Two Novel Skeletal Rearrangements Involving in the C Ring of C_{19}-Diterpenoid Alkaloid Deltaline Derivatives

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Treatment of compounds 2 and 5, both from the C_{19}-diterpenoid alkaloid deltaline 1, with 5% NaOH methanol (room temperature, 16 h) and NaOH-*N*,*N*-dimethylformamide (reflux, 10 h) led to the two novel skeletal rearrangement products 4 (90%) and 6 (62%), respectively, involving Wagner–Meerwein rearrangement and Grob fragmentation. Their structures were fully characteristized based on 2D NMR and HR-MS data.

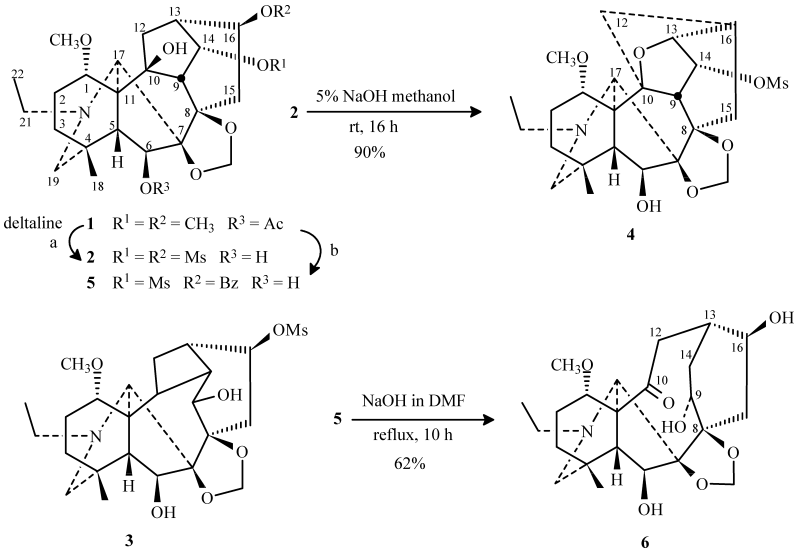
Key words C_{19}-diterpenoid alkaloid; deltaline; Wagner–Meerwein rearrangement; Grob fragmentation; 9,10-seco C_{19}-diterpenoid alkaloid

The diterpenoid alkaloids are a group of complex natural products, displaying many interesting chemical properties.[1,2] In the course of our intensive investigations of the chemistry of this class alkaloids,[3—13] two novel skeletal rearrangements involving in the C ring of C_{19}-diterpenoid alkaloids, *e.g.*, derivatives (**2**, **5**) of deltaline (**1**) have been obtained. We report here the characterization of these novel rearrangement products based on the 2D-NMR.

Results and Discussion

Deltaline (**1**) isolated from *Delphinium bonvalotti* Franch[14] was subjected to *O*-demethylation (6.5% HBr–HOAc, 85 °C, 20 h), followed by 5% NaOH hydrolysis and subsequent mesylation (MsCl, pyridine, room temperature, 2 h), to afford the dimesylate **2** (64%). An attempt to prepare **3** from **2** by treatment with 5% NaOH methanol (room temperature, 16 h) produced the rearrangement product **4** as white amorphous powder in 90% yield (Chart 1). HR-MS of **4** showed a molecular ion $[M+H]^+$ at *m/z* 498.2142, corresponding to $C_{24}H_{35}NO_8S$.

