*m*CPBA Oxidation of Acetyllycoctonine and Its New Products

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Treatment of a lycoctonine-type alkaloid acetyllycoctonine (4) with *m*CPBA at room temperature led to acetyllycoctonine *N*-oxide (5) as the major product together with other interesting compounds 6—12 as the minor products, which were derived from oxidation involving the nitrogen atom[1)] and Cope elimination as well as Polonovski-like fragmentation. All of those new compounds (5—12) were fully characterized.

Key words C_{19}-diterpenoid alkaloid; acetyllycoctonine; oxidation involving nitrogen atom; *N*-oxidation

The diterpenoid alkaloids are a synthetic or structurally modified target for a long time due to their complex and diversities displaying a lot of interesting chemical reactions [1,2] and several biological activities.[3,4] Some papers [5—9] reported that treatment of the aconitine-type alkaloids and their derivatives with *m*CPBA lead to the main products the *N*-oxides together with the by-products, the amides or the *N*,*O*-mixed ketal. In contrast, oxidation of the lycoctonine-type alkaloids with *m*CPBA has been reported rarely yet besides deltaline (**1**) containing 7,8-methoxylene and ajacine (**2**) having the 7,8-glycol group. The former gave the *N*-oxide in high yield of 95.8%, but the latter only in lower yield of 20%.[6] In conjunction with our ongoing research program, we have found that treatment of a lycoctonine-type alkaloid acetyllycoctonine (**4**) with *m*CPBA afforded not only the major compound acetyllycoctonine *N*-oxide (**5**) but also the interesting by-products (**6**—**12**). This paper deals with the isolation and structural elucidation of these new compounds (**5**—**12**).

Results and Discussion

When acetyllycoctonine (**4**) derived from lycoctonine (**3**) reacted with *m*CPBA at room temperature for 30 min, followed by a column chromatography (silica gel H, $CHCl_3$–MeOH system), the major product acetyllycoctionine *N*-oxide (**5**) (31%) was obtained together with the other new interesting minor compounds **6** (0.9%), **7** (2.8%), **8** (8.5%), **9** (7.2%), **10** (1.3%), **11** (1.5%), and **12** (1.5%).

Compound **5** has the molecular formula, $C_{27}H_{43}NO_9$, based on its HR-MS. The ^{1}H- and ^{13}C-NMR spectra of **5** showed the characteristic signals at δ_H 1.41 (3H, t, J=6.6 Hz) and δ_C 8.8 (q) for an *N*-ethyl group.[5,6] This led to determine readily the structure of **5**. ^{13}C-NMR comparison of **4** and **5** (Table 1) showed the differences of the δ values of many carbons, *e.g.* C-1, C-2, C-4, C-6, C-7, C-10, C-12, C-13, C-18, especially in C-17, C-19, C-21, and C-22, due to the *N*-oxidation effect.[5,6]

The molecular formulae of compounds **6** ($C_{27}H_{41}NO_9$) and **7** ($C_{25}H_{37}NO_9$) were derived from their HR-MS. As compared with **7**, the ^{1}H- (^{13}C-) NMR and MS spectra of **6** showed the appearance of an additional *N*-ethyl group (δ_H 1.10 t, J=7.2 Hz; δ_C 43.6 t, 11.9 q) and more 28 mass units corresponding to the CH_2CH_2 moiety of the *N*-ethyl group in **6**. The ^{13}C-NMR data of both the compounds **6** and **7** also exhibited the distinctive lactam group at δ_C 169.9 s and 173.3 s, respectively. The structures of these two compounds, thus, were assigned to be **6** and **7**. As showed in Table 1, apparently, because of the presence of the electron-donating *N*-ethyl group, the d value of C-19 in **6** shifted upfield as compared with **7**.

