Synthesis of Benzo[*c*][1,8]phenanthrolin-6-one Through Cyclization of *N*-(Isoquinol-5-yl)-2-bromo-benzamide Derivatives.

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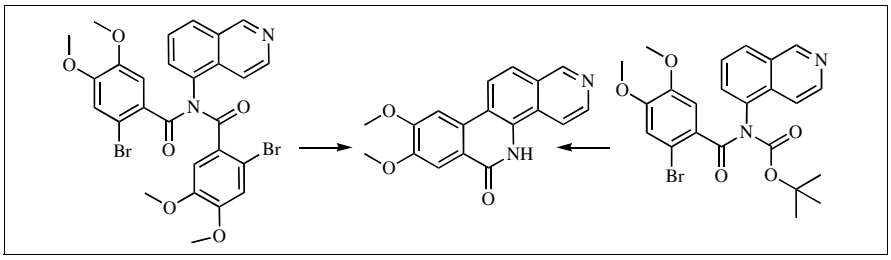

In the course of our search for compounds with potential antitumor properties we have undertaken the synthesis of benzo[*c*][1,8]phenanthroline derivatives. Our project required the preparation of 8,9-dimethoxy benzo[*c*][1,8]phenanthrolin-6-ones. This was first attempted by the lithiumdiisopropylamide cyclization of *N*-(isoquinol-5-yl)-2-bromo-4,5-dimethoxybenzamide. The reaction led to 40% of the unexpected internal Diels-Alder adduct 3,4-dimethoxy-6*H*-pyrido[2,3-*i*]6,8a-ethenoindolo[*cd*]isoquinoline-2(1*H*)-one, which arose from a benzyne intermediate. In a second and more successful approach, the internal biaryl palladium diacetate-assisted coupling reaction of properly *N*-protected *N*-(isoquinol-5-yl)-2-bromo-4,5-dimethoxybenzamide was studied. The optimisation of the protecting group necessary for this procedure led to a 64% yield of the target compound starting from *N,N*-(isoquinol-5-yl)-*bis*-(2-bromo-4,5-dimethoxybenzamide).

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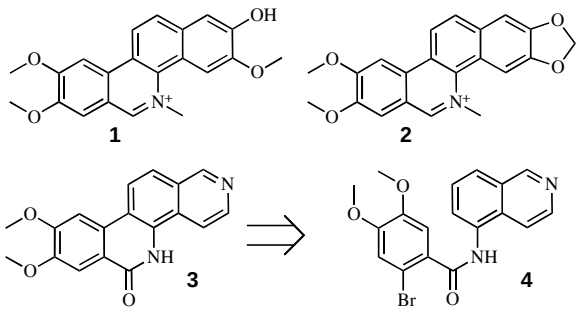
The phenanthridine nucleus is found in a variety of natural alkaloids as well as in synthetic compounds of biological importance [1-3]. Since 1970, the benzo[*c*]-phenanthridine alkaloids have been the focus of interest for their biological effects such as their potential antitumor properties [4,5]. A topoisomerase I inhibition has been described in the case of fagaronine (**1**), nitidine (**2**) [6-8] as well as synthetic compounds also featuring the benzo[*c*]phenanthridine ring system [9,10]. Recently LaVoie's group developed many cytotoxic benzo[*i*]phenanthridines, dibenzo[*c,h*]cinnoline derivatives and novel 5*H*-dibenzo[*c,h*]1,6-naphthyridin-6-one derivatives with antitumor effects [11-18]. All these compounds are strong topoisomerase I inhibitors. With the aim of synthesizing new antitumoral compounds, we attempted to replace the benzo[*c*]phenanthridine ring system by a benzo[*c*][1,8]-phenanthroline [19]. We report in this paper our results on the synthesis of the benzo[*c*][1,8]phenanthrolin-6-one **3** *via* the key cyclization of *N*-(isoquinol-5-yl)-2-bromo-4,5-dimethoxybenzamide (**4**) either using the Kessar benzyne cyclization [20, 21] or a palladium-assisted intramolecular biaryl coupling reaction [22].

