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A Biomimetic Synthesis of a Novel Seco Indole Alkaloid, 11-Methoxygelsemamide

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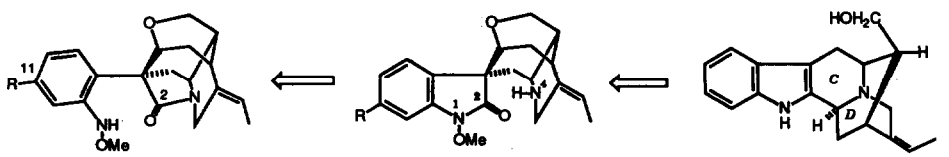
Abstract: A new type of *Gelsemium* alkaloid, 11-methoxygelsemamide (**2**), having a 1,2-secoindole system, was synthesized for the first time from a sarpagine type indole alkaloid, gardnerine (**6**), based on a suggested biogenetic sequence.

Introduction

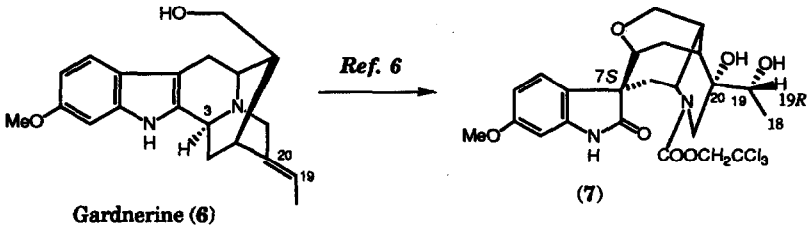
From *Gelsemium elegans* Benth. (Loganiaceae),[1] an original plant of Chinese folk medicine "Kou-Wen", two novel alkaloids, gelsemamide (**1**) and 11-methoxygelsemamide (**2**), have been isolated by Cordell *et al.*[2] The characteristic of these two alkaloids are the presence of both an *N*-methoxyaniline and a novel aliphatic part having a cage structure. Biogenetically, **1** and **2** might be derived from the humantenine-type oxindole alkaloids, such as rankinidine (**3**) and humantenirine (**4**), by bond-cleavage between the N_1 and C_2 and bond-formation between the N_4 and C_2 positions. The humantenine-type oxindole alkaloids, the precursor of (**1**) and (**2**), would be formed from the sarpagine-type indole alkaloid, such as koumidine (**5**), by the C/D ring cleavage, oxidative transformation to the oxindole derivative, and introduction of a methoxy group onto the N_1 function, as illustrated in scheme I. During the chemical study on the *Gelsemium* alkaloids,[3] we were interested in the unusual structure as well as the biomimetic chemical synthesis of these two seco indole alkaloids. Here we describe the successful accomplishment of the first synthesis of 11-methoxygelsemamide (**2**) from the indole alkaloid, gardnerine (**6**).[4]



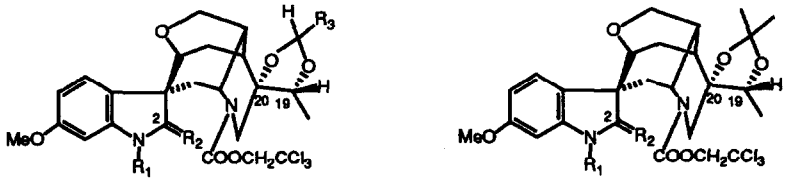
Scheme I

Results and Discussion

A major alkaloidal constituent of *Gardneria nutans*, gardnerine (**6**),[5] was converted to the oxindole derivative (**7**), having a humantenine-type skeleton, according to the method published in a previous paper.[6] This compound has the *S* configuration at the spiro C_7 center and the glycol system at the C_{19}-C_{20} position would be converted to the ethylidene side chain in the later reaction stage. The next requirement for the synthesis of the humantenine-type alkaloid was the preparation of an N_1-methoxy oxindole function. For this task, reduction of the oxindole function in **7** to the secondary amine followed by oxidation leading to the hydroxamic acid was needed. The 19,20-diol function in **7** was then initially protected with cyclic orthoformate, which was considered to directly transform into the olefinic compound after preparation of an N_1-methoxy oxindole function. But, reduction of the cyclic orthoformate (**8**) with borane dimethylsulfide complex (BH_3•SMe_2)



