

## ***m*-CHLOROPERBENZOIC ACID OXIDATION OF CORYNANTHE-TYPE INDOLE ALKALOID, MITRAGYNINE, AFFORDED UNUSUAL DIMERIZATION PRODUCTS**

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**Abstract** – The *m*-chloroperbenzoic acid oxidation of a Corynanthe-type indole alkaloid, mitragynine (**1**), in the presence of trifluoroacetic acid produced unusual dimeric compounds (**3** and **4**), both of which had a linkage between the C-7 and C-12' positions in the indole part of the starting material.

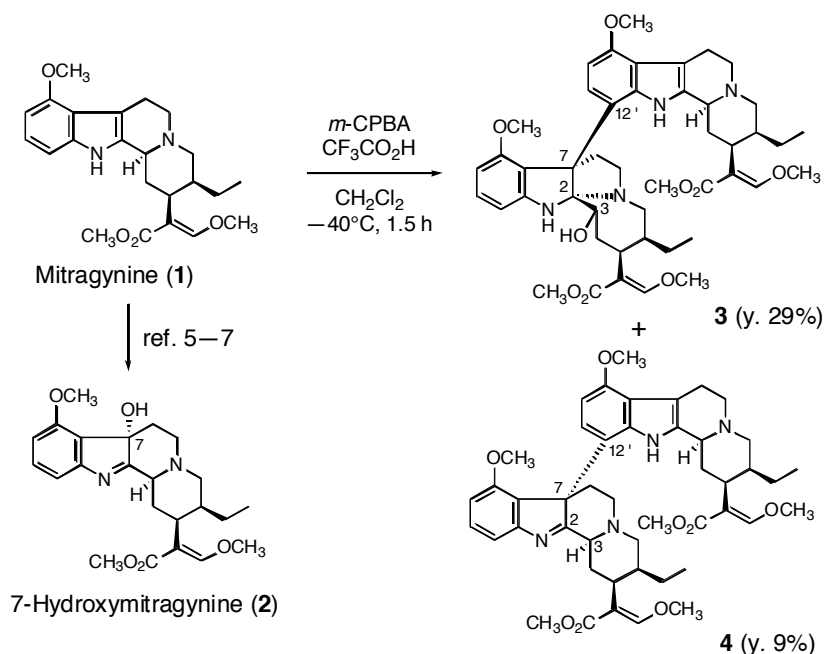
### **INTRODUCTION**

In our recent chemical and pharmacological study<sup>1</sup> on the rubiaceous plant, *Mitragyna speciosa*, which has been traditionally used in tropical countries as a substitute for opium,<sup>2</sup> we have found that 7-hydroxymitragynine (**2**),<sup>3</sup> a minor constituent of this plant, exhibited highly potent opioid agonistic property *in vitro* and *in vivo* experiments in mice.<sup>4</sup> In particular, **2** displayed efficient antinociception when administered orally to mice in the tail-flick and hot plate tests, exhibiting superior advantage over morphine as regards the ability to induce antinociception *via* oral administration. Inspired by this result, we investigated<sup>5–7</sup> the preparation of **2** from mitragynine (**1**), a major component of *M. speciosa*.<sup>3, 8</sup> Gueller and Borschberg have reported an efficient procedure for transforming Aristotelia-type indole alkaloids into 7-hydroxyindolenine derivatives using *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of trifluoroacetic acid.<sup>9</sup> When we applied this method to mitragynine (**1**), a Corynanthe-type indole alkaloid, unexpected dimerization products were obtained. We describe herein the structures and the possible mechanisms for the formation of these compounds.

### **RESULTS AND DISCUSSION**

The *m*-CPBA oxidation of indole alkaloids possessing two nitrogen atoms, i.e., aromatic and aliphatic amino groups, in the molecule generally gives the *N*-oxide derivatives of the alkylamino part.

