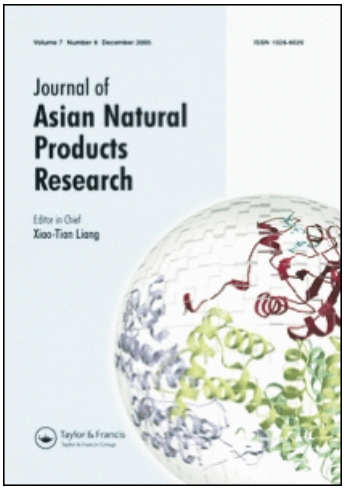

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An effective *O*-demethylation of some C_{19}-diterpenoid alkaloids with HBr–glacial acetic acid

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The aconitine-type alkaloids talatisamine (**1**), 8,14-diacetyltalatisamine (**11**), and compound **3**, the lycoctonine-type alkaloid deltaline (**5**), and the 7,17-*seco* C_{19}-diterpenoid alkaloids **7** and **9** were treated with HBr–glacial acetic acid to give useful *O*-demethylated derivatives **2**, **2,** **4**, **6**, **8**, and **10** respectively in good to high yields (49–90%).

Keywords: C_{19}-diterpenoid alkaloid; *O*-demethylation; talatisamine; 8,14-diacetyltalatisamine; 7,17-*seco* C_{19}-diterpenoid alkaloid

1. Introduction

The diterpenoid alkaloids are a synthetic or structurally modified target and for a long time, due to their complex diversities, have displayed alot of interesting chemical reactions [1,2] and several biological activities [3,4]. It is emphasized that in the studies on the structure–activity relationship of these class of alkaloids, various modifications including the *O*-demethylation, which is one of the most common methods for the chemical transformation besides SAR, are often carried out. Many *O*-demethylations using $ZnCl_2$–5% HCl [5], HCl or HNO_3 [6], *N*-acetyl-*N*-deethylisopyrochasmanine [7,8], 30% HBr–HOAc [9], HBr–HOAc [10], Me_3SiI [11], $AlCl_3$/NaI [11], and 50% H_2SO_4 [12,13] have been reported. However, most of the above-mentioned methods are not very useful owing to lower yields or structurally limited substrates. Therefore, the *O*-demethylation of C_{19}-diterpenoid alkaloids is still worthy of further research. After a series of studies, the *O*-demethylation of compounds (**1**, **3**, **5**, **7**, and **9**) using HBr–HOAc (20 equiv.) at 50–80°C for 7–20 h furnished the corresponding *O*-demethylated products (**2**, **4**, **6**, **8**, and **10**) in good to high yields (49–90%; Figure 1). Herein, we describe a useful method for *O*-demethylation with five new non-naturally occurring C_{19}-diterpenoid alkaloids.

2. Results and discussion

Preliminary trials under various conditions showed that *O*-demethylation of C_{19}-diterpenoid alkaloids strongly depended upon the amount of HBr–HOAc and the reaction temperature rather than on the concentration of HBr, and the *O*-demethylation at high temperature led to a reduction in the reaction time. For example, 8,14-diacetyltalatisamine (**11**) was reacted with 9–18-fold mmol of 3.7–6.5% HBr–HOAc at room temperature, which resulted in 16,18-*O*-demethyl product **2** with the yield of 51.8%. But, treatment of **11** with 20-fold mmol of 6.5% HBr–HOAc at the same temperature resulted in **2** with high yield (70.0%). For the substrate **5**, only changing the reaction temperature from room temperature to 50–80°C using the same

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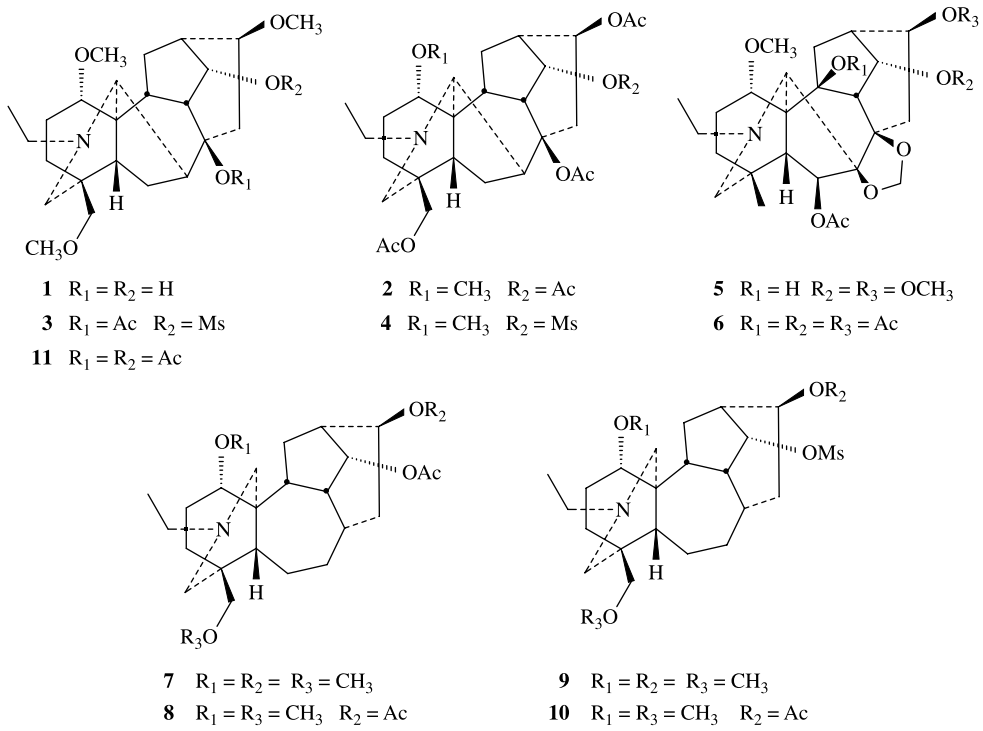