Compounds **8** and **9** have the same formula, $C_{34}H_{46}NO_{11}Cl$, which was assigned by HR-ESI-MS *m*/*z* 680.2823 (M+H, Cacld 680.2831) for **8** and *m*/*z* 702.2662 (M+Na, Cacld 702.2651) for **9**. Their ^{1}H- and ^{13}C-NMR spectra are very similar except for C-17, C-19 and C-21 (Table 1). In the ^{1}H- (^{13}C-) NMR spectra of **8** and **9**, a 1H-quartet signal at *ca.* δ_H 6.3 (J=5.4 Hz) and a 3H-doublet sig-

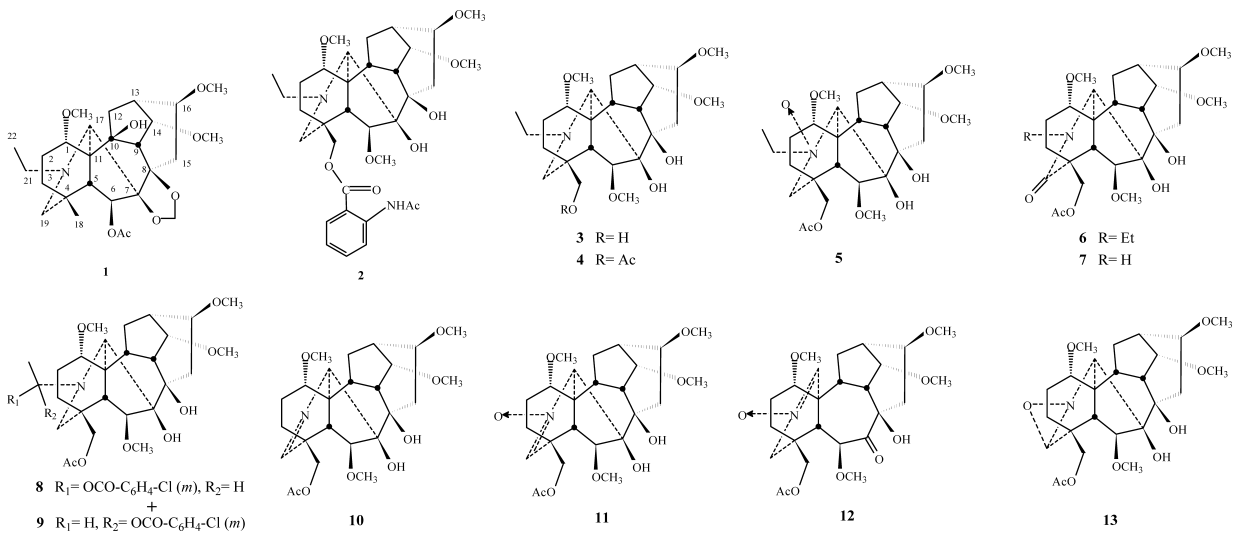

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Table 1. ^{13}C-NMR Data of Compounds **4**—**11**

