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SYNTHESIS OF DERIVATIVES OF CHLORIN P_6 TRIMETHYL ESTER

Guang-Fan Han, Wei Dai, Wen-Tao Zhang, Zheng Xing, and Yu-Yuan Zhao

School of Material Science and Engineering, Jiangsu University of Science and Technology, Zhenjiang, Jiangsu, China

The Vilsmeier reaction of nickel(II) chlorin P_6 trimethyl ester with 3-dimethyl-amino-acrolein yielded nickel(II) chlorin P_6 20-(2-formylvinyl) trimethyl ester and nickel(II) chlorin P_6 3-(1-hydroxyethyl)-3-devinyl-20-(2-formylvinyl) trimethyl ester. Also, the outgrowths of nickel(II) chlorin P_6 20-(2-formyl) trimethyl ester and nickel(II) chlorin P_6 3-(2-formylvinyl)-3-devinyl-20-(2-formyl) trimethyl ester were obtained by Vilsmeier reaction with dimethylformamide. By treating the derivatives of nickel(II) 20-(2-formyl)-chlorin and nickel(II) 3-(2-formylvinyl)-20-(2-formyl)-chlorin with trifluoracetic acid, the removal of the central nickel(II) ion was accomplished. The derivatives of 20-(2-formyl)-chlorin and 3-(2-formylvinyl)-20-(2-formyl)-chlorin demonstrated considerable bathochromic shift of the major absorption band in the red region of the optical spectrum.

Keywords: Chlorin P_6 trimethyl ester; formyl-; formylvinyl-; photodynamic therapy; Vilsmeier reaction

Photodynamic therapy (PDT) is a very active field treatment the modality for cure of tumors, based on the formation of reactive species by illuminating a photosensitizer in the presence of oxygen.[1] PDT utilizes the ability of a selectively retained photosensitizer to elicit an efficient photodynamic reaction upon activation with tissue-penetrating light. An ideal photosensitizer should have definite structure in chemistry, good amphiphilicity, reasonable stability, and lack of toxic compounds with longer wavelength absorption near or beyond 700 nm.[2,3] As the degradation products of a natural product, chlorophyl, chlorins derivatives have a good tumor photodynamic curative effect.[4]

From early research in relative compound of chlorins, the presence and position of the substitutes in the parent chlorins made a remarkable difference in biological activities.[5] It has great influence in bioactivity by the substituent at the 20-meso-position hydrogen of chlorines.[7–10] Substituents at the 3-position and 20-meso-position can extend absorption wavelength of visible spectra, which is an important parameter to measure anticancer efficacy in PDT.[4,6] In our experiment,

