Tetrahedron Letters 57 (2016) 3215–3217

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diocollettines A, an unusual tricyclic diarylheptanoid derivative from the rhizomes of *Dioscorea collettii*

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ARTICLE INFO

Article history:
Received 1 May 2016
Revised 6 June 2016
Accepted 12 June 2016
Available online 14 June 2016

Keywords:
Tricyclic diarylheptanoid
Dioscorea collettii
Absolute configuration
Cytotoxicity

ABSTRACT

An unprecedented diarylheptanoid derivative with 6/5/5 fused rings, diocollettines A (**1**), together with five known compounds (**2**–**6**) were isolated from the rhizomes of *Dioscorea collettii*. The structures were elucidated by extensive NMR spectroscopic analysis, together with HR-ESI-MS techniques. The absolute configuration of compound **1** was unambiguously confirmed by comparison of experimental data with calculated electronic circular dichroism (ECD) spectra and single-crystal X-ray diffraction analysis. Compound **1** exhibited moderate cytotoxicity against NCL-H460.

Introduction

Plants of *Dioscorea* genus (Dioscoreaceae) have been reported to be rich in a variety of compounds, such as steroid saponins,[1] diarylheptanoids,[2,3] and phenolic compounds.[4,5] Some species of *Dioscorea* have been used extensively as herbal medicine for the treatment of gastric diseases, urethra infection, bone injuries, and rheumatic arthritis for a long time. Extensive phytochemistry and pharmacological studies showed that compounds obtained from *Dioscorea* genus had a wide spectrum of antimicrobial,[6,7] anti-neuroinflammatory,[2] anti-inflammatory,[8] and anti-tumor properties.[9,10] *Dioscorea collettii*, known as 'Charuishuyu' in China, belongs to *Dioscorea* genus (Dioscoreaceae) and is widely distributed in Myanmar, India, and southwest of China. Despite the significant biological activities of compounds obtained from *Dioscorea* genus, only a limited number of phytochemical studies of *D. collettii* have been published so far. Previous studies on the phytochemistry of *D. collettii* revealed the presence of several steroid saponins.[11,12]

In our ongoing search for novel bioactive from the *Dioscorea* genus,[13] the chemical constituents of *D. collettii* have been investigated in depth. A novel diarylheptanoid derivative named diocollettines A (**1**), together with five known compounds (**2**–**6**) were isolated. Compound **1** possesses an unprecedented heterocyclic structure with five chiral centers in which two tetrahydrofuran rings and one tetrahydropyran ring are fused to construct a tricyclic ring system. Herein, the isolation, structure elucidation, and cytotoxicities against NCL-H460 of compounds **1**–**6** were reported (Fig. 1).

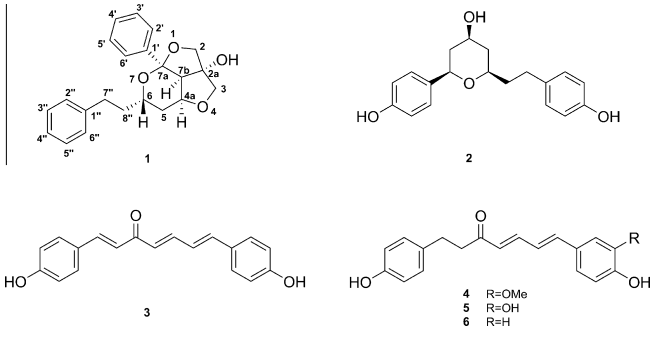

Figure 1. Chemical Structures of compounds **1**–**6**.

