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A novel approach to the taxane ABC ring system through chemical conversion from C_{19}-diterpenoid alkaloid deltaline

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Dedicated to venerated Professor Xiao-Tian Liang on the occasion of his 85th birthday

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ABSTRACT

A novel approach to the highly functionalized taxane ABC ring system through chemical conversion of the C_{19}-diterpenoid alkaloid deltaline (**1**) was achieved in six steps (**1**→**17**) in 18% overall yield mainly by Grob fragmentation, fission of the $\Delta^{9(14)}$ double bond, followed by aldol condensation, and Pelletier's cleavage process.

1. Introduction

In spite of some remarkable successes, including six total syntheses[1] and a plethora of ingenious synthetic designs, the convenient practical assembly of the full-functionalized taxane core structure or the synthesis of structurally simplified analogs, remains a significant challenge, and substantial excellent studies are still in progress.

Numerous methods to synthesize the ABC system of the taxoid nucleus have been published,[2] among which the most important is to construct simultaneously the BC ring, following the completion of A ring. However, a method to derive the taxoid core nucleus from natural products using the C_{19}-diterpenoid alkaloids as the starting material was not reported previously. On the other hand, whereas the structure–activity relationships of the taxoids, e.g., paclitaxel, are well studied,[3] there is no information available for the simplified nor-taxoids without the methyl groups at C-8, C-12, and C-15, and this attracted our attention. Obviously, this study may form the basis for searching for more active taxoids with lower toxicity.

The diterpenoid alkaloids are a group of highly oxygenated, complex natural products displaying a plethora of interesting chemistry.[4] They were isolated mainly from *Aconitum* and *Delphinium* plants (Ranunculaceae) as rich sources.[5] During the course of studies on the development of a novel method for the construction of the unique taxane tricyclo[9.3.1.$0^{3,8}$]pentadecane nucleus based on the chemical conversion of C_{19}-diterpenoid alkaloids, as early as 1994, we initiated a decade long research program using yunaconitine, a C_{19}-diterpenoid alkaloid, as the starting material according to the strategy shown in Scheme 1.[6] Though repetitive studies were conducted, substantial success was not achieved. After a long search, it became apparent that deltaline (**1**) could be isolated from *Delphinium bonvalotii* Franch. on the kilogram scale, and thus we designed two strategies to convert deltaline (**1**) to taxane-like compounds according to Scheme 2, but these attempts also failed.[7] Based on these studies, we now present an alternative strategy, depicted in Scheme 3, which represents a novel construction of the unique taxane ABC system core. As shown in Scheme 3, after the O-demethylation and selective mesylation (path a), the mesylate (A) was subjected to Grob fragmentation (path b) to give the olefin B, followed by fission of the C(9)–C(14) double bond leading to the key intermediate C (path c). Subsequent aldol condensation–acetalation (path d) of C furnished hemiacetal D. Finally, protection using CH_3I–NaH (path e), followed

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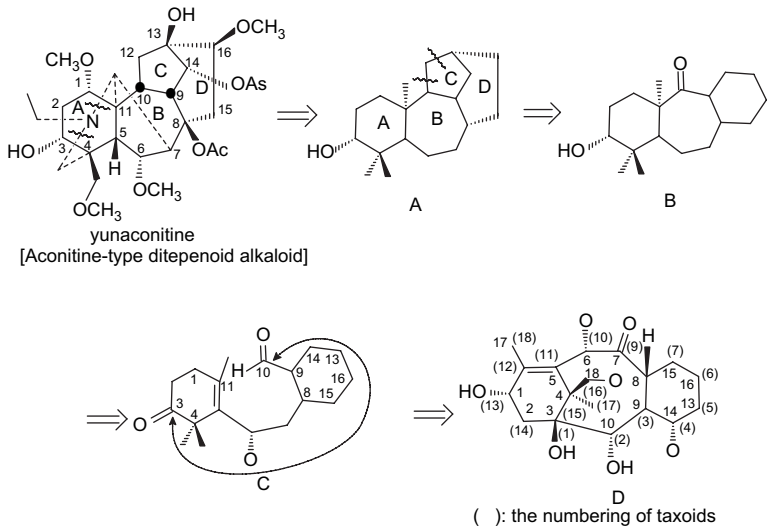
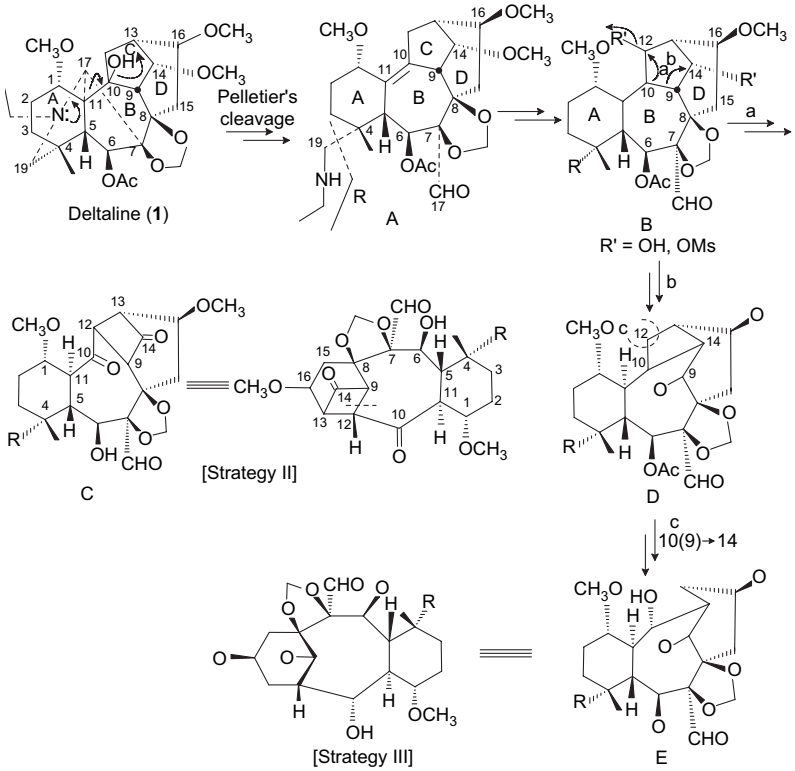


Scheme 1. Approach to the taxane-like ABC system from yunaconitine by strategy I.

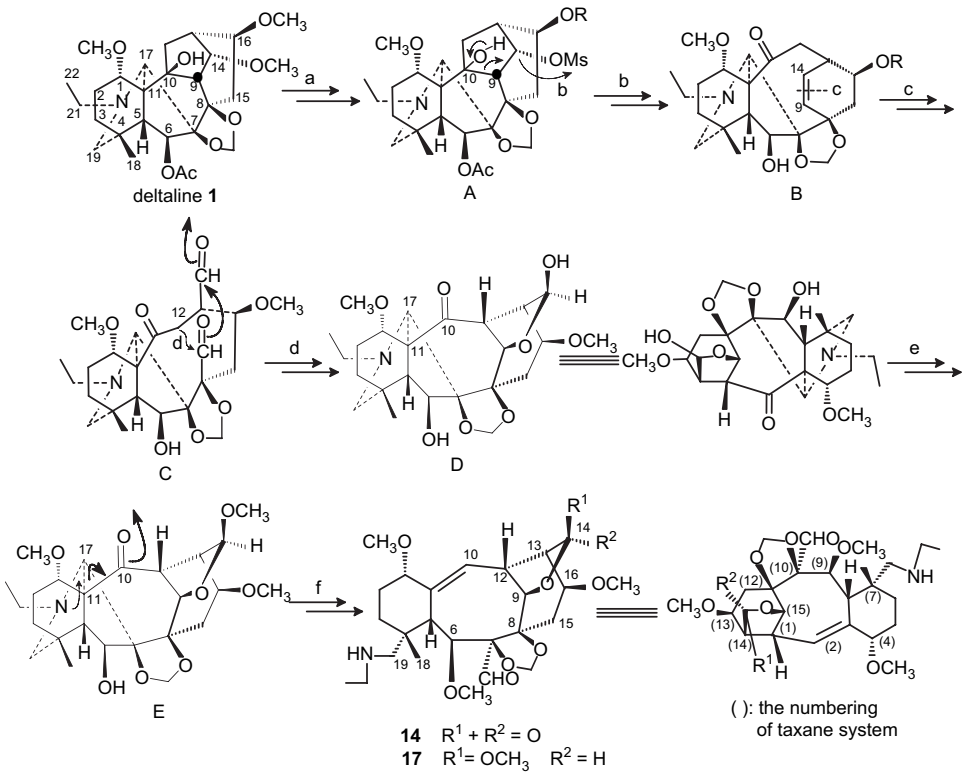
by Pelletier's cleavage[8] (path f), produced the desired taxane-like cores **14** and **17**. In this paper, we report some details of this novel and stereospecific approach to the taxane-like ABC ring system from deltaline (**1**).

