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Novel synthesis of 12,13-*seco* norditerpenoid alkaloids via semipinacol rearrangement and reaction with Br_2–HOAc

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Abstract—Treatment of 14-methylsulfonyl pseudaconine **3** with DMF–NaOH at 150°C for 10 h afforded the desired C-nor and 12,13-*seco* norditerpenoid alkaloids 16α-methoxyl ketone **7** (70%) and 16β-methoxyl ketone **8** (15%) as a pair of epimers. Reaction of **7** with Br_2–HOAc at room temperature for 1.5–2 h produced the phenols **9** (40%), **10** (10%) and **13** (29%). Whereas, treatment of **8** with Br_2–HOAc under same conditions as the case for **7** gave phenolic compound **9** (38%) besides the by-product α-bromoketone **14** (25%).

1. Introduction

Many norditerpenoid alkaloids display important biological activities[1] and are a synthetic or structural modified target.[2] We have previously reported on the synthesis of various derivatives of norditerpenoid alkaloids for evaluation of their biological activities.[3] After many unsuccessful attempts to cleave the 12,13-bond of norditerpenoid alkaloids, we finally found that 12,13-*seco* norditerpenoid alkaloids can be prepared via a semipinacol rearrangement followed by reaction with Br_2–HOAc. Herein, we wish to report the isolation and characterization of these novel 12,13-*seco* norditerpenoid alkaloids.

2. Results and discussion

The semipinacol rearrangement is very useful for cleavage and formation of the C–C bonds in organic molecules.[4] We attempted to access the 12,13-*seco* norditerpenoid alkaloids as shown in Scheme 1: tosylation of diol **A** afforded sulfonate ester **B** that gave rise to ketone **C** via a semipinacol rearrangement, subsequent treatment with HX (X=Br, Cl) to give the desired alkyl halide.

The norditerpenoid alkaloid pseudaconine **2** was chosen as the starting material from hydrolysis of yunnaconitine **1** available to us in kilogram quantities. Treatment of **2** with MsCl (3.0 mmol) instead of TsCl in pyridine at room temperature gave compound **3** in good yield (77%) besides the minor by-products **4** and **5**. The site(s) of sulfonation were ascertained by the respective downfield shifts of the corresponding compounds. Treatment of **5** with glacial acetic acid in an attempt to perform a Wagner–Meerwein rearrangement produced only the eliminative compound **6**. The NMR spectra of **6** showed distinctive signals at δ_H 5.79 (1H, d, J=9.7 Hz), 5.99 (1H, dd, J=9.7, 3.5 Hz); δ_C 137.6, 124.9, for a disubstituted double bond. After optimization of the reaction conditions, it was finally found that reaction of **3** with NaOH in DMF under drastic conditions (150°C, 10 h) afforded the desired rearrangement products, the 12,13-*seco* norditerpenoid alkaloids **7** (70%) and **8** (15%) as a pair of C-16 epimers. The MS (EI and HREI) of both compounds showed the same molecular ion (M^+) at *m/z* 465 corresponding to the formula $C_{25}H_{39}NO_7$. The IR and ^{13}C NMR spectra of **7** and **8** exhibited characteristic signals at 1707 cm^{-1}, δ_C 211.1 and 1709 cm^{-1}, δ_C 208.7, respectively, for six-membered cyclic ketones, attributed to C-13 due to the presence of the multi-bond ^1H–^{13}C correlations between H-12, H-14 and C-13 in the HMBC spectrum (Table 1). In comparison to the NMR spectra of compound **3**, those of compounds **7** and **8** showed the disappearance of the signals of the OMs group and the appearance of one ketone group at C-13, in addition to the upfieled shift of H-14 from 4.70 (d, J=5.2 Hz) to 2.90 (dd, J=16.8, 10.0 Hz) and 2.93 (dd, J=9.6, 6.4 Hz), in compounds **7** and **8**, respectively. These observations suggest that **3** could rearrange to **7** and **8** as shown in Scheme 2. The NOESY spectrum (Fig. 3) of **7** displayed the key correlations of H-9 with H-6β, H-15β and H-16β, indicating a *cis*-fused C/D ring system and the configuration at C-16. Finally, our hypothetical structure of **7** was confirmed by its 2D-NMR (Table 1) and single crystal X-ray analysis

Keywords: norditerpenoid alkaloid; 12,13-*seco* norditerpenoid alkaloid; semi-pinacol rearrangement; aromatization.

