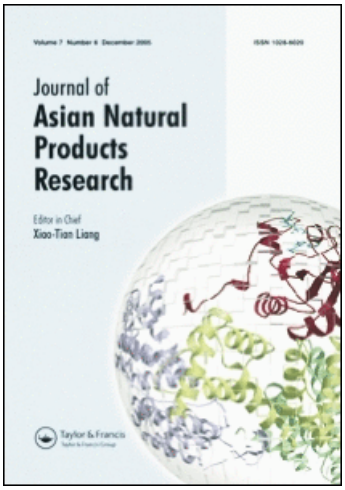

Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

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To cite this Article He, Ya-Mei , Zou, Chun-Lan , Chen, Qiao-Hong and Wang, Feng-Peng(2007) 'New formation of imines of C_{19}-diterpenoid alkaloids by heating with DMSO', Journal of Asian Natural Products Research, 9: 8, 713 — 720
To link to this Article: DOI: 10.1080/10286020600979803
URL: http://dx.doi.org/10.1080/10286020600979803

Journal of Asian Natural Products Research, Vol. 9, No. 8, December 2007, 713–720

New formation of imines of C_{19}-diterpenoid alkaloids by heating with DMSO

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(Received 23 March 2006; revised 29 June 2006; in final form 5 July 2006)

Treatment of some C_{19}-diterpenoid alkaloids (**3**, **6**, **10** and **12**) with anhydrous DMSO at 100–170°C for 3–7 h led to the formation of the corresponding imines (**4**, **7/8**, **11**, **13/14**) in 65–83% yield, respectively. This is a new simpler formation of the imines of the C_{19}-diterpenoid alkaloids.

Keywords: Imine formation; C_{19}-Diterpenoid alkaloid; Dimethyl sulphoxide Talatisamine

1. Introduction

In our continuing investigation on the chemistry of diterpenoid alkaloids [1], displaying a lot of interesting chemistry [2,3] and important biological activities, an attempt to carry out the Wagner–Meerwein rearrangement of compound **1** using DMSO led, surprisingly, to the imine **2**, which is a new preparation of imines of the C_{19}-diterpenoid alkaloids. Preparation methods of imines of C_{19}-diterpenoid alkaloids have been summarised, including oxidation with CrO_3/pyridine [4], $KMnO_4$ [5], Pb $(OAc)_4$ [6], or NBS [7–10], rearrangement of chloroamines [11] as well as heating some oxazolidine-containing or having *O*, *N*-mixed acetal diterpenoid alkaloids with Ac_2O-Pyridine [2,12,13]. However, most of them, except for the NBS method reported by us, are not very useful owing to low yields [8,9] or structurally limited substrates. Therefore, application of DMSO to the conversion of amines in the C_{19}-diterpenoid alkaloids into imines is worthy of further research. In 1994, Jinbo *et al.* [14] reported the oxidation of secondary amines to imines using activated DMSO. Interestingly, this conversion for the tertiary amines such as the C_{19}-diterpenoid alkaloids using only DMSO rather than activated DMSO reagent has not yet been reported. Thus, we have found a useful method for the formation of imines of C_{19}-diterpenoid alkaloids by heating with dry DMSO. In order to observe the application of preparation of imines by DMSO mentioned above, we focused our attention on the different C_{19}-diterpenoid alkaloids and the optimisation of the reaction conditions. In this paper, we wish to report the preparation of imines of C_{19}-diterpenoid alkaloids by heating with dry DMSO.