1 $R_1 = R_2 = H$
2 $R_1 = CH_3$ $R_2 = Ac$
3 $R_1 = Ac$ $R_2 = Ms$
4 $R_1 = CH_3$ $R_2 = Ms$
5 $R_1 = H$ $R_2 = R_3 = OCH_3$
6 $R_1 = R_2 = R_3 = Ac$
11 $R_1 = R_2 = Ac$

7 $R_1 = R_2 = R_3 = CH_3$
8 $R_1 = R_3 = CH_3$ $R_2 = Ac$
9 $R_1 = R_2 = R_3 = CH_3$
10 $R_1 = R_3 = CH_3$ $R_2 = Ac$

Figure 1. Substrates and products of *O*-demethylation.

amount and concentration of HBr–HOAc led largely to a reduction of the reaction time from 7 d to 20–53 h. Based on the above-mentioned results, an effective *O*-demethylation of the C_{19}-diterpenoid alkaloids could be achieved in good yields (65–85%) by heating the substrates with 20 equivalents of 6.5% HBr–HOAc at 50–80°C for 20–53 h.

The *O*-demethylation using various substrates, such as the aconitine-type (e.g., talatisamine (**1**) and **3**), the lycoctonine-type (e.g., deltaline (**5**)), and the 7,17-*seco* type (e.g., **7** and **9**), under optimization conditions as described above indicated that both the aconitine- and lycoctonine-type alkaloids (**1**, **3**, and **5**) furnished the expected *O*-demethylated products (**2**, **4**, and **6**) in excellent yields (81–90%) with the easy sequence for the *O*-demethylation of this class of alkaloids to be the 16- and 18-OCH_3 or the 14- and 16-$OCH_3 \gg$ the 1-OCH_3.

In summary, the *O*-demethylation of C_{19}-diterpenoid alkaloids can be carried out in excellent yields by heating the alkaloids with 20 equivalents of 6.5% HBr–HOAc at 50–80°C for 20–53 h. To the best of our knowledge, this method provided the most simple and convenient *O*-demethylation for the C_{19}-diterpenoid alkaloids.

3. Experimental

3.1 General experimental procedures

Melting points were ascertained by thermal values analysis using a microscope and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 341 polarimeter. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$, with TMS as internal standard, on a Varian Unity INOVA 400/54 NMR spectrometer. MS spectra were measured on Finnigan LCQ and Micromass Auto Ultima-Tof spectrometer. Silica gel H (Qingdao Sea Chemical Factory, Qingdao, China) was used for TLC and column chromatography.

3.2 Substrate preparation

Compounds **1** [14], **5** [15], **11** [16], **3**, **7**, and **9**: these compounds were separated or prepared in our laboratory.

Compound **3**. This compound was prepared from talatisamine (**1**), which was treated with methanesulfonyl chloride (MsCl)–pyridine, followed by Ac_2O–TsOH. Compound **3**: mp 76–78°C; $[\alpha]_D$ − 4.2 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 1.98 (3H, s, OAc), 3.02 (3H, s, OMs), 3.26, 3.28, and 3.30 (each 3H, s, 3 × OMe), 4.82 (1H, t, $J = 4.8$ Hz, H-14β); ^{13}C NMR (100 MHz) see Table 1; ESIMS *m/z* 542 ([M + H]$^+$, 100%); HRESIMS *m/z* 542.2763 [M + H]$^+$ (calcd for $C_{27}H_{44}NO_8S$, 542.2782).

