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Synthesis and crystal structure of 7,9-dideacetyl-1-deoxybaccatinVI

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7,9-dideacetyl-1-deoxybaccatinVI was synthesized from 1-deoxybaccatinVI and its crystal structure was determined by X-ray crystallographic techniques. The compound ($C_{33}H_{42}O_{11}\cdot 2CH_4O$) crystallizes into monoclinic space group $P2_1$ with unit cell parameters: $a = 8.654(17)$ Å, $b = 16.470(5)$ Å, $c = 12.671(3)$ Å, $\beta = 97.63(2)^\circ$, and $Z = 2$. The X-ray results demonstrated that the reaction of 7,9,10-Trideacetyl-1-deoxy-baccatinVI with Ac_2O in tetrahydrofuran, using $CeCl_3$ as catalyst, yielded monoacetylated product 7,9-dideacetyl-1-deoxy baccatinVI In the structure, the six-membered A ring exhibits boat conformation, the eight-membered B ring adopts boat-chair conformation, and the six-membered C ring exhibits a sofa conformation.

KEY WORDS: Crystal structure; conformation; 7,9-dideacetyl-1-deoxybaccatinVI.

Introduction

A naturally occurring diterpenoid Paclitaxel (taxol),[1–3] isolated from the bark of the Pacific yew (*Taxus brevifolia*), has proved to be one of the most important new anticancer drug introduced in the last decades, owing to its great potential in the successful treatment of wide types of cancer, a unique antitumor mechanism of action, and complex molecular architecture. In order to fully understand the compound' mechanism of action and determine the structural features essential for their biological activity, extensive structure–activity relationship (SAR) studies on taxoids have been performed.[4] These studies suggested 1-hydroxyl group is not necessary for the activity of paclitaxel.[5] To explain these SAR, studies have focused on the determination of the conformation of either active or inactive taxoids. The naturally occurring 1-deoxybaccatinVI (**1**)[6,7] served as precursor for the preparation of 1-deoxypaclitaxel analog. In continuing our studies on 1-deoxybaccatinVI,[8] we focus on structural modifications of the diterpenoid and conformational changes as an area of interest. Herein, we report the synthesis (Scheme 1) and crystal structure of 7,9-dideacetyl-1-deoxybaccatinVI (**3**).

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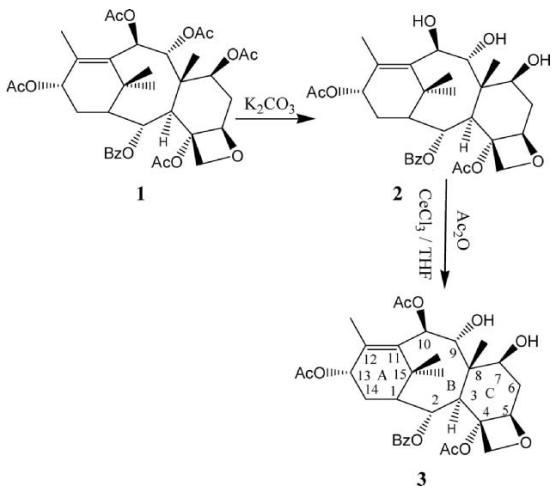
Experimental

*Synthesis of 7,9,10-trideacetyl-1-deoxy-baccatinVI (**2**)*

To a solution of **1** (349.4 mg, 0.5 mmol) in methanol (20 mL) at room temperature was added dropwise potassium carbonate (2.0 mL, 1.3 N in



Scheme 1.