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http://dx.doi.org/10.1016/j.tetlet.2016.06.047
0040-4039/

Compound **1**, obtained as a colorless solid, was found to possess a molecular formula of $C_{22}H_{24}O_4$ by its HRESIMS peak at *m*/*z* 353.1752 $[M+H]^+$ (calcd for $C_{22}H_{25}O_4$, 353.1753), indicating 11 degrees of unsaturation. Its UV spectrum exhibited absorption maxima at 195, 205, and 256 nm. In the ^{1}H NMR data (Table 1) (600 MHz, DMSO-d_6), ten aromatic proton signals between δ_H 7.54 and 7.14 indicated the presence of two mono-substituted benzene rings, which was supported by the hydrogen signals at δ_H 7.54 (2H, d, *J* = 7.5 Hz, H-2′, 6′), 7.35 (2H, t, *J* = 7.2 Hz, H-3′, 5′), 7.28 (1H, t, *J* = 7.2 Hz, H-4′), 7.24 (2H, t, *J* = 7.2 Hz, H-3″, 5″), 7.19 (2H, d, *J* = 7.3 Hz, H-2″, 6″), 7.14 (1H, t, *J* = 7.0 Hz, H-4″). Additionally, two oxymethylene groups at δ_H 4.01 (1H, d, *J* = 9.2 Hz, H_a-2), 3.76 (1H, d, *J* = 9.2 Hz, H_b-2), 3.90 (1H, d, *J* = 8.6 Hz, H_a-3), 3.50 (1H, d, *J* = 8.6 Hz, H_b-3); two oxymethine protons at δ_H 4.29 (1H, m, H-4a), 3.97 (1H, m, H-6); three methylene groups at δ_H 2.64 (1H, m, H_a-7″) and 2.61 (1H, m, H_b-7″), 1.79 (1H, d, *J* = 14.3 Hz, H_a-5) and 1.62 (1H, t, *J* = 12.9 Hz, H_b-5), 1.72 (1H, m, H_a-8″) and 1.67 (1H, m, H_b-8″); one methine proton at δ_H 2.61 (1H, m, H-7b) was observed. The presence of one proton signal at δ_H 5.46 (HO-2a) indicated the presence of one hydroxyl group, which was unambiguously designated by the HSQC experiment. The ^{13}C NMR and DEPT spectra revealed 22 carbon signals, attributable to 12 aromatic carbon signals assignable to two mono-substituted benzene rings, five methylenes (two oxymethylenes), three methines (two oxymethines), and two quaternary carbons (Table 1).

The 11 degrees of unsaturation inherent in the molecular formula of compound **1**, coupled with data showing the presence of two benzene rings, indicated that diocollettines A (**1**) possesses another three rings to fulfill the unsaturation requirement. In the ^{1}H–^{1}H COSY spectrum (Fig. 2), the correlation of H_{ab}-7″ (δ_H 2.61, 2.64) /H_{ab}-8″ (δ_H 1.67, 1.72)/H-6 (δ_H 3.97)/H_{ab}-5 (δ_H 1.62, 1.79)/H-4a (δ_H 4.29)/H-7b (δ_H 2.61) revealed the –CH_2-CH_2-CH-CH_2-CH-CH- (C-7/C-8/C-6/C-5/C-4a/C-7b) subunit in compound **1**. One phenyl group attached to C-7″ was clarified by the correlations from H_{ab}-7″ to C-2″/C-6″ (δ_C 128.4), H_{ab}-7″ to C-1″ (δ_C 141.9), and H_{ab}-8″ to C-1″ in the HMBC spectrum (Fig. 2). The linkages of C-6/5/4a/7b as well as the HMBC correlations from H-4a and H-6 to C-7a (δ_C 107.5), together with the downfield chemical shifts of C-6 (δ_C 63.7) and C-7a (δ_C 107.5), established a tetrahydropyran ring-A. The correlations from H-2′, H-6′ to C-7a, and from H-7b to C-1′ (δ_C 144.6) in the HMBC spectrum revealed that the other phenyl group was connected to C-7a. The signals of the oxymethylene carbon at δ_C 78.3 (C-2) and the quaternary carbon at δ_C 87.7 (C-2a), together with the HMBC correlations of H_{ab}-2 with C-2a (δ_C 87.7), C-7b (δ_C 52.6) and H-7b with C-2a, C-2 (δ_C 78.3) indicated the connectivity of C-7b/C-2a/C-2. Then, a tetrahydrofuran ring-B was proposed by the correlations of H_{ab}-2 with C-7a in the HMBC spectrum, combined with the downfield chemical shift of C-2 (δ_C 78.3). In the HMBC spectrum, the correlations of an active proton δ_H 5.46 (s, HO-2a) with C-2a, C-7b, and C-2 suggested the hydroxyl was linked to C-2a. The cross peaks between H_{ab}-3 with C-2, C-2a, and C-7b in the HMBC spectrum indicated the direct connection between C-3 (δ_C 76.7) and C-2a. The established linkage of C-4a/C-7b/C-2a/C-3 as well as the downfield chemical shift of C-3 (δ_C 76.7) and C-4a (δ_C 75.1), together with the HMBC correlations of H_{ab}-3 with C-4a, constructed a tetrahydrofuran ring-C, which met its unsaturation degree. Thus, the planar structure of compound **1**, shown in Figure 1, was established to possess an unprecedented 6/5/5 ring-fused system.

