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Studies on the relative reactivity of three hydroxyl groups in aconitine

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The relative reactivity of three hydroxyl groups in aconitine toward acetylation, chlorination, sulfonylation, and oxidation has been studied in this paper. The reduction of C-3 ketone and C-15 ketone derivatives of aconitine was also investigated. It was found that (1) the relative reactivity of three hydroxyl groups toward acetylation, chlorination, and sulfonylation is 3-OH > 13-OH > > 15-OH; (2) 3-OH is much more reactive than 15-OH toward oxidation; and (3) reduction of the carbonyl group at C-3 with $NaBH_4$ generated a pair of C-3 epimers, while the reduction products of the carbonyl group at C-15 depend largely on the specific reducing agent and the absolute configuration of 16-OCH_3. When the substrate has 16β-OCH_3, its carbonyl group at C-15 can be reduced with $NaBH_4$ to yield exclusively the 15α-OH-containing product. Upon replacement of reducing agent $NaBH_4$ with $LiAlH_4$, the C-15 carbonyl group can be reduced to yield a pair of C-15 epimers. On the other hand, when the substrate has 16α-OCH_3, C-15 carbonyl group can only be reduced to generate 15α-OH-containing product.

Keywords: aconitine; regioselective reaction; oxidation; chlorination; sulfonation

1. Introduction

Aconitine represents the first example of diterpenoid alkaloid, which was isolated by Geiger from *Aconitum napellus* L. in 1833 [1]. Its structural complexity and physiological properties, especially its toxicity toward heart and nerve system, have stimulated scientists' strong attention to its sources, chemical reactions, and medicinal chemistry [2]. Aconitine is not only the key toxic component in the famous traditional Chinese medicine including Chuan Wu, Fu Zi, and Cao Wu, but is also applied to many pharmacological investigations as a tool drug [2]. Its derivative, 3-acetylaconitine, has been approved for clinical treatment of various pains in China [3]. In addition to the biological activities, some chemical reactions of aconitine, including N-deethylation [4,5], N-oxidation [6], amidation [5–8] and formation of nitrones [9], pyrolysis [10,11], deoxydation [12], methanolysis [13], O-demethylation [14–16], selective hydrolysis [17], and introduction of sugar [18], have been reported. As part of our ongoing research project, we attempt to semi-synthesize the analogs of diterpenoid alkaloids for structure–activity relationship study. In this paper, we wish to report the regioselective reactions, including acetylation, chlorination, sulfonation, and oxidation of three hydroxyl groups in aconitine.

2. Results and discussion

It has been reported by Pelletier's research group [16] that treatment of aconitine (**1**)

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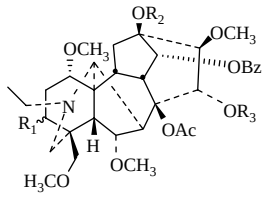
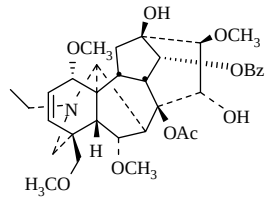
with acetic anhydride in pyridine or acetic chloride at room temperature could generate various acetylated products (**2**–**4**) (Figure 1). This paper has mentioned that 3-OH is most reactive toward acetylation, but no detailed description on the relative reactivity of three hydroxyl groups toward acetylation has been reported. It was observed by us that acetylated products of aconitine depended strongly upon the amount of catalyst (such as TsOH) and reaction time. Reaction of aconitine (**1**) with acetic anhydride in the presence of 1.1 equivalent of TsOH at room temperature yielded 3-acetylaconitine (**2**, 43%), together with 48% starting material. 3,13-Diacetylaconitine (**3**) was exclusively obtained in 92% yield when the reaction time was prolonged to 12 h, while 3,13,15-triacetylaconitine (**4**) was obtained in 97% yield only when the amount of TsOH was increased to 2 equivalents and the reaction time was prolonged to 48 h. The ^{1}H and ^{13}C NMR spectral data of compounds **2**–**4** are consistent with those reported in the literature [16,19,20]. The above-mentioned results indicated that the relative reactivity of three hydroxyl groups in aconitine toward acetylation is 3-OH > 13-OH > > 15-OH.

Treatment of aconitine (**1**) with $SOCl_2$ at room temperature for 12 h generated exclusively compound **5** in 89% yield. The ^{1}H and ^{13}C NMR spectra of **5** showed the presence of a two-substituted double bond (δ_H 6.06, dd, $J = 10.0$ and 3.2 Hz, H-2; δ_H 5.79, d, $J = 12.5$ Hz, H-3; δ_C 125.5, 137.7 d). Its structure was identified based on the



1 R^1=αOH R^2=R^3=H
2 R^1=αOAc R^2=R^3=H
3 R^1=αOAc R^2=Ac R^3=H
4 R^1=αOAc R^2=R^3=Ac
6 R^1=αOMs R^2=R^3=H
7 R^1=αOTs R^2=R^3=H
11 R^1=βOH R^2=R^3=H
12 R^1=βOAc R^2=R^3=H



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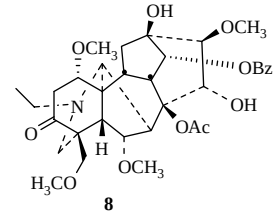

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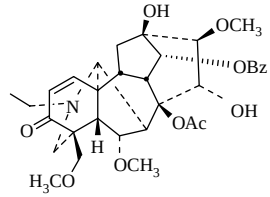

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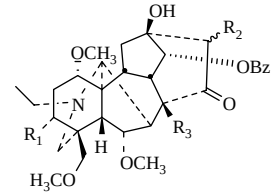
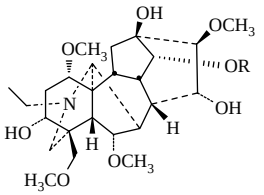
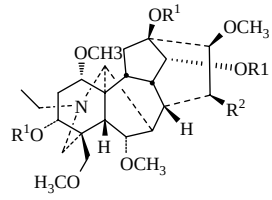


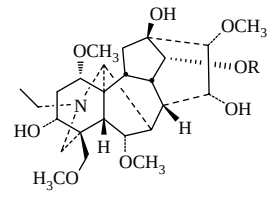
10 R^1=OAc R^2=βOCH$_3$ R^3=OAc
13 R^1=OH R^2=βOCH$_3$ R^3=H
14 R^1=OH R^2=αOCH$_3$ R^3=H



15 R=Bz
16 R=H



17 R^1=H R^2=OH
18 R^1=Ac R^2=OAc



19 R=Bz
20 R=H

Figure 1. Structures of compounds **1**–**20**.

comparison of its NMR data with those in the literature [21,22]. Obviously, compound **5** was produced through a chlorination–elimination process, suggesting that the 3-hydroxyl group in aconitine is easier to be replaced by chlorine than the other two hydroxyl groups.

