

Crystal Structure of Cucubaldiol, a Novel Norsesquiterpenoid Incorporating a Bicyclo[2.2.2]octene Ring System from *Cucubalus baccifer* (Caryophyllaceae)

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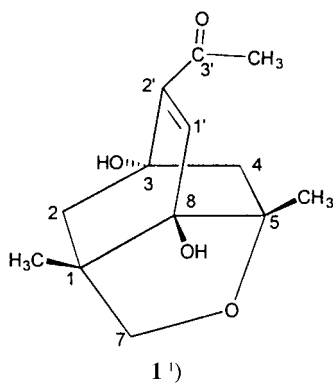
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Cucubaldiol (**1**), a novel norsesquiterpenoid incorporating a bicyclo[2.2.2]octene ring system, was isolated from the whole plants of *Cucubalus baccifer* L. Its structure was determined on the basis of spectroscopic data especially by 2D-NMR and X-ray diffraction analyses.

1. Introduction. – *Cucubalus baccifer* L. (Caryophyllaceae) is a folk medicine in China used for pulmonary tuberculosis (in oral) and scrofula (external use) [1]. During our phytochemical investigation of this plant, cucubaldiol (**1**)¹⁾, a new C₁₃ norsesquiterpenoid incorporating a bicyclo[2.2.2]octene ring system, was isolated. This paper describes its structural elucidation.



2. Results and Discussion. – Cucubaldiol (**1**) was isolated as cubic crystals from the AcOEt extract in a yield of 0.000083%. The molecular formula C₁₃H₁₈O₄ was deduced from its EI-MS in combination with the ¹³C-NMR and DEPT spectra, and was further confirmed by HR-EI-MS (*M*⁺ at *m/z* 238.1210; calc. 238.1205). The ¹³C-NMR and DEPT spectra exhibited three Me, three CH₂, one CH, and six quaternary C-atoms.

¹⁾ Arbitrary numbering; for the systematic name, see *Exper. Part*.

The ^1H , ^1H -COSY experiment revealed no correlations, except for geminal couplings. Hence, the structure determination was initiated by the study of the 2D-HMBC interactions (*Table*). However, two structures including **1** and its enantiomer are possible if only the NMR data are considered. The value of the optical rotation (see *Exper. Part*) suggests, that this compound is optically active.

Table. ^1H - and ^{13}C -NMR, and HMBC Data of **1** (CDCl_3)^a. Arbitrary numbering¹).

	$\delta(\text{H})$	$\delta(\text{C})^{\text{b}}$	HMBC ^c
C(1)		47.4 (s)	H–C(1'), H–C(2), H–C(7), Me–C(1)
H _a –C(2)	1.97 (d, $J = 12.5$) ^a	52.7 (t)	H–C(4), H–C(7), Me–C(1)
H _b –C(2)	1.57 (dd, $J = 12.5, 3.5$)		
C(3)		71.7 (s)	H–C(1'), H–C(2), H–C(4)
H _a –C(4)	2.02 (d, $J = 13.2$)	51.7 (t)	H–C(2), Me–C(5),
H _b –C(4)	1.62 (dd, $J = 13.2, 3.5$)		
C(5)		85.0 (s)	H–C(1'), H–C(4), H–C(7), Me–C(5)
H _a –C(7)	3.74 (d, $J = 8.2$)	78.3 (t)	H–C(2), Me–C(1)
H _b –C(7)	3.70 (d, $J = 8.1$)		
C(8)		83.9 (s)	H–C(2), Me–C(1)
H–C(1')	6.79 (s)	141.5 (d)	
C(2')		144.5 (s)	H–C(1'), H–C(2), H–C(4), Me–C(3')
C(3')		199.4 (s)	H–C(1'), Me–C(3')
CH ₃ –C(1)	0.98 (s)	19.2 (q)	H–C(2), H–C(7)
CH ₃ –C(5)	1.16 (s)	22.1 (q)	H–C(4)
CH ₃ –C(3')	2.34 (s)	25.9 (q)	

^a) δ in ppm, J in Hz. ^b) Multiplicity was established by DEPT data. ^c) Hetero correlation of the indicated proton(s) with the C-atom(s) listed in the same row.

The resonance at δ 199.4 (C(3')¹) is characteristic of a carbonyl group. The signals at δ 144.5 and 141.5 indicate the presence of a conjugated C=C bond. The chemical shifts at δ 71.7 (C(3)), 83.9 (C(8)), 85.0 (C(5)), and 78.3 (C(7)) can be attributed to C-atoms bearing an O-atom. Comparison of the ^{13}C -NMR spectrum of **1** with that of drummondone A, which is a norsesquiterpenoid with a bicyclo[2.2.2]octane ring system and has been isolated as a natural product from *Sesbania drummondii* [2], indicates that they are similar to some extent. The significant difference between the ^{13}C -NMR spectrum of **1** and drummondone A are the absence in **1** of the resonances at δ 26.3 and 55.0 characteristic of C(1') and C(2'), respectively, in drummondone A; instead, two signals at δ 141.5 and 144.5 are clearly observed in **1**, in accord with the presence of a C=C bond between C(1') and C(2').

