有机化学 DOI: 10.6023/cjoc202309005 研究简报
Chinese Journal of Organic Chemistry NOTE

土坛树中高度氧化的杜松烷型倍半萜及其生物活性研究

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摘要 从海南民间药用植物土坛树树皮中分离得到 2 个新的高度氧化的杜松烷型倍半萜类化合物 alansalene A (**1**)和 2,7-二羟基-4-异丙基-1-甲基-6-萘醛(**5**)以及 5 个已知的同系物, 通过 NMR、HR-ESI-MS 等多种现代波谱技术确定了其化学结构. 体外抗炎活性显示, 化合物 alangene D (**2**)具有突出的抗炎活性, 其 IC_{50}=(2.98±0.11) μmol/L 强于阳性对照药物地塞米松[IC_{50}=(39.62±0.12) μmol/L]. 体外 α-葡萄糖苷酶抑制活性显示, 化合物 alangene F (**3**)和 2,7-二羟基-4-异丙基-6-甲基萘-1-甲醛(**6**)表现出强的 α-葡萄糖苷酶抑制活性, 其 IC_{50} 值为分别为(111.85±1.80)和(18.55±0.68) μmol/L [阳性对照阿卡波糖 IC_{50}=(478.75±27.14) μmol/L].

关键词 土坛树; 高度氧化; 倍半萜; 抗炎; α-葡萄糖苷酶抑制

Studies on the Highly Oxidized Cadinane Sesquiterpenes from *Alangium salviifolium* and Their Bioactivities

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Abstract Two new highly oxidized cadinane sesquiterpenes of alansalene A (**1**) and 2,7-dihydroxy-4-isopropyl-1-methyl-6-naphthaldehyde (**5**), and five known analogues were isolated from the barks of *Alangium salviifolium*, which is a folk medicinal plant in Hainan. The structures were elucidated by spectroscopic methods (1D and 2D NMR, HR-ESI-MS). Compound alangene D (**2**) exhibited stronger anti-inflammatory activity *in vitro* with IC_{50} value of (2.98±0.11) μmol/L to that of dexamethasone [IC_{50}=(39.62±0.12) μmol/L]. Alangene F (**3**) and 2,7-dihydroxy-4-isopropyl-6-methylnaphthalene-1-carbaldehyde (**6**) displayed potential α-glucosidase inhibitory activities with IC_{50} values of (111.85±1.80) and (18.55±0.68) μmol/L, respectively, which were stronger than that of acarbose [IC_{50}=(478.75±27.14) μmol/L].

Keywords *Alangium salviifolium*; highly oxidization; sesquiterpene; anti-inflammatory; α-glucosidase inhibitory

1 Introduction

Alangium salviifolium, also known as 'Ge-she-luo', belongs to the genus *Alangium* (Alangiaceae) and comprises about 30 species growing mainly in tropical and subtropical Asia and Oceania. Among them, nine species growing in China.[1] *A. salviifolium* is a tall thorny tree and mainly distributed in Hainan, Guangdong, and Guangxi of China.[2]

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Received September 4, 2023; revised October 31, 2023; published online November 15, 2023.
Project supported by the Key R&D Projects in Hainan Province-Social Development (Nos. ZDYF2022SHFZ286, ZDYF2021SHFZ072), the National Natural Science Foundation of China (No. 21662012), the Innovation Platform for Academicians of Hainan Province (No. YSPTZX202030), and the Central Government Guides Local Science and Technology Development (No. ZY2022HN08), and the Hainan Normal University "Innovative Entrepreneurship Training Program for College Students" (No. 202311658005).
海南省重点研发项目(Nos. ZDYF2022SHFZ286, ZDYF2021SHFZ072)、国家自然科学基金(No. 21662012)、海南省院士创新平台(No. YSPTZX202030)、中央引导地方科技发展专项(No. ZY2022HN08)及海南师范大学"大学生创新创业训练计划"(No. 202311658005)资助项目.
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It is a well-known traditionally used medicinal plant in India and has a wide spectrum of biological activities, such as anti-arthritic, antidiabetic, analgesic, anti-inflammatory, diuretic, antiepileptic and antifungal.[3-4]

