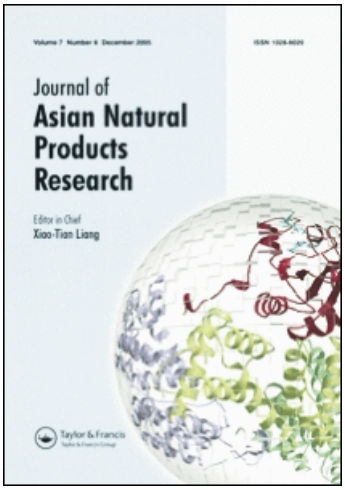

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Further studies on the synthesis of 7,17-*Seco* norditerpenoid alkaloids

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FURTHER STUDIES ON THE SYNTHESIS OF 7,17-*SECO* NORDITERPENOID ALKALOIDS

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Following the report on the synthesis of the 7,17-*seco* compounds [Wang, F.P., Yang, J.S., Chen, Q.H., Yu, L. and Li, B.G. (2000), *Chem. Pharm. Bull.* **48**, 1912–1916], further studies on the reaction optimization for cleavage of the C(7),C(17) bond led to the 7,17-*seco* norditerpenoid alkaloids (e.g. **4**, **9**) in nearly 90% yield.

Keywords: Norditerpenoid alkaloid; 7,17-*seco* Norditerpenoid alkaloid; Fragmentation; Biological activity

INTRODUCTION

The norditerpenoid alkaloids are a group of highly oxygenated complex natural products displaying a lot of interesting chemical reactions [1] and important biological activities [2,3], and are therefore a synthetic or structurally modified target. In the course of this investigation, we have reported a series of structural modifications of the norditerpenoid alkaloids [4–6]. Herein, we describe in detail the highly efficient synthesis of the 17,7-*seco* norditerpenoid alkaloids that are key compounds for the evaluation of biological activities.

RESULTS AND DISCUSSION

As previously mentioned, although the cleavage of the C(17)–C(7) bond of the norditerpenoid alkaloids has already been reported before 2000 [1], most of the reactions led to complicated products with low yields [7,8] or difficult purification [9]. Recently, we reported a new method for the synthesis of the 7,17-*seco* norditerpenoid alkaloids *via* reduction of the corresponding 8-chloro derivatives in moderate yields (46–60%) [4].

Mechanistically, there are at least two reaction processes in pathways a or b (Scheme 1). As for these moderate yields, we rationalized that reactivity toward nucleophilic attack of methanol enhanced the formation of **A** in pathway b but decreased the yields of the 7,17-*seco* compounds in pathway a (Scheme 1).

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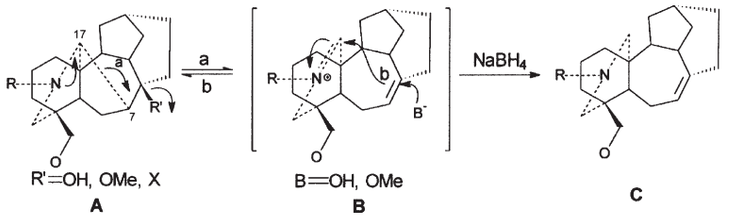