2. Results and discussion

The synthesis was initiated with deltaline (**1**), which afforded **3** in 64% overall yield for the two steps, including the O-demethylation as modified by us[9] and $KMnO_4$ oxidation to avoid the influence of the N-atom. The IR and ^{13}C NMR spectra of **3** exhibited distinct signals for a lactam at 1648 cm^{-1} and δ_C 169.5. After considerable investigation of various alternative pathways, it was found that the selective acylation of **4** from the hydrolysis of **3** using BzCl in the presence of Ag_2O–KI[10] (40 °C, 2 h) furnished **5a** (45%) and **5b** (50%). The latter could be recycled for the preparation of additional **5a**. Following mesylation to yield **6**, exposure to 5% NaOH methanol (reflux, 3 h) permitted Grob fragmentation to **7**, which on methylation afforded the desired product **8**, as a result of one-pot procedure, in a 70% isolated yield (Scheme 4). The molecular formula of **7**, $C_{23}H_{31}NO_7$, was established by the HR-ESIMS, and the ^{13}C NMR spectra of **7** showed a lactam group (1683 cm^{-1}, δ_C 172.4), a ketone group (1642 cm^{-1}, δ_C 213.9), and a cis-disubstituted double bond (1642 cm^{-1}; δ_H 6.26 d, J=10.0 Hz, δ_H 5.92 dd, J=10.0, 6.0 Hz; δ_C133.9 d, 127.8 d). From the HMBC correlations of C-10/H-1, H-5, and H-17, as well as H-9/C-13 and C-15, and H-14/C-8 and C-16, the ketone

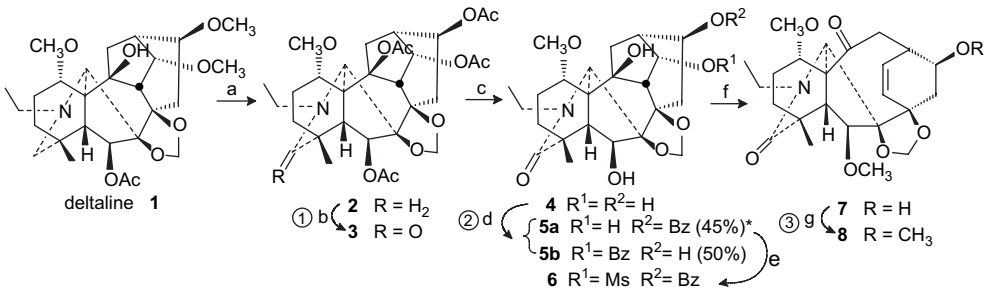


Scheme 2. Approach to the taxane-like ABC system from deltaline by strategies II and III.



Scheme 3. Conversional synthetic strategy IV of the taxane core starting from deltaline (**1**).

group and the double bond in **7** were assigned to C-10 and to between C-9 and C-14, e.g., $\Delta^{9(14)}$, respectively. The structure of **7** was established based on 2D NMR spectral analysis (Table 1). After osmylation, HIO_4 oxidation of **9** provided easy access to the key intermediate **10** (70%). Compared with **9**, the ^1H and ^{13}C NMR spectra of **10** ($C_{25}H_{35}NO_9$, HR-ESIMS) displayed an additional hemiacetal moiety (δ_H 5.58 d, J=3.2 Hz, δ_C 95.8 d; δ_H 5.44 d, J=6.0 Hz, δ_C 75.0 d), which was located by the 2D NMR spectrum between C-14 and C-9 (Table 2). The absolute configuration of C-14 in **10** was determined as *S* due to the NOESY observation between H-14 and H-15 (Table 2). Subsequent reduction using B_2H_6 (THF, reflux, 1.5 h) furnished **11** (96%). The ^{13}C NMR spectrum of **11** showed the absence of the lactam group and the acetal moiety, as compared with **10**. Attempted treatment of **11** under various basic conditions to initiate Grob fragmentation–hydrolysis in order to prepare the target taxane core failed. To overcome this difficulty, an alternative approach using Pelletier's cleavage[8] was used. Reduction using B_2H_6, followed by selective protection of the 9-, 14-hydroxyl groups of **12** by the oxidation (Ag_2CO_3, reflux, 17 h)[11] to the lactone **13** (30%) was carried out. The IR and ^{13}C NMR spectra of **13**, as a single compound, exhibited characteristic signals at 1790 cm^{-1} and δ_C 173.6 for a γ-lactone moiety. Finally, starting from **13**, according to Pelletier's cleavage,[8] the desired target taxane-like core **14** was achieved in a 78% isolated yield (Scheme 5). The IR, ^1H, and ^{13}C NMR spectra of **14** ($C_{25}H_{37}NO_8$, HR-ESIMS) showed an additional aldehyde group (1719 cm^{-1}; δ_H 9.58 s; δ_C 200.9 d) and a trisubstituted double bond (δ_H 5.47 d, J=2.0 Hz; δ_C 125.5 d, 137.9 s) as compared with those of **13**. Location of the double bond was achieved according to the HMBC correlations of C-2/H-4 and H-8 or H-2/C-4, C-8, C-14, and C-15, as well as C-3/H-5 and H-9 (using the taxoid numbering) (Table 3). The structure of **14** was determined by 2D NMR spectral analysis (Table 3), and comparison with the data for **18**, whose structure was established based on X-ray crystallographic analysis. However, owing to the long reaction time and the toxicity of osmylation, attention was turned to the alternative route for the taxane core shown in Scheme 6. As described in Scheme 6, starting with the olefin **8**, the acetal **15** via **10** was prepared in 70% yield through one-pot procedure via O_3 oxidation followed by an aldol condensation–acetalation–methylation process. The HR-ESIMS of **15** gave the quasi-molecular ion peak at *m*/*z* 530.2335



Scheme 4. (a) 6.5% HBr–HOAc, 85 °C, 50 h, 85%; (b) $KMnO_4$, acetone–H_2O–glacial acetic acid, room temperature, 1 h, 75%; (c) 5% NaOH methanol, reflux, 1 h, 100%; (d) BzCl, Ag_2O–KI, THF, 40 °C, 2 h, **5a**: 90% yield after removing 50% of the recovered **5b**; (e) MsCl, pyridine, room temperature, 2 h, 100%; (f) 5% NaOH methanol, reflux, 3 h, 88%; (g) CH_3I, NaH, room temperature, 4 h, 80% (* after recovering the starting material from **5b**, 90%).

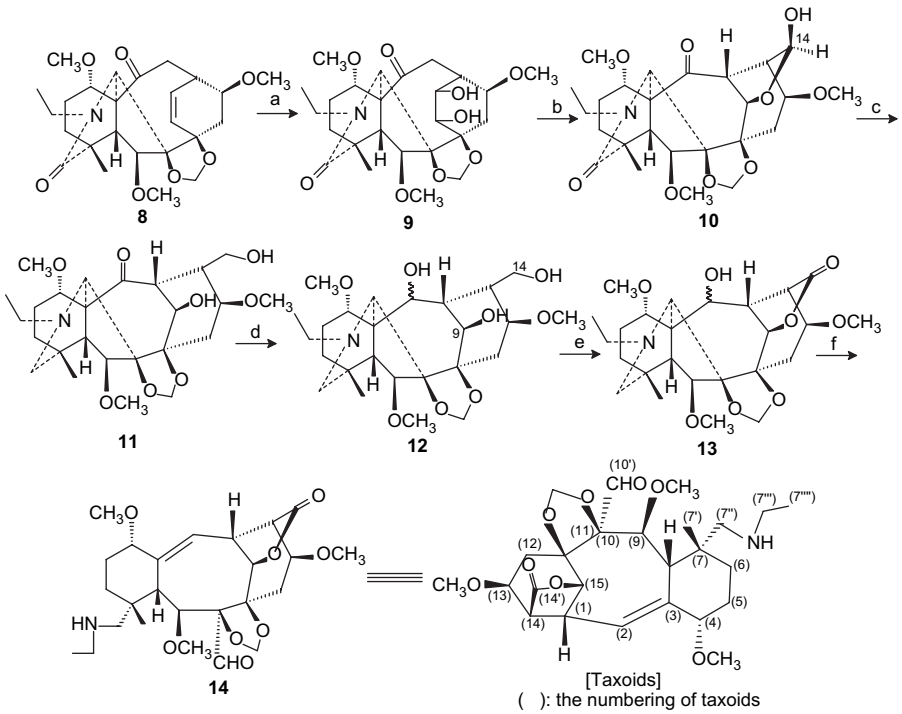
Table 1
NMR data for compound **7**

Carbon	δ_C	δ_H mult (J in Hz)	^{1}H–^{1}HCOSY	HMBC (H→C)	NOESY
1	78.9 d	3.23 dd (10.0, 8.0)	H-2α, H-2β	C-10, C-17, C-1′	H-3β
2	26.4 t	1.58 m (hidden) (α)	H-1, H-2β, H-3α, H-3β	—	H-1′, H-21
		2.17 m (β)	H-1, H-2α, H-3α, H-3β	C-4, C-11	—
3	36.3 t	1.32 m (β)	H-2β, H-2α, H-3α	C-5	—
		1.92 m (α)	H-2β, H-2α, H-3β	C-1, C-5	H-18
4	42.7 s	—	—	—	—
5	53.8 d	2.40 d (3.2)	H-17 (W-type)	C-3, C-7, C-10, C-17	H-1, H-3β, H-18
6	81.6 d	4.03 d (11.2)	6-OH	C-4, C-11, C-17	H-18, OCH_2O
7	98.2 s	—	—	—	—
8	81.3 s	—	—	—	—
9	133.9 d	6.26 d (10.0)	H-14	C-13, C-15	—
10	213.9 s	—	—	—	—
11	62.5 s	—	—	—	—
12	48.5 t	2.88 d (10.8) (β)	H-12α, H-13	C-11, C-16	—
		3.89 d (10.8) (α)	H-12β, H-13	C-14, C-16	H-15α, H-16, H-17, H-1′
13	41.0 d	2.89 m (hidden)	H-16, H-12	C-9, C-15	H-15β
14	127.8 d	5.92 dd (10.0, 6.0)	H-9, H-13	C-8, C-16	—
15	45.1 t	1.52 m (hidden) (β)	H-15α, H-16	C-7	H-13
		2.79 m (hidden) (α)	H-15β, H-16	C-7, C-9	—
16	72.3 d	4.42 t (7.2)	H-13, H-14, H-15α, H-15β	C-12, C-14	H-17
17	63.9 d	4.21 d (3.2)	H-5 (W-type)	C-5, C-6, C-10, C-19, C-21	H-16
18	21.2 q	1.32 s	—	C-3, C-5, C-19	H-3α, H-5, H-6
19	172.4 s	—	—	—	—
21	43.9 t	2.82 m (hidden)	H-21 (δ 4.25), H-22	C-17, C-19	—
		4.25 m	H-21 (δ 2.82), H-22	C-17, C-19	—
22	12.6 q	1.19 t (7.2)	H-21	—	—
1′	56.1 q	3.33 s	—	C-1	—
OCH_2O	91.4 t	4.98 s	—	C-8	H-6
		5.03 s	—	C-7, C-8	—
6-OH	—	2.33 d (11.2)	—	—	—

corresponding to the $C_{26}H_{37}NO_9Na$ which is 14 times units than that of **10**. The ^{1}H and ^{13}C NMR spectra of **15** were very similar to those of **10**, except for C-12 (δ_C 54.8 d), C-14 (δ_C 102.4 d), and C-15 (δ_C 35.6 t), indicating that **15** was the methyl ether of **10**. Another target taxane-like core compound **17**, representing a new class of nor-taxanes without the 16-, 17-, 18-, and 19-methyl groups, but with oxygenation at C-15, was afforded by B_2H_6 reduction of **15**, followed by Pelletier's cleavage of **16** as described above, in a 64%