Similarly, treatment of aconitine (**1**) with MsCl or TsCl catalyzed by 4-dimethylaminopyridine (DMAP) at room temperature for 1 h or 20 h yielded exclusively **6** (81%) or **7** (85%). The H-3 signal in the ^{1}H NMR spectra of **6** and **7** is downshifted to $\delta_H \sim 4.70$, indicating that the hydroxyl group at C-3 is esterified. This suggested that only the hydroxyl group at C-3 of aconitine was sulfonated under this reaction condition. The hydroxyl group at C-15 cannot be sulfonated even at elevated reaction temperature and prolonged reaction time. Compounds **6** and **7** were fully characterized on the basis of its ^{1}H and ^{13}C NMR data (Table 1) and HR-ESI-MS.

Treatment of aconitine (**1**) with 1 equivalent of Jones reagent at room temperature for 30 min yielded ketones **8** (61%) and **9** (19%). The ^{13}C NMR spectrum of **8** (Table 1) showed a ketone signal at δ_C 214.6, and its ^{1}H NMR spectrum lacks the signal of H-3 when compared with that of aconitine. This supported that the hydroxyl group at C-3 in aconitine was oxidized to ketone. The NMR spectra of compound **9** exhibited the signals at δ_H 6.27 (1H, d, $J = 10.4$ Hz) and at δ_H 6.46 (1H, d, $J = 10.0$ Hz) for an α,β-unsaturated ketone. Comparison of the NMR data of **9** with those of aconitine indicated the absence of resonances corresponding to a methoxyl group. The structure of **9** was confirmed by its ^{1}H and ^{13}C NMR data (Section 3 and Table 1, respectively). The formation of **8** or **9** suggested that the hydroxyl group at C-3 is more reactive than that at C-15 toward oxidation with Jones reagent. The hydroxyl group at C-15 in compound **2** can only be oxidized with 5 equivalents of Jones reagent for 12 h to form ketone **10** (83%). The ^{13}C NMR spectrum (Table 1) of **10** showed the presence of a ketone carbonyl group at δ_C 205.0 (s), which can be readily assigned at C-15 by its ^{1}H (^{13}C) NMR and HR-ESI-MS. This also supported that the hydroxyl group at C-3 is more reactive than that at C-15 toward oxidation.

Reduction of compound **8** with $NaBH_4$ at room temperature for 1 h yielded aconitine (**1**) as a major product along with a minor one. The minor product was established as **11** by analyzing its ^{1}H and ^{13}C NMR data (Table 1) and HR-ESI-MS. To determine the relative configuration of 3-OH in **11**, its 3-acetyl derivative **12** was prepared by reaction of **11** with acetic anhydride in pyridine. Comparison of the ^{1}H NMR spectrum of **12** with that of **11** indicated the presence of an additional acetyl group (δ 2.05, s). In the NOE difference spectrum (NOEds) experiment, the correlation between H-3 (δ 5.37, brs, $W_{1/2} = 4.8$ Hz) and H-19 (δ 2.59,ABq, $J = 11.8$ Hz) indicated the β-orientation of 3-OH in compound **11**.

We next attempt to investigate the effect of configuration of 16-OCH_3 on the reductive products of the 15-carbonyl-containing compound. Consequently, compounds **13** and **14**, each of them has a ketone carbonyl group at C-15, were prepared by pyrolysis of aconitine (**1**) based on the procedure reported in the literature [11]. The NMR data of compounds **13** and **14** were consistent with those reported in the literature [11]. No 2D NMR data of these two compounds has been reported in the literature [11], so we confirmed the structure of **14**, except for comparison with those in the literature [11], by analyzing its 2D NMR data. All ^{1}H and ^{13}C signals of compound **14** were assigned based on its 2D NMR data (Table 2). This also confirmed the structure of **13**. In the NOEds of **14**, the key correlation between H-16 (δ 3.86, s) and H-2′, 6′ (δ 7.98, d, $J = 7.6$ Hz) suggested the α-orientation of 16-OCH_3 in compound **14**.

Refluxing of compound **13** with $NaBH_4$ in THF for 14 h generated

Table 1. ^{13}C NMR spectral data of compounds **6**–**12**, **15**, and **17**–**19** (100 MHz, for ^{13}C, $CDCl_3$).

