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Occurrence of a New Dimeric Compound of 5-Oxotaxinine A through Diels-Alder Cycloaddition

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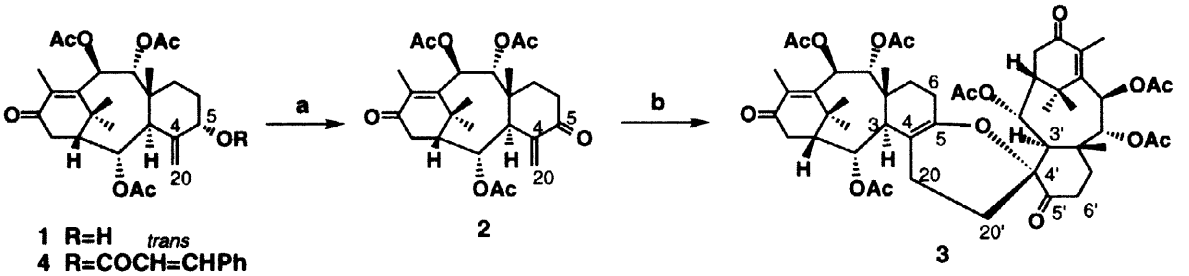
Abstract: Oxidation of taxinine A (**1**) with tetrapropylammonium perruthenate afforded 5-oxotaxinine A (**2**) which subsequently gave a new dimeric compound (**3**) through regio- and stereo-specific Diels-Alder cycloaddition. The relative stereostructure of **3** was established by spectral data and X-ray analysis.

In our studies on various chemical derivatization from taxinine (**4**), one of major taxoids obtained from Japanese yew *Taxus cuspidata*,[1~3] we recently found that oxidation of taxinine A (**1**) yielded 5-oxotaxinine A (**2**) which subsequently afforded a new dimeric compound (**3**) through Diels-Alder cycloaddition. In this paper we describe the formation of **3** from **2** and the stereostructure of **3**.

Oxidation of taxinine A (**1**), which was derived from taxinine (**4**),[4] with tetrapropylammonium perruthenate (TPAP)[5] yielded 5-oxotaxinine A (**2**, 80%).[6,7] The structure of **2** was elucidated by spectral data including FDMS and 2D NMR. It was found that **2** was allowed to stand at room temperature to occur a new



Scheme 1. a) TPAP, 4-Methylmorpholine *N*-oxide, CH_3CN, MS 4Å, rt., 2h, 80 %; b) Table 1

Table 1. Effect of Temperature on Formation of Dimeric Compound **3** from 5-Oxotaxinine A (**2**)

concentration of **2** (mmol/L)	solvent	temperature (°C)	time (h)	yield (%) of **3**
1.7	PhH	20	8	50
1.7	PhH	40	8	69
1.7	PhH	80	8	75
	none	80	8	99

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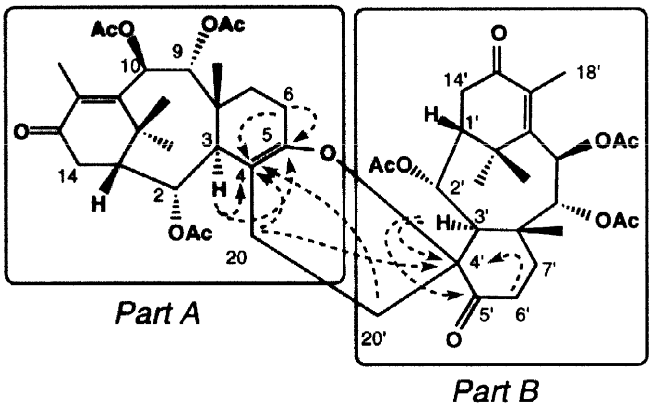

Figure 1. HMBC Correlations of the Dimer (**3**) of 5-Oxotaxinine A (**2**)

Table 2. ^{1}H and ^{13}C NMR Data of the Dimer (**3**) of 5-Oxotaxinine A (**2**) in Acetone-d_6