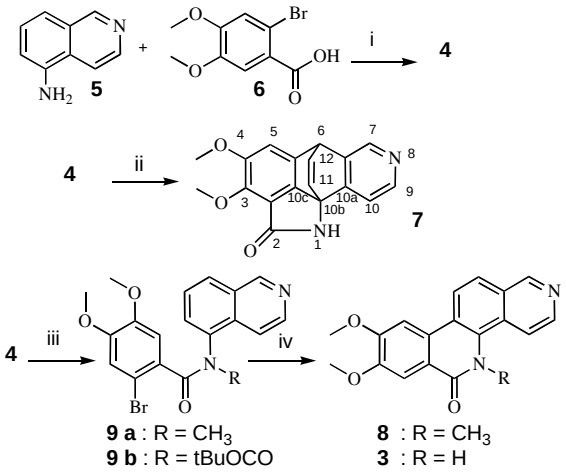
Scheme I



The preparation of the benzamide **4** was achieved by the reaction of 5-aminoisoquinoline (**5**) with the chloride of acid **6** which was prepared using thionyl chloride. In a first cyclization attempt we used the lithium diisopropylamide-mediated method as reported by Kessar for the synthesis of benzophenanthridines [23]. Unexpectedly, these conditions led to 40% of the 3,4-dimethoxy-6*H*-pyrido[2,3-*i*]6,8a-ethenoindolo[*cd*]isoquinoline-2(1*H*)-one (**7**) along with traces of the target compound **3** and unreacted material **4**. Compound **7** results from an internal Diels-Alder reaction between a benzyne intermediate and the isoquinoline ring system. The structure was established by an extensive NMR study and it is noteworthy that such cycloaddition has actually been reported previously in a related case [24]. In a second approach, a palladium-assisted intramolecular biaryl coupling reaction reported by Harayama for the synthesis of several *N*-substituted benzo[*c*]phenanthridin-6-one was attempted [25-29]. From the unprotected amide **4** no cyclized compound **3** could be detected as trials only

led to the recovery of the starting material. This confirmed the necessity of the protection of this amide function to achieve the cyclization. The *N*-methylated amide **9a** was obtained by alkylation of **4** and subjected to the palladium-assisted cyclization conditions. As previously described for the synthesis of various lactams, the suggested mechanism of this reaction involves first a palladium oxidative insertion into the carbon-halogen bond which can be followed by an intramolecular regioselective C-H activation [30-33]. From the highly polar reaction products we could isolate 44% of the target *N*-methyl benzo[*c*][1,8]phenanthrolin-6-one **8**. However, since a *N*-demethylation of this compound without any *O*-demethylation remains a challenge, we prepared the *Boc*-protected amide **9b** by treatment of **4** with di-*tert*-butyl dicarbonate [34]. The palladium-assisted cyclization of **9b** led to the unprotected target compound **3**. Thus a *Boc* protecting group turned out to resist the cyclization reaction although it is readily cleaved on the reaction product. The low 26% yield observed reflects, aside from the fact that compound **3** is highly polar, the difficulties encountered in the treatment of this reaction in which the palladium salt is used quantitatively.

Scheme II

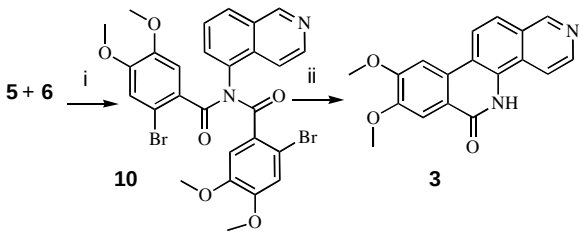


i : $SOCl_2$,4-DMAP ; ii : LDA, THF ; iii : Boc_2O, 4-DMAP or NaH, CH_3I; iv : Ag_2CO_3, DPPP, $PdOAc_2$, *t*-Bu_3P

Another option arose as, in the course of an alternate preparation of amide **4** using the carbodiimide EDCI, we could isolate not only 20% of **4** but also 32% of the bisbenzamide **10**. Thus, we used this already protected precursor and, under the previous palladium-assisted cyclization conditions, we obtained the target benzo[*c*]-[1,8]phenanthrolin-6-one **3** in a much improved 64% yield.

In conclusion, this preliminary study of the cyclization of *N*-(isoquinol-5-yl)-2-bromo-benzamide led us to investigate the reaction products using either a strong base or a palladium-assisted method. In the first instance we could isolate the product of an unexpected internal Diels Alder reaction between a benzyne and an isoquinoline. In the second approach we demonstrated that a *Boc* protecting group is compatible with the palladium-assisted cyclization method. Moreover, the much better yield of the benzo[*c*][1,8]phenanthrolin-6-one **3** obtained from bisbenzamide **10** paves the way for an efficient preparation of original benzo[*c*][1,8]phenanthroline analogues of the antitumor benzo[*c*]phenanthridine alkaloids.

