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

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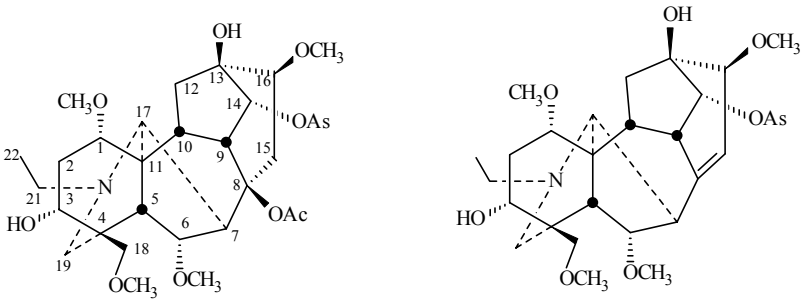
Abstract A new *N*,19-*seco*-norditerpenoid alkaloidal compound (**5**) possessing an oxaziridine group from yunaconitine (**1**) was furnished by using a new method in five steps involving acetylation, imination, quaternization, formation of *N*,*O*-mixed ketal, and oxidation in 50% overall yields.

The norditerpenoid alkaloids are a group of highly oxygenated complex natural products displaying a lot of interesting chemical reactions[1] 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]

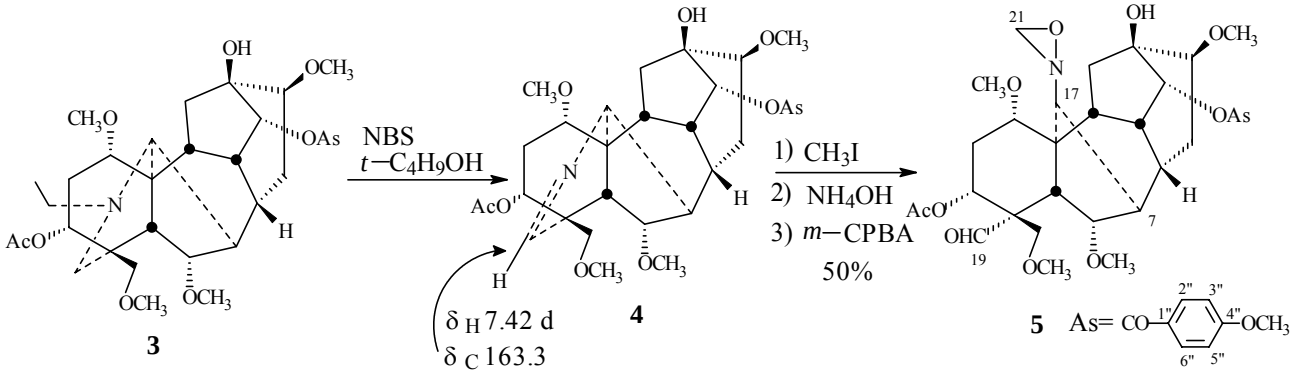
In the course of this investigation, we recently reported a series of structural modifications of the norditerpenoid alkaloids.[4] Herein, we report in detail a new synthesis of *N*,19-*seco*-norditerpenoid alkaloidal compounds for evaluation of the biological activities.

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 intermedicte *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 ℃, in vacuum for 5 min) and afforded compound (**2**) in 81% yield. To this end, hydrogenation of **2** in the presence of PtO_2 as a catalyst followed by acetylation with Ac_2O/pyridine resulted in the formation of **3** in 80% yield. The MS



1 As= CO-C_6H_4-OCH_3(*p*) **2**

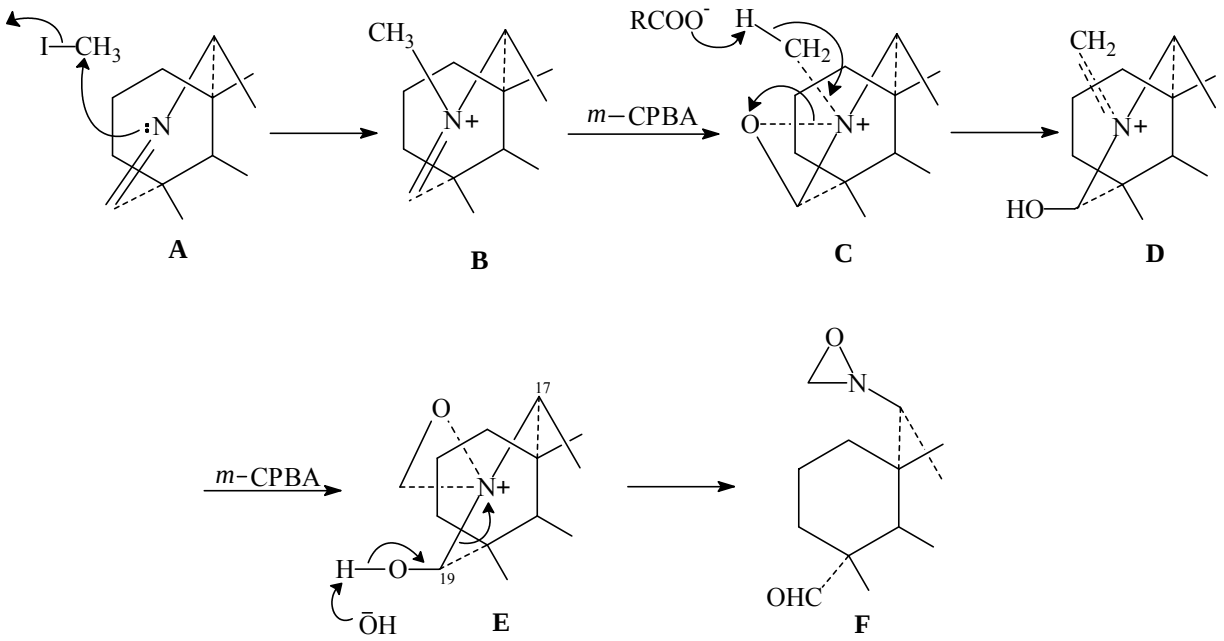
(HR-FAB) spectrum of compound (**3**) showed the pseudo molecular ion (M^++H) at *m/z* 644 corresponding to the formula $C_{35}H_{50}NO_{10}$. As compared with **2**, its NMR spectra exhibited the absence of a trisubstituted double bond, leading easy to determine the structure of **3**. Reaction of **3** with NBS-*t*-C_4H_9OH using a method developed by us[4c] afforded the imine **4** (Scheme 1). The molecular



