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Preparation of the *N*,19-*seco* Norditerpenoid Alkaloids from Norditerpenoid Alkaloid Yunaconitine

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Abstract: The synthesis of a new *N*,19-*seco* norditerpenoid alkaloid **7** bearing nitro group from yunaconitine **1** as the starting material through a series of steps was described.

Keywords: Norditerpenoid alkaloid, *N*,19-*seco* norditerpenoid alkaloid, yunaconitine.

The norditerpenoid alkaloids are a group of highly oxygenated complex natural products displaying a lot of interesting chemical reactions[1]. They were isolated mainly from *Aconitum* and *Delphinium* plants (*Ranunculaceae*)[2].

In the course of this investigation, we currently reported a series of structural modifications of the norditerpenoid alkaloids[3]. Herein, we report the synthesis of *N*,19-*seco* norditerpenoid alkaloids for evaluation of their biological activities.

In 1960, Büchi *et al*[4] reported that the norditerpenoids bearing an imine *N*-oxide reacted with HIO_4 to afford the *N*,19-*seco* lactones. Here we used a slight variant procedure of this method to get much improved yields, with the unambiguous assignments of ^1H (^{13}C) signals for the desired product **7**. We first synthesized the new norditerpenoid alkaloid **4** starting from **1**[5] *via* **2**→**3**[6,7], followed by the reaction with NBS developed by us[3b] to give the imine **5** [9] (overall 37% yield). The 1-OCH_3 of **1** was removed to avoid complications encountered in certain chemical transformations[3j], which will not be detailed here. The MS (EI and HREIMS) of **5** showed the molecular ion (M^+) at *m/z* 543 corresponding to the formula $C_{25}H_{37}NO_{10}$. In comparison with **4**, the spectral data of compound **5** exhibited an additional imine group (δ_H 7.58, brs; δ_C 165.4 d). Treatment of **5** with *m*-CPBA at room temperature furnished compound **6**[11] in 74% yield. The molecular formula $C_{25}H_{37}NO_{11}S$ of **6** was inferred from its HREIMS. As compared with **5**, the ^{13}C NMR spectrum of **6** showed the upfield shifts of C-11 and C-19 from 50.4 and 165.4 to 46.2 and 137.1, respectively, as well as the downfield shift of C-17 from 63.6 to 76.8 due to *N*-oxidation[10]. Treatment of the *N*-oxide **6** with an excess of HIO_4 (7.0 equiv.) in MeOH at room temperature afforded the desired *N*,19-*seco* compound **7**[12] in 63% yield. The formula $C_{24}H_{33}NO_{13}S$ of **7** was confirmed by its HREIMS and ^{13}C NMR data. The NMR spectra of **7** showed two methoxyl groups (δ_H 3.27, 3.38; δ_C 58.7 q, 59.2 q), one acetyl group (δ_H 1.93; δ_C 169.6 s, 20.6 q), and a methylsulfonyl group (δ_H 3.18; δ_C 38.3 q). Its IR and ^{13}C NMR spectra displayed the presence of a γ-lactone (1768 cm^{-1}; δ_C 174.6 s). Finally, the structure of **7** was confirmed by its 1D and 2D NMR (^1H-^1H COSY, HMQC, HMBC) spectra (**Table 2**).

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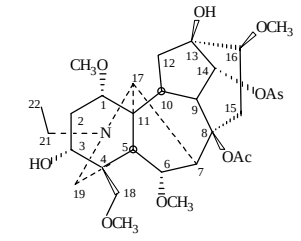
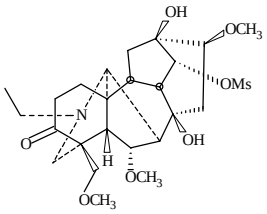
The formation of **7** can be explained by the mechanism depicted in **Figure 1**: HIO_4 oxidized **6** to an intermediate A, and then, the 6α-hydroxyl group, formed by the 6-*O*-demethylation, attacked the carboxyl group leading to the formation of **7**.



yunaconitine **1**

As=CO-C_6H_4-OCH_3(*p*)



