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BUDDLEDIN C FROM *Pulicaria prostrata* AND SELECTIVE SYNTHESIS OF ITS EPOXY DERIVATIVE

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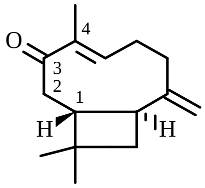
The structure of the sesquiterpene ketone buddledin C isolated from Pulicaria prostrata *(Gilib.) Aschers., was confirmed by XSA. The stereochemistry of its epoxide, which was formed selectively by treating it with hydrogen peroxide in alkaline solution, was proposed based on quantum-chemical and molecular-mechanical calculations.*

Key words: *Pulicaria prostrata*, buddledin C, caryophyllane-type sesquiterpene, XSA, epoxidation, quantum-chemical calculations.

Five species of plants of the genus *Pulicaria* grow in the CIS. Of these, four are indigenous to Kazakhstan [1].

We isolated the flavonoid sorbifoline [2], the guaianolide gaillardine [3], triterpenoids and sterols [4], and caryophyllane sesquiterpenoids [5, 6] from the aerial part of plants of the genus *Pulicaria*.

A volatile crystalline compound with melting point and specific optical rotation similar to those of buddledin C (3-keto-*trans*-caryophyllene, **1**), a component of *Buddleja davidii* Franch. (Buddlejaceae) [7], was easily isolated by steam distillation during preparation of essential oil from the aerial part of the unstudied species *P. prostrata* (Gilib.) Aschers. The structure of **1** was previously established using spectral data and chemical correlation with buddledin A (2β-acetoxy-3-keto-*trans*-caryophyllene), for which the absolute configuration was also determined [8].



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We confirmed the previously proposed structure [7] of **1** by performing an x-ray structure analysis (XSA). Table 1 gives the bond lengths and angles in **1** (Fig. 1), which are normal within uncertainty limits [9]. The exceptions are slightly elongated C1–C9, C1–C11, and C10–C11 bonds and C11C1C9, C1C9C10, and C10C11C1 angles that differ from 90° owing to steric strain in the four-membered ring and are similar to those observed in related compounds [10]. The nine- and four-membered rings are *trans*-fused. The HC1C9H torsion angle is -162.5°. The C-8 methylene has the β-orientation (HC9C8C15 torsion angle -168.7°). The four-membered ring is not planar and adopts the more preferred folded conformation. The dihedral angle between its two component planes is 20.3°. The nine-membered ring adopts a distorted chair—chair conformation [11]. Table 2 gives the intracyclic torsion angles. A comparison of these angles in **1** compared with those in the previously studied buddledin A [8] (Table 2) showed that the corresponding angles differed by less than 10°. The exceptions were C5–C6 and C6–C7 ($\Delta\varphi$ 16.6 and 12.3°, respectively).

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TABLE 1. Bond Lengths (d, Å) and Angles (ω, deg) in **1**

Bond	d	Angle	ω	Angle	ω
O1-C3	1.223 (4)	C2C1C9	123.1 (3)	C8C9C1	122.4 (3)
C1-C2	1.531 (4)	C2C1C11	119.1 (3)	C10C9C1	87.4 (3)
C1-C9	1.558 (5)	C9C1C11	88.7 (3)	C9C10C11	90.0 (3)
C1-C11	1.561 (5)	C3C2C1	112.8 (3)	C13C11C12	111.5 (3)
C2-C3	1.495 (5)	O1C3C4	121.8 (4)	C13C11C10	116.5 (3)
C3-C4	1.474 (6)	O1C3C2	121.3 (4)	C12C11C10	111.7 (3)
C4-C5	1.330 (5)	C4C3C2	116.6 (3)	C13C11C1	116.0 (3)
C4-C14	1.503 (6)	C5C4C3	118.6 (4)	C12C11C1	112.3 (3)
C5-C6	1.471 (6)	C5C4C14	124.8 (4)	C10C11C1	86.6 (3)
C6-C7	1.540 (6)	C3C4C14	116.5 (3)		
C7-C8	1.517 (6)	C4C5C6	127.2 (4)		
C8-C15	1.314 (6)	C5C6C7	108.0 (3)		
C8-C9	1.525 (6)	C8C7C6	112.9 (3)		
C9-C10	1.533 (5)	C15C8C7	120.6 (4)		
C10-C11	1.552 (5)	C15C8C9	122.0 (4)		
C11-C13	1.515 (5)	C7C8C9	117.4 (4)		
C11-C12	1.524 (5)	C8C9C10	118.4 (3)		

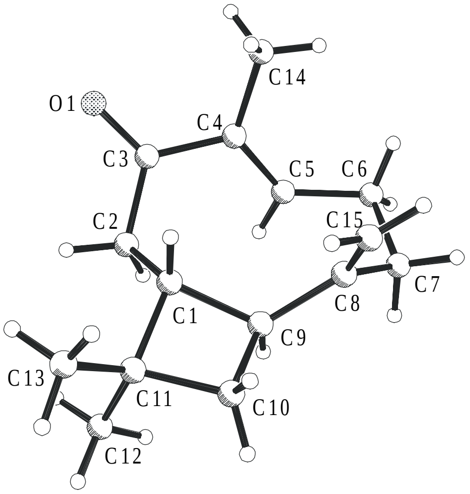

Fig. 1. Structure of **1**.

