Further Studies on Synthesis of the 12,13-*seco* Norditerpenoid Alkaloids

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After a series of optimization for the reaction conditions (reagents, reaction temperature, *etc.*), treatment of the sulfonates 4, 8, 13 and 15 with 8% NaOH (room temperature, 24 h) *via* a semipinacol rearrangement afforded the corresponding C-nor compounds 5, 9, 12 and 16, as the major of a pair of epimer at C-16, to an excellent extent, in 95%, 92%, 100% and 90% yield, respectively. The 12,13-*seco* compounds 21 and 22 (23) were obtained in 20% and 60% yield, respectively, by treating 5 with Br_2–glacial HOAc (room temperature, 24 h). Treatment of the C-nor compounds 5 or 6, 16 or 17, and 28 from 10 with $SOCl_2$–anhydrous benzene (room temperature, overnight) afforded the 12,13-*seco* compounds 24, 26 and 30 in 70% or 100%, 40% and 66% yield, respectively. When treatment of the C-nor compound 29 from 9 under same conditions gave the 12,13-*seco* products 30, 31 and 32 in 33%, 26% and 20% yield. When treating 21 or 24, and 26 with 5% KOH in EtOH afforded the 12,13-*seco* compounds 25 and 27 quantitatively, respectively. The compound 31 converted to 30 quantitatively by treatment with Na_2CO_3 in MeOH. All of the new compounds were isolated and fully characterized.

Key words norditerpenoid alkaloid; yunaconitine; 12,13-*seco* norditerpenoid alkaloid

In the previous paper of this series,[1] we reported the synthesis of the 12,13-*seco* norditerpenoid alkaloids from the norditerpenoid alkaloids. This is the key stage in the modification of the norditerpenoid alkaloids for evaluation of their biological activities. Herein, we have continued to describe in detail the further synthesis of the 12,13-*seco* norditerpenoid alkaloids.

Results and Discussion

In our investigation toward the modification of the bioactive norditerpenoid alkaloids, the synthesis of 12,13-*seco* norditerpenoid alkaloids is one of most difficult steps, which has not been reported in the literature before. After a series of unsuccessful experiments,[2,3] we finally found that the 12,13-*seco* norditerpenoid alkaloids can be synthesized *via* a semipinacol rearrangement followed by reaction with Br_2–HOAc.[1] This is the first novel access to the 12,13-*seco* norditerpenoid alkaloid recently reported by us.

To investigate further the effect of the A ring structures on the reaction, we have prepared a series of C-nor compounds (Chart 1), with different structural moieties of the A ring. The α,β-unsaturated ketone methyl sulfonate **4**, $C_{25}H_{37}NO_9S$ (high resolution electron impact (HR-EI)-MS), was obtained using yunaconitine **1**[4] as the starting material *via* **2**[4] and **3** in three steps in nearly quantitative overall yields (Chart 2). The ^{1}H- and ^{13}C-NMR spectra of **4** indicated the presence of an α,β-unsaturated ketone moiety (δ_H 6.20, 6.37, each 1H, d, J=10.2 Hz; δ_C 146.6 d, 132.0 d, 200.4 s) and a methylsulfonyl group (δ_H 3.11, 3H s; δ_C 38.5 q) which can be assigned at C-14 due to observation of the one-proton signal at δ_H 4.75 (d, J=6.2 Hz), attributable to H-14β. The reaction of **4** with NaOH was carried out in *N*,*N*-dimethylformamide (DMF) at 150 °C for 6.5 h to give compounds **5** and **6** as a pair of epimers in 68% and 5% yield, respectively. Both compounds **5** and **6** have the same molecular formula $C_{24}H_{33}NO_6$ (HR-EI-MS). The ^{1}H- and ^{13}C-NMR spectra of **5** and **6** showed three aliphatic methoxyl groups (δ_H 3.26, 3.40, 3.48, each 3H, s; δ_C 58.2 q, 58.3 q, 59.0 q for **5**; δ_H 3.25, 3.34, 3.37, each 3H, s; δ_C 58.0 q, 58.4 q, 58.9 q for **6**), a carbonyl group (δ_C 211.6, s for **5**; δ_C 212.1 s for **6**) and an α,β-unsaturated ketone (δ_H 6.21, 6.26, each 1H, d, J=10.0 Hz; δ_C 144.9 d, 132.4 d, 200.6 s for **5**; δ_H 6.19, 6.26, each 1H, d, J=10.0 Hz; δ_C 145.1 d, 132.2 d, 200.8 s for **6**). Their structures were determined on the basis of spectra compared, in particular, with compounds **9**[1] and **10**,[1] which were obtained from **8**.[1] The δ values of H-1 in the ^{1}H-NMR spectra of compounds **4**, **5** and **6** displayed higher than the general cyclohexenone, possibly due to the presence of a steric hindrance between H-1 and H-12α in the these rigid molecules. Similarly, when compound **3** was subjected to treatment subsequently through reduction with H_2/Pd–C, sulfonation and semipinacol rearrangement, another pair of the C-nor compounds **12** and **14** in 37% and 10% yield, respectively, were afforded (Chart 3). Both compounds **12** and **14** have the same molecular formula $C_{24}H_{35}NO_6$ (HR-EI-MS). Their ^{1}H- and ^{13}C-NMR spectra showed the absence of OMs group but two carbonyl groups (δ_H 216.9 s, 212.2 s for **12**; δ_C 217.2 s, 212.7 s for **14**). The structures of **12** and **14** were confirmed on the basis of comparison of the NMR spectra with those of the analogues such **5**, **6**, **9** and **10** (Table 1). When the same reaction conditions were applied to **15** from the 3-ketone **13** by protection with ethylene glycol, 48% and 10% yields of compounds **16** and **17**, respectively, were also obtained as a pair of epimers (Chart 4). Their structures were also confirmed by comparison of the NMR spectra with the analogues **5**, **6**, **9**, **10**, **12** and **14** (Table 1). It should be noted that we have synthesized the C-nor compounds **5**/**6**, **9**/**10**, **12**/**14** and **16**/**17**, as epimeric pairs at C-16, only in moderate yields (37—70%). It is apparent that this is possibly due to the vigorous reaction conditions (NaOH, high temperature). However, the attempt to enhance the yields of the resulting products using **8** in pyridine as the starting material at 140 °C for 12 h resulted in the formation of the compounds **9** and **10** in poor yields (3%, 18%, respectively). This implies that the strong base, *e.g.*, NaOH, is necessary for a semipinacol rearrangement. After a series of optimization for the reaction conditions, we have fortunately found that reactions of the compounds **4**, **8**, **13** and **15** with 8% NaOH carried out under the standard conditions in methanol at room temperature for 24 h gave the corresponding C-nor products **5**, **9**, **12** and **16**,

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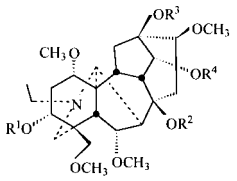
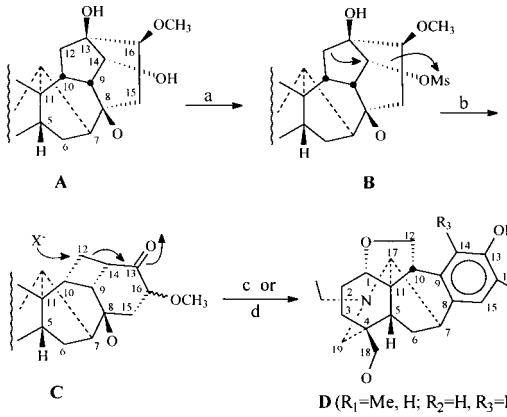


1 R1= R3=H R2=Ac R4=As

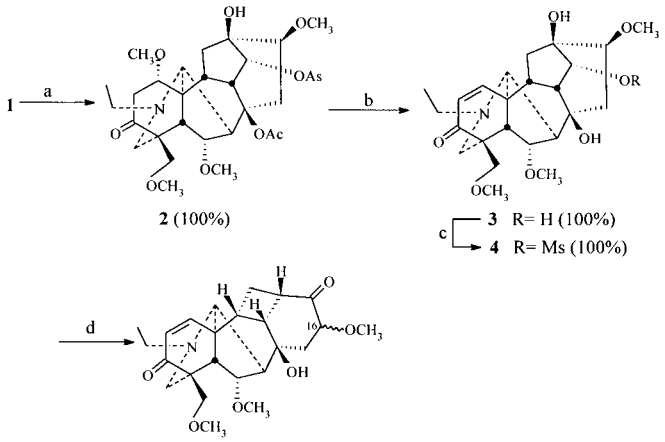
7 R1= R2=R3=R4=H



a). 3 equiv. MsCl/pyridine, r.t (~80% yield); b). method A: DMF/NaOH, 150℃, 14h (~68% yield); method B: 8% NaOH in MeOH, rt, 24h (90~100% yield)

c). Br_2 (1.2 equiv) in HOAc, rt, 1.5h or 1h; d). Br_2 (2.0 equiv) in HOAc, rt, 2h.

Chart 1



2 (100%)

3 R= H (100%)

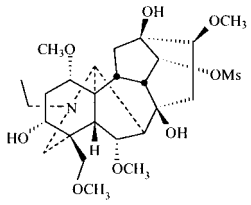
4 R= Ms (100%)

5 (16α-OCH_3)

6 (16β-OCH_3)

a). Jones reagent, 0℃, 20 min; b). 5% NaOH, in MeOH, 55℃, 0.5h; c). MsCl-Pyridine, rt, 4h; d). method A: NaOH in DMF, 150℃, 6.5h; (**5**: 68%; **6**: 5%); method B: 8% NaOH in MeOH, rt, 24h (**5**: 95%; **6**: no detected).

