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A Novel 16,24-Dehydrobiladiene-*ab* System: The Reaction of Xanthobilirubic acid methyl ester with Bromine

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Summary. On treating xanthobilirubic acid methyl ester with bromine in methanol, a red bile pigment, which was assigned the hitherto unknown 16,24-dehydrobiladiene-*ab* constitution, is obtained in 20% yield. In addition, the corresponding mesobiliverdin-XIIIα, mesobilirubin-XIIIα, 14-formyl-tripyrrinone, and two diastereomeric 15,16-dimethoxybiladienes-*ab* could be isolated from the reaction mixture. The mechanistic aspects of this reaction are discussed.

Keywords. 16,24-Dehydrobiladiene-*ab*; Biladiene-*ab*; Xanthobilirubic acid methyl ester; Mesobilirubin-XIIIα; Mesobiliverdin-XIIIα; 14-Formyl-tripyrrinone; 15,16-Dimethoxy-biladienes-*ab*.

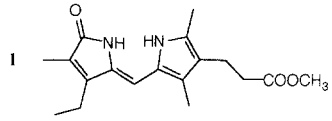
Ein neuer 16,24-Dehydrobiladien-*ab* – Chromophor: Die Reaktion von Xanthobilirubinsäuremethylester mit Brom

Zusammenfassung. Der Umsatz von Xanthobilirubinsäuremethylester mit Brom in Methanol ergibt in 20-prozentiger Ausbeute ein rotes Pigment, für das die bislang nicht bekannte 16,24-Dehydrobiladien-*ab*-Konstitution abgeleitet wurde. Darüber hinaus konnte das entsprechende Mesobiliverdin-XIIIα, Mesobilirubin-XIIIα, 14-Formyltripyrrinon, und zwei diastereomere 15,16-Dimethoxybiladiene-*ab* aus der Reaktionsmischung isoliert werden. Die mechanistischen Aspekte dieser Reaktion werden diskutiert.

Introduction

The biladiene-*ab* chromophor occurs in phycoerythrobilin, which is covalently bound to a protein to form phycoerythrin. This pigment acts together with phycocyanin and allophycocyanin as an antenna system in the photosynthetic apparatus of red and blue-green algae. The total synthesis of phycoerythrobilin was accomplished in 1978 by *Gossauer* [1]. It turned out to be much more complicated than other bile pigment syntheses, such as those of bilatrienes-*abc*, biladienes-*ac*, and bilenes-*b* [2], because of the unsymmetrical constitution of this system. There are several ways to

synthesize biladienes-*ab*: first, they are produced by the condensation of 4,5-dihydrodipyrrinones with dipyrrinones [2]; second, biladienes-*ac* undergo acid catalyzed tautomerization to yield biladienes-*ab*, or dipyrrinones condense with formaldehyde in the presence of hydrobromic acid [3]; third, oxidative rupture of porphyrins by bromine in methanol leads to 15,16-dimethoxybiladienes-*ab* [4].



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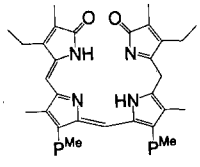
About ten years ago when *Ribó*'s group studied the bromination and nitration of dipyrrinones, amongst them xanthobilirubic acid methyl ester (**1**), they mentioned that the bromination of **1** in methanol yielded an untractable colored mixture. Following this lead, the investigation of this reaction provided an entry to a novel chromophoric system of the 16,24-dehydro-biladiene-*ab* type, which will be described in the following.

Results and Discussion

Synthetic Aspects

Bromine is used in numerous reactions of pyrrole chemistry as an oxidative agent to investigate the reactivities of bile pigments [1, 5, 6] and to synthesize verdins from 1,19-*bis*-(*tert*-butoxycarbonyl)-biladienes-*ac* or 1,19-*bis*-(*tert*-butoxycarbonyl)-bilenes-*b* [7, 8]. Treatment of **1** with bromine in methanol is known to yield mesobiliverdin (**7**) [9]. This reaction constitutes the first useful synthetic method for the preparation of symmetrically substituted rubins as advanced by *Fischer* [9]. The mechanism of this reaction could be envisaged to be similar to that of the formation of 4,5-dihydrodipyrrins by heating bromomethylpyrroles [10].