SCHEME 1

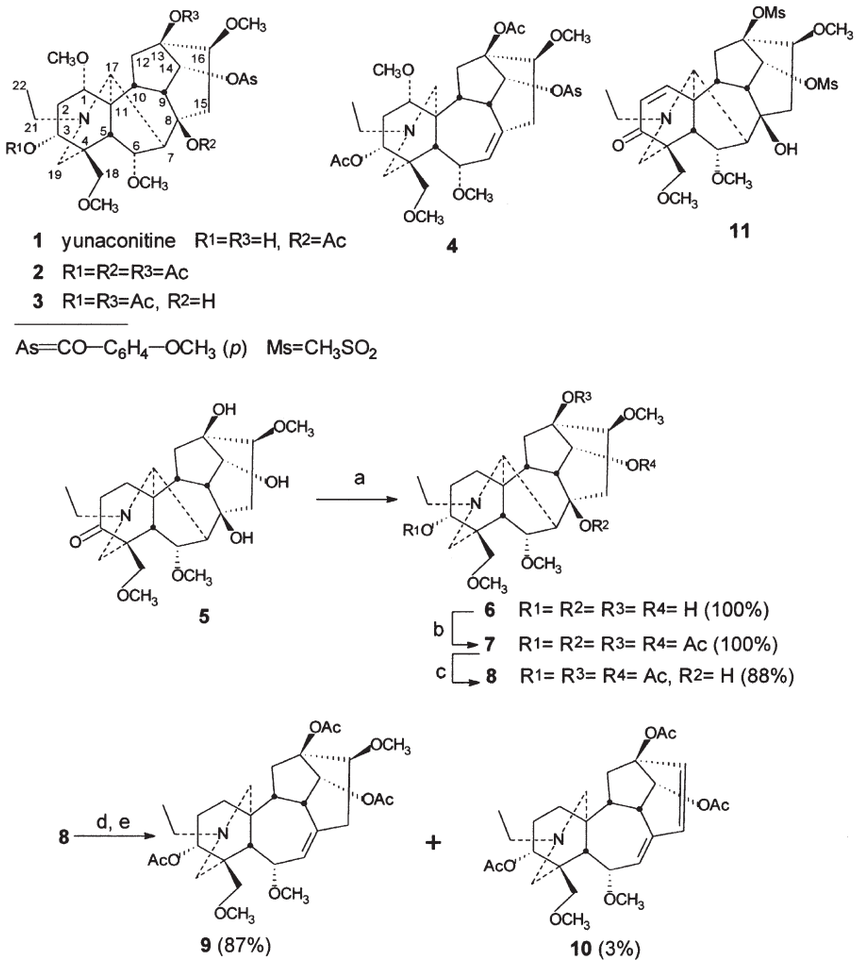
To gain mechanistic understanding of the reaction, we reinvestigated the cleavage of the C(7)−C(17) bond of the norditerpenoid alkaloids *via* a method developed by us [4]. Compound **3** [4] was prepared from the starting material yunaconitine (**1**)[†] via **2** [4] in two steps (82% overall yield). According to this method [4], one-pot treatment of **3** in anhydrous benzene with $SOCl_2$ at room temperature overnight followed by evaporation to dryness afforded a residue, which, in anhydrous THF instead of CH_3OH, reacted with $NaBH_4$ at room temperature for 4.5 h to give **4** in 81% yield. Similarly, the 7,17-*seco* norditerpenoid alkaloids without 1α-methoxy group (**9**) as the major product (87%), and **10** were synthesized from **8**, which was obtained from **5** in three steps (Scheme 2). The MS (EI and HREIMS) of both compounds **9** and **10** showed their molecular ions at *m/z* 563 and 531 corresponding to the formulae $C_{30}H_{45}NO_9$ and $C_{29}H_{41}NO_8$, respectively. The NMR spectra of **9** showed the presence of three methoxyl groups (δ_H 3.21, 3.33, 3.34; δ_C 55.9 q, 57.6 q, 58.8 q), three acetyl groups (δ_H 2.05, 2.06, 2.10; δ_C 170.2 s, 170.5 s, 170.6 s; 21.2 q, 21.4 q, 21.5 q), an *N*-ethyl group (δ_H 0.98 t, $J = 7.2$ Hz; δ_C 51.9 t, 13.4 q), and a trisubstituted double bond (δ_H 5.66, brs; δ_C 127.1 d, 131.9 s). Its structure could be determined easily by comparison of spectral data with the known 7,17-*seco* alkaloid **4** [4]. In comparison to the NMR spectra of **9**, those of compound **10** exhibited the presence of an additional conjugated double bond (δ_H 5.58, $J = 5.8$ Hz; 5.59 d, $J = 9.6$ Hz; 6.24 d, $J = 9.6$ Hz; δ_C 125.3 d, 135.4 s, 128.5 d, 129.4 d) and the absence of a methoxyl group, leading us to assign its structure as **10**. However, further investigation showed that the 7,17-*seco* norditerpenoid alkaloids bearing an α,β-unsaturated ketone from **11**[‡] cannot be obtained under similar reaction conditions. This implies that the α,β-unsaturated unit of the A ring, instead of the 1α-methoxyl group, was unfavorable for the cleavage of the C(17)−C(7) bond, in addition to the solvent factors.

EXPERIMENTAL SECTION

General Experimental Procedure

Melting points are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter. ^1H and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or a Varian INOVA-400/54 spectrometer. MS spectra were obtained with a VG Auto-spec 3000 mass spectrometer. Column chromatography was carried out on silica gel H (10−40 μm). All of the silica gel GF_{254} and silica gel H were purchased from Qingdao Sea Chemical Factory, China.

[†]Yunaconitine (**1**) was purchased from Kunming Institute of Botany, China.
[‡]The preparation of **11** was carried out according to the literature [10].