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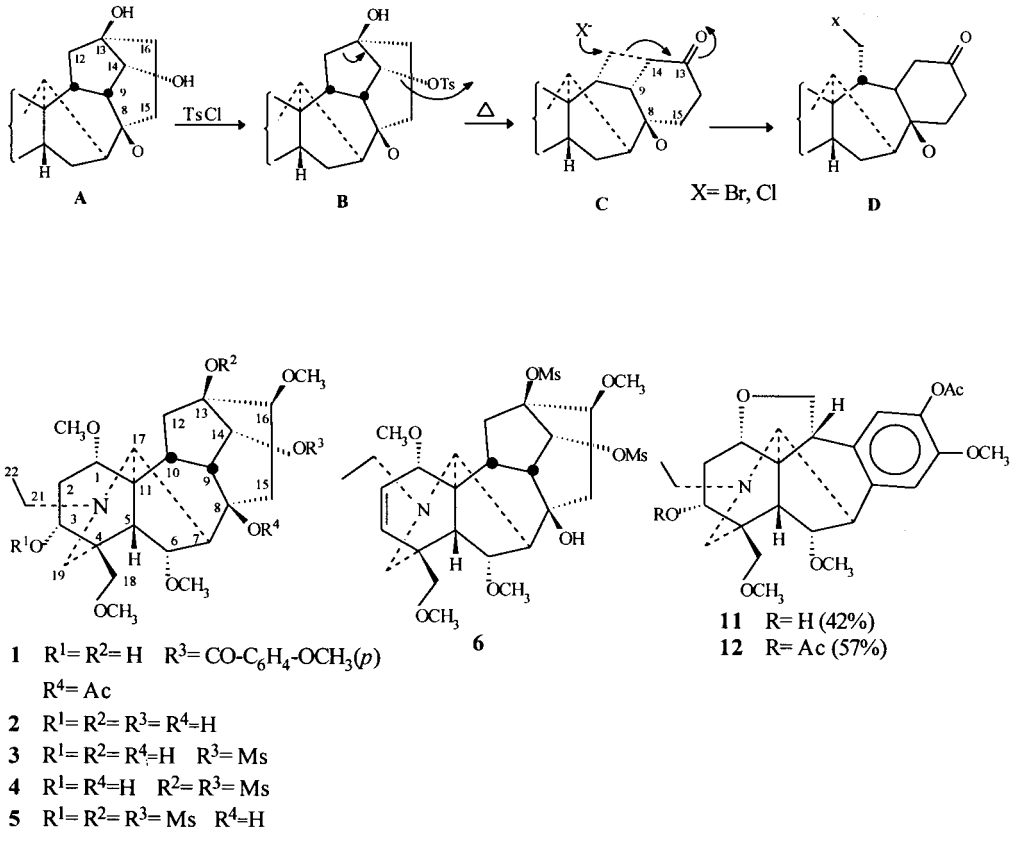
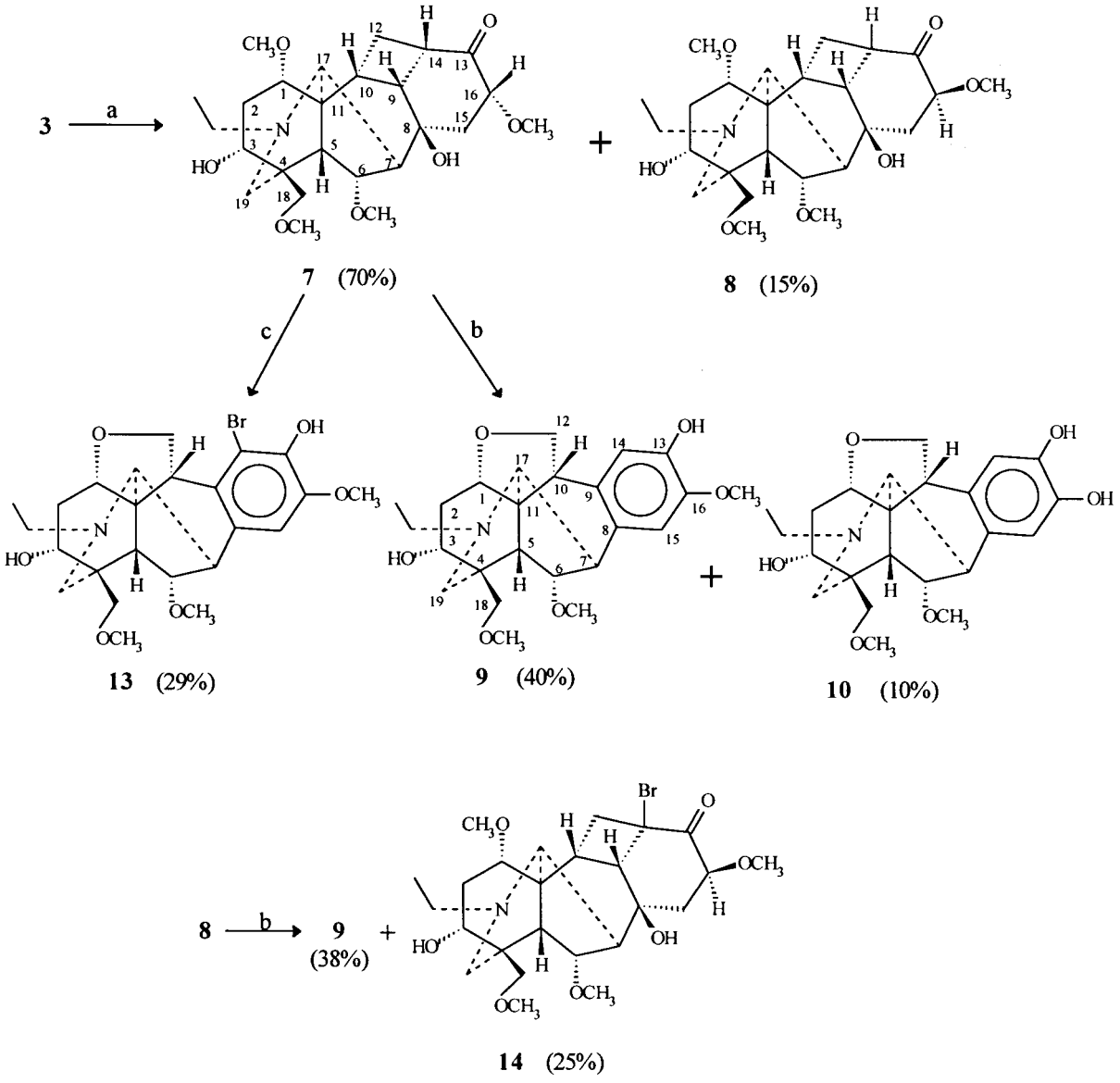


Scheme 1.