Previous phytochemical investigations on *A. salviifolium* led to alkaloids, glycosides, and terpenoids, some of which showed anti-inflammatory, antibacterial, and cytotoxic activities.[5-8] Such as, salicin isolated from *A. chinense* ameliorates rheumatoid arthritis (RA), 10-*O*-demethylcephaeline from *A. salviifolium* exhibited potent cytotoxic activity against human lung carcinoma (A549) and breast adenocarcinoma (MCF-7) with ED_{50} values of 0.013 and 0.062 μmol/L, respectively.[6] In search for bioactive and structurally diverse natural products from *A. salviifolium*, two new cadinane sesquiterpenes and five analogues (Figure 1) were isolated from the ethyl acetate extracts of the barks of *A. salviifolium*. Meanwhile, the cytotoxic activity, anti-inflammation, and *α*-glucosidase inhibitory of all the compounds were evaluated.

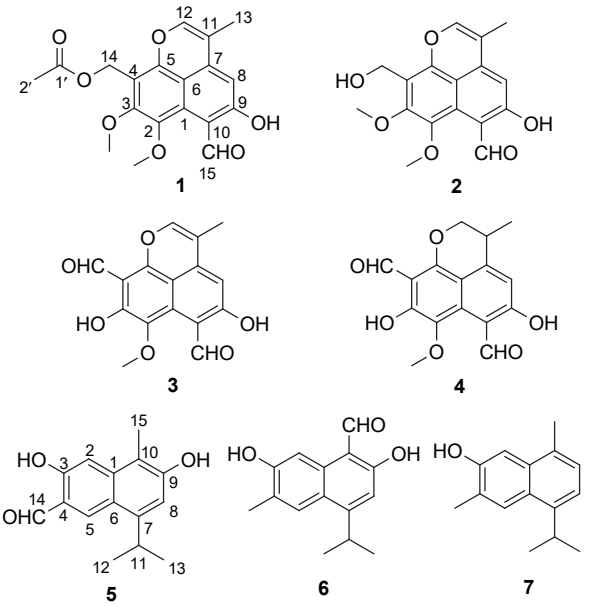

Figure 1 Cadinane sesquiterpenes constituents from *A. salviifolium*.

2 Results and discussion

2.1 Structure elucidation

Alansalene A (**1**) was obtained as a yellow amorphous powder. The molecular ion peak was determined by HR-ESI-MS at *m/z* 381.0940 $[M+Na]^+$ (calcd for $C_{19}H_{18}O_7Na$, 381.0950), corresponding to a molecular formula $C_{19}H_{18}O_7$ and indicating eleven degrees of unsaturation. Its IR spectrum showed absorptions due to the hydroxy (3437 cm^{-1}), chelated aldehyde (1628 cm^{-1}), and aromatic (1351 and 1111 cm^{-1}) groups. The ^1H NMR spectrum (Table 1) exhibited the signals for a chelated hydroxy group at δ_H 14.77 (s, 1H, OH-9), an aldehyde proton at δ_H 10.96 (s, 1H, H-15), two olefinic protons at δ_H 7.07 (d, *J*=1.4 Hz, 1H, H-12) and 6.34 (s, 1H, H-8), one methylene at δ_H 5.28 (s, 2H, H-14), two methoxyl groups at δ_H 4.02 (s, 3H, OCH_3-3) and 3.81 (s, 3H, OCH_3-2), and two methyl groups at δ_H 2.08 (s, 3H, H-2') and 1.95 (d, *J*=1.4 Hz, 3H, H-13). The ^{13}C NMR (Table 1) and DEPT spectra of **1** revealed a total of 19 signals, including an aldehyde carbonyl at δ_C 196.5, eleven quaternary carbons, two methine groups, one methylene, two methoxy carbons, and two methyl carbons. The 1D NMR data indicated that **1** was a highly oxidized cadinane sesquiterpene, and the structure of **1** was similar to that of alangene D (**2**),[9] except for the presence of an acetyl group δ_C 171.2 and 21.2/δ_H 2.08 (s, 3H, H-2') in **1**. The HMBC correlations (Figure 2) from H-2' (δ_H 2.08) to C-1' (δ_C 171.2), and from H-14 (δ_H 5.28) to C-1' (δ_C 171.2), as well as the downfield chemical shift of C-14 (δ_C 56.0), confirmed the acetyl group located at C-14. Therefore, the structure of **1** was identified as alansalene A.

