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Serratustones A and B Representing a New Dimerization Pattern of Two Types of Sesquiterpenoids from *Chloranthus serratus*

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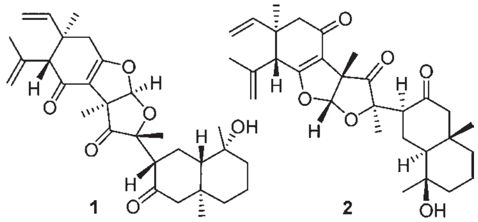
ABSTRACT



Serratustones A (1) and B (2), featuring a new carbon skeleton and representing a novel dimerization pattern of two different types of sesquiterpenoids, were isolated from *Chloranthus serratus*. Their structures with absolute configuration were determined on the basis of a detailed explanation of spectroscopic data, X-ray crystallography, and CD analysis in combination with ECD calculation.

Sesquiterpenoid dimers are a class of natural products of plant origin with both fascinating structural complexity and biological significance,[1] which has attracted attention of not only pharmacologists[2] but also synthetic chemists.[3] Plants of the Chloranthaceae family are well-known in scientific literature for their ability to produce novel disesquiterpenoids,[1] while to date they have been reported to yield only lindenane-type sesquiterpenoid dimers[1,4] that are believed to be biosynthesized from two monomers involving an *endo* Diels–Alder cycloaddition as the key step in most cases.[5] The plant of *Chloranthus serratus* (Thunb.) Roem. et Schult., a perennial herb growing mainly in southern China, has long been applied in remedies of traditional Chinese medicine to promote blood circulation and remove blood stasis.[6] Previous chemical studies of this species by our group[7] and other researchers[8] have led to the isolation of a number of amides, sesquiterpenoids, and lindenane-type sesquiterpenoid dimers. As an extension of structurally diverse and novel constituents, two additional sesquiterpenoid dimers with a new skeleton, namely serratustones A (**1**) and B (**2**), were further

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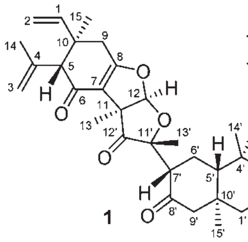
discovered from the same plant material. The absolute structures of **1** and **2** were characterized on the basis of spectroscopic data, single crystal diffraction analysis, and CD spectra as well as ECD calculation. Serratustones A (**1**) and B (**2**) represent the first examples of nonlindenane-type sesquiterpenoid dimers from the Chloranthaceae family, which was biosynthetically formed from a novel dimerization pattern of an elemane and an eudesmane by involving aldol condensation as the key step (Scheme 1).[9] This report describes the extraction, isolation, and structure elucidation, together with a discussion on the plausible biosynthetic pathway to the formation, of the two fascinating dimers.



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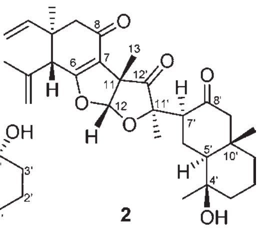