Table 1. ^{1}H and ^{13}C NMR data of compound **7**

No.	δ_H	Mult (J=Hz)	δ_C	HMBC (H→C)
1	3.08	dd (10.8, 7.2)	80.9 d	C-10, C-11, C-17, C-1′
2	2.19	m (hidden) (β)	34.4 t	C-1, C-3, C-4
	2.52	dd (11.2, 5.6) (α)		C-1, C-3, C-4
3	3.71	dd (12.8, 5.2)	71.6 d	C-4, C-5, C-18
4	–	–	42.2 s	–
5	1.84	d (6.4)	47.3 d	C-3, C-4, C-6, C-7, C-11, C-17, C-18
6	3.97	dd (6.4, 1.6)	83.5 d	C-8, C-17, C-6′
7	2.00	d (1.6)	52.0 d	C-6, C-8, C-15, C-17
8	–	–	76.5 s	–
9	2.28	dd (16.8, 10.0)	43.7 d	C-8, C-11, C-12
10	3.67	dd (11.2, 10.0)	44.5 d	C-8, C-11, C-12
11	–	–	47.8 s	–
12	2.28	m (hidden) (β)	30.6 t	C-11
	2.58	m (hidden) (α)		C-11, C-13
13	–	–	211.1 s	–
14	2.90	dd (16.8, 10.0)	38.8 d	C-8, C-10, C-12, C-13
15	2.05	dd (9.6, 5.2) (β)	39.8 t	C-8, C-9, C-13, C-16
	2.51	dd (9.6, 8.8) (α)		C-13, C-16
16	4.15	dd (8.8, 5.2)	79.1 d	C-15, C-16′
17	3.36	d (5.6)	61.5 d	C-5, C-21
18	3.56	ABq (9.0)	76.1 t	C-3, C-4, C-18′
	3.75	ABq (9.0)		C-3, C-4, C-5, C-18′
19	2.21	ABq (11.2)	46.7 t	C-3, C-4, C-5
	2.98	ABq (11.2)		C-3, C-4, C-5, C-17
21	2.43	q (7.0)	48.6 t	C-22
22	1.05	t (7.0)	13.2 q	C-21
1′	3.17	s	55.9 q	C-1
6′	3.37	s	58.1 q	C-6
16′	3.50	s	58.1 q	C-16
18′	3.32	s	59.0 q	C-18

(Fig. 1). Similarly, the structure of **8** was determined unambiguously on the basis of comparison of its 2D-NMR spectra (Table 4, Fig. 4) with those of **7**. Changes of the chemical shifts for C-7, C-8, C-9, C-13, C-14 and C-15 caused by epimerization at C-16 in the ^{13}C NMR spectra of **8** were observed. The 12,14-bond cleavages were tried on compound **7** with Br_2–HOAc under different conditions because **7** did not undergo reaction with HBr or HCl. First, treatment of **7** in glacial acetic acid with Br_2 (1.2 equiv.) in HOAc afforded two major products **9** (40%) and **10** (10%) as white amorphous powders. The MS (HREI) showed the molecular ions (M^+) at m/z 431.2335 and 417.2150 corresponding to $C_{24}H_{33}NO_6$ for **9** and $C_{23}H_{31}NO_6$ for **10**, respectively. Their NMR spectra suggested the presence of aromatic moieties (δ_H 6.59, 6.52, each 1H, s; δ_C 137.3, 129.0, 144.0, 107.4, 114.1, 144.7, for **9**; δ_H 6.84, 7.04, each 1H, s; δ_C 138.3, 128.1, 145.1, 116.4, 113.0, 145.4, for **10**) and new methylene carbon (δ 73.4) but the loss of one methoxyl group. These changes suggested the formation of a tetrahydrofuran moiety. As compared with **9**, the ^{1}H (^{13}C) NMR spectra of compound **10** showed the absence of an aromatic methoxyl group but the presence of an additional phenolic hydroxyl group by comparison of the MS spectra for both compounds. In order to confirm unambiguously the structure of compound **9**, the acetyl derivatives **11** (42%) and **12** (a colorless rhombic crystals, 57%) were prepared from diol **9**. The structure of **12** was proved by the single crystal X-ray analysis (Fig. 2), leading to confirmation of the structures of **9** and **10**. All the ^{1}H and ^{13}C signals of compound **9** were assigned by its 2D-NMR spectra (Table 4). It is worth noting



Scheme 2. (a) DMF–NaOH, 150°C, 10 h; (b) Br_2 (1.2 equiv.) in HOAc, rt, 1.5 h or 1 h; (c) Br_2 (2 equiv.) in HOAc, rt, 2 h.

that when compound **7** was treated with Br_2 (2 equiv.) in HOAc, another new compound **13** (29%) was formed. As compared with **9**, compound **13** has only an additional bromine atom, locating at C-14 by ^{13}C NMR, and concomitant shift changes of the carbons C-8, C-13, C-14 and C-15 were observed. Thus, the structure of compound **13** was determined simply by comparison of the ^{13}C NMR data with those of **9**.

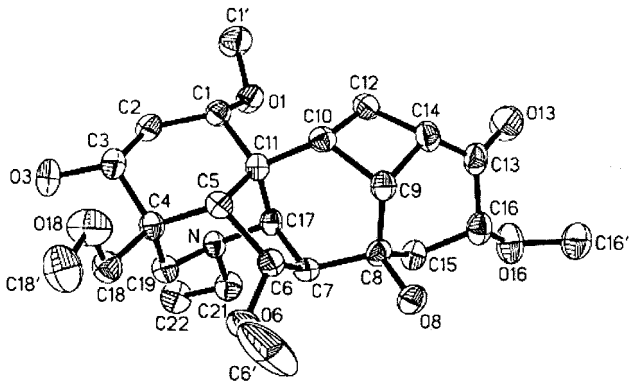


Figure 1. ORTEP drawing of **7**.

Finally, it was interesting to find that treatment of compound **8** with Br_2 (1.2 equiv.) in HOAc under the same conditions as for **7** gave the α-bromoketone **14** (25%) along with **9** (38%). Comparison of the ^{13}C NMR spectra (Table 4) of compounds **8** and **14** displayed differences only in the signals of carbons C-5, C-9, C-10, C-12, C-13 and C-14, strongly suggesting the bromine atom in **14** to be located at C-14.

In conclusion, a novel first access to the 12,13-*seco* norditerpenoid alkaloids, with aromatization of the D ring in the final products, has been developed. The amount of bromine in the cleavage reactions has a strong influence on the 12,13-*seco* norditerpenoid alkaloids. The results described here should prove helpful for similar modifications of other norditerpenoid alkaloids.