Table 1 ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) data of compounds **1** and **5**

No.	**1**[a]		**5**[b]	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1		128.5 (C)		142.1 (C)
2		143.0 (C)	7.19, s	108.2 (CH)
3		154.3 (C)		157.1 (C)
4		110.2 (C)		120.8 (C)
5		148.2 (C)	8.47, s	134.1 (CH)
6		115.1 (C)		122.3 (C)
7		141.2 (C)		148.0 (C)
8	6.34, s	105.2 (CH)	6.95, s	113.9 (CH)
9		170.1 (C)		157.4 (C)
10		110.2 (C)		112.8 (C)
11		112.7 (C)	3.71～3.73, m	29.5 (CH)
12	7.07, d (1.4)	144.1 (CH)	1.37, d (6.8)	24.1 (CH_3)
13	1.95, d (1.3)	13.4 (CH_3)	1.37, d (6.8)	24.1 (CH_3)
14	5.28, s	56.0 (CH_2)	10.10, s	197.4 (CH)
15	10.96, s	196.5 (CH)	2.34, s	10.6 (CH_3)
1'		171.2 (C)		
2'	2.08, s	21.2 (CH_3)		
2-OCH_3	3.81, s	59.2 (CH_3)		
3-OCH_3	4.02, s	61.9 (CH_3)		
OH-9	14.77, s			

[a] Measured in $CDCl_3$; [b] Measured in CD_3OD.

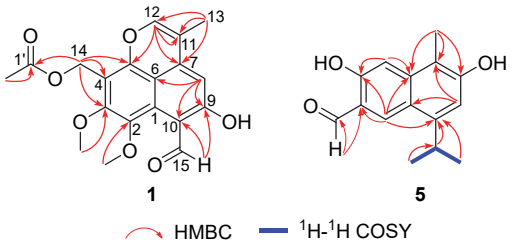

Figure 2 Key HMBC and ^1H-^1H COSY correlations for compounds **1** and **5**

2,7-Dihydroxy-4-isopropyl-1-methyl-6-naphthaldehyde (**5**) was isolated as a yellow solid power. Its molecular formula was defined as $C_{15}H_{16}O_3$ with eight degrees of unsaturation from its HR-ESI-MS ion at *m/z* 243.1021 [M−

H]$^-$ (calcd for $C_{15}H_{15}O_3$, 243.1021). Its IR spectrum showed absorptions due to the hydroxy (3429 cm^{-1}), chelated aldehyde (1624 cm^{-1}), and aromatic (1350 and 1121 cm^{-1}) groups. The ^{1}H NMR spectrum of compound **5** (Table 1) showed resonances of one aldehyde group at δ_H 10.10 (s, 1H, H-14), three aromatic protons at δ_H 8.47 (s, 1H, H-5), 7.19 (s, 1H, H-2) and 6.95 (s, 1H, H-8), three methyl groups at δ_H 2.34 (s, 3H, H-15) and 1.37 (d, 6H, J=6.8 Hz, H-12/13), and one methine proton at δ_H 3.71～3.73 (m, 1H, H-11). The ^{1}H-^{1}H COSY correlations (Figure 2) of H-11/H-12/13, showed that the structure contains an isopropyl group. The ^{13}C NMR (Table 1) and DEPT showed 15 carbon signals, including one aldehyde carbon, three methyl groups, one sp^3 methine group, three aromatic methine groups, and seven quaternary carbons. Detailed analysis of 1D NMR data suggested that **5** was a highly oxidized cadinane sesquiterpene. The NMR data closely resembled those of 2,7-dihydroxycadalene.[10] The only difference between them was the presence of additional an aldehyde group at the C-4 position in **5** instead of methyl in 2,7-dihydroxycadalene. The HMBC correlations (Figure 2) from the aldehyde proton (H-14) to C-4 (δ_C 120.8) and C-3 (δ_C 157.1) revealed that the aldehyde group was attached at C-4. Further analysis of the HMBC correlations from H_3-12 to C-7 and C-11, from H-5 to C-7, C-4, C-3 and C-1, from H-2 to C-10, C-4, C-3 and C-6, from H_3-15 to C-10, C-9 and C-1, from H-8 to C-10, C-6 and C-11, leading to the proposed structure of **5** as shown in Figure 1, and named as 2,7-dihydroxy-4-isopropyl-1-methyl-6-naphthaldehyde.

