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Calyciphylline C, a novel *Daphniphyllum* alkaloid from *Daphniphyllum calycinum*

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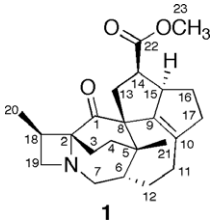
Abstract—Calyciphylline C (**1**), a novel *Daphniphyllum* alkaloid with unprecedented fused-hexacyclic ring system, has been isolated from the leaves of *Daphniphyllum calycinum* (Daphniphyllaceae), and the structure and relative stereochemistry were elucidated on the basis of spectroscopic data.

Daphniphyllum alkaloids are a family of fused-heterocyclic natural products elaborated by the trees of the genus *Daphniphyllum* (Daphniphyllaceae).[1,2] These ring systems have attracted great interest as challenging targets for total synthesis[3] as well as biosynthetic studies.[4] In our search for structurally unique and biogenetically interesting *Daphniphyllum* alkaloids,[5] a novel *Daphniphyllum* alkaloid, calyciphylline C (**1**),[6] was isolated from the leaves of *Daphniphyllum calycinum*. In this Letter, we describe the isolation and structure elucidation of **1**.



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The leaves of *D. calycinum* were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted to pH 10 with saturated Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (hexane/EtOAc, 1:0→0:1, and then $CHCl_3$/MeOH, 1:0→0:1) followed by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to afford calyciphylline C (**1**, 0.00019% yield).

Calyciphylline C (**1**) showed that the pseudomolecular ion peak at *m*/*z* 370 $(M+H)^+$ in the ESIMS, and the molecular formula, $C_{23}H_{31}NO_3$, was established by HRESIMS [*m*/*z* 370.2375, $(M+H)^+$, Δ −0.7 mmu]. IR absorptions implied the presence of ester and keto carbonyl (1730 and 1700 cm^{-1}, respectively) functionality. ^1H and ^{13}C NMR spectra of **1** showed some broad signals, indicating that **1** exists in several interconverting conformations. ^1H and ^{13}C NMR data of **1** (Table 1) revealed 23 carbons signals due to one tetrasubstituted double bond, two carbonyls, three sp^3 quaternary carbons, four sp^3 methines, nine sp^3 methylenes, two methyls, and one methoxy group. Among them, two methylenes (δ_C 57.1, δ_H 2.87, and 2.61; δ_C 58.8, δ_H 3.04, and 2.96) and one quaternary carbon (δ_C 76.7) were ascribed to those bearing a nitrogen.

The gross structure of **1** was elucidated by the analyses of 2D NMR data including ^1H–^1H COSY, HMQC, and HMBC spectra in CD_3OD (Fig. 1). The ^1H–^1H COSY spectrum of **1** revealed four structural units **a** (C-3–C-4), **b** (C-18–C-19 and C-20), **c** (C-6–C-7 and C-12, and C-11–C-12), and **d** (C-13–C-17). HMBC correlations were observed for H_2-19 to C-7 (δ_C 57.1) and H_2-7 and H_2-19 to C-2 (δ_C 76.7), suggesting that C-2, C-7, and C-19 were connected to each other through a nitrogen

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Table 1. ^{1}H and ^{13}C NMR data of calyciphylline C (**1**) in CD_3OD

Position	δ_H	δ_C
1	—	214.9 s
2	—	76.7 s
3a	2.29 (1H, m)	24.7 t
3b	1.51 (1H, m)	
4a	1.98 (1H, m)	36.4 t
4b	1.88 (1H, m)	
5	—	41.7 s
6	1.98 (1H, m)	51.5 d
7a	2.87 (1H, m)	57.1 t
7b	2.61 (1H, m)	
8	—	61.9 s
9	—	144.7 s
10	—	136.2 s
11	2.15 (2H, m)	27.4 t
12a	2.15 (1H, m)	27.9 t
12b	1.71 (1H, m)	
13a	2.78 (1H, m)	41.6 t
13b	1.98 (1H, m)	
14	3.11 (1H, m)	43.5 d
15	3.99 (1H, m)	58.0 d
16a	1.98 (1H, m)	30.8 t
16b	1.32 (1H, m)	
17a	2.61 (1H, m)	43.5 t
17b	2.33 (1H, m)	
18	3.04 (1H, m)	27.8 d
19a	3.04 (1H, m)	58.8 t
19b	2.96 (1H, m)	
20	1.13 (3H, br s)	15.1 q
21	1.24 (3H, s)	27.7 q
22	—	177.5 s
23	3.67 (3H, s)	52.6 q

atom. HMBC cross-peaks for H_2-4 and H_3-20 to C-2 indicated the connectivities of units **a** and **b** through C-2. The presence of a ketone at C-1 was suggested by the HMBC correlation for H-13 and H-18 to C-1 (δ_C 214.9). The connectivity of C-1 and C-13 to C-9 through C-8 was implied by HMBC correlations for H_2-13 to C-1, C-8 (δ_C 61.9), and C-9 (δ_C 144.7). The connectivity of C-21 to C-4, C-6, and C-8 through C-5 was implied by HMBC correlations for H_2-4 to C-6 (δ_C 51.5) and C-21 (δ_C 27.7), H-6 to C-5 (δ_C 44.9), H_2-13 to C-5,