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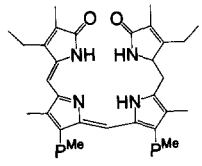

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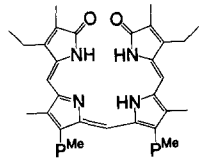

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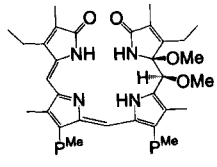

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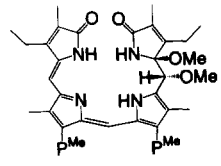

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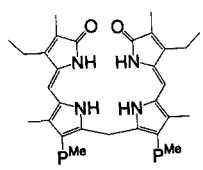

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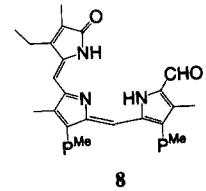

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To synthesize biladienes-*ab* as model compounds of phycoerthrobilin, the reaction of dipyrrinones, like **1**, with bromine in methanol was considered. In principle, the mesobiliverdin produced in this reaction [9] could then undergo an acid catalyzed rearrangement [5] to yield the desired chromophoric system.

A complex mixture of pigments was obtained by treating **1** with bromine in methanol. This mixture was separated by careful column chromatography on silica. The pigments were eluted in the order **8** > **5** > **4** > **2** > **6** > **7**. The resulting six pigment fractions were structurally assigned by means of spectroscopic measurements as discussed in detail below. The relative yields of the products **2** and **4–8** changed considerably with the relative amounts of bromine used as shown in Table 1. With an equimolar amount of bromine, the main product was verdin **4** with only small amounts of **2** and **5–8**. These latter materials became more prominent when bromine was used in a ratio of 1:2. However, the desired biladiene-*ab* **3** could not be detected in any of these cases. Moreover, if the reaction mixture contained additional hydrogen bromide, the relative yields changed in favor of the novel chromophoric system of **2**. The importance of this acid for the formation of pigments, especially of **2**, was proven by adding anhydrous potassium carbonate to the reaction mixture before adding bromine. Only if sufficient hydrobromic acid was added afterwards the reaction mixture turned colored and the products **2** and **4–8** were formed. Upon lowering the temperature, the yields of **6** and **7** were strongly enhanced. Addition of the acid induced also a pronounced enhancement of the methanol addition products **5** and **6** (Table 1).

Table 1. Yields (%) of pigments **2** and **4–8** from the reaction of **1** with bromine in methanol

solvent	**1**:Br_2 mol:mol	°C	time	**2**	**4**	**5**	**6**	**7**	**8**
MeOH	1:1.0	40–50	2 hr	6	33	8	4	3	5
MeOH	1:1.2	40–50	2 hr	8	28	7	6	5	4
MeOH	1:1.5	40–50	2 hr	7	25	7	6	7	5
MeOH	1:2.0	0	2 hr	9	27	6	17	18	7
MeOH	1:2.0	40–50	30 min	11	35	6	10	8	6
MeOH + a	1:2.0	30	30 min	11	27	16	14	3	8
MeOH + b	1:2.0	30	30 min	20	28	9	18	11	12
MeOH + c	1:2.0	40	30 min	20	5	8	20	5	14

a: 1 ml HBr (40%) in MeOH; b: 1 ml HBr (40%) in MeOH + 10 ml CH_2Cl_2; c: *THF* (v/v, 1:1)

Structural Assignments from Spectroscopic Data

The long wavelength absorption peak of **2** was observed at 560 nm in methanol. Upon complexation with zinc ions it was shifted to 622 nm, and upon acidification it shifted again to 566 nm. Thus, **2** displayed the characteristic behavior of biladienes-*ab*.

The ^{1}H NMR spectrum of pigment **2** in acetone-d_6 solution displayed a rather good resolution. However, in deuteriochloroform solution, in which the compound was partly protonated by a trace of acid, the resolution was low. It was remarkable that there was an AB system at 3.22 ppm, as could be corroborated by a ^{1}H, ^{1}H COSY experiment (Table 2). This indicated that there was a $-CH_2-$ group and not a $-CH=$ group at position 15, and that there was no proton in positions 14 and 16. The ^{13}C NMR spectrum showed two peaks at 155.58 and 164.33 ppm, which were assigned to two C=N carbon atoms. Usually, there is only one C=N group peak to be found in the ^{13}C NMR spectra of bile pigments [11]. The chemical shifts of the methine protons corresponded [2] to *Z*-configurations at the exocyclic double bonds.