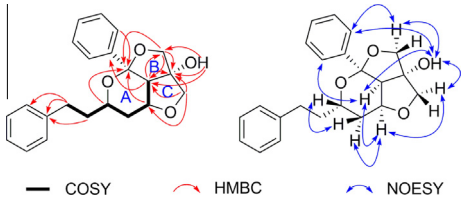

Figure 2. ^{1}H–^{1}H COSY, key HMBC, and NOESY correlations of diocollettines A (**1**).

The relative stereochemistry of diocollettines A was elucidated by an analysis of the NOESY spectrum (Fig. 2). The correlations of H_b-2/HO-2a, H_b-2/H-2′, HO-2a/H_b-3, HO-3a/H-7b, HO-2a/H-2′, H_b-3/H-4a, H-4a/H_b-5, H-4a/H-7b, H-7b/H-6′, and H_a-5/H-6 strongly indicated the same orientation of H-2′, H-6′, HO-2a, H-4a, and H-7b while H-6 was in the other orientation.

The absolute configuration of compound **1** was determined by comparing the experimental with the computational electronic circular dichroism (ECD) spectra (Fig. 3). The calculated ECD curve of

Table 1
^{1}H, ^{13}C NMR data, and HMBC correlations of diocollettines A (**1**) in DMSO[a]

No.	δ_H, mult (*J* in Hz)[b]	δ_C	HMBC (H→C)
2	a: 4.01, d (9.2) b: 3.76, d (9.2)	78.3, CH_2	C-2a, C-3, C-7a, C-7b
2a		87.7, C	
3	a: 3.90, d (8.6) b: 3.50, d (8.6)	76.7, CH_2	C-2, C-2a, C-4a, C-7b
4a	4.29, m	75.1, CH	C-6, C-7a
5	a: 1.79, d (14.3) b: 1.62, t (12.9)	32.1, CH_2	C-4a, C-7b, C-8″
6	3.97 (1H, m)	63.7, CH	C-4a, C-7a, C-7″, C-8″
7a		107.5, C	
7b	2.61, m	52.6, CH	C-2, C-2a, C-3, C-1′
1′		144.6, C	
2′, 6′	7.54, d (7.5)	125.8, CH	C-7a
3′, 5′	7.35, t (7.2)	127.9, CH	C-1′
4′	7.28, t (7.2)	127.6, CH	
1″		141.9, C	
2″, 6″	7.19, d (7.3)	128.4, CH	C-7″
3″, 5″	7.24, t (7.2)	128.3, CH	C-1″
4″	7.14, t (7.0)	125.7, CH	C-2″, C-6″
7″	a: 2.64, m b: 2.61, m	30.9, CH_2	C-6, C-1′, C-2″, C-6″, C-8″
8″	a: 1.72, m b: 1.67, m	36.8, CH_2	C-6, C-1′, C-7″
2a-OH	5.46, s		C-2, C-2a, C-7b

[a] ^{1}H NMR was measured at 600 MHz, ^{13}C NMR spectrum was measured at 150 MHz.
[b] Lower-field methylene signals were labeled as 'a' and higher-field signals as 'b'.