Table 2
NMR data for compounds **10** and **15**

Carbon no.	**10**					**15**
	δ_C	δ_H mult (J in Hz)	^{1}H–^{1}HCOSY	HMBC (H→C)	NOESY	δ_C
1	81.2 d	4.48 dd (10.4, 7.2)	H-2α, H-2β	C-10, C-17, C-1′	H-5	81.4 δ
2	24.8 t	1.51 m (α)	H-1, H-2β, H-3α, H-3β	C-4	—	24.9 t
		2.10 m (β)	H-1, H-2α, H-3α, H-3β	C-4, C-11	H-1′	
3	35.4 t	1.42 m (β)	H-2β, H-2α, H-3α	C-1, C-5, C-18, C-19	H-18, H-22	35.5 t
		1.92 m (α)	H-2β, H-2α, H-3β	C-1, C-5, C-18, C-19	H-18	
4	43.5 s	—	—	—	—	43.6 s
5	57.1 d	1.87 d (2.8)	H-17 (W-type)	C-3, C-10, C-18, C-19	H-6′, H-18	57.2 d
6	93.4 d	3.80 s	—	C-4, C-8, C-11, C-17, C-6′	H-18, OCH_2O	93.5 d
7	92.7 s	—	—	—	—	92.7 s
8	85.8 s	—	—	—	—	86.0 s
9	75.0 d	5.44 d (6.0)	H-12	C-7, C-13, C-14, C-15	H-6′	75.0 d
10	210.4 s	—	—	—	—	210.5 s
11	63.6 s	—	—	—	—	63.7 s
12	56.0 d	3.92 dd (6.4, 4.8)	H-9, H-13	C-8, C-11, C-14, C-16	—	54.8 τ
13	49.0 d	2.80 t (4.0)	H-12, H-16	C-9, C-15	H-16′	48.4 d
14	95.8 d	5.58 d (3.2)	14-OH	C-9, C-12, C-16	H-15β	102.4 d
15	38.4 t	1.83 dd (13.6, 10.8) (β)	H-15α, H-16	C-7	H-14	35.6 τ
		2.38 dd (14.0, 6.4) (α)	H-15β, H-16	C-7, C-9, C-13	H-16′, H-17	
16	72.8 d	4.02 m	H-13, H-15α, H-15β	C-14, C-16′	H-17	72.9 d
17	63.0 d	4.43 d (2.8)	H-5 (W-type)	C-5, C-6, C-7 C-10, C-19, C-21	H-15α, H-16, H-21, H-22	63.0 d
18	20.5 q	1.26 s	—	C-3, C-5, C-19	H-3β, H-5, H-6, H-6′	20.6 q
19	171.3 s	—	—	—	—	717.3 s
21	42.8 t	2.89 m	H-21 (δ 4.31), H-22	C-17, C-19	H-17	42.9 t
		4.31 m	H-21 (δ 2.89), H-22	C-17, C-19	H-17	
22	12.2 q	1.16 t (7.2)	H-21	—	H-1′, H-17	12.3 q
1′	56.4 q	3.27 s	—	C-1	—	56.4 q
6′	58.0 q	3.26 s	—	C-6	H-18	58.2 q
14′	—	—	—	—	—	56.6 q
1′6	56.5 q	3.37 s	—	C-16	H-1′	56.5 q
OCH_2O	91.4 t	4.99 s	—	C-7, C-8	H-6, H-6′	92.9 t
		5.13 s	—	C-7, C-8	H-15α	
14-OH	—	3.87 d (3.2)	H-14	—	—	



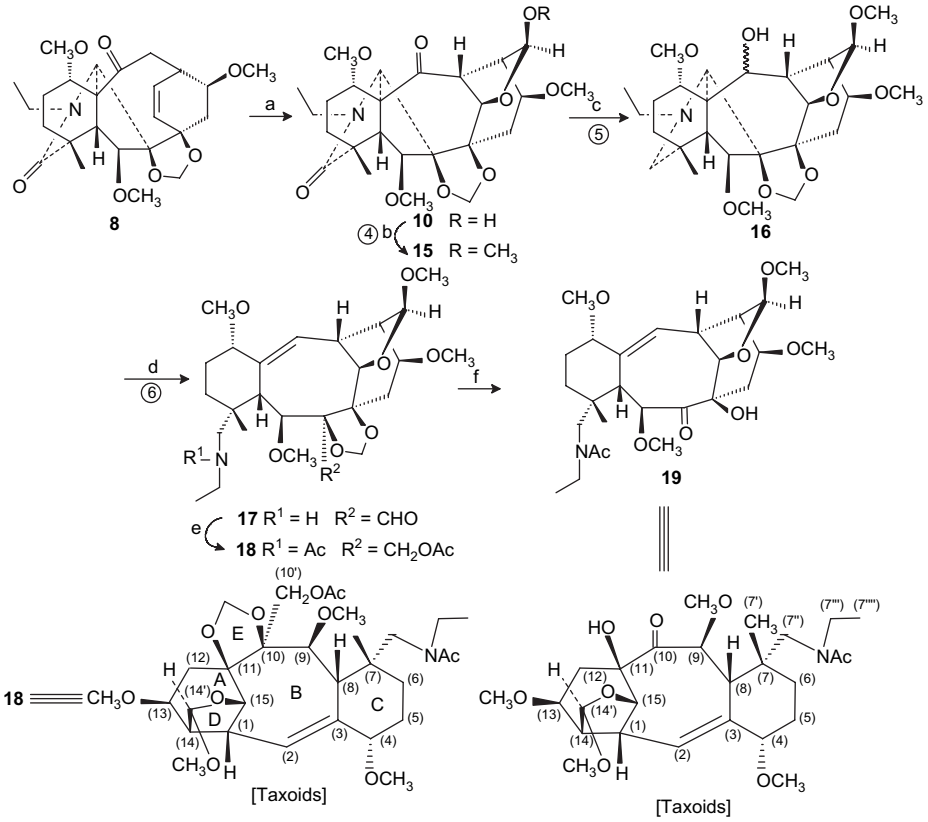
Scheme 5. (a) OsO_4, NMO, 5 h, 100%; (b) HIO_4, THF, aq Na_2SO_3, 70%; (c) B_2H_6, THF, reflux, 1.5 h, 96%; (d) B_2H_6, THF, reflux, 20 h, 52%; (e) Ag_2CO_3, Celite, toluene, reflux, 17 h, 30%; (f) (i) $SOCl_2$–pyridine, room temperature, 1 h, (ii) CH_3OH–H_2O (9:1), 70 °C, 2 h, 78%.

isolated yield (Scheme 6). The ^1H and ^{13}C NMR spectra of **16** (see Section 4) showed distinct twin signals, implying that it is the epimeric pair at C-10. The ^1H and ^{13}C NMR spectra of **17**, as compared with those of **14**, showed the absence of the γ-lactone group, leading to noticeable differences, especially in C-1, C-2, C-8, C-11, C-14, and C-14′ (Tables 3 and 4). The structure of **17**, including the absolute configuration based on a derivation from the known C_{19}-diterpenoid alkaloid deltaline (**1**),[12] was established unambiguously by the 2D NMR (Table 4) and single crystal X-ray analysis (Fig. 1) of the analogue **18** prepared by N-acetylation and

Table 3
NMR data for compound **14**[a]

Carbon	δ_C	δ_H mult (*J* in Hz)	^1H–^1H COSY	HMBC (H→C)
1	41.7 d	3.71 m (hidden)	H-2, H-14, H-15	C-3, C-11, C-13, C-14′
2	125.5 d	5.47 d (2.0)	H-1	C-4, C-8, C-14, C-15
3	137.9 s	—	—	—
4	80.9 d	3.65 m (hidden)	H-5α, H-5β	C-2, C-6, C-8, C-4′
5	25.0 t	1.79 m (hidden) (α)	H-4, H-5β, H-6α, H-6β	C-7
		1.93 m (β)	H-4, H-5α, H-6α, H-6β	C-3, C-7
6	27.3 t	1.23 m (β)	H-5α, H-5β, H-6α	C-4, C-8, C-7′, C-7″
		1.82 m (hidden) (α)	H-5α, H-5β, H-6β	C-7′
7	36.8 s	—	—	—
8	42.0 d	2.75 d (7.2)	H-9	C-2, C-4, C-6, C-10, C-7′
9	84.5 d	4.16 d (7.2)	H-8	C-3, C-11, C-9′, C-10′
10	91.3 s	—	—	—
11	83.6 s	—	—	—
12	30.5 t	1.83 m (hidden) (β)	H-12α, H-13	C-10
		2.64 dd (15.6, 6.4) (α)	H-12β, H-13	C-10, C-14, C-15
13	71.8 d	3.68 m (hidden)	H-12α, H-12β, H-14	C-13′
14	44.5 d	2.99 m	H-1, H-13	C-12, C-15
15	77.5 d	6.16 d (5.2)	H-1	C-12, C-14, C-14′
4′	55.4 q	3.31 s	—	C-4
7′	26.7 q	1.38 s	—	C-6, C-8, C-7″
9′	61.7 q	3.39 s	—	C-9
10′	200.9 d	9.58 s	—	—
13′	56.6 q	3.44 s	—	C-13
14′	173.1 s	—	—	—
7″	57.6 t	2.79 m (hidden)	H-7″ (δ 3.22)	C-8
		3.22 m (hidden)	H-7″ (δ 2.79)	—
7‴	44.2 t	3.01 m (hidden)	H-7‴ (δ 3.27), H-7⁗	C-7⁗
		3.27 m (hidden)	H-7‴ (δ 3.01), H-7⁗	C-7⁗
7⁗	11.2 q	1.49 t (7.2)	H-7‴	—
OCH_2O	91.7	5.33 s	—	C-10, C-11
		5.80 s	—	C-10, C-11
NH	—	7.14 br s	—	—

[a] The numbering of taxoids.