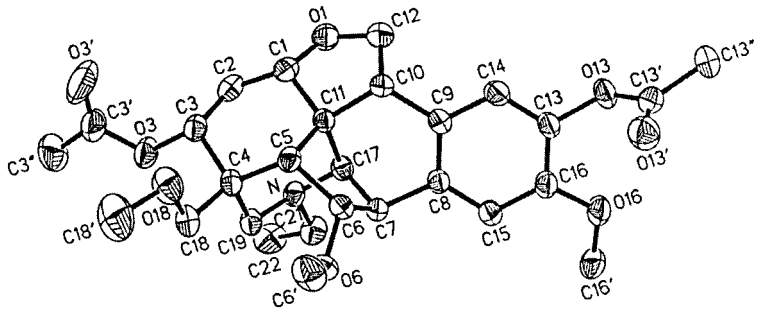


Figure 2. ORTEP drawing of **12**.

3. Experimental

3.1. General

Melting points were determined on a Kofler block (uncorrected); optical rotations were measured in a 1.0 dm tube with a PE-341 polarimeter at 20±1°C. IR spectra were recorded on a Nicolet 200 SXV spectrometer; MS spectra were obtained with a Spec-3000 VG 7070 E GC/MS/DES instrument; ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or Varian INOVA-400/54 spectrometer, in $CDCl_3$ with TMS as internal standard; Silica gel GF_{254} and H (10–40 μm, Qingdao Sea Chemical Factory, China) were used for TLC, Chromatotron and CC. Spots on chromatograms were detected with modified Dragendorff's reagent. Only key signals in the ^{1}H NMR spectra are reported.

3.1.1. Compound 2. A solution of yunnaconitine (**1**) (4 g, 6 mmol) in an 8% NaOH solution in methanol (60 mL) was heated at 60°C for 30 min, and evaporated in vacuo to give a residue that was diluted with H_2O (5 mL), and extracted with $CHCl_3$ (10 mL×4). The combined chloroform solutions were dried over anhydrous Na_2SO_4 and after removal of the solvent pseudaconine (**2**) (2.92 g, 99.6% yield) was obtained as white amorphous powder that was identified by comparison of mp (92–92°C, lit.[5]; 91–92°C), $[\alpha]_D^{20}$=+49.8 (*c* 0.56, $CHCl_3$) [lit.[5] +49 ($CHCl_3$)], TLC (silica gel GF_{254}, ether–acetone/4:1; $CHCl_3$/MeOH/9:1) and an $^{1}H(^{13}C)$ NMR data with the authentic sample.

3.1.2. Compounds 3, 4, 5 and 6. To a mixture of MsCl (0.09 mL, 1.15 mmol) and pyridine (2 mL), pseudaconine (**2**, 185 mg, 0.38 mmol) was added and the solution was allowed to stand at room temperature for 1 day. The crude reaction mixture was subjected to column chromatography on silica gel H (30 g) using cyclohexane–acetone (7:3) as eluent to yield compounds **3** (165 mg, 77%), **4** (10 mg, 4%) and **5** (15 mg, 6%).

Compound **3**. White amorphous powder; mp 129–130°C; R_f (50% cyclohexane–acetone) 0.31; $[\alpha]_D^{20}$=+22.3 (*c* 0.34, $CHCl_3$); ν_{max}(KBr) 3432 (OH), 2922, 2840, 1638, 1454, 1352, 1180, 1095 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.70 (1H, d, *J*=5.2 Hz, H-14β), 4.02 (1H, d, *J*=6.7 Hz, H-6β), 3.66 (1H, d, *J*=5.9 Hz, H-3β), 3.42, 3.29, 3.29, 3.19 (each 3H, s, OCH_3×4), 3.09 (3H, s, SO_2CH_3), 1.05 (3H, t, *J*=7.0 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$), 85.9 (C-14), 82.4 (C-6), 82.4 (C-16), 82.1 (C-1), 77.3 (C-18), 74.8 (C-13), 73.4 (C-8), 71.7 (C-3), 61.2 (C-17), 59.0 (C-18′), 58.0 (C-16′), 57.6 (C-6′), 55.7 (C-1′), 53.2 (C-7), 50.2 (C-11), 48.7 (C-21), 48.5 (C-5), 47.6 (C-9), 47.0 (C-19), 43.1 (C-4), 42.1 (C-15), 41.2 (C-10), 38.4 (14-SO_2CH_3), 35.2 (C-2), 33.5 (C-12), 13.3 (C-22); *m/z* (EI) 561 (3 M^+), 546 (3 M−15), 530 (100% M−31); HRMS (EI): M^+ found 561.2598. $C_{26}H_{43}NO_{10}S$ requires 561.2607.

Compound **4**. White amorphous powder; mp 137–139°C; R_f (50% cyclohexane–acetone) 0.28; $[\alpha]_D^{20}$=+23.1 (*c* 0.38, $CHCl_3$); ν_{max}(KBr) 3420 (OH), 2918, 2840, 1635, 1350, 1178, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.02 (1H, d, *J*=5.1 Hz, H-14β), 3.39, 3.29, 3.29, 3.23 (each 3H, s, OCH_3×4), 3.14, 3.06 (each 3H, s, O_3SCH_3×2), 1.11 (3H, t, *J*=6.9 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$) 90.1 (C-13), 84.1 (C-1), 82.2 (C-6), 82.2 (C-14), 79.9 (C-16), 77.0 (C-18), 72.6 (C-8), 71.5 (C-3), 61.4 (C-17), 59.0 (C-18′), 57.5 (C-16′), 57.0 (C-6′), 55.7 (C-1′), 52.8 (C-7), 50.1 (C-11), 48.9 (C-21), 47.7 (C-5), 47.3 (C-19), 43.3 (C-9), 43.2 (C-4), 41.9 (C-15), 41.5 (C-10), 40.2 (13-SO_2CH_3), 39.1 (14-SO_2CH_3), 34.8 (C-2), 30.0 (C-12), 13.4 (C-22); *m/z* (EI) 639 (2 M^+,) 608 (100%); HRMS (EI): M^+, found 639.2396, $C_{27}H_{45}NO_{12}S_2$, requires 639.2383.