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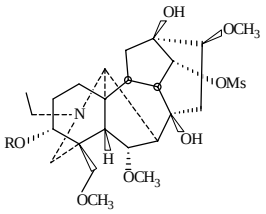
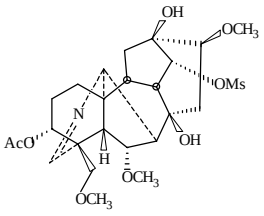


3 R= H
4 R= Ac



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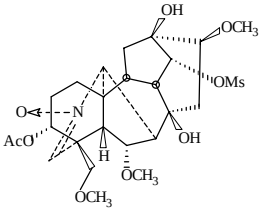

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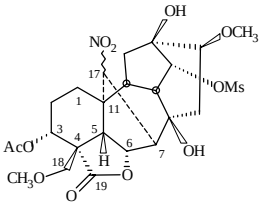

7

Table 1 ^{13}C NMR data of compounds **2**, **3**, **4**, **5**, and **6** ($CDCl_3$, 50 MHz)

No.	**2**	**3**	**4**	**5**	**6**
1	24.9 t	28.7 t	26.0 t	26.2 t	25.4 t
2	38.5 t	28.9 t	28.6 t	28.3 t	27.3 t
3	217.4 s	74.4 d	74.1 d	73.5 d	73.9 d
4	53.0 s	43.0 s	42.3 s	45.7 s	46.1 s
5	44.1 d	53.2 d	53.3 d	60.5 d	60.8 d
6	82.3 d	82.5 d	82.2 d	81.9 d	81.4 d
7	52.7 d	48.8 d	46.9 d	45.7 d	44.8 d
8	74.5 s	73.9 s	74.0 s	74.7 s	74.6 s
9	47.6 d	47.7 d	47.8 d	46.7 d	46.5 d
10	40.3 d	41.0 d	40.9 d	41.2 d	40.4 d
11	45.7 s	46.0 s	48.9 s	50.4 s	46.2 s
12	37.1 t	36.8 t	36.9 t	36.4 t	36.2 t
13	74.7 s	74.7 s	74.8 s	72.1 s	71.6 s
14	85.4 d	82.1 d	83.0 d	83.2 d	81.6 d
15	43.1 t	42.8 t	42.8 t	41.7 t	41.2 t
16	82.0 d	85.7 d	85.8 d	85.2 d	84.5 d
17	64.5 d	63.7 d	63.4 d	63.6 d	76.8 d
18	75.5 t	77.2 t	72.0 t	71.3 t	71.2 t
19	48.3 t	48.9 t	48.9 t	165.4 d	137.1 d
21	52.9 t	47.1 t	47.9 t	--	--
22	12.8 q	13.3 q	13.3 q	--	--
6'	58.2 q	57.6 q	57.6 q	57.4 q	57.4 q
16'	58.0 q	58.1 q	57.8 q	58.1 q	58.2 q
18'	59.0 q	59.1 q	58.8 q	59.0 q	59.0 q
3-OAc	--	--	170.2 s	169.9 s	169.8 s
			21.1 q	20.9 q	20.9 q
14-OMs	38.5 q	38.4 q	38.4 q	38.4 q	38.5 q

In summary, the cleavage of the *N*-C(19) bonds of the norditerpenoid alkaloids according to Büchi *et al* [4] through oxidation of the imine N-oxides with HIO_4 has been studied, a novel *N*,19-*seco* norditerpenoid alkaloid bearing the nitro group **7** was prepared in moderate yields.