Scheme 1

formula $C_{33}H_{43}NO_{10}$ of compound (**4**) inferred from its HR-FABMS and ^{13}C NMR spectra. In comparison to the NMR spectra of **3**, those of **4** showed the absence of an *N*-ethyl group and the apearance of an imine group (δ_H 7.42, d, *J*=1.0 Hz; δ_C 163.3 d). When **4** was subjected to treatment with CH_3I-conc. NH_4OH 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 $C_{34}H_{46}NO_{12}$. As compared with **4**, the IR and NMR spectra of **5** displayed the presence of an additional formyl group (1730 cm^{-1}, δ_H 10.31 s; δ_C 202.2 s) and the oxaziridine moiety [δ_H 3.94, 4.08 (each 1H, ABq, *J*=10.0 Hz; δ_C 76.3 t), as well as the absence of the imine group. The HMBC spectrum of **5** showed the multi-bond ^1H-^{13}C correlations between H-19 and C(4), H_2-21 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 CH_3I 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. ^{1}H- 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.

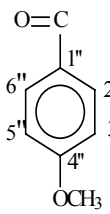
Pyroyunaconitine (2). An amorphous fine powder yunaconitine (400 mg) (**1**) purchased from Kunming Institute of Botany in 250 mL of a round-bottomed flask was heated under reduced pressure (20 mm Hg) at 205-210℃ for 5 min. After cooling, the residue was chromatographed over silica gel H (6 g) column eluting with cyclohexane-acetone (4:1) to give the product (white amorphous powder, 295 mg, 81%). ^{1}H NMR (200 MHz): δ1.08 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.23, 3.27, 3.31, 3.38, 3.83 (each 3H, s, 5×OCH_3), 4.24 (1H, d, *J*=6.6 Hz, H-6β), 4.91 (1H, d, *J*=2.6 Hz, H-15), 5.55 (1H, d, *J*=6.4 Hz, H-14β), 6.89, 7.98