Compound **5**. White amorphous powder; mp 172–173°C; R_f (50% cyclohexane–acetone) 0.61; $[\alpha]_D^{20}$=+9.3 (*c* 0.41, $CHCl_3$). ν_{max} (KBr) 3438 (OH), 2920, 2820, 1640, 1450, 1350, 1180, 1100 cm^{-1}, δ_H (200 MHz, $CDCl_3$) 5.00 (1H, d, *J*=5.1 Hz, H-14β), 4.70 (1H, d, *J*=5.6 Hz, H-3β), 3.37, 3.34, 3.25, 3.22, (each 3H, s, OCH_3×4), 3.13, 3.05, 2.99, (each 3H, s, O_3SCH_3×3), 1.05 (3H, t, *J*=7.1 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$) 90.1 (C-13), 84.0 (C-14), 82.5 (C-16), 81.4 (C-1), 81.0 (C-6), 79.6 (C-3), 72.6 (C-8), 71.0 (C-18), 61.0 (C-17), 58.4 (C-18′), 57.7 (C-16′), 57.0 (C-6′), 56.1 (C-1′), 53.3 (C-7), 49.5 (C-11), 48.8 (C-21), 47.8 (C-5), 47.0 (C-19), 45.8 (C-9), 42.9 (C-4), 41.8 (C-15), 41.1 (C-10), 40.2 (13-SO_2CH_3), 39.1 (14-SO_2CH_3), 37.9 (14-SO_2CH_3), 34.7 (C-2), 33.8 (C-12), 13.4 (C-22); *m/z* (EI) 621 (2 $M^+-CH_3SO_3H$) 606 (100%); HRMS (EI): 717.2186, $C_{28}H_{47}NO_{14}S_3$ requires 717.2158.

To a solution of compound **5** (50 mg, 0.07 mmol) in glacial acetic acid (13 mL) was added water (5 mL). The solution was heated at 130°C for 1 h and basified to pH 11 with NH_4OH solution, and then extracted with $CHCl_3$ (5 mL×3). The combined chloroform solutions were dried over anhydrous Na_2SO_4 and evaporation of the solvent in vacuo gave *compound* **6** (30 mg, 80%) as a white amorphous powder, mp 158–159°C; R_f (50%

cyclohexane–acetone) 0.70; $[\alpha]_D^{20}=+32.0$ (*c* 0.46, $CHCl_3$); ν_{max} (KBr) 3430 (OH), 2920, 2820, 1638, 1450, 1350, 1175, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.99 (1H, dd, *J*=9.7, 3.5 Hz, H-2), 5.79 (1H, d, *J*=9.7 Hz, H-3), 3.38, 3.34, 3.31, 3.30 (each 3H, s, OCH_3×4), 3.14, 3.07 (each 3H, s, CH_3SO_2×2), 1.08 (3H, t, *J*=7.0 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$) 137.6 (C-2), 124.9 (C-3), 89.1 (C-13), 84.3 (C-14), 83.0 (C-16), 81.8 (C-6), 79.9 (C-1), 78.1 (C-18), 74.0 (C-8), 59.2 (C-18′), 58.0 (C-17), 57.7 (C-16′), 57.0 (C-6′), 56.1 (C-1′), 52.6 (C-21), 50.4 (C-7), 48.7 (C-11), 47.6 (C-19), 47.3 (C-5), 47.3 (C-9), 43.5 (C-15), 41.4 (C-10), 40.7 (C-4), 40.2 (3-SO_2CH_3), 39.1 (14-SO_2CH_3), 33.1 (C-12), 12.6 (C-22); *m/z* (EI) 621 (11 M^+), 606 (23 M^+-15), 590 (19% M^+-31); HRMS (EI) 621.2273, $C_{27}H_{43}NO_{11}S_2$ requires 621.2277.

3.1.3. Compounds 7 and 8. To a solution of compound **3** (160 mg, 0.28 mmol) in DMF (10 mL) was added NaOH (30 mg), and the resulting solution heated under reflux at 150°C for 10 h. After work up, the crude reaction mixture was chromatographed on silica gel H (10 g) eluting with cyclohexane–acetone (9:1) to give compounds **7** (95 mg, 70%) and **8** (20 mg, 15%).

Compound **7**. Colorless rhombic crystals; mp 214–215°C; R_f (70% cyclohexane–acetone) 0.36; $[\alpha]_D^{20}=+86.9$ (*c* 0.68, $CHCl_3$); ν_{max} (KBr) 3496 (OH), 2966, 2913, 2871, 2807, 1707 (C=O, six-membered cyclic ketone), 1458, 1103 cm^{-1}; δ_H (400 MHz, $CDCl_3$) and δ_C (100 MHz, $CDCl_3$) see Table 1; NOESY see Fig. 3; *m/z* (EI) 465 (14 M^+), 434 (100% M^+-31); HRMS (EI): 465.2718, $C_{25}H_{39}NO_7$ requires 465.2726; Crystal structure for **7**: a colorless orthorhombic crystal from acetone was mounted

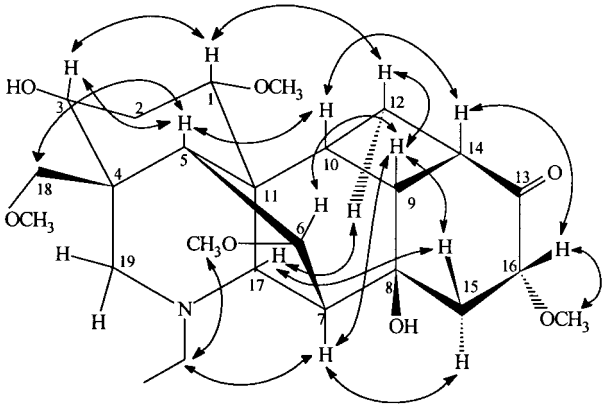


Figure 3. Key NOESY correlations of **7**.