Figure 1 A plausible mechanism for formation of **7** from **6**

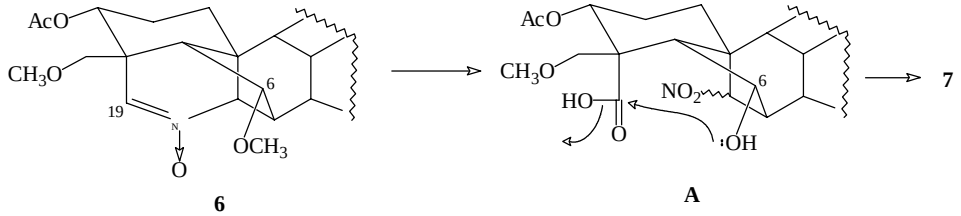

Table 2 NMR data of compound **7** ($CDCl_3$, ^1H: 400 MHz; ^{13}C: 100 MHz)

No.	δ_H	Mult (*J*=Hz)	δ_C	HMBC (H→C)
1	1.38	m (hidden)	21.2 t	C-3, C-11, C-17
	2.25	m (W1/2=24.0)		C-2, C-3, C-11, C-17
2	1.57	m (W1/2=14.4)	24.6 t	C-1, C-3, C-4, C-11
3	4.86	t (5.2)	67.0 d	C-1, C-5, C-18, C-19, 3-OAc
4	--	--	51.0s	--
5	2.69	d (6.8)	49.4 d	C-4, C-7, C-10, C-17, C-18, C-19
6	5.07	d (6.8)	82.4 d	C-5, C-8, C-11, C-17
7	2.96	br.s	58.4 d	C-5, C-6, C-8, C-9, C-15, C-17
8	--	--	72.8 s	--
9	2.19	m (hidden)	45.7 d	C-8, C-12, C-13, C-14
10	2.35	m	44.2 d	C-8, C-11, C-17
11	--	--	49.0 s	--
12	1.40	m (hidden)	35.2 t	C-10, C-11, C-13, C-14, C-16
	1.99	m (hidden)		C-9, C-13, C-16
13	--	--	75.8 s	--
14	4.49	d (4.8)	84.7 d	C-8, C-13, C-16
15	2.03	m (hidden)	42.4 t	C-7, C-8, C-9, C-13, C-16
	2.63	dd (14.8, 8.8)		C-7, C-8, C-9, C-13, C-16
16	3.40	m (hidden)	81.7 d	C-12, C-13, C-14, C-16'
17	4.13	br.s	89.5 d	C-5, C-6, C-7, C-8, C-10, C-11
18	3.42	ABq (8.8)	77.0 t	C-3, C-4, C-5, C-18'
	3.44	ABq (8.8)		C-3, C-4, C-5, C-18'
19	--	--	174.6 s	--
16'	3.38	s	58.7 q	C-16
18'	3.27	s	59.2 q	C-18
3-OAc	1.93	s	20.6 q	--
	--	--	169.6 s	--
14-OMs	3.18	s	38.3 q	--
8-OH	5.38	br.s	--	C-8, C-9
13-OH	4.74	br.s	--	C-13, C-16