Compound **7**. **7** was prepared from 14-acetyltalatisamine according to the method we developed [17], followed by H_2, PtO_2–95% EtOH. Compound **7**: mp 130–132°C; $[\alpha]_D$ −3.2 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.98 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 2.04 (3H, s, OAc), 3.23, 3.26, and 3.29 (each 3H, s, 3 × OMe), 4.64 (1H, t, $J = 4.2$ Hz, H-14β); ^{13}C NMR (100 MHz) see Table 1; ESIMS *m/z* 450 ([M + H]$^+$, 100%); HRESIMS *m/z* 450.3071 [M + H]$^+$ (calcd for $C_{26}H_{44}NO_5$, 450.3059).

Compound **9**. This was prepared from compound **7** which was treated with NaOH–CH_3OH, followed by MsCl–Pyridine. Compound **9**: mp 32–34°C; $[\alpha]_D$ − 24.0 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.01 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 3.05 (3H, s, OMs), 3.28, 3.31, and 3.33 (each 3H, s, 3 × OMe), 4.75 (1H, t, $J = 4.2$ Hz, H-14β); ^{13}C NMR (100 MHz) see Table 1; ESIMS *m/z* 486 ([M + H]$^+$, 100%); HRESIMS *m/z* 486.2867 [M + H]$^+$ (calcd for $C_{25}H_{44}NO_6S$, 486.2884).

3.3 O-Demethylation of C_{19}-diterpenoid alkaloids with HBr–HOAc: general procedure

The C_{19}-diterpenoid alkaloids are dissolved in 6.5% HBr–HOAc and heated at the temperature and for the time shown in the sections below. The reaction solution was poured into ice water and then extracted with $CHCl_3$ after basifying with concentrated NH_4OH to give the residue that was subjected to column chromatography (silica gel H, $CHCl_3$–MeOH) to obtain the pure products.

Compound **2**. Talatisamine (**1**) (2.20 g, 5.23 mmol) and 6.5% HBr–HOAc (131 ml, 0.1 mol) at 80°C for 17 h gave compound **2** (2.38 g, 81%).

Compound **2**. mp 118–120°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 1.94, 2.00, 2.03, and 2.04 (each 3H, s, 4 × OAc), 3.25 (3H, s, OMe), 3.70 and 3.81 (each 1H, ABq, $J = 11.2$ Hz, H_2-18), 4.78 (1H, d, $J = 6.0$ Hz, H-16α), 4.79 (1H, t, $J = 4.8$ Hz, H-14β); ^{13}C NMR (100 MHz) see Table 1; ESIMS *m/z* 562 ([M + H]$^+$, 100%); HRESIMS *m/z* 562.2991 [M + H]$^+$ (calcd for $C_{30}H_{44}NO_9$, 562.3011).

Compound **4**. Compound **3** (1 g, 2.0 mmol) and 6.5% HBr–HOAc (50 ml, 40 mmol) at 50°C for 20 h gave compound **4** (1.1 g, 90%).

Compound **4**. mp 141–143°C; $[\alpha]_D$ −8.2 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.06 (3H, t, $J = 6.8$ Hz, NCH_2CH_3), 1.99, 2.02, and 2.05 (each 3H, s, 3 × OAc), 3.25 (3H, s, OMe), 3.70 and 3.82 (each 1H, ABq, $J = 10.8$ Hz, H_2-18), 4.80 (1H, t, $J = 6.0$ Hz, H-16α), 4.81 (1H, t, $J = 4.4$ Hz, H-14β); ^{13}C NMR (100 MHz) see Table 1; ESIMS *m/z* 598 ([M + H]$^+$, 100%); HRESIMS *m/z* 598.2668 [M + H]$^+$ (calcd for $C_{29}H_{44}NO_{10}S$, 598.2680).

Compound **6**. Deltaline (**5**) (101 mg, 0.2 mmol) and 6.5% HBr–HOAc (5 ml, 4 mmol) at 75–80°C for 20 h gave **6** (45 mg, 85%).

Compound **6**. mp 65–67°C; $[\alpha]_D$ −26.4 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 (3H, s, C_4–CH_3), 1.06 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 2.02, 2.06, 2.06, and 2.09 (each 3H, s, 4 × OAc), 3.25 (3H, s, OMe), 3.53 (1H, dd, $J = 9.6$ and 7.6 Hz, H-1β), 4.20 (1H, d, $J = 5.6$ Hz, H-9β), 4.76 (1H, dd, $J = 9.6$ and 6.0 Hz, H-16α), 4.85 and 4.96 (each 1H, s, OCH_2O), 5.44 (1H, s,

Table 1. ^{13}C NMR spectral data of compounds **2**–**4** and **6**–**10** (100 MHz, $CDCl_3$).