Scheme 6. (a) (i) O_3, CH_2Cl_2, −78 °C, (ii) Me_2S, room temperature, (iii) Na_2SO_3, THF–H_2O, room temperature, 70%; (b) CH_3I, NaH, THF, room temperature, 100%; (c) B_2H_6, THF, reflux, 78%; (d) (i) $SOCl_2$, pyridine, room temperature, (ii) MeOH–H_2O (9:1), reflux, 84%; (e) (i) Ac_2O–pyridine, room temperature, (ii) $NaBH_4$, room temperature, (iii) Ac_2O–pyridine, room temperature, 91%; (f) (i) Ac_2O–pyridine, room temperature, (ii) *m*CPBA/$CHCl_3$, Na_2CO_3, (iii) HOAc–H_2O, 69%.

Table 4
NMR data for compound **17**[a]

Carbon	δ_C	δ_H mult (*J* in Hz)	^1H–^1H COSY	HMBC (H→C)
1	39.7 d	3.44 m (hidden)	H-2, H-15	C-3, C-11, C-13, C-14′
2	127.9 d	5.62 d (2.0)	H-1	C-4, C-8, C-14, C-15
3	136.8 s	—	—	—
4	80.7 d	3.64 br s	H-5α, H-5β	C-2, C-6, C-8, C-4′
5	24.4 t	1.73 m (α)	H-4, H-5β, H-6α, H-6β	—
		1.93 m (β)	H-4, H-5α, H-6α, H-6β	C-3, C-7
6	26.8 t	1.47 m (hidden) (β)	H-5α, H-5β, H-6α	C-4
		1.80 m (α)	H-5α, H-5β, H-6β	C-4, C-7′, C-7″
7	36.5 s	—	—	—
8	44.6 d	2.70 d (8.0)	H-9	C-2, C-4, C-6, C-10, C-7′, C-7″
9	85.7 d	3.95 d (8.0)	H-8	C-3, C-7, C-11, C-9′, C-10′
10	91.8 s	—	—	—
11	85.7 s	—	—	—
12	31.7 t	1.64 dd (14.4, 11.2) (β)	H-12α, H-13	C-10, C-14
		2.34 dd (14.4, 6.0) (α)	H-12β, H-13	C-10, C-14, C-15
13	72.8 d	3.49 m (hidden)	H-14, H-12α, H-12β	C-11, C-13′, C-14′
14	48.3 d	2.57 t (4.0)	H-1, H-13	C-2, C-12, C-15
15	76.4 d	5.32 d (5.6)	H-1	C-12, C-14, C-14′
4′	55.0 q	3.27 s	—	C-4
7′	26.3 q	1.35 s	—	C-6, C-8, C-7″
9′	61.3 q	3.46 s	—	C-9
10′	199.4 d	9.52 s	—	—
13′	56.3 q	3.33 s	—	C-13
14′	101.1 d	4.95 s	—	C-1, C-13, C-15, C-14″
7″	57.4 t	2.82 m	H-7″ (δ 3.22)	C-7′, C-7‴
		3.22 m (hidden)	H-7″ (δ 2.82)	C-6, C-7′
14″	54.9 q	3.41 s	—	C-14′
7‴	44.2 t	3.05 m	H-7‴ (δ 3.26), H-7⁗	C-7″
		3.26 m (hidden)	H-7‴ (δ 3.05), H-7⁗	C-7″
7⁗	11.0 q	1.49 t (7.2)	H-7‴	—
OCH_2O	91.4 t	5.19 s	—	C-10, C-11
		5.59 s	—	C-10, C-11

[a] The numbering of taxoids.

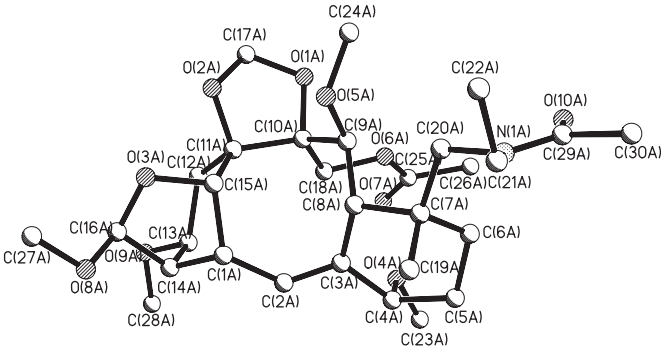


Figure 1. X-ray structure of **18**.

$NaBH_4$ reduction, and acetylation of **17**. The X-ray crystallography data of **18** are listed below: colorless crystals from cyclohexane–acetone are monotectic, space group $P2_1$, a=10.253 (1), b=17.78 (1), c=17.594 (1) Å, β=106.589 (1)°, V=3074.7 (1) Å^3, Z=2, d_x=1.257 g/cm^3. Full-matrix least-squares refinements gave $R(F)$=0.0567, $wR(F)$=0.0523 for 739 parameters and 12,499 reflections with $I \geq 3s(I)$. The X-ray diffraction analysis of **18** showed that the skeleton consists of one eight-membered ring B, two six-membered rings A and C, each with the chair conformation, as well as two five-membered heterocyclic rings D and E, having the envelope form. In addition, the cis-fusion patterns of the A/B, A/D, B/D, and B/E rings were also observed. Therefore, the stereochemistry of C-1, C-8, and the bridge ring of **18** is the same as those of the taxoids, except for the missing 16, 17, 18, and 19-methyl groups. In addition, the NOE relationships between H-14′ (δ_H 4.93 s) and H-12β (δ_H1.52 m) also supported the *S* configuration at C-14′, the same as **10**. Finally, acetylation of **17** with Ac_2O–pyridine, followed by *m*CPBA oxidation and HOAc hydrolysis, furnished compound **19** in 69% yield (Scheme 6). The IR and ^{13}C NMR spectra (Table 6) of **19** ($C_{26}H_{41}NO_8$, HR-ESIMS) showed the distinct ketone and ester signals at 1712 cm^{-1} and δ_C 199.1 s, as well as at 1633 cm^{-1} and δ 171.8 s, 21.6 q, respectively. It is important to point out that the conversion of **1**→**3**, **3**(→**4**)→**5a**, **5a**→**8**, **8**→**15**, **15**→**16**, and **16**→**17** shown in Schemes 4 and 6 and Section 4 was carried out in six steps in an overall yield of 18%.

3. Conclusion

In conclusion, a short, efficient, and effective conversional synthesis, based on diterpenoid alkaloid chemistry, of the taxane-like ABC ring system, and yielding a new class of nor-taxanes, has been developed. The route is mainly based on the Grob fragmentation and Pelletier's cleavage, using readily available starting material, operationally simple reactions employing cheap chemical reagents, and in good overall yield (18% for 6 steps from deltaline **1**). Further research on the synthetic conversion to the taxanes based on the strategy shown in Scheme 3 is continuing.

4. Experimental section

4.1. General methods

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

Table 5
NMR data for compound **18**[a]

Carbon	δ_C	δ_H mult (J in Hz)	^1H–^1H COSY	HMBC (H→C)
1	40.0 d	3.39 m (hidden)	H-2, H-14, H-15	C-3, C-11, C-13, C-14′
2	129.0 d	5.71 s	H-1	C-4, C-8, C-14, C-15
3	139.6 s	—	—	—
4	79.9 d	3.67 m	H-5α, H-5β	C-2, C-6, C-8, C-4′
5	23.3 t	1.55 m (α)	H-4, H-5β, H-6α, H-6β	C-7
		1.86 m (β)	H-4, H-5α, H-6α, H-6β	C-7
6	26.6 t	1.23 m (β)	H-5α, H-5β, H-6α	C-8
		1.78 m (α)	H-5α, H-5β, H-6β	—
7	39.7 s	—	—	—
8	51.3 d	2.69 d (8.4)	H-9	C-2, C-4, C-6, C-10, C-7′
9	86.0 d	3.86 d (9.2)	H-8	C-7, C-11, C-9′, C-10′
10	87.7 s	—	—	—
11	87.6 s	—	—	—
12	32.8 t	1.52 m (β)	H-12α, H-13	C-10
		2.67 m (α)	H-12β, H-13	C-10, C-14, C-15
13	73.0 d	3.31 m	H-14, H-12α, H-12β	C-13′
14	48.8 d	2.58 m	H-1, H-13	C-12, C-15
15	79.7 d	5.28 d (6.0)	H-1	C-10, C-12, C-14, C-14′
4′	55.7 q	3.22 s	—	C-4
7′	26.8 q	0.93 s	—	C-6, C-8, C-7″
9′	60.7 q	3.56 s	—	C-9
10′	66.7 t	4.39 ABq (12.0)	H-10′	C-9, C-11, OCO
13′	56.2 q	3.37 s	—	C-13
14′	101.7 d	4.96 s	—	C-1, C-13, C-15, C-14″
7″	53.0 t	3.33 m (hidden)	H-7″ (δ 3.72)	NCO
		3.72 m	H-7″ (δ 3.33)	NCO
14″	54.9 q	3.42 s	—	C-14′
7‴	45.7 t	3.27 m (hidden)	H-7‴ (δ 3.47), H-7⁗	NCO
		3.47 m	H-7‴ (δ 3.27), H-7⁗	NCO
7⁗	13.5 q	1.18 t (7.2)	H-7‴	—
OCH_2O	91.6 t	4.92 s	—	C-10, C-11
		5.17 s	—	C-10, C-11
NCO	171.8 s	—	—	—
$NCOCH_3$	21.7 q	2.15 s	—	—
OCO	170.4 s	—	—	—
$OCOCH_3$	21.0 q	2.10 s	—	—

[a] The numbering of taxoids.