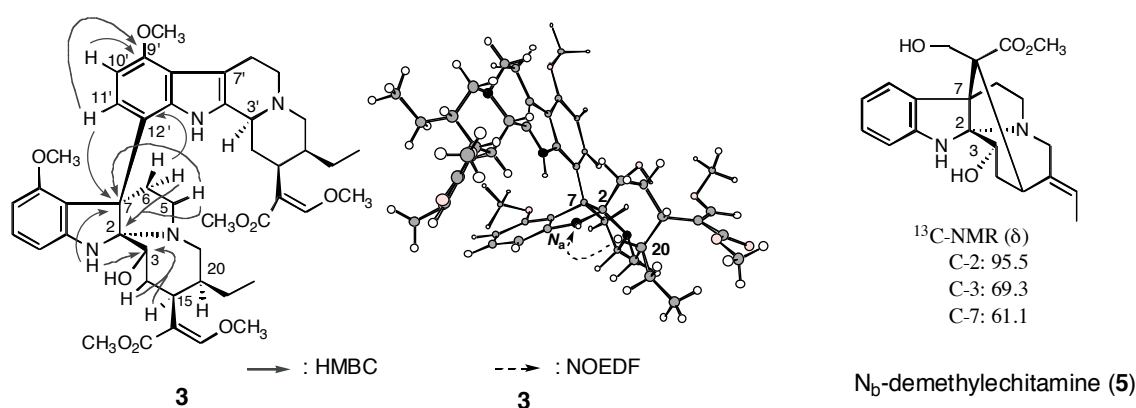
Mitragynine (**1**) afforded an N<sub>b</sub>-oxide derivative under conventional conditions (one equivalent of *m*-CPBA in methylene chloride).<sup>6</sup> To prevent this kind of reaction, Gueller and Borschberg devised a condition for *m*-CPBA oxidation by adding trifluoroacetic acid that protected the lone electron pair of the N<sub>b</sub> by protonation, thereby succeeding in the oxidation of the indole part preferentially to yield 7-hydroxyindolenine derivative in good yield.<sup>9</sup> The application of this protocol (*m*-CPBA, TFA, CH<sub>2</sub>Cl<sub>2</sub>, -40°C, 1.5 h) to mitragynine (**1**), however, resulted in the isolation of two products having unusual structures. (Scheme 1) The structure of major product (**3**) obtained in 29% yield was inferred from spectroscopic data and the chemical reaction as described below. The minor product isolated in 9% yield was proved to be compound (**4**), which was formed by hypervalent iodine {phenyliodine(III) bis(trifluoroacetate)} oxidation of mitragynine (**1**).<sup>5</sup>



**Scheme 1**

The molecular formula (C<sub>46</sub>H<sub>60</sub>N<sub>4</sub>O<sub>9</sub>) determined from the high-resolution FABMS spectrum and the <sup>13</sup>C-NMR spectrum implied that **3** had a dimeric structure. The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra of **3** clearly showed the presence of two sets of fundamental structural units in the starting material (**1**), i.e., two β-methoxyacylic acid methyl ester residues, two ethyl groups, and two 9-methoxy groups on the aromatic ring. Furthermore, the UV absorption bands (298, 244 (sh), 229, and 218 nm) and the <sup>13</sup>C-NMR spectrum that disclosed twenty sp<sup>2</sup> carbons and twenty-six sp<sup>3</sup> carbons including one characteristic aminoacetal carbon (δ 93.6) indicated that **3** contained one indolic and one indoline chromophore. In the <sup>1</sup>H-NMR spectrum, a set of three aromatic protons at δ 6.28 (1H, doublet, *J*=7.6 Hz), δ 6.27 (1H, doublet, *J*=7.6 Hz), and δ 7.00 (1H, doublet of doublet, *J*<sub>1</sub>=*J*<sub>2</sub>=7.6 Hz), which are the same as those of **1**, and a set of *ortho*-coupled protons at δ 6.40 (1H, doublet, *J*=8.3 Hz) and δ 7.15 (1H, doublet, *J*=8.3 Hz) were