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Journal of Asian Natural Products Research
ISSN 1028-6020 print/ISSN 1477-2213 online © 2007 Taylor & Francis
http://www.tandf.co.uk/journals
DOI: 10.1080/10286020600979803

2. Results and discussion

Since 1980, many studies on the chemistry of diterpenoid alkaloids have been carried out in our laboratory. During these studies, we found that heating **1** with DMSO yielded the unexpected imine **2**. While treatment of compound **3** with DMSO at 100–140°C for 12 h also afforded the imine **4** in 56% yield besides the minor immonium salt **5** (16%). Compound **4**, $C_{22}H_{33}NO_5$ (HRMS), was obtained as amorphous powder. Its ^{1}H NMR and ^{13}C NMR spectra showed the typical imine signals at δ_H 8.80 (br s) and δ_C 165.2 (d) and the absence of an *N*-ethyl group. Based on these interesting results, we turned our attention to observation of the reaction, including optimisation of the reaction conditions, the limitation for preparation of the imines of C_{19}-diterpenoid alkaloids.

Preliminary trials under various conditions (table 1) showed that treatment of **3** with dry DMSO at 130°C for 3 h afforded **4** in 82% yield (table 1). The imines could be achieved in excellent yields (65–83%) by heating the substrates (**3**, **6**, **10**, **12**) with dry DMSO at the temperature and for the time shown in table 1. It is quite interesting that the C_{19}-diterpenoid alkaloids having substituent groups at C-3 and C-6, e.g., 3-acetylyunaconitine (**15**), afforded only the *N*-deethyl compounds, probably due to the hindrance of the substitutions at C-3 and C-6. Therefore, this method of formation of imines is obviously more adequate to the C_{19}-diterpenoid alkaloids without substitutions at C-3 and C-6.

It is worth noting that, in this case, the conversion of the tertiary amines (**3**, **6**, **10**, **12**) to the imines (**4**, **7**, **11**, **13**) possibly undergo a process different from that reported by Jinbo *et al*. [14]. Considering the general mechanism for oxidation of alcohols or secondary amines using activated DMSO [15,16], we postulate a process of formation of the imines of the C_{19}-diterpenoid alkaloids (figure 1). First, a nucleophilic attack of the lone-pair electron of the nitrogen atom on the sulphur atom in DMSO [15] led to the intermediate B which produced C by a β-elimination with loss of ethylene, while α-elimination of C afforded the imines D and the intermediate E. The latter was subjected again to an electron transference depicted in figure 1 to regenerate DMSO together with release of methylsulphide via dehydration. The methylsulphide formed by treatment of talatisamine (**3**) with DMSO at 130°C was collected and identified on the basis of its disagreeable odour and distinct signal at δ_H 2.11 (6H, s) in the ^{1}H NMR spectrum [17]. In addition, the key intermediate B also produced the immonium salt F and the *N*-deethyl compound G through α-elimination and electron transference as shown in figure 1, respectively.

Table 1. Reaction with anhydrous DMSO.

Entry	*Substrate*	*Reagent*	*Temperature (°C)*	*Time (h)*	*Product (yield %)*
1	**1**	DMSO†	138	5	**2** (21%)
2	Talatisamine (**3**)	DMSO†	100–140	12	**4** (56%), **5** (16%)
3	Talatisamine (**3**)	Dry DMSO + EtOAc	120	6	**4** (35%)
4	Talatisamine (**3**)	Dry DMSO	100–130	3	**4** (65%), **5** (33%)
5	Talatisamine (**3**)	Dry DMSO	130	3	**4** (82%), **5** (13%)
6	14-Acetyltalatisamine (**6**)	Dry DMSO	130	6‡	**7** (69%), **8** (11%), **9** (15%)
7	8,14-Diacetyltalatisamine (**10**)	Dry DMSO	100	6‡	**11** (83%)
8	Lappaconitine (**12**)	Dry DMSO	100	2	**13** (65%), **14** (15%)
9	3-Acetylyunaconitine (**15**)	Dry DMSO	150	3	**16** (68%)
10	Deltaline (**17**)	Dry DMSO	170	3	**18** (56%)

† No steamed treatment.
‡ The reaction has not finished after 3 h.