The X-ray diffraction data indicate that the structure of **1** should be the enantiomer of 1',2' didehydrodrummondone A. The relative configuration of **1** was determined by molecular-modeling studies and also confirmed by X-ray single-crystal diffraction analysis [3]. A view of the solid-state conformation is provided by the *Figure*. The structure of **1** which contains three six-membered rings in the boat conformation and one five-membered ring in the envelope conformation was very rigid in molecular modeling. Thus, the orientation of the substituents Me–C(1), Me–C(5), OH–C(3), and OH–C(8) were naturally fixed, *i.e.*, the two Me groups were positioned on the β -side and the two OH groups on the α -side of the six-membered ring formed by C(1), C(2), C(3), C(4), C(5), and C(8). In addition, the ^1H - and ^{13}C -NMR data (*Table*) were assigned by the HMQC and HMBC experiments. However, it should be noted that

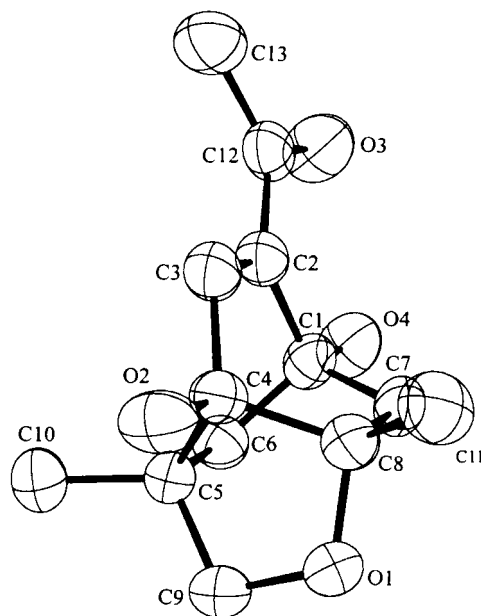


Figure. Perspective view of a molecule of **1**

obvious $\delta(C)$ differences between **1** and drummondone A for the signals of C(1), C(4), C(5), and Me–C(3') were observed. The upfield shift of Me–C(3') in **1** may be attributed to a strong conjugation effect, while the reasons for significant downfield shifts of C(1), C(4), and C(5) remain unclear.

Bioactivities of cucubaldiol were screened by cardiovascular (PP1), anti-cancer (CDC25), antibacteria (PEPT), and antifungus (YNG) bioassays. Unfortunately, no activities were observed at a concentration of 61, 25, 96, and 4 $\mu\text{g/ml}$, respectively.

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Experimental Part

General. M.p.: uncorrected. Optical rotation: *Jasco 20C* polarimeter. ^1H - (400 MHz) and ^{13}C -NMR (100.6 MHz) Spectra: *Bruker AM-400* spectrometer; δ in ppm rel. to SiMe_4 (=0 ppm), J in Hz. MS: *VG-Auto-Spec-3000* mass spectrometer; m/z (rel. %).

Plant Material. The whole plants of *C. baccifer* were collected in Chenggong country of Yunnan province, China, in September 1999. It was identified by Dr. Y. M. Shui, and a voucher specimen (No. 2) was preserved in the Herbarium of Kunming Institute of Botany, *The Chinese Academy of Sciences*.

Extraction and Isolation. The dried whole plants of *C. baccifer* (24.0 kg) were extracted 3 times with 95% EtOH under reflux (3×90 l), for 2, 1, and 1 h, resp. After evaporation of the combined extracts, the residue was suspended in H_2O and then extracted with petroleum ether (60–90°), AcOEt, and BuOH. The AcOEt extract (400.0 g) was decolored on *Diaion HP 20* eluting with a gradient $\text{H}_2\text{O}/\text{MeOH}$ 0:1 \rightarrow 1:0. The 70% MeOH eluate (250.0 g) was subsequently subjected to CC (silica gel 200–300 mesh (2500 g), $\text{CHCl}_3/\text{MeOH}$ 48:1 \rightarrow 8:2, 6500 ml each eluent) to give a fraction (5.0 g), which was resubmitted to CC (silica gel (10–40 μm), petroleum ether/ PrOH 15:1 \rightarrow 5:1) by VLC to afford **1**. Square crystals (CHCl_3). Yield 0.000083%. M.p. 177–

179°. $[\alpha]_D^{25} = +46.3$ ($c = 0.3$, CHCl_3). ^1H - and ^{13}C -NMR: *Table*. EI-MS: 238 (41, M^+), 221 (5), 180 (100), 166 (47), 151 (33), 137 (47), 124 (58), 109 (27). HR-EI-MS: 238.1210 (calc. 238.1205).

Single-Crystal X-Ray Analysis of 1-[(3S,3aR,6S,7aS)-1,3,3a,6,7,7a-Hexahydro-3a,6-dihydroxy-3,7a-dimethyl-3,6-methanobenzofuran-5-yl]ethanone (1). Suitable cubic crystals were grown by slow evaporation of a CHCl_3 soln. of **1**. A colorless crystal measuring $0.20 \times 0.40 \times 1.00$ mm was mounted on a *MAC-DIP-2030 K* diffractometer (MoK_α radiation). M_r 238.28 ($\text{C}_{13}\text{H}_{18}\text{O}_4$); space group $P2_12_12_1$. Unit cell parameters: $a = 8.916$ (1), $b = 9.105$ (1), $c = 15.128$ (1), $V = 1226.7$ (2) \AA^3 , $Z = 4$. $D_{\text{calc}} = 1.289$ g/cm^3 . R_f 0.056, R_w 0.058 ($w = 1/\sigma^2 |F|$), $\text{g.of.} = 6.172$, $(\Delta/\sigma)_{\text{max}} = 0.172$, $\Delta\rho_{\text{min}} = -0.180$ e/\AA^3 , $\Delta\rho_{\text{max}} = 0.230$ e/\AA^3 . Unique reflections: 1222, observed reflections: 1210. The data were collected at $20 \pm 1^\circ$ by the ω - 2θ scan technique to a maximum 2θ value of 50.0° . A total of 1222 reflections were collected. The structure was solved by direct methods and expanded by the *Fourier* technique. The non-H-atoms were refined anisotropically, H-atoms were included but not refined. Crystallographic data for the structure reported in this paper have been deposited with the *Cambridge Crystallographic Data Center* as deposition No. CCDC 160496. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk).

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