Table 6
NMR data for compound **19**[a]

Carbon	δ_C	δ_H mult (J in Hz)	^1H–^1H COSY	HMBC (H→C)
1	39.6 d	3.38 m (hidden)	H-2, H-14, H-15	C-3, C-11, C-13, C-14′
2	128.2 d	5.40 s	H-1	C-4, C-8, C-14, C-15
3	136.7 s	—	—	—
4	80.3 d	3.22 m	H-5α, H-5β	C-2, C-6, C-8, C-4′
5	26.4 t	1.54 m (α)	H-4, H-5β, H-6α, H-6β	—
		1.73 m (β)	H-4, H-5α, H-6α, H-6β	—
6	25.3 t	1.23 m (β)	H-5α, H-5β, H-6α	—
		1.79 m (α)	H-5α, H-5β, H-6β	—
7	40.0 s	—	—	—
8	48.0 d	2.86 d (10.0)	H-9	C-2, C-4, C-6, C-7′
9	89.3 d	3.88 d (10.4)	H-8	C-7, C-11, C-9′
10	199.0 s	—	—	—
11	80.2 s	—	—	—
12	33.1 t	1.18 dd (13.2, 11.2) (β)	H-12α, H-13	C-10, C-15
		2.94 dd (13.2, 6.0) (α)	H-12β, H-13	C-10, C-14, C-15
13	72.2 d	3.26 m	H-14, H-12α, H-12β	C-13′
14	48.5 d	2.48 t (3.2)	H-1, H-13	C-12, C-15
15	79.9 d	5.23 d (5.6)	H-1	C-12, C-14, C-14′
4′	56.3 q	2.96 s	—	C-4
7′	24.4 q	0.91 s	—	C-6, C-8, C-7″
9′	57.6 q	3.30 s	—	C-9
13′	56.2 q	3.30 s	—	C-13
14′	102.2 d	4.90 s	—	C-1, C-13, C-15, C-14″
7″	53.3 t	3.08 m	H-7″ (δ 3.55)	C-7′
		3.55 m	H-7″ (δ 3.08)	C-6
14″	54.9 q	3.39 s	—	C-14′
7‴	45.8 t	3.34 m	H-7‴, H-7⁗	C-7″
7⁗	13.4 q	1.11 t (7.2)	H-7‴	—
NCO	171.7 s	—	—	—
$NCOCH_3$	21.6 q	2.09 s	—	—

[a] The numbering of taxoids.

Finnigan LCQ DECA mass spectrometer; HRMS spectra were obtained with a Bruker BioTOFQ mass spectrometer; ^1H 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 gel GF_{254} and H (10–40 μm, Qingdao Sea Chemical Factory, China) were used for TLC and CC.

4.1.1. Preparation of compound *2*

A solution of deltaline (**1**) (11.0 g, 21.70 mmol) in 6.5% HBr–HOAc (527 ml, w/v) was heated at 85 °C for 50 h. Removal of solvent gave a residue, which was diluted with water (100 ml). Basification (NH_4OH, pH 10), extraction ($CHCl_3$, 200 ml×3), drying (Na_2SO_4), and evaporation in vacuum gave a residue (13.0 g), which was chromatographed over silica gel H (220 g) eluted with cyclohexane–acetone (8:1) to give **2** (11.1 g, 85%). Compound **2**: mp: 64–66 °C; $[\alpha]_D^{20}$ −28.4 (*c* 0.5, $CHCl_3$); IR (KBr): 1739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, s, H_3-18), 1.06 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 2.02, 2.06, 2.06, 2.09 (each 3H, s, OCH_3×4), 3.25 (3H, s, OCH_3), 3.53 (1H, dd, *J*=9.6, 7.6 Hz, H-1β), 4.20 (1H, d, *J*=5.6 Hz, H-9), 4.76 (1H, dd, *J*=9.6, 6.0 Hz, H-16α), 4.85, 4.96 (each 1H, s, OCH_2O), 5.44 (1H, s, H-6α), 5.53 (1H, t, *J*=5.2 Hz, H-14β); ^{13}C NMR (100 MHz, $CDCl_3$) δ 78.3 (d, C-1), 26.7 (t, C-2), 36.3 (t, C-3), 33.5 (s, C-4), 50.7 (d, C-5), 77.3 (d, C-6), 91.0 (s, C-7), 81.3 (s, C-8), 47.2 (d, C-9), 95.4 (s, C-10), 57.3 (s, C-11), 34.4 (t, C-12), 38.5 (d, C-13), 73.8 (d, C-14), 33.7 (t, C-15), 73.2 (d, C-16), 63.1 (d, C-17), 25.3 (q, C-18), 56.4 (t, C-19), 50.1 (t, C-21), 13.6 (q, C-22), 170.6 s, 170.2 s, 170.0 s, 169.7 s, 23.2 q, 21.5 q, 21.2 q, 21.1 q (OAc×4), 55.0 (q, C-1′), 93.9 (t, OCH_2O); ESIMS *m*/*z* 606 $[M+H]^+$; HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{31}H_{44}NO_{11}$: 606.2909, found: 606.2889.

4.1.2. Preparation of compound *3*

Method 1. To a solution of **2** (6.4 g, 10.58 mmol) in acetone–H_2O–glacial acetic acid (165:42:3) (210 ml) under ice bath, $KMnO_4$ (5.0 g, 31.74 mmol) was added. Upon addition was completed, cold bath was removed and the reaction mixture stirred at room temperature for 1 h, to which Na_2SO_3 (5.0 g) in H_2O (20 ml) was added for stopping the reaction. Usual work-up and chromatography (silica gel H, 130 g) using cyclohexane–acetone (5:1) as eluent furnished **3** (4.9 g, 75%). *Method 2*. A solution of deltaline (**1**) (11.0 g, 21.7 mmol) in 6.5% HBr–HOAc (527 ml, w/v) was heated at 85 °C for 50 h. The usual work-up gave the crude **2** (13.0 g) and then exposed to acetone–H_2O–glacial acetic acid (165:42:3) (430 ml) under ice bath, followed by $KMnO_4$ (10.2 g, 65.1 mmol), then the reaction mixture was stirred at room temperature for 1 h, to which Na_2SO_3 (10 g) in H_2O (40 ml) was added for stopping the reaction. The same work-up as method 1 furnished **3** (8.6 g, 64%). Compound **3**: mp: 213–215 °C; $[\alpha]_D^{20}$ −23.0 (*c* 0.5, $CHCl_3$); IR (KBr): 1739, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, s, H_3-18), 1.15 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 2.04, 2.08, 2.08, 2.11 (each 3H, s, OCH_3×4), 2.94–3.02, 3.99–4.08 (each 1H, m, NCH_2CH_3), 3.60 (1H, d, *J*=3.2 Hz, H-17), 3.73 (1H, t, *J*=8.4 Hz, H-1β), 4.10 (1H, d, *J*=5.2 Hz, H-9), 4.78 (1H, dd, *J*=9.6, 5.2 Hz, H-16α), 4.89, 4.97 (each 1H, s, OCH_2O), 5.38 (1H, d, *J*=1.6 Hz, H-6α), 5.55 (1H, t, *J*=5.2 Hz, H-6α); ^{13}C NMR (50 MHz, $CDCl_3$) δ 79.9 (d, C-1), 26.6 (t, C-2), 34.6 (t, C-3), 44.9 (s, C-4), 50.2 (d, C-5), 75.7 (d, C-6), 94.7 (s, C-7), 89.6 (s, C-8), 46.8 (d, C-9), 80.3 (s, C-10), 54.9 (s, C-11), 33.7 (t, C-12), 37.8 (d, C-13), 73.2 (d, C-14), 33.5 (t, C-15), 72.5 (d, C-16), 62.1 (d, C-17), 23.2 (q, C-18), 169.5 (s, C-19), 43.0 (t, C-21), 12.2 (q, C-22), 172.3 s, 170.6 s, 170.2 s, 169.5 s, 21.5 q, 21.3 q, 21.1 q (OAc×4), 54.9 (q, C-1′), 94.1 (t, OCH_2O); ESIMS *m*/*z* 620 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ *m*/*z* calcd for $C_{31}H_{41}NO_{12}Na$: 642.2521, found: 642.2497.

4.1.3. Preparation of compound *4*

A solution of **3** (8.9 g, 14.38 mmol) in 300 ml of 5% NaOH methanol was refluxed for 1 h. Evaporation under reduced pressure, dilution (H_2O, 100 ml), acidification with 10% HCl to pH 4, followed by basification (NH_4OH, pH 10), extraction (*n*-butanol, 250 ml×3), and general work-up gave **4** (6.5 g, 100%). Compound **4**: mp: 234–236 °C; $[\alpha]_D^{20}$ −11.4 (*c* 0.5, CH_3OH); IR (KBr): 3396, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, s, H_3-18), 0.99

(3H, t, J=7.2 Hz, NCH_2CH_3), 3.28 (3H, s, OCH_3), 3.70 (1H, t, J=6.4 Hz, H-1β), 3.76–3.90 (1H, m, H-16), 4.89 (1H, t, J=4.8 Hz, H-14β), 5.11, 5.22 (each 1H, s, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.9 (d, C-1), 26.2 (t, C-2), 34.3 (t, C-3), 45.6 (s, C-4), 50.6 (d, C-5), 75.6 (d, C-6), 90.7 (s, C-7), 81.3 (s, C-8), 49.6 (d, C-9), 78.7 (s, C-10), 52.2 (s, C-11), 36.5 (t, C-12), 38.6 (d, C-13), 72.0 (C-14), 35.3 (t, C-15), 71.1 (d, C-16), 63.3 (d, C-17), 21.7 (q, C-18), 173.0 (s, C-19), 42.2 (t, C-21), 12.5 (q, C-22), 55.2 (q, C-1′), 93.4 (t, OCH_2O); ESIMS m/z 452 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{23}H_{33}NO_8Na$: 474.2098, found: 474.2075.