Scheme III



i : EDCI, 4-DMAP ; ii : Ag_2CO_3, DPPP, $PdOAc_2$, *t*-Bu_3P

EXPERIMENTAL

Melting points were determined on a hot stage Reichert microscope and are uncorrected. Mass spectra (MS) were recorded with a Nermag R-10-10C spectrophotometer using desorption-chemical ionization (DCI-MS; reagent gas: NH_3). UV spectra were (λ_{max} in nm) recorded in spectroscopic grade MeOH on a Beckman DU 640 apparatus. IR Spectra (vmax in cm^{-1}) were obtained from potassium bromide pellets or sodium chloride films on a Perkin-Elmer 257 instrument. Elemental analysis was determined by the microanalyses service of Pierre and Marie Curie University. NMR spectra were recorded at 300 or 400 MHz (^{1}H NMR) and at 75 or 100 MHz (^{13}C NMR) using a Bruker AVANCE-400 and AC-300 spectrometers. The chemical shifts are reported in ppm (δ), and coupling constant (*J*) values are given in hertz (Hz), relative to solvent peaks as internal standards (δ: $CDCl_3$: 7.27 (^{1}H), 77 (^{13}C); DMSO-d_6: 2.50 (^{1}H), 40.6 (^{13}C)). Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), dd (doubledoublet), td (tripledoublet), m (multiplet). All the ^{1}H and ^{13}C signals were unambiguously assigned using 2D NMR techniques. Column chromatographies were performed on Merck silica gel 35-70 μM or 20-45 μM.

General Procedure for Amidation.

Method A.

A solution of thionyl chloride (40.0 mmol, 3.00 mL) was added dropwise to 2-bromo-4,5-dimethoxybenzoic acid (**6**) (4.0 mmol, 1.00 g) dissolved in dichloromethane (150.00 mL, distilled over phosphorus pentoxide). The reaction was stirred at reflux during two hours. The volatiles were removed *in vacuo* and the resulting residue diluted with dichloromethane (150.00

mL). 5-Amino-isoquinoline (**5**) (4.00 mmols, 0.41 g) and 4-dimethylaminopyridine (4-DMAP) (4.00 mmols, 0.32 g) were added and the suspension was stirred at room temperature for 12 hours. The mixture was washed with water, made basic with concentrated sodium hydroxide and then extracted with dichloromethane. The organic layers were dried over magnesium sulfate and then evaporated to dryness under reduced pressure. Trituration of the residue in ethyl acetate followed by a filtration lead to compound **4** in 32% yield.

2-Bromo-*N*-isoquinol-5-yl-4,5-dimethoxybenzamide (**4**).

This compound was obtained as amorphous white solid, ir (potassium bromide): NH 3448, CO 1637, 1535, 1245, C-Br 1026. uv: λ max 288 nm (log ε 3.10); λ max 322 nm (log ε 2.90) ; λ max 353 nm (log ε 2.0). ^{1}H nmr ($CDCl_3$) : δ 9.20 (s, 1H, 1-H), 8.50 (d, 1H, 3-H, J = 6 Hz), 8.46 (s, 1H, NH), 8.33 (d, 1H, 6-H, J = 7 Hz), 7.78 (d, 1H, 8-H, J = 8 Hz), 7.74 (d, 1H, 4-H, J = 6 Hz), 7.60 (dd, 1H, 7-H, J = 7, 8 Hz), 7.43 (s, 6'-H, 1H), 7.00 (s, 1H, 3'-H), 3.87 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3). ^{13}C nmr (CDCl3) : δ 165.2 (CO), 153.2 (C1), 151.6 (C4'), 148.4 (C5'), 143.6 (C3), 131.8 (C8a), 129.7 (C4a), 129.2 (C5) 128.5 (C1'), 127.3 (C7), 125.3 (C8), 124.2 (C6), 116.0 (C3'), 114.1 (C6'), 113.8 (C4), 109.9 (C2'), 56.5 (OCH_3), 56.3 (OCH_3). ms : m/z : 387, 389 (M+H).

Method B.