methanol/water), and the reaction progress was followed by TLC until completion. After careful neutralization (saturated ammonium chloride) and removal of the methanol, the residue was extracted with ethyl acetate and purified by column chromatography on silica gel with ethyl acetate/hexane 3/2 as an eluent to give **2** (186.0 mg, 65%).^{1}H NMR ($CDCl_3$, ppm): δ 1.21 (s, 3H), 1.64–1.69 (m, 1H), 1.77 (s, 3H), 1.80 (s, 3H), 1.86 (s, 3H), 1.92–1.96 (m, 2H), 2.18 (s, 3H), 2.27 (s, 3H), 2.42–2.48 (m, 1H), 2.51–2.58 (m, 1H), 2.89 (d, $J = 5.83$ Hz,1H), 3.16 (s, 1H), 3.65 (s, 1H), 4.16 (d, $J = 8.40$ Hz, 1H), 4.32–4.39 (m, 3H), 4.83 (d, $J = 6.95$ Hz, 1H), 4.92 (d, $J = 10.31$ Hz, 1H), 4.99 (d, $J = 8.81$ Hz, 1H), 5.76 (dd, $J = 2.10$, 5.89 Hz, 1H), 5.97 (t, $J = 8.61$, 8.87 Hz, 1H), 7.47 (t, $J = 7.83$ Hz, 2H), 7.59 (t, $J = 7.42$ Hz, 1H), 8.05 (dd, $J = 7.79$, 1.19 Hz, 2H);^{13}C NMR ($CDCl_3$): δ 12.5, 14.8, 21.2, 22.8, 26.7, 26.9, 31.7, 38.0, 38.2, 44.1, 44.3, 47.4, 69.5, 71.2, 71.8, 74.3, 76.7, 78.9, 81.9, 84.0, 128.6, 129.8, 133.5, 135.2, 137.5, 165.1, 169.3, 170.7; ESI Full MS m/z: 573 $(M + H)^+$, 555 $(M + H\text{-}H_2O)^+$, 495, 373, 331, 313, 295.

*Synthesis of 7,9-dideacetyl-1-deoxybaccatinVI (**3**)*

In a solution of anhydrous **2** (195 mg, 0.34 mmol) in dry tetrahydrofuran (7 mL), cerium(III) chloride heptahydrate (13 mg, 0.035 mmol) and acetic anhydride (0.13 mL, 1.3 mmol) were added, and then stirred at 40°C for 2 h. At the end of this period, the solution was quenched with distilled water and extracted with ethyl acetate. The organic phase was washed with water for three times and dried over anhydrous magnesium sulfate, and concentrated in vacuo to obtain a white solid. Column chromatography of the solid on silica gel with 25% petroleum ether in ethyl acetate solution as an eluent gave the title compound **3** 171 mg in 82% yield. IR ν_{maks} (KBr) cm^{-1}: 3443.8, 1738.5, 1716.9, 1650.3, 1452.4, 1372.1, 1241.3, 969.5, 714.9.^{1}H NMR ($CDCl_3$, ppm): δ 1.15 (s, 3H), 1.63–1.71 (m, 1H), 1.75 (s, 3H), 1.81 (s, 3H), 1.96 (s, 3H), 1.90–2.03 (m, 2H), 2.13 (s, 3H), 2.19 (s, 3H), 2.28 (s, 3H), 2.39–2.50 (m, 1H), 2.51–2.62 (m, 1H), 2.89 (d, $J = 8.4$ Hz, 1H), 4.16 (d, $J = 8.52$ Hz, 1H), 4.37 (d, $J = 8.24$ Hz, 1H), 4.45–4.48 (m, 1H), 4.45 (d, $J = 10.99$ Hz, 1H), 5.00 (d, $J = 8.52$ Hz, 1H), 5.74 (dd, $J = 5.91$, 2.06 Hz, 1H), 5.94 (t, $J = 9.07$, 7.69 Hz, 1H), 6.16 (d, $J = 10.99$ Hz, 1H), 7.47 (t, $J = 7.55$ Hz, 2H), 7.59 (t, $J = 7.42$ Hz, 1H), 8.06 (d, $J = 7.14$ Hz, 2H).^{13}C NMR: δ 12.6, 14.6, 21.1, 21.2, 22.7, 26.5, 26.9, 31.2, 37.9, 38.0, 44.3, 44.6, 47.0, 69.0, 71.5, 73.8, 73.9, 76.6, 77.2, 81.9, 84.0, 128.5, 129.6, 133.4, 134.7, 136.9, 165.0, 169.2, 170.6, 170.7. ESI Full MS m/z: 638, 637 $(M + Na)^+$. The colorless single crystal was cultured from a mixture solution of methanol and water (9:1.v/v) by slow evaporation at room temperature.