In summary, the imines of diterpenoid alkaloids can be prepared in excellent yields by heating with dry dimethyl sulphoxide (DMSO) at 100–170°C for 3–7 h. To the best of our knowledge, this method provided the most simple and convenient preparation of the imines of C_{19}-diterpenoid alkaloids. Further studies on the utilisation of the method for other different substrates besides the diterpenoid alkaloids are currently in progress.

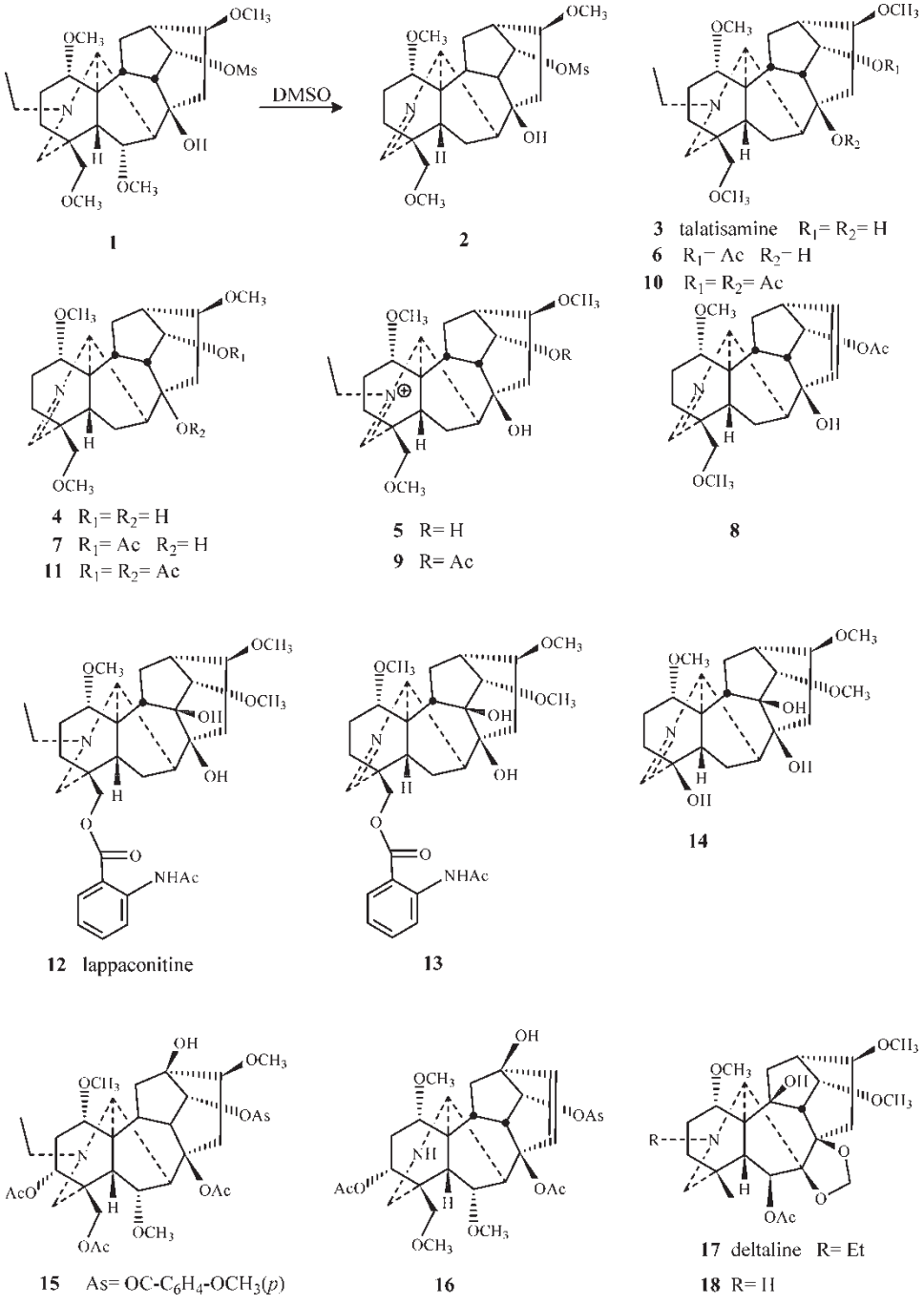


Figure 1. Structures of compounds 1–18.