Position	6	7	8	9	10	11	12	15	17	18	19
1	83.3	83.2	83.0	147.0	82.6	83.2	82.7	83.5[a]	83.5[a]	82.8[a]	83.8[a]
2	36.1	36.3	42.4	131.9	34.6	35.8	35.8	33.5	33.7	31.4	30.0
3	80.9	80.9	214.6	200.2	71.4	79.2	74.1	71.8[a]	71.8[a]	71.8[a]	72.1[a]
4	42.8	42.7	49.5	48.9	42.4	42.3	42.2	43.1	43.8	42.6	43.1
5	46.5	45.2	43.5	48.3	47.6	44.5	46.5	46.9	44.8	46.0	42.8
6	81.5	81.6	81.0	82.2	81.5	81.2	81.3	85.0[a]	84.9[a]	82.1[a]	85.3[a]
7	45.2	45.3	44.3	44.8	46.1	44.2	44.7	39.5	43.6	43.2	42.6
8	91.7	91.6	91.9	91.8	83.1	91.9	91.9	40.6	43.1	42.9	39.2
9	44.5	44.5	43.5	43.0	44.5	44.7	44.3	37.3	40.6	41.0	38.9
10	40.3	40.2	41.2	37.3	41.7	40.3	40.4	41.5	41.9	42.9	47.0
11	49.4	49.2	49.5	50.7	49.9	49.4	48.9	50.4	50.3	50.0	50.8
12	33.6	33.1	34.5	37.9	34.6	33.5	31.2	36.4	37.2	35.4	39.6
13	73.9	73.9	74.0	74.1	74.9	74.1	75.2	75.0	76.1	84.2	79.2
14	78.7	78.6	78.8	78.8	77.3	78.8	78.8	80.4[a]	78.6[a]	74.5[a]	81.3[a]
15	78.7	78.6	78.7	78.6	205.0	78.9	78.8	72.1[a]	67.8[a]	69.8[a]	64.6[a]
16	90.0	89.9	89.5	89.9	88.5	90.1	90.1	94.1[a]	86.7	85.2[a]	84.8[a]
17	60.6	60.3	60.6	61.3	60.1	61.0	61.0	61.7	62.1	61.6	60.1
18	70.7	70.5	75.6	71.7	71.4	81.3	77.0	77.3	77.2	72.0	77.5
19	48.9	48.7	52.6	50.7	48.8	50.2	51.5	49.0	50.2	49.1	48.8
21	46.5	46.5	48.1	48.9	47.6	48.8	49.4	47.4	48.8	47.8	47.4
22	13.3	13.2	12.5	12.9	13.2	13.3	13.0	13.3	13.5	13.3	13.3
1-OCH_3	56.5	56.3	56.1	–	56.2	56.3	56.2	56.0	56.1	56.2	56.1
6-OCH_3	58.2	57.9	58.0	58.2	58.1	57.9	57.8	57.9	57.9	58.1	57.6
16-OCH_3	61.0	60.9	61.3	60.5	60.7	61.4	61.4	61.6	61.4	61.6	60.7
18-OCH_3	58.4	58.3	58.9	58.9	58.8	58.9	59.0	59.1	59.2	58.8	59.1
C=O	172.3	172.2	172.5	172.3	167.4	172.4	170.4	–	–	171.0	–
CH_3	21.3	21.2	21.4	21.3	21.1	21.4	21.4	–	–	20.7	–
C=O	–	–	–	–	170.3	–	172.4	–	–	170.7	–
CH_3	–	–	–	–	21.2	–	21.3	–	–	20.8	–

Table 1 – *continued*

Position	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**15**	**17**	**18**	**19**
C=O	–	–	–	–	–	–	–	–	–	170.5	–
CH_3	–	–	–	–	–	–	–	–	–	20.9	–
C=O	–	–	–	–	–	–	–	–	–	170.2	–
CH_3	–	–	–	–	–	–	–	–	–	21.6	–
OOC	166.0	165.9	165.9	165.8	166.6	166.0	166.1	166.2	–	–	166.8
1′	129.5	129.6	129.6	129.6	129.4	129.8	129.6	129.7	–	–	129.2
2′, 6′	129.6	129.5	129.6	129.4	130.1	129.6	129.7	129.8	–	–	129.7
3′, 5′	128.6	128.5	128.6	128.7	128.3	128.6	128.6	128.5	–	–	128.6
4′	133.3	133.2	133.3	133.4	133.3	133.2	133.3	133.2	–	–	133.6

Notes: **6**: 38.3 (OMs); **7**: 129.5, 129.6, 129.6, 127.5, 127.5, 134.9, 21.5 (OTs).
[a] The assignments were based on the HMQC spectrum of **15**, **17**, **18,** and **19**, respectively.

Table 2. NMR spectral data of compounds **13** and **14** (400 MHz for ^{1}H, 100 MHz for ^{13}C, $CDCl_3$).

	13		**14**			
Position	δ_C	δ_C [11]	δ_H mult (*J* in Hz)	δ_C	δ_C [11]	HMBC
1	83.4	83.5	3.07 hidden	83.5	83.4	C-11, C-10, 1-OCH_3
2	34.0	34.1	2.07 m, 2.34 m	33.9	32.5	C-11, C-4
3	71.4	71.6	3.71 hidden	71.6	71.6	C-5, C-18
4	43.0	43.5	–	43.5	43.6	–
5	48.0	48.1	2.08 hidden	48.3	48.0	C-7, C-18, C-19
6	83.9	84.0	3.91 d (6.8)	83.9	84.0	C-4, C-8, 6-OCH_3
7	42.3	42.5	2.74 hidden	41.6	41.9	C-5, C-9, C-15
8	48.4	48.5	2.46 hidden	48.9	49.0	C-17
9	38.5	38.6	2.92 m	38.5	38.5	C-12, C-15
10	43.4	43.1	2.21 m	44.6	44.6	C-1, C-17
11	50.8	50.9	–	51.0	51.2	–
12	35.9	36.1	1.81 m, 2.96 m	32.9	33.8	C-11, C-14, C-16
13	76.4	76.6	–	77.3	77.4	–
14	79.4	79.5	5.43 d (4.8)	78.4	78.5	C-8, C-16
15	211.8	211.8	–	211.8	211.7	–
16	89.0	89.2	3.86 s	86.0	86.0	C-8, C-12, 16-OCH_3
17	61.7	61.7	2.96 brs	61.5	61.6	C-5, C-6, C-10
18	76.1	76.2	3.70, 3.62 ABq (9.2, 9.2)	76.6	76.6	C-3, C-5, 18-OCH_3
19	47.2	47.4	2.40 d (11.6) 2.92 hidden	47.2	47.6	C-3, C-5, C-17
21	49.1	49.1	2.64 hidden 2.73 hidden	49.2	49.4	C-17, C-19
22	13.3	13.3	1.07 t (6.8)	13.3	13.2	C-21
1-OCH_3	56.1	56.1	3.20 q	56.0	56.0	C-1
6-OCH_3	57.9	57.9	3.24 q	57.7	57.9	C-6
16-OCH_3	61.8	61.9	3.84 q	62.2	62.3	C-16
18-OCH_3	59.1	59.2	3.34 q	59.1	59.2	C-18
COO	167.1	167.1	–	165.9	166.0	–
1′	129.5	133.2	–	133.6	133.6	–
2′, 6′	129.8	129.8	7.98 d (7.6)	129.7	129.6	COO, C-4′
3′, 5′	128.4	129.6	7.47 t (7.6)	129.2	129.3	C-1′
4′	133.2	128.4	7.61 t (7.6)	128.6	128.6	C-2′, C-6′