The IR and $^1H(^{13}C)$-NMR spectra of **4** exhibited only characteristic signals at 1354 cm^{-1}, δ_H 3.11 (3H, s), δ_C 38.9 (q) for one methylsulfonyl group that was attributed to C-14 due to the chemical shift of H-14 (δ 4.69, d, J=5.6 Hz). As compared with **2**, the ^{13}C-NMR spectrum of **4** clearly showed significant changes in the chemical shifts of C-9, C-10, C-11, C-12, C-13, C-15, and C-16 caused by the skeletal rearrangement. The ^1H–^1H COSY and HMBC spectra of **4** lacked the correlations between H_2-12 and H-13 but showed the key HMBC correlation of H-16 and C-10 (Fig. 1), indicating that sodium hydroxide treatment of **2** led to the abeo 12(13)→16 migration to give **4** *via* the Wagner–Meerwein rearrangement shown in Chart 2. This deduction was also supported strongly by the presence of oxygenated and nonoxygenated methines at δ 60.4 and δ 34.5 attributed to C-13 and C-16, respectively, based on the HMBC correlations of H-9 (δ 4.21)/C-13, H-15 (δ 1.61, 2.15)/C-12, C-13, H-14 (δ 4.69)/C-16, and H_2-12 (δ 1.68, 2.05)/C-16 (Fig. 1), when compared with **2**. In addition, the ^{13}C-NMR spectrum of **4** exhibited the characteristic signals at δ 65.5 (C-10), 40.8 (C-9),



a). (1). 6.5% HBr-HOAc, 85 °C, 20 h; (2). MsCl, tr, 2 h, 85 °C; b). (1). 6.5% HBr-HOAc, 85 °C, 20 h; (2). 5% NaOH, 60 °C, 1 h; (3). KI, Ag_2O, BzCl, 30 °C, 22 h, 40%

Chart 1

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77.8 (C-14), and 60.4 (C-13) of a tetrahydrofuran moiety due to the ^{1}H–^{1}H COSY correlation between H-9/H-14, and H-14/H-13, as well as the HMBC correlations of H-13/C-10 and H-9/C-13 (Fig. 1). The structure of **4** was thus determined on the basis of this evidence, especially in NMR (Table 1, Fig. 1).

In connection with our ongoing program on the development of novel conversional synthetic strategies to access taxanes from C_{19}-diterpenoid alkaloids,[15,16] we have attempted to construct the taxane-like core C starting from **5** *via* Wagner–Meerwein rearrangement (path a) followed by the rupture of C-12 (path b) and Pelletier's cleavage[17] (path c) shown in Chart 2. However, treatment of **5** with sodium hydroxide under reflux for 10 h led to the unexpected compound **6** in 62% yield (Chart 2).

The IR (1688 cm^{-1}) and NMR (δ_C 214.7) spectra of **6**, $C_{23}H_{33}NO_6$ (HR-MS), showed an extra ketone group as compared with those of **5**. Comparison of the ^{13}C-NMR spectra of **5** and **6** showed large differences, including many the carbon-13 signals, except for a few signals, *e.g.*, C-2, C-3, C-18, and C-22 (Table 2), as described above, also implying the possibility of skeletal rearrangement. The ^{1}H- and ^{13}C-NMR spectra of **6** with the same saturation degree (n=7) as **5** showed an additional ketone group at δ_C 214.7 attributed to C-10 due to the HMBC correlations of C-10/H-1 (δ 3.43), H-17 (δ 3.91), H-5 (δ 2.32) (Table 2) and the absence of ester groups caused by alkaline hydrolysis in addition to the mesyl group as compared with **5**, indicating that the C-10 ketone group might be derived from the Grob fragmentation shown in Chart 3. As compared with **5**, the ^{1}H- and ^{13}C-NMR spectra of **6** also displayed an extra methene (δ_H 1.82, 2.18) and an additional signal at δ_H 4.33 (d, J=7.6 Hz), which were located at H_2-14 and H-9, showing the HMBC correlations of H_2-14/C-8, C-12, and C-16 as well as H-9/C-13, C-15, and C-7 (Fig. 2), respectively. In addition, the configuration of C-9 bearing the newly formed hydroxyl group was deduced to be *R* due to the observation of NOE relationships between H-9 (δ 4.33) and H-15β (δ 1.78) a well as H-9 and H-13 (δ 2.40) (Fig. 3) in the NOESY spectrum of **6**. Obviously, the 9-OH, 16-OCH_3 and 8-OCH_2– in the chair conformation of ring C in **6** were located as equatorial bonds. Therefore the structure of **6** was established based on its 2D-NMR spectrum (Fig. 2) including the ^{1}H- and ^{13}C-NMR spectra (Table 1).

