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OXIDATION PRODUCTS OF STRICTOSAMIDE BY IODOSOBENZENE DIACETATE

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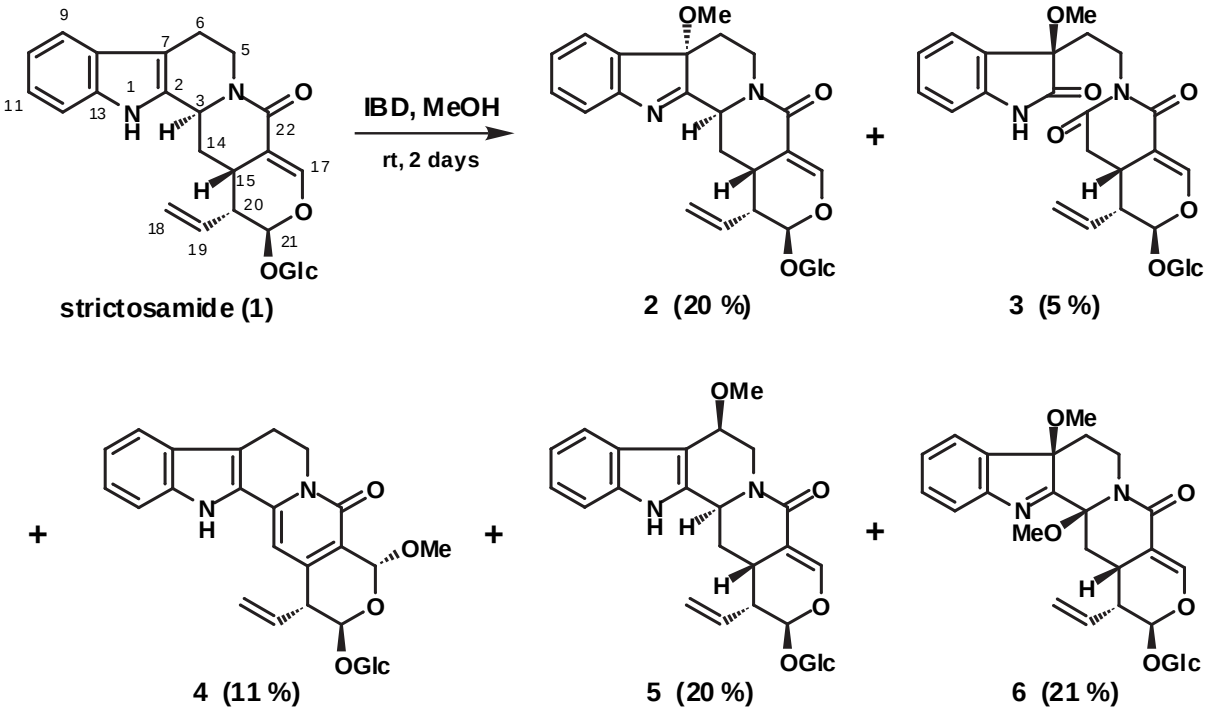
Abstract - Oxidation of strictosamide (**1**), a representative monoterpene indole alkaloid, by iodosobenzene diacetate (IBD) gave compounds (**2** ~ **6**), among them the structure of **3** corresponded to an oxindole derived through oxidative cleavage between C-2 and C-3 of **1**. A plausible mechanism of formation of **2** ~ **6** from strictosamide (**1**) by IBD oxidation is proposed.

Naturally occurring oxindole alkaloids have been found to possess interesting biological activity.[1] Some oxindole alkaloids, such as 3-oxo-7-hydroxy-3,7-secorhynchophylline,[2] Us-7, and Us-8,[3] may be biosynthetically generated through oxidation from a representative monoterpene indole alkaloid, strictosidine, which is a precursor of strictosamide (**1**)[4] isolated from plants of genera *Rhazya* (Apocynaceae), *Nauclea* (Rubiaceae), and *Uncaria* (Rubiaceae). Therefore, we examined oxidation reaction of strictosamide (**1**) from which oxindole alkaloids could be generated. In this paper we describe oxidation reaction of strictosamide (**1**) by iodosobenzene diacetate (IBD) and propose a plausible mechanism of formation of oxidation products (**2** ~ **6**) from **1**.