compounds **15** (18%) and **16** (30%). The ^{1}H NMR spectrum of **15** is characteristic of a signal at δ 4.45 (dd, $J = 10.4$ and 6.4 Hz) for H-15, indicating that the carbonyl group at C-15 in compound **13** was reduced. The key correlation between H-15 and H-2′, 6′ (δ 8.04, d, $J = 7.2$ Hz) in its NOEds indicated that the hydroxyl group at C-15 in **15** is α-oriented. Comparison of the ^{1}H NMR spectrum of **16** with that of **15** indicated that the signal at δ 4.49 (dd, $J = 10.4$ and 6.4 Hz) can be located to H-15β in compound **16** and the resonance at δ 3.79 ($J = 4.8$ Hz) can be assigned to H-14β (Figure 2) [2]. In conjunction with its HR-ESI-MS data, it is readily determined that compound **16** was the hydrolyzed product of **15**. Finally, all of the ^{1}H and ^{13}C NMR data of **16** were assigned based on its 2D NMR data (Table 3).

However, reaction of compound **13** with $LiAlH_4$ yielded compound **17** (36%) in addition to compound **16** (46%). These two compounds exhibited identical molecular formulae ($C_{25}H_{41}NO_8$) and identical substitution pattern ($OCH_3 \times 4$, $OH \times 4$) in their ^{1}H and ^{13}C NMR spectra

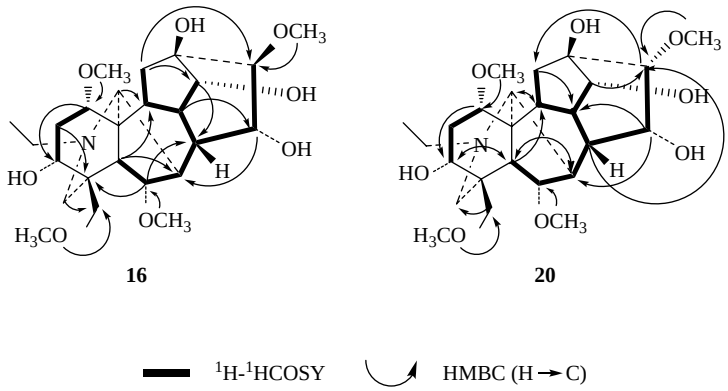


Figure 2. Key $^{1}H-^{1}H$ COSY and HMBC correlations of compounds **16** and **20**.

(Tables 1 and 3). Therefore, compound **17** is very likely the C-15 epimer of compound **16**. However, the β-orientation of the hydroxyl group at C-15 in **17** cannot be directly assigned by the chemical shift and coupling constant of H-15. In the ^{1}H NMR spectrum of compound **18**, the global acetyl derivative of **17**, the one

Table 3. ^{1}H and ^{13}C NMR spectral data of compounds **16** and **20** (400 MHz for ^{1}H, 100 MHz for ^{13}C).

	16[a]		**20**[b]	
Position	δ_H mult (J = Hz)	δ_C	δ_H mult (J = Hz)	δ_C
1	3.10 hidden	83.1 d	3.28 hidden	83.0 d
2	1.92 m, 2.38 m	32.7 t	2.60 m	31.4 t
3	3.83 dd (6.8, 4.8)	71.3 d	4.83 m	69.4 d
4	–	43.0 s	–	43.9 s
5	2.06 d (6.8)	46.1 d	2.36 d (6.0)	44.2 d
6	3.99 d (6.4)	84.9 d	4.14 d (6.4)	85.5 d
7	2.52 hidden	39.6 d	2.90 hidden	40.5 d
8	2.72 hidden	40.6 d	3.10 hidden	43.9 d
9	2.41 m	39.5 d	2.60 m	40.5 d
10	1.91m	41.5 d	2.00 hidden	43.0 d
11	–	50.4 s	–	51.3 s
12	2.06 m, 2.52 m	37.0 t	2.65 m, 2.90 m	40.5 t
13	–	76.4 s	–	80.5 s
14	3.79 d (4.8)	78.5 d	4.49 d (4.8)	78.9 d
15	4.49 dd (10.4, 6.4)	71.4 d	5.47 t (9.2)	65.2 d
16	3.30 hidden	93.9 d	4.42 d (8.4)	87.4 d
17	3.06 s	62.1 d	–	62.5 d
18	3.68, 3.57 ABq (8.4, 8.8)	77.2 t	3.82, 3.86 ABq (9.6)	75.8 t
19	2.54 m 2.74 m	49.0 t	3.06 hidden 2.90 hidden	49.6 t
21	2.58 hidden 3.02 m	48.0 t	2.90 hidden 3.10 m	49.6 t
22	1.16 t (7.2)	12.9 q	1.28 t (6.8)	11.8 q
1-OCH_3	3.26 s	55.8 q	3.27 s	55.3 q
6-OCH_3	3.30 s	57.9 q	3.25 s	58.1 q
16-OCH_3	3.64 s	61.9 q	3.72 s	61.0 q

[a] $CDCl_3$; [b] C_5D_5N.

proton doublet signal at δ_H 5.32 (d, $J = 4.8$ Hz) can readily be assigned to H-14 [2]. The resonances at δ_H 4.86 (dd, $J = 12.0$ and 6.0 Hz) and δ_H 5.15 (dd, $J = 8.4$ and 4.4 Hz) were assigned to H-3β and H-15α based on the key correlations with C-3 (δ_C 71.8 d) and C-15 (δ_C 69.8 d), respectively, in its HMQC spectrum. The correlation between OAc-15 and OCH_3-16β in its NOEds and coupling constant (dd, $J = 8.4$, and 4.4 Hz) of H-15 led to confirm the β-orientation of 15-OAc of **18**.