*Crystal structure determination of **3***

A summary of the crystallographic information is given in Table 1, and selected bond distances and angles are listed in Tables 2 and 3, respectively. The selected crystal was mounted on a ENRAF-NONIUS CAD4 diffractometer. Diffraction data were measured at 20°C using graphite monochromated Mo Kα ($\lambda = 0.071073$ nm) radiation. The structure was solved by direct methods and refined by full-matrix least squares method on $F_{obs}{}^2$ by using the SHELXTL 97 software

Table 1. Crystal Data and Other Crystallographic Details

Empirical formula	$C_{33}H_{42}O_{11}\cdot 2CH_4O$
Formula weight	678.75
Temperature (K)	292(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
Cell dimensions	
a (Å)	8.6540(17)
b (Å)	16.470(5)
c (Å)	12.671(3)
α (°)	90.00(2)
B (°)	97.63(2)
Γ (°)	90.00(2)
Volume (Å^3)	1790.0(8)
Z	2
Density (calc.) (mg/m^3)	1.259
Absorption coefficient (mm^{-1})	0.096
F(0 0 0)	728
Crystal size (mm)	0.50 × 0.40 × 0.30
θ range for data collection (°)	1.62–25.18
Max., Min. transmission	0.9719, 0.9537
Index ranges	$-10 \le h \le 10$ $-1 \le k \le 19$ $-15 \le l \le 15$
Reflections collected	7174
Independent reflections	3594 [$R_{int} = 0.0372$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3594/1/447
Goodness-of-fit on F^2	1.003
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0404$, $wR_2 = 0.0854$
R indices (all data)	$R_1 = 0.0939$, $wR_2 = 0.1024$
Largest diff. peak and hole (eÅ^{-3})	0.138 and −0.135
CCDC deposit no.	283053

package. All non-H atoms were anisotropically refined. The hydrogen atoms were located by geometry calculation and riding on the related parent atoms.

Table 2. Bond Lengths (Å) of **3**

C(1)–C(14)	1.539(6)	C(6)–C(7)	1.514(6)
C(1)–C(15)	1.549(5)	C(7)–C(8)	1.548(5)
C(1)–C(2)	1.540(5)	C(8)–C(9)	1.563(5)
C(2)–C(3)	1.572(5)	C(9)–C(10)	1.522(5)
C(3)–C(4)	1.552(5)	C(10)–C(11)	1.512(6)
C(3)–C(8)	1.574(5)	C(11)–C(12)	1.333(5)
C(4)–C(20)	1.510(6)	C(11)–C(15)	1.529(5)
C(5)–O(5)	1.448(5)	C(12)–C(13)	1.515(6)
C(5)–C(6)	1.494(6)	C(13)–C(14)	1.536(6)
O(5)–C(20)	1.432(5)		

Table 3. Bond Angles (°) of **3**

C(14)–C(1)–C(15)	110.4(3)	C(6)–C(7)–C(8)	114.1(3)
C(14)–C(1)–C(2)	113.9(3)	C(7)–C(8)–C(9)	111.5(3)
C(2)–C(1)–C(15)	113.5(3)	C(19)–C(8)–C(3)	112.7(3)
C(1)–C(2)–C(3)	118.9(3)	C(7)–C(8)–C(3)	104.9(3)
C(4)–C(3)–C(2)	112.7(3)	C(9)–C(8)–C(3)	113.1(3)
C(4)–C(3)–C(8)	111.4(3)	C(10)–C(9)–C(8)	120.7(3)
C(2)–C(3)–C(8)	114.0(3)	C(11)–C(10)–C(9)	115.2(3)
C(20)–C(4)–C(5)	85.3(3)	C(12)–C(11)–C(10)	119.6(3)
C(20)–C(4)–C(3)	121.9(3)	C(12)–C(11)–C(15)	119.3(3)
C(3)–C(4)–C(5)	118.3(3)	C(10)–C(11)–C(15)	119.9(3)
O(5)–C(5)–C(6)	114.2(4)	C(11)–C(12)–C(13)	118.7(3)
O(5)–C(5)–C(4)	90.4(3)	C(12)–C(13)–C(14)	112.9(3)
C(6)–C(5)–C(4)	119.9(3)	C(1)–C(14)–C(13)	115.5(3)
C(20)–O(5)–C(5)	91.4(3)	C(11)–C(15)–C(1)	103.7(3)
C(5)–C(6)–C(7)	116.4(3)	O(5)–C(20)–C(4)	92.0(3)

Results and discussion

The compound **3** crystallized in monoclinic system, space group $P2_1$. The structure of molecule **3** with atomic labeling is shown in Fig. 1. The crystals include two methanol molecules, not shown in Fig. 1 for sake of clarity.

