

A NEW ACCESS TO THE CLEAVAGE OF THE N-19 BOND OF NORDITERPENOID ALKALOIDS AND THEIR DERIVATIVES BY FORMATION OF OXAZIRIDINES

Qiao-Hong Chen, Liang Xu, and Feng-Peng Wang*

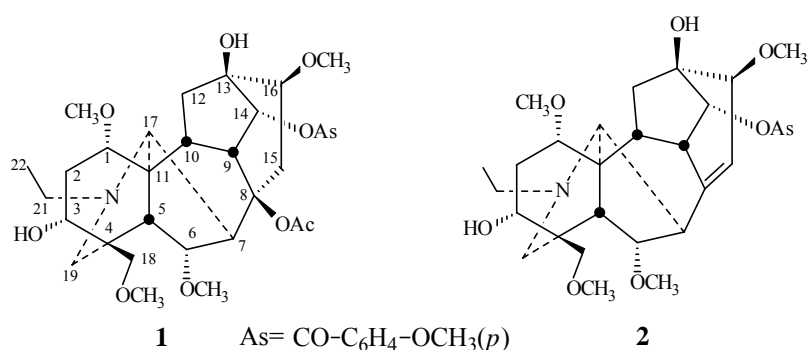
Department of Chemistry of Medicinal Natural Products, West China College of Pharmacy, Sichuan University, No. 17, Duan 3, Renmin Nan Road, Chengdu 610041, P. R. China

Abstract A new *N,19-seco*-norditerpenoid alkaloidal compound (**5**) possessing an oxaziridine group from yunaconitine (**1**) was furnished by using a new method in five steps involving acetylation, imination, quaternization, formation of *N,O*-mixed ketal, and oxidation in 50% overall yields.

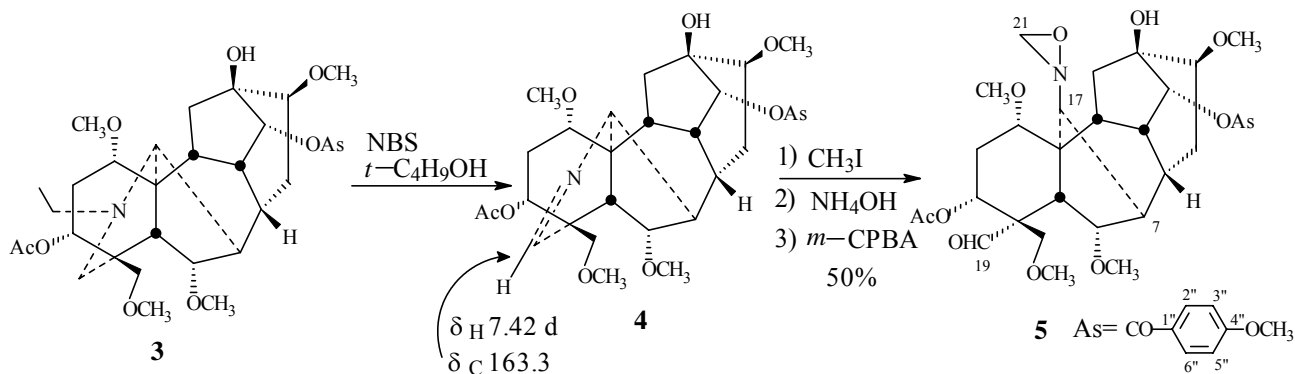
The norditerpenoid alkaloids are a group of highly oxygenated complex natural products displaying a lot of interesting chemical reactions¹ and several biological activities,² which are a synthetic or structural modified target. They were isolated mainly from both *Aconitum* and *Delphinium* plants (*Ranunculaceae*) as a rich source.³

In the course of this investigation, we recently reported a series of structural modifications of the norditerpenoid alkaloids.⁴ Herein, we report in detail a new synthesis of *N,19-seco*-norditerpenoid alkaloidal compounds for evaluation of the biological activities.