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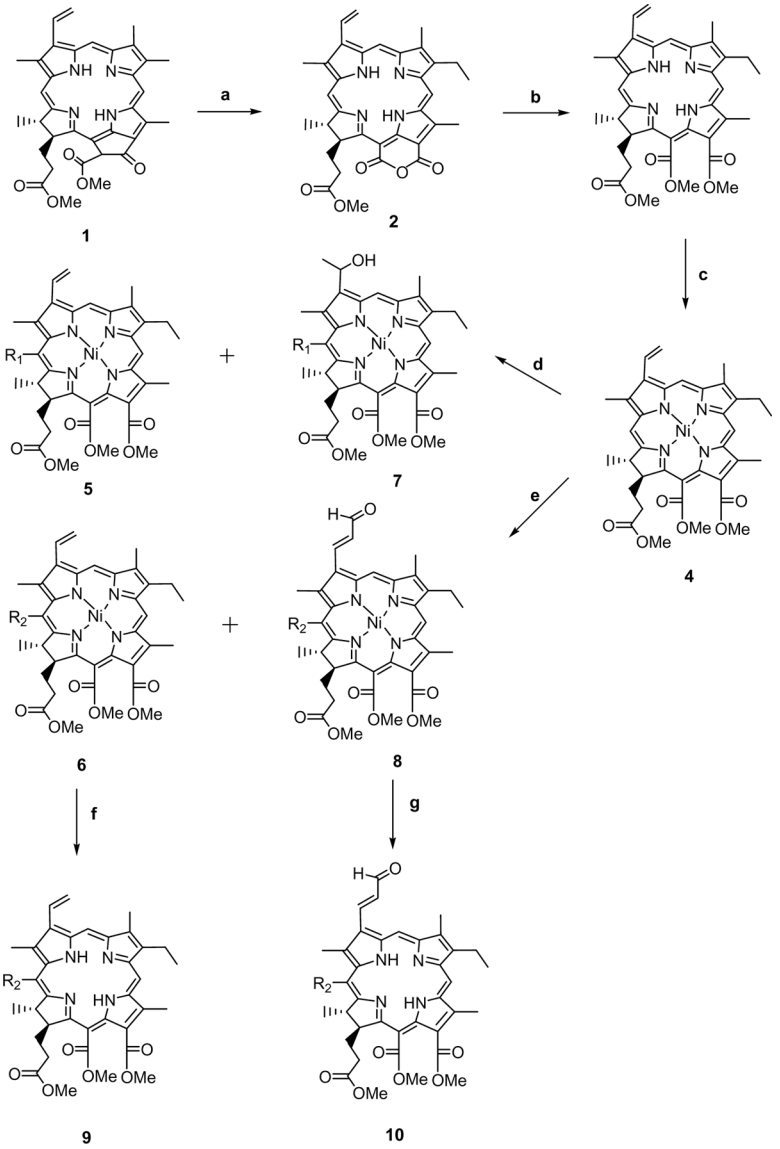
Address correspondence to Guang-Fan Han, School of Material Science and Engineering, Jiangsu University of Science and Technology, Zhenjiang, Jiangsu, China. E-mail: gf552002@yahoo.com.cn

formyl and formylvinyl structures were selected as substituted function groups introduced to the 20-meso-position and the 3-position in the conjugated region and electron-withdrawing formyl group to extend absorption wavelength. In this work, several novel derivatives (**5**–**10**) of chlorin P_6 trimethyl ester were obtained by the Vilsmeier reaction (Scheme 1).



Scheme 1. $R_1 = CH{=}CHCHO$; $R_2 = CHO$ (a) air, Et_2O, propanol, KOH, rt; (b) $NaOH/CH_3OH$, rt; (c) $Ni(AcO)_2$, 65°C; (d) $DMF/POCl_3$, 0°C; (e) 3-DMA/$POCl_3$, 0°C; (f) TFA, rt; and (g) TFA, rt.

RESULTS AND DISCUSSION

In our approach, methyl pheophorbide-*a* (MP-*a*, **1**) was used as a starting material and converted into purpurin-18-methyl ester (**2**) by atmospheric oxidization. Chlorin P_6 trimethyl ester (**3**) was obtained by reaction with NaOH from **2** in methanol solution in good yield. Then, the reaction of **3** with excess nickel acetate in methanol was employed after reflux for 12 h, **3** was converted into its nickel complex (**4**) (Scheme 1). The maximum absorption of compound **4** was observed at 666 nm.