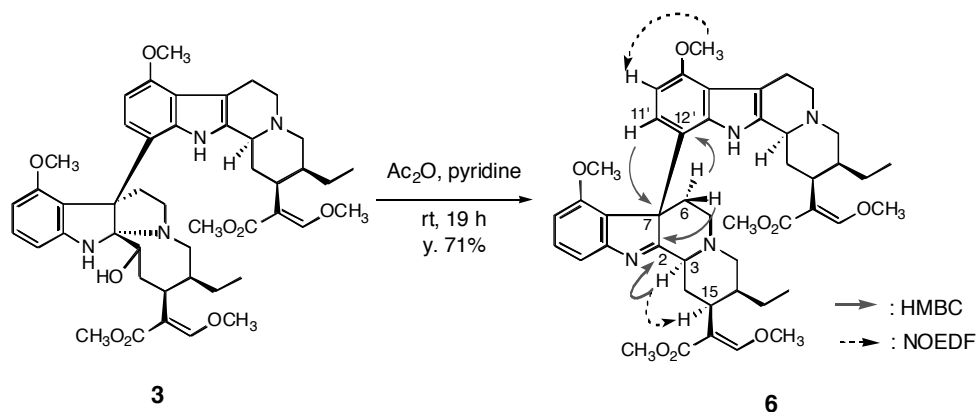
observed. These indicated that one of the two units was intact as regards the substituent mode on the benzene ring and the other unit had a substituent at the C-10 or C-12 position. In the  $^1\text{H}$ -detected heteronuclear multiple-bond correlation (HMBC) spectrum (Figure 1), connectivities were observed between the two *ortho*-coupled protons ( $\delta$  6.40 and 7.15) and an aromatic carbon ( $\delta$  153.9), that could be assigned as C-9' based on its chemical shift, as well as between the *ortho*-coupled proton ( $\delta$  7.15) and a quaternary carbon ( $\delta$  54.5) that could be assigned as C-7 based on the fact that this carbon showed HMBC cross-peaks with the protons at  $\text{N}_a$ , C-5 and C-6. These findings indicated the presence of a bridge between C-7 in the indoline part and C-12' on the indole ring of another unit. In the indoline part of the dimeric structure, three characteristic signals in the  $^{13}\text{C}$ -NMR spectrum, i.e.,  $\delta$  93.6, 70.5, and 54.5, were observed compared with those in mitragynine (**1**). These chemical shifts were very similar to those (see Figure 1) of a known indole alkaloid,  $\text{N}_b$ -demethylechitamine (**5**),<sup>10</sup> which contained a 3-hydroxy-pyrrolidinoindoline residue in the molecule.



**Figure 1**

The presence of this function was supported by the HMBC cross-peaks between the quaternary aminoacetal carbon ( $\delta$  93.6) and the protons at  $\text{N}_a$ , C-5, C-6, and C-14, and between the secondary hydroxyl carbon ( $\delta$  70.5) and the protons at  $\text{N}_a$ , C-14, and C-15. The remaining part of dimer (**3**) was revealed to have the structure of mitragynine itself, except for a substituent at C-12', based on the reasons mentioned above and on the comparison of the  $^{13}\text{C}$ -NMR spectra of **3** and **1**. To elucidate the stereochemistry of the newly formed chiral centers in **3**, differential nuclear Overhauser effect (NOEDF) experiments were carried out. The clear NOE observed between H-20 and  $\text{N}_a$ -H, as shown in Figure 1, indicated that the  $\text{N}_b$  group was attached to the C-2 position from the  $\alpha$ -side, implying a C2(*R*) configuration. This finding suggested that the substituent (an indole ring) at C-7 was attached from the  $\beta$ -side, because the bicyclo[3.3.0]octane ring system could only assume the *cis*-fused form. However, significant information of the stereochemistry of the secondary hydroxyl group at C-3 could not be

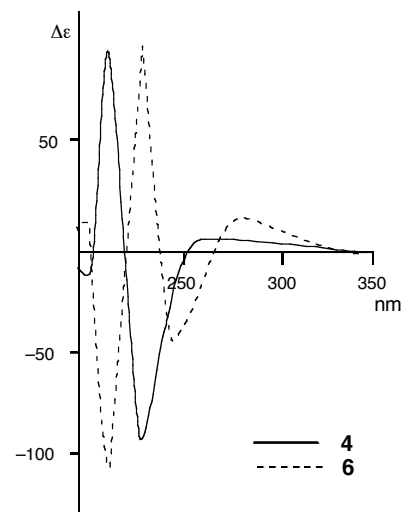
obtained from the NOEDF experiments. Thus, we attempted to prepare the acetyl derivative of **3**. Under conventional conditions (acetic anhydride in pyridine at room temperature), we obtained an unexpected compound (**6**) in 71% yield. (Scheme 2)