Similarly, reaction of compound **14** with $NaBH_4$–THF under reflux for 4 h yielded compounds **19** (11%) and **20** (43%). The ^{1}H NMR spectrum of **19** exhibited four methoxy groups (δ 3.28, 3.29, 3.30, 3.62) and a benzoyl (OBz) group (δ_H 7.47, t, $J = 7.6$ Hz; δ_H 7.61, t, $J = 7.6$ Hz; δ_H 8.01, d, $J = 7.2$ Hz). Its molecular formula was determined as $C_{32}H_{45}NO_9$ based on its HR-ESI-MS and ^{13}C NMR experiments. In the NOEds of **19**, selective irradiation of H-15 (δ 4.62,t, $J = 9.2$ Hz) resulted in the signal enhancement of H-2′, 6′ (δ 8.01, d, $J = 7.2$ Hz), indicating the α-orientation of 15-OH in compound **19**. Comparison of the NMR and HR-ESI-MS data of **20** with those of **19** suggested that compound **20** is the hydrolyzed product of **19**. The hydroxyl group at C-15 was established as α-oriented based on the coupling constant ($J = 9.2$ Hz) of H-15 (δ 5.47, t) in the ^{1}H NMR spectrum of **20**.

It is worth noting that the reduction of compound **14** with $LiAlH_4$ or diisobutylaluminum hydride (DIBAL-H) still generated 15α-OH-containing compound **20**.

In conclusion, the hydroxyl group at C-3 in aconitine (**1**) is more reactive than that at C-13 or C-15 toward acetylation, sulfonylation, chlorination, and oxidation. The relative reactivity of three hydroxyl groups in aconitine toward acetylation and oxidation is 3-OH > 13-OH > > 15-OH and 3-OH > 15-OH, respectively. In this study, neither 13- or/and 15-chlorinated aconitine nor 13- or/and 15-sulfonated aconitine was observed. The reduction products of 3-ketone derivative (**8**) with $NaBH_4$ are a pair of C-3 epimers, while the reduction products of 15-ketone derivatives (**13** and **14**) depend greatly on the reducing agents and the configuration of 16-OCH_3. When the substrate has 16β-OCH_3, its carbonyl group at C-15 can be reduced with $NaBH_4$ to yield exclusively the 15α-OH-containing product. Replacement of reducing agent $NaBH_4$ with $LiAlH_4$, the C-15 carbonyl group can be reduced to give a pair of C-15 epimers. On the other hand, when the substrate has 16α-OCH_3, C-15 carbonyl group can only be reduced to generate the 15α-OH-containing product.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured in a 1.0 dm cell with a Perkin-Elmer 341 polarimeter (Perkin-Elmer, Waltham, MA, USA); HRMS were obtained with a BrukerBioTOFQ mass spectrometer (Bruker Daltonics, Karlsruhe, Germany); ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or a Varian INOVA-400/54 spectrometer (Varian, Palo Alto, CA, USA), with TMS as internal standard; silica gel GF_{254} and silica gel H (10–40 mm, Qingdao Chemical Factory, Qingdao, China) were used for thin layer chromatography (TLC) and column chromatography (CC). Zones on TLC (silica gel G) plates were detected with the modified Dragendorff's reagent. Aconitine was provided by our research group.

3.2 Synthesis of derivatives of aconitine

3.2.1 Compound 2

Compound **2** (white amorphous powder, 460 mg, 43%) from aconitine (**1**, 1000 mg, 1.55 mmol) was prepared according to the literature [19,20]. The structure of **2** was identified based on comparison of the ^{1}H and ^{13}C NMR data with those in the literature [19,20]. HR-ESI-MS

m/z: 688.3326 $[M + H]^+$ (calcd for $C_{36}H_{50}NO_{12}$, 688.3333).

3.2.2 Compound 3

Compound **3** (white amorphous powder, 390 mg, 92%) from compound **2** (400 mg, 0.58 mmol) was prepared according to the literature [16]. The structure of **3** was identified based on comparison of the ^1H and ^{13}C NMR data with those in the literature [16]. HR-ESI-MS *m/z*: 730.3446 $[M + H]^+$ (calcd for $C_{38}H_{52}NO_{13}$, 730.3439).

3.2.3 Compound 4

Compound **4** (white amorphous powder, 102 mg, 97%) from compound **3** (100 mg, 0.14 mmol) was prepared according to the literature [16]. Compound **4** was identified based on comparison of the ^1H and ^{13}C NMR data with those in the literature [16]. HR-ESI-MS *m/z*: 772.3547 $[M + H]^+$ (calcd for $C_{40}H_{54}NO_{14}$, 772.3544).

3.2.4 Compound 5

Compound **5** (white amorphous powder, 43 mg, 89%) from aconitine (**1**, 50 mg, 0.077 mmol) was prepared according to the literature [21,22]. The structure of **5** was identified based on comparison of the ^1H and ^{13}C NMR data with those in the literature [21,22]. HR-ESI-MS *m/z*: 628.3182 $[M + H]^+$ (calcd for $C_{34}H_{46}NO_{10}$, 628.3122).

3.2.5 Compound 6

Aconitine (**1**, 150 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (5 ml), and DMAP (28 mg, 0.23 mmol), Et_3N (0.1 ml), and MsCl (0.05 ml) were added. The mixture was stirred at room temperature for 1 h. Extraction ($CHCl_3$, 5 ml × 3), drying (Na_2SO_4), and evaporation afforded the residue, which was purified by CC (silica gel, $CHCl_3$–MeOH, 100:1) to give compound **6** (white amorphous powder, 131 mg, 81%). **6**: $[\alpha]_D^{20}$ + 13.9 (*c* 1.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 3.03, 3.20, 3.27, 3.72 (each 3H, s $OCH_3 \times 4$), 3.04 (3H, s, OMs), 4.75 (1H, dd, $J = 12.8$ and 5.6 Hz, H-3β), 4.87 (1H, d, $J = 4.8$ Hz, H-14β), 7.46 (2H, t, $J = 7.6$ Hz, H-3′, 5′), 7.58 (1H, t, $J = 7.6$ Hz, H-4′), 8.03 (2H, d, $J = 7.6$ Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 724.2994 $[M + H]^+$ (calcd for $C_{35}H_{50}NO_{13}S$, 724.3003).

