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Novel reactions of lycoctonine analogs: unusual pyrolysis of C4–COOH and hydrogenolysis of *N*–C6 bond

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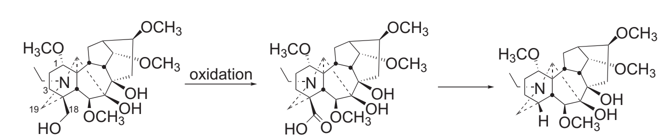
ABSTRACT

Pyrolysis of carboxylic acid group at C-4 of **2**, an oxidation product from the C_{19}-diterpenoid alkaloid lycoctonine **1**, generated an unexpected but novel rearranged product **13** (37%). The structure of **13** was confirmed by its 2D NMR data and its single crystal X-ray crystallographic analysis. In addition, hydrogenolysis of **13** in the presence of acetic acid yielded the *N*–C6 bond fission products **16** and **17**, which represents the first hydrogenolysis involving the breakage of the *N*–C6 bond of the diterpenoid alkaloids. Some new observations on the oxidation of lycoctonine **1** were described as well.

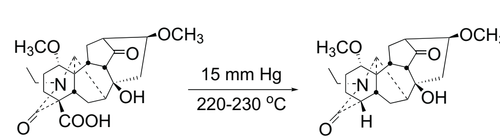
1. Introduction

Lycoctonine (**1**) was firstly isolated from *Aconitum lycoctonum* L in 1886.[1] As a diterpenoid alkaloid with the widest distribution, it extensively exists in around 80 plants of the genera, *Delphinium Aconitum* and *Consolida*.[2] The chemical reactions, especially the oxidation, of lycoctonine have made great contributions to the skeletal structure establishment of the diterpenoid alkaloids before the 1970's.[3–14] For example, investigation on its oxidative products by Edwards and Marion indicated that lycoctonine possesses a methylene group adjacent to the nitrogen and a primary hydroxyl group, and a vicinal glycol moiety.[3] The first successful skeleton establishment of the C_{19}-diterpenoid alkaloids was based on the X-ray crystallographic analysis of the derivative of lycoctonine.[8] However, the oxidation products of lycoctonine from the earlier investigations were poorly characterized due to the unavailable techniques of separations and spectroscopy at that time. Recently, Benn et al. revisited the structures of some oxidation products of lycoctonine and provided the insightful summarization on the relationship between the oxidation products of lycoctonine and specific oxidants.[1]

As part of our ongoing research project, we attempted to semi-synthesize the C_{18}-diterpenoid alkaloid **3** from the C_{19}-diterpenoid alkaloid lycoctonine **1** through the oxidation of its primary hydroxyl group followed by decarboxylation (Scheme 1). It has been reported that decarboxylation of the diterpenoid alkaloid **4** could be completed under vacuum to generate decarboxylated product **5** in 98% yield (Scheme 2).[15] However, in our present study, heating the carboxylic acid **2** under vacuum gave us an unexpected rearranged product instead. In this paper, we wish to report this novel rearranged product and its unusual hydrogenolysis, as well as some new observations on the oxidation of lycoctonine.



Scheme 1. Attempt to convert the C_{19}-diterpenoid alkaloid lycoctonine to the C_{18}-diterpenoid alkaloids.



Scheme 2. Decarboxylation of **4**.

2. Results and discussion

As summarized by Benn et al.,[1] the oxidation products of lycoctonine are greatly dependent on the specific oxidants. For example, oxidation of lycoctonine with chromic acid yields preferably lycoctonal (**6**), a primary hydroxyl oxidation product. In

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contrast to its behavior with chromic acid, oxidation of lycoctonine with permanganate in neutral, weakly acidic, or alkaline solution affords lactam **7**, a C-19 methylene oxidation product. Intriguingly, further oxidation of lactam with chromic acid gives a product (**12a**) of C4–C18 bond fission. This kind of bond fission could be avoided in the presence of oxalic acid.

In order to make carboxylic acid **2** from lycoctonine (**1**), we have tried different oxidants. As shown in Scheme 3, treatment of lycoctonine with PCC only yielded lycoctonal (**6**) in poor yield (16%); while oxidation with $KMnO_4$ could generate lactam **7** in 60% yield. These results are consistent with those described in the literature.[1] In addition, we have observed the following new oxidation of lycoctonine: (1). alkaloid **10**, with all hydroxyl groups in lycoctonine protected, was oxidized with $KMnO_4$ followed by deprotection to generate lactam **7** in an excellent yield (93%); (2) Swern oxidation of lycoctonine gave us Pinacol rearrangement products **8** (47%) and **9** (12%), together with minor lycoctonal (**6**); (3) the oxidative status of *N*-atom has significant influence on the oxidation with Dess–Martin Periodinance (DMP): oxidation of lycoctonine with DMP provided us with complicated products, while oxidation of lactam **7** with DMP yielded **11** in an excellent yield (94%); (4) the normal Jones oxidation of lycoctonine could generate the expected carboxylic acid **2**, but in a poor yield (8%); and (5) inspired by the solid phase synthesis, we found that the strong acidic cation resin loaded with lycoctonine could smoothly react with Jones reagent to generate carboxylic acid **2** in 56% yield, as well as a C4–C18 fission product **12** in 22% yield.

methoxyl groups (δ_H 3.32, 3.36, 3.37, each 3H, s; δ_C 57.3 q, 57.1 q, 56.7 q), an exocyclic double bond (δ_C 146.3s; δ_C 111.8t; δ_H 4.73, 2H, t, J=2.8 Hz), and a ketone carbonyl group (δ_C 213.2s). The ^{13}C NMR of **13** showed the absence of the C-18 carboxyl group, as compared with **2**. The ketone carbonyl group could be assigned at C-7 due to the correlations from H_2-15 (δ_H 1.65, 2.44) and H-9 (δ_H 2.32, m) to C-7 (δ_C 213.2s) in the HMBC spectrum (Fig. 1), which indicated that the vicinal glycol moiety in **2** had undergone Pinacol rearrangement. The exocyclic double bond was located at C-4 and C-19 on the basis of the HMBC correlations from H_2-3 (δ_H 2.21, 2.60) and H-5 (δ_H 2.62) to C-19, from H_2-19 to C-3 (δ_C 28.3) and C-5 (δ_C 48.6), and from H-6 to