The molecular ion peak of **2** appeared in its mass spectrum at $m/z = 614$, and the peak at $m/e = 493$ corresponded the characteristic fragment shown in Fig. 1. The high resolution mass measurement of **2** yielded its formula weight as 614.3079. This value compared favorably with the calculated one of 614.3094 for $C_{35}H_{42}N_4O_6$. Although the molecular mass of mesobiliverdin-XIIIα (**4**) was also 614, the properties of these two compounds were quite different. Thus, the constitution of **2** derived from the NMR spectra and the absorption spectrum was well in accordance with the mass spectrum. Accordingly, a bile pigment containing a dehydrolactam moiety attached to the biladiene-*ab* chromophore was obtained for the first time. Such dehydrolactam structural fragments are uncommon in bile pigments [2].

Table 2. ^{1}H, ^{1}H COSY experiment for **2** (acetone-d_6, δ relative to internal *TMS*)

Correlation peak 1			Correlation peak 2			
ppm	multiplicity	J/HZ	ppm	multiplicity	J/HZ	group
1.11	t	7.65	2.30	q	7.65	CH_2CH_3 at C-17
			2.40	q	7.65	
1.18	t	7.65	2.61	q	7.65	CH_2CH_3 at C-3
2.51	t	7.48	2.91	t	7.48	CH_2CH_2 at C-8
2.54	t	7.48	2.93	t	7.48	CH_2CH_2 at C-12
3.13	d	14.61	3.31	d	14.61	CH_2 at C-15

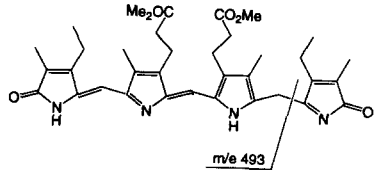
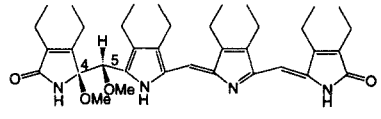


Fig. 1. Mass fragmentation of **2** by EI and FAB methods

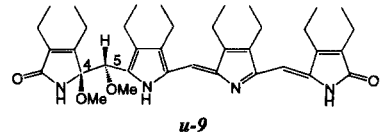
Remarkably, in the case of **2** this led to a novel chromophoric system, which was constitutionally isomeric to the bilatrienes-*abc*.

The absorption spectrum of **4** contained the typical two band system of verdins at 630 and 360 nm. The constitutional assignment of **4** followed easily from the ^{1}H NMR spectrum. Besides the characteristic signals of the methyl, methylene, and methine signals, it exhibited also those of the corresponding side chains of (*Z*, *Z*, *Z*)-mesobiliverdin-XIIIα dimethyl ester (**4**) [12].

The compounds **5** and **6** were characterized by the typical absorption spectra of biladienes-*ab*. The structural aspects of the two diastereomeric compounds **5** and **6** could also be derived mainly from their ^{1}H NMR spectra and from comparisons with those of the corresponding octaethyl derivatives [4, 6]. These two diastereomers of *l*- and *u*- configuration could be envisaged as the 4,5-methanol adducts of mesobiliverdin-XIIIα dimethyl ester (**4**). As shown in Table 3, the chemical shifts of **5** and **6** were found to be very similar to those described for *l*- and *u*-2, 3, 7, 8, 12, 13, 17, 18-octaethyl-4,5-dimethoxy-4,5-dihydro-1,19-dioxo-21*H*,24*H*-bilin (*l*-**9**, *u*-**9**) which were obtained from the oxidation of octaethylbilindione by means of various reagents [4, 6]. The methine chemical shifts were characteristic [2] of *Z* configurations at the exocyclic double bonds. The mass spectral data of **5** and **6** were also in agreement with the constitutions assigned from the NMR spectra. Moreover, **5** proved to be identical with the compound described in Ref. [13].



l-**9**



u-**9**

From the absorption spectrum of **7**, a rubinoid chromophor was immediately evident. The question about the structural details of **7** could then be settled unequivocally because the ^{1}H NMR literature data of (*Z*, *Z*)-mesobilirubin-XIIIα dimethyl ester [12] fitted well with the experimental ones.