In dichloromethane (65.00 mL, distilled over phosphorus pentoxide) under an inert atmosphere, acid (3.8 mmol, 1.00 g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (3.8 mmol, 0.73 g), 4-DMAP (3.8 mmol, 0.46 g) and 5-amino-isoquinoline (**5**) (3.8 mmol, 0.55 g) were added successively. This was stirred at room temperature during 24 hours. The mixture was made acid with aqueous hydrochloric acid 1 *M* and then extracted with dichloromethane. The organic layers were dried over magnesium sulfate and then evaporated to dryness under reduced pressure. Trituration of the reaction mixture in ethyl acetate followed by filtration lead to compound **10** in 27% yield. The aqueous layer was then cautiously made basic to pH 12 with concentrated sodium hydroxide and extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate, evaporated to dryness under reduced pressure. A trituration of the mixture reaction in ethyl acetate followed by a filtration lead to compound **4** in 20% yield.

bis-(2-Bromo-4,5-dimethoxybenzoyl)(isoquinolin-5-yl)azane (**10**)

This compound was obtained as amorphous white solid, ir (potassium bromide): 2579, NH-CO 1716, CO 1630, C-Br 1021 cm^{-1}. uv: λ max 202 nm (log ε 8.20); λ max 279 nm (log ε 7.30). ^{1}H nmr ($CDCl_3$): δ 9.27 (s, 1H, H1), 8.66 (d, 1H, 3-H, J = 5 Hz), 8.12 (d, 1H, 4-H, J = 5 Hz), 7.92 (dd, 1H, 8-H, J = 7, 1 Hz), 7.78 (dd, 1H, 6-H, J = 7, 1 Hz), 7.56 (t, 1H, 7-H, J = 7 Hz), 7.43 (s, 2H, 3'-H+ 3''-H), 6.90 (s, 2H, 6'-H+ 6''-H), 3.87 (s, 6H, 2 x OCH_3), 3.65 (s, 6H, 2 x OCH_3). ^{13}C nmr ($CDCl_3$): δ 165.3 (CO), 153.2 (C1), 151.5/148.8 (C4'+ C4''/C5' + C5''), 143.6 (C3), 131.8 (C8a), 129.7 (C4a), 129.2 (C5) , 128.5 (C1'+ C1''), 127.3 (C6), 125.3 (C8), 124.2 (C7), 116.0 (C3' + C3''), 114.1 (C4), 113.7 (C6' + C6''), 109.9 (C2' + C2''), 56.4 (OCH_3), 56.3 (OCH_3). ms: m/z : 629, 631, 633 (M+H).

2-Bromo-*N*-methyl-(isoquinol-5-yl)-4,5-dimethoxybenzamide (**9a**).

Sodium hydride (50% in oil 1.2 mmol, 0.06 g) was dissolved in dry dimethylformamide (10.00 mL) and **4** (0.4 mmol, 0.15 g) was slowly added. Methyl iodide (1.2 mmol, 64.60 mL) was added and the suspension was stirred for one hour. After removal of the solvent under reduced pressure, the residue was dissolved in dichloromethane (50.00 mL) and washed with brine (50.00 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. Column chromatography of the residue over silica gel (eluent: dichloromethane/methanol 90/10) afforded **9a** as an amorphous white solid (0.11 g , 71%,). ir (potassium bromide): 2443, CO 1660, 1504, 1252, C-Br 1021 cm^{-1}. uv: λ max 205 nm (log ε 3.70) ; λ max 270 nm (log ε 3.80). ^{1}H nmr ($CDCl_3$): δ 9.36 (s, 1H, 1-H), 8.64 (d, 1H, 3-H, J = 6 Hz), 7.86 (m, 2H, 8-H and 4-H), 7.67 (d, 1H, 6-H, J = 7 Hz), 7.47 (t, 1H, 7-H, J = 7 Hz), 6.78 (s, 1H, 3'-H), 6.36 (s, 1H, 6'-H), 3.70 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.24 (s, 3H, N-CH_3). ^{13}C nmr ($CDCl_3$): δ 169.4 (CO), 153.0/149.5 (C4'/C5'), 147.3 (C1), 143.8 (C3), 130.8 (C8a), 130.0 (C6), 129.6 (C4a) 128.8 (C5), 128.0 (C8), 127.8 (C1'), 127.3 (C7), 115.5 (C3'), 115.3 (C4), 110.5 (C2'), 110.2 (C6'), 55.9 (OCH_3), 55.5 (OCH_3), 30.8 (N-CH_3). ms: m/z : 401, 403 (M+H).