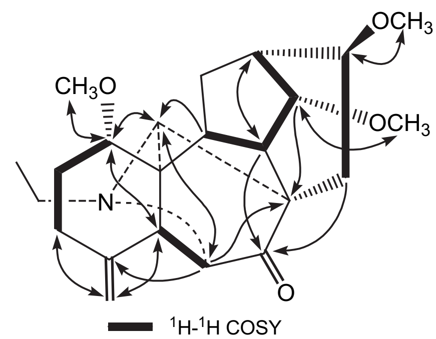
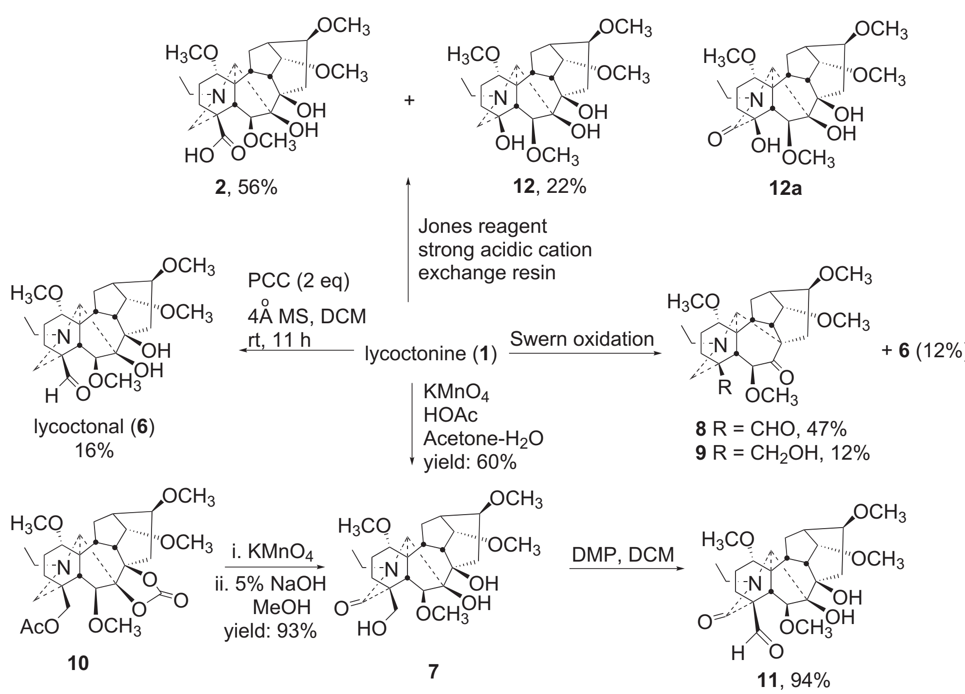


Fig. 1. Key ^1H–^1H COSY and HMBC correlations of **13**.



Scheme 3. Oxidation of lycoctonine.

With carboxylic acid **2** in hand, we attempted to make the C_{18}-diterpenoid alkaloid **3** employing the similar procedure as described in the literature.[15] Very intriguingly, heating **2** under vacuum (15 mm Hg) at 220 °C for 25 min generated an unexpected but novel rearranged product **13** (37%) instead of **3**. The structure of this novel product was elucidated using the 1D and 2D NMR experiment, as well as by X-ray crystallographic analysis. Its ESIMS showed a quasimolecular ion peak at m/z 388 $[M+1]^+$ and its NMR spectroscopic patterns are quite different from those of its starting material **2**. The NMR (^1H, ^{13}C, and HMQC) data feature an *N*-ethyl group (δ_C 13.9 q, δ_H 1.07, 3H, t, J=7.2 Hz; δ_C 43.1t, δ_H 2.45, 2.69, each 1H, m), three C-4. This suggested that the bond between *N*-atom and C-19 was broken. Similarly, three methoxyl groups could be readily assigned at C-1, C-14, and C-16 on the basis of the related correlations in the HMBC spectrum (Fig. 1), implying the disappearance of the methoxyl group at C-6 in **2**. In addition, the newly formed *N*–C6 bond was evident from the critical HMBC correlations between H-17 (δ_H 3.82) and C-6 (δ_C 73.3), and between H-6 and C-17 (δ_C 70.7), as well as from the W-type coupling (1.6 Hz) between H-6 and H-17. Finally, our proposed structure of **13** was confirmed by its X-ray crystallographic analysis (Fig. 2). The formation of **13** might be explained by the mechanism depicted in Scheme 4. Firstly,

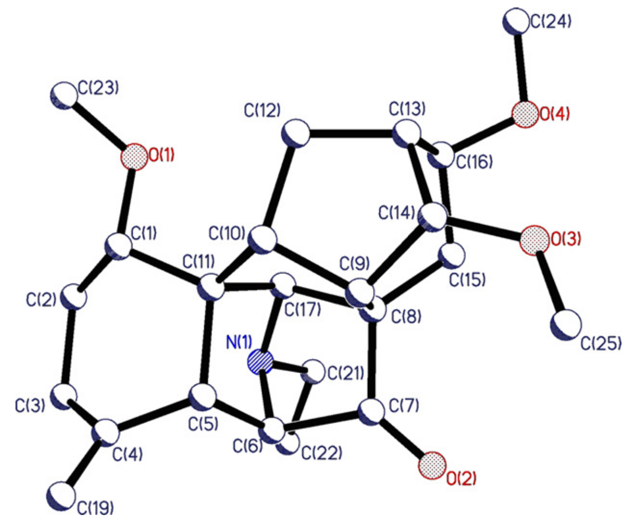
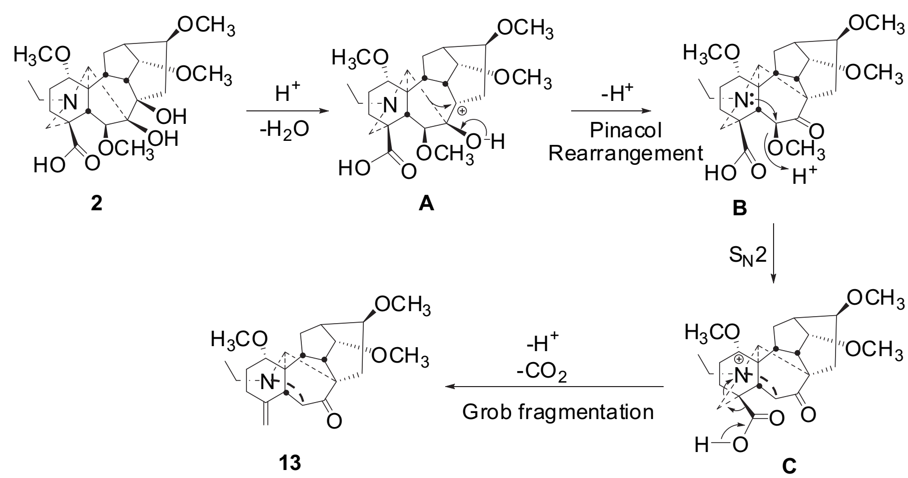