2

Serratustone A (**1**)[10] displayed a sodiated molecular ion $[M + Na]^+$ at m/z 519.2704 (calcd 519.2723) in the HR-ESI(+)MS analysis, consistent with a molecular formula of $C_{30}H_{40}O_6$ incorporating 11 degrees of unsaturation. The IR spectrum showed the presence of hydroxyl (3430 cm^{-1}), carbonyl (1765 and 1689 cm^{-1}), and vinyl (1657 and 1632 cm^{-1}) groups. The NMR data ($CDCl_3$, Supporting Information (SI) Table S1) of **1**, with the aid of DEPT and HSQC (SI Figure S4) experiments, revealed resonances suggestive of a monosubstituted terminal double bond (δ_H 5.73, H-1; 4.99 and 4.94, H_2-2; δ_C 145.7, C-1; 113.3, C-2), a disubstituted double bond (δ_H 5.02 and 4.80, H_2-3; δ_C 115.2, C-3; 141.4, C-4), a tetrasubstituted double bond (δ_C 114.9, C-7; 175.0, oxygenated, C-8), and three carbonyls (δ_C 192.5, C-6; 208.9, C-8′; 209.9, C-12′). Other characteristic signals included an olefinic methyl (δ_C 25.0, C-14), five tertiary methyls (δ_C 16.5, 19.0, 23.2, 25.6, and 30.7; C-13, C-15′, C-13′, C-15, and C-14′, respectively), one sp^3 oxygenated methine (δ_C 115.1, C-12), and two sp^3 oxygenated quaternary carbons (δ_C 71.4, C-4′; 83.2, C-11′). In addition, the only remaining proton that was distinguished by HSQC data was supportive of a hydroxy group in agreement with the IR spectrum. These observations accounted for 6 out of the 11 degrees of unsaturation requiring **1** to be pentacyclic and suggested a likely disesquiterpenoid skeleton for **1** based on the fact that plants of the Chloranthaceae family were rich sources of sesquiterpenoid dimers.[1] While the lindenane-type dimeric sesquiterpenoids were common metabolites from this plant family,[1] the NMR properties of compound **1** were apparently distinct from those previously reported data implying an unusual framework and/or a novel dimerization pattern.

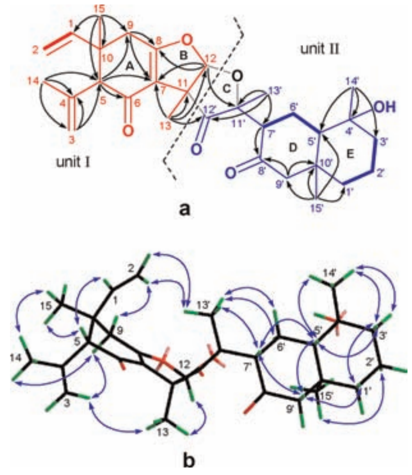

Figure 1. (a) $^1H-^1H$ COSY (bold —) and selected HMBC correlations (→) for **1**. (b) Key ROESY correlations (↔) for **1**.

Analyses of $^1H-^1H$ COSY data (Figure 1a) for **1** exhibited three structural fragments (C-1 to C-2, C-1′ to C-3′, and C-5′ to C-7′), which only provided limited information for the structural elucidation. Fortunately the acquisition of excellent HMBC data (Figure 1a) enabled us to connect these fragments as well as the isolated methines, methylenes, and methyls across those deprotonated carbons and heteroatoms and defined the planar structure of **1** as shown. More specifically, the HMBC correlations from H_3-15 to C-1, C-5, C-9, and C-10 attached the monosubstituted vinyl, CH-5, CH_2-9, and Me-15 to C-10; the cross-peaks of H_3-14 to C-3, C-4, and C-5 linked the isopropenyl to C-5; the correlations from H-5 to C-6, C-7, and C-9 and from H_2-9 to C-7 and C-8 indicated a cyclohexenone motif (ring A) as drawn; the cross-peaks of H_3-13 to C-7, C-11, and C-12, together with H-12 to C-7 and C-8, established a dihydrofuran (ring B) functionality fused with ring A with 13-Me linking to C-11. The structural unit I of **1** was thereby (Figure 1a, in red) characterized representing an elemane-type sesquiterpenoid. Similarly, the structural unit II (Figure 1a, in blue) of an eudesmane-type sesquiterpenoid was also constructed on observing the following HMBC correlation networks of H_3-14′/C-3′, C-4′, and C-5′; H_3-15′/C-1′, C-5′, C-9′, and C-10′; H-7′ and H-9′/C-8′; and H_3-13′/C-7′, C-11′, and C-12′. Finally, the connection of the two units (I and II) via a 3-ketotetrahydrofuran ring (ring C) was fixed by the key HMBC correlations of H_3-13/C-12′ and H-12/C-11′ (Figure 1a) and supported by the deshielded C-12 (δ_C 115.1) and C-11′ (δ_C 83.2) carbon signals, indicating that a new carbon framework of sesquiterpenoid dimer was formed by a C-11–C-12′ linkage.