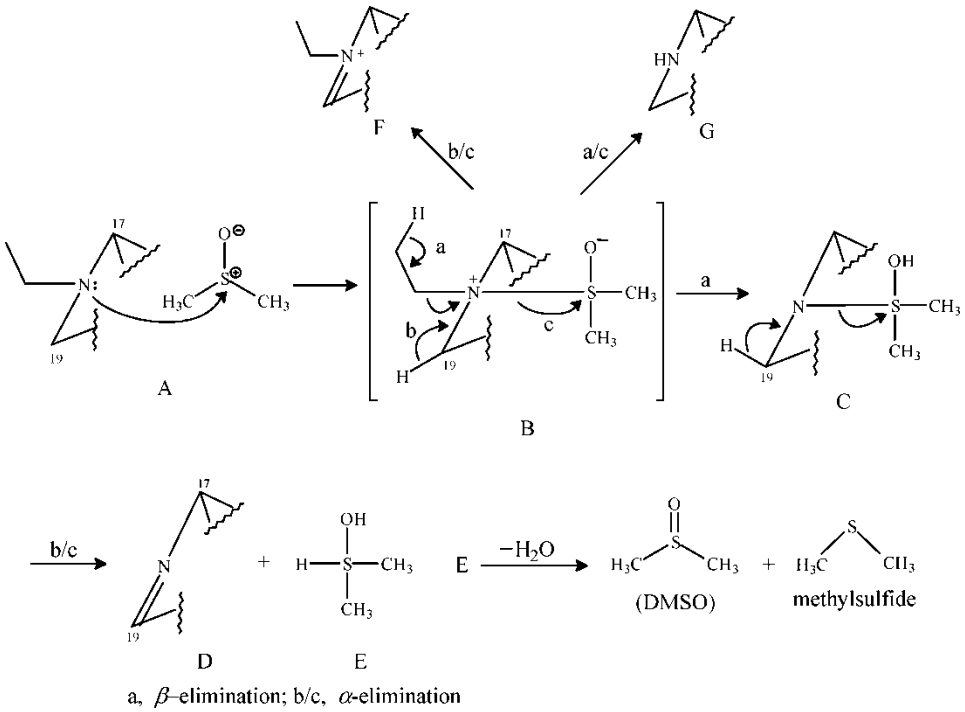


Figure 2. A possible mechanism for formation of compounds **2**, **4**, **6**, **7**, **11**, **13**, **14**, **16**, and **18**.

3. Experimental

3.1 General experimental procedures

Melting points were determined on a Kofler block and are uncorrected; optical rotations were measured in a 1.0 dm cell with a Jasco Dip-370 polarimeter at 20 ± 1°C; IR spectra were recorded on a Nicolet 200 SXV spectrometer; MS spectra were obtained with a Finnigan LCQ and Micromass Auto Spec Ultima-Tof spectrometer; ^{1}H NMR and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or a Varian INOVA-400/54 spectrometer, with TMS as internal standard; Silica GF_{254} and gel H (10−40 μm, Qingdao Sea Chemical Factory, China) were used for TLC and CC. Only key signals for all products in the ^{1}H NMR spectra are reported.