A plausible process for the formation of compounds **4** and **6** is depicted in Chart 3. Wagner–Meerwein rearrangement of **2** leads to the intermediate A, in which an attack of the C-10 hydroxyl group on the carbonium at C-13 gives **4**. In contrast, compound **5** was subjected only to Grob fragmentation followed by hydration to furnish the ketene **6**. In general, olefin can be hydrated under acid conditions. However, it also underwent a possible nucleophilic addition in the presence of alkaline.[18]

In summary, we have continued to investigate the chem-

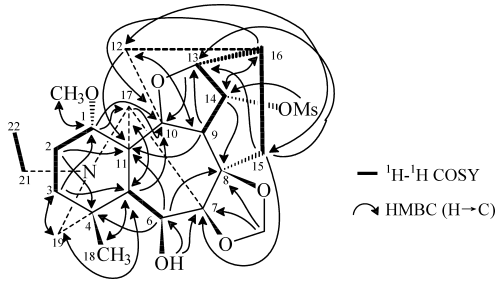


Fig. 1. Key ^{1}H–^{1}H COSY and HMBC Correlations of **4**

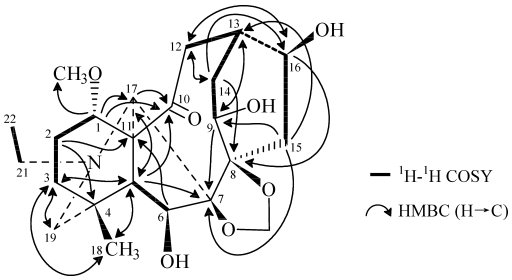


Fig. 2. Important ^{1}H–^{1}H COSY and HMBC Correlations of **6**

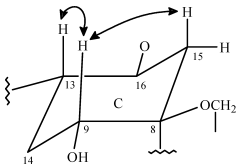


Fig. 3. The Partial NOE Relationships of **6**

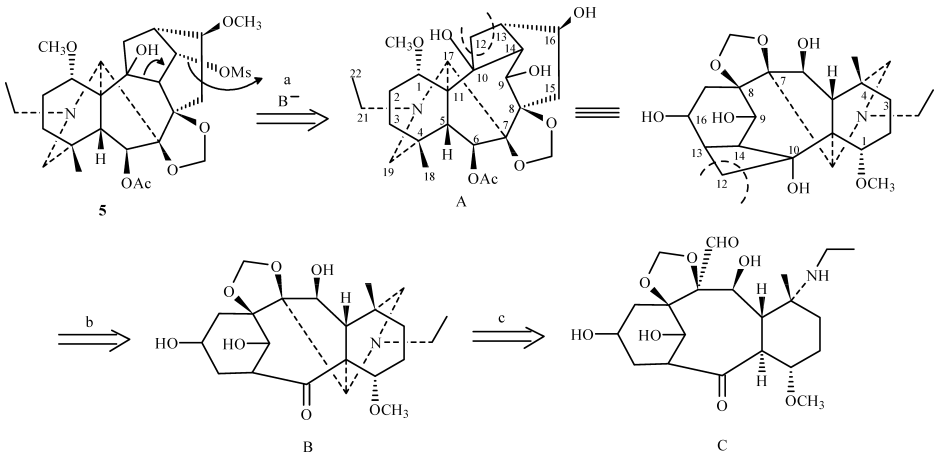
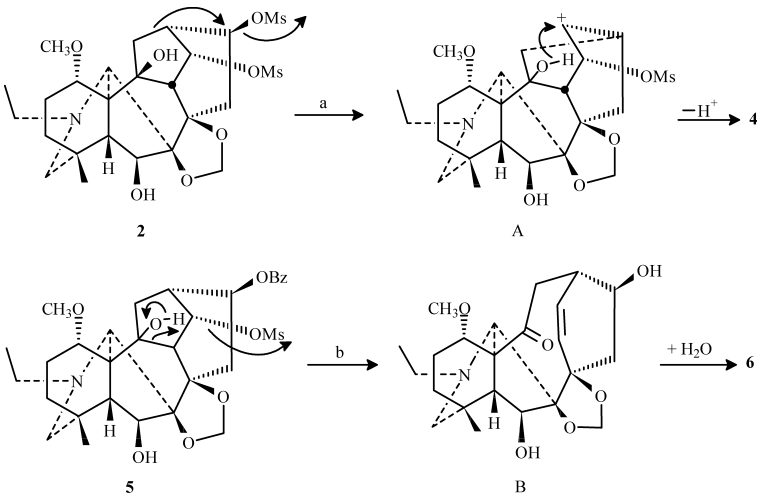


