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TETRAHEDRON

Stereochemical Studies on the *Uncaria* Alkaloid, 3-Oxo-7-hydroxy-3,7-secorhynchophylline: The Absolute Configuration of 3-Hydroxyoxindole Derivatives

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Abstract: 3-Oxo-7-hydroxy-3,7-secorhynchophylline (**1**), an oxindole alkaloid found in *Uncaria attenuata*, was prepared from isorhynchophylline (**2**), and two diastereomers ascribable to C7 of the natural and semi-synthetic **1** were separated by chiral column chromatography. The absolute configuration at C7 was elucidated by comparison of the CD spectra with those of the known oxytryptophan derivatives (**8a** and **8b**). Further, the absolute configuration of some natural products having a 3-substituted-3-hydroxyoxindole moiety was deduced by utilizing the new CD spectral finding obtained in the present study.

Keyword: Alkaloids; Oxidation; Configuration; Circular dichroism.

INTRODUCTION

A number of indole and oxindole alkaloids have so far been isolated from the *Uncaria* plants and have been found to possess pharmacologically significant activities.[1] The chemical investigation of *Uncaria attenuata* Korth (*U. salaccensis* Bakh. f. nom prois) in Thailand was first carried out by UK-Thai researchers,[2] resulting in the isolation of many Corynanthe- and heteroyohimbine-type indole and oxindole alkaloids. Later, we reinvestigated the constituents of this plant and found a new type of oxindole alkaloids, *i.e.*, salacin,[3] Us-7, Us-8,[4] and 3-oxo-7-hydroxy-3,7-secorhynchophylline (**1**).[3] Among them, the structure of **1** was determined by spectroscopic analysis and chemical transformation from rhynchophylline or isorhynchophylline (**2**). However, the stereochemistry at the C7 position remains undetermined as yet, because both the natural and semi-synthetic (**1**) have been obtained as an inseparable epimeric mixture ascribable to the C7 position. In the present study, we re-examined this subject and obtained new findings regarding the circular dichroism (CD) spectra, which were quite useful for analyzing the absolute configuration of the quaternary center in the 3-hydroxyoxindole derivatives, on which we describe in this paper.

RESULTS AND DISCUSSION

3-Oxo-7-hydroxy-3,7-secorhynchophylline (**1**) was prepared from the known alkaloid, isorhynchophylline (**2**), as follows. The *N*b function in **2** was oxidized with *m*-CPBA and the resulting *N*-oxide (**3**) was subjected to a modified Polonovski reaction using trifluoroacetic anhydride. The reaction proceeded in a regioselective manner