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[9] Dewick, P. M. In *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; John Wiley & Sons, Ltd.: Chichester, 2004; p 16.

[10] **Serratustone A (1):** Colorless crystals (MeOH); mp 207–210 °C; $[\alpha]^{20}_D = -111$ (c 0.1, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 264 (3.85) nm; CD (MeOH) λ ($\Delta\varepsilon$) 232 (+0.3), 265 (+24.5), 292 (−22.0) nm; IR (KBr, disk) ν_{max} 3430, 2921, 1765, 1689, 1657, 1632, 1388, 1276, 1060, 927 cm^{-1}; for ^1H and ^{13}C NMR data, see Supporting Information Table S1; ESI(+)MS m/z 519.3 $[M + Na]^+$, 1015.6 $[2M + Na]^+$; HR-ESI(+)MS m/z 519.2704 $[M + Na]^+$ (calcd for $C_{30}H_{40}O_6Na$, 519.2723).

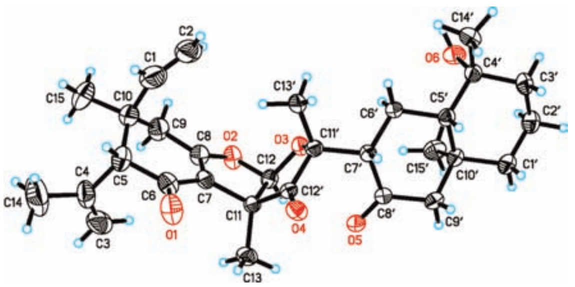

Figure 2. Single-crystal X-ray structure of **1**.

The relative configuration of **1** was determined on the basis of ROESY experiment (Figure 1b). H-9α showed remarkable correlations with both H-3b and H_3-14 suggestive of a *quasi* 1,3-diaxial relationship for H-9α and 5-isopropenyl (C-3 to C-14 via C-4), and they were arbitrarily assigned in an α-orientation, thus leaving H-9β and H-5 *quasi* equatorial and β-oriented. Consequently, the cross-peak of H_3-14/H_3-15 indicated an equatorially positioned Me-15 and hence an axial and β-configured 10-vinyl. The ROESY correlation of H_2-2/H_3-13′ suggested a coplanar relationship for the C1−C2 fragment and Me-13′, while further observation of correlations of H-12/H_3-13 and H_3-13/H-3b confirmed the *cis* conjunction for the heterocyles B and C and supported H-12, Me-13, and 5-isopropenyl being cofacial. As for the structure unit II, the ROESY correlation pairs of H-5′/H-7′, H-7′/H-9′β, and H-9′β/H-1′β indicated that H-5′, H-7′, H-9′β, and H-1′β were all axially located and were randomly assigned as in a β-configuration, thereby resulting in Me-15′ being α-oriented. In addition, Me-14′ was assumed to be equatorially located and thus β-configured on the basis of the cross-peaks of H_3-14′/H_2-3′ and H-5′. Finally, Me-13′ and H-7′ were tentatively, due to the rotary nature of the C-7′−C-11′ bond, determined to have a *cis* relationship based on the observation of ROESY correlations of H_3-13′ with H-7′ and H_2-6′, together with consideration of the remarkable steric hindrance resulting from the bulky substituents at both sides. The relative stereochemistry of **1** was eventually secured by the performance of a single crystal X-ray diffraction experiment (Figure 2) with the result being in good accordance with that acquired in solution for **1** from ROESY data.