Treatment of strictosamide (**1**) with IBD (1 eq.) in MeOH at room temperature for 2 days yielded compounds (**2**) (20%), (**3**) (5%), (**4**) (11%), (**5**) (20%), and (**6**) (21%) (Scheme 1). The structures of **2** ~ **6** were elucidated by spectral data including MS and 2D NMR spectrometries as follows.

Compound (**2**) was shown to have the molecular formula, $C_{27}H_{32}N_2O_9$, by HRFABMS [*m/z* 529.2194 $(M+H)^+$, Δ +0.8 mmu]. The ^1H and ^{13}C NMR spectra of **2** revealed the presence of a methoxy group (δ_H 2.88; δ_C 53.3) and an imine (δ_C 182.8) from comparison with those of strictosamide (**1**). The presence of the imine at C-2 was deduced from HMBC correlations of H-6a and H-14b to the imino carbon. HMBC correlations of the methoxy protons, H-5a, H-6a, and H-9 to C-7 (δ_C 88.9) indicated that the methoxy group was attached to C-7, while a NOESY correlation between MeO-7 and H-3 suggested that the methoxy group was α-oriented.

Dedicated to the celebration of the 75th birthday of Professor Yuichi Kanaoka



Scheme 1

The molecular formula, $C_{27}H_{32}N_2O_{11}$, of compound (**3**) was established by HRFABMS spectrum [*m/z* 561.2050 $(M+H)^+$, Δ -3.4 mmu]. The ^1H-^1H COSY spectrum revealed connectivities of C-5 to C-6, C-9 to C-12, C-14 to C-15, C-18 to C-21, C-15 to C-20, and C-1' to C-6'. HMBC correlations of H-9 to C-7 (δ_C 72.5) and C-13 (δ_C 144.4), H-12 to C-8 (δ_C 129.2), H_2-6 to C-2 (δ_C 180.2) and C-7, a methoxy protons (δ_H 3.02) to C-7 indicated the presence of an oxindole ring, in which a methoxy group was attached to C-7. HMBC correlations of H_2-5 to C-3 (δ_C 174.4) and C-22 (δ_C 168.6), H_2-14 to C-3, and H-17 to C-22 revealed the presence of a glutarimide moiety (C-3, C-14 - C-16, C-22, and N-4), which was connected to the dihydropyran ring. The absolute configuration at C-7 was elucidated to be *R*, since a positive Cotton curve at the region of 300-260 nm and a negative curve at the region of 260-230 nm were observed in the CD spectrum of **3**.[5]

Compound (**4**) was shown to have the molecular formula, $C_{27}H_{30}N_2O_9$, by HRFABMS spectrum [*m/z* 549.1868 $(M+Na)^+$, Δ +1.9 mmu]. The ^1H and ^{13}C NMR and HMQC spectra of **4** indicated the presence of one methoxy (δ_H 3.65, s; δ_C 57.0), one acetal (δ_H 5.69, s; δ_C 98.3), and one pyridone ring (δ_H 6.68, s, H-14; δ_C 140.4, C-3, 102.6, C-14, 149.8, C-15, 122.0, C-16). The presence of the pyridone ring (C-3, N-4, C-14 to C-16, and C-22) was also supported by HMBC correlations of H-14 to C-2, C-3, and C-16 and H-20 to C-15 and the UV spectrum of **4**. HMBC correlations of the methoxy protons and C-17 (δ_C 98.3), and H-17 to C-15, C-16, and C-21 indicated that the methoxy group was attached to C-17. The α-orientation of the methoxy group at C-17 was deduced from a NOESY correlation between H-17 and H-20.

The molecular formula, $C_{27}H_{32}N_2O_9$, of compound (**5**) was established by HRFABMS spectrum [*m/z* 529.2183 $(M+H)^+$, Δ -0.3 mmu]. The ^1H and ^{13}C NMR and HMQC spectra of **5** indicated the presence of one methoxy (δ_H 3.57, s; δ_C 57.5) and one oxymethine (δ_H 4.67; δ_C 74.6). HMBC correlations between the methoxy protons and C-6 (δ_C 74.6), and the oxymethine proton to C-2 (δ_C 137.9), C-5 (δ_C 46.7), and C-7 (δ_C 112.0) revealed that the methoxy group was attached to C-6, while a NOESY correlations of H-3 to H-5b (δ_H 3.02) and H-5a (δ_H 5.35) to MeO-6 indicated that the methoxy group was β-oriented.