Nickel(II) chlorin P_6 20-(2-formylvinyl) trimethyl ester (**5**) and nickel(II) chlorin P_6 3-(1-hydroxyethyl)-3-devinyl-20-(2-formylvinyl) trimethyl ester (**7**) were prepared by the treatment of **4** with dimethylformamide (DMF) in $POCl_3$ at 0°C (Scheme 1). In the correlation (COSY) spectrum of **5**, one hydrogen at δ 7.42 (dd, $J = 11.4$ Hz, 17.75 Hz) is coupled to one hydrogen at δ 5.93 (d, $J = 11.35$ Hz) and the other hydrogen at δ 5.8 (d, $J = 17.8$ Hz). It is clear that the peaks at δ 7.42, δ 5.93, and δ 5.8 are due to the hydrogen atoms of the vinyl group in position 3 of compound **5**. Two hydrogen atoms at δ 3.3 are coupled to the three hydrogen atoms at δ 1.4. It is quite obviously the ethyl group in position 8. One hydrogen atom at δ 4.3 is coupled to the three hydrogen atoms at δ 1.3, which showed the H18 and the methyl group at C18. Two hydrogen atoms at δ 1.7 are coupled to the two hydrogen atoms at δ 2.3 and one hydrogen atom at δ 5.0, which allowed us to assign the H17 and the ethyl group at C17. The 2-formylvinyl group in position 20 was confirmed by the coupling relationship between the hydrogen at δ 5.7 (dd, $J = 7.8$ Hz, 15.35 Hz) and δ 9.6 (d, 7.79 Hz), δ 8.2 ($J = 15.31$ Hz). In the ^{1}H NMR spectra of **5**, two singlet peaks at δ 8.7 and δ 8.6 with one-proton intensity were assigned to H5 and H10 respectively, and the six singlet peaks to the methyl groups at C2, C7, and C12 and three ester groups. Mass spectra of compound **5** exhibited an intensive peak of molecular ions, m/z 735.4 [M^+]. As the COSY spectrum of **7** shows, one hydrogen atom at δ 5.8 is coupled to the three hydrogen atoms at δ 2.0. In the meantime, the mass spectra of compound **7** exhibited an intensive peak of molecular ions, m/z 753.5 [M^+], which is just larger than the molecular weight of compound **5** with 18. It is clear that the vinyl group in position 3 was converted to the hydroxyethyl group by deoxidization. The absorptions maxima of these compounds were observed at 692 and 698 nm, respectively.

A significant shift (by 26 nm) of the absorption maximum to long wavelengths was observed when a hydrogen atom in position 20 was replaced by a formylvinyl group for **5**. There is also a significant shift (by 32 nm) of the absorption maximum to long wavelengths observed when the both structures of positions 3 and 20 were changed for **7**. Constructing conjugated group at 20-meso and deoxidizing in position 3 greatly increased wavelength absorption. Nickel(II) chlorin P_6 20-(2-formyl) trimethyl ester (**6**) and nickel(II) chlorin P_6 3-(2-formylvinyl)-20-(2-formyl) trimethyl ester (**8**) were obtained from **4** by the Vilsmeier reaction with 3-dimethylaminoacrolein (3-DMA). In the ^{1}H NMR spectra of **6**, the single at δ 10.82 with one-proton intensity was assigned to the hydrogen of 20-CHO-group. The analysis of the other groups of compound **6** according to the ^{1}H NMR and COSY spectra was similar to the explanation of the compound **5**. Compound **8** is the same as **6** but one hydrogen atom of the vinyl group in the 3-position was replaced by a formyl group. In the COSY spectra of compound **8**, the coupling relationship of the

hydrogen at δ 9.9 (d, $J = 7.6$ Hz), δ 8.2 (d, $J = 16.15$ Hz), and δ 6.8 (dd, $J = 7.6$ Hz, 16.15 Hz) allowed us to assigned the structure of the 2-formylvinyl group. Mass spectra of these compounds exhibited intensive peaks of molecular ions at m/z 709.22 (**6**) and 737.32 (**8**). The absorptions maxima of these compounds are observed at 685 and 715 nm, respectively, which are significant changes compared with the absorption maximum of **4**. The treatment of **6** and **8** with dichloromethane and then trifluoroacetic acid resulted in two compounds, **9** and **10**, without the central nickel(II) ion. The Qy absorptions, as the longest absorption band in chlorin, in products **9** and **10** displayed a red shift compared with corresponding absorption band in nickel chlorin, **6** and **8**. This change was attributed to the extension of the conjugated system by removing nickel, which shortened the conjugated carbonyl group by withdrawing electron outside the macrocycle.