Chart 2



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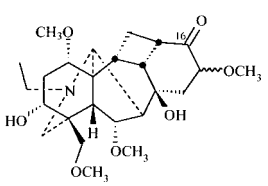
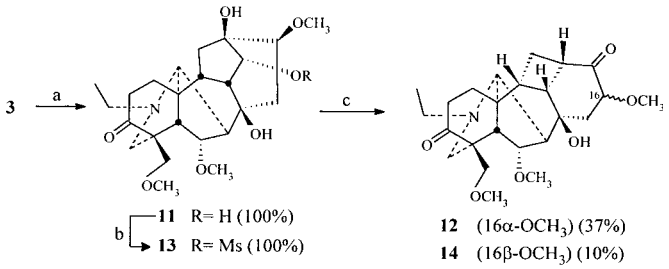


9 (16α-OCH_3)

10 (16β-OCH_3)



11 R= H (100%)

13 R= Ms (100%)

12 (16α-OCH_3) (37%)

14 (16β-OCH_3) (10%)

a). H_2. Pd/C; b). MsCl-pyridine, 40℃, 1.5h; c). method A: NaOH in DMF, 150℃, 12h (**12**: 37%; **14**: 10%); method B: 8% NaOH in MeOH, rt, 24h (**12**:100%; **14**: no detected)

Chart 3

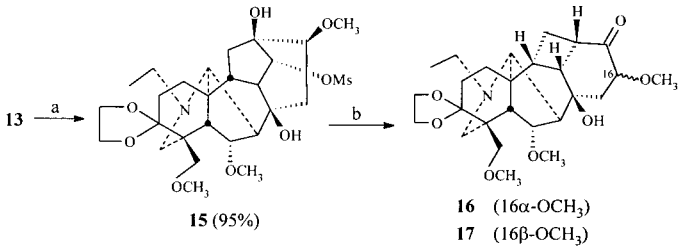
Table 1. ^{13}C-NMR Data of Compounds **5**, **6**, **9**, **10**, **12**, **14**, **16** and **17**

No.	5	6	9	10	12	14	16	17
1	144.9 d	145.1d	80.9	81.0	22.6 t	22.7 t	25.1 t	25.5 t
2	132.4 d	132.2 d	34.4	34.3	38.5 t	38.7 t	30.9 t	31.0 t
3	200.6 s	200.8 s	71.6	72.0	216.9 s	217.2 s	112.7 s	112.9 s
4	47.2 s	47.0 s	42.2	42.4	43.4 s	43.4 s	43.3 s	43.3 s
5	48.1 d	48.4 d	47.3	47.6	44.1 d	44.5 d	46.1 d	47.0 d
6	83.0 d	82.5 d	83.5	82.9	83.8 d	83.4 d	84.1 d	84.0 d
7	52.2 d	50.4 d	52.0	50.3	51.5 d	49.9 d	51.7 d	50.1 d
8	77.3 s	74.0 s	76.5	72.7	77.3 s	74.1 s	76.9 s	73.9 s
9	43.8 d	46.7 d	43.7	46.8	44.0 d	47.2 d	44.0 d	46.4 d
10	40.2 d	40.8 d	44.5	44.3	42.8 d	43.5 d	43.5 d	44.0 d
11	50.4 s	50.4 s	47.8	47.8	52.4 s	52.5 s	45.1 s	45.1 s
12	27.4 t	28.0 t	30.6	31.3	27.1 t	27.7 t	27.5 t	28.1 t
13	211.6 s	212.1 s	211.1	208.7	212.2 s	212.7 s	212.4 s	212.7 s
14	37.7 d	35.3 d	38.8	36.3	37.6 d	35.3 d	38.1 d	35.7 d
15	42.2 t	40.3 t	39.8	37.5	42.1 t	40.5 t	41.6 t	39.9 t
16	79.1 d	81.9 d	79.1	80.7	79.1 d	82.2 d	79.2 d	82.0 d
17	61.5 d	61.2 d	61.5	61.5	66.1 d	66.0 d	65.0 d	64.8 d
18	71.6 t	71.8 t	76.1	76.9	74.4 t	74.7 t	73.1 t	73.2 t
19	48.7 t	48.6 t	46.7	46.9	48.6 t	48.5 t	48.6 t	48.5 t
21	50.9 t	50.9 t	48.6	48.7	52.2 t	52.3 t	50.2 t	50.2 t
22	12.8 q	12.8 q	13.2	13.1	12.9 q	13.0 q	13.1 q	13.0 q
1′	—	—	55.9	55.8	—	—	—	—
6′	58.2 q	58.0 q	58.1	57.7	58.0 q	57.9 q	58.0 q	58.0 q
16′	58.3 q	58.4 q	58.1	58.1	58.1 q	58.3 q	58.2 q	58.2 q
18′	59.0 q	58.9 q	59.0	59.1	58.9 q	58.9 q	58.7 q	58.9 q
O–CH_2 | O–CH_2	—	—	—	—	—	—	64.3 t 65.2 t	64.3 t 65.7 t

to an excellent extent, in 95%, 92%, 100% and 90% yield, respectively. Therefore, this successful optimization provided a good base for us to further synthesize the final 12,13-*seco* products *via* cleavage of the C(12)–C(14) bond of the C-nor compounds. In addition to the context of this discussion on the semipinacol rearrangement, it is of interest to note that only the major one of two spots on TLC of the resulting products before work-up were observed but finally obtaining the major products bearing the 16α-methoxyl groups, apparently by an epimerization process under the alkaline conditions from the 16β-OCH_3 group to the 16α-OCH_3 group.

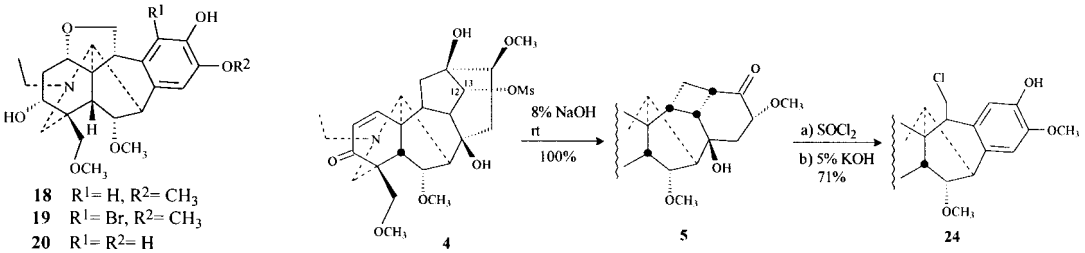
This is plausible for the C-nor compounds bearing the 16α-OCH_3 group without the de-stabilizing interaction between the 16-OCH_3 and the 8β-OH group.

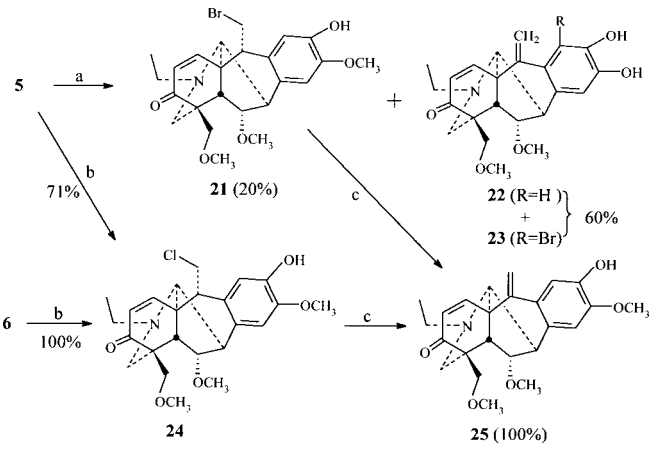
Recently, we reported the preparation of the key intermediates **18**, **19** and **20** using different eq of Br_2 in HOAc from **9** in 40%, 29% and 10% yield, respectively.[1)] But, the results



a). glycol/anhydrous benzene, TsOH, reflux, 5h; b). method A: NaOH in DMF, 160℃, 15h (**16**: 48%; **17**: 10%); method B: 8% NaOH in MeOH, rt, 24h (**16**: 90%; **17**: no detected)

Chart 4





a). Br_2-glacial HOAc, rt, 4h; b). $SOCl_2$-anhydrous benzene, rt, overnight; c). 5% KOH in EtOH, 50℃, 30min.

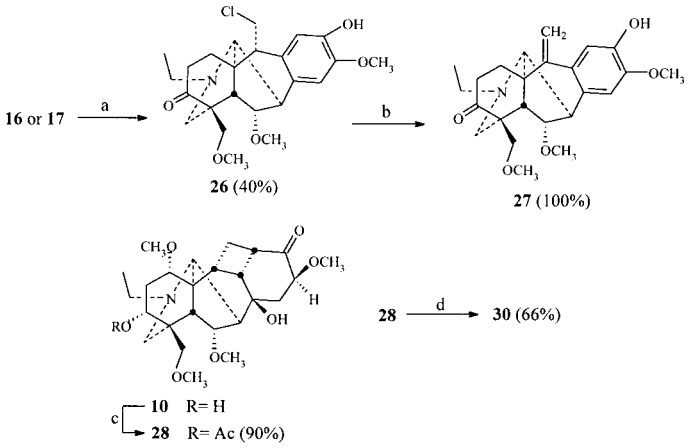
Chart 5

obtained in further study clearly indicated that cleavage of the C(12)–C(14) bond with aromatization of the D ring greatly depended on the structures of the substrates and the exact reaction conditions.