Fig. 2. ORTEP drawing of **13**.

addition to the normal reduction products **14** and **15**. The mixture of **16** and **17** cannot be separated by conventional chromatography. Its ESIMS showed two quasimolecular ion peaks at m/z 390 $[M+1]^+$ and 392 $[M+1]^+$. Comparison between the NMR spectra of the mixture with compound **13** showed that the mixture of **16** and **17** possesses a methylene (δ_C 43.1t and 40.8t) at C-6 instead of a methine (δ_C 73.3d) in **13**, suggesting that the bond between the *N*-atom and C-6 was broken. This is the first example of hydrogenolysis of diterpenoid alkaloids involving the breakage of the bond between *N*-atom and C-6. However, continued hydrogenolysis of the normal reduction products **14** and **15** cannot lead to the fission of the bond between the *N*-atom and C-6. Treatment of **13** directly with acid only resulted in the formation of isomeric olefin **18**. Further hydrogenolysis of the mixture of **16** and **17** led to the slow conversion of **16** to **17**. The configuration of the newly formed methyl group at C-19 in **14** was assigned as the β orientation based on NOEds experiment. Selective irradiation of CH_3-19 (δ_H 0.93, d, J=6.4 Hz) resulted in signal enhancement of H-6β (δ_H 3.05, d, J=1.6 Hz). Similarly, irradiation of CH_3-19 in **15** and **17** gave signal enhancement of CH_3-22, suggesting the α orientation of CH_3-19 in **15** and **17**.

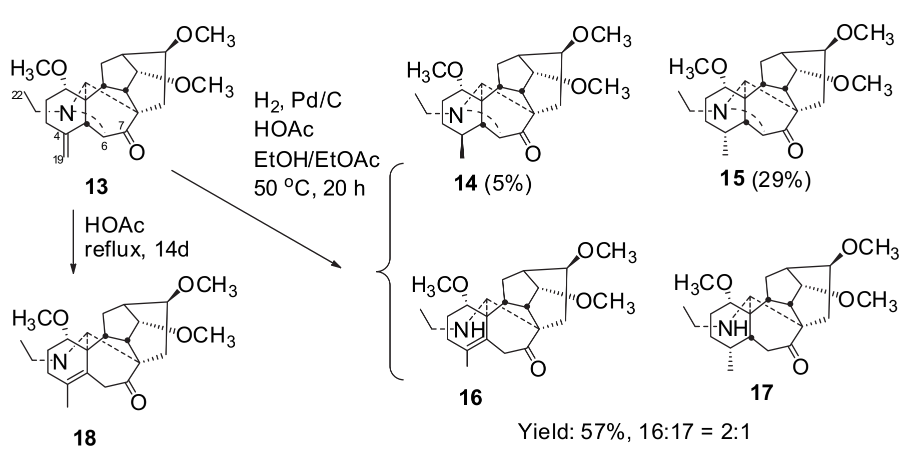


Scheme 4. A plausible mechanism for the formation of **13**.

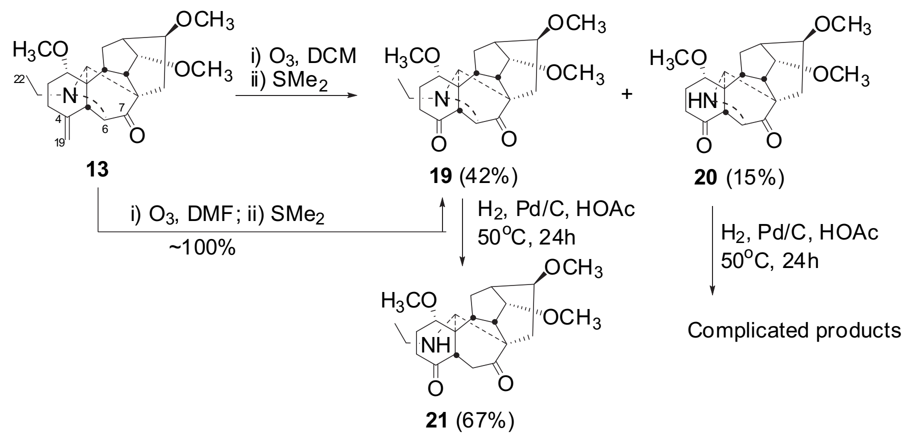
compound **2** might undergo acid-mediated Pinacol rearrangement under heating in vacuo to give intermediate B. The lone pair electron on the *N*-atom in intermediate B might attack C-6 and push the departure of OCH_3-6 to provide ammonium C. Finally, Grob-type fragmentation of the quaternary ammonium salt C could generate the enone **13**.

Further investigation on the hydrogenolysis of **13** resulted in some interesting compounds as well. Hydrogenolysis of **13** in the presence of acid yielded a mixture of **16** and **17** (Scheme 5) in

It is also interesting to find that the products from the ozonolysis of **13** are greatly dependent on the reaction solvents. Using dichloromethane as a reaction solvent, diketone **19** (42%) and its *N*-deethyl derivative **20** (15%) are major products (Scheme 6), together with some other minor byproducts. However, ozonolysis of **13** in DMF led to its nearly quantitative conversion to diketone **19**, implying that DMF might suppress the *N*-atom-involving oxidation.[16,17] In addition, hydrogenolysis of **19** catalyzed by Pd–C could generate the *N*–C6 bond fission product **21**, while the *N*-deethyl derivative



Scheme 5. Hydrogenolysis of **13**.



Scheme 6. Ozonolysis of **13** and rupture of the *N*-C(6) bond in **19**.

20 yielded the complicated products under the same reaction condition. This indicated that the substituted pattern of the *N*-atom is probably the critical factor to the fission of the bond between the *N*-atom and C-6.

3. Conclusion

In conclusion, heating carboxylic acid **2**, an oxidation product of lycoctonine, in vacuo furnished a novel rearranged product **13**. The hydrogenolysis and ozonolysis of **13** were explored as well, from which we found for the first time that the bond between the *N*-atom and C-6 in **13** could be broken by hydrogenolysis. In addition, we have made some new observations on the oxidation of lycoctonine. Especially, inspired by the solid phase synthesis, we found that the strong acidic cation resin loaded with lycoctonine could smoothly react with Jones reagent to generate carboxylic acid **2** in 56% yield.

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 Finnigan LCQ DECA mass spectrometer; HRMS spectra were obtained with a Bruker BioTOFQ mass spectrometer; ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AC-E 200 or a Varian INOVA-400/54 spectrometer, with TMS as internal standard; silica gel GF_{254} and H (10–40 mm, Qingdao Sea Chemical Factory, China) were used for TLC and CC.