Five known compounds were isolated and identified as alangene D (**2**),[9] alangene F (**3**),[9] alangene C (**4**),[9] 2,7-dihydroxy-4-isopropyl-6-methyl-naphthalene-1-carbaldehyde (**6**),[11] 7-hydroxycadalin (**7**)[12] (Figure 1) by comparing their spectroscopic data with the reported ones.

Compounds **1**～**7** were evaluated for their inhibitory potencies on nitric oxide (NO) release from lipopolysaccharide (LPS)-stimulated RAW264.7 cells, while dexamethasone was used as a positive control. The results showed that compound **2** with IC_{50} value of (2.98±0.11) μmol/L, which were stronger than dexamethasone [IC_{50}=(39.62±0.12) μmol/L] (Table 2).

Table 2 Anti-inflammatory activity of compounds **1**～**7** on LPS-induced NO production in RAW264.7 cells

Compound[a]	IC_{50}[b]/(μmol•L^{-1})
2	2.98±0.11
Dexamethasone[c]	39.62±0.12

[a] The compounds with IC_{50} values >100 μmol•L^{-1} were not listed in the table; [b] Values represent means±SD of the triplicate experiment; [c] Positive control.

Compounds **1**～**7** were evaluated for α-glucosidase inhibitory activity, while acarbose was used as the positive control. Among them, compounds **3** and **6** displayed inhibitory activities with IC_{50} values of (111.85±1.80) and (18.55±0.68) μmol/L, respectively, which were comparable to that of acarbose [IC_{50}=(478.75±27.14) μmol/L] (Table 3).

Table 3 α-glucosidase inhibitory activity of compounds **1**～**7**

Compound[a]	IC_{50}[b]/(μmol•L^{-1})
3	111.85±1.80
6	18.55±0.68
Acarbose[c]	478.75±27.14

[a] The compounds with IC_{50} values >200 μmol•L^{-1} were not listed in the table; [b] Values represent means±SD of the triplicate experiment; [c] Positive control.

Compounds **1**～**7** were evaluated for their cytotoxic activities *in vitro* (doxorubicin hydrochloride was used as a positive control). Compounds **1** and **5** showed weak cytotoxic activities against human cancer cell lines (SGC-7901, K562, A549, BEL) with IC_{50} values ranging from 30.60 μmol/L to 72.88 μmol/L (Table 4).

Table 4 Cytotoxicity of compounds **1**～**7** in cancer cell lines

Compd.[a]	SGC-7901[b]	K562[b]	A549[b]	BEL[b]
1	59.49±3.07	30.60±1.38	61.18±0.65	72.88±1.64
5	55.18±3.11	45.27±0.63	39.20±1.40	49.62±0.57
Doxorubicin hydrochloride[c]	0.06±0.01	0.55±0.01	1.51±0.06	3.79±0.22

[a] The compounds with IC_{50} values >100 μmol•L^{-1} were not listed in the table; [b] Values represent means±SD of the triplicate experiment; [c] Positive control.