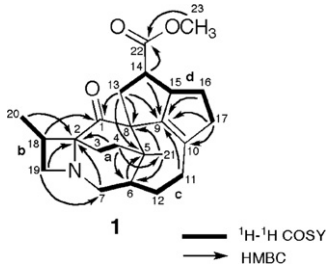


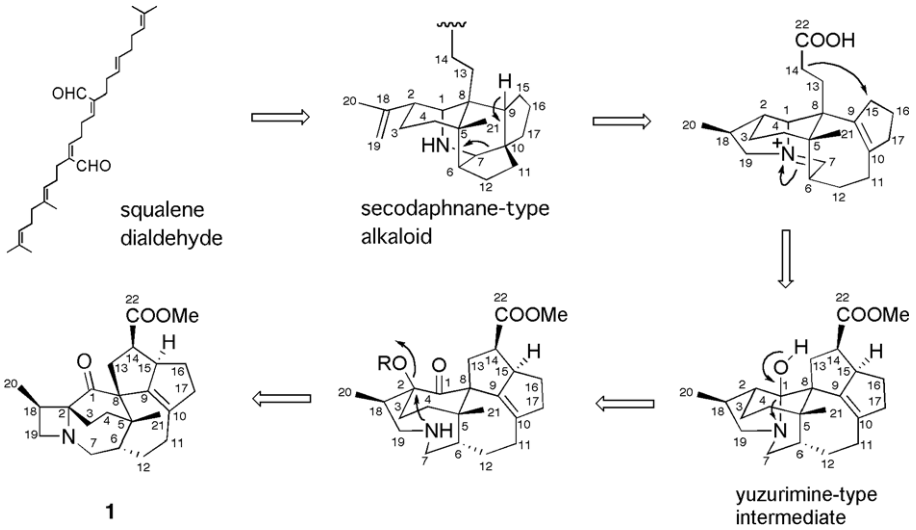
Figure 1. Selected 2D NMR correlations for calyciphylline C (**1**).

and H_3-21 to C-6 and C-8. HMBC cross-peaks for H_2-11 and H_2-17 to C-9 and H_2-17 to C-10 (δ_C 136.2) indicated the connectivities of units **c** and **d** through C-10. In addition, the HMBC correlation for H-14 and H-16 to C-9 indicated the connectivity of C-9 to C-16 through C-15. A methoxy group was attached to C-22 by HMBC correlations for H_3-23 and H-14 to C-22 (δ_C 177.5). Thus, the gross structure of calyciphylline C was assigned as **1**.

The relative stereochemistry of **1** was deduced from NOESY correlations as shown in Figure 2. NOESY correlations of H_3-20/H-3, H-3/H-4, H-4/H_3-21, and H_3-21/H-6 indicated β-orientations of C-20, C-3, C-4, C-21, and H-6. On the other hand, α-orientations of H-14 and H-15 were deduced from NOESY correlation of H-14/H-15.

A plausible biogenetic pathway for calyciphylline C (**1**) is proposed as shown in Scheme 1. Calyciphylline C (**1**) might be generated from secodaphnane-type alkaloid[7] through an yuzurimine-type intermediate with cleavage of the N-1–C-1 bond followed by the formation of the N-1–C-2 bond.

Calyciphylline C (**1**) is a novel *Daphniphyllum* alkaloid having an unprecedented fused-hexacyclic ring system (one four-, two five-, one six-, and two seven-membered rings). Investigations on the absolute stereochemistry and the solution conformation of **1** are currently carried out.



Scheme 1. Plausible biogenetic path of calyciphylline C (**1**).

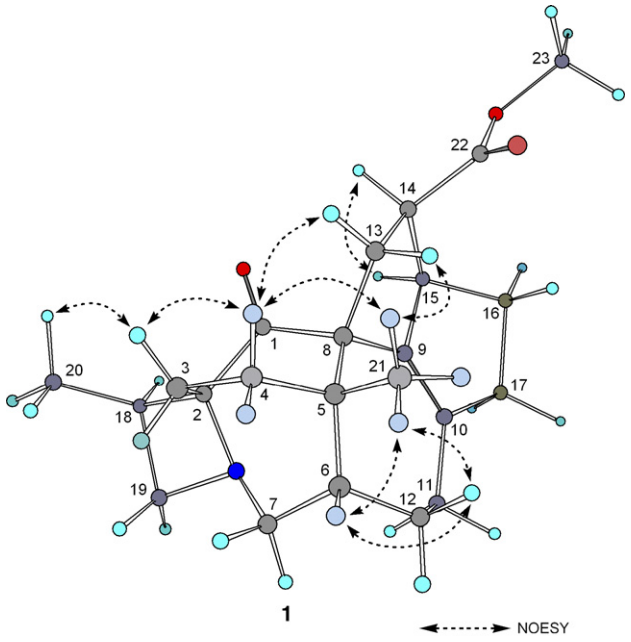


Figure 2. Selected NOESY correlations and relative stereochemistry for calyciphylline C (**1**).

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6. *Calyciphylline C* (**1**). A colorless solid; $[\alpha]_D^{18}$ −21.5 (*c* 0.2, MeOH); IR (neat) ν_{max} 1730 and 1700 cm^{-1}; UV (MeOH) λ_{max} 215 nm (ε 4762); ^1H and ^{13}C NMR data (Table 1); ESIMS *m/z* 370 $(M+H)^+$; HRESIMS *m/z* 370.2375 (M+H; calcd for $C_{23}H_{32}NO_3$, 370.2382).
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