Accordingly, as an important part of our continuing synthetic study of the 12,13-*seco* norditerpenoid alkaloids, we have further studied the role of the structures of the A ring in the cleavage of the C(12)–C(14) bond of the C-nor compounds. Treatment of the C-nor compound **5** with 1.2 eq Br_2 in HOAc at room temperature for 4 h afforded the 12,13-*seco* intermediate **21**, and the mixture of **22** and **23** in 20% and 60% yield, respectively. The molecular formula ($C_{24}H_{30}NO_5Br$) of compound **21** inferred from its HR-EI-MS and ^{13}C-NMR spectra. Its ^{1}H- and ^{13}C-NMR spectra showed an *exo*-methylene group double bond (δ_H 5.02, 5.53, each 1H, br s; δ_C 151.7 s, 110.0 t). Compounds **22** and **23** have the molecular formula $C_{23}H_{27}NO_5$ (HR-EI-MS) and $C_{23}H_{26}NO_5Br$ (HR-EI-MS), respectively. Their ^{1}H- and ^{13}C-NMR spectra showed the presence of an *exo*-methylene group double bond and an α,β-undsaturated ketone (Table 2 and the Experimental). Cleavage of the C(12)–C(14) bond in **5** by the method recently reported from our laboratory[1] gave the 12,13-*seco* product **24** in good yield (71%) and a clear-cut reaction (Chart 5). The molecular formula $C_{24}H_{30}NO_5Cl$ of **24** can be established by its HR-EI-MS. Its structure was confirmed easy by comparison of the NMR data (Table 2) with **21**. Similarly, reaction of the C-nor compounds **6**, **16** (**17**) and **28** in the presence of only $SOCl_2$ in benzene instead of Br_2 in HOAc at room temperature resulted in the forma-

Table 2. ^{13}C-NMR Data of Compounds **21**, **24**, **26**, **22**/**23**, **25** and **27**

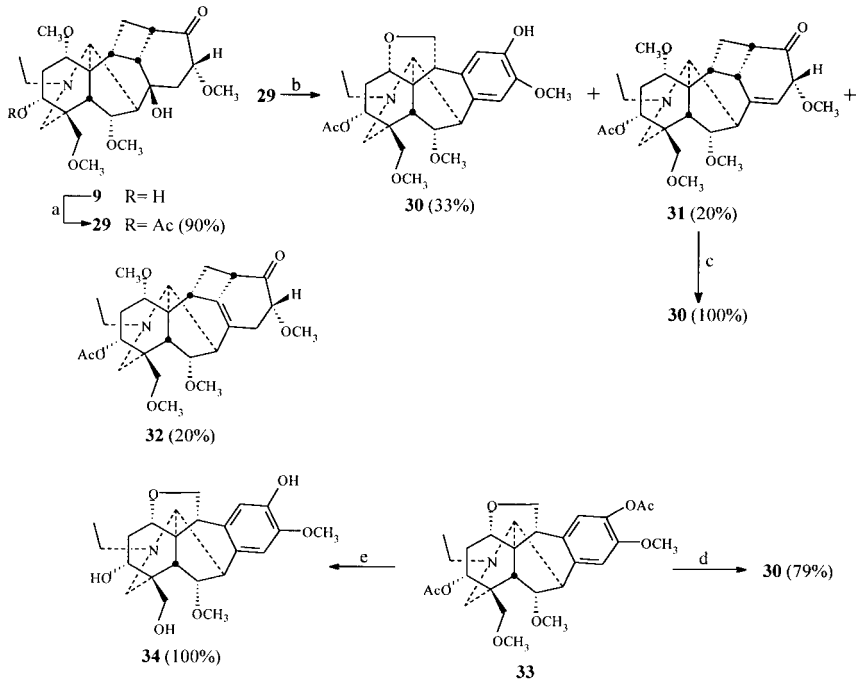
No.	21	24	26	22/23	25	27
1	147.5 d	147.4 d	26.6 t	150.4 (149.7) d	149.5 d	27.1 t
2	132.7 d	132.8 d	39.5 t	132.2 (131.9) d	132.0 d	40.2 t
3	200.2 s	200.2 s	214.9 s	201.7 (201.6) s	200.8 s	217.6 s
4	50.7 s	50.4 s	45.6 s	51.6 (51.6) s	50.0 s	47.4 s
5	47.8 d	49.0 d	49.9 d	46.7 (46.3) d	47.3 d	45.5 d
6	91.9 d	91.7 d	93.5 d	91.7 (91.4) d	91.7 d	91.9 d
7	51.0 d	50.7 d	49.9 d	51.5 (52.2) d	51.3 d	47.7 d
8	139.4 s	139.5 s	140.2 s	138.4 (136.4) s	138.0 s	137.7 s
9	126.7 s	125.9 s	127.4 s	126.2 (127.9) s	127.0 s	127.7 s
10	46.0 d	49.0 d	45.2 d	151.6 (151.5) s	151.7 s	155.7 s
11	48.8 s	45.9 s	52.4 s	51.8 (51.8) s	51.8 s	52.0 s
12	36.2 t	45.9 t	47.8 t	110.3 (112.1) t	111.0 t	108.7 t
13	143.9 s	143.9 s	143.6 s	142.6 (143.0) s	144.2 s	143.9 s
14	106.9 d	106.9 d	106.5 d	111.6 (107.3) d	106.7 d	106.3 d
15	113.9 d	113.7 d	113.9 d	111.2 (111.0) d	110.7 d	110.7 d
16	145.1 s	145.0 s	144.8 s	144.4 (140.8) s	146.3 s	145.8 s
17	65.5 d	65.9 d	69.6 d	67.7 (67.9) d	68.0 d	72.3 d
18	71.4 t	71.3 t	72.8 t	71.7 (71.7) t	71.5 t	74.5 t
19	49.1 t	49.2 t	49.0 t	49.3 (49.1) t	49.1 t	48.9 t
21	50.8 t	50.6 t	50.9 t	50.9 (50.9) t	50.9 t	52.0 t
22	12.8 q	12.7 q	13.1 q	12.6 (12.5) q	12.8 q	12.8 q
6′	58.6 q	58.1 q	58.3 q	58.5 (58.9) q	58.6 q	58.3 q
16′	55.9 q	55.9 q	55.8 q	—	56.0 q	55.8 q
18′	59.1 q	58.5 q	58.9 q	59.2 (59.2) q	59.1 q	58.9 q



a). $SOCl_2$-anhydrous benzene, rt, overnight; b). 5% KOH in EtOH, rt, 2h;

c). Ac_2O-pyridine rt, 12h; d). $SOCl_2$-anhydrous benzene, rt, overnight

Chart 6



a). Ac_2O/pyridine, rt, 12h b). $SOCl_2$-anhydrous benzene, rt, overnight; c). Na_2CO_3 in MeOH, rt, overnight. d). 40% HBr, CH_2Cl_2, r.t; 2h; e). 40% HBr, CH_2Cl_2, 80℃, 3h

Chart 7

tion of the 12,13-*seco* products **24**, **26**, and **30** in 100%, 40% and 66% yield, respectively (Charts 5, 6). But, when the similar reaction conditions were applied to the C-nor compound bearing the 1α-OCH_3 group (**29**), the 12,13-*seco* compound **30** was obtained in 33% yield besides the by-products **31** and **32**. Both compounds **31** and **32** have the same molecular formula $C_{27}H_{39}NO_7$ (HR-EI-MS). Their ^{1}H- and ^{13}C-NMR spectra showed characteristic signals at δ_H 5.34, 1H, br s; δ_C 145.3 s, 116.0 d for a trisubstituted double bond in **31**, δ_C 136.8 s, 134.2 s for a tetrasubstituted double bond in **32**. The former (**31**) was converted to **30** upon treatment with Na_2CO_3 (Chart 7). The results of the studies mentioned above indicated the following points: 1). the 1α-OCH_3 group of the C-nor molecules such as **9**, **10** could participate in the cleavage reaction but was not in itself necessary; 2). the α,β-unsaturated ketone or the 3-ketone of the A ring (*e.g.*, **5** or **13**, **14**) also may enhance slightly the yields of the resulting products; 3). it is apparent that $SOCl_2$ in benzene instead of Br_2 in HOAc should be used in the cleavage C-nor compounds not bearing the 1-OCH_3 group.