CONCLUSIONS

Introduction of hydroxy groups in chlorins is known to significantly change the hydrophilicity of such compounds. The hydroxyl group attached to 3-position of compound **7** was obtained by the reaction with HCl hydrolyzed by phosphoryl chloride. The Vilsmeier reaction is used in various industrial processes to attach an aldehyde group to an aromatic compound. The major product, the aldehyde group, attached to 20-meso aromatic compound nickel(II) chlorin P_6 20-(2-formyl) trimethyl ester obtained by the Vilsmeier reaction. In this reaction with dimethylformamide, the aldehyde group attached to the 3-positon, and compound **8** was unexpectedly obtained in a novel synthetic method. All the compounds (**5**–**10**) showed significant changes, which met the requirements of an improved photodynamic therapeutic agent.

EXPERIMENTAL

Methyl pheophorbide-*a* was obtained according to the Smith method, whereas purpurin-18-methyl ester and chlorin P_6 trimethyl ester followed Refs. 9 and 10, respectively.

Nickel(II) Chlorin P_6 Trimethyl Ester (4)

$Ni(AcO)_2$ in methanol (30 mL) was added to compound **3** (300 mg, 0.48 mmol) in dichloromethane (50 mL) and was then stirred at 65°C for 12 h. After it cooled, water (400 ml) was added to the mixture and then extracted with dichloromethane (20 ml). The combined organic layers were washed with water (2×50 mL) and dried over Na_2SO_4, and the solvent was removed under vacuum. After esterification by diazomethane, the residue was purified with a silica-gel column with hexane–ethyl acetate (2:1, v/v) to give **4** (60%). Mp 162–163°C. UV-vis ($CHCl_3$) λ max: 413 (1.288), 504 (0.097), 547 (0.131), 666 (0.536); ^{1}H NMR ($CDCl_3$) δ: 1.49 (d, $J = 6.8$ Hz, 3H, 18^1-Me), 1.55 (t, $J = 7.2$ Hz, 3H, 8^2-Me), 1.62–1.69 (m, 2H, 17^1-CH_2), 2.30–2.37 (m, 2H, 17^2-CH_2), 3.02, 3.02, 3.31, 3.59, 3.83, 4.13 (each s, each 3H, 18H, Me+OMe), 3.50 (q, $J = 7.2$ Hz, 2H, 8^1-CH_2), 4.01 (m, 1H, H17), 5.23 (m, 1H, H18), 5.94 (d, $J = 11.5$ Hz, 1H, 3^2-CH_2), 6.01 (d, $J = 17.7$ Hz, 1H, 3^2-CH_2), 7.70 (dd, $J = 17.8$ Hz,

11.6 Hz, 1H, 3^1−CH), 7.86 (s, 1H, H20), 9.00, 8.86 (each s, each 1H, 2H, H5 and H10); IR (KBr) υ: 1717 (C=O), 1612 (C=C) cm^{-1}. Anal. calcd. for $C_{36}H_{38}N_4NiO_6$: C, 63.46; H, 5.62; N, 8.22; found: C, 63.41; H, 5.57; N, 8.26.

Nickel(II) Chlorin P_6 20-(2-Formylvinyl) Trimethyl Ester (5)