Serratustone B (**2**)[11] displayed a sodiated molecular ion $[M + Na]^+$ at m/z 519.2706 in the HR-ESI(+)MS analysis, corresponding to a molecular formula of $C_{30}H_{40}O_6$ and indicative of a structural isomer of **1**. Analysis of the IR, UV, and NMR data (SI Table S1) supported this hypothesis and revealed high structural similarities for the two cometabolites. Detailed comparison of their ^{1}H and ^{13}C NMR data (SI Table S1) revealed major differences mainly existent in the A ring with significantly shifted resonances for CH-5 ($\Delta\delta_C$ 11.5; $\Delta\delta_H$ 0.16), C-6 ($\Delta\delta_C$ 16.5), C-8 ($\Delta\delta_C$ 17.3), and CH_2-9 ($\Delta\delta_C$ 12.5; $\Delta\delta_H$ 0.11 and 0.11), which was suggestive of a different substitution pattern and/or an altered fused manner for A and B rings. The HMBC experiment (SI Figure S1) confirmed the above conclusion exhibiting key correlations from H-5 and H-12 to C-6, and from H_2-9 to C-8, and also facilitated the establishment of a planar structure for **2** as drawn. The relative stereochemistry of **2** was assigned with the aid of ROESY data (SI Figure S1). In particular, the ROESY correlations of H-5/H-1 and H_3-15, H_3-14/H_3-15, and H-9α/H-3b suggested identical configurations for C-5 and C-10 of **2** with those of **1**, while the cross-peaks between H-12 and H_3-13 and between H-3b and H_3-13′ indicated a *cis*-fusion pattern for B and C rings as in **1** but, most noteworthy, an opposite orientation for H-12, Me-13, and Me-13′ compared with their counterparts in **1**. Similarly, the relative configurations for the left stereocenters of the eudesmane part were also considered to the reverse of those in **1** inferred from further explanation of ROESY data (SI Figure S1).

The absolute configurations of compounds **1** and **2** were determined by a CD exciton chirality method and were secured by calculation of electronic circular dichroism (ECD) spectra using density functional theory (DFT). The UV of **1** exhibited a strong absorption at λ_{max} 264 nm attributable to the conjugated α,β-unsaturated ketone (Woodward's rule gave ca. λ_{max} 267 nm).[12] The first negative cotton effect at λ_{max} 292 ($\Delta\varepsilon$ −22.0) and the second positive cotton effect at λ_{max} 265 ($\Delta\varepsilon$ +24.5) in the CD spectrum of **1** (Figure 3) arising from the exciton coupling between the two chromophores of an α,β-unsaturated ketone and the adjacent Δ^3 double bond indicated a negative chirality for **1**. The absolute configuration of **1** was therefore assigned as depicted. Similarly, the absolute configuration of **2** was also established (Figure 3).

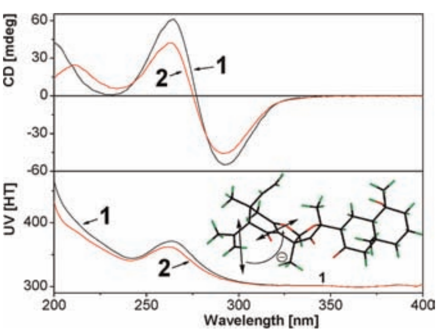

Figure 3. CD and UV spectra of **1** and **2** (in MeOH), and the stereoview of **1** (arrows denote the electronic transit n dipole of the chromophores).

The calculation of electronic circular dichroism (ECD) using time-dependent density functional theory (TDDFT),

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[11] **Serratustone B (2):** White amorphous powder; $[\alpha]^{20}_D = -174$ (c 0.1, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 262 (3.78) nm; CD (MeOH) λ ($\Delta\varepsilon$) 234 (+3.5), 264 (+25.5), 292 (−27.7) nm; IR (KBr, disk) ν_{max} 3500, 2929, 1763, 1705, 1660, 1626, 1384, 1030, 930, 756 cm^{-1}; for ^{1}H and ^{13}C NMR data, see Supporting Information Table S1; ESI(+)MS m/z 519.3 $[M + Na]^+$, 1015.7 $[2M + Na]^+$; HR-ESI(+)MS m/z 519.2706 $[M + Na]^+$ (calcd for $C_{30}H_{40}O_6Na$, 519.2723).