After Büchi *et al.*⁵ reported the synthesis of *N,19-seco*-norditerpenoid alkaloids from the norditerpenoid alkaloids bearing an imine *N*-oxide in 1960, no chemistry on the cleavage of *N*-C(19) bond of the norditerpenoid alkaloids has been reported yet. Many attempts to cleave the *N*-C(19) bond of norditerpenoid alkaloids failed. But, we finally found that *N,19-seco* norditerpenoid alkaloids can be completed *via* an oxidation of the intermediate *N,O*-mixed ketal with *m*-CPBA to form the oxaziridine. To prevent the effect of the 8-OAc group on the reaction, we accomplished the following. According to the literature,⁶ yunaconitine (**1**)⁷ was exposed to these reaction conditions (205~210 °C, in vacuum for 5 min) and afforded compound (**2**) in 81% yield. To this end, hydrogenation of **2** in the presence of PtO₂ as a catalyst followed by acetylation with Ac₂O/pyridine resulted in the formation of **3** in 80% yield. The MS



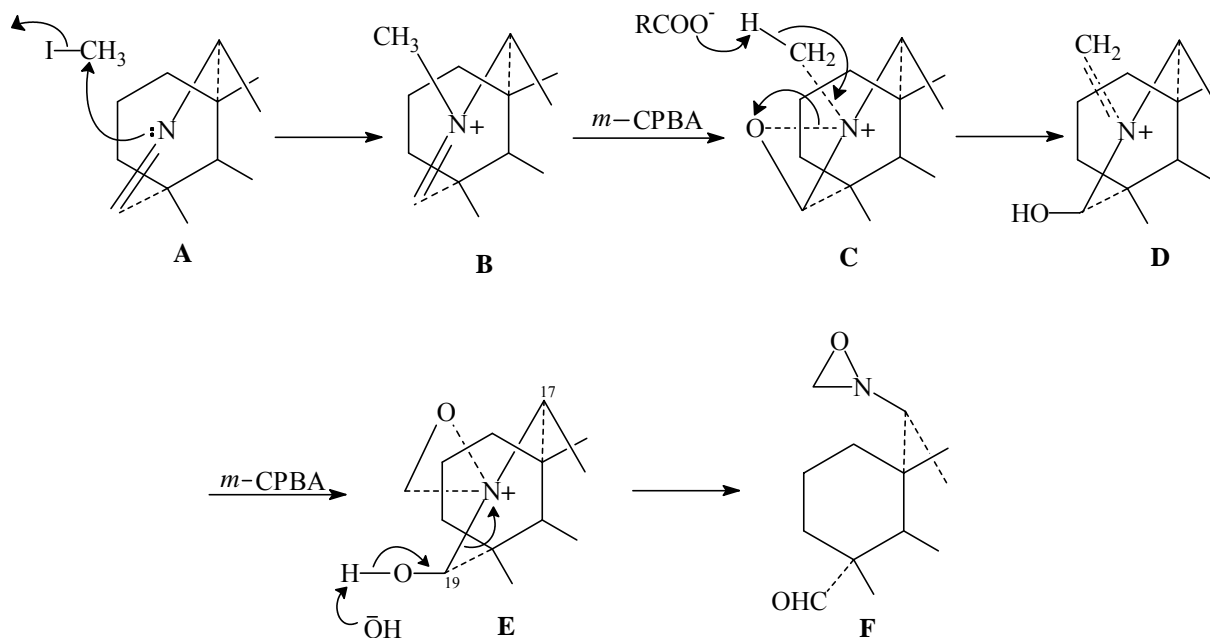
(HR-FAB) spectrum of compound (**3**) showed the pseudo molecular ion ($M^+ + H$) at m/z 644 corresponding to the formula C₃₅H₅₀NO₁₀. As compared with **2**, its NMR spectra exhibited the absence of a trisubstituted double bond, leading easy to determine the structure of **3**. Reaction of **3** with NBS-*t*-C₄H₉OH using a method developed by us^{4c} afforded the imine **4** (Scheme 1). The molecular