Carbon	**4**[10)]	**5**	**6**	**7**	**8**	**9**	**10**	**11**
1	84.0	87.4	83.5	83.6	83.6	83.7	81.9	81.7
2	26.1	23.7	25.0	25.1	26.2	26.4	20.0	20.6
3	31.9	30.2	28.3	28.5	30.8	30.7	24.5	26.6
4	37.2	39.4	47.2	47.1	39.1	39.2	46.1	42.1
5	43.3	49.0	49.1	49.2	49.9	49.7	42.9	42.9
6	90.9	88.8	91.9	91.7	90.4	90.4	90.6	90.7
7	88.5	83.9	85.9	85.3	87.4	87.1	86.5	84.8
8	77.5	78.3	76.4	76.2	77.1	77.1	77.0	76.4
9	50.4	43.0	42.7	42.8	43.4	43.4	42.9	42.8
10	38.1	47.8	45.2	44.6	45.7	45.8	45.3	46.1
11	49.0	50.0	48.7	48.5	49.0	49.6	50.5	50.6
12	28.7	30.6	29.3	28.6	28.4	28.3	30.4	30.3
13	46.1	36.1	37.5	37.7	37.7	37.7	38.0	38.0
14	84.0	83.0	81.9	81.7	83.0	82.3	83.9	83.9
15	33.7	33.5	33.2	33.1	34.1	34.0	33.1	33.3
16	82.6	81.5	81.3	81.4	82.4	82.1	80.7	80.0
17	64.6	76.9	63.2	59.2	68.5	67.5	64.2	77.7
18	69.1	71.2	66.2	65.6	68.4	68.3	65.7	66.2
19	52.4	69.4	169.9	173.3	55.3	57.1	167.5	136.2
21	51.0	68.6	43.6	—	97.6	98.5	—	—
22	14.1	8.8	11.9	—	19.0	18.9	—	—
1-OCH_3	55.7	56.1	55.1	55.7	55.1	55.4	56.3	56.3
6-OCH_3	57.8	57.5	57.8	57.8	57.7	57.7	57.7	57.8
14-OCH_3	58.0	58.2	58.5	58.5	58.2	58.2	58.6	58.7
16-OCH_3	56.3	56.8	56.3	56.4	56.3	55.9	56.4	56.5
18-OCO	170.9	170.3	170.3	170.2	170.5	170.6	170.4	170.3
CH_3	20.8	20.5	20.7	20.7	20.6	20.6	20.6	20.6
21-OCO	—	—	—	—	164.1	163.8	—	—
1′	—	—	—	—	132.4	132.0	—	—
2′	—	—	—	—	129.6	129.7	—	—
3′	—	—	—	—	134.2	134.5	—	—
4′	—	—	—	—	129.3	129.5	—	—
5′	—	—	—	—	127.7	127.8	—	—
6′					132.7	133.0		