**Scheme 2**

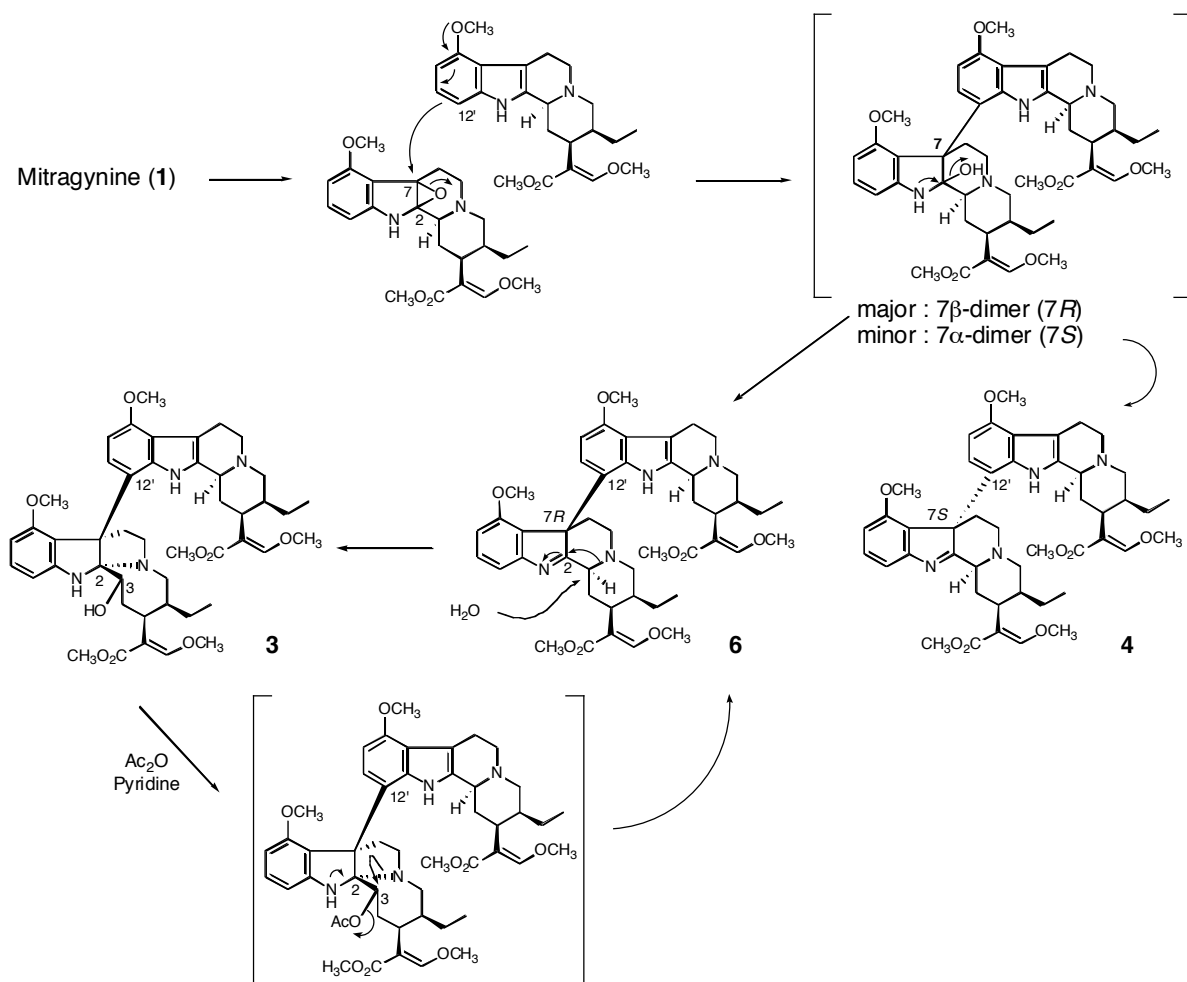
The molecular formula ( $C_{46}H_{58}N_4O_8$ ) determined from the high-resolution FAB-MS spectrum and the  $^1H$ -NMR spectrum indicated that **6** was not the acetate derivative but the dehydration product. The UV absorption bands and the  $^1H$ - and  $^{13}C$ -NMR spectra were very similar with those of **4** and the molecular formula was identical to that of **4**. In particular, the aminoacetal carbon in **3** disappeared and instead, a characteristic indolenine carbon ( $\delta$  191.3) was observed in the  $^{13}C$ -NMR spectrum. The HMBC cross-peaks between the imine carbon ( $\delta$  191.3) and the protons at C-3 and C-6 supported the indolenine structure. The stereochemistry of the newly formed chiral center at C-3 was deduced to be *S* from the observation of NOE between H-3 and H-15. (Scheme 2) From these data, the structure of the dimeric compound was deduced to be formula (**6**), which was an epimer of **4** at the C-7 position. Actually, in the CD spectra, both compounds displayed the opposite Cotton sign in the 200–260 nm region, as shown in Figure 2.