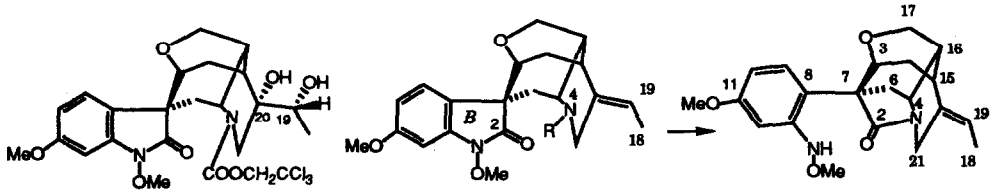
Gardnerine (**6**) (**7**)



R_1=H, R_2=O, R_3=OMe: (**8**)
R_1=H, R_2=H_2, R_3=H: (**9**)

R_1=OMe, R_2=O, R_3=OMe: (**15**)

R_1=H, R_2=O: (**10**)
R_1=H, R_2=H_2: (**11**)
R_1=OH, R_2=O: (**12**)
R_1=OMe, R_2=O: (**13**)



(**14**)

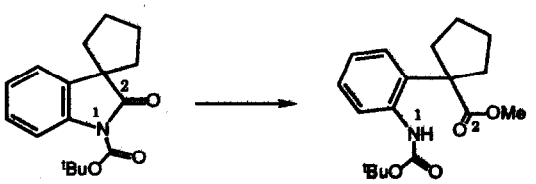
R=$COOCH_2CCl_3$: (**16**)
R=H: Humantenirine (**4**)

11-Methoxygelsemamide (**2**)

Scheme II

afforded the methylenedioxy derivative (**9**). The protecting group of the diol in **7** was then changed to dimetyl acetal, and the lactam residue of the acetonide (**10**) was reduced again with the BH_3•SMe_2 complex to yield the secondary amine (**11**) in quantitative yield. Treatment of the amine (**11**) with the urea hydrogen peroxide addition compound (H_2O_2•H_2NCONH_2) and a catalytic amount of sodium tungstate (Na_2WO_4•$2H_2O$) in aq. MeOH at 10-18°C gave the hydroxamic acid (**12**),[4,7] which was methylated with diazomethane to yield N_1-methoxy oxindole (**13**) in 31% overall yield from **11**. In the ^1H nmr spectrum of **13**, the characteristic signals of the N_1-methoxy group were observed at δ 3.98 and 3.97 ppm (total 3H, each singlet).[8] Next, a vicinal diol function in the humantenine skeleton was converted to the ethylidene double bond as follows. After removal of the acetal group in **13** with aqueous 80% AcOH, the diol **14** was converted to cyclic orthoformate (**15**) by treatment with trimethyl orthoformate in the presence of pyridinium *p*-toluenesulfonate (PPTS), which was refluxed in acetic anhydride[9] for 5h to provide the 19*Z*-olefinic compound **16** in 77% overall yield from **14**. The N_4-protecting group in compound (**12**) was removed with activated zinc in AcOH to furnish humantenirine (**4**) {mp. 166-167°, $[\alpha]_D^{23}$ -153° (*c* 0.40 in MeOH)} in 88% yield. The ^1H, ^{13}C-nmr, Uv, Mass, $[\alpha]_D$ and m.p. were identical with those of the natural product reported in the literature.[10]

To create the gelsemamide skeleton, we first attempted the bond formation between the N_4 and C_2 position in **4** using sodium hydride in aprotic solvents, which could be expected the generation of N_4 anion and subsequent its attack to the C_2 carbonyl function. But, the starting material was only recovered. From a stereomodel analysis, it could be presumed that in this rigid system the distance between N_4 and C_2 was too far to occur the desired bond connection. While, we found in the model experiments that treatment of the *N*-Boc derivative (**17**) of the spiro oxindole[11] with alkaline solution (1. KOH, aq. THF, 2. CH_2N_2) gave the *N*-C_2 seco oxindole derivative (**18**) (Scheme III). This observation indicated that the carbonyl function of the oxindoles, which possessed an electron withdrawing group on the nitrogen function, was susceptible to nucleophilic addition. Based on this knowledge, humantenirine (**4**) was treated with NaOMe in dry MeOH to yield the target natural product, 11-methoxygelsemamide (**2**) {mp. 141-142°, $[\alpha]_D^{22}$ +215° (*c* 0.145 in MeOH)} in 78% yield. This reaction would proceed *via* B ring cleavage by the attack of methoxide anion at the C_2 position and subsequent amide formation between the C_2 ester group and the N_4 function in the resultant flexible molecule. The synthetic 11-methoxygelsemamide (**2**) was identical with the natural compound based on comparison of their spectroscopic data (^1H, ^{13}C-nmr, Uv, Mass, High mass, Cd, $[\alpha]_D$ and m.p.) reported in the literature.[2]