Phosphorus oxychloride (0.8 mL, 8.0 mmol) was added dropwise to a solution of 3-dimethyl-aminoacrolein (0.8 mL, 8.0 mmol) in dichloromethane (10 mL), and the mixture was stirred at 0°C for 15 min. This mixture was then added to a solution of nickel chlorin (**4**) (250 mg, 0.36 mmol) in dichloromethane (50 mL) with continuous stirring at 0°C. The final mixture was then warmed up to room temperature and stirred for 18 h. Saturated aqueous $NaHCO_3$ (100 mL) was then added, and the solution was stirred overnight. The mixture was extracted with dichloromethane, the combined organic layers were washed with water (3×200 mL) and dried over sodium sulfate, and the solvent was removed under vacuum. The resulting residue was chromatographed on a silica-gel column with hexane–ethyl acetate (2:1, v/v) to provide **5** as green solid (45%). Mp 168–169°C; UV-vis ($CHCl_3$) λ max: 409 (0.668), 692 (0.345); ^{1}H NMR ($CDCl_3$) δ: 1.37 (d, $J = 6.8$ Hz, 3H, 18^1-Me), 1.45 (t, $J = 7.2$ Hz, 3H, 8^2-Me), 1.92–2.22 (m, 2H, 17^1-CH_2), 2.29–2.37 (m, 2H, 17^2-CH_2), 2.82, 2.89, 3.17, 3.60, 3.78, 4.01 (each s, each 3H, 18H, Me+OMe), 3.32 (q, $J = 7.2$ Hz, 2H, 8^1-CH_2), 4.37–4.41 (m, 1H, H17), 5.03–5.07 (m, 1H, H18), 5.77 (dd, $J = 15.4$, 7.8 Hz, 1H, 20^2−CH), 5.80 (d, $J = 11.2$ Hz, 1H, 3^2−CH), 5.93 (d, $J = 17.6$ Hz, 1H, 3^2−CH), 7.42 (dd, $J = 11.2$, 17.6 Hz, 1H, 3^1−CH), 8.29 (d, $J = 15.4$ Hz, 1H, 20^1−CH), 8.60, 8.70 (each s, each 1H, 2H, H5 and H10), 9.69 (d, $J = 7.8$ Hz, 1H, 20^3−CHO); EI/MS m/z (%): 735.4 (M^+, 100), 316.3 (32), 288.3 (42). IR (KBr) υ: 1726 (C=O), 1613 (C=C) cm^{-1}. Anal. calcd. for $C_{39}H_{40}N_4NiO_7$: C, 63.69; H, 5.48; N, 7.26; found: C, 63.61; H, 5.45; N, 7.69.

Nickel(II) Chlorin P_6 20-(2-Formyl) Trimethyl Ester (6)

This compound **6** was obtained from nickel chlorin (**4**) by the Vilsmeier reaction with dimethylformamide in the yield of 35% as a green solid. Mp 175–176°C, UV-vis ($CHCl_3$) λ max: 387 (0.292), 426 (0.344), 685 (0.240); ^{1}H NMR ($CDCl_3$) δ: 1.33 (d, $J = 6.8$ Hz, 18^1-Me), 1.47 (t, $J = 7.2$ Hz, 3H, 8^2-Me), 1.82–1.72 (m, 2H, 17^1-CH_2), 2.39–2.27 (m, 2H, 17^2-CH_2), 2.85, 2.96, 3.15, 3.60, 3.79, 4.08 (each s, each 3H, 18H, Me+OMe), 3.30 (q, $J = 7.2$ Hz, 2H, 8^1-CH_2), 4.72 (m, 1H, H17), 5.01 (m, 1H, H18), 5.77 (d, $J = 11.2$ Hz, 1H, 3^2−CH), 5.98 (d, $J = 17.6$ Hz, 1H, 3^2−CH), 7.41 (dd, $J = 11.2$, 17.6 Hz, 1H, 3^1−CH), 8.63, 8.50 (s, each 1H, 2H, H5 and H10), 10.82 (s, 1H, 20^1−CHO); EI/MS m/z (%): 709.22 (M^+, 100), 677.37 (24) 295.12 (16). IR (KBr) υ: 1727 (C=O), 1623 (C=C) cm^{-1}; Anal. calcd. for $C_{37}H_{38}N_4NiO_7$: C, 62.64; H, 5.40; N, 7.90; found: C, 62.61; H, 5.37; N, 7.93.