The halogen-containing 12,13-*seco* norditerpenoid alkaloids such as **21**, **24** and **26** were subjected to treatment with

Table 3. ^{13}C-NMR Data of Compounds **29**, **31**, **32**, **30**, **33** and **34**

No.	**29**	**31**	**32**	**30**	**33**	**34**
1	80.5 d	81.0 d	80.6 d	79.9	79.8 d	80.2 d
2	31.4 t	31.1 t	30.6 t	30.4	30.3 t	34.3 t
3	71.4 d	71.5 d	71.6 d	72.7	72.6 d	75.5 d
4	41.4 s	41.5 s	41.0 s	42.6	42.6 s	43.8 s
5	45.2 d	46.3 d	47.5 d	44.3	45.1 d	47.0 d
6	83.8 d	84.6 d	93.6 d	92.0	91.3 d	91.4 d
7	52.0 d	46.7 d	49.1 d	49.1	48.8 d	49.2 d
8	76.3 s	145.3 s	136.8 s	137.6	137.8 s	137.6 s
9	43.6 d	41.4 d	134.2 s	129.0	128.6 s	129.0 s
10	44.7 d	43.3 d	42.0 d	44.6	44.4 d	44.1 d
11	47.6 s	48.4 s	45.8 s	51.1	51.1 s	51.3 s
12	30.5 t	29.4 t	27.7 t	73.6	73.5 t	73.5 t
13	211.4 s	208.8 s	209.4 s	143.9	144.3 s	143.9 s
14	38.8 d	36.6 d	56.9 d	114.0	122.1 d	107.3 s
15	39.9 t	116.0 d	38.3 t	107.3	109.0 d	114.0 d
16	79.2 d	80.5 d	79.6 d	144.0	149.0 s	144.6 s
17	61.3 d	69.5 d	67.8 d	66.5	66.2 d	66.8 d
18	71.4 t	71.5 t	71.3 t	72.0	71.9 t	67.7 t
19	47.4 t	47.6 t	47.8 t	47.7	47.7 t	46.7 t
21	48.6 t	48.9 t	49.2 t	48.8	48.8 t	49.0 t
22	13.2 q	13.0 q	13.0 q	12.9	12.9 q	13.1 q
1′	56.1 q	56.2 q	55.9 q	—	—	—
6′	58.1 q	57.9 q	57.9 q	58.2	58.3 q	58.2 q
16′	58.2 q	58.4 q	58.3 q	55.9	55.8 q	56.0 q
18′	58.7 q	58.8 q	58.8 q	58.9	58.9 q	—
3-OAc	170.2 s	170.1 s	170.1 s	170.0	169.9 s	—
	21.1 q	21.0 q	21.0 q	21.0	21.0 q	—
13-OAc	—	—	—	—	168.9 s	—
	—	—	—	—	20.5 q	—

5% KOH in ethanol under conditions (room temperature, or 50 °C; 30 min or 2 h, respectively) resulting in elimination to produce the 12,13-*seco* compounds bearing the $\Delta^{10(12)}$ double bonds (**25**, **27**) in nearly quantitative yields (Charts 5, 6).

It is worthy of note that our attempts to cleavage of the tetrahydrofuran ring of **33** using a variety of reagents (*e.g.*, SeO_2, H_2/Pd–C, $HClO_4$ or HBr) were not successful. Only compounds **30** and **34** were obtained by reaction of **33** with 40% HBr in CH_2Cl_2 at room temperature for 2 h and 80 °C for 3 h, respectively (Chart 7). The molecular formula of both analogues **30** ($C_{26}H_{35}NO_7$) and **34** ($C_{23}H_{31}NO_6$) was determined by their HR-EI-MS. The structures of **30** an **34** were determined by comparison of the NMR spectra with the known compound **33.**[1)]

In summary, we have continued to investigate further the nature of the stereoselectivity of the key cleavage reactions of C(12)–C(13) bonds and to develop practical protocols for this purpose. Meanwhile, a series of new norditerpenoid alkaloids were obtained. This is very useful for studies of the chemistry of this class of alkaloids.

Experimental

General Experimental Procedures Melting points are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter at 20±1 °C. ^{1}H- and ^{13}C-NMR spectra were measured on a Bruker AC-E 200 or a Varian INOVA-400/54 spectrometer, in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; IR spectra were recorded on a Perkin-Elmer 983 spectrometer; MS were obtained with a VG Auto spec-3000 mass spectrometer; TLC was performed on silica gel GF_{254} percolated plates, sprayed with a modified Dragendoff's reagent for detection; Column chromatography was carried out on Silica gel H (10—40 μm); All silica gel GF_{254} and silica gel H used in the experiments were purchased from the Qingdao Sea Chemical.

Compound 2 To a solution of yunaconitine **1** (1066 mg, 1.62 mmol) in acetone (20 ml), Jone's reagent (1.75 ml, 4.85 mmol) was added dropwise under ice bath. After this, the solution was stirred for 20 min. Deluting (H_2O, 20 ml), basifying (NH_4OH, pH=11), extraction ($CHCl_3$, 20 ml×5), drying (Na_2SO_4) afforded the product as colorless needle crystals, 1063 mg (100%). *Rf* 0.72 (cyclohexane/acetone=1 : 1); mp 180—180.5 °C; IR (KBr) cm^{-1}: 3450 (OH), 2977, 2820, 1723 (COO), 1605, 1511, 1459, 1373, 1259, 1171, 1099; ^{1}H-NMR (200 MHz) δ: 0.98 (3H, t, J=7.2 Hz, $\underline{N}CH_2\underline{CH}_3$), 1.35 (3H, s, 8-OAc), 3.14, 3.14, 3.16, 3.52 (each 3H, s, OCH_3×4), 3.47, 3.69 (each 1H, ABq, J=8.2 Hz, H_2-18), 3.82 (3H, s, Ar-OCH_3), 4.06 (1H, d, J=6.0 Hz, H-6β), 4.89 (1H, d, J=5.2 Hz, H-14β), 6.89, 7.96 (each 2H, AA′BB′, J=9.0 Hz, Ar-H); ^{13}C-NMR (50 MHz) δ: 83.5 (d, C-1), 42.3 (t, C-2), 214.5 (s, C-3), 53.3 (s, C-4), 47.4 (d, C-5), 83.2 (d, C-6), 44.0 (d, C-7), 85.6 (s, C-8), 44.7 (d, C-9), 41.1 (d, C-10), 49.8 (s, C-11), 34.3 (t, C-12), 74.5 (s, C-13), 78.4 (d, C-14), 40.2 (t, C-15), 81.0 (d, C-16), 60.9 (d, C-17), 75.7 (t, C-18), 52.9 (t, 19) 47.6 (t, C-21), 12.5 (q, C-22), 56.0 (q, C-1′), 58.7 (q, C-6′), 57.8 (q, C-16′), 58.9 (q, C-18′), 165.7 (s, ArCO), 122.2, (s, C-1 ″), 131.5 (d, C-2 ″, 6 ″), 113.7 (d, C-3 ″, 5 ″), 163.4 (s, C-4 ″), 55.3 (q, ArOCH_3), 169.8 (s, OAc), 21.4 (q, OAc); EI-MS *m/z* (%) 657 (M^+, 2), 642 (M−15, 2), 626 (M−31, 29), 625 (M−32, 66), 565 (100).

Compound 3 A solution of 3-dehydroyunaconitine (**2**) (1063 mg, 1.62 mmol) in 5% methanolic NaOH (25 ml) was heated at 55 °C for 30 min. Removal of solvent, deluting (H_2O, 10 ml), extraction ($CHCl_3$, 10 ml×5), drying (Na_2SO_4) and evaporation afforded the product as white amorphous powder, 726 mg (100%). *Rf* 0.33 (cyclohexane/acetone=1 : 1); IR (KBr) cm^{-1}: 3481 (OH), 2972, 2889, 2820, 1670 (CO), 1456, 1391, 1243, 1198, 1095, 1021, 970, 937, 752, 620; ^{1}H-NMR (200 MHz) δ: 1.02 (3H, t, J=6.8 Hz, $\underline{N}CH_2\underline{CH}_3$), 3.28, 3.37, 3.44 (each 3H, s, OCH_3×3), 4.11 (1H, d, J=6.8 Hz, H-6β), 4.23 (1H, d, J=6.4 Hz, H-14β), 6.23 (1H, d, J=10.2 Hz, H-2), 6.43 (1H, d, J=10.2 Hz, H-1); ^{13}C-NMR (50 MHz) δ: 147.7 (d, C-1), 131.6 (d, C-2), 200.6 (s, C-3), 49.2 (s, C-4), 48.8 (d, C-5), 81.5 (d, C-6), 52.9 (d, C-7), 74.6 (s, C-8), 48.7 (d, C-9), 37.8 (d, C-10), 50.9 (s, C-11), 38.3 (t, C-12), 76.3 (s, C-13), 79.2 (d, C-14), 43.4 (t, C-15), 82.7 (d, C-16), 61.1 (d, C-17), 72.0 (t, C-18), 48.6 (t, C-19), 51.3 (t, C-21), 12.9 (q, C-22), 57.9 (q, C-6′), 58.0 (q, C-16′), 59.0 (q, C-18′); EI-MS *m/z* (%) 449 (M^+, 100), 434 (M−15, 60), 418 (M−31, 75).