(each 2H, AA'BB' system, *J*=8.8 Hz, Ar-H). The structure of **2** was identified by comparison of ^{1}H NMR and TLC ($CHCl_3$/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℃; $[\alpha]_D^{20}$ +40.0° (c 0.45, $CHCl_3$); *Rf* 0.52 ($CHCl_3$-MeOH=95:5); IR_{max}^{KBr} cm^{-1}: 3459 (OH), 2929, 1732, 1711, 1606, 1512, 1456, 1367, 1254, 1169; ^{1}H NMR (200 MHz): δ1.09 (3H, t, *J*=7.2 Hz, *N*CH_2*CH*$_3$), 2.01 (3H, s, OAc), 3.18, 3.23, 3.24, 3.38, 3.85 (each 3H, s, 5×OCH_3), 4.84 (1H, d, *J*=6.6 Hz, H-3β), 4.90 (1H, d, *J*=5.6 Hz, H-14β); ^{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 (*C*O-Ar), 170.2 (*C*OCH_3); EIMS (%) 643 (M^+, 10), 628 (M-15, 15), 612 (M-31, 100); HRFABMS *m/z*: 644.3435, calcd for $C_{35}H_{50}NO_{10}$ (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℃ for 3.5 h. Evaporation to dryness, basifing (10% NH_4OH, 20 mL), extraction ($CHCl_3$, 10 mL×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℃; $[\alpha]_D^{20}$ +83.3° (c 0.42, $CHCl_3$), *Rf* 0.48 ($CHCl_3$-MeOH = 95:5); IR_{max}^{KBr} cm^{-1}: 3443 (OH), 2988, 1710, 1637 (N=C), 1605, 1512, 1459, 1369, 1163, 1104; ^{1}H NMR (200 MHz): δ2.07 (3H, s, OAc), 3.21, 3.21, 3.27, 3.41, 3.86 (each 3H, s 5×OCH_3), 4.97 (1H, d, *J*=4.8 Hz, H-14β), 5.10 (1H, dd, *J*=8.2, 5.6 Hz, H-3β), 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): δ20.9 (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	^{1}H COSY	HMBC (H→C)
1	3.34 *dd* (5.6, 12.0)	83.9 *d*	H-2α, H-2β	C(1'), C(10)
2	1.78 *dd* (12.0, 24.8) (α)	30.6 *t*	H-1, H-2β, H-3	C(1), C(3), C(4), C(11)
	2.23 *m* (β)		H-1, H-2α, H-3	C(1), C(3), C(4), C(11)
3	4.94 *dd* (2.8, 12.8)	69.3 *d*	H-2α, β	C(1), C(2), C(19)
4	—	52.9 *s*	—	—
5	2.87 *d* (8.4)	50.7 *d*	H-6	C(4), C(6), C(7), C(10), C(17), C(18), C(19)
6	3.64 *d* (8.4)	85.6 *d*	H-5	C(5), C(7), C(8), C(6'), C(17)
7	2.17 *d* (hidden)	51.7 *d*	H-8	C(6), C(8), C(9), C(11), C(17)
8	2.56 *m*	32.4 *d*	H-7, H-9, H-15	C(6), C(7), C(9), C(17)
9	2.56 *m*	36.7 *d*	H-8, H-10, H-14	C(7), C(8)
10	2.14 *m*	46.1 *d*	H-9, H-12	C(8), C(9), C(17)
11	—	52.2 *s*	—	—
12	2.11 *m* (β)	33.9 *t*	H-10, H-12α	C(10), C(11), C(13), C(14), C(16)
	1.96 *m* (α)		H-10, H-12β	C(10), C(11), C(13), C(14), C(16)
13	—	76.5 *s*	—	—
14	4.88 *d*	79.6 *d*	H-9	C(13), C(16)
15	1.17 *m*	30.6 *t*	H-8, H-16	C(7), C(8), C(16)
16	3.42 *dd* (4.4, 9.2)	85.2 *d*	H-15	C(8), C(13), C(15), C(16')
17	2.17 *s*	74.0 *d*	—	C(5), C(6), C(10), C(20)
18	3.64 ABq (10.0)	70.3 *t*	H-18 (3.19)	C(4), C(18')
	3.19 ABq (10.0)		H-18 (3.64)	C(4), C(18')
19	10.31 *s*	202.2 *d*	—	C(4), C(18)
21	4.08 ABq (10.0)	76.3 *t*	H-21 (3.94)	C(17)
	3.94 ABq (10.0)		H-21 (4.08)	C(17)
1'	3.32 *s*	55.6 *q*	—	C(1)
6'	3.16 *s*	57.5 q	—	C(6)
16'	3.45 *s*	58.2 *q*	—	C(16)
18'	3.30 *s*	59.1 *q*	—	C(18)
OAc	—	170.0 *s*	—	—
	2.01 *s*	20.9 *q*	—	C(3')
	—	166.3 *s*	—	—
	1" —	122.3 *s*	—	—
	2", 6" 7.99 AA'BB' (8.4)	131.7 *d*	H-3"	C(4"), C(6"), 14(CO)
	3", 5" 6.90 AA'BB' (8.4)	113.8 *d*	H-2"	C(1"), C(4"), C(5")
	4" —	163.5 *s*	—	—
	3.85 *s*	55.3 *q*	—	C(4")

(C-19), 163.3 (C-4"), 166.5 [O*C*O-C_6H_4-OCH_3(*p*)], 170.1 (*C*OCH_3); 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 $C_{33}H_{44}NO_{10}$ (M^++1) 614.2965.

Compound (**5**). To a solution of compound (**4**) (373 mg, 0.61 mmoL) in methanol (5 mL), CH_3I (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. NH_4OH (5 mL) in CH_2Cl_2 (5 mL) for 10 min. The water layer was extracted with CH_2Cl_2 (5 mL×3). The organic layer was dried (Na_2SO_4) and evaporated to afford the compound (**5**), which was dissolved in CH_2Cl_2 (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% Na_2CO_3 (8 mL). After vigorously stirring, the organic layer was separated and the water layer was extracted with CH_2Cl_2 (8 mL ×3), and drying the CH_2Cl_2 layer with Na_2SO_4, 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℃; $[\alpha]_D^{20}$ +30.8° (c 0.78, $CHCl_3$); *Rf* 0.54 ($CHCl_3$-MeOH=97:3); IR_{max}^{KBr} cm^{-1}: 3459 (OH), 2928, 2825, 1730, 1709, 1606, 1512, 1461, 1366, 1256, 1107; ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz): Table 1; EIMS (%) 659 (M^+, 10), 629 (M-31, 6), 614 (9); HRFABMS *m/z* 660.3025, calcd for $C_{34}H_{46}NO_{12}$ (M^++1) 660.3020.

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