4.1.1. Preparation of compound ***6***. To a solution of **1** (300 mg, 0.64 mmol) in CH_2Cl_2 (12 ml) were added sequentially 4 Å molecular sieve 250 mg and PCC (250 mg, 1.28 mmol), and the mixture was stirred at 25 °C for 11 h. The reaction mixture was then passed through a flash column eluting with petroleum ether–diethyl ether (1:1). The residue obtained was chromatographed over silica gel H eluting with petroleum ether–diethyl ether (2:1) to give **6** (white amorphous powder, 47 mg, 16%): mp: 61–63 °C; $[\alpha]_D^{20}$ +38.4 (*c* 0.50, $CHCl_3$); IR (KBr): 3418, 2955, 2926, 2838, 1716, 1646, 1460, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.24, 3.25, 3.31, 3.38 (each 3H, s, $OCH_3\times4$), 3.95 (1H, s, H-6α), 9.45 (1H, s, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7 (d, C-18), 91.8 (d, C-16), 88.6 (s, C-7), 83.7 (d, C-6), 83.6 (d, C-1), 82.5 (d, C-14), 77.6 (s, C-8), 64.7 (d, C-17), 59.2 (q, C-16′), 57.8 (q, C-14′), 56.2 (q, C-6′), 56.0 (q, C-1′), 50.9 (t, C-19), 49.7 (t, C-21), 49.7 (s, C-11), 48.6 (d, C-5), 48.3 (s, C-4), 45.9 (d, C-9), 43.3 (d, C-13), 37.9 (d, C-10), 33.5 (t, C-15), 29.8 (t, C-12), 28.9 (t, C-3), 25.1 (t, C-2), 14.0 (q, C-22). ESIMS *m/z* 464 ([M−H]$^{+}$, 100), 465 ([M]$^{+}$, 32); HR-ESIMS [M+H]$^{+}$ *m/z* calcd for $C_{25}H_{40}NO_7$: 466.2805, found: 466.2794.

4.1.2. Preparation of compound ***7***. To a solution of **1** (500 mg, 1.07 mmol) in acetone–water/4:1 (15 ml) were added sequentially HOAc (0.5 ml) and $KMnO_4$ (340 mg, 2.14 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of saturated Na_2SO_3 solution. The insolvable material was filtered off, and the filtrate was concentrated prior to be diluted with H_2O (20 ml). The mixture was basified with ammonium hydroxide to pH>9, and extracted with chloroform (20 ml×3). The extracts were dried over Na_2SO_4, and the chloroform was removed in vacuum. The residue obtained was chromatographed (silica gel H, petroleum ether–acetone 2:1) to give **7** (pale yellow amorphous powder, 310 mg, 60%). *Alternative method*: To a solution of **10** (104 mg, 0.19 mmol) in acetone–water/4:1 (4 ml) were added sequentially HOAc (0.1 ml) and $KMnO_4$ (92 mg, 0.58 mmol), and the mixture was stirred at 0 °C for 30 min. A similar work-up procedure as described in the first method was employed to give a residue, which was diluted with 5% NaOH–MeOH (3 ml). The mixture was stirred at 50 °C for 30 min, and the methanol was removed by evaporation. The residue was diluted with H_2O (15 ml), the mixture was extracted with chloroform (15 ml×3), and the extracts were dried over Na_2SO_4. After removing the solvents, the residue was purified over column chromatography (silica gel H, petroleum ether–acetone 2:1) to yield **7** (87 mg, 93%): mp: 84–86 °C; $[\alpha]_D^{20}$ +48.3 (*c* 0.30, $CHCl_3$); IR (KBr): 3426, 2934, 1618, 1462, 1206, 1088 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.21, 3.37 (each 3H, s, $OCH_3\times2$), 3.43 (6H, s, $OCH_3\times2$), 3.66 (1H, t, *J*=4.4 Hz, H-14β), 3.00, 4.08 (each 1H, m, NCH_2CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.9 (s, C-19), 91.3 (d, C-16), 86.0 (s, C-7), 83.6 (d, C-1), 82.0 (d, C-6), 81.4 (d, C-14), 76.5 (s, C-8), 67.3 (t, C-18), 63.2 (d, C-17), 58.7 (q, C-16′), 57.8 (q, C-14′), 56.4 (q, C-6′), 55.2 (q, C-1′), 51.1 (d, C-5), 48.1 (s, C-11), 47.7 (s, C-4), 44.9 (d, C-9), 43.4 (t, C-21), 42.7 (d, C-13), 37.4 (d, C-10), 33.3 (t, C-15), 28.7 (t, C-12), 28.6 (t, C-3), 24.5 (t, C-2), 11.9 (q, C-22). ESIMS *m/z* 482 ([M+H]$^{+}$, 100), 504 ([M+Na]$^{+}$, 92); HR-ESIMS [M+H]$^{+}$ *m/z* calcd for $C_{25}H_{40}NO_8$: 482.2754, found: 482.2747.