3.2 Substrate preparation

3.2.1 Compound 1. **1** was prepared from talatisamine (**3**) by TsCl. 1: δ_H (200 MHz, $CDCl_3$): 1.07 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 3.11 (3H, s, SO_2CH_3), 3.27, 3.29, 3.30 (each 3H, s, $OCH_3 \times 3$), 4.93 (1H, t, $J = 4.9$ Hz, H-14β); δ_C (50 MHz, $CDCl_3$): 85.1 (C-1), 26.0 (C-2), 32.1 (C-3), 38.3 (C-4), 38.5 (C-5), 25.0 (C-6), 44.5 (C-7), 73.4 (C-8), 46.3 (C-9), 45.4 (C-10), 48.8 (C-11), 28.4 (C-12), 46.1 (C-13), 81.6 (C-14), 40.9 (C-15), 82.5 (C-16), 61.8 (C-17), 79.3 (C-18), 53.1 (C-19), 49.4 (C-21), 13.3 (C-22), 56.0 (C-1′), 56.0 (C-16′), 58.3 (C-18′), 38.9 (SO_2CH_3); (EI-MS) *m/z*: 499 (2, M^+), 484 (5), 468 (100).

3.2.2 Compounds. **3** [18], **6** [18], **10** [20], **12** [19], **15** [20], and **17** [20] were separated or prepared by our laboratory.

Table 2. ^{13}C NMR data of compounds **2**, **4**, **5**, **7**, **8**, **9**, and **11**.

No.	*2*	*4*	*5*	*7*	*8*	*9*	*11*
1	81.2	83.3	80.2	81.0	75.6	80.0	82.4
2	26.8	25.5	19.9	24.3	23.5	19.4	23.5
3	23.8	27.1	28.3	28.2	32.3	29.2	29.6
4	48.8	47.6	48.0	49.3	47.9	47.5	48.5
5	38.9	37.3	37.7	35.8	35.3	37.1	40.8
6	25.2	27.1	24.9	26.9	27.1	24.4	26.4
7	41.0	39.3	39.4	41.4	41.3	39.4	39.4
8	72.8	72.3	72.2	73.1	73.3	72.3	75.2
9	53.4	42.6	38.3	41.6	44.6	37.4	41.0
10	44.2	52.4	53.7	53.2	49.2	54.1	49.2
11	49.0	42.9	42.7	44.8	49.4	43.1	44.2
12	28.3	25.6	24.2	25.0	24.5	23.9	24.4
13	44.9	46.2	42.5	44.0	43.6	42.1	47.9
14	81.9	84.7	81.7	83.2	83.2	81.7	85.0
15	40.5	37.5	39.6	40.3	129.6	37.1	38.7
16	82.6	75.4	84.5	76.2	131.1	75.4	75.5
17	61.7	62.7	67.6	62.1	62.7	66.8	61.6
18	75.5	75.1	73.1	75.6	75.6	73.0	75.5
19	164.3	165.2	178.2	164.5	164.6	177.4	164.1
21	–	–	55.9	–	–	55.8	–
22	–	–	13.6	–	–	13.4	–
1-OCH_3	55.9	56.1	56.3	55.8	55.9	56.2	56.1
16-OCH_3	56.1	56.5	56.4	55.8	–	56.2	56.5
18-OCH_3	59.4	59.5	59.4	59.4	59.3	56.3	59.5
8-OAC	–	–	–	–	–	–	170.8
	–	–	–	–	–	–	21.2
14-OAC	–	–	–	170.6	170.1	170.8	169.1
	–	–	–	21.2	21.0	21.2	22.2
SO_2CH_3	–	–	–	–	–	–	–

3.3 Treatment of C_{19}-diterpenoid alkaloids with DMSO: general procedure for table 1

To a solution of the C_{19}-diterpenoid alkaloids (0.17–0.20 mmol) dry DMSO (1 ml) was added and the reaction mixture was heated at the temperature and for the time shown in table 1. After evaporation in a vacuum, the residue was subjected to column chromatography on silica gel ($CHCl_3$/MeOH) to give the pure product.