Nickel(II) Chlorin P_6 3-(1-Hydroxyethyl)-3-devinyl-20-(2-formylvinyl) Trimethyl Ester (7)

This compound was obtained with 3-dimethyl-aminoacrolein by the Vilsmeier reaction (20%) as a green solid. Mp 178–179°C; UV-vis ($CHCl_3$) λ max: 424 (0.883), 574 (0.119), 698 (0.518).^{1}H NMR($CDCl_3$) δ: 1.34 (d, $J = 7.0$ Hz, 3H, 18^1-Me), 1.43 (t,

$J = 7.62$ Hz, 3H, 8^2-Me), 1.68–1.82 (m, 2H, 17^1-CH_2), 2.02 (d, $J = 6.64$ Hz, 3^2-CH_3), 2.21–2.34 (m, 2H, 17^2-CH_2), 2.70, 2.88, 3.10, 3.58, 3.75, 4.05 (each s, each 3H, Me+OMe), 3.35 (q, $J = 7.8$ Hz, 2H, 8^1-CH_2), 4.31–4.36 (m, 1H, H18), 5.03–5.07 (m, 1H, H17), 5.65 (dd, $J = 7.7$, 15.4 Hz, 1H, 20^2-CH), 5.82 (q, $J = 6.59$ Hz, 1H, 3^1-CH), 8.25 (d, $J = 15.4$ Hz, 1H, 20^1-CH), 8.67, 9.05 (each s, each 1H, 2H, 2H, H5 and H10), 9.66 (d, $J = 7.8$ Hz, 1H, 20^3-CHO); EI/MS m/z (%): 753.5 (M^+, 100), 735.3 (15), 316.4 (18), 288.2 (27). IR (KBr) υ: 1726 (C=O), 1619 (C=C) cm^{-1}. Anal. calcd. for $C_{39}H_{42}N_4NiO_8$: C, 62.17; H, 5.62; N, 7.44; found: C, 62.12; H, 5.66; N, 7.49.

Nickel(II) Chlorin P_6 3-(2-Formylvinyl)-3-devinyl-20-(2-formyl) Trimethyl Ester (8)

This compound was obtained with dimethylformamide by the Vilsmeier reaction (25%) as a green solid. Mp 165–166°C; UV-vis ($CHCl_3$) λ max: 392 (0.200), 435 (0.217), 715 (0.199); ^{1}H NMR ($CDCl_3$) δ: 1.30 (d, $J = 6.8$ Hz, 18^1-Me), 1.45 (t, $J = 7.2$ Hz, 3H, 8^2-Me), 1.30 (d, $J = 6.8$ Hz, 18^1-Me), 2.31–2.34 (m, 2H, 17^1-CH_2), 2.41–2.44 (m, 2H, 17^2-CH_2), 2.86, 3.04, 3.13, 3.57, 3.77, 4.06 (each s, each 3H, 18H, Me+OMe), 3.28 (q, $J = 7.2$H, 2H, 8^1-CH_2), 4.75–4.78 (m, 1H, H17), 5.05–5.08 (m, 1H, H18), 6.86 (dd, $J = 7.6$, 16.15 Hz, 1H, 3^2-CH), 8.24 (d, $J = 16.15$ Hz, 1H, 3^1-CH), 8.64, 8.58 (each s, each 1H, 2H, H5 and H10), 9.95 (d, $J = 7.6$ Hz, 1H, 3^2-CHO), 10.77 (s, 1H, 20^1-CHO); EI/MS m/z (%): 737.32 (M^+, 100), 705.45 (38), 735.38 (20). IR (KBr) υ: 1732 (C=O), 1623 (C=C) cm^{-1}. Anal. calcd. for $C_{38}H_{38}N_4NiO_8$: C, 61.89; H, 5.19; N, 7.60; found: C, 61.96; H, 5.13; N, 7.58.