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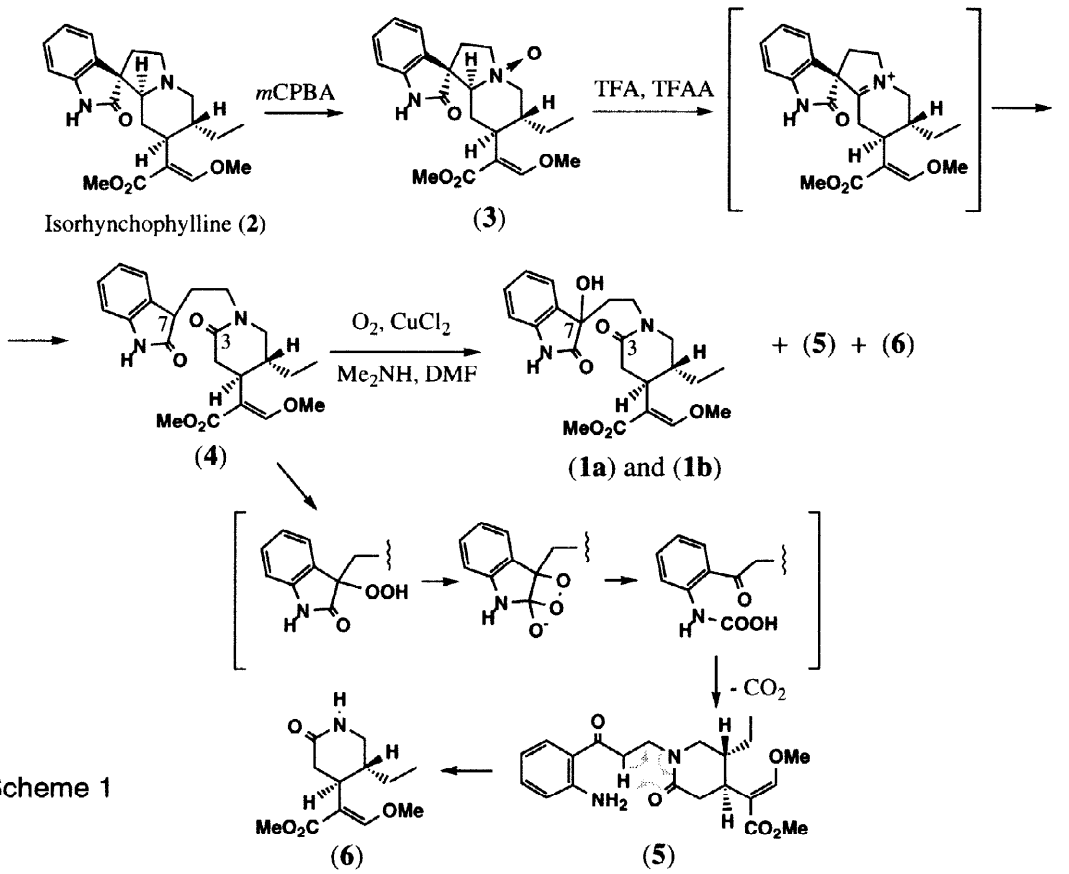
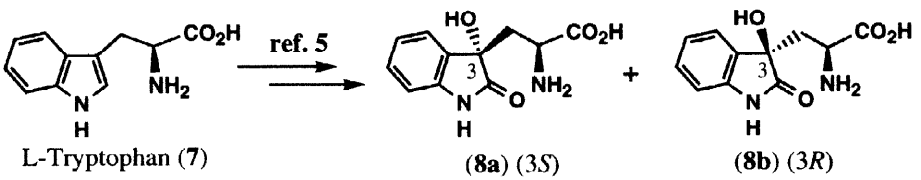
to give the 3,7-*seco* derivative (**4**) in 54% yield. Subsequently, a hydroxy group was introduced to the C7 position in **4** employing $CuCl_2$-catalyzed oxidation ($CuCl_2$, dimethyl amine, oxygen atmosphere in DMF). Under this condition, the desired compound (**1**) was obtained in 30% yield together with two structurally interesting side products (**5**) and (**6**) in 22% and 35% yield, respectively. The synthetic compound **1** was revealed to be identical with the natural product by comparison of their chromatographic behavior, UV, ^{1}H- and ^{13}C-NMR, and mass spectra. The compound **5** exhibited the characteristic UV absorption (230.5, 366.5 nm), suggesting the presence of 2-aminoacetophenone chromophor, and was elucidated to be the 2,7-*seco* derivative by analyzing the NMR data, including the HMQC and HMBC spectra. The second by-product (**6**) possesses the fundamental *D*-ring unit of Corynanthe-type indole alkaloids, which would be produced *via* retro-Michael type reaction of **5** as proposed in Scheme 1.