3.4 Reactions for table 1

3.4.1 Compound 2. Compound **1** [18] (260 mg, 0.52 mmol) and DMSO (12 ml) gave **2** (50 mg, 21%).

Compound **2**: R_f (95% $CHCl_3$/CH_3OH) 0.36; $[\alpha]_D^{20} = +14.9$ (*c* 0.5, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 3.10 (3H, s, SO_2CH_3), 3.18, 3.29, 3.32 (each 3H, s, $OCH_3 \times 3$), 4.93 (1H, t, $J = 4.8$ Hz, H-14β), 7.19 (1H, s, H-19); δ_C (50 MHz, $CDCl_3$), see table 2; *m*/*z* (ESI) 470 (3, $[M + H]^+$), 454 (15, M-CH_3), 440 (32), 424 (46); HRESI-MS *m*/*z* 470.2207 $[M + H]^+$(calcd for $C_{23}H_{36}NO_7S$, 470.2204).

3.4.2 Compounds 4 and 15. Talatisamine (**3**) (100 mg, 0.24 mmol) and dry DMSO (1 ml) gave **4** (76 mg, 82%), **5** (13 mg, 13%) as amorphous powder and methylsulphide (7 mg, colourless liquid).

Compound **4**: Mp 96–97°C; R_f (95% $CHCl_3$/CH_3OH) 0.44; $\alpha_D^{20} = +21.3$ (*c* 0.95, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 3.21, 3.34, 3.39 (each 3H, s, $OCH_3 \times 3$), 7.27 (1H, br s, H-19);

δ_C (50 MHz, $CDCl_3$), see table 2; *m/z* (ESI) 392 (100, $[M + H]^+$); HRESI-MS *m/z* 392.2415 $[M + H]^+$(cald for $C_{22}H_{34}NO_5$, 392.2431).

Compound **5**: Mp 99–100°C; R_f (83% $CHCl_3/CH_3OH$) 0.37; $\alpha_D^{20} = -12.0$ (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 3.23, 3.38, 3.41 (each 3H, s, $OCH_3 \times 3$), 4.22 (1H, t, $J = 4.7$ Hz, H-14β), 8.80 (1H, br s, H-19); δ_C (50 MHz, $CDCl_3$), see table 2; *m/z* (EI) 420 (100, $[M + H]^+$); HRESI-MS *m/z* 420.5626 $[M + H]^+$(calcd for $C_{24}H_{38}NO_5$, 420.5679).

Methylsulphide: liquid with strong disagreeable odour. δ_H (400 MHz, $CDCl_3$) 2.11 (6H, s).

3.4.3 Compounds 7, 8, and 9. 14-Acetyltalatisamine (**6**) (100 mg, 0.22 mmol) and dry DMSO (1 ml) gave **7** (65 mg, 69%), **8** (10 mg, 11%), and **9** (15 mg, 15%).

Compound **7**: Mp 103–104°C; R_f (95% $CHCl_3/CH_3OH$) 0.43; $\alpha_D^{20} = +52.9$ (*c* 1.55, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.06 (3H, s, 14-OAc), 3.22, 3.25, 3.35 (each 3H, s, $OCH_3 \times 3$), 4.85 (1H, t, $J = 4.8$ Hz, H-14β), 7.23 (1H, br s H-19); δ_C (50 MHz, $CDCl_3$), see table 2; *m/z* (ESI) 434 (100, $[M + H]^+$); HRESI-MS *m/z* 434.2551 $[M + H]^+$(calcd for $C_{24}H_{36}NO_6$, 434.2537).

Compound **8**: Mp 107–108°C; R_f (95% $CHCl_3/CH_3OH$) 0.37; $\alpha_D^{20} = +48.3$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.04 (3H, s, 14-OAc), 3.20, 3.36 (each 3H, s, $OCH_3 \times 2$), 4.86 (1H, t, $J = 4.8$ Hz, H-14β), 5.69 (1H, dd, $J = 7.6$, 2 Hz, H-15), 5.90 (1H, d, $J = 8$ Hz, H-16), 7.24 (1H, br s H-19); δ_C (50 MHz, $CDCl_3$), see table 2; *m/z* (ESI) 402 (100, $[M + H]^+$); HRESI-MS *m/z* 402.2266 $[M + H]^+$(calcd for $C_{23}H_{32}NO_5$, 402.2275).