	^{1}H^a		J(Hz)	^{13}C^a		HMBC (^{1}H)		^{1}H		J(Hz)	^{13}C		HMBC (^{1}H)
1	2.17	brdd		47.8	d	16,17	1'	2.12	m		49.0	d	14'a,16',17'
2	5.67	brdd		72.0	d	3	2'	5.71	dd	4.4, 2.1	71.2	d	1',3',14'a, 14'b
3	3.12	brd		42.8	s	1,2,9,19	3'	2.63	d	4.4	51.0	d	1',2',19', 20'
4				101.7	s	20',3,6a, 20a	4'				85.0	s	3',6'b,20a
5				146.9	s	3,6b	5'				206.4	s	6'a,6'b,7'a, 20'
6a	2.26	m		25.5	t		6'a	2.92	m		33.3	t	
6b	1.99	m					6'b	2.21	m				
7a	2.08	m		29.0	t	9,19	7'a	2.21	m		32.9	t	9',19'
7b	1.42	ddd	12.6, 10.6, 6.0				7'b	1.62	m				
8				42.8	s	2,6a,9,19	8'				43.6	s	2',9',19'
9	6.02	d	10.7	75.9	d	19	9'	5.95	d	10.5	75.5	d	19'
10	5.86	d	10.7	73.3	d		10'	5.89	d	10.5	72.9	d	
11				151.7	s	10,16,17,18	11'				150.4	s	16',17',18'
12				138.5	s	14a,18	12'				137.9	s	18'
13				199.3	s	1,14a,18	13'				199.8	s	14'a,14'b, 18'
14a	2.80	dd	19.5, 6.3	36.8	t		14'a	3.24	d	19.8	36.0	t	
14b	2.41	d	19.5				14'b	2.61	dd	19.8, 6.8			
15				40.0	s	1,10,14a,16 17	15'				38.8	s	10',14'a, 14'b,16',17'
16	1.78	s		25.4	q	17	16'	1.74	s		25.4	q	17'
17	1.13	s		37.2	q	16	17'	1.10	s		37.1	q	16'
18	1.97	s		13.6	q		18'	1.90	s		13.6	q	
19	1.01	s		18.5	q	7b,9	19'	1.26	s		18.9	q	7'a
20a	2.75	d	1.0	26.3	t	20'	20'	2.29	m		22.1	t	
20b	1.30	m											
AcO	2.11	s		170.7^b	s		AcO	2.11	s		170.5^c	s	
	2.03	s		169.9^b	s			2.02	s		169.8^c	s	
	2.00	s		169.8^b	s			2.00	s		169.4^c	s	
				21.5	q						21.4	q	
				20.7	q						20.7	q	
				20.6	q						20.6	q	

a) δ in ppm, b) interchangeable, c) interchangeable dimeric compound **3** (Scheme 1).[6,8] Compound **3** was generated from **2** in benzene at 20 ~ 80 °C in 50 ~ 75 % yield, and the dimeric reaction without solvent at 80°C proceeded quantitatively (Table 1). Compound **3** was shown to have the molecular formula, $C_{52}H_{68}O_{16}$, by HRFABMS [*m/z* 949.4572 $(M+H)^+$, Δ -1.4 mmu], indicating a dimer of 5-oxotaxinine A (**2**). The ^1H NMR (Table 2) spectrum of **3** showed proton signals due to each pair of three acetyl methyls, three oxymethines, and four methyls. Each pair of these signals was assigned to be owing to parts A and B, corresponding to each half moiety of the dimer (Fig. 1) by 2D NMR (^1H-^1H COSY, HMQC, and HMBC) data. HMBC correlations of H-3, H-6a, and H-20a to C-4 (δ 101.7), H-3 and H-6b to C-5 (δ 146.9) indicated the presence of an enol (C-4, C-5, and O-5) in part A, while the presence of an α-oxyketone (O-4', C-4', C-5', and O-5') was deduced from HMBC correlations of H-3' and H-6'b to C-4' (δ 85.0), H-3', H_2-6', and H-20' to C-5' (δ 206.4) in part B. ^1H-^1H COSY connectivities between H_2-20 and H_2-20' and HMBC correlations of H-20a to C-4' and H-20' to C-4 revealed that **3** possessed a dihydropyran ring (C-4, C-5, O-5, C-4', C-20' and C-20), which was supported by comparison with olefin chemical shifts (δ 99.2 and 144.0) of a dihydropyran reported.[9] Thus the structure of **3** was assigned to be a dimer of compound **2**. Relative stereochemistry at the spiro carbon (C-4') of **3** was deduced from the NOESY spectrum. The cross peaks for H-6'a/H_3-19', H-6'a/H_2-20', and H_3-19'/H_2-20' indicated that C-4' had *R** configuration (Fig. 2). Compound **3** was crystallized from *i*-PrOH and H_2O to give prisms of space group $P2_12_12_1$. The crystal structure was solved by the direct method and refined by a full-matrix least-squares method to R=0.084 and R_W=0.249 using 2002 ($I>2\sigma$ (I)) observed reflections.[10] The relative stereostructure of **3** was established by the X-ray analysis as shown in Fig. 3, which corresponded to that elucidated by NMR data.