Scheme 1

Taking the formation mechanism into consideration, we can easily recognize that the C7 position of **1** is the epimeric center. Actually, the 500MHz ^{1}H-NMR spectrum of natural and semi-synthetic 3-oxo-7-hydroxy-3,7-secorhynchophylline (**1**) reveals it to be a diastereomeric mixture. All attempts at the separation of this diastereomeric mixture using normal- and reverse-phase chromatographies were unsuccessful. However, good separation was obtained when chiral column chromatography (CHIRALCEL OD, mobile phase; 50% *n*-hexane/EtOH) was used. The spectroscopic data including the ^{1}H- and ^{13}C-NMR, mass and UV spectra of these diastereomers (fast eluted compound **1a** and slow eluted compound **1b**) are very similar, excepting the Cotton curves in the CD spectra. As shown in Figure 1, the antipodal curves ascribed to the C7 chiral center in **1a** (UV λmax; 204.6, 242.2, 295.4 nm) and **1b** (UV λmax; 204.4, 242.0, 295.4 nm) were observed. In order to determine the absolute configuration at C7 of **1a** and **1b**, we prepared the optically active 3-hydroxyoxindole

derivatives (**8a** and **8b**),[5] whose absolute configuration was already assigned by transformation to a related pair of diastereomers of known stereochemistry.[6] According to Labroo's procedure,[5] L-tryptophan (**7**) was converted to two 3-hydroxyoxytryptophans (**8a** and **8b**) (Scheme 2), which were respectively identical with the reported compounds in all respects. One diastereomer (**8a**) ($[\alpha]_D$ -19.9°) assigned to be C3(*S*) configuration exhibited a negative Cotton effect at the long-wave region (300-260 nm) and a positive curve at shorter wave region (260-220 nm) in the CD spectrum, while the other diastereomer (**8b**)) ($[\alpha]_D$ +36.7°) having C3(*R*) configuration showed the entirely antipodal curve of **8a**. Comparison of these CD data with those of (**1a** and **1b**) led us to conclude that **1a** (fast eluted compound) and **1b** (slow eluted compound) have C7(*S*) and C7(*R*) configuration, respectively.



Scheme 2

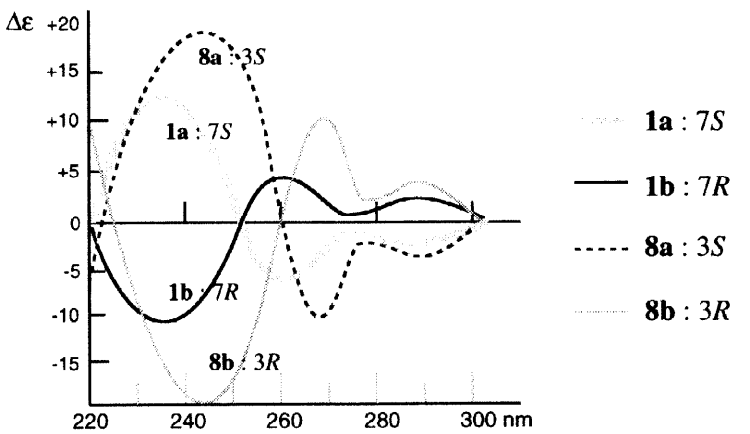
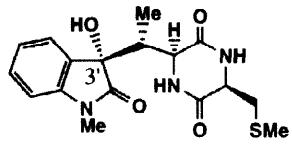
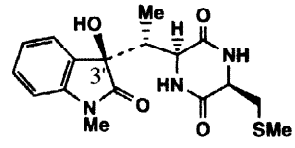


Fig. 1 Comparison of CD spectra (in MeOH) of **1a,b** and **8a,b**

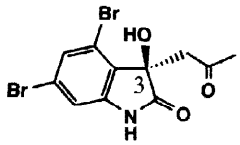
Recently, many natural products carrying the 3-hydroxyoxindole residue have been found from marine resources. (Fig. 2) Laatsch *et al.* have isolated two diketopiperazines named maremycin A (**9**) and B (**10**)[7] from the culture broth of marine *Streptomyces*, and tentatively assigned the absolute configuration at the quaternary center of the hydroxyoxindole moiety by utilizing the Force-field calculation and NMR data. By applying our present findings concerning the CD spectral details, the stereochemistry of the 3' position in **9** and **10** could be deduced to be (*S*) and (*R*), respectively, which is the same conclusion with the tentative assignment in the original literature. Kamano *et al.* have found four hydroxyoxindole alkaloids, convolutamydines A - D (**11-14**),[8] from marine bryozoan, the absolute configuration of which, however, has not yet been elucidated. In the literature all these natural products were reported to exhibit a negative Cotton effect at around 225 - 250 nm in the CD spectra, suggesting that their absolute configuration would be (*R*) form.