17 18

Scheme III

In conclusion, we succeeded in the first synthesis of a novel seco indole alkaloid, 11-methoxygelsemamide (**2**) from the sarpagine-type alkaloid, gardnerine (**6**), using a suggested biogenetic sequence. The absolute configuration of the new alkaloid **2** is hereby chemically confirmed.

Experimental

M.p.s were measured on a Yamato MP-21 apparatus and are uncorrected. IR spectra were measured with a Hitachi 260 spectrophotometer, and UV spectra were measured in ethanol with a Hitachi U3400 spectrophotometers. ^{1}H NMR spectra were recorded on a JEOL JNM A 500 (500 MHz) spectrometer with tetramethylsilane as internal standard. *J*-Values are given in Hz. ^{13}C NMR spectra were measured with a JEOL JNM A-500 (125.65 MHz) spectrometer with tetramethylsilane as internal standard. Mass spectra were taken with a JEOL JMS-AM20 or a JEOL JMS-HX110 spectrometer. CD spectra were measured with a JASCO J-500A spectrometer for solutions in MeOH. Thin layer chromatography was performed on Merck precoated Silica gel 60F-254 plates. Column chromatography utilized Merck Silica gel 60 (70-230 mesh) and prepacked column [Kusano CPS-HS-221-05 (for medium pressure column chromatography)].

Compounds (**7** and **8**) were prepared from gardnerine (**6**) according to the reported procedure.[6]

Reduction of the Cyclic Orthoformate (8) Borane-methyl sulfide complex (10.0 M solution in THF, 68 µl, 0.678 mmol) was added to a solution of **8** (40 mg, 0.068 mmol) in dry THF (1 ml) at 0 °C and the mixture was heated under reflux for 3 h. Cold 5% aq. sodium carbonate solution was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in methanol (2 ml) and trimethylamine *N*-oxide dihydrate (38 mg, 0.339 mmol) was added to the solution. The reaction mixture was heated under reflux for 2 h. The solvent was evaporated *in vaccuo*. The residue was purified by SiO_2 open column chromatography with ethyl acetate-hexane (3:1) to yield the secondary amine (**9**) (38 mg, quant.) as an amorphous powder. Uv (EtOH) : 297, 207 nm. Ir ($CHCl_3$) : 1710 cm^{-1}. ^{1}H-nmr (500MHz, $CDCl_3$) δ : 3.75 (3H, s, OMe), 5.10 and 4.90 (each 1H, s, -OCH_2O-), 1.25 (3H, d, J = 6.6 Hz, 18-H_3). Ms m/z : 548 (M^++2, 2.5%), 546 (M^+, 2.5%), 160 (100).

Preparation of the Acetonide (10) *p*-Toluene sulfonic acid mono hydrate (338 mg, 1.777 mmol) and 2,2-dimethoxypropane (0.73 ml, 5.937 mmol) were added to a solution of **7** (650 mg, 1.182 mmol) at 0 °C and the mixture was heated under reflux for 1 h. Cold 5% aq. sodium carbonate solution was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by SiO_2 open column chromatography with ethyl acetate-hexane (1:1) to give the acetonide (**10**) (680 mg, 98%) as an amorphous powder. Uv (EtOH) : 260, 216 nm. Ir ($CHCl_3$) : 1710, 1160, 1115 cm^{-1}. ^{1}H-nmr (500 MHz, $CDCl_3$) δ : 3.79 (3H, s, Ar-OMe), 1.50

and 1.49 (3H, each s, Me), 1.45 (3H, d, J = 6.3 Hz, 18-H_3), 1.36 (3H, s, Me). Ms m/z : 590 (M^++2, 3%), 588 (M^+, 3), 176 (100). High ms (Fab, NBA) Calcd for $C_{26}H_{32}N_2O_7Cl_3$ (MH), 589.1275. Found 589.1270.