Chart 2

Table 1. ^{1}H- and ^{13}C-NMR Data of Compounds **2**, **4**, **5** and **6**

No.	**2**	**4**		**5**[a)]	**6**	
	δ_C	δ_C	δ_H Mult (J=Hz)	δ_C	δ_C	δ_H Mult (J=Hz)
1	79.8 d	76.0 d	3.30 dd (10.8, 7.2)	80.1 d	87.1 d	3.43 dd (10.8, 7.2)
2	26.4 t	25.3 t	1.98 m (α)	26.6 t	25.1 t	1. 90 m (α)
			2.19 m (β)			2.50 m (hidden) (β)
3	37.0 t	36.5 t	1.20 ddd (16.0, 4.8, 2.4) (β)	37.3 t	38.8 t	1.46 ddd (13.2, 4.8, 2.8) (α)
			1.55 ddd (12.4, 4.4, 2.8) (α)			1.58 ddd (13.2, 5.2, 2.4) (β)
4	33.6 s	34.3 s	—	33.6 s	31.9 s	—
5	49.5 d	53.2 d	1.71 s	50.2 d	54.3 d	2.32 s
6	79.0 d	79.6 d	4.32 s	79.7 d	81.9 d	4.05 s
7	92.6 s	94.3 s	—	92.5 s	102.8 s	—
8	81.3 s	81.2 s	—	82.0 s	88.3 s	—
9	51.3 d	40.8 d	4.21 d (5.6)	51.4 d	79.7 d	4.33 d (7.6)
10	79.8 s	65.5 s	—	80.7 s	214.7 s	—
11	55.5 s	48.6 s	—	55.7 s	63.5 s	—
12	36.6 t	23.5 t	1.68 m (hidden) (β)	36.8 t	39.9 t	2.61 m (β)
			2.05 m (hidden) (α)			2.78 m (α)
13	39.8 d	60.4 d	3.80 d (0.8)	39.7 d	32.0 d	2.40 m
14	78.8 d	77.8 d	4.69 d (5.6)	76.8 d	25.9 t	1.82 m (β)
						2.18 m (α)
15	34.0 t	17.8 t	1.61 m (β)	33.8 t	36.1 t	1.78 dd (16.8, 2.0) (β)
			2.15 m (α)			2.76 m (hidden) (α)
16	76.7 d	34.5 d	2.65 m (hidden)	72.9 d	70.2 d	4.13 m
17	63.6 d	65.2 d	3.34 d (2.4)	63.3 d	65.4 d	3.91 s
18	25.4 q	25.2 q	0.96 s	25.4 t	25.4 q	0.92 s
19	56.9 t	57.4 t	2.33 dd (12.0, 2.4)	57.1 t	56.1 t	2.50 ABq (11.2)
			2.69 d (11.6)			
21	50.4 t	50.2 t	2.65 m (hidden)	50.3 t	51.0 t	2.80 m
			2.76 m			
22	13.8 q	13.8 q	1.04 t (7.2)	13.8 q	13.9 q	1.06 t (7.2)
1′	55.3 q	55.0 q	3.21 s	55.3 q	56.4 q	3.20 s
O$\underline{CH_2}$O	93.5 t	93.9 t	5.05 s	93.5 t	91.7 t	4.98 s
			5.19 s			5.05 s
14-OMs	38.7 q	38.2 q	3.06 s	38.5 q	—	—
16-OMs	38.9 q	—	—	—	—	—
6-OH	—	2.91 s	—	—	—	—