Table 2. 2D-NMR Data of Compound **12**

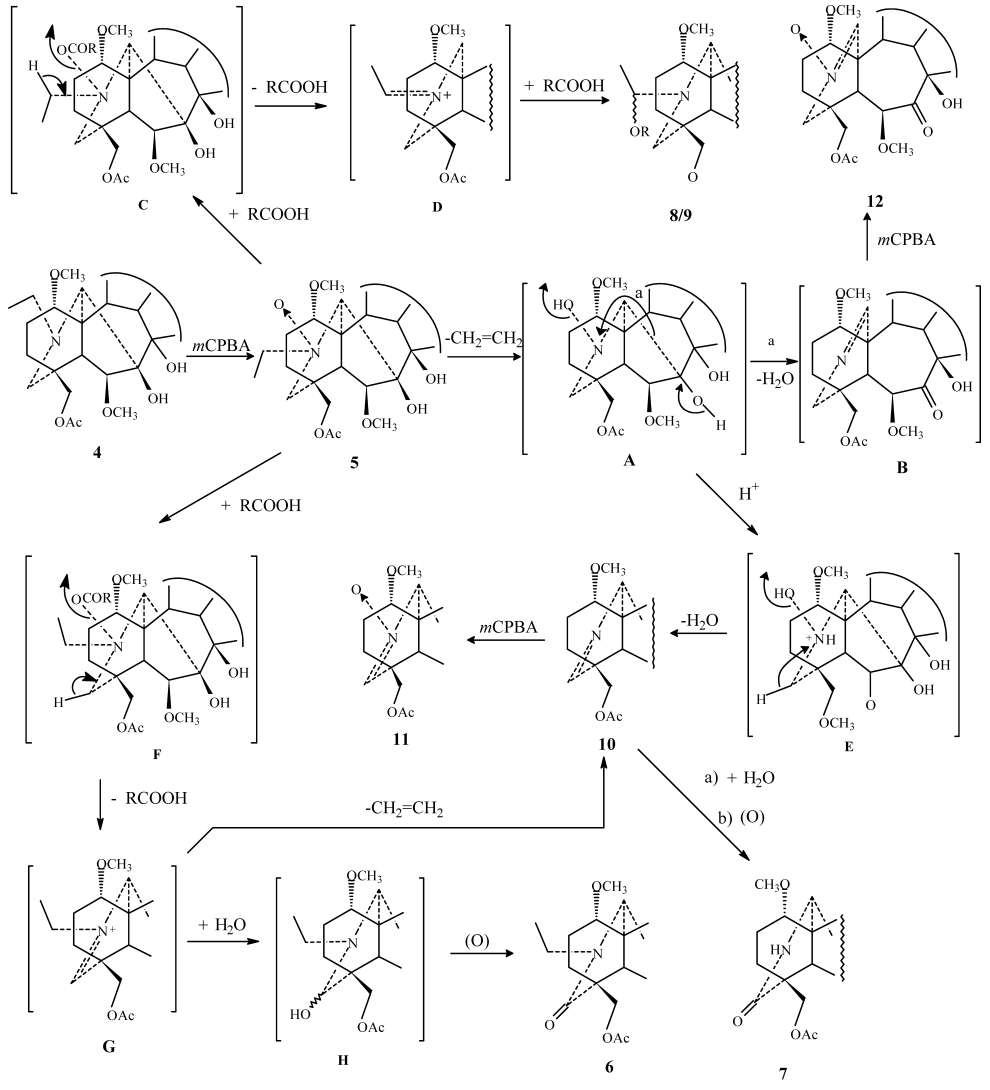
Carbon	δ_H	δ_C	HMBC (H→C)
1	3.09 dd (15.2, 4.4)	91.7 d	C-10, C-11, C-17
2	1.19—1.29 m (α)	23.5 t	C-1
	2.03—2.05 m (β)		—
3	1.60—1.64 m (β)	33.1 t	C-2, C-4, C-19
	1.87—1.90 m (α)		C-1, C-2, C-5
4	—	39.2 s	—
5	2.13 s	49.5 d	C-1, C-4, C-6, C-7, C-11, C-17, C-18, C-19
6	3.77 d (1.6)	88.6 d	C-4, C-5, C-7, C-8, C-11
7	—	207.7 s	—
8	—	74.8 s	—
9	3.78—3.80 m	40.6 d	C-8, C-11, C-12, C-14, C-15
10	2.47—2.53 m	45.2 d	C-1, C-8, C-9, C-11, C-12, C-13, C-14, C-17
11	—	46.0 s	—
12	1.48 dd (15.6, 7.6) (β)	28.1 t	C-10, C-13, C-14, C-16
	2.11—2.18 m (α)		C-13, C-14
13	2.63—2.65 m	36.2 d	C-14, C-15
14	3.35—3.36 m	80.3 d	C-8, C-13
15	1.58 dd (17.2, 6.4) (α)	33.5 t	C-8, C-14
	2.47—2.53 m (β)		C-8, C-9, C-13
16	3.78—3.80 m	84.2 d	C-8, C-12, C-14, C-15
17	7.06 s	136.6 d	C-5, C-10, C-19
18	3.88 ABq (12.0)	67.7 t	C-3, C-4, C-5, C-19, O<u>CO</u>CH_3
	4.24 ABq (11.6)		C-3, C-4, C-5, C-19, O<u>CO</u>CH_3
19	3.56 ABq (16.8)	62.8 t	C-3, C-4, C-5, C-17
	3.79—3.82 hidden		C-3, C-4, C-5, C-17, C-18
1-OCH_3	3.25 s	56.3 q	C-1
6-OCH_3	3.38 s	58.4 q	C-6
14-OCH_3	3.31 s	57.0 q	C-14
16-OCH_3	3.45 s	58.1 q	C-16
18-OCO	—	170.2 s	—
CH_3	2.09 s	20.6 q	O<u>CO</u>CH_3

nal at around δ_H 1.5 (J=5.4 Hz) were attributed to H-21 and H_3-22, respectively, implying the presence of a oxygenated substitution at the C-21 position and also that compounds **8** and **9** are a pair of epimers.