Compound **9**: Mp 99–101°C; R_f (83% $CHCl_3/CH_3OH$) 0.35; $\alpha_D^{20} = -10.4$ (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.49 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 2.07 (3H, s, 14-OAc), 3.17, 3.32, 3.41 (each 3H, s, $OCH_3 \times 3$), 4.39 (1H, d, $J = 6.8$ Hz, H-6β), 4.86 (1H, t, $J = 4.8$ Hz, H-14β), 8.69 (1H, br s H-19); δ_C (50 MHz, $CDCl_3$), see table 2; *m/z* (ESI) 430 (100, $[M + H]^+$); HRESI-MS *m/z* 430.2603 $[M + H]^+$(calcd for $C_{25}H_{36}NO_5$, 430.2588).

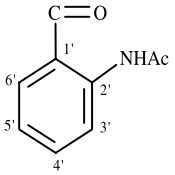
3.4.4 Compound 11. 8,14-Acetyltalatisamine (**10**) (100 mg, 0.2 mmol) and dry DMSO (1 ml) gave **11** (78 mg, 83%).

Compound **11**: Mp 88–89°C; R_f (97% $CHCl_3/CH_3OH$) 0.52; $\alpha_D^{20} = +64.5$ (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.90, 2.01 (each 3H, s, OAc × 2), 3.20, 3.31, 3.31 (each 3H, s, $OCH_3 \times 3$), 4.79 (1H, t, $J = 4.6$ Hz, H-14β), 7.14 (1H, br s, H-19); δ_C (50 MHz, $CDCl_3$), see table 2; *m/z* (ESI) 476 (100, $[M + H]^+$); HRESI-MS *m/z* 476.2637 $[M + H]^+$(calcd for $C_{26}H_{38}NO_7$, 476.2643).

3.4.5 Compounds 13 and 14. Lappaconitine (**12**) [19] (100 mg, 0.17 mmol) and dry DMSO (1 ml) gave **13** (59 mg, 65%) and **14** (10 mg, 15%).

Compound **13**: Mp 105–106°C; R_f (95% $CHCl_3/CH_3OH$) 0.31; $\alpha_D^{20} = +52.4$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.18 (3H, s, OAc), 3.22, 3.31, 3.41 (each 3H, s, $OCH_3 \times 3$), 7.03 (1H, t, $J = 7.4$ Hz, H-5′), 7.52 (1H, t, $J = 7.3$ Hz, H-4′), 7.96 (1H, d, $J = 8.0$ Hz, H-3′), 8.68 (1H, d, $J = 8.4$ Hz, H-6′), 11.0 (1H, br s, NHAc); δ_C (50 MHz, $CDCl_3$), see table 3; *m/z* (ESI) 554 (100, $[M + H]^+$); HRESI-MS *m/z* 554.5948 $[M + H]^+$(calcd for $C_{30}H_{38}N_2O_8$, 554.5956).

Table 3. ^{13}C NMR data of compounds **13**, **14**, **16**, and **18**.

