The MIC was the lowest of the substances that prevented visible growth of micro-organisms.

Acknowledgements

The authors gratefully acknowledge the support from the Academy of Sciences for the Developing World (TWAS) and the Chinese Academy of Sciences (CAS) through a CAS-TWAS fellowship to SVTS at the Shanghai Institute of Materia Medica, Shanghai, China.

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