Reduction of the Acetonide (10) Borane-methyl sulfide complex (10.0 M solution in THF, 102 µl, 1.02 mmol) was added to a solution of **10** (30 mg, 0.052 mmol) in dry THF (1 ml) at 0 °C and the mixture was heated under reflux for 3 h. Cold 5% aq. sodium carbonate solution was added to the mixture and the whole was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was dissolved in methanol (1 ml) and trimethylamine *N*-oxide dihydrate (28 mg, 0.252 mmol) was added to the solution. The reaction mixture was heated under reflux for 3 h. The solvent was evaporated *in vaccuo*. The residue was purified by SiO_2 open column chromatography with ethyl acetate-hexane (1:1) to yield the secondary amine (**11**) (30 mg, quant.) as an amorphous powder. Uv (EtOH) : 297, 205 nm. Ir ($CHCl_3$) : 1710, 1165 cm^{-1}. ^{1}H-nmr (500MHz, $CDCl_3$) δ : 3.74 (3H, s, OMe), 1.47 (3H, br-s, Me), 1.37 (3H, d, J = 6.3 Hz, 18-H_3), 1.35 (3H, s, Me). Ms m/z : 576 (M^++2, 4%), 574 (M^+, 4), 160 (100). High ms (Fab, NBA) Calcd for $C_{26}H_{34}N_2O_6Cl_3$ (MH), 575.1482. Found 575.1475.

Preparation of the N_a-Methoxyoxindole (12) Sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$, 24 mg, 0.073 mmol) and urea hydrogen peroxide addition compound ($H_2NCONH_2 \cdot H_2O_2$, 227 mg, 2.413 mmol) were added to a solution of the secondary amine (**11**) (139 mg, 0.241 mmol) in 10% aq. methanol (3.3 ml) at 0 °C and the mixture was stirred at 10°~18° for 3.5 h. Cold water was added to the mixture and the whole was extracted with 5% methanol-chloroform. The extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by SiO_2 open column chromatography with ethyl acetate-hexane (1:1). The resulting hydroxamic acid (**12**) was dissolved in methanol (1.5 ml) and a ether solution of diazomethane (1 ml) was added to a solution at 0 °C. The mixture was stirred at room temperature for 1 h. Further ether solution of diazomethane (1 ml) was added to the reaction mixture at 0 °C and the mixture was stirred at room temperature for 1.5 h. After the solution was evaporated under reduced pressure, the residue was purified by SiO_2 open column chromatography with ethyl acetate-hexane (3:7) to afford the N_1-methoxy oxindole (**13**) (47 mg, 31%) as an amorphous powder. Uv (EtOH) : 292 (sh), 285, 219 nm. Ir ($CHCl_3$) : 1715, 1635, 1175 cm^{-1}. ^{1}H-nmr (500MHz, $CDCl_3$) δ : 3.98 and 3.97 (3H, each s, N_1-OMe), 3.84 and 3.83 (3H, each s, Ar-OMe), 1.493 and 1.488 (3H, each s, Me), 1.45 (3H, d, J = 6.4 Hz, 18-H_3), 1.36 (3H, s, Me). Ms m/z : 620 (M^++2, 8%), 618 (M^+, 8), 174 (100). High ms (Fab, NBA) Calcd for $C_{27}H_{34}N_2O_8Cl_3$ (MH), 619.1380. Found 619.1387.

Preparation of the Diol (14) A solution of the N_1-methoxy oxindole (**13**) (20 mg, 0.032 mmol) in 80% aq. acetic acid (0.5 ml) was refluxed for 3.5 h. After the addition of cold water, the reaction mixture was basified with 10% aq. sodium carbonate solution and the

whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by SiO_2 open column chromatography with 10% methanol-chloroform to afford the diol (**14**) (18 mg, 96%) as an amorphous powder. Uv (EtOH) : 293 (sh), 285, 218 nm. Ir ($CHCl_3$) : 1715, 1630, 1120 cm^{-1}. ^1H-nmr (500MHz, $CDCl_3$) δ : 3.98 and 3.97 (3H, each s, N_1-OMe), 3.84 and 3.83 (3H, each s, Ar-OMe). Ms *m/z* : 580 (M^++2, 1%), 578 (M^+, 2), 95 (100). High ms (Fab, NBA) Calcd for $C_{24}H_{29}N_2O_8Cl_3$ (MH), 578.0990. Found 578.0988.