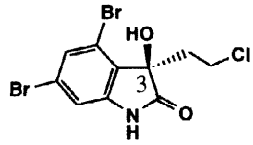
Maremycin A (**9**)



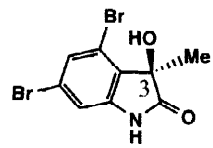
Maremycin B (**10**)



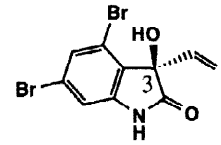
Convolutamydine A (**11**)



Convolutamydine B (**12**)



Convolutamydine C (**13**)



Convolutamydine D (**14**)

Fig. 2

EXPERIMENTAL

General UV: recorded in MeOH. JASCO U-560. ^{1}H and ^{13}C NMR spectra: recorded at 500 and 125.65 MHz, respectively. (ppm, *J* in Hz with TMS as int. standard.) JEOL JNM A-500. EI-MS: direct probe insertion at 70 eV. JEOL JMS-AM20. FAB-MS: JEOL JMS-HX110. CD: JASCO J-720WI. Optical Rotation: JASCO DIP-140. TLC: precoated Kieselgel 60 F_{254} plates (Merck, 0.25 mm thick). Column Chromatography: Kieselgel 60 [Merck, 70-230 (for open chromatography) and 230-400 mesh (for flash chromatography)]. Silica gel prepacked column Kusano CPS-HS-221-05 (for medium-pressure liquid chromatography). DAICEL CHIRAL CELL OD and YMC SH-347-7 ODS (for high-performance column chromatography). Abbreviations used are: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), shoulder (sh).

Preparation of isorhynchophylline *N*-oxide (**3**)

To a stirred solution of **2** (334 mg, 0.867 mmol) in CH_2Cl_2 (20 ml) was added *m*-CPBA (224 mg, 1.301 mmol) at 0℃. After the reaction mixture was stirred for 40 min at room temperature, the solution was concentrated under reduced pressure. The residue was purified by Al_2O_3 column chromatography (2% MeOH/$CHCl_3$) to afford 320 mg (y. 92%) of **3** as a colorless amorphous powder. EI-MS m/z (%): 400 (M^+, 26), 384 (100), 239 (86). HR-MS (FAB): found 401.2070, calcd for $C_{22}H_{29}N_2O_5$; 401.2077. IR ν max (KBr) cm^{-1} : 3400, 2970, 1710. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.78 (3H, t, *J*=7.3, $H_3$18), 1.09 (1H, m, H19), 1.43 (1H, m, H19), 2.42 (1H, ddd, *J*=16.2, 13.2, 13.2, H15), 2.43 (1H, ddd, *J*=12.7, 2.1, 2.1, H14), 2.53 (1H, m, H6), 2.54 (1H, ddd, *J*=13.0, 7.4, 3.0, H6), 2.88 (1H, dd, *J*=15.2, 15.2, H21), 2.90 (1H, ddd, *J*=12.7, 12.7, 2.1, H14), 3.10 (1H, m, H5), 3.57 (1H, ddd, *J*=15.4, 15.4, 3.0, H20), 3.62 (3H, s, OMe), 3.63 (1H, m, H5), 3.71 (3H, s, OMe), 3.86 (1H, dd, *J*=15.2, 3.0, H3), 3.88 (1H, dd, *J*=16.8, 14.1, H21), 6.91 (1H, d, *J*=7.7, H12), 7.04 (1H, t, *J*=7.6, H10), 7.18 (1H, t, *J*=7.6, H11), 7.26 (1H, s, H17), 8.23 (1H, d, *J*=7.7, H9), 10.47 (1H, s, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 10.5 (C18), 23.3 (C19), 25.6 (C14), 33.3 (C20), 36.1 (C6), 38.7 (C15), 51.2 (OMe), 55.3 (C7), 61.9 (OMe), 68.7 (C21), 68.6 (C5), 80.2 (C3), 109.8 (C12), 110.3 (C16), 122.2 (C10), 128.1 (C9), 128.5 (C11), 131.5 (C8),142.8 (C13), 160.2 (C17), 168.9 (C22), 182.3 (C2).