Compound 4 A mixture of compound **3** (450 mg, 1.0 mmol) in pyridine (30 ml) and MsCl (0.15 ml, 2.0 mmol) was stirred at room temperature for 4 h. Removal of solvent, basifying (10% Na_2CO_3), extraction ($CHCl_3$, 20 ml×5), drying (Na_2SO_4), evaporation and crystallization afforded the product as colorless needle crystals, 526 mg (100%). mp 111—111.5 °C; *Rf* 0.52 (cyclohexane/acetone=1 : 1); $[\alpha]_D^{20}$ +106.0° (c=1.00, $CHCl_3$); IR (KBr) cm^{-1}: 3458 (OH), 2930, 2825, 1671 (CO), 1453, 1347, 1175, 1121, 1097, 981, 885; ^{1}H-NMR (200 MHz) δ: 0.96 (3H, t, J=7.0 Hz, $\underline{N}CH_2\underline{CH}_3$), 2.43 (2H, q, J=7.2 Hz, $N\underline{CH}_2CH_3$), 3.11 (3H, s, 14-$OSO_2\underline{CH}_3$), 3.23, 3.34, 3.41 (each 3H, s, OCH_3×3), 3.76, 3.85 (each 1H, ABq, J=8.0 Hz, H_2-18), 4.08 (1H, d, J=4.0 Hz, H-6β), 4.75 (1H, d, J=6.0 Hz, H-14β), 6.20 (1H, d, J=10.2 Hz, H-2), 6.37 (1H, d, J=10.2 Hz, H-1); ^{13}C-NMR (50 MHz) δ: 146.6 (d, C-1), 132.0 (d, C-2), 200.4 (s, C-3), 49.4 (s, C-4), 48.7 (d, C-5), 81.6 (d, C-6), 53.8 (d, C-7), 74.6 (s, C-8), 47.3 (d, C-9), 37.6 (d, C-10), 50.8 (s, C-11), 37.6 (t, C-12), 74.7 (s, C-13), 85.2 (d, C-14), 42.9 (t, C-15), 82.0 (d, C-16), 60.6 (d, C-17), 71.9 (t, C-18), 48.8 (t, C-19), 51.4 (t, C-21), 12.8 (q, C-22), 58.2 (q, C-6′), 58.0 (q, C-16′), 59.0 (q, C-18′), 38.5 (q, OMs); EI-MS *m/z* (%) 527 (M^+, 87), 512 (M−15, 35), 496 (M−31, 45), 449 (48); HR-EI-MS *m/z* 527.2187 (Calcd for $C_{25}H_{37}NO_9S$, 527.2189).

Compounds 5 and 6 Method A: To a solution of compund **4** (526 mg, 1.0 mmol) in DMF (30 ml), NaOH (100 mg) was added and the solution was heated at 150 °C for 6.5 h. Removal of solvent, deluting (H_2O), extraction ($CHCl_3$, 25 ml×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, cyclohexane/acetone=3 : 1) afforded the pure products as white amorphous powder, **5** (290 mg, 68%) and **6** (20 mg, 5%).

Method B: A mixture of compound **4** (100 mg, 0.19 mmol) in 8% methanolic NaOH (5 ml) was stirred at room temperature for 24 h. Removal of solvent, deluting (H_2O), extraction ($CHCl_3$, 5 ml×4), drying (Na_2SO_4) and evaporation afforded the product as white amorphous powder **5**: 78 mg (95%); *Rf* 0.66 (cyclohexane/acetone=1 : 1); $[\alpha]_D^{20}$ +105.9° (c=1.02, $CHCl_3$); IR (KBr) cm^{-1}: 3447 (OH), 2927, 2824, 1719 (CO), 1668 (CO), 1455, 1398, 1321, 1207, 1120, 973; ^{1}H-NMR (200 MHz) δ: 0.96 (3H, t, J=7.0 Hz, $\underline{N}CH_2\underline{CH}_3$), 3.26, 3.40, 3.48 (each 3H, s, OCH_3×3), 3.56, 3.86 (each 1H, ABq, J=8.4 Hz, H_2-18), 4.00 (1H, dd, J=6.0, 2.0 Hz, H-6β), 4.19 (1H, dd, J=13.0, 4.9 Hz, H-16β), 6.21 (1H, d, J=10.0 Hz, H-2), 6.26 (1H, d, J=10 Hz, H-1); ^{13}C-NMR (50 MHz) δ see Table 1; EI-MS *m/z* (%) 431(M^+, 100), 416 (M−15, 50), 400 (M−31, 38) HR-EI-MS *m/z* 431.2282 (Calcd for $C_{24}H_{33}NO_6$, 431.2307); **6**: *Rf* 0.85 (cyclohexane/acetone=1 : 1); IR (KBr) cm^{-1}: 3532 (OH), 2930, 2826, 1712 (CO), 1667 (CO), 1457, 1384, 1310, 1187, 1113, 973; ^{1}H-NMR (200 MHz) δ: 0.92 (3H, t, J=7.2 Hz, $\underline{N}CH_2\underline{CH}_3$), 3.25, 3.34, 3.37 (each 3H, s, OCH_3×3), 3.66, 3.83 (each 1H, ABq,

J=8.4 Hz, H_2-18), 3.96 (1H, exchangeable in D_2O, 8-OH), 4.08 (1H, dd, J=6.2, 2.2 Hz, H-6β), 6.19 (1H, d, J=10.0 Hz, H-2), 6.26 (1H, d, J=10.0 Hz, H-1); ^{13}C-NMR (50 MHz) see Table 1; EI-MS m/z (%) 431 (M^+, 100), 416 (M−15, 54), 400 (M−31, 60), 399 (60); HR-EI-MS m/z 431.2354 (Calcd for $C_{24}H_{33}NO_6$ 431.2307).

Compound 8 To a solution of pseudaconine (**7**)[5] (185 mg, 0.38 mmol) in pyridine (10 ml), MsCl (0.09 ml, 1.15 mmol) was added and the solution was stirred at room temperature for 2 h. Removal of solvent, basifying (10% Na_2CO_3), extraction ($CHCl_3$, 10 ml×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, cyclohexane/acetone/diethylamine= 4 : 2 : 0.1) afforded the product as white amorphous powder, 165 mg (78%); It was idenfied by comparison of TLC (silica gel G, Rf 0.31, cyclohexane/acetone=1 : 1) with the authentic sample.

Compounds 9 and 10 Method A: To a solution of Compound **8** (160 mg, 0.28 mmol) in DMF (8 ml), NaOH (30 mg) was added and the solution was heated at 150 °C for 24 h. Removal of solvent, deluting (H_2O, 8 ml), extraction ($CHCl_3$, 8 ml×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, cyclohexane/acetone=5 : 1) afforded the pure products as white amorphous powder, **9** (95 mg, 70%) and **10** (20 mg, 15%).

Method B: A solution of Compound **8** (470 mg, 0.84 mmol) in pyridine (20 ml) was refluxed at 140 °C for 12 h. Removal of solvent and column chromatography (silica gel H, petroleum/acetone=3 : 1) afforded the products (**9**: colorless needle crystals, 12 mg, 3%; **10**: white amorphous powder, 71 mg, 18%. besides the starting material (250 mg).

Method C: A solution of 14-methylsulfonyl pseudaconine (**10**) (670 mg, 1.194 mmol) in 8% methanolic NaOH (35 ml) was stirred at room temperature for 12 h. Removal of solvent, deluting (H_2O, 30 ml), extraction ($CHCl_3$, 30 ml×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, petroleum/acetone=3 : 1) afforded the product **9** as colorless needle crystals, 513 mg (92%) The structures of **9** and **10** were identified by comparison of TLC (cyclohexane/acetone=7 : 3, *Rf*: 0.36 for **9**; 0.63 for **10**).

Compound 13 To a solution of Compound **11** (1.58 g, 3.50 mmol) in pyridine (50 ml), MsCl (0.55 ml, 7.10 mmol) was added and the solution was heated at 40 °C for 1.5 h. Removal of solvent, basifying (10% Na_2CO_3), extraction ($CHCl_3$, 25 ml×3), drying (Na_2SO_4) and evaporation in vacuum and crystallization (ether/acetone) afforded the pure product as colorless needle crystals, 1.86 g, (100%). mp 118.5—119 °C; Rf 0.60 (cyclohexane/acetone= 1 : 1); $[\alpha]_D^{20}$ −51.1° (c=0.94, $CHCl_3$); IR (KBr) cm^{-1}: 3505 (OH), 3324 (OH), 2962, 2894, 2836, 1720 (CO), 1454, 1343, 1180, 1092, 869; ^{1}H-NMR (200 MHz) δ: 0.97 (3H, t, J=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.10 (3H, s, 14-$OSO_2\underline{CH_3}$), 3.17, 3.34, 3.40 (each 3H, s, OCH_3×3), 3.45, 3.84 (each 1H, ABq, J=7.8 Hz, H_2-18), 4.11 (1H, d, J=6.4 Hz, H-6β), 4.71 (1H, d, J=3.4 Hz, H-14β); ^{13}C-NMR (50 MHz) δ: 24.9 (t, C-1), 38.5 (t, C-2), 217.4 (s, C-3), 53.0 (s, C-4), 44.1 (d, C-5), 82.3 (d, C-6), 52.7 (d, C-7), 74.5 (s, C-8), 47.6 (d, C-9), 40.3 (d, C-10), 45.7 (s, C-11), 37.1 (t, C-12), 74.7 (s, C-13), 85.4 (d, C-14), 43.1 (t, C-15), 82.0 (d, C-16), 64.5 (d, C-17), 75.5 (t, C-18), 48.3 (t, C-19), 52.9 (t, C-21), 12.8 (q, C-22), 58.2 (q, C-6′), 58.0 (q, C-16′), 59.0 (q, C-18′), 38.5 (q, OMs); EI-MS m/z (%) 529 (M^+, 76), 514 (M−15, 63), 498 (M−31, 37), 469 (35), 454 (44), 438 (24); HR-EI-MS m/z 529.2351 (Calcd for $C_{25}H_{39}NO_9S$ 529.2345).

Compounds 12 and 14 Method A: To a solution of compound **13** (213 mg, 0.40 mmol) in DMF (13 ml), NaOH (90 mg) was added and the solution was heated at 150 °C for 12 h. Removal of solvent, deluting (H_2O, 15 ml), extraction ($CHCl_3$, 15 ml×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, petroleum/acetone=3 : 1) afforded the products as white amorphous powder (**12**: 65 mg, 37%; **14**: 18 mg, 10%).