The possible mechanism for the formation of these dimeric compounds is depicted in Scheme 3. Under acidic conditions, *m*-CPBA preferentially reacts with the indole part in mitragynine (**1**) to yield the 2,7-epoxy intermediate,<sup>11</sup> which is subjected to electrophilic aromatic substitution in the presence of another mitragynine (**1**). The elimination of one water molecule from the resulting hemiaminoacetal intermediates affords dimers (**4**) and (**6**) possessing an indolenine residue. Although the reason is obscure, in the case of



**Figure 2.** CD spectra of compounds (**4**) and (**6**)

$\beta$ -isomer (**6**), further rearrangement occurs to give the echitamine-type compound (**3**) having a pyrrolidinoindoline chromophore. When **3** is treated with acetic anhydride in pyridine, the resulting 3-acetoxy group acts as a leaving group, promoting the reconstruction of the indolenine derivative (**6**).



**Scheme 3**

## EXPERIMENTAL

**General** UV: recorded in MeOH on a JASCO V-560 instrument. <sup>1</sup>H and <sup>13</sup>C-NMR spectra: recorded on a JEOL JNM A-400, JNM A-500, JNM ECP-400, or JNM ECP-600 spectrometer; *J* values are given in Hz. EI-MS: direct probe insertion at 70 eV recorded on a JEOL JMS GC-mate spectrometer. FAB-MS: recorded on a JEOL JMS-HX110 mass spectrometer. CD: recorded on a JASCO J-720WI spectrometer. TLC: precoated Kieselgel 60 F<sub>254</sub> plates (Merck, 0.25 mm thick). Column chromatography: Kieselgel 60 [Merck, 70-230 (for open chromatography)], aluminum oxide 90 [Merck, 70-230 (for open chromatography)].

### *m*-CPBA oxidation of mitragynine (**1**)

To a stirred solution of mitragynine (**1**) (100.0 mg, 0.25 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (4.0 mL) was added trifluoroacetic acid (0.1 mL). After stirring for 5 min at -40°C under argon atmosphere, a solution of *m*-