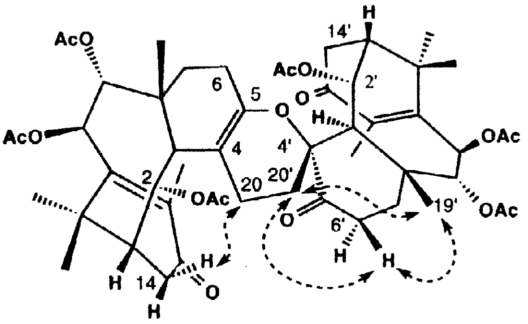

Figure 2. Relative Stereochemistry of the Dimer (**3**) of 5-Oxotaxinine A (**2**)

Dotted arrows denote NOESY correlations

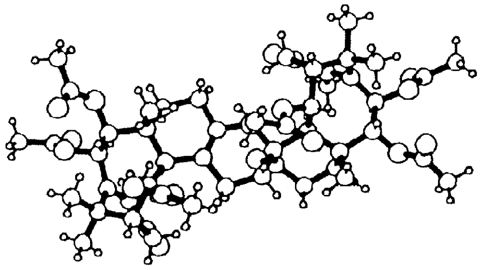

Figure 3. ORTEP Drawing of Compound **3**

The formation of **3** from **2** is considered to be derived through regio- and stereo-specific Diels-Alder cycloaddition between the enone (C-20, C-4, C-5, and O-5) of one molecule and the exomethylene (C-4' and C-20') of another one, in which the exomethylene approached to the enone. Similar dimerization has been also reported for formation of bistheonellasterone from theonellasterone.[11] Although many natural and derivatized taxoids have been reported, compound **3** is the first example of dimeric taxoids. This type of dimeric reaction could be applied for other taxoids possessing an exomethylene and a ketone at C-4 and C-5, respectively. Such dimerization of other taxoids and bioactivities of the products are currently investigated.

