Preparation and Properties of 1,1′-Disubstituted $\Delta^{2,2'}$-Bi-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one Dimers with a Twisted C=C Bond

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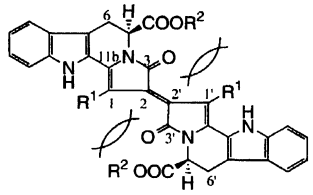
1,1′-Dimethyl and 1,1′-dichloro derivatives of the titled dimeric compound were prepared. A twisting of the central C^2=$C^{2'}$ double bond in the above-mentioned dimers was suggested based on the bathochromism observed in the absorption spectra. The 1,1′-dimethyl dimer was autoxidized at the enamine-type C^1=C^{10b} double bond to give 1,10b-dioxygenated products, while the 1,1′-dichloro dimer underwent a chlorine–hydrogen exchange to yield a 1,1′-dihydro compound upon heating in *n*-BuOH and 1,1,2,2-tetrachloroethane. These reactions might result from a strain around the twisted C^2=$C^{2'}$ double bond of the 1,1′-disubstituted dimers.

Twisting of the C=C bonds in ethylene derivatives is caused by a steric hindrance of bulky substituents; also, *N*,*N*′-dimethylindigo has a twisted central C^2=$C^{2'}$ double bond.[1,2] In a previous paper we reported on the preparation and X-ray analysis of a 1,1′-bis(ethoxycarbonyl)trichotomine derivative **1a**. The central C^2=$C^{2'}$ double bond of **1a** was twisted because of steric interactions between the C^1-substituent and the $C^{3'}$-carbonyl group, and between the $C^{1'}$-substituent and the C^3 carbonyl group.[3] Subsequently, 1,1′-dialkyltrichotomine derivatives **1b** were prepared and clarified to have a twisted C^2=$C^{2'}$ double bond similar to that of **1a** based on absorption spectral comparisons.[4] It is reported that *N*,*N*′-dimethylindigo undergoes autoxidation at the central C^2=$C^{2'}$ double bond to give *N*-methylisatin.[2] A 1,1′-dimethyltrichotomine derivative **1b** (R^1 = Me) is autoxidized at the C^1=C^{11b} double bond to afford 1,11b-dioxygenated compounds; the reactivity was attributed to relief of the twisting of the C^2=$C^{2'}$ double bond.[4] A blue pigment, trichotomine (**1c**), was isolated from *Clerodendron trichotomum* Thunb, and suggested to be biosynthesized from L-tryptophan and 2-oxoglutaric acid.[5,6] We anticipated the occurrence of a trichotomine-type pigment, such as **2** biosynthesized from 2-arylethylamine and 2-oxoglutaric acid.[7] The chromophore of **1c** is regarded as being a $\Delta^{2,2'}$-dilactam conjugated with π-electron rich indole rings, while that of **2** is conjugated with phenyl rings bearing electron-withdrawing acetoxy groups. We thus planned to compare the properties of the 1,1′-disubstituted derivatives of **2** with those of the 1,1′-disubstituted trichotomine derivatives. In this paper, we wish to report on the preparation and properties of a 1,1′-dimethyl $\Delta^{2,2'}$-bi-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3(2*H*)-one dimer **3** and a 1,1′-dichloro dimeric compound **4**.