2-Bromo-*N*-*tert*-butyloxycarbonyl-*N*-(isoquinol-5-yl)-4,5-dimethoxybenzamide (**9b**).

Triethylamine (0.2 mmol, 0.34 mL) was added dropwise in a solution of **4** (0.2 mmol, 0.03 g) in dichloromethane at room temperature. Di-*tert*-butyl dicarbonate (0.5 mmol, 0.12 mL) and 4-DMAP (0.2 mmol, 0.03 g) were then added and the suspension was stirred for one hour at room temperature. The solvents were removed under reduced pressure and the residue was purified by a flash chromatography on silica gel eluting with dichloromethane/methanol (90/10 v/v) to afford **9b** as white crystal (0.12 g, quant.) m.p. = 101-102°C. ir (potassium bromide): 2299, 1740,CO 1682, 1255 cm^{-1}. uv: λ max 216 nm (log ε 4.4) ; λ max 273 nm (log ε 3.2). ^{1}H nmr ($CDCl_3$): δ 9.34 (s, 1H, 1-H), 8.61 (d, 1H, 3-H, J = 6 Hz), 8.04 (d, 1H, 8-H, J = 8 Hz), 7.82 (d, 1H, 6-H, J = 7 Hz), 7.71 (m, 2H, 4-H and 7-H), 7.02 (s, 1H, 3'-H), 7.01 (s, 1H, 6'-H), 3.91 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 1.20 (s, 9H, 3 x CH_3). ^{13}C nmr (CDCl3): δ 170.0 (CO), 153.0 (C1), 151.7 (CO-(Boc)), 150.8/148.6 (C4'/C5'), 144.0 (C3), 134.6 (C8a), 133.7 (C4a), 130.7 (C5), 130.3 (C6), 129.3 (C1'), 128.4 (C8), 127.1 (C7), 115.4 (C3'), 115.0 (C4), 112.0 (C6'), 109.9 (C2'), 84.2 ($C(CH_3)_3$), 56.3 (2 x OCH_3), 27.8 ($C(CH_3)_3$). ms: m/z : 487, 489 (M+H).

Anal. Calcd. for $C_{22}H_{23}BrN_2O_5.H_2O$. C, 56.54; H, 4.83; N, 5.90. Found C, 56.67; H, 4.72; N, 5.75.

3,4-Dimethoxy-*6H*-6,10b-ethenoindolo[1,7-*fg*]isoquinolin-2(1*H*)-one (**7**).

Under an inert atmosphere (argon), a 2 *M* lithium diisopropylamide solution in tetrahydrofuran (4.0 mmols, 2.00 mL) was added at -78°C under argon to a solution of the compound **4** (0.7 mmol, 0.26 g) in anhydrous tetrahydrofuran (16.00 mL, distilled over sodium/benzophenone). The reaction mixture was stirred at -78°C for 4 hours and allowed to warm to room temperature within 16 hours. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in dichloromethane (50.00 mL) and washed with water (50.00 mL). The organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure. Column

chromatography of the residue over silica gel (eluent: dichloromethane/methanol 90/10) afforded **7** as white crystals (0.08 g, 31%). m.p. = 298°C. ir (potassium bromide): NH 3405, CO 1671, 1456, 1385 cm^{-1}. uv (in MeOH): λ max 213 nm (log ε 2.79); λ max 262 nm (log ε 3.02); λ max 342 nm (log ε 2.29); λ max 361 nm (log ε 2.18); λ max 318 nm (log ε 2.11). ^1H nmr (DMSO-d_6): δ 9.61 (s, 1H, NH), 8.62 (s, 1H, 7-H), 8.33(d, 1H, 9-H, J = 5 Hz), 7.43 (d, 1H, 10-H, J = 5 Hz), 7.13 (dd, 1H, 12-H, J = 7, 5 Hz), 6.90 (d, 1H, 11-H, J = 5 Hz), 6.89 (s, 1H, 5-H), 5.88 (d, 1H, 6-H, J = 7 Hz), 4.10 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3). ^{13}C nmr (DMSO-d_6) : δ 171.3 (CO), 153.2 (C10a), 152.1 (C4), 148.4 (C3), 148.3 (C10c), 147.0 (C9), 142.6 (C7), 140.2 (C6a) 140.0 (C12), 137.8 (C11), 128.1 (C5a), 118.5 (C2a), 114.7 (C10), 108.8 (C5), 66.3 (C10b), 60.3 (OCH_3), 56.8 (OCH_3), 42.7 (C6). ms : m/z : 307 (M+H).