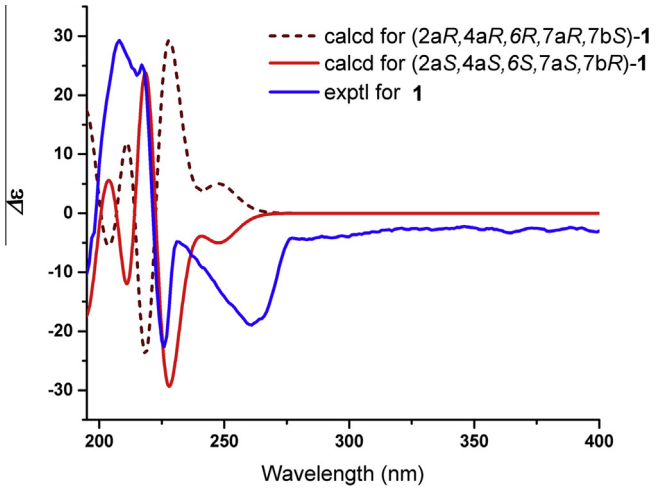

Figure 3. Comparison of the experimental CD spectrum of compound **1** with calculated ECD spectra for (2a*R*,4a*R*,6*R*,7a*R*,7b*S*)-**1** and (2a*S*,4a*S*,6*S*,7a*S*,7b*R*)-**1** in MeOH. σ = 0.25 eV; shift = 30 nm.

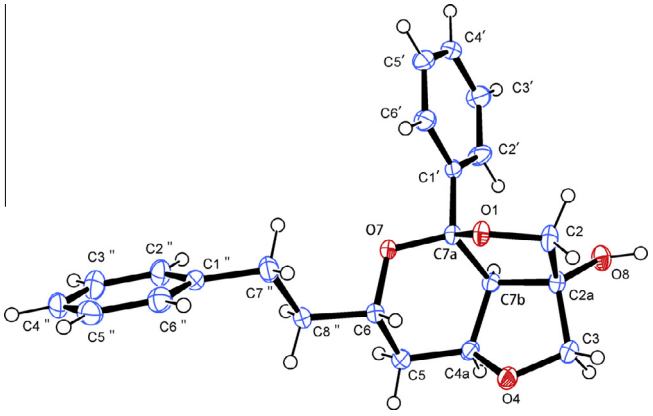

Figure 4. Single-crystal X-ray structure of diocollettines A (**1**).

enantiomeric configuration of (2a*R*,4a*R*,6*R*,7a*R*,7b*S*)-**1** matched well with the experimental one, assigning unambiguously the absolute configuration of compound **1** as (2a*S*,4a*S*,6*S*,7a*S*,7b*R*)-**1**. Furthermore, crystallization of compound **1** was carried out in cyclohexane/dichloromethane, giving triclinic crystals suitable for X-ray crystallographic analysis. These crystals further confirmed the planar structure and the absolute configuration of compound **1** (deposition number: CDCC 1477278; Fig. 4).

The remaining known compounds were identified as (1*R*,3*S*,5*R*)-1,7-bis(4-hydroxyphenyl)-1,5-epoxy-3-hydroxyheptane (2),[3,14] 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (3),[15] Tsaokoarylone (4),[16] diarylcomosols I (5),[17] 1,7-bis(4-hydroxyphenyl)hepta-4*E*,6*E*-dien-3-one (6).[18] Their structures were established by comparison of their NMR spectroscopic data and optical rotation with those reported in the literature.

Compounds **1**–**6** were tested for theirs cytotoxicity against human lung cancer NCL-H460 cell lines. The results indicated compound **4** had strong cytotoxic activity with IC_{50} = 0.23 μM in these compounds. Compound **1** showed a moderate cytotoxic activity with IC_{50} = 20.15 μM while compound **2** showed no activity with IC_{50} >100 μM.

Acknowledgment

This research was financially supported by a grant from the National Natural Science Foundation of China (No. 81173487).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.06.047. These data include MOL files and InChiKeys of the most important compounds described in this article.

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