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6. **2**. Colorless needle crystals (cyclohexane-acetone); mp 118.5-119°C; *Rf* 0.60 (cyclohexane-acetone=1:1); $[\alpha]_D^{20}$ -51.1 (c 0.94, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J*=7.2 Hz, *N*CH_2CH_3), 3.10 (s, 3H, OMs), 3.17, 3.34, 3.40 (s, each 3H, 3×OCH_3), 3.45, 3.84 (ABq, each 1H, *J*=7.8 Hz, H_2-18), 4.11 (d, 1H, *J*=6.4 Hz, H-6β), 4.71 (d, 1H, *J*=3.4 Hz, H-14β); EIMS *m/z* (%) 529 (M^+, 76), 516 (M-15, 63), 498 (M-31, 37), 469 (35), 454 (44), 438 (24); HREIMS *m/z* calcd for $C_{25}H_{39}NO_9$ (M^+) 529.2345, found 529.2351.
7. **3**. White amorphous powder, mp 108-108.5°C; *Rf* 0.52 (cyclohexane-acetone=1:1); $[\alpha]_D^{20}$ +2.0 (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (t, 3H, *J*=7.0 Hz, *N*CH_2CH_3), 2.33, 2.98 (ABq, each 1H, *J*=11.2 Hz, H_2-19), 2.47 (q, 2H, *J*=7.0 Hz, *NCH*$_2$$CH_3$), 3.13 (s, 3H, OMs), 3.32, 3.33, 3.42 (s, each 3H, 3×OCH_3), 3.65, 3.88 (ABq, each 1H, *J*=9.0 Hz, H_2-18), 4.71 (d, 1H, *J*=5.2 Hz, H-14β); EIMS *m/z* (%) 531 (M^+, 100), 516 (M-15, 93), 500 (M-31, 18); HREIMS *m/z* calcd for $C_{25}H_{41}NO_9S$ (M^+) 531.2502, found 531.2512.
8. **4**. White amorphous powder, mp 123-124°C; *Rf* 0.80 (cyclohexane- acetone=1:1); $[\alpha]_D^{20}$ +24.5 (c 0.98, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (t, 3H, *J*=7.2 Hz, *N*CH_2*CH*$_3$), 2.01 (3H, s, OAc), 2.93, 3.89 (each 1H, ABq, *J*=8.6 Hz, H_2-19), 3.09 (s, 3H, OMs), 3.22, 3.35, 3.38 (s, each 3H, 3×OCH_3), 4.04 (d,1H, *J*=6.2 Hz, H-6β), 4.68 (d, 1H, *J*=5.2 Hz, H-14β), 4.95 (dd, 1H, *J*=10.4, 5.6 Hz, H-3β); EIMS *m/z* (%) 573 (M^+,7), 558 (M-15, 5), 514 (100); HREIMS calcd for $C_{27}H_{43}NO_{10}S$ (M^+) 573.2607, found 573.2562.
9. **5**. White amorphous powder, 70 mg (37%). mp 136-136.5°C; *Rf* 0.36 (cyclohexane-acetone=1:1); $[\alpha]_D^{20}$ +75.2 (c 1.09, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.04 (s, 3H, OAc), 3.10 (s, 3H, OMs), 3.27, 3.28, 3.40 (s, each 3H, 3×OCH_3), 3.56, 4.16 (ABq, each 1H, *J*=8.8 Hz, H_2-18), 3.65 (brs, OH), 3.91 (brs, OH), 4.09 (d,1H, *J*=6.8 Hz, H-6β), 4.71 (d, 1H, *J*=5.0 Hz, H-14β), 5.02 (dd, 1H, *J*=9.6, 4.6 Hz, H-3β), 7.58 (brs, 1H, H-19); EIMS *m/z* (%) 543 (M^+, 3), 484 (M-59, 100); HREIMS *m/z* calcd for $C_{25}H_{37}NO_{10}S$ (M^+) 543.2138, found 543.2166.
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11. **6**. White amorphous powder, 221 mg (74%). mp 164-165°C; *Rf* 0.27 ($CHCl_3$- MeOH=9:1); $[\alpha]_D^{20}$ -34.0 (c 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (s, 3H, OAc), 3.13 (s, 3H, OMs), 3.29, 3.31, 3.42 (s, each 3H, 3×OCH_3), 3.42, 4.20 (ABq, each 1H, *J*=8.2 Hz, H_2-18), 3.58, 3.96 (brs, each 1H, OH), 4.72 (d, 1H, *J*=5.0 Hz, H-14β), 5.03 (dd, 1H, *J*=9.0, 4.4 Hz, H-3β), 6.83 (brs,1H, H-19); EIMS *m/z* (%) 559 (M^+, 13), 543 (8), 542 (M-17, 9), 500 (M-59, 14), 484 (100); HREIMS *m/z* calcd for $C_{25}H_{37}NO_{11}S$ (M^+) 559.2087, found 559.2112.
12. **7**. White amorphous powder, 60 mg (63%). mp 158-159°C; *Rf* 0.65 ($CHCl_3$- MeOH=9:1); $[\alpha]_D^{20}$ -11.6 (c 1.03, $CHCl_3$); EIMS *m/z* (%) 575 (M^+, 7), 559 (17), 515 (M-60, 14), 484 (26); HREIMS *m/z* calcd for $C_{24}H_{33}NO_{13}S$ (M^+) 575.1672, found 575.1641.

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