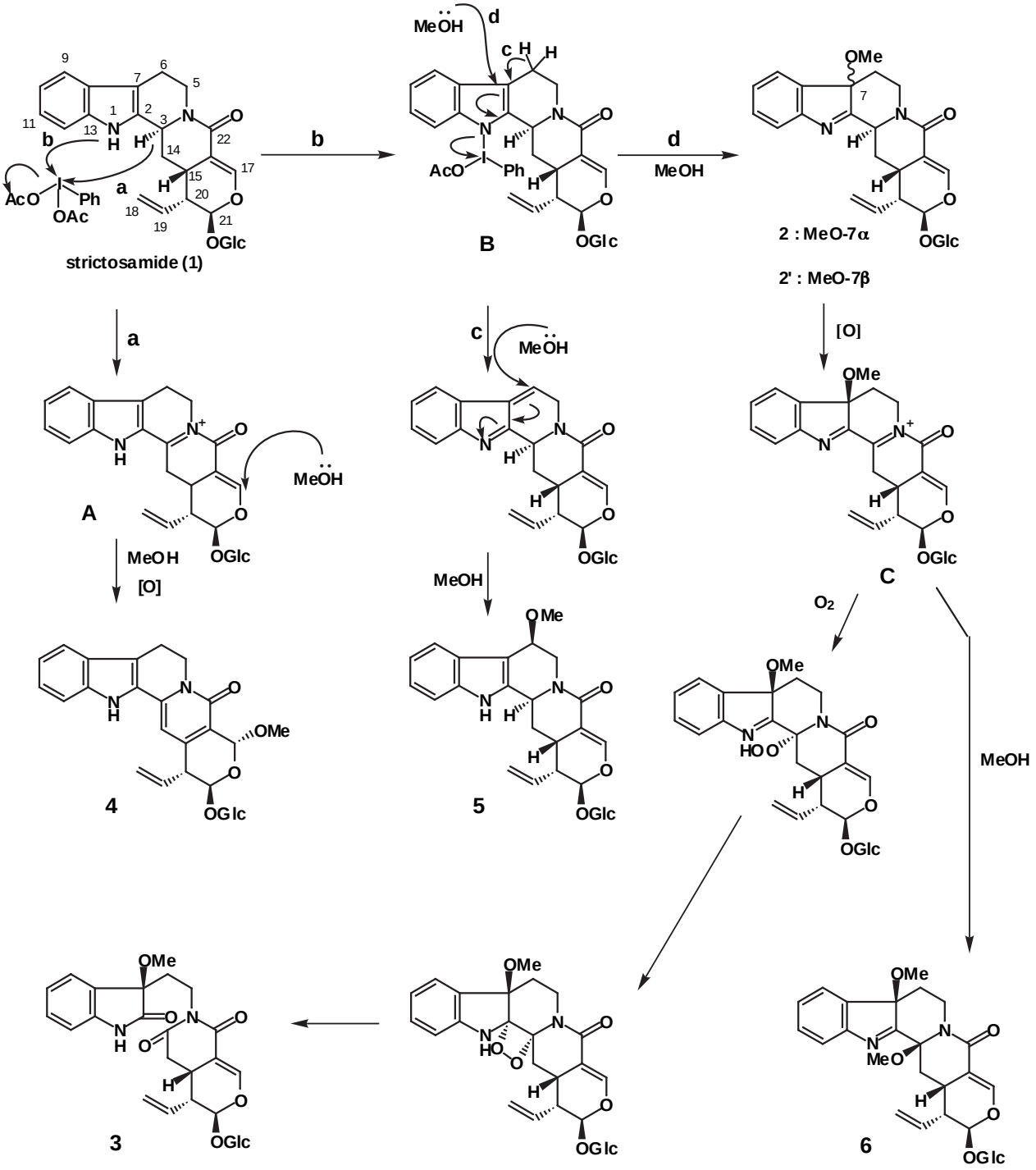
Compound (**6**) was shown to have the molecular formula, $C_{28}H_{34}N_2O_{10}$, by HRFABMS [*m/z* 559.2260 $(M+H)^+$, Δ -3.2 mmu]. The ^1H and ^{13}C NMR and HMQC spectra of **6** indicated the presence of two methoxy groups (δ_H 3.03, s; δ_C 55.0 and δ_H 3.40, s; δ_C 53.2) and one imine (δ_C 180.7). The presence of the imine at C-2 was deduced from an HMBC correlation of H-6a to the imino carbon. HMBC correlations of the methoxy protons (δ_H 3.03), H-5a, H-6a, and H-9 to C-7 (δ_C 88.9) and the methoxy protons (δ_H 3.40), H-14a, and H-15 to C-3 (δ_C 90.4) indicated that the two methoxy groups were attached to C-7 and C-3, while NOESY correlations of MeO-3 to H-15 and MeO-7 revealed that both methoxy groups were β-oriented.