Scheme 1

formula C₃₃H₄₃NO₁₀ of compound (**4**) inferred from its HR-FABMS and ¹³C NMR spectra. In comparison to the NMR spectra of **3**, those of **4** showed the absence of an *N*-ethyl group and the appearance of an imine group ($\delta_{\text{H}} 7.42$, d, $J=1.0$ Hz; $\delta_{\text{C}} 163.3$ d). When **4** was subjected to treatment with CH₃I-conc. NH₄OH and *m*-CPBA, the oxaziridine-containing *N*,19-*seco* compound (**5**) (Scheme 1) was produced in 50% overall yield from **1**. The MS (FAB and HR-FAB) spectrum of compound (**5**) showed its molecular ion ($M^+ + H$) at m/z 629 corresponding to the pseudo formula C₃₄H₄₆NO₁₂. As compared with **4**, the IR and NMR spectra of **5** displayed the presence of an additional formyl group (1730 cm⁻¹, $\delta_{\text{H}} 10.31$ s; $\delta_{\text{C}} 202.2$ s) and the oxaziridine moiety [$\delta_{\text{H}} 3.94, 4.08$ (each 1H, ABq, $J=10.0$ Hz; $\delta_{\text{C}} 76.3$ t), as well as the absence of the imine group. The HMBC spectrum of **5** showed the multi-bond ¹H-¹³C correlations between H-19 and C(4), H₂-21 and C(17), leading to confirm the location of the formyl group and oxaziridine moiety in **5**. Finally, the structure of **5** was determined by 1D- and 2D- NMR spectra (Table 1). The formation of **5** can be explained by the mechanism depicted in Scheme 2. First, reaction of the imine **A** with CH₃I afforded the intermediate **B** that was oxidized by peracid through a Baeyer-Villiger type process^{8,9} to form **C**, and then, ring closure in **C** with loss of MCBA gave **D** that carries out the second peracid

oxidation to form the intermediate **E** followed by attacking of OH^- to afford the oxaziridine **F** (*N*, 19-seco compound (**5**)).



Scheme 2 A plausible mechanism for formation from **4** to **5**

In summary, one new *N*,19-seco norditerpenoid alkaloidal compound (**6**) possessing an oxaziridine group have been synthesized from yunaconitine (**1**) in five steps mainly including acetylation, imination, quaternarization, formation of *N*,*O*-mixed ketals and oxidation in 50% overall yields. This is a new method for cleavage of the *N*,*C*(19) bond of the norditerpenoid alkaloids and their derivatives.

EXPERIMENTAL

General Experimental Procedure. Melting points were uncorrected. IR spectrum was measured on a Perkin-Elmer spectrophotometer. Optical rotation was measured with a JASCO DIP-370 polarimeter. ^1H - and ^{13}C - NMR spectra were measured on a Bruker AC-200 and a Varian Unity 400/45 spectrometers, in CDCl_3 with TMS as the internal standard. HRFABMS spectrum was obtained from a AutoSpec-3000 spectrometer.

Pyroyunaconitine (2). An amorphous fine powder yunaconitine (400 mg) (**1**) purchased from Kunming Institute of Botany in 250 mL of a round-bottomed flask was heated under reduced pressure (20 mm Hg) at 205-210 $^\circ\text{C}$ for 5 min. After cooling, the residue was chromatographed over silica gel H (6 g) column eluting with cyclohexane-acetone (4:1) to give the product (white amorphous powder, 295 mg, 81%). ^1H NMR (200 MHz): δ 1.08 (3H, t, $J=7.2$ Hz, NCH_2CH_3), 3.23, 3.27, 3.31, 3.38, 3.83 (each 3H, s, $5\times\text{OCH}_3$), 4.24 (1H, d, $J=6.6$ Hz, H-6 β), 4.91 (1H, d, $J=2.6$ Hz, H-15), 5.55 (1H, d, $J=6.4$ Hz, H-14 β), 6.89, 7.98