SCHEME 2

3α,13-Diacetylyunaconitine (2)

To a solution of yunaconitine (**1**) (200 mg, 0.30 mmol) in Ac_2O (6 ml), TsOH (213 mg) was added and the solution was heated at 60°C for 6 h followed by pouring into ice–water. Basification (NH_4OH, pH = 11), extraction ($CHCl_3$, 15 ml × 3), drying (Na_2SO_4) and removal of solvent afforded the product as a white amorphous powder, 220 mg (97%), which was identified by comparison of its TLC (silica gel GF_{254}, R_f 0.70, cyclohexane/acetone = 1 : 1) with that of an authentic sample.

Compound 3

A solution of 3α,13-diacetylyunaconitine (**2**) (253 mg, 0.33 mmol) in diglyme/H_2O (4:1, v/v) (7 ml) was refluxed for 12 h. Evaporation *in vacuo* and column chromatography (silica gel H: 8 g, $CHCl_3$/MeOH = 95 : 5) afforded the product as a white amorphous powder, 210 mg

(88%), which was identified by comparison of its TLC (silica gel GF_{254}, R_f 0.15, chloroform/acetone = 9 : 1) with that of an authentic sample.

Compound 4

A mixture of compound **3** (51 mg, 0.072 mmol), anhydrous benzene (2 ml) and $SOCl_2$ (0.05 ml) was stirred at room temperature overnight. Evaporation *in vacuo* to dryness gave a residue, to which $NaBH_4$ (51 mg) in THF (2 ml) was added and the solution was allowed to stand at room temperature for 5 h. Removal of solvent, dilution with H_2O (8 ml), extraction ($CHCl_3$, 8 ml × 4), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, $CHCl_3$/MeOH = 100 : 1) afforded the pure product as a white amorphous powder, 40 mg (81%), which was identified by comparison of its TLC (silica gel G, R_f 0.56, cyclohexane/acetone = 1 : 1) with that of an authentic sample.

Compound 5

To a solution of yunaconitine (**1**) (1066 mg, 1.62 mmol) in acetone (20 ml), Jones's reagent (1.75 ml, 4.85 mmol) was added dropwise in an ice–water bath. Next, the reaction solution was stirred at 0°C for 20 min. Dilution with H_2O (20 ml), basification (NH_4OH, pH = 11), extraction ($CHC1_3$, 20 ml × 5), drying (Na_2SO_4), and removal of solvent afforded the residue (1063 mg), which was dissolved in 5% NaOH methanol (25 ml) and the solution was heated at 55°C for 30 min. Removal of solvent, dilution with H_2O, extraction ($CHCl_3$, 10 ml × 5), drying (Na_2SO_4), removal of solvent afforded a white amorphous powder (726 mg, 100%). A mixture of the above-mentioned white powder (100 mg, 0.22 mmol) in 95% EtOH (5 ml) and 10% Pd–C (18 mg) in 95% EtOH (5 msl) was hydrogenated under hydrogen gas at room temperature for 5.5 h. After filtration, removal of solvent and crystallization (95% EtOH) afforded the product as colorless needle crystals, 102 mg (98%). mp 157.5–158°C; $[\alpha]_D^{20}$ − 91.8 (*c* 0.98, $CHCl_3$); R_f 0.45 ($CHCl_3$/MeOH = 9 : 1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (3H, t, J = 7.2 Hz, NCH_2CH_3), 3.09, 3.26, 3.31 (each 3H, s, 3 × OCH_3), 3.72, 4.03, 4.82 (each 1H, brs, 3 × OH), 4.13 (1H, d, J = 6.4 Hz, H-6β); ^{13}C NMR (100 MHz, DMSO-d_6) see Table I; EIMS *m/z* (%) 451 (M^+, 97), 436 (M − 15, 86), 420 (M − 31, 59), 391 (42), 376 (62), 360 (48); HREIMS *m/z* calcd for $C_{24}H_{37}NO_7$ (M^+) 451.2570, found 451.2563.

Compound 6

A mixture of compound **5** (100 mg, 0.22 mmol) in MeOH (3 ml) and $NaBH_4$ (110 mg) was stirred at room temperature for 30 min. Removal of solvent afforded the product as white amorphous powder, 104 mg (100%). $[\alpha]_D^{20}$ + 15.1 (*c* 1.06, $CHCl_3$); R_f 0.38 ($CHCl_3$/MeOH = 9 : 1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.09 (3H, t, J = 7.2 Hz, NCH_2CH_3), 3.32 (6H, s, 2 × OCH_3), 3.42 (3H, s, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) see Table I; EIMS *m/z* (%) 453 (M^+, 100), 438 (M − 15, 91), 422 (M − 31, 28), 409 (29), 390 (52); HREIMS *m/z* calcd for $C_{24}H_{39}NO_7$ (M^+) 453.2726, found 453.2743.