a) C_6H_5COO: 166.0 (Ar-COO), 130.1 (C-1″), 129.6 (C-2″, 6″), 128.4 (C-3″, 5″), 133.0 (C-4″).



a). Wagner-Meerwein rearrangement; b) Grob fragmentation

Chart 3. Plausible Mechanism for Formation of Compounds **4** and **6**

istry of C_{19}-diterpenoid alkaloids and found two novel skeletal rearrangement products involved in Wagner–Meerwein rearrangement and Grob fragmentation. Further study of the role of **6** in constructing the taxane-like ABC ring system is underway in our laboratory.

Experimental

General Melting points were determined on a Kofler block (uncorrected). Optical rotations were measured in a 1.0-dm cell with a PE-314 polarimeter at 20±1 °C. IR spectra were recorded on a Nicolet 200 SXV spectrometer. MS spectra were obtained with a Auto-Spec-3000 instrument. ^{1}H- and ^{13}C-NMR spectra were acquired on a Bruker Ac-E 200 or a Varian

INOVA-400/54 spectrometer, with TMS as an internal standard. Silica gel GF_{254} and H (10—40 μm, Qingdao Sea Chemical Factory, China) were used for TLC and CC.

Compound 2 A solution of deltaline **1** (2.28 g, 4 mmol) in 6.5% HBr–HOAc (112 ml, w/v) was heated at 85 °C for 20 h. The reaction mixture was evaporated to dryness. Diluting (H_2O, 20 ml), basifying (conc. NH_4OH, pH 10), extraction ($CHCl_3$, 15 ml×3), drying (Na_2SO_4), and the removal of solvent gave a residue to which 5% NaOH methanol (50 ml) was added. This mixture was heated at 60 °C for 1 h to give a residue, and after a general work-up, water (15 ml) was added. Extraction (*n*-butanol, 15 ml×3), drying (Na_2SO_4), and evaporation afforded a residue that was dissolved in pyridine (20 ml). To this solution MsCl (19 ml, 24 mmol) was added and this mixture was allowed to stand at room temperature for 2 h. A general work-up gave crude **2**, which was chromatographed over silica gel H (50 g) eluted with cyclohexane–acetone (5 : 1) to afford **2** (1.52 g, 64%) as a white amorphous powder. mp 94—96 °C; $[\alpha]_D^{20}$ −23.4° (c=0.5, $CHCl_3$); IR (KBr): 3384, 1348 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.94 (3H, s, H_3-18), 1.05 (3H, t, J=7.2 Hz, $NCH_2\underline{CH_3}$), 3.05, 3.11 (each 3H, s, OMs×2), 3.23 (3H, s, OCH_3), 3.58 (1H, dd, J=10.0, 7.6 Hz, H-1β), 3.83 (1H, d, J=5.2 Hz, H-9), 4.26 (1H, s, H-6α), 4.76 (1H, dd, J=9.6, 4.4 Hz, H-16α), 5.05, 5.18 (each 1H, s, OCH_2O), 5.42 (1H, t, J=5.2 Hz, H-14β); ^{13}C-NMR (100 MHz, $CDCl_3$): see Table 1. ESI-MS m/z 594 $[M+H]^+$; HR-ESI-MS m/z 594.2011 $[M^+]$, Calcd for $C_{25}H_{40}NO_{11}S_2$, 594.2037.