Method B: A solution of compound **13** (85 mg, 0.16 mmol) in 8% methanolic NaOH (5 ml) was stirred at room temperature for 24 h. Removal of solvent, deluting (H_2O, 5 ml), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4) and evaporation to dryness afforded the product as white amorphous powder (**12**: 70 mg, 100%), Rf 0.50 (cyclohexane/acetone=1 : 1). **12**: $[\alpha]_D^{20}$ −23.3° (c=1.03, $CHCl_3$); IR (KBr) cm^{-1}: 3447 (OH), 2928, 2853, 1716 (CO), 1455, 1113, 975; ^{1}H-NMR (200 MHz) δ: 0.97 (3H, t, J=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.23, 3.39, 3.48 (each 3H, s, OCH_3×3), 3.54, 3.65 (each 1H, ABq, J=8 Hz, H_2-18), 4.02 (1H, dd, J=6.0, 2.2 Hz, H-6β), 4.18 (1H, dd, J=13.0, 5.2 Hz, H-16α); ^{13}C-NMR (50 MHz) see Table 1; EI-MS m/z (%) 433 (M^+, 64), 418 (M−15, 100), 402 (M−31, 20); HR-EI-MS m/z 433.2449 (Calcd for $C_{24}H_{35}NO_6$, 433. 2464); **14**: Rf 0.78 cyclohexane/acetone=1 : 1; $[\alpha]_D^{20}$ −24.7° (c=0.81, $CHCl_3$); IR (KBr) cm^{-1}: 3517 (OH), 2922, 2853, 1716 (CO), 1456, 1377, 1196, 1111, 974; ^{1}H-NMR (200 MHz) δ: 0.97 (3H, t, J=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.20, 3.29, 3.34 (each 3H, s, OCH_3×3), 3.50, 3.72 (each 1H, ABq, J=8.0 Hz, H_2-18), 3.85 (1H, br s, exchangeable in D_2O, 8-OH), 4.05 (1H, dd, J=6.0, 2.2 Hz, H-6β); ^{13}C-NMR (50 MHz) see Table 1; EI-MS m/z (%) 433 (M^+, 86), 418 (M−15, 100), 402 (M−31, 20); HR-EI-MS m/z 433.2426 (Calcd for $C_{24}H_{35}NO_6$ 433.2464).

Compound 15 To a solution of compound **12** (500 mg, 0.95 mmol) in anhydrous benzene (30 ml), a mixture of TsOH (200 mg) and glycol (3 ml) was added and the solution was refluxed for 5 h under dropwise addition of benzene (50 ml) using a water separator. Basifying (10% Na_2CO_3, pH>9), separating the water layer, extraction ($CHCl_3$, 20 ml×2), drying (Na_2SO_4) and removal of solvent afforded the product as white amorphous powder, 511 mg, (95%). Rf 0.57 (ether/acetone=9 : 1); $[\alpha]_D^{20}$ +13.0° (c=0.77, $CHCl_3$); IR (KBr) cm^{-1}: 3481 (OH), 2927, 1633, 1452, 1358, 1273, 1173, 1108, 1032, 979; ^{1}H-NMR (200 MHz) δ: 1.07 (3H, t, J=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.09 (3H, s, 14-$OSO_2\underline{CH_3}$), 3.23, 3.32, 3.39 (each 3H, s, OCH_3×3), 3.46, 3.58 (each 1H, ABq, J=9.2 Hz, H_2-18), 3.86—4.00 (4H, m, O–CH_2–CH_2–O); ^{13}C-NMR (50 MHz) δ: 28.2 (t, C-1), 30.6 (t, C-2), 112.7 (s, C-3), 45.3 (s, C-4), 46.8 (d, C-5), 82.3 (d, C-6), 53.4 (d, C-7), 73.9 (s, C-8), 47.8 (d, C-9), 40.7 (d, C-10), 45.6 (s, C-11), 36.8 (t, C-12), 74.8 (s, C-13), 85.8 (d, C-14), 42.9 (t, C-15), 82.8 (d, C-16), 63.4 (d, C-17), 73.5 (t, C-18), 48.7 (t, C-19), 50.6 (t, C-21), 13.4 (q, C-22), 58.1 (q, C-6′), 58.0 (q, C-16′), 58.9 (q, C-18′), 38.5 (q, OMs), 64.3 (t, OCH_2), 65.0 (t, OCH_2); EI-MS m/z (%) 573 (M^+, 72), 558 (M−15, 51), 542 (M−31, 29), 528 (100), 486 (59); HR-EI-MS m/z 573.2568 (Calcd for $C_{27}H_{43}NO_{10}S$, 573.2607).

Compounds 16 and 17 Method A: To a solution of compound **15** (780 mg, 1.36 mmol) in DMF (60 ml), NaOH (375 mg) was added and the solution was heated at 160 °C for 15 h. Removal of solvent, deluting (H_2O, 50 ml), extraction ($CHCl_3$, 45 ml×3), drying (Na_2SO_4), evaporation to dryness and column chromatography (silica gel H, ether/acetone=95 : 5) afforded the pure products (**16**, colorless needle crystals, 310 mg, 48%; **17**, white amorphous powder, 65 mg, 10%); **16**: 0.49 (cyclohexane/acetone= 1 : 1); $[\alpha]_D^{20}$ +70.6° (c=0.85, $CHCl_3$); IR (KBr) cm^{-1}: 3453 (OH), 2923, 2811, 1717 (CO), 1633, 1450, 1379, 1200, 1161, 1109; ^{1}H-NMR (200 MHz) δ: 1.01 (3H, t, J=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.25, 3.40, 3.52 (each 3H, s, OCH_3×3), 3.8—4.0 (4H, m, OCH_2CH_2O), 4.15 (1H, dd, J=13.4, 4.8 Hz, H-16β); ^{13}C-NMR (50 MHz) see Table 1; EI-MS m/z (%): 477 (M^+, 88), 462 (M−15, 68), 466 (M−31, 35), 432 (M−45, 100), 390 (87); HR-EI-MS m/z 477.2742 (Calcd for $C_{26}H_{39}NO_7$, 447.2726); **17**: Rf 0.71 (cyclohexane/acetone=1 : 1); $[\alpha]_D^{20}$ +15.0° (c=1.33, $CHCl_3$); IR (KBr) cm^{-1}: 3523 (OH), 2923, 2809, 1714 (CO), 1450, 1379, 1274, 1198, 1159, 1111, 1041, 947; ^{1}H-NMR (200 MHz) δ: 1.01 (3H, t, J=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.23, 3.29, 3.36 (each 3H, s, OCH_3×3), 3.82—3.97 (4H, m, OCH_2CH_2O); ^{13}C-NMR (50 MHz) see Table 1; EI-MS m/z (%) 477 (M^+, 51), 462 (M−16, 50), 445 (M−32, 37), 432 (M−45, 100), 391 (50); HR-EI-MS m/z 477.2738 (Calcd for $C_{26}H_{39}NO_7$, 477.2726).

Method B: A solution of compound **15** (90 mg, 0.16 mmol) in 8% methanolic NaOH (5 ml) was stirred at room temperature for 24 h. Removal of solvent, deluting (H_2O, 5 ml), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4) and evaporation to dryness afforded the product **16** as white amorphous powder, 67 mg (90%).

Compounds 21, 22 and 23 To a solution of compound **5** (280 mg, 0.65 mmol) in glacial acetic acid (7 ml), Br_2 (0.035 ml, 0.69 mmol) was added dropwise and the solution was stirred at room temperature 4 h. Basifying (saturated Na_2CO_3, pH>9), extraction ($CHCl_3$, 25 ml×3), drying (Na_2SO_4), removal of solvent and column chromatography (silica gel H, cyclohexane/acetone=3 : 1) afforded the pure products (**21**: white amorphous powder, 65 mg, 20%; **22**+**23**: white amorphous powder, 170 mg, 60%). **21**: Rf 0.63 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +142.8° (c=0.77, $CHCl_3$); IR (KBr) cm^{-1}: 3408 (OH), 2924, 2852, 1671 (CO), 1510, 1457, 1400, 1303, 1211, 1106, 758; ^{1}H-NMR (200 MHz) δ: 0.93 (3H, t, J=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.28, 3.33 (each 3H, s, OCH_3×2), 3.90 (3H, s, Ar-OCH_3), 4.15 (1H, dd, J=11.7, 3.5 Hz, H-12), 6.42 (1H, d, J=10.4 Hz, H-1), 6.64 (1H, s, H-15), 6.88 (1H, s, H-14), 7.25 (1H, d, J=10.4 Hz, H-2); ^{13}C-NMR (50 MHz) see Table 2; EI-MS m/z (%) 493 (M_1^+, 50), 491 (M_2^+, 50), 478 (M_1−15, 13), 476 (M_2−15, 13), 462 (M_1−31, 50), 460 (M_2−31, 50), 412 (M−Br, 100); HR-EI-MS m/z 491.1299 (Calcd for $C_{24}H_{30}NO_5Br$, 491.1307); **22**: ^{1}H-NMR (200 MHz) δ: 0.95 (3H, t, J=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.29, 3.31 (each 3H, s, OCH_3×2), 4.92, 5.45 (each 1H, br s, H_2-12), 6.36 (1H, d, J=10.0 Hz, H-2), 6.68 (1H, s, H-15), 6.70 (1H, d, J=10.0 Hz, H-1), 7.08 (1H, s, H-14); ^{13}C-NMR (50 MHz) see Table 2; EI-MS m/z (%) 397 (M^+, 100), 382 (M−15, 34), 366 (M−31, 63); HR-EI-MS m/z 397.1900 (Calcd for $C_{23}H_{27}NO_5$, 397.1889). **23**: ^{1}H-NMR (200 MHz) δ: 0.95 (3H, t, J=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.29, 3.31 (each 3H, s, OCH_3×2), 5.03, 5.53 (each 1H, br s, H_2-12), 6.37 (1H, d, J=10.0 Hz, H-2), 6.66 (1H, s, H-15), 6.68 (1H, d, J=10.0 Hz, H-1), 7.11 (1H, s, H-14); ^{13}C-NMR (50 MHz) see Table 2; EI-MS m/z (%) 477 (M_1^+, 17), 475 (M_2^+, 17), 462 (M_1−15, 5), 460 (M_2−15, 5), 446 (M_1−31, 8), 444 (M_2−31, 7); HR-EI-MS m/z 475.1011 (Calcd for $C_{23}H_{26}NO_5Br$, 475.0994).