Preparation of olefinic compound (16) from the diol (14) Pyridinium *p*-toluenesulfonate (30 mg, 0.119 mmol) and trimethyl orthoformate (144 μl, 1.308 mmol) were added to a solution of **14** (76 mg, 0.131 mmol) in dry THF (2 ml) and the mixture was stirred at room temperature for 17 h. The solution was passed through a short column of silica gel (1 g, ethyl acetate) and concentrated. The resulting 1,3-dioxolane (**15**) was dissolved in acetic anhydride (1.5 ml) and the mixture was refluxed under argon for 5 h. After the addition of cold water, the reaction mixture was basified with 10% aq. sodium carbonate solution and the whole was extracted with $CHCl_3$. The organic layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by MPLC with ethyl acetate-hexane (1:2) to give the olefinic compound (**16**) (55 mg, 77%) as an amorphous powder. Uv (EtOH) : 291 (sh), 284, 261, 217 nm. Ir ($CHCl_3$) : 1710, 1635, 1120 cm^{-1}. ^1H-nmr (500MHz, $CDCl_3$) δ : 5.69 and 5.65 (1H, each br-q, J = 6.8 Hz, 19-H), 3.97 and 3.96 (3H, each s, N_1-OMe), 3.833 and 3.830 (3H, s, Ar-OMe), 1.76 (br-d, J = 6.8 Hz) and 1.74 (br-d, J = 7.1 Hz) (3H, 18-H_3). Ms *m/z* : 546 (M^++2, 12 %), 544 (M^+, 14), 174 (100). High ms (Fab, NBA) Calcd for $C_{24}H_{28}N_2O_6Cl_3$ (MH), 545.1013. Found 545.1005.

Preparation of Humantenirine (4) Zinc dust (60 mg, 0.918 mmol) was added to a solution of the olefinic compound (**16**) (23.7 mg, 0.043 mmol) in acetic acid (0.5 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was filtered and diluted with ice-water. The mixture was basified with a cold aq. NH_4OH solution and the whole was extracted with 5% methanol-chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by SiO_2 pencil column chromatography with 5-10% methanol-chloroform to afford humantenirine (**4**) (14.1 mg, 88%) as prism. m.p. 166-167 °C (AcOEt) (lit.[10] 167-170 °C). $[\alpha]_D^{23}$ -153° (*c* 0.40 in MeOH) {lit.[10] $[\alpha]_D^{20}$ -135° (*c* 0.56 in MeOH)}. Uv (EtOH) : 293 (sh), 285, 218 nm. ^1H-nmr (500MHz, $CDCl_3$) δ : 7.30 (1H, d, J = 8.3 Hz, 9-H), 6.63 (1H, dd, J = 8.3 and 2.3 Hz, 10-H), 6.56 (1H, d, J = 2.3 Hz, 12-H), 5.24 (1H, q, J = 6.6 Hz, 19-H), 4.29 (1H, d, J = 10.5 Hz, 17-H), 4.03 (1H, dd, J = 10.5 and 4.6 Hz, 17-H), 3.98 (3H, s, N_1-OMe), 3.89 (1H, d, J = 16.9 Hz, 21-H), 3.83 (3H, s, OMe), 3.71 (1H, m, 5-H), 3.52 (1H, d, J = 8.3 Hz, 3-H), 3.33 (1H, d, J = 16.9 Hz, 21-H), 2.61 (1H, m, 15-H), 2.41 (1H, dd, J = 15.4 and 7.6 Hz, 14-H), 2.31 (1 H, dd, J = 15.4 and 6.4 Hz, 14-H), 2.31 (1H, dd, J = 16.0 and 3.4 Hz, 6-H), 2.22 (1H, m, 16-H), 2.18 (1H, dd, J = 16.0 and 3.4 Hz, 6-H), 1.60 (3H, d, J = 6.6 Hz, 18-H_3). ^{13}C-nmr (125.65 MHz, $CDCl_3$) δ : 174.6 (s, C-2), 74.1 (d, C-3), 56.4 (d, C-5), 34.2 (t, C-6), 54.3 (s, C-7), 123.0 (s, C-8), 126.0 (d, C-9), 108.0 (d, C-10),