Compound 7

A mixture of 1-demethoxypseudaconine (**6**) (104 mg, 0.23 mmol) in Ac_2O (4 ml) and TsOH (110 mg) was heated at 60°C for 3 h. After this, the reaction solution was poured into ice water and basification (NH_4OH, pH = 11), extraction ($CHCl_3$, 10 ml × 3), drying (Na_2SO_4), removal of solvent and crystallization (MeOH) afforded the product as colorless needle crystals, 150 mg (100%). mp 179–180°C; $[\alpha]_D^{20}$ + 11.9 (*c* 1.01, $CHCl_3$); R_f 0.75

TABLE I ^{13}C NMR data of compounds **5**–**10**

Number	Compound **5**	Compound **6**	Compound **7**	Compound **8**	Compound **9**	Compound **10**
1	24.7 t	28.9 t	25.9 t	25.9 t	27.8 t	24.6 t
2	38.9 t	29.1 t	28.6 t	28.6 t	38.4 t	36.8 t
3	216.7 s	74.9 d	74.2 d	74.8 d	74.8 d	74.5 d
4	52.5 s	43.0 s	42.1 s	42.2 s	42.8 s	43.9 s
5	43.8 d	49.3 d	46.7 d	46.9 d	47.6 d	43.1 d
6	82.3 d	82.5 d	80.1 d	79.4 d	80.2 d	75.0 d
7	52.4 d	52.0 d	42.7 d	44.9 d	127.1 d	125.3 d
8	74.0 s	73.9 s	85.6 s	74.5 s	131.9 s	135.4 s
9	48.3 d	49.1 d	48.3 d	53.9 d	53.9 d	42.8 d
10	40.5 d	41.4 d	40.9 d	41.9 d	40.7 d	39.9 d
11	45.2 s	45.7 s	46.0 s	46.1 s	37.5 s	38.6 s
12	38.4 t	37.2 t	37.1 t	37.2 t	37.2 t	29.0 t
13	76.2 s	76.5 s	81.1 s	82.0 s	83.9 s	83.1 s
14	78.3 d	79.1 d	77.0 d	77.4 d	79.3 d	81.4 d
15	43.5 t	43.0 t	39.7 t	42.8 t	44.7 t	128.5 d
16	83.3 d	83.1 d	83.7 d	83.4 d	82.9 d	129.4 d
17	64.3 d	64.5 d	63.2 d	68.7 d	57.0 t	54.2 d
18	75.6 t	77.6 t	71.7 t	72.0 t	72.2 t	73.7 t
19	47.8 t	48.8 t	48.8 t	48.8 t	50.7 t	50.7 t
21	52.9 t	47.1 t	47.5 t	47.8 t	51.9 t	51.2 t
22	13.1 q	13.5 q	13.3 q	13.4 q	13.4 q	11.7 q
6′	57.5 q	57.4 q	57.7 q	57.8 q	55.9 q	57.7 q
16′	58.3 q	57.9 q	57.7 q	57.9 q	57.6 q	–
18′	58.7 q	59.1 q	58.1 q	58.8 q	58.8 q	58.1 q
OAc	–	–	169.4 s	170.2 s	170.2 s	170.3 s
	–	–	170.3 s	170.4 s	170.5 s	170.4 s
	–	–	170.5 s	170.6 s	170.6 s	170.9 s
	–	–	170.5 s	–	–	–
	–	–	21.0 q	21.1 q	21.2 q	21.2 q
	–	–	21.1 q	21.2 q	21.4 q	21.2 q
	–	–	21.1 q	21.3 q	21.5 q	21.5 q
	–	–	22.1 q	–	–	–

($CHCl_3$/MeOH = 9 : 1); ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (3H, t, $J = 7.0$ Hz, NCH_2CH_3), 1.97, 2.01, 2.06, 2.09 (each 3H, s, 4 × OAc), 3.20, 3.25, 3.32 (each 3H, s, 3 × OCH_3), 4.88 (1H, d, $J = 5.2$ Hz, H-14β), 4.95 (1H, d, $J = 5.4$ Hz, H-3β); ^{13}C NMR (50 MHz, $CDCl_3$) see Table I; EIMS *m/z* (%) 621 (M^+, 13), 606 (M − 15, 6), 590 (M − 31, 2), 578 (M − 43, 7), 562 (M − 59, 100); HREIMS *m/z* calcd for $C_{32}H_{47}NO_{11}$ (M^+) 621.3149, found 621.3112.