Compounds **10** and **11** have the molecular formulae $C_{25}H_{37}NO_8$ (HR-EI-MS m/z 479.2500 Cacld 479.2519) and $C_{25}H_{37}NO_9$ (HR-EI-MS m/z 495.2456 Cacld 495.2468), respectively. They also possess the same unsaturated degree (n=8) but the presence of difference of 16 mass units between **10** and **11** in the MS spectra, indicating that **11** is possibly derived from the *N*-oxidation of **10**. The ^{1}H- and ^{13}C-NMR spectra of **10** and **11** exhibited the distinctive imine signals (**10**: δ_H 7.72 br s, δ_C 167.5 d; **11**: δ_H 6.77 d, J=1.2 Hz, δ_C 136.2 d). In addition, their ^{13}C-NMR spectra (Table 1) are similar except for C-4, C-7, C-17 and C-19. It is worthy to note that changes of the δ values caused by the *N*-oxidation from **10** to **11** corresponding to **4**→**5** are less together with a great upfield-shift of the δ value of C-19 in the ^{13}C-NMR spectra of **11** as compared with those of **10**.

Compound **12**, $C_{25}H_{37}NO_9$ (HR-EI-MS m/z 495.2473 Cacld 495.2468), was obtained as a white amorphous powder with smaller *Rf* value (0.43) on TLC (petroleum ether–acetone 1 : 1). The ^{1}H- and ^{13}C-NMR spectra of **12** showed the presence of four methoxyl groups (δ_H 3.25 s, 3.31 s, 3.38 s, 3.45 s), an acetyl group (δ_H 2.09 s, δ_C 170.2 s, 20.6 q), an imine group (δ_H 7.06 s, δ_C 136.6 d), and a ketone group (δ_C 207.7s). Its structure was confirmed by 2D-NMR spectra. It is also a novel artifact 17,7-seco C_{19}-diterpenoid alkaloid.

Finally, our results together with the data on the oxidation involved the nitrogen atom of diterpenoid alkaloids[1)] led us to propose a plausible process from **4** to compounds **5**—**12** depicted in Chart 1: *m*-CPBA oxidation of acetyllycoctonine (**4**) first produces the *N*-oxide **5**, and then, **5** was subjected to a Cope elimination to give the intermediate A in company with loss of a molecular ethylene. Cleavage of the C_{17}–C_7 bond in A *via* a Polonovski-like process formed the imine ketone B followed by treating with *m*-CPBA to afford **12**. The salt D formed from A under acid condition gave **10a** through an α-elimination of water, *m*CPBA oxidation of **10** afforded competitively the nitrone **11** instead of the oxaziridine **13**.[9,11)] Another pathway of formation of **10** involved possibly in a Cope elimination of the intermediate **G**, and continued the



R=OC-C$_6$H$_5$Cl(*m*)

Chart 1

reaction of **10** with H_2O followed by oxidation led to form **7**. On the other hand, esterification of **5** with (*m*)Cl–C_5H_6COOH gave the intermediates **C** and **F**, leading to produce a pair of regioisomeric immonium salts **D** and **G**. The former reacted with (*m*)Cl–C_5H_6COOH to form a pair of epimer **8** and **9**, the latter in the presence of H_2O gave the intermediate **H** followed by oxidation into **6**.

Expenimental

General Experimental Procedure Melting points were uncorrected. IR spectra were recorded on a Nicolet FT-IR 200SXV spectrometer. Optical rotations were measured with a JASCO DIP-370 polarimeter. ^{1}H- and ^{13}C-NMR spectra were acquired on a Varian INOVA 400/54 or a Bruker AC-E 200 spectrometer in $CDCl_3$ with TMS as internal standard. MS spectra were obtained on Finnigan LCQ and Micromass Auto Spec Ultima-Tof spectrometer.