Compound 24 Method A: To a solution of compound **5** (35 mg, 0.08 mmol) in anhydrous benzene (2 ml), $SOCl_2$ (0.6 ml) was added and the solution was first stirred at room temperature overnight, to which then 10% Na_2CO_3 (2 ml) was added and stirred continuously for 5 min. Extraction ($CHCl_3$, 3 ml×3), drying (Na_2SO_4), removal of solvent and column chromatography (silica gel H, cyclohexane/acetone=3 : 1) afforded the products as white amorphous powder, 21 mg (71%).

Method B: To a solution of compound **6** (23 mg, 0.05 mmol) in anhydrous benzene (1 ml), $SOCl_2$ (0.4 ml) was added dropwise and the solution was stirred at room temperature overnight. Basifying (10% Na_2CO_3, pH>9), extraction ($CHCl_3$, 3 ml×3), drying (Na_2SO_4) and removal of solvent afforded the product as white amorphous powder, 25 mg (100%). *Rf* 0.73 (cyclohexane/acetone=1 : 1); $[\alpha]_D^{20}$ −4.4° (*c*=0.45, $CHCl_3$); IR (KBr) cm^{-1}: 3422 (OH), 2925, 2852, 1729 (CO), 1671 (CO), 1510, 1457, 1370, 1304, 1241, 1107, 1043, 978, 753; ^{1}H-NMR (200 MHz) *δ*: 0.94 (3H, t, *J*=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.29, 3.34 (each 3H, s, OCH_3×2), 3.91 (3H, s, Ar-OCH_3), 4.12 (1H, dd, *J*=12.6, 1.8 Hz, H-12), 4.30 (1H, dd, *J*=12.6, 3.4 Hz, H-12), 6.42 (1H, d, *J*=10.4 Hz, H-1), 6.65 (1H, s, H-15), 6.92 (1H, s, H-14), 7.21 (1H, d, *J*=10.4 Hz, H-2); ^{13}C-NMR (50 MHz) see Table 2; EI-MS *m/z* (%) 449 (M_1, 11), 447 (M_2, 29), 411 (M−HCl, 100); HR-EI-MS *m/z* 447.1821 (Calcd for $C_{24}H_{30}NO_5Cl$, 447.1812).

Compound 25 Method A: A solution of compound **21** (30 mg, 0.06 mmol) in 5% ethanolic KOH (2 ml) was heated at 50 °C for 30 min. Removal of solvent, deluting (H_2O, 3 ml), extraction ($CHCl_3$, 3 ml×3), drying (Na_2SO_4) and evaporation afforded the product as white amorphous powder, 25 mg (100%).

Method B: A solution of compound **24** (25 mg, 0.056 mmol) in 5% ethanolic KOH (2 ml) was heated at 50 °C for 30 min. Removal of solvent, deluting (H_2O, 3 ml) extraction ($CHCl_3$, 3 ml×3), drying (Na_2SO_4) and evaporation afforded the product as white amorphous powder, 23 mg (100%). *Rf* 0.70 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +120.4° (*c*=0.98, $CHCl_3$); IR (KBr) cm^{-1}: 3420 (OH), 2925, 2853, 1716 (CO), 1672 (CO), 1608, 1504, 1455, 1350, 1307, 1207, 1109; ^{1}H-NMR (200 MHz) *δ*: 0.93 (3H, t, *J*=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 2.55 (2H, q, *J*=7.2 Hz, $\underline{NCH_2}CH_3$), 2.45, 2.66 (each 1H, ABq, *J*=10.4 Hz, H_2-19), 2.63 (1H, br s, H-17), 2.91 (1H, d, *J*=6.4 Hz, H-5), 3.21 (1H, d, *J*=1.4 Hz, H-7), 3.29, 3.34 (each 3H, s, OCH_3×2), 3.68, 3.90 (each 1H, ABq, *J*=10.0 Hz, H_2-18), 3.72 (1H, d, *J*=6.2 Hz, H-6*β*), 3.93 (3H, s, Ar-OCH_3), 5.02, 5.53 (each 1H, br s, H_2-12), 6.36 (1H, d, *J*=10.0 Hz, H-2), 6.68 (1H, s, H-15), 7.10 (1H, d, *J*=10.0 Hz, H-1), 7.15 (1H, s, H-14); ^{13}C-NMR (50 MHz) *δ*: see Table 2; EI-MS *m/z* (%) 411 (M^+, 100), 396 (M−15, 43), 380 (M−31, 65), 366 (44); HR-EI-MS *m/z* 411.2052 (Calcd for $C_{24}H_{29}NO_5$, 411.2045).

Compound 26 To a solution of compound **16** or compound **17** (100 mg, 0.21 mmol) in anhydrous benzene (5 ml), $SOCl_2$ (0.5 ml) was added dropwise and the solution was stirred at room temperature overnight. Removal of solvent, basifying (10% Na_2CO_3, pH>9), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4), evaporation and column chromatography (silica gel H, cyclohexane/acetone=3 : 1) afforded the product as white amorphous powder, 30 mg (40%). *Rf* 0.83 (cyclohexane/acetone=1 : 1); $[\alpha]_D^{20}$ +48.3° (*c*=0.58, $CHCl_3$); IR (KBr) cm^{-1}: 3425 (OH), 2927, 2852, 1714 (CO), 1627, 1510, 1453, 1372, 1241, 1206, 1106; ^{1}H-NMR (400 MHz) *δ*: 1.01 (3H, t, *J*=6.8 Hz, $\underline{N}CH_2\underline{CH_3}$), 2.56 (2H, q, *J*=6.8 Hz, $\underline{NCH_2}CH_3$), 3.27, 3.28 (each 3H, s, OCH_3×2), 3.90 (3H, s, Ar-OCH_3), 6.61 (1H, s, H-15), 6.88 (1H, s, H-14); ^{13}C-NMR (100 MHz) see Table 2; EI-MS *m/z* (%) 451 (M_1^+, 15), 449 (M_2^+, 45), 420 (M_1−31, 50), 418 (M_2−31, 100); HR-EI-MS *m/z* 449.1972 (Calcd for $C_{24}H_{32}NO_5Cl$, 449.1969).

Compund 27 A solution of compound **26** (45 mg, 0.1 mmol) in 5% ethanolic KOH (3 ml) was stirred at room temperature for 2 h overnight. Removal of solvent, deluting (H_2O, 5 ml), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4) and evaporation to dryness afforded the product as white amorphous powder, 43 mg (100%). *Rf* 0.52 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +144.5° (*c*=1.01, $CHCl_3$); IR (KBr) cm^{-1}: 3451 (OH), 2928, 2845, 1714 (CO), 1610, 1502, 1451, 1351, 1308, 1246, 1209, 1109, 966, 876; ^{1}H-NMR (200 MHz) *δ*: 0.97 (3H, t, *J*=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.22, 3.30 (each 3H, s, OCH_3×2), 3.91 (3H, s, 16-OCH_3), 3.55, 3.72 (each 1H, ABq, *J*=8.0 Hz, H_2-18), 5.25, 5.47 (each 1H, br s, H_2-12), 6.64 (1H, s, H-15), 7.08 (1H, s, H-14); ^{13}C-NMR (50 MHz) see Table 2; EI-MS *m/z* (%) 413 (M_1^+, 60), 398 (M−15, 13), 382 (M−31, 100); HR-EI-MS *m/z* 413.2210 (Calcd for $C_{24}H_{31}NO_5$, 413.2202).

Compound 28 To a solution of compound **10** (242 mg, 0.52 mmol) in pyridine (5 ml), Ac_2O (1 ml) was added and the solution was stirred at room temperature for 2 h. Removal of solvent, basifying (10% Na_2CO_3, pH>9), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4) and evaporation afforded the product as white amorphous powder, 262 mg (100%). *Rf* 0.72 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +34.9° (*c*=0.63, $CHCl_3$); ^{1}H-NMR (200 MHz) *δ*: 1.07 (3H, t, *J*=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 2.06 (H, s, OAc), 3.15, 3.22, 3.32, 3.37 (each 3H, s, OCH_3×4), 2.93, 3.87 (each 1H, ABq, *J*=8.6 Hz, H_2-18), 4.29 (1H, br s, exchangeable in D_2O, 8-OH), 4.91 (1H, dd, *J*=12.6, 5.0 Hz, H-3*β*); IR (KBr) cm^{-1}: 3519 (OH), 2927, 2822, 1734 (COO), 1716 (CO), 1452, 1378, 1244, 1101, 974; ^{13}C-NMR (50 MHz) *δ*: 80.9 (d, C-1), 31.5 (t, C-2), 71.7 (d, C-3), 41.4 (s, C-4), 45.4 (d, C-5), 83.4 (d, C-6), 50.4 (d, C-7), 73.0 (s, C-8), 47.1 (d, C-9), 44.3 (d, C-10), 47.7 (s, C-11), 31.3 (t, C-12), 209.3 (s, C-13), 36.4 (d, C-14), 37.7 (t, C-15), 80.8 (d, C-16), 61.2 (d, C-17), 71.7 (t, C-18), 47.4 (t, C-19), 48.7 (t, C-21), 13.3 (q, C-22), 56.1 (q, C-1′), 57.9 (q, C-6′), 58.2 (q, C-16′), 58.8 (q, C-18′), 170.2 (s, OAc), 21.1 (q, OAc); EI-MS *m/z* (%) 507 (M^+, 9), 492 (M−15, 6), 476 (M−31, 100), 448 (89), 416 (83); HR-EI-MS *m/z* 507.2819 (Calcd for $C_{27}H_{41}NO_8$, 507.2832).