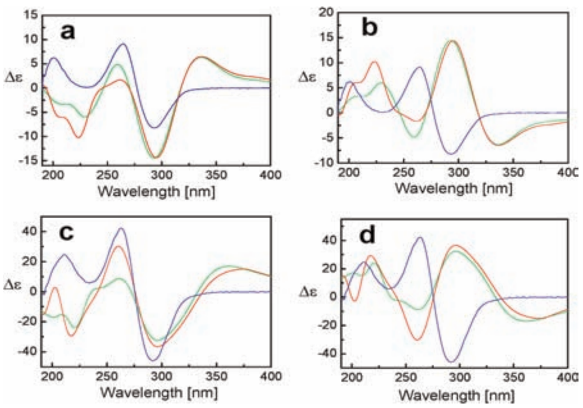


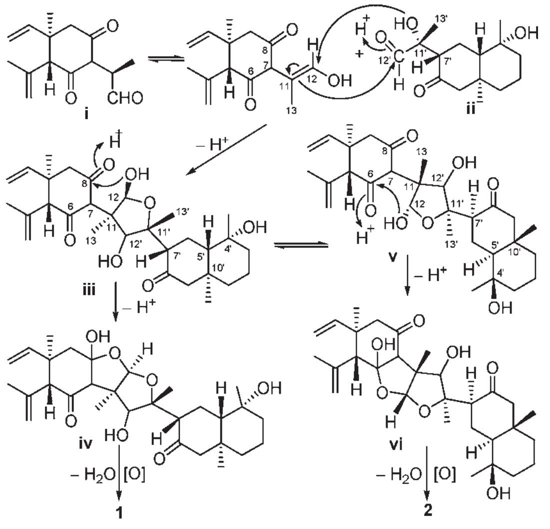
Figure 4. Calculated ECD spectra of **1** (a) and **2** (c), and those of the enantiomers of **1** (b) and **2** (d); experimental ECD (blue); calculated ECD in gas phase (green) and in MeOH (red).

which has demonstrated great success in determining the absolute configurations of chiral molecules,[13] was applied to secure the absolute configurations of **1** and **2** as assigned above. The calculated ECD curves of compounds **1** and **2**, and their enantiomers in both gas phase and methanol, were illustrated in Figure 4. The calculated ECD of **1** and **2** matched very well with the experimental data, while the calculated ECD curves of their enantiomers were opposite to the experimental ones, confirming the absolute structures of compounds **1** and **2** as assigned by the experimental CD method.

A plausible biosynthetic pathway of **1** and **2** is speculated in Scheme 1. Compounds **1** and **2** are structural isomers and are proposed to be the dimers of two different sesquiterpenoids of an elemane type (**i**) and an eudesmane type (**ii**). Two sesquiterpenoids (**i** and **ii**) would be initially linked by involving an aldol condensation as the key step to give the intermediate **iii**. Intermediate **iii** would readily be transformed into the key semiketal **iv**, which after dehydration and oxidation would produce **1**. Similarly, the rotamer **v** (via a counterclockwise rotation of the C-7–C-11 bond) underwent a cascade reaction yielding **2** with a reversed relative stereochemistry of rings C–E as compared with **1**.

In vitro evaluation of compounds **1** and **2** against HL-60 (leukemia) and A-549 (lung cancer) tumor cell lines showed that they were inactive. Compounds **1** and **2** were also tested *in vitro* in a DGAT-1 inhibitory assay, but neither of them were active (SI section S1).

Scheme 1. Plausible Biosynthetic Pathway of **1** and **2**



Serratustones A (**1**) and B (**2**) represent a new carbon skeleton that is formed by involving a novel dimerization pattern of two different types of sesquiterpenoids of an elemane and an eudesmane. We propose to name this compound scaffold serratustone. We believe that the discovery of this novel skeleton will surely attract interest from researchers in related scientific communities, especially synthetic chemists.

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Supporting Information Available. Experimental procedures; 1D and 2D NMR, ESI(±)MS, IR spectra of serratustones A (**1**) and B (**2**); Crystallographic data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.