Preparation of Compounds (5)—(12) To acetyllycoctonine (**4**) (1.28 g, 2.52 mmol) prepared from lycoctonine (**3**) with acetic anhydride in $CHCl_3$ (30 ml) *m*CPBA (2.15 g, 12.6 mmol) was added, and this solution was stirred at room temperature for 30 min. Evaporation in vacuum to give a residue, which was subjected to column chromatography on silica gel H (total amount of 200 g) using $CHCl_3$–MeOH (98 : 2→9 : 1)→petroleum–acetone–H_2O (50 : 50 : 1) as eluents yield the major compound (**5**) (399 mg, 31%), and the minor ones (**6**) (37 mg, 2.8%), (**7**) (12 mg, 0.9%), (**8**) (146 mg, 8.5%), (**9**) (123 mg, 7.2%), (**10**) (15 mg. 1.3%), (**11**) (20 mg, 1.5%), and (**12**) (20 mg, 1.5%).

Compound **5**: White amorphous powder, $C_{27}H_{43}NO_9$, HR-ESI-MS *m*/*z* 526.3021 (M+H, Cacld 526.3010), mp 128—129 °C, $[\alpha]_D^{20}$ +23.3° (*c*=1.965, $CHCl_3$); IR (cm^{-1}): 3460 (OH), 1741 (COO). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.41 (3H, t, *J*=6.6 Hz, N-$CH_2\underline{CH_3}$); 2.04 (3H, s, OAc); 3.24, 3.27, 3.36, 3.37 (each 3H, s, 4×OCH_3); 3.58 (1H, t, *J*=4.4 Hz, H-14β); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; ESI-MS: *m*/*z* 526 (M+1, 100).

Compound **6**: White amorphous powder, $C_{27}H_{41}NO_9$, HR-EI-MS *m*/*z* 523.2774 (M$^+$, Cacld 523.2781), mp 80—81 °C, $[\alpha]_D^{20}$ +26.6° (*c*=1.330, $CHCl_3$); IR (cm^{-1}): 3479 (OH), 1746 (COO), 1633 (CONR). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.10 (3H, t, *J*=7.2 Hz, N-$CH\underline{CH_3}$); 2.06 (3H, s, OAc), 3.20, 3.35, 3.36, 3.41 (each 3H, s, 4×OCH_3), 3.64 (1H, t, *J*=4.4 Hz, H-14β), 3.76 (1H, s), 3.93 (1H, s), 4.06 (1H, m), 4.27, 4.59 (2H, ABq, *J*=12.0 Hz, H_2-18); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m*/*z* 523 (M$^+$, 20), 505 (M−18, 90), 490 (45), 432 (50).

Compound **7**: White amorphous powder, $C_{25}H_{37}NO_9$, HR-EI-MS *m*/*z* 495.2470 (M$^+$, Cacld 495.2468), mp 97—98.5 °C, $[\alpha]_D^{20}$ +64.9° (*c*=0.535, $CHCl_3$); IR (cm^{-1}): 3465 (OH), 1741 (COO), 1661 (CONH). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.08 (3H, s, OAc), 3.26, 3.34, 3.40, 3.43 (each 3H, s, 4×OCH_3); 3.65 (1H, t, *J*=4.4 Hz, H-14β); 4.29, 4.58 (each 1H, ABq, *J*=12.0 Hz, H_2-18); 6.25 (1H, d, *J*=4.4 Hz, NH); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m*/*z* 495 (M$^+$, 15), 480 (M−15, 85), 464 (M−31, 20).