A plausible mechanism of formation of compounds (**2** ~ **6**) from strictosamide (**1**) by IBD oxidation in MeOH is proposed as shown in Scheme 2. In the first step IBD induces the oxidation of C-3 (pathway **a**) or N-1 (pathway **b**) of **1**, resulting in generation of intermediates (**A**) and (**B**), respectively. Oxidation of ring D of **A** and addition of MeOH to C-17 give compound (**4**), while the dehydration at C-6 of **B** (pathway **c**) and then addition of MeOH to C-6 afford compound (**5**). On the other hand, addition of MeOH to C-7 of **B** (pathway **d**) give compound (**2**) (MeO-7α) and the stereoisomer (**2'**) (MeO-7β). Dehydration at C-3 of **2'** followed by addition of MeOH to C-3 yield compound (**6**). Oxidation at C-3 of **C** followed by formation of a peroxy ring at C-2 and C-3 and then cleavage of the C-2 – C-3 bond afford compound (**3**). Oxindole alkaloids with a hydroxy group at C-7 in place of the methoxy group like **3** may be obtained from plants of Apocynaceae or Rubiaceae.

EXPERIMENTAL

General Methods. ^1H and ^{13}C NMR spectra were recorded on 500 and 600 MHz spectrometers. The 3.35 ppm resonance of residual CHD_2OD and 49.8 ppm of CD_3OD were used as internal references, respectively. FABMS was measured by using glycerol as a matrix.

Oxidation of Strictosamide (1) by Iodosobenzene Diacetate (IBD): To a solution of strictosamide (**1**, 20 mg, 40 μmol) in MeOH (1.0 mL) was added IBD (13 mg, 40 μmol). The solution was stirred at rt for 2 days, and the reaction mixture was concentrated in vacuo. The residue was applied to C_{18} HPLC (Develosil ODS HG-5, 1.0 x 25 cm, Nomura Chemical, MeOH/H_2O, 7:3, UV detection at 254 nm) to afford compounds (**2**) (4.3 mg, t_R 9.6 min), (**3**) (1.2 mg, t_R 8.0 min), (**4**)



Scheme 2

(2.2 mg, t_R 12.4 min), (**5**) (4.3 mg, t_R 10.8 min), and (**6**) (4.9 mg, t_R 13.6 min).

Compound (2): A colorless amorphous solid; IR (KBr) ν_{max} 3436, 1644, and 1065 cm^{-1}; UV (MeOH) λ_{max} 208 (ε 19000) and 238 (15000) nm; ^1H NMR (CD_3OD): δ 7.65 (1H, d, J = 7.5 Hz, H-