3 Conclusions

Two new cadinane sesquiterpenes (**1** and **5**) and five known analogues (**2**～**4**, **6** and **7**) were obtained from the barks of *A. salviifolium*. Their structures were determined by extensive analysis. The results of anti-inflammatory activity screening showed that **2** exhibited strong anti-inflammatory activity with IC_{50} value of (2.98±0.11) μmol/L. Compounds **3** and **6** displayed pronounced α-glucosidase inhibitory activities with IC_{50} values of (111.85±1.80) and (18.55±0.68) μmol/L, respectively. Compounds **1** and **5** showed moderate cytotoxic activities against four human cancer cell lines with IC_{50} values ranging from 30.60 μmol/L to 72.88 μmol/L. These findings enriched the chemical diversity of the constituents from *A. salviifolium* and provided a few promising lead compounds for further development of anti-inflammatory and anti-diabetic drugs.

4 Experimental section

4.1 General experimental procedures

The NMR spectra were recorded on Bruker AV 400 NMR spectrometers using TMS as an internal standard. HR-ESI-MS spectra were performed on an Agilent 6210 ESI/TOF mass spectrometer. Ultra Performance Liquid Chromatography (UPLC) was performed on a Thermo Fisher Ultimate 3000. Semi-preparative HPLC was performed on an Agilent 1260 LC series with a DAD detector using an Agilent Eclipse XDB-C_{18} column (9.4 mm×250 mm, 5 μm). IR spectra were recorded on a Nicolet 6700

spectrophotometer. Column chromatography (CC) was carried out on silica gel (100～200, 200～300 mesh, Qingdao Haiyang Chemical Co., Ltd, China) and C_{18} ODS-A (50 μm, YMC, Japan). TLC analysis was performed on precoated silica gel GF_{254} plates (Qingdao Haiyang Chemical Co., Ltd, China).

4.2 Plant material

A. salviifolium was collected in December 2021 from Haikou Crater National Geopark, Hainan Island, China. The species was authenticated as *A. salviifolium* by Dr. Yu-Kai Chen (Hainan Normal University, Hainan, China). A voucher specimen (No. 20211220) was deposited at the Key Laboratory of Tropical Medicinal Resource Chemistry of the Ministry of Education, Hainan Normal University.

4.3 Extraction and isolation

The dried barks of the *A. salviifolium* (20 kg) were crushed and extracted with petroleum ether (PE) (30 L×2, each for 3 d), ethyl acetate (EtOAc) (30 L×2, each for 3 d), and 95% ethanol (EtOH) (30 L×2, each for 5 d) successively. The extracts were condensed *in vacuo* to obtain different solvent crude extracts. Subsequently, the EtOAc crude extract (141.0 g) was subjected to silica gel vacuum liquid column (VLC) eluted with PE/EtOAc (V∶V=100∶1～0∶1) to give 25 fractions (Fr.1～Fr.25).

Fr.4 (10.636 g) was separated by ODS column chromatography (CC) with methanol (CH_3OH)/H_2O as eluent (V∶V=3∶2～1∶0) to obtain 18 fractions (Fr.4.1～Fr.4.18). Fr.4.2 was separated by semi-preparative HPLC eluting by 48% acetonitrile in water to obtain **5** (3.0 mg, t_R=60 min, flow rate=3 mL/min). Fr.4.3 was purified by semi-preparative HPLC eluting by 58% acetonitrile in water to yield **6** (7.8 mg, t_R=30 min) and **4** (5.5 mg, t_R=36 min, flow rate=2.5 mL/min). Fr.4.4 was divided into 9 fractions (Fr.4.4.1～Fr.4.4.9) by a silica gel CC eluting with PE/EtOAc (V∶V=10∶1～1∶0), Fr.4.4.2 was dissolved in CH_3OH and recrystallized to obtain **3** (12.3 mg). Fr.4.4.3 was separated by semi-preparative HPLC eluting by 62% acetonitrile in water to yield **7** (2.0 mg, t_R=20 min, flow rate=2.5 mL/min). Similarly, Fr.4.4.5 was purified by semi-preparative HPLC eluting with 70% acetonitrile in water to afford **1** (3.6 mg, t_R=15 min, flow rate=2.5 mL/min). Fr.4.9 was subjected to silica gel CC eluting with PE/EtOAc (V∶V=8∶1～1∶0) to yield 6 fractions (Fr.4.9.1～Fr.4.9.6). Fr.4.9.4 was dissolved in CH_3OH and purified to get **2** (22.3 mg).