4.1.3. Preparation of compounds ***8*** *and* ***9***. To a solution of TFAA (0.1 ml, 0.71 mmol) in dry CH_2Cl_2 (2 ml) was added, under argon, DMSO (0.1 ml, 1.41 mmol) in dry CH_2Cl_2 (1 ml), and the mixture was stirred at −40 °C for 30 min. And then a solution of compound **1** (200 mg, 0.43 mmol) in dry CH_2Cl_2 (5 ml) was added to the reaction mixture. The reaction was allowed to proceed for additional 3 h prior to the addition of Et_3N (0.3 ml, 2.15 mmol). The reaction temperature was warmed to room temperature, and the reaction mixture was diluted with H_2O (10 ml) and basified with ammonia hydroxide to pH>9. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 ml). The organic layers were combined and dried over Na_2SO_4, the organic solvents were removed under reduced pressure, and the residue was purified by column chromatography (silica gel H, cyclohexane–acetone 5:1) to furnish **8** (white amorphous powder, 90 mg, 47%), **9** (white amorphous powder, 23 mg, 12%), and **6** (white amorphous powder, 24 mg, 12%). Compound **8**: mp: 195–197 °C; $[\alpha]_D^{20}$ +48.4 (*c* 0.50, $CHCl_3$); IR (KBr): 2947, 2912, 2820, 1720, 1461, 1386, 1128, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.18 (1H, s, H-6α), 3.37 (1H, t, *J*=4.0 Hz, H-14β), 3.22, 3.25, 3.34, 3.43 (each 3H, s, $OCH_3\times4$), 9.46 (1H, s, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4 (d, C-18), 199.7 (s, C-7), 87.4 (d, C-16), 83.1 (d, C-1), 82.9 (d, C-6), 78.5 (d, C-14), 65.8 (d, C-17), 59.4 (q, C-16′), 58.9 (s, C-8), 57.1 (q, C-14′), 56.7 (q, C-6′), 55.9 (q, C-1′), 52.3 (s, C-11), 50.6 (s, C-4), 49.7 (t, C-21), 48.6 (d, C-5), 48.0 (t, C-19), 45.3 (d, C-9), 42.6 (d, C-13), 39.4 (d, C-10), 31.1 (t, C-15), 26.0 (t, C-12), 25.8 (t, C-3), 19.9 (t, C-2), 9.7 (q, C-22). ESIMS *m/z* 470 ($[M+Na]^+$, 100), 448 ($[M+H]^+$, 42); HR-ESIMS $[M+H]^+$ *m/z* calcd for $C_{25}H_{38}NO_6$: 448.2699, found: 448.2696. Compound **9**: mp: 96–98 °C; $[\alpha]_D^{20}$ +4.5 (*c* 0.20, $CHCl_3$); IR (KBr): 3432, 2933, 2825, 1719, 1641, 1459, 1379, 1205, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=6.8 Hz, NCH_2CH_3), 3.21, 3.84 (each 1H, ABq, *J*=12.0 Hz, H_2-18), 3.89 (1H, s, H-6α), 3.46 (1H, s, H-17), 3.35 (1H, t, *J*=4.0 Hz, H-14β), 3.26, 3.27, 3.38, 3.55 (each 3H, s, $OCH_3\times4$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7 (s, C-7), 83.6 (d, C-16), 83.3 (d, C-1), 83.0 (d, C-6), 79.3 (d, C-14), 69.6 (t, C-18), 66.0 (d, C-17), 59.6 (q, C-16′), 59.1 (s, C-8), 57.1 (q, C-14′), 56.7 (q, C-6′), 56.1 (t, C-19), 55.6 (q, C-1′), 51.2 (s, C-11), 49.1 (d, C-5), 48.3 (t, C-21), 45.5 (d, C-9), 42.4 (d, C-13), 40.4 (s, C-4), 39.6 (d, C-10), 31.4 (t, C-15), 28.9 (t, C-12), 26.0 (t, C-3), 20.4 (t, C-2), 9.8 (q, C-22). ESIMS *m/z* 450 ($[M+H]^+$, 100); HR-ESIMS $[M+H]^+$ *m/z* calcd for $C_{25}H_{40}NO_6$: 450.2703, found: 450.2704.

*4.1.4. Preparation of compound **11**.* To a solution of **7** (310 mg, 0.64 mmol) in CH_2Cl_2 (15 ml) was added DMP (408 mg, 0.96 mmol), and the mixture was stirred at 0 °C for 1.5 h prior to be quenched with saturated Na_2SO_3. The organic layer was separated and the aqueous layer was re-extracted with CH_2Cl_2 (15 ml×2). The combined organic phases were dried over Na_2SO_4 and concentrated under vacuum. The residue was subjected to column chromatography (silica gel H, cyclohexane–acetone 5:1) to yield **11** (white amorphous powder, 290 mg, 94%). Compound **11**: mp: 77–79 °C; $[\alpha]_D^{20}$ +63.7 (*c* 1.15, $CHCl_3$); IR (KBr): 3455, 2940, 2828, 1720, 1636, 1462, 1206, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (3H, t, *J*=6.8 Hz, NCH_2CH_3), 3.67 (1H, t, *J*=4.4 Hz, H-14β), 3.06, 4.14 (each 1H, m, NCH_2CH_3), 3.23, 3.36, 3.38, 3.43 (each 3H, s, $OCH_3\times4$), 10.24 (1H, s, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.6 (d, C-18), 168.7 (s, C-19), 94.2 (d, C-16), 85.7 (s, C-7), 83.5 (d, C-1), 82.1 (d, C-6), 80.9 (d, C-14), 76.9 (s, C-8), 62.8 (d, C-17), 60.6 (s, C-11), 59.8 (q, C-16′), 57.9 (q, C-14′), 56.4 (q, C-6′), 55.5 (q, C-1′), 49.1 (d, C-5), 47.7 (s, C-4), 44.8 (d, C-9), 43.6 (t, C-21), 42.7 (d, C-13), 37.5 (d, C-10), 33.1 (t, C-15), 29.6 (t, C-12), 28.5 (t, C-3), 24.4 (t, C-2), 11.9 (q, C-22). ESIMS *m/z* 480 ($[M+H]^+$, 100), 502 ($[M+Na]^+$, 41); HR-ESIMS $[M+H]^+$ *m/z* calcd for $C_{25}H_{38}NO_8$: 480.2597, found: 480.2586.

*4.1.5. Preparation of compounds **2** and **12**.* The wet strong acidic cation exchange resin (100 g) was mixed with 10% hydrochloric acid, and the resin was stood overnight prior to be washed to neutral with deionized water. The resin, followed by a solution of compound **1** (1.9 g, 4.07 mmol) in 0.5 N HCl (12 ml), was loaded onto a column, which was eluted with deionized water until the eluent being neutral. The substrate-containing resin was poured into a beaker (500 ml), to which Jones reagent (8 ml) was added. The reaction mixture was stirred at room temperature for 24 h prior to be washed to neutral with deionized water. The subsequent resin was eluted with 10% $NH_3\cdot H_2O$, and the solvents were evaporated under reduced pressure. The residue obtained was chromatographed over silica gel H eluting with petroleum ether–acetone (2:1) to give **12** (pale yellow amorphous powder, 0.4 g, 22%) and with $CHCl_3$–MeOH (3:1) to give **2** (pale yellow amorphous powder, 1.1 g, 56%). Compound **12**: mp: 93–95 °C; $[\alpha]_D^{20}$ +35.5 (*c* 0.20, $CHCl_3$); IR (KBr): 3435, 2936, 2824, 1655, 1458, 1403, 1323, 1092, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (3H, t, *J*=6.8 Hz, NCH_2CH_3), 3.61 (1H, t, *J*=4.4 Hz, H-14β), 3.24, 3.34 (each 3H, s, $OCH_3\times2$), 3.42 (6H, s, $OCH_3\times2$), 4.08 (1H, s, H-6α), 4.26 (1H, br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 89.6 (d, C-16), 88.7 (s, C-7), 83.8 (d, C-1), 83.7 (d, C-14), 82.7 (d, C-6), 77.6 (s, C-8), 69.9 (s, C-4), 64.0 (d, C-17), 58.2 (q, C-16′), 57.7 (q, C-14′), 57.6 (t, C-19), 56.2 (q, C-6′), 56.1 (q, C-1′), 55.8 (d, C-5), 50.5 (s, C-11), 50.4 (t, C-21), 45.8 (d, C-9), 43.3 (d, C-13), 38.3 (d, C-10), 37.3 (t, C-15), 33.3 (t, C-12), 28.7 (t, C-3), 26.8 (t, C-2), 14.0 (q, C-22). ESIMS *m/z* 476 ($[M+Na]^+$, 100), 454 ($[M+H]^+$, 85); HR-ESIMS $[M+H]^+$ *m/z* calcd for $C_{24}H_{40}NO_7$: 454.2805, found: 454.2795. Compound **2**: mp: 138–140 °C; $[\alpha]_D^{20}$ +31.8 (*c* 0.50, CH_3OH); IR (KBr): 3482, 2949, 2827, 1645, 1592, 1457, 1367, 1328, 1222, 1084 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.32, 3.35, 3.41, 3.45 (each 3H, s, $OCH_3\times4$), 3.63 (1H, t, *J*=4.0 Hz, H-14β); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.6 (s, C-18), 91.6 (d, C-16), 86.5 (s, C-7), 83.9 (d, C-1), 82.9 (d, C-14), 82.9 (d, C-6), 78.4 (s, C-8), 64.4 (d, C-17), 58.5 (d, C-16′), 57.8 (q, C-14′), 56.3 (q, C-6′), 55.9 (q, C-1′), 51.3 (t, C-19), 51.2 (t, C-21), 49.1 (s, C-11), 48.6 (d, C-5), 46.1 (s, C-4), 44.6 (d, C-9), 43.1 (d, C-13), 38.0 (d, C-10), 33.3 (t, C-15), 29.6 (t, C-12), 29.5 (t, C-3), 23.1 (t, C-2), 12.3 (q, C-22). ESIMS *m/z* 504 ($[M+Na]^+$, 90), 482 ($[M+H]^+$,52), 436($[M-COOH]^+$, 100); HR-ESIMS $[M+H]^+$ *m/z* calcd for $C_{25}H_{40}NO_8$: 482.2754, found: 482.2757.