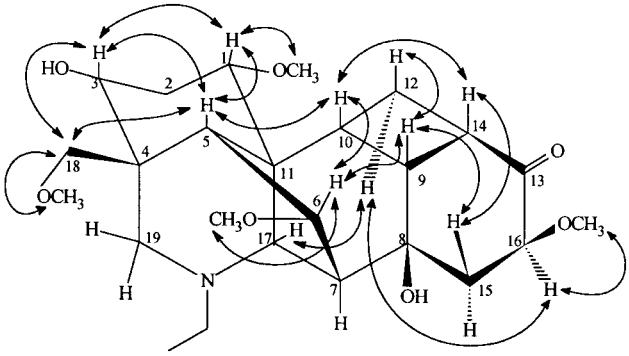


Figure 4. Key NOESY correlations of **8**.

Table 2. ^1H and ^{13}C NMR data of compound **9**

No.	δ_H	Mult (*J*=Hz)	δ_C	HMBC (H→C)	NOESY
1	3.71	m (hidden)	80.6 d	C-2, C-11, C-17	H-3, H-5, H-12β
2	2.17	m (hidden) (β)	33.5 t	C-1, C-3, C-4, C-11	H-12α
	3.14	dd (12.0, 10.0 (α)			
3	3.98	dd (10.0, 5.2)	75.4 d	C-4, C-5, C-19	H-18
4	–		43.5 s	–	–
5	1.90	d (6.4)	47.0 d	C-10, C-11, C-17, C-19	H-1, H-3, H-7, H-18
6	3.72	hidden	91.7 d	C-4, C-7, C-8, C-17, C-6′	H-10, H-18, H-18′
7	3.05	t (8.4)	49.3 d	C-5, C-9, C-11, C-15, C-17	H-5, H-12β
8	–	–	137.3 s	–	–
9	–	–	129.0 s	–	–
10	2.98	br.s (*W*1/2=8.4)	44.4 d	C-5, C-8, C-9, C-11, C-14, C-7	H-1, H-14
11	–		51.3 s	–	–
12	3.73	dd (9.6, 8.4) (α)	73.4 t	C-1, C-9, C-11	H-2, H-17
	4.37	dd (9.6, 8.0) (β)		–	H-1, H-7
13	–		144.0 s	–	–
14	6.59	s	107.4 d	C-8, C-9, C-10, C-13	H-10, H-16′
15	6.52	s	114.1 d	C-7, C-8, C-13, C-16	
16	–		144.7 s	–	–
17	2.98	br.s (*W*1/2=8.4)	66.7 d	C-5, C-6, C-7, C-19, C-21	H-12β, H-6′, H-21
18	3.43	ABq (9.0)	78.4 t	C-3, C-4, C-5, C-18′	H-3, H-5
	3.95	ABq (9.0)		C-3, C-4, C-5, C-18′	H-5, H-6
19	2.46	ABq (12.0)	47.1 t	C-3	H-17
	3.26	ABq (12.0)		C-4, C-5, C-17, C-18	H-21
21	2.48	m (hidden)	48.8 t	C-22	H-17, H-19
22	1.05	t (6.8)	13.1 q	C-21	H-17, H-19
6′	3.35	s	58.0 q	C-6	H-17
16′	3.86	s	55.9 q	C-16	H-14, HO-13
18′	3.35	s	59.3 q	C-18	H_2-18
13-OH	5.83	br.s			H-16′

on a P_4 four circle diffractometer and exposed to graphite-monochromated MoKα irradiation. The unit cell parameters are a=9.160 (2) Å, b=12.862 (2) Å, c=10.307 (10) Å in space group $P2_12_12_1$, of the 3771 measured with $1.98<\theta<27.50°$ scan, 3116 were independently observed at the level of $F_0>4\sigma$ (F_0). The structure was solved by the direct method using the program SHELXTL and the atomic squares on F^2 method. The final R indexes [$I > 2\sigma(I)$] was R^1=0.0375, $WR2$=0.0840.

Compound **8**. White amorphous powder; mp 90–91°C; R_f (70% cyclohexane–acetone) 0.63; $[\alpha]_D^{20}$=+67.0 (*c* 0.41, $CHCl_3$); ν_{max} (KBr) 3407 (OH), 2927, 2854, 2820, 1709 (C=O, six-membered cyclic ketone), 1450, 1100 cm^{-1}; δ_H (400 MHz, $CDCl_3$) and δ_C (100 MHz, $CDCl_3$) see Table 4; NOESY see Fig. 4; *m/z* (EI) 465 (8 M^+), 434 (85 M^+-31), 422 (90%); HRMS (EI): 465.2705, $C_{25}H_{39}NO_7$ requires 465.2726.

3.1.4. Compounds 9 and 10. To a solution of compound **7** (270 mg, 0.58 mmol) in glacial acetic acid (10 mL), was added Br_2 (0.035 mL, 0.68 mmol) in HOAc (3 mL) dropwise and the solution was stirred at room temperature for 1.5 h. After basifying to pH>9 with the NH_4OH solution was extracted with $CHCl_3$ (15 mL×5) and the combined chloroform solutions were dried over anhydrous Na_2SO_4. Evaporation in vacuo afforded a residue (255 mg) that was separated on a column (silica gel H 10 g) eluting with hexane–acetone (5:1) to afford **9** (100 mg, 40%) and **10** (24 mg, 10%).

Compound **9**. White amorphous powder; mp 134.5–136°C; R_f (70% cyclohexane–acetone) 0.39; $[\alpha]_D^{20}$=+140.0 (*c* 0.35, $CHCl_3$); ν_{max} (KBr) 3420 (OH), 2920, 2840, 1620, 1590, 1510, 1450, 1100 cm^{-1}; δ_H (400 MHz, $CDCl_3$) and δ_C (100 MHz, $CDCl_3$) see Table 2; *m/z* (EI) 432 (40 M^++1), 416 (43 M^+-15), 400 (100% M^+-31); HRMS (EI): 431.2335, $C_{24}H_{33}NO_6$ requires 431.2307).