*4.1.4. Preparation of compounds **5a** and **5b***

To a solution of **4** (2.3 g, 5.10 mmol) in fresh THF (100 ml), were added sequentially KI (169 mg, 1.02 mmol), Ag_2O (1.77 g, 7.65 mmol), and BzCl (1.1 ml, 9.18 mmol) under argon steam and the mixture was heated at 40 °C for 2 h, to which water (3 ml) was added to stop the reaction. A general work-up procedure gave a residue, which was diluted with H_2O (20 ml). Basifying (NH_4OH, pH 10), extraction ($CHCl_3$, 30 ml×3), drying (Na_2SO_4), evaporation, and column chromatography (silica gel H, 75 g, $CHCl_3$–MeOH 95:5 to 19:1) furnished **5a** (1.27 g, 45%, after recovering the starting material from **5b**, 90%) and **5b** (1.42 g, 50%). The latter was hydrolyzed with 5% NaOH methanol to recover the starting material **4** for the next use. Compound **5a**: mp: 148–150 °C; $[\alpha]_D^{20}$ −19.8 (*c* 0.5, $CHCl_3$); IR (KBr): 3422, 1712, 1623 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.29 (3H, s, H_3-18), 2.93–2.98, 3.97–4.03 (each 1H, m, NCH_2CH_3), 3.25 (3H, s, OCH_3), 3.43 (1H, d, J=5.2 Hz, H-9), 3.65 (1H, d, J=3.2 Hz, H-17), 3.76 (1H, t, J=8.4 Hz, H-1α), 4.18 (1H, br s, H-6α), 4.80 (1H, t, J=4.8 Hz, H-14β), 5.05, 5.22 (each 1H, s, OCH_2O), 5.12–5.14 (1H, m, H-16α), 7.43–8.04 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.2 (d, C-1), 26.5 (t, C-2), 33.3 (t, C-3), 45.4 (s, C-4), 50.8 (d, C-5), 75.3 (d, C-6), 90.4 (s, C-7), 82.4 (s, C-8), 50.8 (d, C-9), 79.9 (s, C-10), 53.3 (s, C-11), 37.1 (t, C-12), 39.7 (d, C-13), 73.4 (d, C-14), 34.4 (t, C-15), 71.5 (d, C-16), 62.6 (d, C-17), 21.7 (q, C-18), 173.7 (s, C-19), 43.1 (t, C-21), 12.3 (q, C-22), 55.0 (q, C-1′), 93.8 (t, OCH_2O), 165.9 (s, Ar–*C*OO), 129.9 (s, C-1″), 129.5 (d, C-2″, 6″), 128.3 (d, C-3″, 5″), 133.1 (d, C-4″); ESIMS m/z 556 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{30}H_{37}NO_9Na$: 578.2361, found: 578.2338. Compound **5b**: mp: 266–268 °C; $[\alpha]_D^{20}$ −18.0 (*c* 0.5, $CHCl_3$); IR (KBr): 3520, 3378, 1716, 1621 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.27 (3H, s, H_3-18), 2.91–2.96, 3.98–4.03 (each 1H, m, NCH_2CH_3), 3.22 (3H, s, OCH_3), 3.60 (1H, d, J=2.8 Hz, H-17), 3.70 (1H, d, J=4.8 Hz, H-9), 3.78 (1H, t, J=8.8 Hz, H-1β), 3.87 (1H, br d, J=8.8 Hz, H-16α), 5.10, 5.19 (each 1H, s, OCH_2O), 5.77 (1H, t, J=4.8 Hz, H-14β), 7.37–7.59 (5H, m, Ar–H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 79.7 (d, C-1), 24.7 (t, C-2), 32.7 (t, C-3), 43.4 (s, C-4), 48.6 (d, C-5), 73.7 (d, C-6), 88.3 (s, C-7), 79.3 (s, C-8), 46.4 (d, C-9), 78.0 (s, C-10), 51.0 (s, C-11), 36.0 (t, C-12), 38.3 (d, C-13), 72.7 (d, C-14), 35.3 (t, C-15), 68.3 (d, C-16), 60.8 (d, C-17), 20.1 (q, C-18), 171.1 (s, C-19), 40.5 (t, C-21), 10.7 (q, C-22), 91.6 (t, OCH_2O), 53.2 (q, C-1′), 164.1 (s, Ar–*C*OO), 128.8 (s, C-1″), 127.9 (d, C-2″, 6″), 126.8 (d, C-3″, 5″), 131.2 (d, C-4″); ESIMS m/z 556 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{30}H_{37}NO_9Na$: 578.2361, found: 578.2338.

*4.1.5. Preparation of compounds **6** and **7***

Alcohol **5a** (1.65 g, 2.97 mmol) was first mesylated with MsCl (0.82 ml, 8.91 mmol) in dry pyridine (60 ml) at room temperature for 2 h, stopping the reaction with H_2O, and the usual work-up gave **6**, and then exposed to 5% sodium hydroxide–methanol (60 ml) under reflux for 3 h. Evaporation under reduced pressure, dilution (H_2O, 100 ml), extraction ($CHCl_3$, 100 ml×3), drying (Na_2SO_4), and evaporation in vacuum gave a residue (1.29 g), followed by chromatography (silica gel H, 25 g; cyclohexane–acetone 6:1) furnished **7** (1.13 g, 88%). Compound **6**: mp: 152–154 °C; $[\alpha]_D^{20}$ −33.9 (*c* 0.8, $CHCl_3$); IR (KBr): 3412, 1713, 1623, 1354 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.30 (3H, s, H_3-18), 2.93–2.98, 3.97–4.04 (each 1H, m, NCH_2CH_3), 3.09 (3H, s, OMs), 3.26 (3H, s, OCH_3), 3.63 (1H, d, J=3.2 Hz, H-17), 3.74 (1H, d, J=5.6 Hz, H-9), 3.77 (1H, t, J=8.8 Hz, H-1β), 4.21 (1H, d, J=0.8 Hz, H-6α), 5.06, 5.24 (each 1H, s, OCH_2O), 5.11 (1H, dd, J=9.2, 2.4 Hz, H-16α), 5.49 (1H, t, J=5.2 Hz, H-14β), 7.44–8.11 (5H, m, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.6 (d, C-1), 26.6 (t, C-2), 33.0 (t, C-3), 45.4 (s, C-4), 51.0 (d, C-5), 78.8 (d, C-6), 93.3 (s, C-7), 81.4 (s, C-8), 49.2 (d, C-9), 79.5 (s, C-10), 53.5 (s, C-11), 36.5 (t, C-12), 38.8 (d, C-13), 75.1 (d, C-14), 34.7 (t, C-15), 72.1 (d, C-16), 62.5 (d, C-17), 21.8 (q, C-18), 173.2 (s, C-19), 43.1 (t, C-21), 12.4 (q, C-22), 55.0 (q, C-1′), 93.8 (t, OCH_2O), 166.1 (s, Ar–*C*OO), 130.0 (s, C-1″), 129.7 (d, C-2″, 6″), 128.5 (d, C-3″, 5″), 133.2 (d, C-4″), 38.3 (q, OMs); ESIMS m/z 634 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{31}H_{39}NO_{11}SNa$: 656.2136, found: 656.2108. Compound **7**: mp: 68–70 °C; $[\alpha]_D^{20}$ +22.6 (*c* 0.5, $CHCl_3$); IR (KBr): 3518, 3389, 1683, 1642 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) see Table 1; ESIMS m/z 434 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{23}H_{31}NO_7Na$: 456.1993, found: 456.1982.

*4.1.6. Preparation of the key intermediate **8***

The olefin-ketone **8**, employed as the key intermediate, could be synthesized by one-pot mesylation–Grob fragmentation–methylation procedure. Alcohol **5a** (1.65 g, 2.97 mmol) was first mesylated with MsCl (0.82 ml, 8.91 mmol) in dry pyridine (60 ml) at room temperature for 2 h, then exposed to 5% sodium hydroxide–methanol (60 ml) under reflux for 3 h. Finally, the C-6 and C-16 hydroxyl groups were protected using CH_3I (1.65 ml, 26.10 mmol) and NaH (935 mg, 39.14 mmol) in THF (50 ml) at room temperature for 4 h (TLC monitoring). Adding H_2O to stop the reaction, and the usual work-up, followed by chromatography (silica gel H, 30 g; cyclohexane–acetone 7:1), furnished **8** (962 mg, 70%). Compound **8**: mp: 67–69 °C; $[\alpha]_D^{20}$ +30.6 (*c* 0.5, $CHCl_3$); IR (KBr): 2935, 1699, 1649 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.30 (3H, s, H_3-18), 3.20 (1H, dd, J=10.0, 8.0 Hz, H-1α), 3.29, 3.30, 3.26 (each 3H, s, OCH_3×3), 3.60 (1H, d, J=12.0 Hz, H-6α), 3.85 (1H, t, J=7.2 Hz, H-16), 4.21 (1H, d, J=2.8 Hz, H-17), 2.70–2.79, 4.21–4.31 (each 1H, m, NCH_2CH_3), 4.89, 5.05 (each 1H, s, OCH_2O), 5.85 (1H, dd, J=10.0, 6.8 Hz, H-14), 6.08 (1H, d, J=10.0 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.8 (d, C-1), 26.3 (t, C-2), 36.0 (t, C-3), 43.0 (s, C-4), 49.8 (d, C-5), 90.3 (d, C-6), 97.3 (s, C-7), 81.5 (s, C-8), 133.2 (d, C-9), 213.9 (s, C-10), 61.5 (s, C-11), 49.4 (t, C-12), 35.7 (d, C-13), 126.7 (d, C-14), 43.9 (t, C-15), 80.8 (d, C-16), 63.7 (d, C-17), 21.5 (q, C-18), 172.5 (s, C-19), 41.2 (t, C-21), 12.5 (q, C-22), 55.9 (q, C-1′), 57.9 (q, C-6′), 56.1 (q, C-16′), 91.0 (t, OCH_2O), ESIMS m/z 484 $[M+Na]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{25}H_{35}NO_7Na$: 484.2306, found: 484.2295.