12), 7.50 (1H, t, *J* = 7.5 Hz, H-11), 7.48 (1H, d, *J* = 7.5 Hz, H-9), 7.41 (1H, d, *J* = 2.0 Hz, H-17), 7.38 (1H, t, *J* = 7.5 Hz, H-10), 5.67 (1H, dt, *J* = 16.8 and 10.6 Hz, H-19), 5.39 (1H, dd, *J* = 16.8 and 1.9 Hz, H-18a), 5.37 (1H, dd, *J* = 10.6 and 1.9 Hz, H-18b), 5.50 (1H, d, *J* = 1.9 Hz, H-21), 4.80 (1H, br s, H-3), 4.68 (1H, m, H-5a), 4.68 (1H, d, *J* = 8.0 Hz, H-1'), 3.96 (1H, dd, *J* = 12.5 and 1.9 Hz, H-6'a), 3.73 (1H, m, H-6'b), 3.55 (1H, m, H-15), 3.40 (1H, m, H-3'), 3.35 (1H, m, H-5b), 3.34 (1H, m, H-5'), 3.30 (1H, m, H-4'), 3.20 (1H, m, H-2'), 2.88 (3H, s, MeO-7), 2.85 (1H, m, H-20), 2.61 (1H, dt, *J* = 13.7 and 1.9 Hz, H-6a), 2.48 (1H, dd, *J* = 13.7 and 5.0 Hz, H-14a), 2.05 (1H, td, *J* = 13.7 and 6.0 Hz, H-14b), 1.45 (1H, m, H-6b); ^{13}C NMR (CD_3OD): δ 182.8 (C-2), 166.3 (C-22), 155.8 (C-13 and C-17), 138.3 (C-8 and C-19), 131.7 (C-11), 128.9 (C-10), 125.3 (C-9), 125.1 (C-12), 121.5 (C-18), 109.5 (C-16), 101.4 (C-1'), 99.2 (C-21), 88.9 (C-7), 79.1 (C-5'), 78.9 (C-3'), 75.4 (C-2'), 72.3 (C-4'), 63.5 (C-6'), 56.3 (C-3), 53.3 (MeO-7), 44.8 (C-20), 40.6 (C-5), 40.5 (C-6), 25.6 (C-15), and 25.1 (C-14); FABMS *m/z* 529 $(M+H)^+$; HRFABMS *m/z* 529.2194 $(M+H)^+$, calcd for $C_{27}H_{33}N_2O_9Na$, 529.2186.

Compound (3): A colorless amorphous solid; IR (KBr) ν_{max} 3430 and 1623 cm^{-1}; UV (MeOH) λ_{max} 208 (ε 29000) and 246 (17000) nm; CD (MeOH) 217 (Δε +1.9), 245 (-5.8), 292 (+3.2), and 328 (-1.0) nm; ^{1}H NMR (CD_3OD): δ 7.59 (1H, d, *J* = 2.3 Hz, H-17), 7.38 (1H, d, *J* = 7.5 Hz, H-9), 7.36 (1H, t, *J* = 7.5 Hz, H-11), 7.16 (1H, t, *J* = 7.5 Hz, H-10), 6.95 (1H, d, *J* = 7.5 Hz, H-12), 5.61 (1H, d, *J* = 1.3 Hz, H-21), 5.58 (1H, m, H-19), 5.36 (1H, dd, *J* = 15.2 and 1.5 Hz, H-18a), 5.27 (1H, dd, *J* = 12.0 and 1.5 Hz, H-18b), 4.71 (1H, d, *J* = 8.1 Hz, H-1'), 3.95 (1H, m, H-5a), 3.92 (1H, m, H-6'a), 3.78 (1H, m, H-5b), 3.68 (1H, m, H-6'b), 3.40 (1H, m, H-3'), 3.37 (1H, m, H-5'), 3.32 (1H, m, H-4'), 3.24 (1H, m, H-15), 3.21 (1H, m, H-2'), 3.02 (3H, s, MeO-7), 2.72 (1H, m, H-20), 2.48 (1H, dd, *J* = 16.2 and 5.6 Hz, H-14a), 2.28 (1H, dd, *J* = 16.2 and 15.0 Hz, H-14b), and 2.20 (2H, m, H-6); ^{13}C NMR (CD_3OD): δ 180.2 (C-2), 174.4 (C-3), 168.6 (C-22), 153.2 (C-17), 144.4 (C-13), 133.9 (C-19), 131.8 (C-11), 129.2 (C-8), 126.5 (C-9), 124.8 (C-10), 122.1 (C-18), 112.3 (C-12), 109.6 (C-16), 100.4 (C-1'), 98.4 (C-21), 78.9 (C-5'), 78.6 (C-3'), 75.3 (C-2'), 72.5 (C-7), 72.0 (C-4'), 63.3 (C-6'), 53.6 (MeO-7), 44.3 (C-20), 36.3 (C-6), 36.0 (C-5), 35.4 (C-14), and 25.0 (C-15); FABMS *m/z* 561 $(M+H)^+$; HRFABMS *m/z* 561.2050 $(M+H)^+$, calcd for $C_{27}H_{33}N_2O_{11}$, 561.2084.