CPBA (44.0 mg, 0.18 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) was added *via* a syringe. After stirring for 1.5 h at the same temperature, dimethyl sulfide (10  $\mu\text{L}$ ) was added to the reaction mixture and the cold mixture was poured into 28%  $\text{NH}_3$  and  $\text{H}_2\text{O}$  and was extracted with  $\text{CHCl}_3$  three times. The combined organic layer was washed with brine, dried over  $\text{MgSO}_4$  and evaporated. The residue was separated by  $\text{Al}_2\text{O}_3$  column chromatography (30%  $\text{AcOEt}/n$ -hexane) to give **3** (29.1 mg, 29%) and **4** (5.8 mg, 9%), both as amorphous powder. **3**: UV (MeOH)  $\lambda_{\text{max}}$ : 298, 244 (sh), 229, and 218 nm.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  [ppm]: 9.54 (1H, br s,  $\text{N}_a\text{-H}$ ), 7.47 and 7.41 (each 1H, s, H-17 and H-17'), 7.15 (1H, d,  $J=8.3$ , H-11'), 7.00 (1H, dd,  $J=7.6$  and 7.6, H-11), 6.40 (1H, d,  $J=8.3$ , H-10'), 6.28 (1H, d,  $J=7.6$ , H-10), 6.27 (1H, d,  $J=7.6$ , H-12), 3.83 (3H, s, 9'- $\text{OCH}_3$ ), 3.75 and 3.73 (each 3H, s, 17- $\text{OCH}_3$  and 17'- $\text{OCH}_3$ ), 3.72 and 3.66 (each 3H, s, 22- $\text{OCH}_3$  and 22'- $\text{OCH}_3$ ), 3.58 (3H, s, 9- $\text{OCH}_3$ ), 3.12 (1H, br d,  $J=14.0$ , H-6), 3.03 (2H, m, H-3' and H-6'), 2.95 (4H, m, H-6', H-15, H-21 and H-21'), 2.85 (1H, dd like,  $J=11.6$  and 6.1, H-5'), 2.80 (2H, m, H-5 and H-15'), 2.70 (1H, m, H-14), 2.64 (1H, td like,  $J=12.3$  and 5.3, H-6'), 2.48 (1H, td like,  $J=12.3$  and 4.3, H-5'), 2.39 (1H, br d,  $J=8.6$ , H-21), 2.25 (1H, ddd,  $J=12.8$ , 12.8, and 12.8, H-14'), 2.10 (1H, t like,  $J=11.0$ , H-5), 2.05 (1H, m, H-3), 2.02 (1H, m, H-21'), 1.75 (2H, m, H-19 and H-19'), 1.63 (1H, m, H-14'), 1.56 (1H, m, H-20'), 1.52 (1H, m, H-20), 1.49 (1H, m, H-14), 1.20 (2H, m, H-19 and H-19'), 0.85 and 0.82 (each 3H, t,  $J=7.3$ ,  $\text{H}_3\text{-18}$  and  $\text{H}_3\text{-18}'$ ).  $^{13}\text{C-NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  [ppm]: 169.3 and 169.2 (C-22 and C-22'), 160.5 and 160.3 (C-17 or C-17'), 157.9 (C-9), 153.9 (C-9'), 148.5 (C-13), 135.2 (C-13'), 133.4 (C-2'), 129.6 (C-11), 122.7 (C-11'), 118.4 (C-12'), 118.3 (C-8), 116.1 (C-8'), 111.9 and 111.5 (C-16 and C-16'), 106.5 (C-7'), 104.2 and 104.1 (C-10 and C-12), 99.2 (C-10'), 93.6 (C-2), 70.5 (C-3), 61.6 (C-3'), 61.34 and 61.29 (17- $\text{OCH}_3$  and 17'- $\text{OCH}_3$ ), 58.8 (C-21'), 57.8 (C-21), 55.3 (9- $\text{OCH}_3$ ), 55.1 (9'- $\text{OCH}_3$ ), 54.5 (C-7), 53.9 (C-5'), 53.7 (C-5), 51.30 and 51.27 (22- $\text{OCH}_3$  and 22'- $\text{OCH}_3$ ), 40.6 (C-20'), 40.4 (C-20), 39.9 (C-15'), 39.8 (C-15), 29.4 (C-14'), 28.6 (C-6), 24.7 (C-14), 23.9 (C-6'), 19.0 (C-19 and C-19'), 12.9 and 12.8 (C-18 and C-18'). FABMS (NBA)  $m/z$ : 813 [ $\text{MH}^+$ ]. HR-FABMS (NBA): calcd for  $\text{C}_{46}\text{H}_{61}\text{N}_4\text{O}_9$  [ $\text{MH}^+$ ]: 813.4439, found: 813.4432. CD (0.17 mM, MeOH, 24°C),  $\lambda_{\text{nm}}$  ( $\Delta\epsilon$ ): 290 (0), 272 (+2.5), 267 (0), 249 (-31.4), 240 (0), 232 (+77.0), 225 (0), 218 (-66.3), 203 (-0.5). **4**: UV (MeOH)  $\lambda_{\text{max}}$ : 297, 248 (sh), and 232 nm.  $^1\text{H-NMR}$  (600 MHz,  $\text{CDCl}_3$ , -50°C)  $\delta$  [ppm]: 7.43 and 7.40 (each 1H, s, H-17 and H-17'), 7.38 (1H, d,  $J=7.8$ , H-12), 7.34 (1H, d,  $J=7.7$ , H-11'), 7.24 (1H, t,  $J=7.8$ , H-11), 6.90 (1H, br s,  $\text{N}_a\text{-H}$ ), 6.59 (1H, d,  $J=7.8$ , H-10), 6.50 (1H, d,  $J=7.7$ , H-10'), 3.86 (3H, s, 9'- $\text{OCH}_3$ ), 3.79 and 3.58 (each 3H, s, 17- $\text{OCH}_3$  and 17'- $\text{OCH}_3$ ), 3.69 and 3.60 (each 3H, s, 22- $\text{OCH}_3$  and 22'- $\text{OCH}_3$ ), 3.57 (3H, s, 9- $\text{OCH}_3$ ), 3.45 (1H, br d,  $J=14.0$ , H-6), 3.00 (1H, m, H-6'), 2.95 (1H, m, H-21 or H-21'), 2.92 (1H, m, H-3'), 2.90 (1H, m, H-14), 2.87 and 2.78 (each 1H, m, H-15 and H-15'), 2.82 (1H, m, H-6'), 2.80 (1H, m, H-5'), 2.73 (2H, m, H-5), 2.57 (1H, br d,  $J=10.7$ , H-3), 2.38 (1H, q like,  $J=12.9$ , H-14'), 2.32 (1H, m, H-5'), 2.30 (1H, m, H-21 or H-21'), 2.20 (1H, br d,  $J=10.4$ , H-21 or H-21'), 1.68