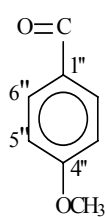
(each 2H, AA'BB' system, $J=8.8$ Hz, Ar-H). The structure of **2** was identified by comparison of ^1H NMR and TLC ($\text{CHCl}_3/\text{MeOH}=7:3$; ether/acetone=9:1) with the authentic sample.¹⁰

Compound (3). To a solution of pyroyunaconitine (**2**) (150 mg, mmol) in 2.5% HCl (1 mL), the pretreated PtO_2 (15 mg) in EtOAc (5 mL) was added and the suspension was stirred under a hydrogen atmosphere at rt overnight. After work-up using a general method, to a residue in pyridine (3 mL) was added acetic anhydride (0.5 mL) and the solution was allowed to stand overnight. Evaporation under reduced pressure gave a residue, which was chromatographed over silica gel H (cyclohexane/acetone=4:1) to give the pure product as white amorphous powder, 130 mg (80%). mp 104-106 °C; $[\alpha]_{\text{D}}^{20} +40.0^\circ$ (c 0.45, CHCl_3); R_f 0.52 ($\text{CHCl}_3\text{-MeOH}=95:5$); $\text{IR}_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3459 (OH), 2929, 1732, 1711, 1606, 1512, 1456, 1367, 1254, 1169; ^1H NMR (200 MHz): δ 1.09 (3H, t, $J=7.2$ Hz, NCH_2CH_3), 2.01 (3H, s, OAc), 3.18, 3.23, 3.24, 3.38, 3.85 (each 3H, s, $5\times\text{OCH}_3$), 4.84 (1H, d, $J=6.6$ Hz, H-3 β), 4.90 (1H, d, $J=5.6$ Hz, H-14 β); ^{13}C NMR (50 MHz): δ 13.6 (C-22), 21.2 (CO- CH_3), 30.2 (C-2), 31.8 (C-8), 33.7 (C-12), 36.5 (C-15), 39.5 (C-9), 41.5 (C-10), 42.4 (C-4), 46.1 (C-5), 46.4 (C-7), 47.8 (C-19), 49.0 (C-21), 50.3 (C-11), 55.4 (4''- OCH_3), 56.5 (C-1'), 58.1 (C-6'), 58.2 (C-16'), 58.8 (C-18'), 60.1 (C-17), 71.8 (C-3), 71.9 (C-18), 75.9 (C-13), 80.1 (C-14), 83.2 (C-1), 85.1 (C-16), 85.6 (C-6), 113.5 (C-3'', C-5''), 122.7 (C-1''), 131.8 (C-2''), C-6''), 163.3 (C-4''), 166.5 (CO-Ar), 170.2 (CO CH_3); EIMS (%) 643 (M^+ , 10), 628 (M-15, 15), 612 (M-31, 100); HRFABMS m/z : 644.3435, calcd for $\text{C}_{35}\text{H}_{50}\text{NO}_{10}$ (M^++1) 644.3434.