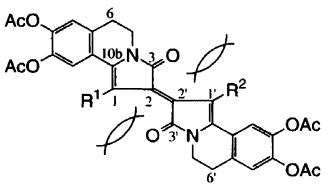
Results and Discussion

Preparation and UV-vis Spectrum of 3. A 1,1′-dimethyl derivative **3** was prepared as follows. Dopamine hydrochloride was reacted with methyl 4,4-dimethoxy-3-methylbutanoate[8] to give condensation products, which were acetylated with acetic anhydride and pyridine to give diacetates **5a** and **5b** in a ratio of 1.3 : 1.0 (Chart 1). The *trans*-relationship between the C^1- and C^{10b}-protons in **5b** was assigned by the NOEs observed between the C^1-methyl group and the C^{10b}-proton in the NOESY experiment. The treatment of **5a** with *N*-bromosuccinimide (NBS) in the presence of MeOH yielded a bromo methoxy compound **6**. The ^{1}H and ^{13}C NMR spectra of **6** coupled with DEPT and COLOC experiments showed the presence of a methoxy group (δ_H = 3.14) on C^{10b} (δ_c = 93.9), and of another quaternary sp^3 carbon (δ_c = 71.7, C^1) bearing a methyl group (δ_H = 2.06). Although the mass spectrum of **6** did not show a molecular ion peak, a peak at *m*/*z* 394 $(M-OMe)^+$ indicated the presence of a bromo substituent, which was located on the C^1. Dehydrobromination of **6** with triethylamine afforded a methoxy olefine **7**. The ^{1}H and ^{13}C NMR spectra of **7** indicated the presence of a methoxy group (δ_H = 3.13) on C^{10b} (δ_c = 91.5) and of a C^1=C^2 double bond (δ_c = 159.5 and 124.9, respectively). Upon heating in AcOEt, **7** underwent autoxidation to give a blueish-green dimer **3**, whose structure was in line with the spectral data (^{1}H and ^{13}C NMR, MS). The ^{13}C NMR signal of C^1 was observed at a lower field (δ = 113.6) relative to that of **2** (δ = 98.3). The formation of **3** could be rationalized by a homolytic fission of the C^{10b}–OMe bond of **7**, followed by a coupling of the resulting two radicals at the C^2, and by dehydrogenation to afford **3**.

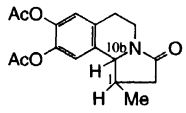
In the UV-vis spectrum of **3**, the λ_{max} was observed at 709 nm, which was shifted to a longer wavelength by 75 nm relative to that of **2** (634 nm).[7] This trend was similar to that observed between **1d** (R^1 = H, 658 nm) and **1b** (R^1 = Me, 715 nm); the latter was suggested to have a twisted C^2=$C^{2'}$ double bond.[4] Accordingly, the bathochromism observed in



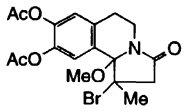
1a R^1=COOEt, R^2=Me
1b R^1=Alkyl, R^2=Me
1c R^1=R^2=H
1d R^1=H, R^2=Me



2 R^1=R^2=H
3 R^1=R^2=Me
4 R^1=R^2=Cl
21 R^1=Cl, R^2=H



5a H^1 / H^{10b} cis
5b H^1 / H^{10b} trans



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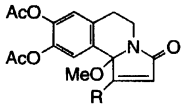
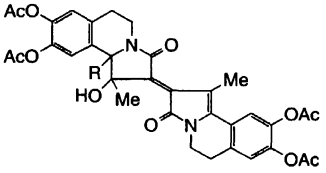
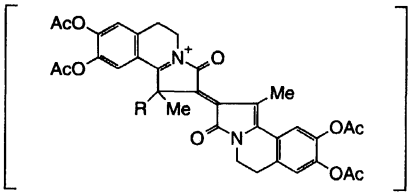


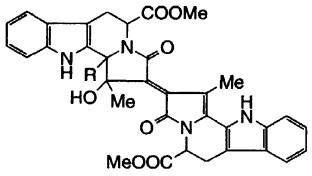
7 R=Me
23 R=Cl



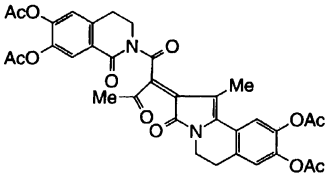
8 R=OMe
10 R=OH



9 R=OH
11 R=OOH



12 R=OH
14 R=OMe



13

Chart 1.

3 might be attributed to a substituent effect of the methyl groups on C^1 and $C^{1'}$, and to twisting of the central C^2=$C^{2'}$ double bond.

Autoxidaton of 3. Attempts to obtain a crystal of **3** suitable for X-ray analysis were unsuccessful, since **3** was not stable in solution. Upon standing in MeOH and CH_2Cl_2 for 2 d, **3** gave a complex mixture of products, from which a small amount of an orange compound **8** (λ_{max} = 476 nm) was obtained. The ^{1}H and ^{13}C NMR spectra of **8** showed the presence of a hydroxy group (δ_H = 7.18, exchangeable with D_2O) on C^1 (δ_c = 82.1) and of a methoxy group (δ_H = 3.26) on C^{10b} (δ_c = 92.3). In the FABMS spectrum of **8**, although no molecular ion peak was found, the observed ion peak at *m/z* 643 $(M-OMe)^+$ could be explained as being a compound such as **9**, supporting the 1-hydroxy-10b-methoxy structure of **8**.