(2H, m, H-19 and H-19'), 1.63 (1H, m, H-14), 1.54 (1H, m, H-6), 1.48 (3H, m, H-14', H-20 and H-20'), 1.10 (2H, m, H-19 and H-19'), 0.79 and 0.75 (each 3H, t,  $J=7.2$ , H<sub>3</sub>-18 and H<sub>3</sub>-18'). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>, -50°C) δ [ppm]: 190.1 (C-2), 170.0 and 169.6 (C-22 and C-22'), 161.5 and 161.4 (C-17 and C-17'), 155.7 (C-9), 154.9 (C-13), 153.5 (C-9'), 134.3 (C-13'), 133.1 (C-2'), 130.2 (C-8), 129.5 (C-11), 121.5 (C-11'), 117.8 (C-7'), 114.0 (C-12), 110.86 and 110.84 (C-16 and C-16'), 110.80 (C-12'), 109.2 (C-10), 107.4 (C-8'), 99.1 (C-10'), 62.4 and 61.5 (17-OCH<sub>3</sub> and 17'-OCH<sub>3</sub>), 62.3 (C-3), 61.0 (C-3'), 59.6 (C-7), 57.6 and 57.4 (C-21 and C-21'), 55.6 (9-OCH<sub>3</sub>), 55.4 (9'-OCH<sub>3</sub>), 53.8 (C-5'), 52.1 and 52.0 (22-OCH<sub>3</sub> and 22'-OCH<sub>3</sub>), 51.2 (C-5), 40.4 and 40.3 (C-20 and C-20'), 39.5 and 38.4 (C-15 and C-15'), 32.4 (C-6), 29.1 (C-14'), 26.6 (C-14), 23.8 (C-6'), 19.1 and 19.0 (C-19 and 19'), 13.0 (C-18 and C-18'). FABMS (NBA)  $m/z$ : 795 [MH<sup>+</sup>]. HR-FABMS (NBA): calcd for C<sub>46</sub>H<sub>59</sub>N<sub>4</sub>O<sub>8</sub> [MH<sup>+</sup>]: 795.4333, found: 795.4324. CD (0.20 mM, MeOH, 24°C), λnm (Δε): 310 (0), 305 (-0.9), 300 (0), 298 (+2.3), 292 (0), 287 (-1.1), 280 (0), 269 (+4.8), 260 (0), 234 (-139.0), 227 (0), 220 (+101.0), 208 (0).