Modified Polonovski reaction of isorhynchophylline *N*-oxide **3**

A mixture of **3** (30 mg, 0.0375 mmol) in trifluoroacetic anhydride (2 ml) and trifluoroacetic acid (2 ml) was heated at 50℃ under argon atmosphere for 8h. The solution was concentrated under reduced pressure and the

residue was basified by the addition of chilled ammonia water. The whole mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (4% i-PrOH/$CHCl_3$) to afford 16 mg (y. 54%) of **4** as a yellow amorphous powder. EI-MS m/z (%) : 400 (M^+, 100), 268 (24), 210 (49). HR-MS (FAB): found 401.2081, calcd for C22H29N2O5; 401.2077. IR ν max ($CHCl_3$) cm^{-1}: 3430, 2950, 1710, 1630, 1420. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.84 (3H, t, *J*=7.3, H18), 1.09 (1H, dqd, *J*=17.5, 7.3, 4.3, H19), 1.45 (1H, dqd, *J*=17.5, 7.3, 3.3, H19), 2.18 (2H, m, H6, H15), 2.24 (1H, m, H20), 2.31 (1H, ddd, *J*=17.8, 12.0, 5.8, H5), 2.71 (1H, ddd, *J*=17.8, 12.0, 6.6, H5), 2.85 (1H, ddd, *J*=11.5, 11.5, 5.2, H6), 2.91, 3.02 (each 0.5H, dd, *J*=11.4, 11.4, H14), 3.26, 3.34 (each 0.5H, dd, *J*=12.0, 5.0, H14), 3.39 (1H, dd, *J*=12.2, 5.2, H21), 3.46 (1H, dd, *J*=11.0, 6.1, H7), 3.69 (3H, s, OMe), 3.81 (3H, s, OMe), 3.83 (1H, m, H21), 6.85 (1H, d, *J*=7.7, H12), 7.05 (1H, d, *J*=7.7, H10), 7.20 (1H, d, *J*=7.7, H11), 7.34 (1H, s, H17), 7.44 (1H, d, *J*=7.7, H9), 7.63 (1H, s, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 11.0 (C18), 23.9 (C19), 27.7 (C6), 34.9 (C15), 36.0 (C14), 37.0 (C20), 43.8 (C7), 44.2 (C21), 51.2 (OMe), 61.6 (OMe), 109.6 (C12), 110.2 (C16), 122.5 (C10), 124.5 (C9), 128.0 (C11), 129.3 (C8),160.3 (C17), 168.0 (C22), 170.2 (C3), 179.8 (C2).

Oxidation of 3,7-seco derivative **4**

A mixture of **4** (50 mg, 0.125 mmol), $CuCl_2$ (100 mg), and dimethylamine (50% aqueous solution, 4 drops) in dimethylformamide (5 ml) was stirred for 24 h at room temperature under O_2 atmosphere. The reaction mixture was diluted with CH_2Cl_2 and then washed with 1N-HCl solution. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (10% MeOH/EtOAc) to afford **1** (15 mg, y. 30%), **5** (10.7 mg, y. 22%) and **6** (10.5 mg, y. 35%). The synthetic **1** was identical with the natural product by comparison of their chromatographic behavior, UV, ^{1}H- and ^{13}C-NMR, and mass spectra. The diastereomers were separated using chiral column chromatography [Column: CHIRAL CELL OD (DAICEL, φ 20 mm x 250 mm), Solvents: n-Hex/EtOH=1/1, Flow rate: 3.0 ml/min], resulting in the isolation of 6.1 mg of **1a** (retention time; 13.4 min) and 4.6 mg of **1b** (retention time; min 14.4 min) from 21.0 mg of the diastereomeric mixture.