In the presence of water, **3** similarly underwent autoxidation to yield an orange compound **10** (λ_{max} = 467 nm). The ^{1}H and ^{13}C NMR spectra of **10** suggested the presence of two hydroxy groups (δ_H = 8.17 and 5.28) on C^1 (δ_c = 80.8) and C^{10b} (δ_c = 87.5), respectively. The FABMS spectrum of **10** did not show a molecular ion peak, but a fragment ion peak at *m/z* 643 $(M-OH)^+$, which could also be assigned to the **9** mentioned above. These spectral data are in line with the C^1, C^{10b}-dihydroxylated structure of **10**.

Under similar conditions mentioned above, **2** was stable and did not undergo autoxidation. The formation of **8** and **10** might proceed via a compound such as **9**, which might be derived from a hydroperoxide **11**. The addition of MeOH and water on C^{10b} of **9** might give **8** and **10**, respectively.

We previously reported that **1b** (R^1 = Me) underwent autoxidation to give a 1,11b-dihydroxylated compound **12** and a 1,11b-seco dicarbonyl compound, whose formation was explained by the O–O bond and the C–C bond fissions of the 1,11b-dioxetane intermediate, respectively.[4] In the autoxidation of **3**, mentioned above, the formation of the corresponding 1,10b-seco dicarbonyl compound **13** was not observed. The difference in the autoxidation products of **3** and **1b** (R^1 = Me) seemed to reflect an electronic effect of a π-electron rich indole ring and of a phenyl ring bearing two electron-withdrawing acetoxy groups.[9] We thus examined the oxidation of **3** and **1b** (R^1 = Me) with mCPBA in order to understand the characteristic reactivity.

Upon a treatment with mCPBA in MeOH and CH_2Cl_2, **3** afforded **8**, which was identical with that obtained above. The oxidation of **1b** (R^1 = Me) with mCPBA in MeOH and CH_2Cl_2 similarly gave a 1-hydroxy-11b-methoxy compound **14**, and that in wet CH_2Cl_2 yielded a 1,11b-dihydroxy compound **12**. On the other hand, in wet CH_2Cl_2, **3** was oxidized with mCPBA to give an orange compound **13** (λ_{max} = 478 nm). The ^{13}C NMR spectrum of **13** indicated the presence of an acetyl group (δ_c = 30.1 and 194.7). The mass spectrum of **13** showed a peak at *m/z* 659 $(M+H)^+$, which was larger by 32 than the $(M+H)^+$ peak of **3** (*m/z* 627). These spectral data supported the 1,10b-seco dicarbonyl structure of **13**. The conversion of **3** into **13** is similar to that of enol ethers into dicarbonyl compounds by peracid oxidation.[10] Accordingly, the formation of **13** could be explained by a series of reac-

tions: 1) epoxidation of the C^1=C^{10b} double bond of **3**, 2) an epoxide ring opening to a compound such as **9**, 3) the addition of mCPBA to C^{10b} of **9**, and 4) a C^1–C^{10b} bond cleavage of the resulting C^1-hydroxy C^{10b}-perester.

Using the above compound **13** as a marker, although we examined the autoxidation products of **3** with TLC, **13** could not be detected. The characteristics observed in the oxidation products of **3** and **1b** (R^1 = Me) might result from the stability of an intermediate, such as **11**, and of a corresponding intermediate formed from **1b** (R^1 = Me). In the autoxidation of **3**, unstable **11** might be changed into **9** in preference to dioxetane formation on C^1 and C^{10b}. In mCPBA oxidation, **9** might easily be oxidized to give **13** in preference to the formation of **10**. Further studies are now in progress.

The formation of **8**, **10**, and **13** might indicate that a strain around the twisted C^2=$C^{2'}$ double bond in **3** is relieved by a decreasing steric interaction between the 1-methyl group and the 3′-carbonyl group.

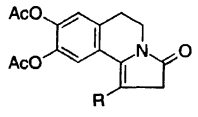
Preparation and Properties of 1,1′-Dichloro Dimeric Compound 4. A chlorine atom is as bulky as a methyl group, and the 1,1′-dichloro dimer **4** was anticipated to have a twisted C^2=$C^{2'}$ double bond.[11] We thus prepared **4** and attempted an autoxidative conversion of **4** into a C^1-hydroxy compound, and then into a C^1-carbonyl compound.