Anal. Calcd. for $C_{18}H_{14}N_2O_2.H_2O$. C, 66.66; H, 4.97; N, 8.64. Found C, 66.92; H, 4.49; N, 8.60.

General Procedure for Cyclization Reaction of Amide **9a** or **9b**.

Under an inert atmosphere silver carbonate (0.8 mmol, 0.16 g) and [1,3-bis-diphenylphosphino)propane] (DPPP) (0.40 mmol, 0.16 g) were successively added to a solution of amide **9a**-**9b** (0.4 mmol) in dimethylformamide (35.00 mL dried over 4 Å molcules sieves). Tributylphosphine (*t*-Bu_3P) (0.4 mmol, 0.10 mL) was then added dropwise prior to the addition of palladium (II) acetate ($Pd(OAc)_2$) (0.40 mmol, 0.08 g). The reaction mixture was heated at reflux during 12 hours. After cooling at room temperature, the undissolved material was removed by filtration. The solvents were then removed using a high vacuum pump. A trituration of the residue in dichloromethane followed by a filtration lead to compound **3** or **8** in 26 and 44% yield, respectively.

8,9-Dimethoxybenzo[*c*][1,8]phenanthrolin-6-one (**3**).

This compound was obtained as an amorphous yellow solid, ir: NH 1664, CO 1652, 1285 cm^{-1}. uv: λ max 260 nm (log ε 3.80); λ max 280 nm (log ε 3.70); λ max 216 nm (log ε 3.0). ^1H nmr ($CDCl_3$): δ 10.1 (s, 1H, NH), 9.35 (s, 1H, 1-H), 8.74 (d, 1H, 3-H, J = 6 Hz), 8.32 (d, 1H, 11-H, J = 9 Hz), 8.11 (d, 1H, 4-H, J = 6 Hz), 8.01 (s, 1H, 7-H), 7.87 (d, 1H, 12-H, J = 9 Hz), 7.74 (s, 1H, 10-H), 4.17 (s, 3H, OCH_3), 4.10 (s, 3H, OCH_3). ^{13}C nmr ($CDCl_3$): δ 161.9 (CO), 154.7/151.2 (C8/C9), 152.9 (C1), 144.0 (C3), 131.3 (C4b), 129.9 (C10a), 128.5 (C4a) 126.5 (C12a), 123.9 (C12), 122.3 (C11), 120.3 (C6a), 117.7 (C10b), 116.2 (C4), 108.8 (C7), 105.9 (C10), 56.8 (2 x OCH_3). ms: m/z : 307 (M+H).

N-Methyl-8,9-dimethoxybenzo[*c*][1,8]phenanthrolin-6-one (**8**).

This compound was obtained as an amorphous yellow solid, ir (potassium bromide): CO 1649, 1514, 1370, 765 cm^{-1}. uv: λ max 214 nm (log ε 2.40); λ max 268 nm (log ε 3.20). ^1H nmr ($CDCl_3$): δ 9.36 (s, 1H, 1-H), 8.64 (d, 1H, 3-H, J = 6 Hz), 8.60 (d, 1H, 11-H, J = 9 Hz), 8.34 (d, 1H, 4-H, J = 6 Hz), 8.22 (s, 1H, 7-H), 7.99 (d, 1H, J = 9, 12-H), 7.69 (s, 1H, 10-H), 4.16 (s, 3H, N-CH_3), 4.08 (s, 3H, OCH_3), 4.06 (s, 3H, OCH_3). ^{13}C nmr ($CDCl_3$): δ 163.5 (CO), 153.7(C1), 151.8 (C8/C9), 150.8 (C3), 135.2 (C4b), 34.2 (C10a), 128.0 (C4a) 127.8 (C12a), 122.9 (C12), 121.6 (C11), 120.4 (C4), 120.1 (C6a), 113.6 (C10b), 108.8 (C7), 103.4 (C10), 56.8 (2 x OCH_3), 35.2 (N-CH_3). ms: m/z : 321 (M+H).

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