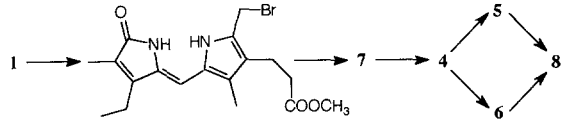
Table 3. Comparison of strategic proton chemical shifts of **5**, *l*-**9**, **6**, and *u*-**9**

Compound	5-H or 15-H	4, 5-OMe	
5	4.50	3.24, 3.41	
l-**9**	4.63	3.19, 3.47	[4]
6	4.41	2.96, 3.28	
u-**9**	4.41	2.98, 3.33	
	4.29	2.96, 3.31	[3]

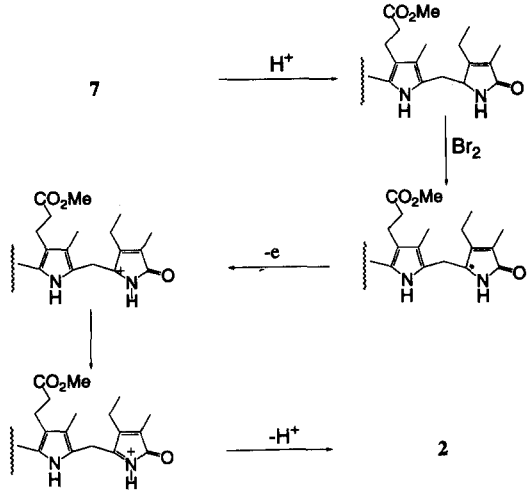
An intense absorption band at 540 nm, which shifted to 600 nm upon protonation to 630 nm and upon addition of zinc ions pointed to a tripyrrin chromophore of **8**. The formyl-tripyrrinone constitution of **8** followed then easily from its ^{1}H NMR spectrum with the formyl and methine signals as the most informative peaks. The shift regions for the latter corresponded to a *Z* configuration at the two exocyclic double bonds. As well, the constitution of the tripyrrinone **8** agreed with its mass spectral data.

Mechanistic Aspects

With respect to the reaction mechanism, we suggested that the treatment of xanthobilirubic acid methyl ester **1** with bromine in methanol would first yield the bromomethyl derivative. This intermediate could then undergo acid catalyzed self condensation in the common way of bile pigment synthesis [2] to yield mesobilirubin-XIIIα dimethyl ester (**7**). This rubin can then be oxidized by excess bromine to the verdin **4**. In the next step, methanol addition to verdin **4** resulted in the formation of the diastereomeric 15,16-dimethoxy-biladienes **5** and **6** as has been well documented in literature for similar systems [5, 14]. These diastereomers would fragment upon further oxidation by an excess of bromine to yield the formyl-tripyrrinone derivative **8** as is also well known from literature.



Alternatively, rubin **7** could be converted to the biladiene-*ab* **3** catalyzed by the strong acid [3]. The novel 16,24-dehydrobiladiene-*ab* **2** could then be produced upon oxidation of **3** *via* an intermediate, which is similar to the one proposed by *Ribó* [14].



Scheme 1

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 MHz instrument with *TMS* as the internal standard. UV-Vis spectra were recorded on a HP-8451A instrument, and the IR spectra on a Perkin-Elmer 983G spectrophotometer. Mass spectra were measured on α Finnigan MS-90 instrument, and melting points were determined with a micro-melting point apparatus. Silica GF_{254} was used for column chromatography.