At first, the autoxidative dimerization of a vinyl chloride **15** was examined, since **2** was prepared from **16** (Chart 2).[7] Compound **15** was prepared from **17**[7] by a treatment with *t*-butyl hypochlorite (*t*-BuOCl) in MeOH and CH_2Cl_2 at room temperature for 24 h in the dark. The ^{13}C NMR spectrum of **15** showed tetra-substituted olefinic carbon signals at δ = 103.4 (C^1) and 131.7 (C^{10b}) along with six phenyl carbon signals. In the COLOC experiment, the cross peak between the C^{10b} signal (δ = 131.7) and the H^5 and H^{10} signals (δ = 3.73 and 8.08, respectively) supported the presence of a double bond between C^1 and C^{10b}. The mass spectrum of **15** showed a molecular ion peak at *m/z* 335, which was larger by 34 than that of **16** (M^+ = 301), indicating the presence of a chloro substituent. The C^1 signal of **15**, observed at a lower-field (δ = 103.4) relative to that of **16** (δ = 97.8), suggested the attachment of a chloro substituent on C^1. Compound **15** was obtained from **16** under similar conditions to those described above. Therefore, the formation of **15** from **17** might proceed via a chloro iminium compound **18**, which was obtained from **16**, formed in situ from **17**.

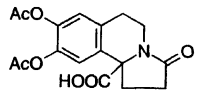
Heating a mixture of **17**, *t*-BuOCl, MeOH, and CH_2Cl_2 under reflux for 5 h yielded a methoxy dichloride **19**, which was also obtained from **15** under similar conditions to those described above. The mass spectrum of **19** showed a molecular ion peak at *m/z* 401, which was larger by 66 (OMe and Cl) than that of **15**, indicating the presence of a methoxy group and two chloro substituents. The ^{1}H and ^{13}C NMR of **19** supported the presence of a methoxy group (δ_H = 3.23) on the C^{10b} (δ_c = 93.7), and of two chloro substituents on the quarternary C^1 (δ_c = 89.7). The formation of **19** could be explained by the addition of methanol to a compound such as **20**, obtained from **15**.[12]

The oxidative dimerization of **15** was examined under similar conditions to those used in the preparation of **2** from **16**.[7] Upon heating in 1,1,2,2-tetrachloroethane under an oxygen atmosphere, **15** underwent autoxidation to give a mixture of dimer **2** and a new dimer **21** in a ratio of 2 : 3. The structure of **2**, bearing hydrogen atoms on C^1 and $C^{1'}$, was confirmed by a ^{1}H NMR comparison. In order to determine the pathway to **2**, the autoxidation of **15** was examined under various conditions. Upon heating in *n*-BuOH, **15** gave **2** and **21** in a ratio of 6 : 1. When crystals of **15** were heated at 170—177 °C for 15 min, they turned blue and yielded **2** and **21** in a ratio of 6 : 1. Hence, we presumed that the initially formed 1,1′-dichloro dimer **4** lost the 1- and/or 1′-chloro substituent by a chlorine–hydrogen exchange via an iminium compound, such as **22a**, and/or by a homolytic cleavage to give a vinyl radical, such as **22b**, which abstracted a hydrogen atom from the solvent and/or the substrate. We thus chose chlorobenzene as a solvent, since it had a large bond-dissociation energy (Ph–H = 111 kcal mol^{-1}).[13] However, upon heating in chlorobenzene for 30 min, **15** gave **2** and **21** in a ratio of 2 : 3, and did not yield the desired **4**.

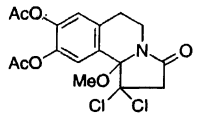
On the other hand, the autoxidation of **19** was examined.



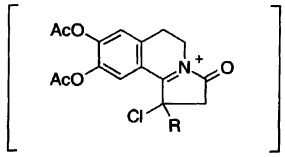
15 R=Cl
16 R=H

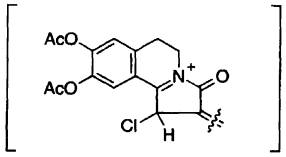


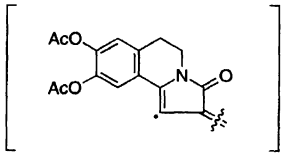
17



19







18 R=H
20 R=Cl

22a

22b

Chart 2.

Upon heating in 1,1,2,2-tetrachloroethane, **19** gave the dimer **21** as the main pigment. The ^{1}H NMR spectrum of **21** indicated five singlet olefinic and aromatic signals at $\delta = 7.14$, 7.16, 7.55, 7.62, and 8.39, and the ^{13}C NMR spectrum showed 32 signals, suggesting an unsymmetrical structure of **21**. The SIMS of **21** showed a peak at *m/z* 633 $(M+H)^+$, which was larger by 34 than the $(M+H)^+$ of **2**. These spectral data suggested the described structure of **21** having a chloro substituent on C^1 and a hydrogen atom on $C^{1'}$. The characteristic ^{13}C NMR signals at $\delta = 103.7$ and 100.6 were assigned to C^1 and $C^{1'}$, respectively. The dimer **21** might be obtained via an iminium compound, such as **22a**, generated from the initially formed **4**.