1a: yellow amorphous powder, EI-MS m/z (%): 416 (M^+, 21), 398 (8), 388 (12), 370 (11), 268 (100). HR-MS (FAB): found 417.2020, calcd for C22H29N2O6; 417.2025. $[\alpha]_D^{20}$: -17.4° (c=0.035, $CHCl_3$). UV λmax nm (MeOH) ; 204.6, 242.2, 295.4. IR ν max ($CHCl_3$) cm^{-1}: 3430, 2950, 1720, 1700, 1680, 1420. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.83 (3H, t, *J*=6.9, H18), 1.07 (1H, m, H19), 1.47 (1H, m, H19), 2.09 (1H, m, H6), 2.23 (2H, m, H6, H20), 2.32 (1H, dd, *J*=17.3, 5.2, H14), 2.71 (1H, dd, *J*=17.1, 12.0, H14), 2.85 (1H, td, *J*=12.0, 5.3, H15), 2.93 (1H, t, *J*=12.0, H21), 3.31 (1H, dd, *J*=12.0, 5.2, H21), 3.40 (1H, m, H5), 3.70 (3H, s, OMe), 3.80 (1H, m, H5), 3.82 (3H, s, OMe), 6.85 (1H, d, *J*=7.6, H12), 7.06 (1H, t, *J*=7.6, H10), 7.23 (1H, t, *J*=7.6, H11), 7.36 (1H, s, H17), 7.48 (1H, d, *J*=7.6, H9), 8.05 (1H, s, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) : δ 10.9 (C18), 23.8 (C19), 34.6 (C15), 35.7 (C6), 35.8 (C14), 36.7 (C20), 42.1 (C5), 51.2 (OMe), 52.7 (C21), 61.7 (OMe), 75.0 (C7), 109.8 (C16), 110.2 (C12), 123.0 (C10), 124.4 (C9), 129.5 (C11), 131.2 (C8), 140.1 (C13), 160.4 (C17), 167.9 (C22), 171.2 (C3), 179.7 (C2).

1b: yellow amorphous powder, EI-MS m/z (%): 416 (M^+, 21), 398 (5), 388 (12), 370 (12), 268 (100). HR-MS (FAB): found 417.2018, calcd for C22H29N2O6; 417.2025. $[\alpha]_D^{20}$: +168.6° (c=0.025, $CHCl_3$). UV λmax nm (MeOH) ; 204.4, 242.0, 295.4. IR ν max ($CHCl_3$) cm^{-1}: 3430, 2950, 1720, 1700, 1680, 1420. ^{1}H-NMR ($CDCl_3$, 500 MHz) : δ 0.83 (3H, t, *J*=6.9, H18), 1.07 (1H, m, H19), 1.45 (1H, m, H19), 2.13 (1H, m, H6), 2.23 (2H, m, H6, H20), 2.31 (1H, dd, *J*=17.3, 5.2, H14), 2.72 (1H, dd, *J*=17.3, 12.0, H14), 2.86 (1H, td, *J*=12.0, 5.3, H15), 2.97 (1H, t, *J*=12.0, H21), 3.24 (1H, dd, *J*=12.0, 5.1, H21), 3.52 (1H, m, H5), 3.69 (3H, s, OMe), 3.72 (1H, m, H5), 3.82 (3H, s, OMe), 6.84 (1H, d, *J*=7.5, H12), 7.06 (1H, td, *J*=7.5, 0.1, H10), 7.23 (1H, td, *J*=7.5, 0.1, H11), 7.36 (1H, s, H17), 7.43 (1H, d, *J*=7.5, H9), 7.98 (1H, s, NH). ^{13}C-NMR ($CDCl_3$, 100 MHz) : δ 10.9 (C18), 23.8 (C19), 34.6 (C15), 35.7 (C6), 35.7 (C14), 36.8 (C20), 42.1 (C5), 51.2 (OMe), 52.7 (C21), 61.6 (OMe), 74.9 (C7), 109.8 (C16), 110.1 (C12), 123.0 (C10), 124.2 (C9), 129.5