4.4 Characterization of compounds

Alansalene A (**1**): Yellow amorphous power. UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 209 (4.74), 239 (4.64), 281 (4.33), 428 (3.93) nm; ^{1}H NMR and ^{13}C NMR data see Table 1; IR (KBr) ν_{max}: 3437, 2356, 1628, 1351, 1111, 476 cm^{-1}; HR-ESI-MS calcd for $C_{19}H_{18}O_7Na$ [M+Na]$^+$ 381.0950, found 381.0940.

2,7-Dihydroxy-4-isopropyl-1-methyl-6-naphthaldehyde (**5**): Yellow amorphous power. UV (MeOH) λ_{max} [log ε/(L•mol^{-1}•cm^{-1})]: 221 (4.34), 245 (4.41), 283 (4.25), 343 (3.88) nm; ^{1}H NMR and ^{13}C NMR data see Table 1; IR (KBr) ν_{max}: 3429, 1624, 1350, 1121, 473 cm^{-1}; HR-ESI-MS calcd for $C_{15}H_{15}O_3$ [M－H]$^-$ 243.1021, found 243.1021.

4.5 Assay of anti-inflammatory activity

The anti-inflammatory activity was evaluated by determination of NO production in RAW264.7 cell culture supernatants induced by LPS with Griess reagent.[13] The RAW264.7 cells were inoculated in 96-well plates with a density of 1×10^5 cells per well, and treated with samples and positive control (dexamethasone) after 12 h. 1 h later, cells were exposed to 1 μg/mL LPS and cultured at 37 ℃ and 5% (φ) CO_2 for 24 h. Next, 50 μL of culture supernatant and 100 μL of Griess reagent were mixed. The absorbance values at a wavelength of 540 nm were recorded by a microplate reader.

4.6 Assay of α-glucosidase inhibitory

α-Glucosidase inhibitory activity assay of **1**～**7** was performed followed by the procedures as previously described.[14] Briefly, 10 μL of sample [it was dissolved in dimethyl sulfoxide (DMSO) and diluted to different concentrations] was incubated with 100 μL of α-glucosidase solution (0.2 U/mL) at 37 ℃ for 15 min. Then, 40 μL of 2.5 mmol/L *p*-nitrophenyl-α-*d*-glucopyranoside (*p*-NPG) was added and further incubated at 37 ℃ for 15 min. The OD values were measured at 405 nm with a microplate reader. The percentage inhibition was calculated using the following equation:

$$\text{Inhibition}(\%) = [1 - (OD_{compound} - OD_{blank})/(OD_{control} - OD_{blank})] \times 100\%$$

4.7 Assay of cytotoxicity

The following human tumor lines were used: SGC (gastric cancer), K562 (erythroleukemia), A549 (lung cancer) and BEL (liver cancer). All cancer cells were seeded in 96-well plates and cultured for 12 h. The appropriate test compounds and positive control (doxorubicin hydrochloride) were added into triplicate wells at different concentrations and incubated at 37 ℃ and 5% CO_2 for 48 h. Cell viability was measured by 3-(4,5-dimehthylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay[15]. DMSO was used to dissolve the formazan crystals and then the OD values at 490 nm of each well were measured.

Supporting Information 1D and 2D NMR, HR-ESI-MS spectra of compounds **1** and **5**. These materials can be downloaded for free from the website (http://sioc-journal.cn/).

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