Fortunately, upon heating in chlorobenzene, **19** gave the desired 1,1′-dichloro dimer **4** in 52% yield. The mass spectrum of **4** showed a peak at *m/z* 667 $(M+H)^+$, and the ^{1}H and ^{13}C NMR spectra of **4** suggested a symmetrical structure. The characteristic ^{13}C NMR signal at $\delta = 106.9$ was assigned to the C^1 and $C^{1'}$, and the described structure of **4** was in agreement with the spectral data (^{1}H and ^{13}C NMR, MS). The formation of **4** might proceed via a $\Delta^{1,2}$-compound **23**, formed from **19**. In the UV-vis spectrum of **4**, λ_{max} was observed at 719 nm, which was shifted by 85 nm relative to that of **2** (634 nm). The bathochromic shift might be due to a substituent effect of the chloro groups on C^1 and $C^{1'}$, and due to a twisting of the central C^2=$C^{2'}$ double bond.

The dimer **4** was recovered unchanged upon heating in 1,1,2,2-tetrachloroethane for 2 h. However, upon heating in *n*-BuOH and 1,1,2,2-tetrachloroethane, **4** changed into a mixture of **21** and **2**, and then into **2**. A 1,10b-dioxygenated product, such as **8**, was not detected. The dimer **4** might have undergone a chlorine–hydrogen exchange via an iminium compound, such as **22a**. The resulting **2** might be relieved from the strain around the twisted C^2=$C^{2'}$ double bond of **4**, and have a planar C^2=$C^{2'}$ double bond similar to that of **1d**.[14]

Experimental

All of the melting points are uncorrected. UV-vis spectra were measured on a Shimadzu-UV-3100. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC-300 using $CDCl_3$ as a solvent. The mass spectra were obtained on a JEOL-DX303 or a Hitachi M-80.

Preparation of 5a and 5b. A mixture of dopamine hydrochloride (1.90 g, 10 mmol), methyl 4,4-dimethoxy-3-methylbutanoate (2.46 g, 14 mmol), and water (25 ml) was refluxed for 16 h. The resulting solution was cooled in a refrigerator to give a precipitate, which was filtered (1.21 g, 52%). A mixture of the precipitate, acetic anhydride (10 ml), and pyridine (10 ml) was allowed to stand at room temperature for 24 h. The resulting solution was concentrated under reduced pressure to give a residue, which was crystallized from MeOH to yield **5a** and **5b** (as a mixture, 1.26 g, 76%) in a ratio of 1.3 : 1.0 (determined by ^{1}H NMR). The mixture of **5a** and **5b** was separated by recrystallization from MeOH.

5a: Mp 214—215 °C; ^{1}H NMR $\delta = 0.66$ (3H, d, $J = 6.8$ Hz), 2.16 (1H, m), 2.29 (3H, s), 2.30 (3H, s), 2.70—2.98 (5H, m), 4.38 (1H, m), 4.87 (1H, d, $J = 5.1$ Hz), 6.91 (1H, s), and 6.99 (1H, s); ^{13}C NMR $\delta = 15.5$, 20.6, 28.6, 32.3, 36.3, 40.5, 60.1, 121.0, 123.9, 132.2, 133.4, 140.4, 140.8, 168.3, and 172.7. Found: C, 64.11; H, 6.13; N, 4.37%; M^+ 317. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.04; N, 4.41%; M, 317.

5b: Mp 156—158 °C; ^{1}H NMR $\delta = 1.43$ (3H, d, $J = 6.3$ Hz), 2.21—2.41 (2H, m), 2.29 (3H, s), 2.30 (3H, s), 2.62 (1H, dd, $J = 15.5$ and 7.8 Hz), 2.72 (1H, m), 2.85—3.07 (2H, m), 4.24 (1H, m), 4.35 (1H, d, $J = 7.3$ Hz), 6.99 (1H, s), and 7.09 (1H, s); ^{13}C NMR $\delta = 19.7$, 20.6, 28.5, 36.1, 36.8, 40.1, 63.2, 119.5, 123.9, 132.9, 135.6, 140.6, 168.4, and 172.5. HRMS Found: *m/z* 317.1284. Calcd for $C_{17}H_{19}NO_5$: M, 317.1264.