3.2.6 Compound 7

To a solution of aconitine (**1**, 200 mg, 0.31 mmol) in CH_2Cl_2 (5 ml), DMAP (38 mg, 0.31 mmol), Et_3N (0.1 ml), and TsCl (178 mg, 0.92 mmol) were added. The mixture was stirred at room temperature for 20 h. Extraction ($CHCl_3$, 5 ml × 3), drying (Na_2SO_4), and evaporation afforded the residue, which was purified by CC (silica gel, $CHCl_3$–MeOH, 100:1) to give compound **7** (white amorphous powder, 211 mg, 85%). **7**: $[\alpha]_D^{20}$ + 13.0 (*c* 0.5, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 1.37 (3H, s, 8-OAc), 2.43 (3H, s, 4″-CH_3), 3.03, 3.16, 3.17, 3.72 (each 3H, s, $OCH_3 \times 4$), 4.04 (1H, d, $J = 6.4$ Hz, H-6β), 4.76 (1H, dd, $J = 12.8$ and 5.6 Hz, H-3β), 4.84 (1H, d, $J = 4.8$ Hz, H-14β), 7.33 (2H, d, $J = 8.8$ Hz, H-3″, 5″), 7.80 (2H, d, $J = 8.0$ Hz, H-2″, 6″), 7.44 (2H, t, $J = 7.6$ Hz, H-3′, 5′), 7.55 (1H, t, $J = 7.6$ Hz, H-4′), 8.01 (2H, d, $J = 7.2$ Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 800.3314 $[M + H]^+$ (calcd for $C_{41}H_{54}NO_{13}S$, 800.3316).

3.2.7 Compounds 8 and 9

To a solution of aconitine (**1**, 500 mg, 0.77 mmol) in acetone (20 ml), Jones reagent (0.8 ml, 0.77 mmol) was added dropwise under ice water bath. Then the mixture was stirred at 0°C for 0.5 h. The reaction was quenched by anhydrous $NaHSO_3$. The mixture was neutralized

with concentrated NH_4OH. After filtration and evaporation to remove solvent and give a residue, the crude product was purified by CC (silica gel, petroleum ether–EtOAc, 6:1) to afford compounds **8** (white amorphous powder, 300 mg, 61%) and **9** (white amorphous powder, 85 mg, 18%). **8**: $[\alpha]_D^{20}$ + 34.2 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.2 Hz, NCH_2CH_3), 1.40 (3H, s, 8-OAc), 3.19, 3.19, 3.22, 3.77 (each 3H, s, $OCH_3 \times 4$), 4.11 (1H, d, J = 6.0 Hz, H-6β), 4.93 (1H, d, J = 4.8 Hz, H-14β), 7.48 (2H, t, J = 7.6 Hz, H-3′, 5′), 7.59 (1H, t, J = 7.6 Hz, H-4′), 8.04 (2H, d, J = 7.2 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 644.3074 $[M + H]^+$ (calcd for $C_{34}H_{46}NO_{11}$, 644.3071). **9**: $[\alpha]_D^{20}$ + 75.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (3H, t, J = 7.2 Hz, NCH_2CH_3), 1.45 (3H, s, 8-OAc), 3.22, 3.29, 3.79 (each 3H, s, $OCH_3 \times 3$), 4.10 (1H, d, J = 6.4 Hz, H-6β), 4.97 (1H, d, J = 5.2 Hz, H-14β), 6.27 (1H, d, J = 10.4 Hz, H-2), 6.46 (1H, d, J = 10.0 Hz, H-1), 7.48 (2H, t, J = 7.6 Hz, H-3′, 5′), 7.60 (1H, t, J = 7.6 Hz, H-4′), 8.04 (2H, d, J = 7.2 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 612.2809 $[M + H]^+$ (calcd for $C_{33}H_{42}NO_{10}$, 612.2809).

3.2.8 *Compound **10***

To a solution of compound **2** (320 mg, 0.46 mmol) in acetone (15 ml), Jones reagent (4.5 ml, 2.30 mmol) was added dropwise under ice water bath and the solution was stirred at room temperature for 12 h. Then the reaction was quenched by anhydrous $NaHSO_3$. Basification (conc. NH_4OH), filtration, and evaporation to remove the solvent could afford the residue, which was purified by CC (silica gel, cyclohexane–acetone, 15:1) to give compound **10** (white amorphous powder, 264 mg, 83%). **10**: $[\alpha]_D^{20}$ + 4.7 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.2 Hz, NCH_2CH_3), 1.43 (3H, s, 8-OAc), 2.06 (3H, s, 3-OAc), 3.23, 3.25, 3.28, 3.76 (each 3H, s, $OCH_3 \times 4$), 4.19 (1H, d, J = 6.8 Hz, H-6β), 4.89 (1H, dd, J = 10.8 and 6.8 Hz, H-3β), 5.07 (1H, d, J = 4.8 Hz, H-14β), 7.43 (2H, t, J = 7.6 Hz, H-3′, 5′), 7.56 (1H, t, J = 7.2 Hz, H-4′), 8.04 (2H, d, J = 7.2 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 686.3171 $[M + H]^+$ (calcd for $C_{36}H_{48}NO_{12}$, 686.3177).

3.2.9 *Compound **11** and aconitine **(1)***

To a solution of compound **8** (170 mg, 0.26 mmol) in MeOH (5 ml), $NaBH_4$ (200 mg, 5.26 mmol) was added, and the mixture was stirred at room temperature for 12 h. After evaporation of MeOH, a residue was obtained which was diluted in H_2O (5 ml), basified to pH 10 (conc. NH_4OH), extracted ($CHCl_3$, 5 ml × 3), and dried (anhydrous Na_2SO_4). Evaporation of solvent afforded the residue, which was purified by CC (silica gel, cyclohexane–acetone, 10:1) to give compound **11** (white amorphous powder, 20 mg, 12%) and aconitine (**1**, white amorphous powder, 122 mg, 73%). **11**: $[\alpha]_D^{20}$ + 11.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.2 Hz, NCH_2CH_3), 1.35 (3H, s, 8-OAc), 3.15, 3.25, 3.31, 3.72 (each 3H, s, $OCH_3 \times 4$), 4.45 (1H, dd, J = 5.2 and 2.8 Hz, H-15β), 4.86 (1H, d, J = 4.8 Hz, H-14β), 7.44 (2H, t, J = 7.6 Hz, H-3′, 5′), 7.56 (1H, t, J = 7.6 Hz, H-4′), 8.02 (2H, d, J = 7.2 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 646.3231 $[M + H]^+$(calcd for $C_{34}H_{48}NO_{11}$, 646.3227).