Ketone **1** and its 2-acetoxy- and 2-hydroxy-derivatives (buddledins A and B, respectively) are toxic to fish [7]. Considering the availability of **1**, we initiated a study of its chemical modification. Treatment with hydrogen peroxide in alkaline solution [12] formed the expected 4,5-epoxy derivative **2** in high yield (90%). Crystals of the epoxide, which contains an exomethylene (IR spectrum), of empirical formula $C_{15}H_{20}O_3$ (high-resolution mass spectrum) that were suitable for an XSA could not be grown. Therefore, the question of the stereochemistry at C-4 and C-5 was resolved based on the high selectivity for forming this compound from **1**.

According to quantum-chemical calclations (density functional method, PBE/3z, PRIRODA program [13]), the most stable conformer of **1** is the *β*,*β*-conformer [Fig. 2, the exomethylene and C(4)-methyl are both *β*-oriented relative to the plane of the cyclononene ring], which is the most stable of all four found conformations by 3.5 kcal/mol. It should be noted that the calculated geometry of the *β*,*β*-conformer of **1** agrees well with the XSA. The difference in the intracyclic torsion angles is less than 7.8° (Table 2, C2C3C4C5 angle). Molecular-mechanical calculations also confirm that the *β*,*β*-conformer is perferred by 1.8 kcal/mol. Figure 2 shows that the *α*-side is more susceptible to attack. This should lead to formation of 4*α*,5*β*-epoxide **2**.

TABLE 2. Intracyclic Torsion Angles (φ, deg) in **1**: Experimental in the Crystal and Calculated (PBE/3z) in the Gas Phase and in Buddledin A Previously Studied by XSA*

Angle	φ exp.	φ calc.	φ of buddledin A
C1C2C3C4	54.3	59.1	-54.2
C2C3C4C5	31.9	24.1	-25.3
C3C4C5C6	-160.4	-156.3	159.8
C4C5C6C7	106.9	111.9	-123.5
C5C6C7C8	-39.3	-41.4	51.6
C6C7C8C9	84.8	85.7	-82.4
C7C8C9C1	-116.9	-115.6	106.7
C8C9C1C2	93.0	93.2	-100.5
C9C1C2C3	-89.3	-91.0	93.5
C1C11C10C9	-20.3	-19.2	23.5
C11C10C9C1	20.3	19.2	-23.8
C10C9C1C11	-20.2	-19.0	23.7
C9C1C11C10	19.9	19.0	-23.0

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*(-)-Buddledin C ([α]$_D$-314°) was studied so that the absolute configuration of the molecule was different.

TABLE 3. Chemical Shifts and Spin—Spin Constants (J/Hz) of ^{1}H and ^{13}C Atoms in **1** and **2** (δ, ppm, 0 = TMS)

C atom	**1**		**2**	
	δ_H	δ_C	δ_H	δ_C
1	2.19 ddd (11.0, 11.0, 8.0)	55.39 d	2.30 ddd (9.0, 9.0, 7.0)	47.78 d
2	2.41-2.46 m (H-2a, H-2b)	44.85 t	2.46-2.50 m (H-2a, H-2b)	425.50 t
3		206.66 s		207.97 s
4		136.22 s		63.29 s
5	6.29 m	143.56 d	3.02 dd (11.0, 3.0)	61.08 d
6	2.93 dd (15.0, 12.0, H-6a)	30.76 t	2.20 dddd (13.0, 6.0, 3.0, 3.0, H-6a)	28.72 t
	2.27 d (15.0, H-6b)		1.38 d (13.0, 12.0, 11.0, 6.0, H-6b, overlaps with H-14)	
7	2.58 ddd (12.0, 6.0, 3.0, H-7a)	40.31 t	2.51 ddd (12.0, 6.0, 3.0, H-7a)	35.04 t
	1.62 m (H-7b)		2.07 ddd (12.0, 12.0, 6.0, H-7b)	
8		152.97 s		152.46 s
9	2.38 ddd (9.0, 9.0, 9.0)	47.26 d	2.42 ddd (9.0, 9.0, 9.0)	43.43 d
10	1.80 dd (10.0, 8.0, H-10a)	40.80 t	1.98 dd (10.0, 9.0, H-10a)	43.47 t
	1.51 dd (10.0, 8.0, H-10b)		1.61 dd (10.0, 9.0, H-10b)	
11		33.13 s		33.15 s
12	0.99 s (3H)	29.12 q	1.04 s	29.59 q
13	0.98 s (3H)	21.73 q	0.96 s	22.46 q
14	1.63 s (3H)	12.92 q	1.38 s	14.84 q
15	4.93 br.s (H-15a)	111.55 t	5.17 br.s (H-15a)	113.22 t
	4.88 br.s (H-15b)		5.07 br.s (H-15b)	