Preparation of 6. A mixture of **5a** (380 mg, 1.20 mmol), NBS (427 mg, 2.40 mmol), dry MeOH (4 ml), and dry CH_2Cl_2 (24 ml) was stirred at room temperature for 2 h. The solution was partitioned between $CHCl_3$ and water. The organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified with column chromatography (SiO_2–$CHCl_3$), and crystallized from $CHCl_3$–hexane to give **6** (310 mg, 61%): Mp 84—86 °C; ^{1}H NMR $\delta = 2.06$ (3H, s), 2.31 (6H, s), 2.78 (1H, m), 2.90 (1H, d, $J = 16.7$ Hz), 2.96—3.13 (2H, m), 3.14 (3H, s), 3.25 (1H, d, J=16.7 Hz), 4.58 (1H, m), 7.08 (1H, s), and 7.35 (1H, s); ^{13}C NMR $\delta = 20.7$, 24.7, 28.6, 38.1, 48.7, 52.6, 71.7, 93.9, 121.2, 123.0, 130.8, 136.7, 140.9, 142.2, 168.0, and 173.3. HRMS Found: *m/z* 394.0301. Calcd for $C_{17}H_{17}BrNO_5$: M − OMe, 394.0201.

Preparation of 7. A mixture of **6** (120 mg, 0.28 mmol), Et_3N (0.4 ml, 2.9 mmol), and CH_2Cl_2 (12 ml) was allowed to stand at room temperature for 2 d, and concentrated under reduced pressure. The residue was dissolved in $CHCl_3$. The solution was washed with 0.5% HCl and water, and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue, which was purified with column chromatography (SiO_2–AcOEt), and crystallized from AcOEt–hexane to give **7** (64 mg, 66%): Mp 116—118 °C; ^{1}H NMR $\delta = 2.17$ (3H, d, $J = 1.5$ Hz), 2.28 (3H, s), 2.29 (3H, s), 2.61 (1H, m), 2.88 (1H, m), 3.10 (1H, m), 3.13 (3H, s), 4.31 (1H, m), 5.95 (1H, d, $J = 1.5$ Hz), 7.00 (1H, s), and 7.47 (1H, s); ^{13}C NMR $\delta = 13.8$, 20.6, 20.7, 29.3, 35.6, 49.9, 91.5, 123.2, 123.6, 124.9, 132.4, 134.2, 140.4, 141.7, 159.5, 168.1, 168.2, and 171.3. HRMS Found: *m/z* 345.1184. Calcd for $C_{18}H_{19}NO_6$: M, 345.1211.

Preparation of 3. A solution of **7** (50 mg, 0.14 mmol) in AcOEt (10 ml) was refluxed for 3 h. The resulting precipitate was collected by filtration. The filtrate was concentrated under reduced pressure. The residue was purified with column chromatography (SiO_2–AcOEt) to give **3**, which was combined with the precipitate mentioned above. Crystallization from MeOH–$CHCl_3$ gave **3** (as a powder, 32 mg, 71%): UV-vis ($CHCl_3$) 306 (ε 30400), 351 (19700), 671 (25800) and 709 nm (23800); ^{1}H NMR $\delta = 2.32$ (3H×2, s), 2.33 (3H×2, s), 2.34 (3H×2, s), 3.01 (2H×2, t, $J = 6.0$ Hz), 3.79 (2H×2, t, J=6.0 Hz), 7.15 (1H×2, s), and 7.63 (1H×2, s); ^{13}C NMR $\delta = 14.8$, 20.6, 20.7, 29.7, 36.9, 113.6, 123.1, 123.7, 125.7, 134.1, 135.2, 140.9, 141.3, 142.6, 166.3, 168.1, and 168.2. Found: *m/z* 627.1998. Calcd for $C_{34}H_{31}N_2O_{10}$: M+H, 627.1979.

Autoxidation of 3. 1) in MeOH–CH_2Cl_2. A solution of **3** (20 mg, 32 μmol) in MeOH (5 ml) and CH_2Cl_2 (5 ml) was allowed to stand at room temperature for 2 d. The solution turned dark red and did not show a spot of **3** on TLC. Concentration of the solution under reduced pressure gave a residue, which was separated by column chromatography (SiO_2, MeOH–$CHCl_3$) and PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 100) to give **8** (as an oil, 1 mg, 5%): UV-vis ($CHCl_3$) 286 (ε 13700) and 476 nm (4600); ^{1}H NMR $\delta = 1.10$ (3H, s), 2.30 (6H, s), 2.31 (3H, s), 2.32 (3H, s), 2.34 (3H, s), 2.84 (2H, m), 2.93 (2H, m), 3.21—3.33 (2H, m), 3.26 (3H, s), 4.25 (1H, m), 4.67 (1H, m), 7.08 (1H, s), 7.14 (1H, s), 7.18 (1H, s,