Chlorin P_6 20-(2-Formyl) Trimethyl Ester (9)

The nickel(II) chlorin P_6 20-(2-formyl) trimethyl ester was dissolved in dichoromethane (25 mL), and 30% TFA (25 mL) was added and stirred at room temperature. After 5 h, the reaction mixture was poured into a solution of ice water (20 mL), then extracted several times with dichloromethane (2 × 50 mL), and dried over sodium sulfate. The solvent was removed under vacuum. The resulting residue was chromatographed on a silica-gel column with hexane–ethyl acetate (2:1, v/v) to provide **9** (39%). Mp 181–182°C; UV-vis ($CHCl_3$) λ max: 417.4 (1.667), 706 nm (0.578); ^{1}H NMR ($CDCl_3$) δ: 0.37 (brs, 2H, NH), 1.35 (t, $J = 7.0$ Hz, 3H, 8^2-Me), 1.49 (d, $J = 7.5$ Hz, 3H, 18^1-Me), 2.30–2.33 (m, 2H, 17^1-CH_2), 2.40–2.43 (m, 2H, 17^2-CH_2), 2.85, 2.96, 3.15, 3.61, 3.80, 4.08, (each s, each 3H, 18H, Me+OMe), 3.32 (q, $J = 7.2$ Hz, 2H, 8^1-CH_2), 4.73–4.75 (m, 1H, H17), 4.98–5.03 (m, 1H, H18), 5.86 (d, $J = 11.2$ Hz, 1H, 3^2-CH), 5.98 (d, $J = 17.6$ Hz, 1H, 3^2-CH), 7.48 (dd, $J = 11.2$, 17.6 Hz, 1H, 3^1-CH), 8.64, 8.51 (each s, each 1H, 2H, H5 and H10), 10.82 (s, 1H, 20^1-CHO). IR (KBr) υ: 1726 (C=O), 1621 (C=C) cm^{-1}. Anal. calcd. for $C_{37}H_{40}N_4O_7$: C, 68.08; H, 6.18; N, 8.58; found: C, 68.12; H, 6.13; N, 8.56.

Chlorin P_6 3-(2-Formylvinyl)-3-devinyl-20-(2-formyl) Trimethyl Ester (10)

This compound was obtained with nickel(II) chlorin P_6 3-(2-formylvinyl)-3-devinyl-20-(2-formyl) trimethyl ester by reaction with TFA in the yield of 37%

as a green solid. Mp 174–175°C; UV-vis ($CHCl_3$) λ max: 416.4 nm (0.265), 736.8 (0.326); ^{1}H NMR ($CDCl_3$) δ: 0.70 (brs, 2H, NH), 1.47 (t, $J = 7.5$ Hz, 3H, 8^2-Me), 1.68 (d, $J = 6.8$ Hz, 3H, 18^1-Me), 2.31–2.34 (m, 2H, 17^1-CH_2), 2.41–2.44 (m, 2H, 17^2-CH_2), 2.86, 3.04, 3.13, 3.58, 3.77, 4.06 (each s, each 3H, 18H, Me+OMe), 3.33 (q, $J = 7.3$ Hz, 2H, 8^1-CH_2), 4.75–4.78 (m, 1H, H17), 5.05–5.08 (m, 1H, H18), 6.91 (dd, $J = 7.6$, 16.15 Hz, 1H, 3^2-CH), 8.28 (d, $J = 16.2$ Hz, 1H, 3^1-CH), 8.59, 8.65 (each s, each 1H, 2H, H5 and H10), 9.97 (d, $J = 7.0$ Hz, 1H, 3^2-CHO), 10.77 (s, 1H, 20^1-CHO). IR (KBr) υ: 1726 (C=O), 1614 (C=C) cm^{-1}. Anal. calcd. for $C_{38}H_{40}N_4O_8$: C 67.05, H 5.92, N 8.23; found: C, 67.08; H, 5.81; N, 8.19.

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