Compound **8**: White amorphous powder, $C_{34}H_{46}NO_{11}Cl$, HR-ESI-MS *m*/*z* 680.2823 (M+H, Cacld 680.2831), mp 78—79 °C, $[\alpha]_D^{20}$ +18.8° (*c*=0.595, $CHCl_3$); IR (cm^{-1}): 3467 (OH), 3067 (Ar), 1740 (COO), 1640, 1573 (Ar). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.51 (3H, d, *J*=5.4 Hz, N-$CH\underline{CH_3}$); 2.06 (3H, s, OAc); 3.40, 3.41 (each 6H, s, 4×OCH_3); 3.56 (1H, t, *J*=4.4 Hz, H-14β); 6.39 (1H, q, *J*=5.4 Hz, N-$\underline{CH}CH_3$); 7.35—8.06 (4H, m, H-Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; ESI-MS: *m*/*z* 702 (M+Na, 100).

Compound **9**: White amorphous powder, $C_{34}H_{46}NO_{11}Cl$, HR-ESI-MS *m*/*z* 702.2662 (M+Na, Cacld 702.2651), mp 80—81 °C, $[\alpha]_D^{20}$ +22.7° (*c*=2.140, $CHCl_3$); IR (cm^{-1}): 3459 (OH), 3094 (Ar), 1742 (COO), 1663, 1571 (Ar). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.56 (3H, d, *J*=5.6 Hz, N-$CH\underline{CH_3}$); 2.06 (3H, s, OAc); 3.31, 3.26, 3.42, 3.42 (each 3H, s, 4×OCH_3); 6.38 (1H, q, *J*=5.4 Hz, N-$\underline{CH}CH_3$); 7.37—8.12 (4H, m, H-Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; ESI-MS: *m*/*z* 702 (M+Na, 100).

Compound **10**: White amorphous powder, $C_{25}H_{37}NO_8$, HR-EI-MS *m*/*z* 479.2500 (M$^+$, Cacld 479.2519), mp 136—137 °C, $[\alpha]_D^{20}$ +103.8° (*c*=0.530, $CHCl_3$); IR (cm^{-1}): 3466 (OH), 1743 (COO), 1635 (C=N). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 2.09 (3H, s, OAc), 3.13, 3.33, 3.34, 3.39 (each 3H, s, 4×OCH_3); 3.64 (1H, t, *J*=4.4 Hz, H-14β); 4.21, 4.31 (each 1H, ABq, *J*=11.4 Hz, H_2-18); 7.72 (1H, br s, H-19); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m*/*z* 479 (M$^+$, 100), 464 (M−15, 95), 448 (M−31, 90).

Compound **11**: White amorphous powder, $C_{25}H_{37}NO_9$, HR-EI-MS *m*/*z* 495.2456 (M$^+$, Cacld 495.2468), mp 127—128 °C, $[\alpha]_D^{20}$ +21.9° (*c*=0.740, $CHCl_3$); IR (cm^{-1}): 3449 (OH), 1742 (COO), 1599 (C=N). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.10 (3H, s, OAc); 3.22, 3.34, 3.40, 3.42 (each 3H, s, 4×OCH_3); 3.67 (1H, t, *J*=4.4 Hz, H-14β), 3.98 (1H, d, *J*=0.8 Hz, H-6β), 4.15, 4.19 (2H, ABq, *J*=11.2 Hz, H_2-18), 6.77 (1H, d, *J*=1.2 Hz, H-19); ^{13}C-NMR (50 MHz, $CDCl_3$): see Table 1; EI-MS: *m*/*z* 495 (M$^+$, 30), 480 (M−15, 72), 464 (M−31, 60).

Compound **12**: White amorphous powder, $C_{25}H_{37}NO_9$, HR-EI-MS *m*/*z* 495.2473 (M$^+$, Cacld 495.2468), mp 131—132 °C, $[\alpha]_D^{20}$ −3.4° (*c*=0.670, $CHCl_3$); IR (cm^{-1}): 3429 (OH), 1739 (COO), 1708 (CO), 1578 (C=N). ^{1}H-(400 MHz) and ^{13}C-NMR (100 MHz, $CDCl_3$) see Table 2; EI-MS: *m*/*z* 495 (M$^+$, 40), 479 (M−16, 35), 464 (M−31, 60).

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