Bromination procedure

Method A: 300 mg (0.95 mmol) xanthobilirubic acid methyl ester **1** [15] were dissolved in 300 ml argon saturated methanol. The mixture was stirred at 40–50 °C for 15 min under an argon atmosphere. Then bromine (as specified in Table 1) dissolved in 70 ml methanol was added dropwise over 30 min. The solution changed from yellow *via* light yellow to colorless. After 10 s, the mixture became suddenly purple-red and then dark green. The mixture was stirred for another 30 min after all bromine was added. TLC (eluent: dichloromethylene/ethyl acetate/carbon tetrachloride = 2/1/1, v/v/v) showed that the reaction was finished. The cooled reaction mixture was treated with 50 ml saturated aqu. $NaHCO_3$ and 150 ml dichloromethane. The organic layer was separated and the aquous layer was extracted with dichloromethane (3 × 30 ml). The combined extracts were washed successively with water (2 × 50 ml), saturated aqueous $NaHCO_3$(2 × 50 ml), water (2 × 50 ml), brine (50 ml), and then dried over anhydrous sodium sulfate. After removing the solvent, the residue was dissolved in the minimum amount of dichloromethane, and then chromatographed on a silica GF_{254} column with CH_2Cl_2/EtOAc/CCl_4 = 2/1/1 (v/v/v) as an eluent. Six fractions were eluted in the following order: **8** > **5** > **4** > **2** > **6** > **7**. The yields are given in Table 1.

Method B: 30 mg **1** (0.095 mmol) and 1.0 g anhydrous potassium carbonate (7.2 mmol = 7.6 molequiv.) were added to 50 ml anhydrous deoxygenated and argon saturated methanol. The mixture was stirred at 40–50 °C for 20 min under an argon atmosphere; then, 10 mg bromine (1.94 mmol = 2.04 molequiv) dissolved in 50 ml methanol were carefully added over 10 min. The color of the solution became light yellow. The reaction mixture remained unchanged for two days at room temperature, and only starting material was present according to TLC. To this mixture, several ml HBr (40% in acetic acid) were added to neutralize the potassium carbonate. After 5 min, the color of the mixture changed from light yellow *via* purple and red-blue to dark green. The mixture was allowed to stir for another 30 min and then treated following the workup of *Method A*. The result remained the same.

3,17-diethyl-2,7,13,18-tetramethyl-8,12-dimethoxycarbonylethyl-1,15,19, 21H-tetrahydro-1,19-dioxo-bilin (**2**; $C_{35}H_{42}N_4O_6$)

Fraction #4; m.p.: 220 °C (dec); ^{1}H NMR (acetone-d_6, δ, 500 MHz): 1.11 (*t*, J = 7.65 Hz, CH_2CH_3), 1.18 (*t*, J = 7.65 Hz, CH_2CH_3), 1.69 (s, CH_3), 1.92 (s, CH_3), 2.03 (s, CH_3), 2.09 (s, CH_3), 2.30, 2.40 (2q, J = 7.65 Hz, $2CH_2CH_3$), 2.51 (t, J = 7.48 Hz, $CH_2CH_2CO_2$), 2.54 (t, J = 7.48 Hz, $CH_2CH_2CO_2$), 2.60 (t, J = 7.48 Hz, $CH_2CH_2CO_2$), 2.91 (t, J = 7.48 Hz, $CH_2CH_2CO_2$), 3.21 (AB-system, J = 14.61 Hz, CH_2), 3.85 (s, OCH_3), 3.59 (s, OCH_3), 6.14 (s, –CH=), 7.06 (s, –CH=) ppm; ^{1}H, ^{1}H COSY: see Table 2; ^{13}C NMR (acetone-d_6, δ): 8.20, 8.44, 9.18, 9.66, 12.08, 14.77, 18.15, 18.99. 129.37, 129.69, 131.68, 132.37, 134.08, 136.78, 142.57, 143.65, 147.73, 148.62, 155.58, 164.33, 171.23, 172.32, 172.53, 173.53 ppm; UV-Vis ($CHCl_3$): λ_{max} = 330 (22500), 560 (16200) nm (ε); UV-Vis ($CHCl_3$ + $Zn(OAc)_2$): λ_{max} = 340 (28800), 622 (38100) nm (ε); UV-Vis ($CHCl_3$ + $Zn(OAc)_2$ + *TFA*): λ_{max} = 330 (22600), 566 (26600) nm (ε); IR (KBr) ν = 1734, 1702, 1685, 1627, 1600, 1432, 1363, 1296, 1195, 1163 cm^{-1}; MS (EI, 70 eV): *m/e* (%) = 614 (M^+, 100), 493 (60), 467 (20), 330 (58), 302 (38), 209 (22), 31 (47); *m/e* (calcd.; M^+) for $C_{35}H_{42}N_4O_6$: 614.3049, obsd.: 614.3094.