The cyclooctane ring B adopts the most stable boat-chair conformation, as shown by the torsion angles with atoms C(1) and C(9) as the ends. This ring is *trans*fused along the C(3)–C(8) bond to the six- membered ring C, which exhibits a chair conformation flattened in C(4) [atoms C(7) and C(4) deviated by −0.613 Å and 0.197 Å, respectively, from the mean plane of the other four atoms]. Ring A, "double-bridged" to the central ring, exhibits the 1,3-di-planar boat conformation with C(11) only 0.317 Å and C(15) 1.031 Å fully above the mean plane of the atoms C(13), C(12), C(14), and C(1). The solid-state conformation of **3** is very close to that of the baccatin derivatives resolved by X-ray analysis: 1-deoxybaccatinVI,[6] 9-dihydro-13-acetyl-baccatin III,[9] 10-deacetyl baccatin III,[10] baccatin III,[11] taxol[12]and docetaxel,[13] showing that the presence of the 9-hydroxy function, removal of oxygen function at 1-position and deacylation at 7-position and 9-position have a minimal effect on the conformation of the taxol skeleton. The relative orientation of the carboxyl and benzene groups of benzoyl, which has been the subject of discussions in some papers, deviates

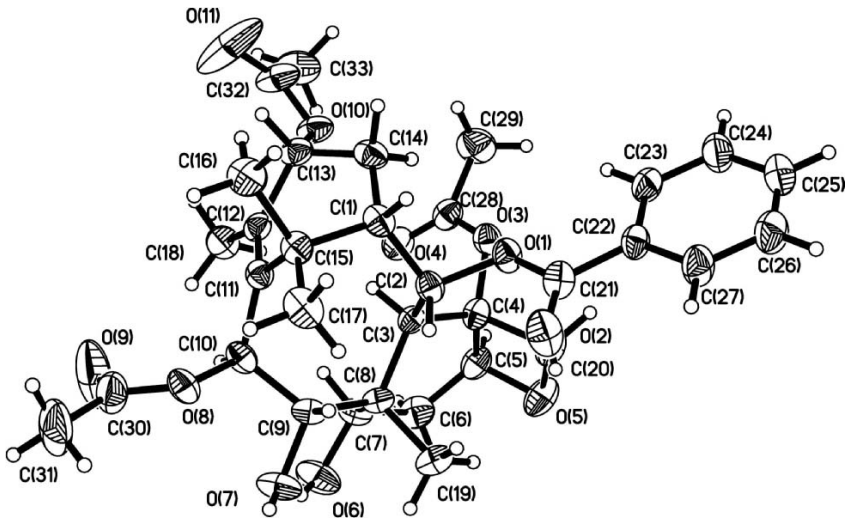


Fig. 1. The molecular structure and labeling scheme of **3** with 30% probability of ellipsoids.

from coplanarity [atoms O(2) and O(1) deviated by −0.011 Å and 0.064 Å, respectively, from the plane of atoms C(21), C(22), C(23), C(24), C(25), C(26), and C(27)]. This study, in conjunction with the earlier studies on related baccatin derivation reveals that the benzoyl group exhibits an unexpected conformational flexibility that may be relevant to the bioactivity of taxanes.

Four corresponding dihedral angles differ by nearly 5° [C(3)–C(8)–C(9)–C(10), C(8)–C(9)–C(10)–C(11), C(12)–C(13)–C(14)–C(1), C(13)–C(14)–C(1)–C(2)] (53°, −61°, −23°, 104° in **3** versus −57°, 65°, 27°, −107° in **1**). Accompanying these differences are shorter bond lengths at C(3)–C(8), C(6)–C(7), and C(13)–C(14) of **3**. The observation of a shorter C(3)–C(8), C(6)–C(7), and C(13)–C(14) bond lengths in **3** (1.57 Å, 1.514 Å, 1.536 Å versus 1.592 Å, 1.539 Å, 1.552 Å in **1**) supports Gabetta's contention that "linear strain in baccatin III derivatives is affected by acylation and by the substitution pattern of the diterpenoid core."[11]

It can be noted that all the hydroxyl groups are engaged in hydrogen bonds. The folded conformation is stabilized by strong intramolecular hydrogen bonds between HO(6) and O atom of HO(7) with the following characteristics: O(6)–H···O(7) = 2.544 Å, H···O(7) = 1.794 Å, O(6)–H···O(7) = 149.5°, and between HO(7) and O(8) with the following characteristics: O(7)–H···O(8) = 2.649 Å, H···O(8) = 2.616 Å, O(7)–H···O(8) = 83.2° [O (13)–H···O (6), 2.706 Å, $x-1$, y, $z-1$], [O (7)–H···O (12), 2.615 Å, x, y, $z+1$], the methanol molecule and the methanol molecule [O (12)–H···O (13), 2.615 Å] also contribute to the crystal packing.

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