*4.1.6. Preparation of compound **13**.* Acid **2** (1.0 g, 2.08 mmol) in a round bottomed flask (100 ml) was heated at 220 °C under 15 mm Hg for 25 min. After cooling to room temperature, the residue was chromatographed over silica gel H eluting with petroleum ether–acetone (13:1) to give **13** (white amorphous powder, colorless crystal after recrystallizing from acetone, 298 mg, 37%). Compound **13**: mp: 132–133 °C; $[\alpha]_D^{20}$ +49.0 (*c* 0.50, $CHCl_3$); IR (KBr): 3063, 2937, 2830, 1743, 1638, 1459, 1383, 1313, 1201, 1096, 998, 942, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.34 (1H, hidden, H-1), 1.94 (2H, m, H-2), 2.21 (1H, m, H-3α), 2.60 (1H, m, H-3β), 2.62 (1H, s, H-5), 3.10 (1H, d, *J*=1.6 Hz, W-type, H-6β), 2.32 (1H, m, H-9), 2.04 (1H, m, H-10), 2.13 (2H, m, H-12), 2.30 (1H, m, H-13), 3.54 (1H, t, *J*=3.2 Hz, H-14β), 1.65 (1H, m, H-15α), 2.43 (1H, m, H-15β), 3.46 (1H, t, *J*=8.4 Hz, H-16), 3.82 (1H, d, *J*=1.6 Hz, W-type, H-17), 4.73 (2H, t, *J*=2.8 Hz, H-19), 2.45 (1H, m, H-21a), 2.69 (1H, m, H-21b), 1.07 (3H, t, *J*=7.2 Hz, H-22), 3.32 (3H, s, 1-OCH_3), 3.37 (3H, s, 14-OCH_3), 3.36 (3H, s, 16-OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.2 (s, C-7), 146.3 (s, C-4), 111.8 (t, C-19), 83.8 (d, C-16), 82.3 (d, C-14), 80.5 (d, C-1), 73.3 (d, C-6), 70.7 (d, C-17), 57.3 (q, C-14′), 57.1 (q, C-16′), 56.7 (q, C-1′), 56.3 (s, C-11), 52.6 (d, C-5), 52.0 (s, C-8), 48.8 (d, C-9), 47.9 (d, C-10), 43.1 (t, C-21), 39.9 (d, C-13), 30.5 (t, C-12), 28.3 (t, C-3), 26.9 (t C-15), 24.3 (t, C-2), 13.9 (q, C-22). ESIMS *m/z* 388 ($[M+H]^+$, 100); HR-ESIMS $[M+H]^+$ *m/z* calcd for $C_{23}H_{34}NO_4$: 388.2488, found: 388.2477.

The crystal structure for **13**: a colorless orthorhombic crystal from acetone was mounted on a P_4 four circle diffractometer and exposed to graphite-monochromated Mo Kα irradiation. The unit cell parameters are *a*=8.5766 (17) Å, *b*=12.623 (3) Å, *c*=19.423 (4) Å, *V*=2102.7 (7) $Å^3$, *Z*=4, d_x=1.224 g/cm^3, in space group $P2_12_12_1$, of the 4131 measured with $2.65\leq\theta\leq26.00°$ scan, 3402 were independently observed at the level of $F_0>4\sigma$ (F_0). The structure was solved by the directed method using the program SHELXL-97 and the atomic parameters were refined by the full-matrix least squares on F^2 method. The final *R* indices [$I>2\sigma$ (I)] was *R*1=0.0620, *wR*2=0.0605. CCDC reference number: CCDC 790141.