Mesobiliverdin-XIIIα dimethyl ester (**4**)

Fraction #3; m.p.: 240–42 °C (Ref. [12]: 244–45 °C); IR, UV-Vis, and ^{1}H NMR agreed with literature data [12].

l-3,17-diethyl-2,7,13,18-tetramethyl-8,12-dimethoxycarbonylethyl-4,5-dimethoxy-1,4,5,19,21,24-hexahydro-1,19-dioxo-22H-bilin (**5**)

Fraction #2; m.p.: 240–42 °C (Ref. [13]: 244–45 °C). IR, UV-Vis, and ^{1}H NMR agreed with literature data [13].

u-3,17-diethyl-2,7,13,18-tetramethyl-8,12-dimethoxycarbonylethyl-4,5-dimethoxy-1,4,5,19,21,24-hexahydro-1,19-dioxo-22H-bilin (**6**; $C_{37}H_{48}N_4O_8$)

Fraction #5; m.p.: 168–170 °C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.22 (m, $2CH_2CH_3$), 1.85 (s, CH_3), 1.94 (s, CH_3), 2.05 (s, CH_3), 2.08 (s, CH_3), 2.55 (m, $4CH_2$), 2.95 (m, $4CH_2$), 2.96 (s, OMe), 3.28 (s, OMe), 3.66 (s, $COCH_3$), 3.69 (s, $COCH_3$), 4.41 (s, CH-15), 5.92 (s, CH-5), 6.28 (s, NH), 6.88 (s, CH-10) ppm; IR (KBr): $\nu = 3260$, 1740, 1720, 1620, 1590, 1428 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 320$ (42000), 519 (30200), 553 (30700) nm (ε); UV-Vis ($CHCl_3$ + Zn $(OAc)_2$): $\lambda_{max} = 340$ (55600), 573 (18000), 640 (35000) nm (ε); UV-Vis ($CHCl_3$ + *TFA*): $\lambda_{max} = 325$ (30700), 545 (53000) nm (ε); MS (FAB, NBA): *m/e* (%) = 676 (2; M^+), 644 (25), 522 (100), 154 (59).

Mesobilirubin-XIIIα dimethyl ester (**7**)

Fraction #6; m.p.: 210–212 °C (Ref. [12]: 244–45 °C); IR, UV-Vis, and ^{1}H NMR agreed with literature data [12].

3-Ethyl-14-formyl-2,7,13-trimethyl-8,12-dimethoxycarbonylethyl-1-oxo-15H,17H-tripyrrin (**8**; $C_{28}H_{33}N_3O_6$)

Fraction #1; m.p.: 192–94 °C; ^{1}H NMR ($CDCl_3$, δ, 400 MHz): 1.15 (t, CH_2CH_3), 1.98 (s, CH_3), 2.05 (s, CH_3), 2.30 (s, CH_3), 2.40 (s, CH_3), 2.43 (t, J = x.x Hz, CH_2CH_2COO), 2.45 (t, CH_2CH_2COO), 2.47 (t, CH_2CH_2COO), 2.55 (t, CH_2CH_2COO), 3.67 (s, $COCH_3$), 3.71 (s, $COCH_3$), 5.29 (s, CH-5), 6.14 (s, CH-10), 9.58 (s, 2NH), 9.82 (s, –CHO) ppm; IR (KBr): $\nu = 3320$, 2860, 1730, 1712, 1700 cm^{-1}; UV-Vis ($CHCl_3$): $\lambda_{max} = 322$ (60100), 480 (18200), 510 (26000) nm (ε); UV-Vis ($CHCl_3$ + $Zn(OAc)_2$): $\lambda_{max} = 340$ (49000), 540 (8000), 580 (17000) 630 (22000) nm (ε); UV-Vis ($CHCl_3$ + *TFA*): $\lambda_{max} = 330$ (49000), 562 (56000) 600 (52000) nm (ε); MS (FAB, NBA): *m/e* (%) = 507 (3; M^+), 493 (100), 154 (20), 137 (20), 90 (13).

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