(C11), 131.2 (C8), 140.1 (C13), 160.4 (C17), 167.9 (C22), 171.1 (C3), 179.6 (C2).

5: yellow amorphous powder, EI-MS m/z (%): 388 (M^+, 2), 279 (9), 242 (14), 149 (100). HR-MS (FAB): found 389.2082, calcd for $C_{21}H_{29}N_2O_5$; 389.2077. UV λmax nm (MeOH) ; 203.0, 230.5, 366.5. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.83 (3H, t, *J*=7.4, H18), 1.08 (1H, m, H19), 1.45 (1H, m, H19), 2.30 (1H, m, H20), 2.43 (1H, dd, *J*=17.3, 4.5, H14), 2.87 (1H, m, H15), 3.03 (1H, t, *J*=11.3, H21), 3.26 (2H, t-like, *J*=7.0, H6), 3.69 (3H, s, OMe), 3.72 (2H, m, H5), 3.80 (3H, s, OMe), 6.30 (2H, br s, NH_2), 6.63 (1H, dd, *J*=8.0, 8.0, H10), 6.64 (1H, d, *J*=8.0, H12), 7.26 (1H, dd, *J*=8.0, 8.0, H11), 7.37 (1H, s, H17), 7.81 (1H, d, *J*=8.0, H9) ^{13}C-NMR ($CDCl_3$, 100 MHz) : δ 11.0 (C18), 23.9 (C19), 35.0 (C15), 36.0 (C14), 35.7 (C14), 37.1 (C20 or C6), 37.2 (C20 or C6), 44.3 (C5), 51.3 (OMe), 53.5 (C21), 61.7 (OMe), 110.0 (C16), 116.0 (C12), 117.2 (C10), 118.0 (C8), 131.6 (C9), 134.5 (C11), 150.3 (C13), 160.3 (C17), 168.0 (C22), 170.4 (C3), 201.3 (C7).

6: yellow amorphous powder, EI-MS m/z (%): 241 (M^+, 14), 171 (100). HR-MS (FAB): found 242.1393, calcd for $C_{12}H_{20}NO_4$; 242.1392. $[\alpha]_D^{24}$:+35.3°(c=0.34, $CHCl_3$). UV λmax nm (MeOH) ; 237.0. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 0.83 (3H, t, *J*=7.4, H18), 1.08 (1H, m, H19), 1.48 (1H, m, H19), 2.22 (1H, m, H20), 2.33 (1H, dd, *J*=17.6, 5.5, H14), 2.77 (1H, dd, *J*=17.6, 12.1, H14), 2.91 (1H, ddd, *J*=12.1, 12.1, 5.5, H15), 2.95 (1H, dd, *J*=11.3, 11.3, H21), 3.39 (1H, dd, *J*=11.3, 4.5, H21), 3.70 (3H, s, OMe), 3.82 (3H, s, OMe), 5.76 (1H, br s, NH), 7.37 (1H, s, H17). ^{13}C-NMR ($CDCl_3$, 125 MHz) : δ 10.9 (C18), 23.7 (C19), 34.8 (C15), 35.2 (C14), 36.3 (C20), 46.6 (C21), 51.2 (OMe), 61.6 (OMe), 110.2 (C16), 160.3 (C17), 167.9 (CO_2), 172.7 (C3).

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