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References and Notes

1. Kingston, D. G. I.; Molinero, A. A.; Rimoldi, J. M. *Progress in the Chemistry of Organic Natural Products* **1993**, *61*, 1-206 and references cited therein.
2. Appendino, G. *Nat. Prod. Rep.*, **1995**, 349-360.
3. Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994**, *50*, 7401-7416.
4. Bathini, Y.; Micetich, R. G.; Daneshtalab, M. *Synth. Commun.* **1994**, *24*, 1513-1517.
5. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis,* **1994**, 639-666.
6. Taxinine A (**1**, 10 mg) was dissolved in dry CH_3CN (0.25 mL), and then added NMO (10 mg) and Molecular Sieves 4A (crushed and activated, 10 mg) and TPAP (1 mg). After the mixture was stirred at room temperature for 2 h, the solution was applied to a silica gel column (CH_2Cl_2/acetone, 99:1) to afford 5-oxotaxinine A (**2**, 8.0 mg). Compound **2** (3.2 mg) was diluted with benzene (0.4 mL) and kept at 40 °C for 8 h under dark. The solution was subjected to a silica gel column (CH_2Cl_2/acetone, 95:5) to give **3** (2.2 mg, 69%) and **2** (recovered, 0.4 mg).
7. 5-Oxotaxinine A (**2**): A colorless plate; $[\alpha]^{27}_D$ +76.4° (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 1744, 1677, and 1234 cm^{-1}; UV (MeOH) λ_{max} 266 (ε 4900) and 207 nm (6400); ^1H NMR (C_6D_6) δ 6.35 (1H, dd, J = 3.2 and 1.5 Hz, H-20a), 6.26 (1H, d, J = 10.5 Hz, H-9), 6.06 (1H, d, J = 10.5 Hz, H-10), 5.71 (1H, dd, J = 4.0 and 1.8 Hz, H-2), 5.37 (1H, dd, J = 2.6 and 1.5 Hz, H-20b), 3.36 (1H, m, H-3), 2.81 (1H, dd, J = 19.7 and 7.0 Hz, H-14a), 2.43 (1H, d, J = 19.7 Hz, H-14b), 2.25 (1H, ddd, J = 19.2, 11.0, and 8.0 Hz, H-6a), 2.22 (3H, s, H-18), 2.07 (1H, ddd, J = 19.2, 8.1, and 1.5 Hz, H-6b), 1.88 (1H, m, H-1), 1.84 (1H, ddd, J = 13.8, 8.0, and 1.5 Hz, H-7a), 1.73 (3H, s, H-16), 1.69 (3H, s, AcO), 1.66 (3H, s, AcO), 1.56 (3H, s, AcO), 1.35 (1H, ddd, J = 13.8, 11.0, and 8.1 Hz, H-7b), 1.03 (3H, s, H-19), and 0.92 (3H, s, H-17); ^{13}C NMR (C_6D_6): δ_C 198.4 (s, C-5), 197.7 (s, C-13), 169.2 (s, AcO), 168.9 (s, AcO), 168.1 (s, AcO), 150.4 (s, C-11), 142.6 (s, C-4), 138.3 (s, C-12), 127.4 (t, C-20), 75.2 (d, C-9), 72.9 (d, C-10), 69.5 (d, C-2), 47.7 (d, C-1), 46.4 (d, C-3), 41.6 (s, C-8), 38.4 (q, C-17), 37.2 (t, C-14), 37.1 (s, C-15), 33.6 (t, C-6), 27.8 (t, C-7), 25.5 (q, C-16), 20.6 (q, AcO), 20.3 (q, AcO), 20.2 (q, AcO), 19.3 (q, C-19), and 14.1 (q, C-18); NOESY correlations (C_6D_6, H/H): 1/16, 1/17, 2/9, 2/16, 2/19, 3/7b, 3/14b, 3/18, 6a/19, 7a/19, 7b/3, 7b/10, 7b/18, 9/16, 9/19, 10/18, and 14b/20b; HRFDMS *m/z* 474.2250 $(M+H)^+$, calcd for $C_{26}H_{34}O_8$, 474.2253.
8. Compound **3**: A colorless plate; $[\alpha]^{30}_D$ +80.8° (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 1746, 1678, 1233, and 1026 cm^{-1}; UV (MeOH) λ_{max} 265 (ε 10800) and 208 nm (10800); ^1H and ^{13}C NMR (Table 1); HMBC correlations (Table 1); NOESY correlations (acetone-d_6, H/H): 1/16, 1/17, 2/9, 2/16, 2/19, 3/7b, 3/10, 3/18, 6a/19, 7b/10, 7b/18, 9/16, 9/19, 14a/6'a, 14a/6'b, 16/17, 19/20, 1'/16', 1'/17', 2'/9', 2'/16', 2'/19', 3'/7'b, 3'/10', 3'/14'b, 3'/19', 3'/20'b, 6a'/20', 6'b/19', 7'b/10', 9'/16', 9'/19', 10'/18', 14'a/17', 14'b/20'b, 16'/17', and 19'/20'; HRFABMS *m/z* 949.4572 $(M+H)^+$, calcd for $C_{52}H_{69}O_{16}$, 949.4586.
9. Kalinowski, H.; Berger, S.; Braun, S. *In Carbon-13 NMR Spectroscopy*, **1988**, 370, John Wily & Sons Ltd.
10. X-ray Crystallography of **3**. Compound **3** was obtained as a colorless prism from *i*-PrOH/H_2O. Compound **3** was crystallized as orthorhobic system, space group $P2_12_12_1$ with one molecule per asymmetric unit. Cell constants were: a = 17.775(4) Å, b = 9.050(3) Å, c = 33.581(3) Å, β = 90.00°, and V = 5402.1(20) $Å^3$. All unique reflections with $3° < 2\theta < 125°$ were collected on a Rigaku AFC-5 diffractometer using graphite-monochromated CuKα radiation and employing ω-2θ scan mode. In 4846 collected reflections 2002 reflections ($I > 2\sigma(I)$) were judged as observed and used for the structure determination and refinement. The structure was solved by direct method and refined by a full-matrix least-squares method with anisotropic thermal parameters [SHELXL93 program].[12] The positions of H atoms were obtained from a difference Fourier map and were included in the final refinement. The residual factors were R=0.084 and R_w=0.249 for 2002 observed reflections.[13]
11. Kobayashi, M.; Kawazoe, K.; Katori, T.; Kitagawa, I. *Chem. Pharm. Bull.* **1992**, *40*, 1773-1778.
12. Sheldrick, G. M. SHELXL93. Program for the Refinement of Crystal Structure, University of Göttingen, Göttingen, 1993.
13. Lists of structure factors, anisotropic distancement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AS1088).