160.2 (s, C-11), 94.6 (d, C-12), 139.9 (s, C-13), 30.0 (t, C-14), 34.2 (d, C-15), 34.7 (d, C-16), 67.0 (t, C-17), 12.6 (q, C-18), 117.7 (d, C-19), 139.4 (s, C-20), 41.1 (t, C-21), 63.4 (q, N_1-OMe), 55.6 (q, OMe). Ms *m/z* : 370 (M^+, 29%), 339 (14), 164 (86), 108 (100).

Preparation of 11-Methoxygelsemamide (2) Sodium methoxide (6.7 mg, 0.124 mmol) was added to a solution of humantenirine (4) (9.2 mg, 0.025 mmol) in dry methanol (1 ml) at 0°C and the mixture was heated under reflux for 5 h. Additional sodium methoxide (2.7 mg, 0.050 mmol) was added to the reaction mixture at 0°C and the mixture was then heated for 6 h. Cold water was added to the mixture and the whole was extracted with chloroform. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by SiO_2 open column chromatography with ethyl acetate-hexane (1:1) to afford 11-methoxygelsemamide (**2**) (7.2 mg, 78%) as prism. m.p. 141-142 °C (MeOH) (lit.[2] 140 °C). $[\alpha]_D^{22}$ +215° (*c* 0.145 in MeOH) {lit.[2] $[\alpha]_D$ +215.5° (*c* 0.2 in MeOH)}. Uv (EtOH) : 283, 212 nm. ^{1}H-nmr (500MHz, $CDCl_3$) δ : 9.67 (1H, s, N_1-H), 7.06 (1H, d, *J* = 8.5 Hz, 9-H), 6.88 (1H, dd, *J* = 2.8 and 0.9 Hz, 12-H), 6.39 (1H, br-dd, *J* = 8.5 and 2.7 Hz, 10-H), 5.35 (1H, qt, *J* = 6.9 and 2.7 Hz, 19-H), 4.74 (1H, br-d, *J* = 17.1 Hz, 21-H), 4.67 (1H, br-d, *J* = 4.7 Hz, 3-H), 4.19 (1H, dd, *J* = 10.4 and 2.5 Hz, 17-H), 3.98 (1H, dd, *J* = 9.0 and 4.9 Hz, 5-H), 3.85 (1H, dd, *J* = 10.4 and 1.8 Hz, 17-H), 3.80 (3H, s, OMe), 3.64 (3H, s, N_1-OMe), 3.51 (1H, br-d, *J* = 17.1 Hz, 21-H), 2.55 (1H, d, *J* = 11.5 Hz, 6-H), 2.45 (2H, m, 14-H and 15-H), 2.32 (1H, dd, *J* = 11.5 and 5.4 Hz, 6-H), 2.24 (1H, m, 16-H), 1.85 (1H, m, 14-H), 1.57 (3H, dt, *J* = 6.9 and 1.5 Hz, 18-H3). ^{13}C-nmr (125.65 MHz, $CDCl_3$) δ : 181.8 (s, C-2), 79.7 (d, C-3), 54.2 (d, C-5), 31.6 (t, C-6), 60.5 (s, C-7), 117.3 (s, C-8), 128.3 (d, C-9), 105.1 (d, C-10), 160.1 (s, C-11), 99.7 (d, C-12), 149.0 (s, C-13), 32.7 (t, C-14), 37.3 (d, C-15), 36.6 (d, C-16), 68.2 (t, C-17), 12.7 (q, C-18), 119.2 (d, C-19), 140.7 (s, C-20), 42.1 (t, C-21), 62.2 (q, N_1-OMe), 55.2 (q, OMe). Ms *m/z* : 370 (M^+, 89%), 339 (100), 295 (21), 174 (22), 162 (51), 132 (34), 117 (24), 109 (29), 91 (32), 79 (34), 77 (39). High ms (Fab, NBA) Calcd for $C_{21}H_{26}N_2O_4$, 370.1893. Found 370.1892. Cd Δε nm (*c* 0.27 mmol/l, MeOH, 25 °C) : -4.4 (286), +24.4 (239).

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