No.	***13***	***14***	***16***	***18***	*No.*	***13***	***14***	***16***	***18***
1	82.3	82.7	80.3	81.3	18-OCH_3	–	–	58.8	56.1
2	23.2	19.5	31.7	26.9		169.0	–	–	–
3	27.0	29.6	71.6	39.2		25.5	–	–	–
4	88.6	77.1	49.9	33.8		167.1	–	–	–
5	48.1	46.8	48.2	50.2					
6	26.9	29.1	81.8	28.8	1	141.8	–	–	–
7	41.3	42.3	42.3	91.7	2′	115.1	–	–	–
8	75.4	75.1	73.7	81.4	3′	120.2	–	–	–
9	88.0	76.5	47.0	49.9	4′	134.7	–	–	–
10	36.8	36.5	45.4	83.8	5′	122.3	–	–	–
11	53.8	54.7	42.6	55.8	6′	130.8	–	–	–
12	26.9	27.5	40.6	34.5	3-OAc	–	–	170.2	–
13	52.4	30.7	76.8	43.7		–	–	21.1	–
14	89.7	88.8	82.0	81.5	6-OAc	–	–	–	169.7
15	44.2	35.3	129.8	36.3		–	–	–	21.3
16	81.3	81.0	134.8	77.5	14-OAs	–	–	113.9	–
17	62.1	68.9	63.7	64.9		–	–	113.9	–
18	–	–	71.9	25.5		–	–	131.7	–
19	159.2	176.3	50.3	59.4		–	–	131.7	–
21	–	57.1	–	–		–	–	163.9	–
22	–	12.6	–	–		–	–	167.0	–
1-OCH_3	56.2	56.3	56.6	55.7		–	–	55.4	–
6-OCH_3	–	–	57.6	57.6		–	–	–	93.8
14-OCH_3	56.4	56.3	–	–					
16-OCH_3	57.9	57.1	–	–					

Compound **14**: Mp 99–100°C; R_f (83% $CHCl_3$/CH_3OH) 0.33; $\alpha_D^{20} = -50.9$ (*c* 1.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$)1.50 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 3.17, 3.34, 3.44 (each 3H, s, $OCH_3 \times 3$), 8.59 (1H, br s, H-19); δ_C (50 MHz, $CDCl_3$) see Table 3; *m/z* (ESI) 422 (100, $[M + H]^+$); HRESI-MS *m/z* 422.5067 $[M + H]^+$(calcd for $C_{23}H_{36}NO_6$, 422.5081).

3.4.6 Compound 16. 3-Acetylyunaconitine (**15**) (100 mg, 0.14 mmol) and dry DMSO (1 ml) gave **16** (62 mg, 68%).

Compound **16**: Mp 152–153°C; R_f (95% $CHCl_3$/CH_3OH) 0.35; $\alpha_D^{20} = +66.9$ (*c* 0.95, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.06 (3H, s, 3-OAc), 3.23, 3.23, 3.35, 3.86 (each 3H, s, $OCH_3 \times 4$), 4.90 (1H, dd, $J = 5.6$, 6.8 Hz, H-3), 5.18 (1H, dd, $J = 2.0$, 4.8 Hz, H-14β), 5.59 (1H, dd, $J = 2.0$, 7.6 Hz, H-15), 5.90 (1H, d, $J = 9.6$ Hz, H-16), 6.92 ~ 7.91 (Ar-H); δ_C (50 MHz, $CDCl_3$), see table 3; *m/z* (ESI) 599 (5, $[M + H]^+$), 628 (100); HRESI-MS *m/z* 599.6758 $[M + H]^+$(calcd for $C_{32}H_{41}NO_{10}$, 599.6766).

3.4.7 Compound 18. Deltaline (**17**) (100 mg, 0.2 mmol) and dry DMSO (1 ml) gave **18** (53 mg, 52%).

Compound **18**: Mp 193–194°C; R_f (97% $CHCl_3/CH_3OH$) 0.47; $\alpha_D^{20} = -17.8$ (*c* 1.2, $CHCl_3$), $C_{25}H_{36}NO_8$, δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t,18-CH_3), 2.07 (3H, s, 6-OAc), 3.28, 3.32, 3.44 (each 3H, s, $OCH_3 \times 3$), 4.12 (1H, t, $J = 4.8$ Hz, H-14β); δ_C (50 MHz, $CDCl_3$), see table 3; *m/z* (ESI) 480 (4, $[M + H]^+$); HRESI-MS *m/z* 480.5255 $[M + H]^+$(calcd for $C_{25}H_{37}NO_8$, 480.5260).

Acknowledgements

Financial support for this research was provided by the National Natural Science Foundation of China (No. 30472075). We also thank Professor Xiao-Tian Liang, Institute of Materia Medica, Chinese Academy of Sciences, Beijing, for helpful discussion on the manuscript.

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