*4.1.7. Preparation of compound **9***

To a solution of **8** (428 mg, 0.93 mmol) in *t*-BuOH–THF–H_2O (10:3:1, 15 ml) NMO (1.34 mg, 11.44 mmol) and OsO_4 (64 mg, 0.25 mmol) were added and the reaction solution was stirred at room temperature for 5 h, then, to this solution 10 ml of saturated Na_2SO_3 solution was added and stirred vigorously for 15 min. The removal of solvent, basification (NH_4OH, pH 10), extraction ($CHCl_3$, 20 ml×3), drying (Na_2SO_4), and evaporation afforded compound **9** (460 mg, 100%). Compound **9**: mp: 180–182 °C; $[\alpha]_D^{20}$ +43.2 (*c* 0.6, $CHCl_3$); IR (KBr): 3406, 2927, 1689, 1641 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (3H, t, J=7.2 Hz, NCH_2CH_3), 1.36 (3H, s, H_3-18), 3.15 (1H, dd, J=10.0, 7.6 Hz, H-1β), 3.32, 3.34, 3.43 (each 3H, s, OCH_3×3), 3.80 (1H, t, J=8.8 Hz, H-16α), 4.21 (1H, t, J=4.4 Hz, H-14), 4.39 (1H, d, J=3.2 Hz, H-17), 4.50 (1H, d, J=5.2 Hz, H-9); ^{13}C NMR (50 MHz, $CDCl_3$) δ 81.2 (d, C-1), 26.2 (t, C-2), 35.4 (t, C-3), 43.9 (s, C-4), 49.3 (d, C-5), 92.4 (d, C-6), 95.4 (s, C-7), 81.3 (s, C-8), 68.9 (d, C-9), 212.0 (s, C-10), 61.6 (s, C-11), 43.7 (d, C-12), 39.7 (d, C-13), 62.2 (d, C-14), 35.6 (t, C-15), 80.6 (d, C-16), 62.9 (d, C-17), 21.8 (q, C-18), 172.4 (s, C-19), 46.3 (t, C-21), 12.3 (q, C-22), 56.1 (q, C-1′), 58.2 (q, C-6′), 56.6 (q,

C-16′), 91.0 (t, OCH_2O); ESIMS *m/z* 518 $[M+Na]^+$; HR-ESIMS $[M+Na]^+$ *m/z* calcd for $C_{25}H_{37}NO_9Na$: 518.2361, found: 518.2334.

4.1.8. Preparation of compound **10**

To a solution of **9** (703 mg, 1.42 mmol) in THF (16 ml), $HIO_4\cdot 2H_2O$ (647 mg, 2.84 mmol) was added and the mixture stirred at room temperature for 30 min. After basifying with saturated Na_2SO_3 solution (30 ml) to pH 7–8, the reaction solution was stirred vigorously for 10 h. Evaporation, extraction ($CHCl_3$, 35 ml×3), and the removal of solvent gave a residue that was recrystallized from ether to afford compound **10** (490 mg, 70%). Compound **10**: mp: 181–183 °C; $[\alpha]_D^{20}$ +5.6 (*c* 0.5, $CHCl_3$); IR (KBr): 3378, 1669, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) see Table 2; ESIMS *m/z* 516 $[M+Na]^+$; HR-ESIMS $[M+Na]^+$ *m/z* calcd for $C_{25}H_{35}NO_9Na$: 516.2204, found: 516.2180.

4.1.9. Preparation of compound **11**

To a solution of **10** (197.0 mg, 0.40 mmol) in 10 ml of THF, B_2H_6–THF (1.2 ml, 1.2 mmol) was added and the reaction solution was refluxed for 1.5 h under argon gas steam. Quenching the reaction with H_2O, evaporation, dilution (H_2O, 5 ml), basifying (NH_4OH, pH 10), extraction ($CHCl_3$, 10 ml×3), drying (Na_2SO_4), and the removal of solvent and chromatography (silica gel H, 4.2 g, cyclohexane–acetone 16:1) afforded **11** (184.7 mg, 96%). Compound **11**: mp: 76–78 °C; $[\alpha]_D^{20}$ −24.8 (*c* 0.5, $CHCl_3$); IR (KBr): 3381, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s, H_3-18), 1.03 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.23, 3.24, 3.45 (each 3H, s, OCH_3×3), 3.57 (1H, s, H-6α), 3.60–3.66 (H-14, hidden), 3.74 (1H, dd, *J*=11.2, 6.8 Hz, H-1β), 3.91 (1H, d, *J*=2.0 Hz, H-17), 4.00 (1H, dd, *J*=6.4, 5.2 Hz, H-14), 4.98, 5.15 (each 1H, s, OCH_2O), 5.15 (1H, d, *J*=2.4 Hz, H-9); ^{13}C NMR (50 MHz, $CDCl_3$) δ 83.7 (d, C-1), 25.1 (t, C-2), 36.3 (t, C-3), 31.9 (s, C-4), 58.7 (d, C-5), 91.4 (d, C-6), 94.0 (s, C-7), 86.1 (s, C-8), 64.9 (d, C-9), 213.1 (s, C-10), 63.6 (s, C-11), 55.8 (d, C-12), 35.2 (d, C-13), 64.3 (d, C-14), 37.5 (t, C-15), 76.7 (d, C-16), 64.3 d (d, C-17), 24.7 (q, C-18), 55.6 (t, C-19), 50.1 (t, C-21), 13.9 (q, C-22), 56.3 (q, C-1′), 57.8 (q, C-6′), 57.2 (q, C-16′), 92.2 (t, OCH_2O); ESIMS *m/z* 482 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ *m/z* calcd for $C_{25}H_{39}NO_8Na$: 504.2568, found: 504.2544.

4.1.10. Preparation of compound **12**

To a solution of **11** (192 mg, 0.40 mmol) in THF (5 ml), B_2H_6–THF (1.8 ml, 1.8 mmol) was added and the mixture was refluxed for 20 h under argon gas steam. Quenching with H_2O, evaporation, dilution with H_2O (5 ml), basification (NH_4OH, pH 10), extraction ($CHCl_3$, 10 ml×3), drying (Na_2SO_4), removal of solvent, and chromatography (silica gel H, 5 g, cyclohexane–acetone 5:1) gave compound **12** (100 mg, 51.8%). Compound **12**: mp: 65–67 °C; $[\alpha]_D^{20}$ −5.9 (*c* 0.5, $CHCl_3$); IR (KBr): 3398 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, s, H_3-18), 0.89 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.15 (1H, dd, *J*=10.4, 6.8 Hz, H-1β), 3.34, 3.42, 3.45 (each 3H, s, OCH_3×3), 3.58 (1H, s, H-6α), 3.69–3.75 (1H, m, H-16α), 3.87 (1H, dd, *J*=7.6, 5.6 Hz, H-10), 5.04 (1H, d, *J*=2.4 Hz, H-9), 4.98, 5.12 (each 1H, s, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.1 (d, C-1), 25.4 (t, C-2), 35.6 (t, C-3), 32.2 (s, C-4), 52.8 (d, C-5), 92.8 (d, C-6), 94.1 (s, C-7), 85.1 (s, C-8), 65.9 (d, C-9), 75.9 (d, C-10), 55.0 (s, C-11), 47.9 (d, C-12), 37.6 (d, C-13), 64.2 (t, C-14), 37.4 (t, C-15), 76.8 (d, C-16), 63.0 (d, C-17), 25.6 (q, C-18), 55.4 (t, C-19), 49.9 (t, C-21), 13.8 (q, C-22), 56.7 (q, C-1′), 56.9 (q, C-6′), 58.5 (q, C-16′), 91.8 (t, OCH_2O); ESIMS *m/z* 506 $[M+Na]^+$; HR-ESIMS $[M+Na]^+$ *m/z* calcd for $C_{25}H_{41}NO_8Na$: 506.2724, found: 506.2707.

4.1.11. Preparation of compound **13**

To a solution of **12** (100 mg, 0.21 mmol) in toluene (5 ml), fresh silver carbonate-Celite (936 mg, 1.66 mmol) was added and the reaction solution was refluxed for 17 h. The solution was filtrated, and the filtrate was evaporated to give a residue that was chromatographed (silica gel H, 1.4 g, cyclohexane–acetone 7:1) afforded compound **13** (30 mg, 30%). Compound **13**: mp: 190–192 °C; $[\alpha]_D^{20}$ +2.0 (*c* 0.8, $CHCl_3$); IR (KBr): 3555, 1790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, s, H_3-18), 1.03 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.27 (1H, dd, *J*=10.4, 6.8 Hz, H-1β), 3.35, 3.39, 3.40 (each 3H, s, OCH_3×3), 3.61 (1H, s, H-6α), 3.64 (1H, d, *J*=2.4 Hz, H-17), 3.88–3.93 (1H, m, H-16α), 4.25 (1H, d, *J*=11.2 Hz, H-10), 4.94, 5.14 (each 1H, s, OCH_2O), 5.79 (1H, d, *J*=6.4 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 82.3 (d, C-1), 25.6 (t, C-2), 37.1 (t, C-3), 32.2 (s, C-4), 51.9 (d, C-5), 92.5 (d, C-6), 94.9 (s, C-7), 84.9 (s, C-8), 72.4 (d, C-9), 72.7 (d, C-10), 55.3 (s, C-11), 45.6 (d, C-12), 51.3 (d, C-13), 173.6 (s, C-14), 38.4 (t, C-15), 77.5 (d, C-16), 64.8 (d, C-17), 25.7 (q, C-18), 55.5 (t, C-19), 49.9 (t, C-21), 13.8 (q, C-22), 56.6 (q, C-1′), 58.4 (q, C-6′), 56.6 (q, C-16′), 92.9 (t, OCH_2O); ESIMS *m/z* 502 $[M+Na]^+$; HR-ESIMS $[M+Na]^+$ *m/z* calcd for $C_{25}H_{37}NO_8Na$: 502.2411, found: 502.2416.

4.1.12. Preparation of 4α,9β,13β-trimethoxy-16,17,18,19-nor-7β-methyl-7α-(N-ethylmethylamine)-10,11-dioxymethylen-taxa-2-ene-14β-lide (**14**)

To a solution of **13** (18 mg, 0.038 mmol) in pyridine (1 ml), $SOCl_2$ (0.05 ml) was added and the reaction solution was stirred at room temperature for 1 h. Stopping the reaction with H_2O (0.1 ml), evaporation, basification (saturated $NaHCO_3$ solution), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4), and the removal of solvent gave a residue that was dissolved in a mixture of methanol–H_2O (2 ml, 9:1). The solution was heated at 70 °C for 21 h. Evaporation and chromatography (silica gel H, 500 mg, $CHCl_3$–MeOH 20:0.35→95:5) afforded **14** (13 mg, 78%). Compound **14**: mp: 178–180 °C; $[\alpha]_D^{20}$ −24.3 (*c* 0.6, $CHCl_3$); IR (KBr): 3422, 1786, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) see Table 3; ESIMS *m/z* 480 $[M+H]^+$; HR-ESIMS $[M+H]^+$ *m/z* calcd for $C_{25}H_{38}NO_8$: 480.2592, found: 480.2592.