Compound (4): A colorless amorphous solid; IR (KBr) ν_{max} 3428 and 1644 cm^{-1}; UV (MeOH) λ_{max} 217 (ε 23000), 259 (sh), 369 (10000), and 387 (9300) nm; ^{1}H NMR (CD_3OD): δ 7.62 (1H, d, *J* = 8.0 Hz, H-9), 7.43 (1H, d, *J* = 8.2 Hz, H-12), 7.27 (1H, dd, *J* = 8.2 and 7.8 Hz, H-11), 7.12 (1H, dd, *J* = 8.0 and 7.8 Hz, H-10), 6.68 (1H, s, H-14), 5.69 (1H, s, H-17), 5.56 (1H, d, *J* = 7.4 Hz, H-21), 5.55 (1H, dt, *J* = 17.7 and 9.7 Hz, H-19), 5.50 (1H, br d, *J* = 17.7 Hz, H-18a), 5.48 (1H, br d, *J* = 9.7 Hz, H-18b), 4.85 (1H, d, *J* = 7.9 Hz, H-1'), 4.53 (1H, m, H-5a), 4.36 (1H, m, H-5b), 3.92 (1H, br d, *J* = 11.8 Hz, H-6'a), 3.69 (1H, dd, *J* = 11.8 and 5.3 Hz, H-6'b), 3.65 (1H, s, MeO-17), 3.46 (1H, m, H-20), 3.46 (1H, m, H-3'), 3.35 (1H, m, H-4'), 3.35 (1H, m, H-5'), 3.27 (1H, m, H-2'), and 3.16 (2H, m, H-6); ^{13}C

NMR (CD_3OD): δ 162.8 (C-22), 149.8 (C-15), 141.2 (C-13), 140.4 (C-3), 135.9 (C-19), 129.2 (C-2), 127.6 (C-8), 126.3 (C-11), 122.6 (C-18), 122.0 (C-16), 121.7 (C-9), 121.2 (C-10), 116.5 (C-7), 113.6 (C-12), 102.6 (C-14), 100.3 (C-1'), 98.3 (C-17), 94.8 (C-21), 79.3 (C-3'), 79.0 (C-5'), 75.6 (C-2'), 72.7 (C-4'), 63.5 (C-6'), 57.0 (MeO-17), 50.1 (C-20), 42.8 (C-5), and 21.2 (C-6); FABMS *m/z* 549 $(M+Na)^+$; HRFABMS *m/z* 549.1868 $(M+Na)^+$, calcd for $C_{27}H_{30}N_2O_9Na$, 549.1849.

Compound (5): A colorless amorphous solid; IR (KBr) ν_{max} 3436, 1643, and 1068 cm^{-1}; UV (MeOH) λ_{max} 218 (ε 30000) and 261 (sh) nm; ^1H NMR (CD_3OD): δ 7.57 (1H, d, *J* = 8.1 Hz, H-9), 7.41 (1H, d, *J* = 1.9 Hz, H-17), 7.39 (1H, d, *J* = 7.4 Hz, H-12), 7.16 (1H, dd, *J* = 7.4 and 7.2 Hz, H-11), 7.09 (1H, dd, *J* = 8.1 and 7.2 Hz, H-10), 5.70 (1H, td, *J* = 10.0 and 6.9 Hz, H-19), 5.45 (1H, d, *J* = 1.9 Hz, H-21), 5.37 (2H, m, H-18), 5.35 (1H, m, H-5a), 5.02 (1H, br d, *J* = 5.6 Hz, H-3), 4.67 (1H, br s, H-6), 4.60 (1H, d, *J* = 8.1 Hz, H-1'), 3.96 (1H, dd, *J* = 11.8 and 2.5 Hz, H-6'a), 3.73 (1H, dd, *J* = 11.8 and 6.2 Hz, H-6'b), 3.57 (3H, s, MeO-6), 3.34 (1H, m, H-5'), 3.29 (1H, m, H-4'), 3.22 (1H, m, H-3'), 3.03 (1H, m, H-2'), 3.02 (1H, m, H-5b), 2.95 (1H, m, H-15), 2.71 (1H, ddd, *J* = 10.0, 6.9, and 1.9 Hz, H-20), 2.55 (1H, ddd, *J* = 13.7, 4.4, and 1.3 Hz, H-14a), and 2.08 (1H, td, *J* = 13.7 and 5.6 Hz, H-14b); ^{13}C NMR (CD_3OD): δ 167.8 (C-22), 149.6 (C-17), 138.6 (C-13), 137.9 (C-2), 135.1 (C-19), 129.1 (C-8), 123.7 (C-11), 121.6 (C-10), 121.3 (C-18), 119.8 (C-9), 113.3 (C-12), 112.0 (C-7), 110.8 (C-16), 100.7 (C-1'), 98.3 (C-21), 79.1 (C-5'), 78.9 (C-3'), 78.3 (C-4'), 74.6 (C-6), 72.3 (C-2'), 63.5 (C-6'), 57.5 (MeO-6), 55.7 (C-3), 46.7 (C-5), 45.5 (C-20), 28.0 (C-14), and 25.8 (C-15); FABMS *m/z* 529 $(M+H)^+$; HRFABMS *m/z* 529.2183 $(M+H)^+$, calcd for $C_{27}H_{33}N_2O_9$, 529.2186.