Compound **10**. White amorphous powder; mp 185–186°C; R_f (70% cyclohexane–acetone) 0.20; $[\alpha]_D^{20}$=+132.0 (*c* 0.37, EtOH); ν_{max} (KBr) 3405 (OH), 3220 (OH), 2920, 2880, 2830, 1620, 1608, 1515, 1460, 1100 cm^{-1}; δ_H (200 MHz, C_5D_5N) 7.04, 6.84 (each 1H, s, Ar–H), 4.29 (1H, dd, J=15.6, 9.6 Hz, H-12β), 3.21, 3.17 (each 3H, s, OCH_3×2), 0.81 (3H, t, J=7.1 Hz, NCH_2CH_3); δ_C (50 MHz, C_5D_5N) see Table 3; *m/z* (EI) 417 (49 M^+), 402 (38 M^+-15), 386 (100% M^+-31); HRMS (EI) 417.2150, $C_{23}H_{31}NO_6$ requires 417.2151.

3.1.5. Acetylation of 9: compounds 11 and 12. To a solution of compound **9** (120 mg, 0.27 mmol) in pyridine (5 mL), acetic anhydride (0.5 mL, 4.5 mmol) was added and the solution was stirred at room temperature for 20 h, and then evaporated to dryness under reduced pressure to give a residue (159 mg) that was separated on a column (silica gel H, 5 g) eluting with hexane–acetone (6:1) to afford the compounds **11** (55 mg, 42%) and **12** (82 mg, 57%).

Compound **11**. White amorphous powder; mp 137–138°C; *R*f (70% cyclohexane–acetone) 0.46; $[\alpha]_D^{20}$=+121.4 (*c* 0.70, $CHCl_3$); ν_{max} (KBr) 3420 (OH), 2920, 2860, 1760 (COO), 1615, 1502, 1450, 1200, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.66, 6.61 (each 1H, s, Ar–H), 4.33 (1H, dd, J=9.8, 8.2 Hz, H-12β), 3.78, 3.31, 3.30 (each 3H, s, OCH_3×3), 2.25 (3H, s, OAc), 1.03 (3H, t, J=7.2 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$) see Table 3; *m/z* (EI) 473 (59 M^+), 458 (42 M^+-15), 442 (100 M^+-31), 430 (18), 400 (24%); HRMS (EI) 473.2408, $C_{26}H_{35}NO_7$ requires 473.2413.

Table 3. ^{13}C NMR data of compounds **10**, **11**, **12** and **13**

No.	**10**	**11**	**12**	**13**
1	81.2 d	80.4 d	79.8 d	79.6 d
2	35.1 t	33.4 t	30.3 t	33.4 t
3	70.7 d	75.2 d	72.6 d	74.9 d
4	44.5 s	43.5 s	42.6 s	43.4 s
5	45.5 d	46.9 d	45.1 d	46.4 d
6	92.9 d	91.0 d	91.3 d	91.8 d
7	49.8 d	48.9 d	48.8 d	50.7 d
8	138.3 s	137.9 s	137.8 s	138.8 s
9	128.1 s	128.6 s	128.6 s	129.6 s
10	44.4 d	44.8 d	44.4 d	44.8 d
11	51.9 s	51.2 s	51.1 s	52.2 s
12	73.2 t	73.3 t	73.5 t	72.6 t
13	145.1 s	144.4 s	144.3 s	141.3 s
14	116.4 d	122.1 d	122.1 d	110.9 s
15	113.0 d	109.0 d	109.0 d	106.9 d
16	145.4 s	149.1 s	149.0 s	145.0 s
17	70.7 d	66.3 d	66.2 d	65.8 d
18	74.0 t	78.1 t	71.9 t	78.1 t
19	47.8 t	47.0 t	47.7 t	47.0 t
21	49.1 t	48.8 t	48.8 t	48.8 t
22	13.2 q	13.0 q	12.9 q	13.0 q
6′	58.0 q	58.1 q	58.3 q	58.1 q
16′	–	55.9 q	55.8 q	56.3 q
18′	58.7 q	59.2 q	58.9 q	59.2 q
3-OAc	–	–	169.9 s	–
			21.0 q	
13-OAc	–	169.0 s	168.9 s	–
		20.5 q	20.5 q	–

Compound **12**. Colorless rhombic crystals (95% EtOH); mp 201–202°C; R_f (70% cyclohexane–acetone) 0.52; $[\alpha]_D^{20}$=+123.6 (*c* 0.44, $CHCl_3$); ν_{max} (KBr) 3060, 2928, 2868, 2835, 1755, 1740, 1620, 1508, 1450, 1380, 1250, 1230, 1210, 1120, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.66, 6.59 (each 1H, s, Ar–H), 5.12 (1H, dd, J=11.4, 5.0 Hz, H-3β), 4.32 (1H, dd, J=10.0, 8.2 Hz, H-12β), 3.77, 3.30, 3.19 (each 3H, s, OCH_3×3), 2.24, 2.05 (each 3H, s, OAc×2), 1.01 (3H, t, J=7.1 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$) see Table 3; *m/z* (EI) 515 (60 M^+), 500 (35 M^+-15), 484 (100 M^+-31), 473 (15), 456 (14), 442 (22%); HRMS (EI) 515.2501, $C_{28}H_{37}NO_8$ requires 515.2519; crystal structure for **12**: a colorless orthorhombic crystal from 95% EtOH was mounted on the same instrument and method as **7**. The unit cell parameters are a=8.3730 (10) Å, b=17.916 (2) Å, c=17.934 (2) Å in space group $P2_12_12_1$, of the 3522 measured with $1.61<\theta<26.01°$ scan, 3337 were independently observed at the level of $F_0>4\sigma$ (F_0). The final R indices [$I > 2\sigma(I)$] was R^1=0.0375, $WR2$=0.0703.