*4.1.7. Preparation of compounds **14**–**17**.* To a solution of **13** (210 mg, 0.54 mmol) in 95% EtOH–EtOAc/1:1 (6 ml) were added acetic acid (0.2 ml) and 10% Pd–C (40 mg), and the mixture was stirred at 50 °C in the presence of hydrogen for 20 h. After filtration, the filtrate was concentrated to give a residue, which was diluted with water (15 ml), basified with ammonia hydroxide to pH>9, and extracted with chloroform (15 ml×3). The extracts were dried over Na_2SO_4, and concentrated in vacuum gave a residue, which was chromatographed (silica gel H, petroleum ether–diethyl ether 8:1) to give **14** (colorless oil, 11 mg, 5%), **15** (white amorphous powder, 61 mg, 29%), and a mixture of **16** and **17** (white amorphous powder, 121 mg, 57%, **16**/**17**=2:1). Continued hydrogenolysis of the mixture of **16** and **17** under the same condition for 7 days, the ratio of **16**–**17** was changed from 2:1 to 1:3. Compound **14**: $[\alpha]_D^{20}$ +7.5 (*c* 0.80, $CHCl_3$); IR (KBr): 2924, 2855, 1741, 1459, 1377, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (3H, d, *J*=6.4 Hz, H-19), 1.09 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.05 (1H, d, *J*=1.6 Hz, W-type, H-6β), 3.47 (1H, t, *J*=8.4 Hz, H-16), 3.53 (1H, t, *J*=3.6 Hz, H-14β), 3.78 (1H, d, *J*=1.6 Hz, W-type, H-17), 3.36 (6H, s, OCH_3×2), 3.38 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4 (s, C-7), 83.7 (d, C-16), 82.5 (d, C-14), 79.5 (d, C-1), 71.9 (d, C-6), 71.6 (d, C-17), 57.2 (q, C-14′), 56.7 (q, C-16′), 56.6 (q, C-1′), 55.6 (s, C-11), 52.0 (s, C-8), 53.1 (d, C-5), 48.8 (d, C-9), 48.4 (d, C-10), 43.0 (t, C-21), 40.1 (d, C-13), 30.7 (d, C-4), 30.4 (t, C-12), 27.4 (t, C-3), 26.8 (t, C-15), 24.2 (t, C-2), 22.4 (q, C-19), 13.7 (q, C-22). ESIMS *m*/*z* 390 ($[M+H]^+$, 100); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{23}H_{36}NO_4$: 390.2644, found: 390.2644. Compound **15**: mp: 69–71 °C; $[\alpha]_D^{20}$ −10.1 (*c* 0.80, $CHCl_3$); IR (KBr): 2927, 2865, 2821, 1745, 1460, 1377, 1125, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, d, *J*=6.4 Hz, H-19), 1.06 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.26 (1H, d, *J*=1.6 Hz, W-type, H-6β), 3.46 (1H, t, *J*=8.0 Hz, H-16), 3.52 (1H, t, *J*=3.6 Hz, H-14β), 3.78 (1H, d, *J*=1.6 Hz, W-type, H-17), 3.33, 3.35, 3.36 (each 3H, s, OCH_3×3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.8 (s, C-7), 83.8 (d, C-16), 82.2 (d, C-14), 79.6 (d, C-1), 70.5 (d, C-6), 66.3 (d, C-17), 57.2 (q, C-14′), 57.1 (q, C-16′), 56.7 (q, C-1′), 54.4 (s, C-11), 52.1 (s, C-8), 50.0 (d, C-5), 49.0 (d, C-9), 48.0 (d, C-10), 43.1 (t, C-21), 39.9 (d, C-13), 30.2 (t, C-12), 26.9 (d, C-4), 26.9 (t, C-3), 26.4 (t, C-15), 23.8 (t, C-2), 20.6 (q, C-19), 13.9 (q, C-22). ESIMS *m*/*z* 412 ($[M+Na]^+$, 100), 390 ($[M+H]^+$, 85); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{23}H_{36}NO_4$: 390.2644, found: 390.2640. Compound **16**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, *J*=6.8 Hz, NCH_2CH_3), 1.61 (3H, s, H-19), 3.28, 3.34, 3.38 (each 3H, s, OCH_3×3), 3.52 (1H, t, *J*=3.6 Hz, H-14β), 3.65 (1H, t, *J*=8.0 Hz, H-16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2 (s, C-7), 129.6 (s, C-5), 126.9 (s, C-4), 82.9 (d, C-16), 82.7 (d, C-14), 79.1 (d, C-1), 66.5 (d, C-17), 59.4 (s, C-11), 57.2 (q, C-14′), 56.7 (q, C-16′), 56.1 (q, C-1′), 52.4 (s, C-8), 49.4 (d, C-9), 45.1 (d, C-10), 44.3 (t, C-21), 43.1 (t, C-6), 40.7 (d, C-13), 30.1 (t, C-12), 27.1 (t, C-3), 25.9 (t, C-15), 22.1 (t, C-2), 19.3 (q, C-19), 15.7 (q, C-22). ESIMS *m*/*z* 390 ($[M+H]^+$); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{23}H_{36}NO_4$: 390.2644, found: 390.2649. Compound **17**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, d, *J*=6.4 Hz, H-19), 1.00 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.28, 3.29, 3.37 (each 3H, s, OCH_3×3), 3.49 (1H, t, *J*=3.2 Hz, H-14β), 3.65 (1H, t, *J*=8.0 Hz, H-16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8 (s, C-7), 83.2 (d, C-16), 82.8 (d, C-14), 80.5 (d, C-1), 67.9 (d, C-17), 59.2 (s, C-11), 57.1 (q, C-14′), 56.7 (q, C-16′), 55.9 (q, C-1′), 51.0 (s, C-8), 45.6 (d, C-5), 43.6 (d, C-9), 43.5 (t, C-21), 40.8 (t, C-6), 40.1 (d, C-10), 39.0 (d, C-13), 31.0 (t, C-12), 30.9 (d, C-4), 29.9 (t, C-3), 26.1 (t, C-15), 25.1 (t, C-2), 19.8 (q, C-19), 15.8 (q, C-22). ESIMS *m*/*z* 392 ($[M+H]^+$); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{23}H_{38}NO_4$: 392.2801, found: 392.2810.

*4.1.8. Preparation of compound **18**.* A solution of **13** (80 mg, 0.21 mmol) in acetic acid (15 ml) was refluxed for 14 days. After cooling to room temperature, the reaction mixture was basified with ammonia hydroxide to pH>9, and extracted with chloroform (15 ml×3). The extracts were dried over Na_2SO_4 and concentrated in vacuum gave a residue, which was chromatographed over silica gel H (cyclohexane–acetone (10:1)) to yield **18** (white amorphous powder, 15 mg, 65% based on the recovery of **13**). Compound **18**: mp: 101–103 °C; $[\alpha]_D^{20}$ +8.2 (*c* 0.50, $CHCl_3$); IR (KBr): 2935, 2827, 1746, 1669, 1452, 1381, 1208, 1098 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (3H, t, *J*=6.8 Hz, NCH_2CH_3), 1.76 (3H, s, H-19), 3.33, 3.35, 3.38 (each 3H, s, OCH_3×3), 3.47 (1H, t, *J*=8.4 Hz, H-16), 3.62 (1H, t, *J*=3.2 Hz, H-14β), 3.77 (1H, br s, H-6β), 3.88 (1H, br s, H-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3 (s, C-7), 130.9 (s, C-5), 130.7 (s, C-4), 83.9 (d, C-16), 82.6 (d, C-1), 77.2 (d, C-14), 71.6 (d, C-17), 70.5 (d, C-6), 57.3 (q, C-14′), 57.2 (q, C-16′), 56.8 (q, C-1′), 55.9 (s, C-11), 54.0 (s, C-8), 47.4 (d, C-9), 46.9 (d, C-10), 42.9 (t, C-21), 40.1 (d, C-13), 30.8 (t, C-12), 26.8 (t, C-3), 26.8 (t, C-15), 24.4 (t, C-2), 20.6 (q, C-19), 13.2 (q, C-22). ESIMS *m*/*z* 410 ($[M+Na]^+$, 100); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{23}H_{34}NO_4$: 388.2488, found: 388.2481.