3.2.10 *Compound **12***

Compound **11** (40 mg, 0.062 mmol) was dissolved in pyridine (1 ml) and Ac_2O (0.1 ml), the mixture was stirred at room temperature for 24 h. Removal of pyridine,-diluting (H_2O, 1 ml), basifying to pH 10 (conc. NH_4OH), extraction ($CHCl_3$, 2 ml × 3), drying (anhydrous Na_2SO_4), and

evaporation afforded a residue, which was isolated by CC (silica gel, petroleum ether–acetone, 6:1) to give compound **12** (white amorphous powder, 36 mg, 86%). **12**: $[\alpha]_D^{20}$ + 27.2 (*c* 1.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, t, J = 7.2 Hz, NCH_2CH_3), 1.36, 2.05 (each 3H, s, OAc × 2), 2.62 (1H, ABq, J = 12.0 Hz, H-19), 2.59 (1H, ABq, J = 11.8 Hz, H-19), 3.13, 3.18, 3.24, 3.74 (each 3H, s, OCH_3 × 4), 4.01 (1H, d, J = 6.8 Hz, H-6β), 4.46 (1H, dd, J = 4.4 and 2.8 Hz, H-15β), 4.87 (1H, d, J = 4.8 Hz, H-14β), 5.37 (1H, brs, $W_{1/2}$ = 4.8 Hz, H-3α), 7.46 (2H, t, J = 7.6 Hz, H-3′, 5′), 7.58 (1H, t, J = 7.2 Hz, H-4′), 8.03 (2H, d, J = 8.0 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 688.3337 $[M + H]^+$ (calcd for $C_{36}H_{50}NO_{12}$, 688.3333).

3.2.11 Compounds **13** and **14**

Aconitine (**1**, 3000 mg, 4.65 mmol) was subjected to pyrolysis under 190°C for 40 min in vacuum. The crude product was purified by CC (silica gel, cyclohexane–acetone, 5:1 with 1% Et_2NH) to give compounds **13** (white amorphous powder, 700 mg, 26%) and **14** (red amorphous powder, 1600 mg, 59%). **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, J = 7.2 Hz, NCH_2CH_3), 3.28, 3.30, 3.31, 3.64 (each 3H, s, OCH_3 × 4), 3.94 (1H, d, J = 6.8 Hz, H-6β), 5.19 (1H, d, J = 4.4 Hz, H-14β), 7.43 (2H, t, J = 7.2 Hz, H-3′, 5′), 7.57 (1H, t, J = 7.2 Hz, H-4′), 7.96 (2H, d, J = 7.2 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 2; HR-ESI-MS *m/z*: 586.3031 $[M + H]^+$ (calcd for $C_{32}H_{44}NO_9$, 586.3016). **14**: for ^{1}H and ^{13}C NMR spectral data, see Table 2; HR-ESI-MS *m/z*: 586.3023 $[M + H]^+$ (calcd for $C_{32}H_{44}NO_9$, 586.3016).

3.2.12 Compounds **15** and **16**

To a solution of compound **13** (2500 mg, 4.27 mmol) in anhydrous THF (25 ml), $NaBH_4$ (320 mg, 8.42 mmol) was added, and then the mixture was refluxed for 14 h. The reaction mixture was cooled to room temperature and then quenched by the addition of H_2O (1 ml). The mixture was concentrated to give a residue. After basification (conc. NH_4OH), the subsequent mixture was extracted with dichloromethane (15 ml × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, and the organic solvents were removed under reduced pressure to give the crude product, which was purified by CC (silica gel, cyclohexane–acetone, 2:1, with 1% Et_2NH) to give compounds **15** (white amorphous powder, 450 mg, 18%) and **16** (white amorphous powder, 600 mg, 30%). **15**: $[\alpha]_D^{20}$ − 0.7 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, t, J = 7.2 Hz, NCH_2CH_3), 3.26, 3.29, 3.31, 3.71 (each 3H, s, OCH_3 × 4), 3.77 (1H, dd, J = 9.2 and 4.8 Hz, H-3β), 4.45 (1H, dd, J = 10.4 and 6.4 Hz, H-15β), 4.92 (1H, d, J = 5.2 Hz, H-14β), 7.46 (2H, t, J = 7.6 Hz, H-3′, 5′), 7.59 (1H, t, J = 7.2 Hz, H-4′), 8.04 (2H, d, J = 7.2 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 588.3175 $[M + H]^+$ (calcd for $C_{32}H_{46}NO_9$, 588.3173). **16**: $[\alpha]_D^{20}$ − 1.6 (*c* 0.9, CH_2Cl_2); for ^{1}H and ^{13}C NMR spectral data, see Table 3; HR-ESI-MS *m/z*: 484.2908 $[M + H]^+$ (calcd for $C_{25}H_{42}NO_8$, 484.2910).

3.2.13 Compound **17**

To a solution of compound **13** (300 mg, 0.51 mmol) in anhydrous THF (15 ml), $LiAlH_4$ (44 mg, 3.78 mmol) was added under ice water bath. The mixture was warmed to room temperature and stirred under argon for 7 h. H_2O (1 ml) was added to quench the reaction. After filtering, the mixture was concentrated to give a residue, which was purified by CC (silica gel, petroleum ether–acetone, 2:1, with 1% Et_2NH) to give compounds **17** (white amorphous powder, 90 mg, 36%) and **16**

(120 mg, 48%). **17**: $[\alpha]_D^{20}$ + 4.2 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, *J* = 6.8 Hz, NCH_2CH_3), 2.75 (1H, s, H-17), 3.01 (1H, dd, *J* = 9.2 and 6.4 Hz, H-1β), 3.22, 3.29, 3.30, 3.60 (each 3H, s, OCH_3 × 4), 3.70 (1H, d, *J* = 4.2 Hz, H-14β), 3.94 (1H, d, *J* = 6.4 Hz, H-6β); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 484.2914 $[M + H]^+$ (calcd for $C_{25}H_{42}NO_8$, 484.2910).