Compound 29 To a solution of compound **9** (120 mg, 0.25 mmol) in pyridine (3 ml), Ac_2O (0.5 ml) was added and the solution was stirred at room temperature for 2 h. Removal of solvent, basifying (10% Na_2CO_3, pH>9), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4) and evaporation to dryness afforded the product as white amorphous powder, 130 mg (100%). *Rf* 0.50 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +45.3° (*c*=1.06, $CHCl_3$); IR (KBr) cm^{-1}: 3446 (OH), 2930, 2822, 1733 (COO), 1718 (CO), 1454, 1371, 1246, 1204, 1164, 1103, 1032, 979, 936; ^{1}H-NMR (200 MHz) *δ*: 1.03 (3H, t, *J*=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 2.02 (3H, s, OAc), 3.11, 3.18, 3.34, 3.46 (each 3H, s, OCH_3×4), 2.89, 3.72 (each 1H, ABq, *J*=8.8 Hz, H_2-18), 3.97 (1H, d, *J*=6.4 Hz, H-6*β*), 4.87 (1H, dd, *J*=12.1, 5.4 Hz, H-3*β*); ^{13}C-NMR (50 MHz) see Table 3; EI-MS *m/z* (%) 507 (M^+, 13), 492 (M−15, 14), 496 (M−31, 100), 448 (89), 416 (90); HR-EI-MS *m/z* 507.2833 (Calcd for $C_{27}H_{41}NO_8$, 507.2832).

Compounds 30, 31 and 32 To a solution of compound **29** (346 mg, 0.68 mmol) in anhydrous benzene (18 ml), $SOCl_2$ (1.8 ml) was added dropwise and the solution was stirred at room temperature for 2 h. Basifying (10% Na_2CO_3, pH>9), extraction ($CHCl_3$, 20 ml×3), drying (Na_2SO_4), removal of solvent and column chromatography (silica gel H, petroleum/acetone=5 : 1) afforded the products as white amorphous powder. **30**: 106 mg (33%); *Rf* 0.48 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +160.0° (*c*=0.15, $CHCl_3$); IR (KBr) cm^{-1}: 3426 (OH), 2926, 2854, 1736 (COO), 1621, 1507, 1456, 1372, 1240, 1105, 1025, 989; ^{1}H-NMR (200 MHz) *δ*: 1.02 (3H, t, *J*=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 2.07 (3H, s, OAc), 3.20, 3.31 (each 3H, s, OCH_3×2), 3.84 (3H, s, Ar-OCH_3), 4.36 (1H, dd, *J*=10.0, 8.4 Hz, H-12*β*), 5.13 (1H, dd, *J*=11.4, 5.0 Hz, H-3*β*), 5.60 (1H, br s, exchangeable in D_2O, 13-OH); 6.50 (1H, s, H-15), 6.56 (1H, s, H-14); ^{13}C-NMR (50 MHz) see Table 3; EI-MS *m/z* (%) 473 (M^+, 67), 458 (M−15, 40), 442 (M−31, 100); HR-EI-MS *m/z* 473.2407 (Calcd for $C_{26}H_{35}NO_7$, 473.2413). **31**: 65 mg (20%); *Rf* 0.58 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +155.0° (*c*=0.40, $CHCl_3$); IR (KBr) cm^{-1}: 2926, 2854, 1733 (COO), 1637, 1456, 1371, 1243, 1106, 1032, 980; ^{1}H-NMR (200 MHz) *δ*: 1.04 (3H, t, *J*=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 2.06 (3H, s, OAc), 3.16, 3.21, 3.33, 3.51 (each 3H, s, OCH_3×4), 2.93, 3.86 (each 1H, ABq, *J*=8.8 Hz, H_2-18), 4.01 (1H, d, *J*=6.6 Hz, H-6*β*), 4.90 (1H, dd, *J*=11.8, 5.0 Hz, H-3*β*), 5.34 (1H, br s, H-15); ^{13}C-NMR (50 MHz) see Table 3; EI-MS *m/z* (%) 489 (M^+, 55), 474 (M−15, 39), 458 (M−31, 100); HR-EI-MS *m/z* 489.2734 (Calcd for $C_{27}H_{39}NO_7$, 489.2726); **32**: 65 mg (20%); *Rf* 0.62 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +46.8° (*c*=0.94, $CHCl_3$); IR (KBr) cm^{-1}: 2935, 2827, 1729 (COO), 1645, 1452, 1372, 1243, 1105, 1031, 981; ^{1}H-NMR (200 MHz) *δ*: 1.05 (3H, t, *J*=7.0 Hz, $\underline{N}CH_2\underline{CH_3}$), 2.06 (3H, s, OAc), 3.19, 3.20, 3.30, 3.48 (each 3H, s, OCH_3×4), 2.91, 3.86 (each 1H, ABq, *J*=8.8 Hz, H_2-18), 4.20 (1H, dd, *J*=9.6, 7.2 Hz, H-14*β*), 4.93 (1H, dd, *J*=11.8, 5.8 Hz, H-3*β*); ^{13}C-NMR (50 MHz) see Table 3; EI-MS *m/z* 489 (M^+, 75), 474 (M−15, 100), 496 (M−31, 78); HR-EI-MS *m/z* 489.2707 (Calcd for $C_{27}H_{39}NO_7$, 489.2726).

Compound 30 Method A: A solution of compound **31** (55 mg, 0.10 mmol) in saturated methanolic Na_2CO_3 (3 ml) was stirred at room temperature overnight. Removal of solvent, deluting (H_2O, 5 ml), extraction ($CHCl_3$, 5 ml×3), drying (Na_2SO_4) and evaporation afforded the product as white amorphous powder, 51 mg (99%).

Method B: A solution of compound **33** (70 mg, 0.13 mmol) in 20% acetic $HClO_4$ (7 ml) was heated at 80 °C for 5 h. Basifying (saturated Na_2CO_3, pH>9), extraction ($CHCl_3$, 5 ml×5), drying (Na_2SO_4), removal of solvent and column chromatography (silica gel H, cyclohexane/acetone=5 : 1) afforded the product as white amorphous powder, 32 mg (58%).

Method C: A mixed solution of compound **28** (242 mg, 0.048 mmol) in ahydrous benzene (10 ml) and $SOCl_2$ (1 ml) was stirred at room temperature overnight. Basifying (10% Na_2CO_3, pH>9), extraction ($CHCl_3$, 10 ml×5), drying (Na_2SO_4), removal of solvent gave a residue (260 mg), which was chromatographed over silica gel H (8 g) eluting with cylolhexane–acetone (5 : 1) to afford the product as white amorphous powder, **30** (140 mg, 66%).

Compound 33 A mixture of compound **18** (120 mg, 0.27 mmol) in pyridine (5 ml) and Ac_2O (0.5 ml, 4.5 mmol) was stirred at room temperature for 20 h. Removal of solvent, column chromatography (silica gel H, cyclohexane/acetone=6 : 1) and crystallization (95% EtOH) afforded the product as colorless needle crystals, 80 mg (54%). It was identified by comparion of TLC (silica gel G, cyclohexane/acetone=7 : 3, *Rf* 0.45) with the authentic sample.

Compound 34 To a solution of compound **33** (17 mg, 0.03 mmol) in CH_2Cl_2 (3 ml), 49% HBr (6 drops) was added and the solution was heated at 80 °C for 3 h. Basifying (10% Na_2CO_3, pH>9), extraction ($CHCl_3$, 5 ml×5), drying (Na_2SO_4), evaporation to dryness afforded the product as white amorphous powder, 13 mg (100%). *Rf* 0.22 (cyclohexane/acetone=7 : 3); $[\alpha]_D^{20}$ +28.3° (*c*=1.13, $CHCl_3$); IR (KBr) cm^{-1}: 3365 (OH), 2926, 2854, 1618, 1508, 1459, 1378, 1273, 1230, 1169, 1104, 1012, 870, 759; ^{1}H-NMR (400 MHz) δ: 1.05 (3H, t, *J*=7.2 Hz, $\underline{N}CH_2\underline{CH_3}$), 3.33 (3H, s, OCH_3), 3.87 (3H, s, Ar-OCH_3), 4.38 (1H, t, *J*=8.4 Hz, H-12β), 5.51 (1H, br s, 13-OH), 6.53, 6.60 (each 1H, s, Ar-H); ^{13}C-NMR (200 MHz) see Table 3; EI-MS *m*/*z* (%) 417 (M^+, 34), 403 (M−14, 29), 402 (M−15, 28), 386 (100); HR-EI-MS *m*/*z* 417.2143 (Cald for $C_{23}H_{31}NO_6$, 417.2151).

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References and Notes

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