exchangeable with D_2O), 7.53 (1H, s), and 7.63 (1H, s); ^{13}C NMR δ = 14.5, 20.6, 20.7, 20.8, 22.8, 28.5, 29.8, 36.8, 37.1, 52.3, 82.1, 92.3, 109.5, 123.0, 123.1, 123.4, 123.6, 125.4, 130.0, 134.1, 134.8, 135.0, 138.3, 141.0, 141.3, 142.5, 142.6, 150.5, 165.8, 168.0, 168.1, and 168.2. HRMS Found: *m/z* 643.1894. Calcd for $C_{34}H_{31}N_2O_{11}$: M − OMe, 643.1928.

2) in H_2O–CH_3CN. A mixture of **3** (20 mg, 32 μmol), water (0.6 ml), and CH_3CN (20 ml) was refluxed for 3 h, and then allowed to stand at room temperature for 2 d. The solution was concentrated under reduced pressure to give a residue, which was separated with PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 100) to afford **10** (as an oil, 1 mg, 5%): UV-vis ($CHCl_3$) 280 (ε 13900) and 467 nm (3200); ^1H NMR δ = 1.18 (3H, s), 2.29 (3H, s), 2.31 (3H, s), 2.32 (3H, s), 2.33 (3H, s), 2.34 (3H, s), 2.84 (2H, m), 2.98 (2H, m), 3.34 (2H, m), 4.27 (1H, m), 4.51 (1H, m), 5.28 (1H, s, exchangeable with D_2O), 7.03 (1H, s), 7.16 (1H, s), 7.52 (1H, s), 7.54 (1H, s), and 8.17 (1H, s, exchangeable with D_2O); ^{13}C NMR δ = 14.7, 20.6, 20.7, 22.1, 28.6, 29.7, 35.0, 37.2, 80.9, 87.5, 109.7, 122.9, 123.2, 123.6, 125.2, 132.9, 133.2, 134.7, 135.5, 138.1, 140.9, 141.0, 142.0, 142.6, 149.8, 164.5, 168.1, 168.2, and 168.6. Found: *m/z* 643.1912. Calcd for $C_{34}H_{31}N_2O_{11}$: M − OH, 643.1928.

MCPBA Oxidation of 3. 1) in MeOH–CH_2Cl_2. A mixture of **3** (10mg, 16 μmol), mCPBA (20 mg, 0.12 mmol), and MeOH–CH_2Cl_2 (1 : 3, 5 ml) was stirred at room temperature for 10 min. To the solution was added $NaHSO_3$. The mixture was partitioned between $CHCl_3$ and $NaHCO_3$ aqueous solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was separated with PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 200) to give **8** (as an oil, 4 mg, 36%), which was identical with that described above by ^1H NMR and TLC comparisons.

2) in Wet CH_2Cl_2. To a solution of **3** (10 mg, 16 μmol) in CH_2Cl_2 (saturated with water, 5 ml) cooled in an ice-water was added mCPBA (20 mg, 0.12 mmol). The mixture was stirred for 3 min, and worked up as described above. Separation with PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 200) and crystallization from AcOEt–hexane gave **13** (4 mg, 36%): Mp 212—213 °C; UV-vis ($CHCl_3$) 262 (ε 26400) and 478 nm (5900); ^1H NMR δ = 2.09 (3H, s), 2.28 (3H, s), 2.30 (6H, s), 2.33 (3H, s), 2.46 (3H, s), 2.84—2.99 (3H, m), 3.40 (2H, m), 3.83—4.02 (2H, m), 4.68 (1H, m), 7.10 (1H, s), 7.16 (1H, s), 7.48 (1H, s), and 7.89 (1H, s); ^{13}C NMR δ = 13.9, 20.5, 20.7, 26.9, 29.7, 30.1, 36.8, 42.3, 107.2, 122.6, 123.2, 123.6, 125.0, 125.3, 126.2, 133.5, 135.2, 139.6, 140.4, 140.6, 140.9, 141.4, 142.6, 146.4, 164.1, 166.6, 167.7, 168.0, 168.1, 168.2, 169.5, and 194.7. HRMS Found: *m/z* 659.1884. Calcd for $C_{34}H_{31}N_2O_{12}$: M+H, 659.1877.