3.2.14 Compound **18**

Compound **17** (50 mg, 0.104 mmol) was dissolved in Ac_2O (2 ml), and *p*-TsOH (33 mg, 0.191 mmol) was added. The mixture was stirred for 48 h at room temperature. After basification (conc. NH_4OH), the subsequent mixture was extracted with dichloromethane (2 ml × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, and the organic solvents were removed under reduced pressure to give compound **18** (white amorphous powder, 59 mg, 92%). **18**: $[\alpha]_D^{20}$ − 10.7 (*c* 1.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (3H, t, *J* = 6.8 Hz, NCH_2CH_3), 2.05, 2.06, 2.07, 2.12 (each 3H, s, OAc × 4), 3.20, 3.21, 3.29, 3.30 (each 3H, s, OCH_3 × 4), 3.91 (1H, d, *J* = 6.8 Hz, H-6β), 3.90 (1H, d, *J* = 7.6 Hz, H-16α), 4.86 (1H, dd, *J* = 12.0, 6.0 Hz, H-3β), 5.15 (1H, dd, *J* = 8.4 and 4.4 Hz, H-15α), 5.32 (1H, d, *J* = 4.8 Hz, H-14β); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 652.3344 $[M + H]^+$ (calcd for $C_{33}H_{50}NO_{12}$, 652.3333).

3.2.15 Compounds **19** and **20**

To a solution of compound **14** (2800 mg, 4.78 mmol) in anhydrous THF (30 ml), $NaBH_4$ (360 mg, 9.47 mmol) was added, and the mixture was refluxed for 4 h and then quenched by H_2O (1 ml). Evaporation to remove the solvent afforded the residue; after basification (conc. NH_4OH), the subsequent mixture was extracted with dichloromethane (15 ml × 3). The organic layers were combined and dried over anhydrous Na_2SO_4, and the organic solvents were removed under reduced pressure to give the crude product, which was isolated by CC (silica gel, cyclohexane–acetone, 2:1, with 1% Et_2NH) to give compounds **19** (white amorphous powder, 300 mg, 11%) and **20** (white amorphous powder, 1000 mg, 43%). **19**: $[\alpha]_D^{20}$ − 7.6 (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (3H, t, *J* = 6.8 Hz, NCH_2CH_3), 3.28, 3.29, 3.30, 3.62 (each 3H, s, OCH_3 × 4), 3.76 (1H, dd, *J* = 10.2 and 5.2 Hz, H-3β), 3.87 (1H, d, *J* = 6.4 Hz, H-6β), 4.62 (1H, t, *J* = 9.2 Hz, H-15β), 5.12 (1H, d, *J* = 4.0 Hz, H-14β), 7.47 (2H, t, *J* = 7.6 Hz, H-3′, 5′), 7.61 (1H, t, *J* = 7.6 Hz, H-4′), 8.01 (2H, d, *J* = 7.2 Hz, H-2′, 6′); for ^{13}C NMR spectral data, see Table 1; HR-ESI-MS *m/z*: 588.3166 $[M + H]^+$ (calcd for $C_{32}H_{46}NO_9$, 588.3173). **20**: $[\alpha]_D^{20}$ − 44.6 (*c* 1.8, CH_2Cl_2); for ^{1}H NMR and ^{13}C NMR spectral data, see Table 3; HR-ESI-MS *m/z*: 484.2912 $[M + H]^+$ (calcd for $C_{25}H_{42}NO_8$, 484.2910).

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References

[1] P.L. Geiger, *Justus Liebigs Ann. Chem.* **7**, 269 (1833).
[2] F.P. Wang and Q.H. Chen, in *The Alkaloids: Chemistry and Biology*, edited by G.A. Cordell, vol. 69 (Elsevier Science, San Diego, CA, 2010), pp. 1–570.
[3] D.X. Lu, X. Guo, and X.C. Tang, *Acta Pharm. Sin.* **9**, 216 (1988).
[4] K. Wiesner, M. Götz, D.C. Simmons, and L.R. Fowler, *Collect. Czech. Chem. Commun.* **28**, 2460 (1963).
[5] H.K. Desai, H.P. Chokshi, and S.W. Pelletier, *J. Nat. Prod.* **52**, 1296 (1989).
[6] Y. Bai, H.K. Desai, and S.W. Pelletier, *J. Nat. Prod.* **58**, 929 (1995).
[7] S.W. Pelletier, G.A. Glinski, and N.V. Mody, *J. Am. Chem. Soc.* **104**, 4676 (1982).

[8] P. Kulanthaivel and S.W. Pelletier, *Heterocycles* **26**, 2351 (1987).
[9] E.G. Zinarava, N.N. Kabolinova, V.V. Shereshorets, E.V. Ivanova, E.E. Shults, G.A. Tolstikov, and M.S. Yunusov, *Russian Chem. Bull. Int. Ed.* **50**, 720 (2001).
[10] D.J. Mclaldin and L. Marion, *Can. J. Chem.* **37**, 1071 (1950).
[11] T. Mori, T. Ohsawa, M. Murayama, H. Bando, K. Wada, and T. Amiya, *Heterocycles* **29**, 873 (1989).
[12] T. Mori, M. Murayama, H. Bando, and N. Kawahara, *Chem. Pharm. Bull.* **30**, 2803 (1991).
[13] H.K. Desai, B.S. Joshi, S.A. Ross, and S.W. Pelletier, *J. Nat. Prod.* **52**, 720 (1989).
[14] I.S. Blaglrough, D.J. Hardick, S. Wonnacott, and B.B.L. Potter, *Tetrahedron Lett.* **35**, 3367 (1994).
[15] D.J. Hardick, I.S. Blagbrough, S. Wonnacott, and B.V.L. Patter, *Tetrahedron Lett.* **35**, 3371 (1994).
[16] B.S. Joshi, S.K. Srivastana, A.D. Barber, H.K. Desai, and S.W. Pelletier, *J. Nat. Prod.* **60**, 439 (1997).
[17] S.A. Ross and S.W. Pelletier, *Heterocycles* **32**, 1307 (1991).
[18] N.Sh. Palnats, R.Sh. Shakirov, M.N. Sultankhodzhaev, and S.T. Akramova, *Chem. Nat. Compd.* **29**, 662 (1993).
[19] X. Chang, H. Wang, L. Lu, and Y. Zhu, *Acta Pharm. Sin.* **16**, 474 (1981).
[20] L.M. Liu, H.C. Wang, and Y.L. Zhu, *Acta Pharm. Sin.* **18**, 39 (1983).
[21] S.W. Pelletier and Z. Djarmati, *J. Am. Chem. Soc.* **98**, 2626 (1976).
[22] R.E. Gilman and L. Marion, *Can. J. Chem.* **40**, 1713 (1962).