Carbon	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**10**
1	85.0	85.2	84.0	78.3	90.5	88.3	88.1	90.2
2	24.7	26.3	25.9	26.7	28.5	26.8	27.9	26.4
3	32.2	32.5	31.8	36.3	34.6	34.2	34.3	34.3
4	37.4	38.2	38.3	33.5	39.2	39.1	39.2	39.2
5	42.1	39.3	38.6	50.7	43.0	44.5	45.0	45.6
6	25.0	24.6	24.6	77.3	27.0	24.0	26.9	25.9
7	44.4	43.9	43.5	91.0	26.2	19.2	25.2	18.9
8	79.5	84.7	84.5	81.3	43.6	39.1	42.2	28.5
9	39.2	43.9	43.5	47.2	43.4	43.0	43.7	43.2
10	39.2	41.4	41.3	95.4	43.6	43.9	44.3	44.0
11	52.5	48.6	48.7	57.3	46.2	42.9	44.6	43.0
12	27.9	28.4	28.3	34.4	29.1	28.2	31.0	28.0
13	41.1	45.7	48.7	38.5	33.7	28.6	36.3	37.0
14	74.5	81.1	80.1	73.8	77.6	75.9	80.7	82.2
15	36.2	37.4	36.0	33.7	35.1	31.0	34.3	51.4
16	74.5	82.2	73.9	73.2	81.8	73.2	80.0	73.2
17	61.3	61.6	61.1	63.1	52.5	51.5	51.7	51.8
18	69.1	79.3	69.5	25.3	79.8	73.4	78.5	79.3
19	52.3	52.8	52.3	56.4	55.0	56.9	57.3	54.6
21	49.1	49.2	49.1	50.1	52.2	53.8	53.8	52.4
22	13.4	13.3	13.4	13.6	12.4	14.0	14.2	12.3
1-OCH_3	55.9	56.0	55.9	55.0	56.3	56.7	56.7	56.9
1-OAc	–	–	–	–	–	–	–	–
6-OAc	–	–	–	169.7	171.7	170.6	–	–
				21.5	21.3	21.0		
8-OAc	169.5	169.8	169.8	–	–	–	38.5	38.0
	20.7	22.4	20.7					
10-OAc	–	–	–	170.6	57.3	–	57.0	–
				23.2				
14-OAc	170.0	–	–	170.2	–	170.2	–	170.8
	20.7			21.2		21.2		21.4
14-OMs	–	38.6	38.3	–	59.3	59.2	59.4	59.2
16-OCH_3	–	56.3	–	–	–	–	–	–
16-OAc	170.4	–	170.1	170.0				
	21.2		21.2	21.1				
18-OCH_3	–	59.3	–	–				
18-OAc	170.9	–	170.9	–				
	21.1		22.2					
OCH_2O	–	–	–	93.9				

H-6α), 5.53 (1H, t, $J = 5.2$ Hz, H-14β); ^{13}C NMR (100 MHz, $CDCl_3$) see Table 1; ESIMS *m/z* 606 ([M + H]$^+$, 100%); HRESIMS *m/z* 606.2918 [M + H]$^+$ (calcd for $C_{31}H_{44}NO_{11}$, 606.2909).

Compound **8**. Compound **7** (550 mg, 1.22 mmol) and 6.5% HBr–HOAc (30 ml, 24 mmol) at 50°C for 7 h gave compound **8** (290 mg, 50%).

Compound **8**. mp 154–157°C; $[\alpha]_\Delta$ + 1.4 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 1.98 and 2.06 (each 3H, s, 2 × OAc), 3.26 and 3.28 (each 3H, s, 2 × OMe), 4.67 (1H, t, $J = 4.6$ Hz, H-14β), 4.83 (1H, t, $J = 3.8$ Hz, H-16α); ^{13}C NMR (100 MHz) see Table 1; ESIMS *m/z* 476 ([M − H]$^+$, 100%); HRESIMS *m/z* 478.3175 [M + H]$^+$ (calcd for $C_{27}H_{44}NO_6$, 478.3163).

Compound **10**. Compound **9** (400 mg, 0.82 mmol) and 6.5% HBr–HOAc (20.8 ml, 16.6 mmol) at 80°C for 11 h gave compound **10** (210 mg, 49%).

Compound **10**. mp 133–135°C; $[\alpha]_D$ − 27.2 (*c* 0.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$)δ: 0.98 (3H, t, $J = 6.8$ Hz, NCH_2CH_3), 2.04 (3H, s, OAc), 3.26 and 3.30 (each 3H, s, 2 × OMe), 4.69 (1H, t, $J = 4.6$ Hz, H-14β), 4.83 (1H, t, $J = 4.0$ Hz, H-16α); ^{13}C NMR (100 MHz) see Table 1; ESIMS *m/z* 514 ([M + H]$^+$, 100%); HRESIMS *m/z* 514.2828 [M + H]$^+$ (calcd for $C_{26}H_{44}NO_7S$, 514.2833).

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