### Acetylation of Dimer (3)

To a stirred solution of **3** (20.0 mg, 0.025 mmol) in dry pyridine (0.6 mL) was added Ac<sub>2</sub>O (0.6 mL, 6.36 mmol) at rt under argon atmosphere. After the reaction mixture was stirred for 19 h, it was poured into chilled water and extracted with CHCl<sub>3</sub> three times. The combined organic layer was washed with brine, dried over MgSO<sub>4</sub> and evaporated. The residue was purified by Al<sub>2</sub>O<sub>3</sub> column chromatography (30% AcOEt/*n*-hexane) to give dimer (**6**) (14.2 mg, 71%) as an amorphous powder. **6**: UV (MeOH) λ<sub>max</sub>: 297, 247 (sh), and 227 nm. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ [ppm]: 7.42 and 7.14 (each 1H, s, H-17 and H-17'), 7.34 (1H, d,  $J=8.2$ , H-11'), 7.29 (1H, d,  $J=7.9$ , H-12), 7.20 (1H, dd,  $J=7.9$ , 7.9, H-11), 6.57 (1H, d,  $J=7.9$ , H-10), 6.49 (1H, br s, N<sub>a</sub>-H), 6.48 (1H, d,  $J=8.2$ , H-10'), 3.85 (3H, s, 9'-OCH<sub>3</sub>), 3.73 and 3.52 (each 3H, s, 17-OCH<sub>3</sub> and 17'-OCH<sub>3</sub>), 3.72 and 3.57 (each 3H, s, 22-OCH<sub>3</sub> and 22'-OCH<sub>3</sub>), 3.65 (1H, m, H-6), 3.36 (3H, s, 9-OCH<sub>3</sub>), 3.21 (1H, dd,  $J=13.4$  and 2.5, H-3), 3.10 (1H, td like,  $J=9.8$  and 4.2, H-5), 3.02 (1H, m, H-6'), 2.91~2.81 (6H, m, H-3', H-5', H-6', H-21, H-21', and H-15'), 2.72 (1H, dt,  $J=13.4$  and 4.0, H-15), 2.42 (1H, m, H-5), 2.32 (2H, m, H-5' and H-21'), 2.22 (1H, br d,  $J=9.5$ , H-21), 1.96 (1H, ddd,  $J=13.1$ , 13.1, 13.1, H-14'), 1.60~1.50 (3H, m, H-6, H-20 and H-20'), 1.34 (1H, br d,  $J=13.4$ , H-14), 1.17 (1H, br d,  $J=13.1$ , H-14'), 1.11 and 0.88 (each 1H, m, H-19 and H-19'), 0.75 and 0.65 (each 1H, m, H-19 and H-19'), 0.79 (3H, t,  $J=7.3$ , H<sub>3</sub>-18 or H<sub>3</sub>-18'), 0.69 (3H, t,  $J=7.0$ , H<sub>3</sub>-18 or H<sub>3</sub>-18'). <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>) δ [ppm]: 191.3 (C-2), 169.23 and 169.15 (C-22 and C-22'), 160.32 and 160.22 (C-17 and C-17'), 156.2 (C-9), 156.0 (C-13), 153.3 (C-9'), 134.3 (C-13'), 132.6 (C-2'), 132.1 (C-8), 129.3 (C-11), 122.2 (C-11'), 117.3 (C-7'), 113.3 (C-12), 112.7 (C-12'), 111.6 and 110.9 (C-16 and C-16'), 108.8 (C-10), 106.1 (C-8'), 99.6 (C-10'), 66.0 (C-3), 61.3 and 61.2 (17-OCH<sub>3</sub> and 17'-OCH<sub>3</sub>), 60.7 (C-3'), 58.9 (C-7), 57.8 (C-21'), 55.6 (9-OCH<sub>3</sub>), 55.4 (9'-OCH<sub>3</sub>), 55.1 (C-21), 53.8 (C-5'), 51.3 and 51.0 (22-OCH<sub>3</sub> and 22'-

OCH<sub>3</sub>), 48.7 (C-5), 40.6 and 40.0 (C-20 and C-20'), 39.7 and 39.5 (C-15 and C-15'), 28.8 (C-14'), 28.3 (C-6 and C-14), 23.9 (C-6'), 19.1 and 18.4 (C-19 and 19'), 12.7 and 12.5 (C-18 and C-18'). FABMS (NBA) *m/z*: 795 [MH<sup>+</sup>]. HR-FABMS (NBA): calcd for C<sub>46</sub>H<sub>59</sub>N<sub>4</sub>O<sub>8</sub> [MH<sup>+</sup>]: 795.4333, found: 795.4324. CD (0.12 mM, MeOH, 24°C), λnm (Δε): 320 (0), 290 (+12.6), 267 (0), 243 (-35.1), 238 (0), 232 (+66.6), 226 (0), 220 (-104.0), 205 (0).

## ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid (No. 14370718) for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a JSPS Research Fellowship for Young Scientists to HI.

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