Compound (4). To a solution of compound (**3**) (199 mg, 0.31 mmol) in *t*-butanol (7 mL), NBS (30 mg, 1.86 mmol) was added and the solution was heated at 50 °C for 3.5 h. Evaporation to dryness, basifying (10% NH_4OH , 20 mL), extraction (CHCl_3 , 10 mL \times 2), drying (Na_2SO_4), removal of solvent and column chromatography (silica gel H, cyclohexane/acetone=3:2) afforded the pure product as white amorphous powder, 122 mg (65%). mp 124-126 °C; $[\alpha]_{\text{D}}^{20} +83.3^\circ$ (c 0.42, CHCl_3), R_f 0.48 ($\text{CHCl}_3\text{-MeOH} = 95:5$); $\text{IR}_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3443 (OH), 2988, 1710, 1637 (N=C), 1605, 1512, 1459, 1369, 1163, 1104; ^1H NMR (200 MHz): δ 2.07 (3H, s, OAc), 3.21, 3.21, 3.27, 3.41, 3.86 (each 3H, s $5\times\text{OCH}_3$), 4.97 (1H, d, $J=4.8$ Hz, H-14 β), 5.10 (1H, dd, $J=8.2, 5.6$ Hz, H-3 β), 7.42 (1H, d, $J=1$ Hz, H-19), 6.92, 8.01 (each 2H, AA'BB' system, $J=8.8$ Hz, Ar-H); ^{13}C NMR (50 MHz): δ 20.9 (CO CH_3), 29.4 (C-2), 30.5 (C-15), 33.1 (C-9), 35.8 (C-12), 38.0 (C-8), 41.3 (C-10), 44.3 (C-5), 50.0 (C-11), 50.7 (C-4), 52.7 (C-7), 55.3 (4''- OCH_3), 55.9 (C-1'), 57.7 (C-6'), 58.2 (C-16'), 58.9 (C-18'), 59.0 (C-17), 72.2 (C-18), 72.6 (C-3), 75.9 (C-13), 80.0 (C-14), 82.0 (C-1), 85.1 (C-6), 86.0 (C-16), 113.5 (C-3'', C-5''), 122.5 (C-1''), 131.7 (C-2'', C-6''), 163.3

Table 1 NMR spectral data of compound (**5**)

No.	δ_{H} Multi (J =Hz)	δ_{C}	^1H COSY	HMBC (H \rightarrow C)
1	3.34 <i>dd</i> (5.6, 12.0)	83.9 <i>d</i>	H-2 α , H-2 β	C(1'), C(10)
2	1.78 <i>dd</i> (12.0, 24.8) (α) 2.23 <i>m</i> (β)	30.6 <i>t</i>	H-1, H-2 β , H-3 H-1, H-2 α , H-3	C(1), C(3), C(4), C(11) C(1), C(3), C(4), C(11)
3	4.94 <i>dd</i> (2.8, 12.8)	69.3 <i>d</i>	H-2 α , β	C(1), C(2), C(19)
4	—	52.9 <i>s</i>	—	—
5	2.87 <i>d</i> (8.4)	50.7 <i>d</i>	H-6	C(4), C(6), C(7), C(10), C(17), C(18), C(19)
6	3.64 <i>d</i> (8.4)	85.6 <i>d</i>	H-5	C(5), C(7), C(8), C(6'), C(17)
7	2.17 <i>d</i> (hidden)	51.7 <i>d</i>	H-8	C(6), C(8), C(9), C(11), C(17)
8	2.56 <i>m</i>	32.4 <i>d</i>	H-7, H-9, H-15	C(6), C(7), C(9), C(17)
9	2.56 <i>m</i>	36.7 <i>d</i>	H-8, H-10, H-14	C(7), C(8)
10	2.14 <i>m</i>	46.1 <i>d</i>	H-9, H-12	C(8), C(9), C(17)
11	—	52.2 <i>s</i>	—	—
12	2.11 <i>m</i> (β) 1.96 <i>m</i> (α)	33.9 <i>t</i>	H-10, H-12 α H-10, H-12 β	C(10), C(11), C(13), C(14), C(16) C(10), C(11), C(13), C(14), C(16)
13	—	76.5 <i>s</i>	—	—
14	4.88 <i>d</i>	79.6 <i>d</i>	H-9	C(13), C(16)
15	1.17 <i>m</i>	30.6 <i>t</i>	H-8, H-16	C(7), C(8), C(16)
16	3.42 <i>dd</i> (4.4, 9.2)	85.2 <i>d</i>	H-15	C(8), C(13), C(15), C(16')
17	2.17 <i>s</i>	74.0 <i>d</i>	—	C(5), C(6), C(10), C(20)
18	3.64 ABq (10.0) 3.19 ABq (10.0)	70.3 <i>t</i>	H-18 (3.19) H-18 (3.64)	C(4), C(18') C(4), C(18')
19	10.31 <i>s</i>	202.2 <i>d</i>	—	C(4), C(18)
21	4.08 ABq (10.0) 3.94 ABq (10.0)	76.3 <i>t</i>	H-21 (3.94) H-21 (4.08)	C(17) C(17)
1'	3.32 <i>s</i>	55.6 <i>q</i>	—	C(1)
6'	3.16 <i>s</i>	57.5 <i>q</i>	—	C(6)
16'	3.45 <i>s</i>	58.2 <i>q</i>	—	C(16)
18'	3.30 <i>s</i>	59.1 <i>q</i>	—	C(18)
OAc	—	170.0 <i>s</i>	—	—
	2.01 <i>s</i>	20.9 <i>q</i>	—	C(3')
	—	166.3 <i>s</i>	—	—
	1'' —	122.3 <i>s</i>	—	—
6''	2'', 6'' 7.99 AA'BB' (8.4)	131.7 <i>d</i>	H-3''	C(4''), C(6''), 14(CO)
5''	3'', 5'' 6.90 AA'BB' (8.4)	113.8 <i>d</i>	H-2''	C(1''), C(4''), C(5'')
	4'' —	163.5 <i>s</i>	—	—
	3.85 <i>s</i>	55.3 <i>q</i>	—	C(4'')