Compound 4 To a solution of compound **2** (119 mg, 0.2 mmol), 5% NaOH methanol (15 ml) was added and this reaction solution was stirred at room temperature for 16 h. Evaporation, diluting (15 ml of H_2O), extraction ($CHCl_3$, 15 ml×3), drying (Na_2SO_4), and removal of solvent gave a residue that was chromatographed over silica gel (2 g) eluted with cyclohexane–acetone (8 : 1) to give compound **4** (89 mg, 90%). mp 86—88 °C; $[\alpha]_D^{20}$ −36.5° (c=0.55, $CHCl_3$); IR (KBr): 3525, 1354, 1175 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (100 MHz, $CDCl_3$): see Table 1. ESI-MS m/z 520 $[M+Na]^+$; HR-ESI-MS m/z 498.2142 $[M+H]^+$, Ccalcd for $C_{24}H_{36}NO_8S$, 498.2156.

Compound 5 A solution of deltaline (**1**) (2.5 g, 4.93 mmol) in 6.5% HBr–HOAc (23 ml) was heated at 85 °C for 20 h. and evaporated in a vacuum to give a residue that was heated with 75 ml of 5% NaOH methanol at 60 °C for 1 h. After a general work-up, column chromatography (silica gel H, 40 g, $CHCl_3$–MeOH/95 : 5) afforded a white amorphous powder (1.44 g), to which potassium iodide (110 mg, 0.66 mmol), Ag_2O (1.15 g, 4.95 mmol), and benzoyl chloride (0.43 ml, 3.63 mmol) were added in 50 ml of fresh THF, and then this reaction solution was heated at 30 °C for 22 h under an argon atmosphere. Quenching (H_2O), filtration, and evaporation of the filtrate gave a residue that was diluted with H_2O (10 ml), and basified to pH 9 with concentrated NH_4OH. After extraction with $CHCl_3$ (20 ml×3), the combined chloroform solutions were dried over anhydrous Na_2SO_4. The removal of solvent and column chromatography (silica gel H, 40 g, cyclohexane–acetone/4 : 1) afforded compound **5** (712 mg, 40%). mp 144—146 °C; $[\alpha]_D^{20}$ −35.8° (c=0.07, $CHCl_3$); IR (KBr): 3425, 1714, 1354 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.96 (3H, s, H_3-18), 1.07 (3H, t, J=7.2 Hz, $NCH_2\underline{CH_3}$), 3.07 (3H, s, OMs), 3.26 (3H, s, OCH_3), 3.60 (1H, dd, J=10.0, 7.2 Hz, H-1β), 3.85 (1H, d, J=5.2 Hz, H-9), 4.29 (1H, br s, H-6α), 5.07 (1H, dd, J=9.6, 4.8 Hz, H-16α), 5.04, 5.18 (each 1H, s, $O\underline{CH_2}O$), 5.45 (1H, t, J=5.2 Hz, H-14β), 7.43—8.10 (5H, m, Ar-H); ^{13}C-NMR (100 MHz, $CDCl_3$): see Table 1. ESI-MS m/z 620 $[M+H]^+$; HR-ESI-MS m/z 620.2526 $[M+H]^+$, Calcd for $C_{31}H_{42}NO_{10}S$, 620.2524.

Compound 6 To a solution of compound **5** (54.5 mg, 0.088 mmol) in DMF (2 ml), sodium hydroxide (10 mg) was added, and this mixture solution was refluxed for 10 h. A general work-up gave a residue (42 mg) that was chromatographed over silica gel H (1 g) eluted with cyclohexane–acetone (7 : 1) to afford **6** (white amorphous powder, 19 mg, 62%). mp 55—57 °C; $[\alpha]_D^{20}$ −45.2° (c=0.7, $CHCl_3$); IR (KBr): 3423, 1688 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) and ^{13}C-NMR (100 MHz, $CDCl_3$): see Table 1. ESI-MS m/z 442 $[M+Na\text{-}H_2O]^+$; HR-ESI-MS m/z 442.2202 $[M+Na\text{-}H_2O]^+$, Calcd for $C_{23}H_{33}NO_6Na$, 442.2200.

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