3.1.6. Compound 13. To a solution of compound **7** (110 mg, 0.23 mmol) in glacial acetic acid (5 mL), was added Br_2 (0.025 mL, 0.48 mmol) in HOAc (2 mL) dropwise and the solution was stirred at room temperature for

Table 4. NMR data for compounds **8** and **14**

No.	**8**				**14**
	δ_H	Mult (J=Hz)	δ_C	HMBC (H→C)	δ_C
1	3.09	dd (10.8, 7.2)	81.0 d	C-3, C-10, C-11, C-17, C-1′	81.0 d
2	2.21	m (hidden) (α)	34.3 t	C-1, C-3, C-4	34.0 t
	2.51	m (hidden) (β)		C-1, C-3, C-4	
3	3.70	dd (12.4, 4.4)	72.0 d	C-2, C-18, C-19	71.7 d
4	–	–	42.4 s	–	42.3 s
5	1.79	d (6.4)	47.6 d	C-4, C-7, C-10, C-11, C-17, C-18	50.5 d
6	4.03	dd (6.4, 1.6)	82.9 d	C-4, C-7, C-8, C-6′, C-17	82.9 d
7	2.03	d (2.0)	50.3 d	C-5, C-6, C-8, C-15, C-17	50.5 d
8	–	–	72.7 s	–	73.4 s
9	2.91	dd (9.6, 6.4)	46.8 d	C-8, C-11, C-13	59.5 d
10	2.37	m (hidden)	44.3 d	C-8, C-9, C-12	41.7 d
11	–	–	47.8 s	–	47.2 s
12	2.37	m (hidden) (α)	31.3 t	C-1, C-11, C-13	40.9 t
	2.53	m (hidden) (β)		C-9, C-10, C-16	
13	–	–	208.7 s	–	203.2 s
14	2.93	dd (9.6, 6.4)	36.3 d	C-8, C-10, C-12, C-13	47.4 s
15	2.44	m (hidden)	37.5 t	C-8, C-9, C-16	37.7 t
16	3.59	d (3.2)	80.7 d	C-8, C-13. C-16′	80.4 d
17	3.23	br.s	61.5 d	C-5, C-6, C-8, C-10, C-11	61.4 d
18	3.60	ABq (8.8)	76.9 t	C-5, C-18′	76.5 t
	3.84	ABq (8.8)		C-3, C-4, C-5, C-18′	
19	2.25	ABq (11.2)	46.9 t	C-3, C-4, C-18, C-21	47.0 t
	3.00	ABq (11.2)		C-3, C-21	
21	2.44	m (hidden)	48.7 t	C-22	48.8 t
22	1.08	t (7.1)	13.1 q	C-21	13.0 q
1′	3.18	s	55.8 q	C-1	55.7 q
6′	3.36	s	57.7 q	C-6	57.9 q
16′	3.34	s	58.1 q	C-16	58.6 q
18′	3.31	s	59.1 q	C-18	59.0 q

2 h, and then after being basified to pH>9 with saturated aqueous Na_2CO_3 the solution was extracted with chloroform (15 mL×5). The combined chloroform solutions were dried over anhydrous Na_2SO_4, and then evaporation in vacuo afforded a residue that was chromatographed on a column (Si gel 5 g) eluting with cyclohexane–acetone (6:1) to give **13** as a white amorphous powder (30 mg, 29%); mp 287–288°C; R_f (70% cyclohexane–acetone) 0.53; $[\alpha]_D^{20}$=+143.9 (*c* 0.90, $CHCl_3$); ν_{max} (KBr) 3432 (OH), 2938, 2860, 1610, 1570, 1490, 1470, 1450, 1110 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.55 (1H, s, H-15), 5.96 (1H, brs, exchangeable in D_2O, HO-13), 4.72 (1H, t, J=9.2 Hz, H-12β), 3.86 (3H, s, aromatic methoxyl), 3.30, 3.28 (each 3H, s, OCH_3×2), 1.04 (3H, t, J=7.1 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$) see Table 3; *m/z* (EI) 511 (51 M_1^+), 509 (53 M_2^+), 496 (56 M_1-15), 494 (57 M_2-15), 480 (10 M_1-31), 478 (15 M_2-31), 431 (58), 416 (29), 400 (100%); HRMS (EI): 509.1361 (M_2^+), $C_{24}H_{32}NO_6Br$ requires 509.1413.

3.1.7. Compounds 9 and 14. To a solution of compound **8** (176 mg, 0.38 mmol) in HOAc (7 mL), was added Br_2 (0.023 mL, 0.45 mmol) in HOAc (2 mL) dropwise and the solution was stirred at room temperature for 1 h. After being basified to pH>9 with saturated Na_2CO_3, the solution was extracted with chloroform (10 mL×5). The combined chloroform solutions were dried over anhydrous Na_2SO_4, and evaporated in vacuo to give a residue (172 mg) that was chromatographed on a column (silica gel H, 6 g) eluting with cyclohexane–acetone (6:1) to give **9** (62 mg, 38%) and **14** (42 mg, 25%).

Compound **14**. White amorphous powder; mp 130–131°C; R_f (70% cyclohexane–acetone) 0.70; $[\alpha]_D^{20}$=+10.3 (*c* 0.42, $CHCl_3$). ν_{max} (KBr) 3500 (OH), 2930, 2820, 1725, 1635, 1450, 1100 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.44 (1H, brs, exchangeable in D_2O, OH), 3.90 (1H, dd, J=6.4, 2.0 Hz, H-6β), 3.80, 3.54 (each 1H, ABq, J=9.0 Hz, H_2-18), 3.39, 3.32, 3.27, 3.14 (each 3H, s, OCH_3×4), 1.04 (3H, t, J=7.0 Hz, NCH_2CH_3); δ_C (50 MHz, $CDCl_3$) see Table 4; *m/z* (EI) 545 (14 M_1^+), 543 (14 M_2^+), 530 (15 M_1-15), 528 (17 M_2-15), 514 (100 M_1-31), 512 (100 M_2-31), 434 (87%); HRMS (EI) 543.1814 (M_2^+), $C_{25}H_{38}NO_7Br$ requires 543.1831.

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