*4.1.9. Preparation of compounds **19** and **20**.* The solution of **13** (170 mg, 0.44 mmol) in dichloromethane (8 ml) was flushed with ozone for 15 min at −78 °C prior to the addition of SMe_2 (1 ml). The reaction mixture was then warmed to room temperature and kept stirring for additional 30 min. The dichloromethane was removed under reduced pressure, and the residue was partitioned between water (10 ml) and chloroform (15 ml×3). The chloroform fractions were dried over Na_2SO_4 and concentrated. The residue obtained was purified by column chromatography (silica gel H, cyclohexane–acetone 7:1) to furnished **19** (pale yellow amorphous powder, 72 mg, 42%) and **20** (pale yellow amorphous powder, 24 mg, 15%). *Alternative method*: A solution of **13** (30 mg, 0.08 mmol) in DMF (2 ml) was flushed with ozone for 10 min at −78 °C. The cold bath was removed due to the frozen reaction mixture. When it was thawing, the reaction mixture was flushed with ozone for additional 10 min at −78 °C. This procedure was repeated one more time to make sure that the total ozone flushing time could reach 30 min. And then SMe_2 (0.1 ml) was added to the reaction mixture, which was warmed to room temperature and kept stirring for 2 h. A similar work-up procedure as described in the first method was employed to give pure product **19** (pale yellow amorphous powder, 30 mg, 100%): mp: 196–198 °C; $[\alpha]_D^{20}$ +27.5 (*c* 0.55, $CHCl_3$); IR (KBr): 2934, 2887, 2826, 1749, 1698, 1451, 1384, 1329, 1205, 1125, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, t, *J*=7.2 Hz, NCH_2CH_3), 3.35, 3.36, 3.38 (each 3H, s, OCH_3×3), 3.48 (1H, t, *J*=8.4 Hz, H-16), 3.59 (1H, hidden, H-14β), 3.80 (1H, d, *J*=1.6 Hz, W-type, H-6β), 3.86 (1H, d, *J*=1.6 Hz, W-type, H-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0 (s, C-7), 207.9 (s, C-4), 83.5 (d, C-16), 82.2 (d, C-14), 77.2 (d, C-1), 71.8 (d, C-6), 69.2 (d, C-17), 58.6 (s, C-11), 57.3 (q, C-14′), 56.8 (q, C-16′), 56.5 (q, C-1′), 55.6 (d, C-5), 52.7 (s, C-8), 48.7 (d, C-9), 47.5 (d, C-10), 42.9 (t, C-21), 39.8 (d, C-13), 33.8 (t, C-3), 30.7 (t, C-12), 26.6 (t, C-15), 22.8 (t, C-2), 13.5 (q, C-22). ESIMS *m*/*z* 412 ($[M+Na]^+$, 100); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{22}H_{32}NO_5$: 390.2280, found: 390.2281. Compound **20**: mp: 182–184 °C; $[\alpha]_D^{20}$ +61.2 (*c* 0.25, $CHCl_3$); IR (KBr): 3296, 2940, 2868, 2829, 1757, 1707, 1455, 1379, 1212, 1130, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.28, 3.35, 3.36 (each 3H, s, OCH_3×3), 3.50 (1H, t, *J*=9.2 Hz, H-16), 3.61 (1H, t, *J*=3.2 Hz, H-14β), 3.78 (1H, br s, H-6β), 4.23 (1H, d, *J*=1.6 Hz, W-type, H-17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9 (s, C-7), 206.8 (s, C-4), 83.3 (d, C-16), 82.0 (d, C-14), 75.4 (d, C-1), 71.6 (d, C-6), 64.0 (d, C-17), 60.6 (s, C-11), 57.3 (q, C-14′), 56.8 (q, C-16′), 56.0 (s, C-8), 55.8 (d, C-5), 55.3 (q, C-1′), 47.5 (d, C-9), 45.9 (d, C-10), 40.6 (d, C-13), 32.1 (t, C-3), 31.1 (t, C-12), 24.4 (t, C-15), 22.1 (t, C-2). ESIMS *m*/*z* 400 ($[M+K]^+$, 100), 362 ($[M+H]^+$, 18); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{20}H_{28}NO_5$: 362.1967, found: 362.1963.

*4.1.10. Preparation of compound **21**.* To a solution of **19** (30 mg, 0.08 mmol) in 95% EtOH–EtOAc/1:1 (1 ml) were added acetic acid (0.1 ml) and 10% Pd–C (5 mg), and the mixture was stirred at 50 °C in the presence of hydrogen atmosphere for 24 h. After filtration and concentration, the residue was diluted with water (10 ml), basified with ammonia hydroxide to pH>9, and extracted with chloroform (10 ml×3). The extracts were dried over Na_2SO_4, and the chloroform was removed in vacuum. The residue obtained was chromatographed over silica gel H, eluting with cyclohexane–acetone 10:1, to give **21** (white amorphous powder, 20 mg, 67%): mp: 224–226 °C; $[\alpha]_D^{20}$ +16.3 (*c* 1.25, $CHCl_3$); IR (KBr): 3327, 2947, 2899, 2828, 1722, 1715, 1476, 1448, 1380, 1205, 1129, 1090, 1010, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, t, J=6.8 Hz, NCH_2CH_3), 3.25, 3.36, 3.45 (each 3H, s, $OCH_3\times3$), 3.61 (2H, m, H-14 and H-16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.9 (s, C-7), 208.4 (s, C-4), 82.7 (d, C-16), 82.6 (d, C-14), 79.1 (d, C-1), 67.4 (d, C-17), 58.6 (s, C-11), 57.4 (s, C-8), 57.3 (q, C-14′), 56.8 (q, C-16′), 56.4 (q, C-1′), 46.6 (d, C-5), 44.5 (d, C-9), 44.4 (d, C-10), 43.0 (t, C-21), 40.3 (d, C-13), 36.6 (t, C-6), 34.3 (t, C-3), 30.5 (t, C-12), 27.2 (t, C-15), 26.0 (t, C-2), 15.9 (q, C-22). ESIMS *m*/*z* 414 ($[M+Na]^+$, 100), 392 ($[M+H]^+$, 57); HR-ESIMS $[M+H]^+$ *m*/*z* calcd for $C_{22}H_{34}NO_5$: 392.2437, found: 392.2422.

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