4.1.13. Preparation of compound **15**

To a solution of **8** (1.5 g, 3.25 mmol) in CH_2Cl_2 (75 ml) was passed ozone gas (50–100 cc/min) at −78 °C for 1.5 h until the reaction solution was changed into blue color and then oxygen gas was passed to remove the remained ozone gas. To the reaction mixture was added Me_2S (2 ml) and the solution stirred at room temperature for 30 min. The removal of solvent in vacuum gave a residue, which was dissolved with THF (70 ml). After adding saturated Na_2SO_3 solution (70 ml), the mixture was stirred vigorously at room temperature for 10 h. The usual work-up gave the crude **10** (1.43 g), and followed by recrystallization from ether to furnish **10** (1.12 g, 70%), as colorless needle crystals. To a solution of the crude **10**, as above, (1.12 g, 2.27 mmol) in THF (25 ml) were added sequentially NaH (545 mg, 22.72 mmol) and CH_3I (0.41 ml, 682 mmol) and the reaction mixture was stirred at room temperature for 2 h under argon steam. The general work-up furnished **15** (1.15 g, 100%). Compound **15**: mp: 96–98 °C; $[\alpha]_D^{20}$ +33.0 (*c* 0.5, $CHCl_3$); IR (KBr): 1649, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 1.24 (3H, s, H_3-18), 3.26, 3.26, 3.37, 3.38 (each 3H, s, OCH_3×4), 3.79 (1H, s, H-6α), 3.84 (1H, dd, *J*=6.4, 4.8 Hz, H-12), 3.97–4.02 (1H, m, H-16α), 2.84–2.91, 4.29–4.36 (each 1H, m, NCH_2CH_3), 4.42 (1H, d, *J*=3.2 Hz, H-17), 4.47 (1H, dd, *J*=10.4, 7.2 Hz, H-1β), 4.99, 5.13 (each 1H, s, OCH_2O), 5.07 (1H, s, H-14), 5.40 (1H, d, *J*=6.8 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) see Table 2; ESIMS *m/z* 508 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ *m/z* calcd for $C_{26}H_{37}NO_9Na$: 530.2361, found: 530.2335.

4.1.14. Preparation of compound **16**

To a solution of **15** (1.09 g, 2.16 mmol) in THF (10 ml) was B_2H_6–THF (8.36 ml, 8.63 mmol) and the mixture was refluxed for 6 h. Quenching the reaction with H_2O, evaporation, dilution with H_2O (10 ml), basification (NH_4OH, pH 10), extraction ($CHCl_3$, 15 ml×3), drying (Na_2SO_4), and the removal of $CHCl_3$, followed by chromatography (silica gel H, 30 g, cyclohexane–acetone 13:1) furnished **16** (504 mg, 78%). Compound **16**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.89/

0.89 (3H, s, H_3-18), 1.03/1.02 (3H, t, J=7.2 Hz, NCH_2CH_3), 3.32, 3.36, 3.38, 3.39/3.35, 3.36, 3.38, 3.39 (each 3H, s, $OCH_3\times4$), 3.62/3.57 (1H, s, H-6α), 3.73–3.78/3.73–3.79 (1H, m, H-16α), 3.80/3.59 (1H, d, J=2.4 Hz, H-17), 4.03 (1H, dd, J=10.4, 7.2 Hz, H-1β), 3.72 (1H, dd, J=10.0, 7.2 Hz, H-1β), 4.42 (1H, d, J=10.0 Hz, H-10α), 4.30 (1H, dd, J=11.6, 1.2 Hz, H-10β), 4.92, 5.08/4.92, 5.09 (each 1H, s, OCH_2O), 4.99/4.94 (1H, s, H-14), 5.40/5.37 (1H, d, J=6.4 Hz, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.4/82.6 (d, C-1), 25.5/25.6 (t, C-2), 37.2/37.3 (t, C-3), 33.1/32.2 (s, C-4), 54.0/52.2 (d, C-5), 92.9/92.7 (d, C-6), 94.1/94.3 (s, C-7), 87.0/87.3 (s, C-8), 78.8/74.1 (d, C-9), 74.2/72.9 (d, C-10), 53.8/55.1 (s, C-11), 47.4/48.7 (d, C-12), 44.4/48.1 (d, C-13), 102.4/102.1 (d, C-14), 38.2/38.1 (t, C-15), 73.7/73.8 (d, C-16), 65.5/64.6 (d, C-17), 25.1/25.7 (q, C-18), 55.6/55.7 (t, C-19), 50.0/49.8 (t, C-21), 13.8/13.8 (q, C-22), 59.8 q, 57.9 q, 56.2 q, 54.7 q/58.3 q, 56.7 q, 56.2 q, 54.7 q (C-1′, 6′, 14′, 16′), 92.4/92.4 (t OCH_2O); ESIMS m/z 496 $[M+H]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{26}H_{41}NO_8Na$: 518.2724, found: 518.2699.

4.1.15. Preparation of 4α,9β,13β,14′β-tetramethoxy-10α-formyl-16,17,18,19-nor-7β-methyl-7α-(N-ethylmethylamine)-10β,11β-dioxymethylen-tax-2-ene-14β-acetal (**17**)

Reaction of a solution of **16** (1.10 g, 2.22 mmol) in pyridine (20 ml) with $SOCl_2$ (0.32 ml, 4.44 mmol) at room temperature for 8 min was carried out. Stopping the reaction with H_2O, followed by chilling at 0 °C, and the removal of pyridine, gave a residue. Diluting (H_2O, 15 ml), basification (5% $NaHCO_3$, pH 8), extraction ($CHCl_3$, 20 ml×3), and evaporation gave a residue (1.18 g), which was dissolved in MeOH–H_2O (30 ml, 9:1), and the solution was refluxed for 15 h. The usual work-up, followed by chromatography (silica gel H, 20 g, $CHCl_3$–MeOH 80:1.4 to 95:5), furnished 923 mg of **17** (84%). Compound **17**: mp: 48–50 °C; $[\alpha]_D^{20}$ +61.2 (*c* 0.6, $CHCl_3$); IR (KBr): 3421, 1721, 1650, 1098 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) see Table 4; ESIMS m/z 496 $[M+H]^+$; HR-ESIMS $[M+H]^+$ m/z calcd for $C_{26}H_{42}NO_8$: 496.2905, found: 496.2909.

4.1.16. Preparation of 4α,9β,13β,14′β-tetramethoxy-10α-acetoxymethylen-16,17,18,19-nor-7β-methyl-7α-(N-acetyl-N-ethylmethylamine)-10β,11β-dioxymethylen-tax-2-en-14β-acetal (**18**)

A mixture of **17** (562 mg, 1.14 mmol), Ac_2O (2 ml), and pyridine (2 ml) was stirred at room temperature for 1 h. The reaction solution was evaporated to yield a residue, which was diluted with H_2O (10 ml) and after basifying to pH 8 using NH_4OH solution was extracted with $CHCl_3$ (15 ml×3). Evaporation of the combined $CHCl_3$ solutions gave a residue, to which THF (10 ml) and $NaBH_4$ (110 mg, 2.89 mmol) were added. The reaction solution was stirred at room temperature for 2.5 h. After quenching with H_2O, extraction with $CHCl_3$ (15 ml×3), drying (Na_2SO_4), and the removal of solvent gave a residue, to which Ac_2O (2 ml) and pyridine (2.5 ml) were added, and the mixture was stirred at 50 °C for 12 h. The usual work-up, followed by chromatography (silica gel H, 15 g, cyclohexane–acetone 7:1) furnished **18** (600 mg, 91%). Compound **18**: mp: 173–175 °C; $[\alpha]_D^{20}$ +58.4 (*c* 0.5, $CHCl_3$); IR (KBr): 1739, 1643 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) see Table 5; ESIMS m/z 604 $[M+Na]^+$; HR-ESIMS $[M+Na]^+$ m/z calcd for $C_{30}H_{47}NO_{10}Na$: 604.3092, found: 604.3120.

4.1.17. Preparation of 11-hydroxyl-4α,9β,13β,14′β-tetramethoxy-16,17,18,19-nor-7β-methyl-7α-(N-acetyl-N-ethylmethylamine)-tax-2-en-14β-acetal-10-one (**19**)

A mixture of **17** (152 mg, 0.31 mmol), Ac_2O (1 ml), and pyridine (1 ml) was stirred at room temperature for 1 h. The reaction solution was evaporated to give a residue, which was diluted with H_2O (10 ml) and after basifying to pH 8 using NH_4OH solution, extracted with $CHCl_3$ (10 ml×3). Evaporation of the combined $CHCl_3$ solutions gave a residue, to which were added $CHCl_3$ (5 ml), *m*CPBA (159 mg, 0.46 mmol), and Na_2CO_3 (80 mg). The reaction solution was stirred at room temperature for 22 h. After quenching with H_2O, extraction with $CHCl_3$ (10 ml×3), drying (Na_2SO_4), and the removal of solvent gave a residue, to which 80% HOAc solution was added and the mixture stirred at room temperature for 3.5 h. After basifying to pH 8 with NH_4OH, extraction with $CHCl_3$ (10 ml×3), drying (Na_2SO_4), and the removal of solvent gave a residue that was chromatographed over silica gel H (4 g) eluted with $CHCl_3$–MeOH (60:0.35) to give compound **19** (105 mg, 69%). Compound **19**: mp: 94–96 °C; $[\alpha]_D^{20}$ +22.2 (*c* 0.5, $CHCl_3$); IR 3409, 1712, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) see Table 6; ESIMS m/z 518 $[M+Na]^+$; HR-ESIMS m/z calcd for $C_{26}H_{41}NO_8Na$: 518.2724, found: 518.2695.

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