Compound 8

A solution of compound **7** (910 mg, 1.46 mmol) in diglyme/H_2O (4:1, v/v) (25 ml) was refluxed at 140°C for 12 h. Removal of solvent and column chromatography (silica gel H, cyclohexane/acetone = 2 : 1) afforded the pure product as a white amorphous powder, 763 mg (88%). $[\alpha]_D^{20} + 77.7$ (*c* 1.03, $CHCl_3$); R_f 0.56 (cyclohexane/acetone = 1 : 1); ^1H NMR (200 MHz, $CDC1_3$): δ 1.07 (3H, t, $J = 7.2$ Hz, NCH_2CH_3), 2.01, 2.01, 2.09 (each 3H, s, 3 × OAc), 3.18, 3.26, 3.29 (each 3H, s, 3 × OCH_3), 4.02 (1H, d, $J = 6.6$ Hz, H-6β), 4.89 (1H, dd, $J = 12.2$, 5.2 Hz, H-3β), 5.02 (1H, d, $J = 5.0$ Hz, H-14β); ^{13}C NMR (50 MHz, $CDCl_3$) see Table I; EIMS *m/z* (%) 579 (M^+, 24), 564 (M − 15, 12), 548 (M − 31, 6), 536 (M − 43, 11), 520 (M − 59, 100); HREIMS *m/z* calcd for $C_{30}H_{45}NO_{10}$ (M^+) 579.3043, found 579.3020.

Compounds 9 and 10

To a solution of compound **8** (734 mg, 1.26 mmol) in anhydrous benzene (25 ml), $SOCl_2$ (1 ml) was added dropwise and the solution was stirred at room temperature overnight. Removal of solvent gave a residue, to which was added $NaBH_4$ (600 mg) in THF (50 ml) and the solution was heated at 50°C for 6 h. Evaporation, dilution (H_2O, 30 ml), extraction ($CHCl_3$, 30 ml × 4), drying (Na_2SO_4), removal of solvent and column chromatography (silica gel H, cyclohexane/acetone = 3 : 1) afforded the products **9** (white amorphous powder, 620 mg, 87%) and **10** (white amorphous powder, 21 mg, 3%); **9**: $[\alpha]_D^{20}$ − 16.7 (*c* 0.84, $CHCl_3$); R_f 0.71 (cyclohexane/acetone = 1 : 1); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.98 (3H, t, J = 7.2 Hz, NCH_2CH_3), 2.05, 2.06, 2.10 (each 3H, s, 3 × OAc), 3.21, 3.33, 3.34 (each 3H, s, 3 × OCH_3), 4.00 (1H, d, J = 1.2 Hz, H-6β), 4.99 (1H, dd, J = 11.2, 4.6 Hz, H-3β), 5.03 (1H, brs, W1/2 = 4.6 Hz, H-14β), 5.66 (1H, brs, W1/2 = 4.6 Hz, H-7); ^{13}C NMR (50 MHz, $CDCl_3$) see Table I; EIMS *m/z* (%) 563 (M^+, 49), 548 (M − 15, 38), 532 (M − 31, 29), 520 (M − 43, 45), 504 (M − 59, 100); HREIMS *m/z* calcd for $C_{30}H_{45}NO_9$ (M^+) 563.3094, found 563.3055; **10**: $[\alpha]_D^{20}$ + 23.5 (*c* 0.68, $CHCl_3$); R_f 0.63 (cyclohexane/acetone = 7 : 3); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.04 (3H, t, J = 7.2 Hz, NCH_2CH_3), 2.02, 2.05, 2.06 (each 3H, s, 3 × OAc), 3.23, 3.30 (each 3H, s, 2 × OCH_3), 4.90 (1H, dd, J = 11.4, 5.8 Hz, H-3β), 5.06 (1H, d, J = 4.0 Hz, H-14β), 5.58 (1H, d, J = 5.8 Hz, H-7), 5.59 (1H, d, J = 9.6 Hz, H-15), 6.24 (1H, d, J = 9.6 Hz, H-16); ^{13}C NMR (50 MHz, $CDCl_3$) see Table I; EIMS *m/z* (%) 531 (M^+, 73), 516 (M − 15, 32), 488 (M − 43, 78), 472 (M − 59, 100); HREIMS *m/z* calcd for $C_{29}H_{41}NO_8$ (M^+) 531.2832, found 531.2780.

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