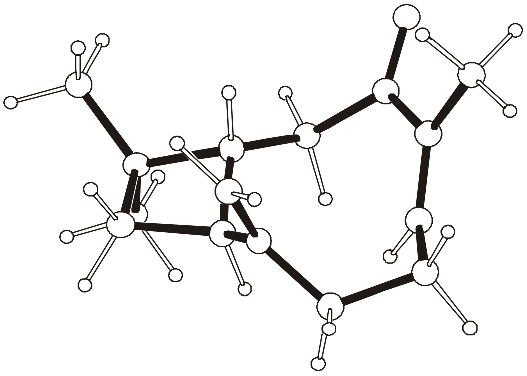
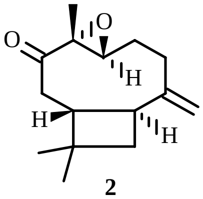


Fig. 2. Most stable conformer of ketone **1**.

PMR spectra of **1** and **2** (Table 3) differ insignificantly with the exception of the signal for H-5, which shifts to strong field after epoxidation of the C4–C5 bond. Signals in the ^{13}C NMR spectra of **1** and **2** also differ insignificantly except for the signals for C-4 and C-5. Signals in the NMR spectra were assigned using two-dimensional ^{13}C—^{1}H (COSY) and ^{1}H—^{1}H (COSY) NMR spectra of **2**.



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EXPERIMENTAL

General Comments. Melting points were determined on a Boetius stage. IR spectra were recorded on a Vector 22 instrument. NMR spectra were recorded on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C). Mass spectra (EI, 70 eV) were obtained in a Finnigan MAT 8200 instrument. Optical rotation was measured (at 580 nm) in a Polamat A polarimeter.

Starting material was collected near the village Balyktykol′sk in Nurin region of Karaganda district during budding (July 2003).

Ketone 1. Compound **1** condensed on the condenser walls as prismatic crystals during steam distillation in a Clevenger apparatus [14] of air-dried *P. prostrata* (100 g). Crystals of **1** also formed in the essential oil, the chemical composition of which we did not investigate. The crystals were harvested, combined, and recrystallized from $CHCl_3$, yield 0.03 g, mp 126-128°C, $[\alpha]_D^{30}$ -314° (*c* 0.35, $CHCl_3$) {lit. [7] mp 129-130°C, $[\alpha]_D$ -316° ($CHCl_3$)}.

XSA of 1. Cell constants and intensities of 1757 reflections were measured on a Syntex $P2_1$ diffractometer at 20°C (Cu Kα-radiation, graphite monochromator, $\theta/2\theta$-scanning, $2\theta \le 177.54°$). The crystals were orthorhombic, $a = 7.433(2)$, $b = 10.773(3)$, $c = 16.618(4)$ Å, V = 1330.7(6) Å^3, $d_{calc} = 1.09$ mg/mm^3, $Z = 4$ ($C_{15}H_{22}O$), space group $P2_12_12_1$.

The structure of **1** was solved by direct methods using the SHELXS-97 program. All nonhydrogen atoms were refined by anisotropic full-matrix least-squares methods using the SHELXL-97 program. Positions of H atoms in **1** were calculated geometrically and set at fixed distances. The final agreement factors were R = 0.0641 and wR = 0.1259 for 966 independent reflections of molecule **1** with $I \ge 2\sigma$.

Atomic coordinates were deposited as CIF files in the Cambridge Crystallographic Data Centre (CCDC284782).

(1*S*,4*R*,6*R*,10*R*)-4,12,12-Trimethyl-9-methylene-5-oxatricyclo[8.2.1.0^{4,6}]tridecan-3-one (2). A solution of **1** (0.200 g) in a mixture of CH_3OH (10 mL) and H_2O_2 (30%, 1 mL) was cooled in an ice bath, treated over 15 min with aqueous NaOH solution (1.5 mL, 10%) with constant stirring, stirred at room temperature for 1 h more, treated with NaCl solution (10 g in 40 mL water), and extracted with diethylether. The extract was dried over Na_2SO_4. The solvent was removed to afford **2** (0.195 g, 90%), mp 105-106°C ($CHCl_3$), $[\alpha]_D^{19.5}$ -140° (*c* 0.32, $CHCl_3$).

IR spectrum (KBr, ν, cm^{-1}): 3067, 1709 (C=O), 1631, 1285 (C–O–C), 890 ($C=CH_2$).
Mass spectrum (EI, 70 eV, m/z, I_{rel}, %): 234 (74) $[M]^+$.

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