(C-19), 163.3 (C-4''), 166.5 [OCO-C₆H₄-OCH₃(*p*)], 170.1 (COCH₃); EIMS (%) 613 (M⁺, 12), 598 (M-OH, 11), 582 (M-31, 5), 568 (M-45, 30), 554 (28); HRFABMS m/z 614.2984, calcd for C₃₃H₄₄NO₁₀ (M⁺+1) 614.2965.

Compound (5). To a solution of compound (**4**) (373 mg, 0.61 mmol) in methanol (5 mL), CH₃I (0.4

mL, 6.42 mmol) was added and the solution was allowed to stand at rt overnight. Evaporation in vacuum afforded the residues, which was treated with conc. NH₄OH (5 mL) in CH₂Cl₂ (5 mL) for 10 min. The water layer was extracted with CH₂Cl₂ (5 mL × 3). The organic layer was dried (Na₂SO₄) and evaporated to afford the compound (**5**), which was dissolved in CH₂Cl₂ (12 mL), *m*-CPBA (42 mg, 2.44 mmol) was added and the solution was stirred at rt for 30 min, then, to which was added 10% Na₂CO₃ (8 mL). After vigorously stirring, the organic layer was separated and the water layer was extracted with CH₂Cl₂ (8 mL × 3), and drying the CH₂Cl₂ layer with Na₂SO₄, removal of solvent and column chromatography (silica gel H, cyclohexane/acetone=4:1) afforded the pure product (compound (**5**)) as white amorphous powder, 277 mg (69%); mp 152-154°C; [α]_D²⁰ +30.8° (c 0.78, CHCl₃); *R*_f 0.54 (CHCl₃-MeOH=97:3); IR_{max}^{KBr} cm⁻¹: 3459 (OH), 2928, 2825, 1730, 1709, 1606, 1512, 1461, 1366, 1256, 1107; ¹H-NMR (400 MHz) and ¹³C-NMR (100 MHz): Table 1; EIMS (%) 659 (M⁺, 10), 629 (M-31, 6), 614 (9); HRFABMS *m/z* 660.3025, calcd for C₃₄H₄₆NO₁₂ (M⁺+1) 660.3020.

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