Compound (6): A colorless amorphous solid; IR (KBr) ν_{max} 3434, 1657, and 1051 cm^{-1}; UV (MeOH) λ_{max} 223 (ε 22000) and 251 (sh) nm; ^1H NMR (CD_3OD): δ 7.66 (1H, d, *J* = 8.1 Hz, H-12), 7.52 (1H, d, *J* = 1.3 Hz, H-17), 7.51 (1H, dd, *J* = 8.1 and 7.5 Hz, H-11), 7.49 (1H, d, *J* = 7.5 Hz, H-9), 7.41 (1H, td, *J* = 7.5 and 1.3 Hz, H-10), 5.65 (1H, dt, *J* = 17.0 and 10.0 Hz, H-19), 5.57 (1H, d, *J* = 1.9 Hz, H-21), 5.44 (1H, dd, *J* = 17.0 and 1.9 Hz, H-18a), 5.35 (1H, dd, *J* = 10.0 and 1.9 Hz, H-18b), 4.74 (1H, d, *J* = 7.5 Hz, H-1'), 4.61 (1H, ddd, *J* = 13.1, 3.7, and 1.9 Hz, H-5a), 3.92 (1H, m, H-6'a), 3.71 (1H, m, H-6'b), 3.67 (1H, m, H-5b), 3.40 (1H, m, H-3'), 3.40 (3H, s, MeO-3), 3.37 (1H, m, H-5'), 3.32 (1H, m, H-4'), 3.26 (1H, m, H-15), 3.21 (1H, m, H-2'), 3.03 (3H, s, MeO-7), 2.81 (1H, ddd, *J* = 10.0, 5.6, and 1.9 Hz, H-20), 2.74 (1H, dd, *J* = 15.0 and 4.4 Hz, H-14a), 2.65 (1H, dt, *J* = 13.1 and 1.9 Hz, H-6a), 2.08 (1H, dd, *J* = 15.0 and 14.3 Hz, H-14b), and 1.43 (1H, td, *J* = 13.1 and 3.7 Hz, H-6b); ^{13}C NMR (CD_3OD): δ 180.7 (C-2), 169.3 (C-8), 167.7 (C-22), 154.3 (C-13), 151.2 (C-17), 134.7 (C-19), 132.0 (C-11), 129.4 (C-10), 125.0 (C-9), 123.8 (C-12), 121.7 (C-18), 109.3 (C-16), 101.0 (C-1'), 98.9 (C-21), 90.4 (C-3), 88.9 (C-7), 78.9 (C-3'), 79.2 (C-5'), 75.5 (C-2'), 72.3 (C-4'), 63.5 (C-6'), 55.0 (MeO-7), 53.2 (MeO-3), 44.9 (C-20), 38.9 (C-6), 35.8 (C-5), 31.1 (C-14), and 24.1 (C-15); FABMS *m/z* 559 $(M+H)^+$; HRFABMS *m/z* 559.2260 $(M+H)^+$, calcd for $C_{28}H_{35}N_2O_{10}$, 559.2292.

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