MCPBA Oxidation of 1b (R^1 = Me). **1) in MeOH–CH_2Cl_2.** A mixture of **1b** (R^1 = Me, 10 mg, 17 μmol), mCPBA (30 mg, 0.17 mmol), and MeOH–CH_2Cl_2 (1:3, 30 ml) was stirred at room temperature for 15 min. The solution was worked up as described above. Separation with PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 20) gave **14** (as an oil, 4 mg, 36%): UV-vis (MeOH) 325 (ε 16500) and 502 nm (19400); ^1H NMR δ = 1.14 (3H, s), 2.59 (3H, s), 3.00 (1H, dd, *J* = 16.3 and 7.0 Hz), 3.37 (1H, dd, *J* = 16.3 and 7.0 Hz), 3.47 (3H, s), 3.65—3.78 (2H, m), 3.68 (3H, s), 3.74 (3H, s), 5.19 (1H, d, *J* = 7.0 Hz), 5.55 (1H, d, *J* = 7.0 Hz), 7.12—7.65 (8H, m), 7.21 (1H, s, exchangeable with D_2O), 8.51 (1H, br s), and 8.64 (1H, br s); ^{13}C NMR δ = 13.6, 22.0, 23.5, 23.6, 49.3, 50.1, 52.5, 52.7, 53.1, 80.5, 91.2, 106.9, 108.7, 111.7, 114.2, 119.1, 119.7, 119.8, 121.1, 123.2, 125.0, 125.5, 125.7, 128.3, 133.6, 133.7, 136.6, 138.9, 146.0, 166.3, 170.1, 170.4, and 171.4. HRMS Found: *m/z* 605.2059. Calcd for $C_{34}H_{29}N_4O_7$: M − OMe, 605.2037.

2) in Wet CH_2Cl_2. To a solution of **1b** (R^1 = Me, 10 mg, 17 μmol) in CH_2Cl_2 (saturated with water, 15 ml) cooled in an ice-water was added mCPBA (30 mg, 0.17 mmol). The mixture was stirred for 2 min, and worked up as described above. Separation with PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 20) gave **12** (as an oil, 1 mg, 10%), which was identical with that reported in a previous paper by ^1H NMR and TLC comparisons.[7]

Preparation of 15. To a solution of **17** (694 mg, 2.0 mmol) in MeOH (1.4 ml) and CH_2Cl_2 (140 ml) was added *t*-BuOCl (1.4 ml, 12 mmol). The solution was kept in a dark place at room temperature for 24 h, and then washed with water and aqueous $NaHCO_3$, and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue, which was purified by column chromatography (SiO_2–$CHCl_3$), and crystallized from MeOH to give **15** (362 mg, 54%): Mp 125—127 °C; UV (MeOH) 208 (ε 29600), 238 (21000), and 307 nm (7330); ^1H NMR δ = 2.31 (3H, s), 2.32 (3H, s), 2 94 (2H, t, *J* = 6.1 Hz), 3.42 (2H, s), 3.73 (2H, t, *J* = 6.1 Hz), 7.12 (1H, s), and 8.08 (1H, s); ^{13}C NMR δ = 20.6, 29.1, 36.7, 43.1, 103.4, 121.6, 123.4, 124.1, 131.7, 133.4, 140.8, 142.2, 168.0, 168.2, and 171.5. Found: C, 57.19; H, 4.19; N, 4.10%; M^+ 335. Calcd for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.17%; M, 335.

Formation of 15. A mixture of **16** (13 mg, 0.043 mmol), *t*-BuOCl (21 mg, 0.19 mmol), MeOH (0.1 ml), and CH_2Cl_2 (2 ml) was left in a dark place at room temperature for 3 h, and then worked up as described above to give **15** almost quantitatively.

Preparation of 19. To a solution of **17** (130 mg, 0.37 mmol) in MeOH (0.4 ml) and CH_2Cl_2 (30 ml) was added *t*-BuOCl (0.40 ml, 3.4 mmol). The solution was refluxed for 5 h, and worked up as described above. Crystallization from MeOH gave **19** (99 mg, 66%): Mp 146—148 °C; ^1H NMR δ = 2.31 (3H, s), 2.32 (3H, s), 2.82 (2H, m), 3.11 (1H, m), 3.22 (1H, d, *J* = 16.2 Hz), 3.23 (3H, s), 3.60 (1H, d, *J* = 16.2 Hz), 4.59 (1H, ddd, *J* = 12.9, 5.4, and 1.6 Hz), 7.11 (1H, s), and 7.67 (1H, s); ^{13}C NMR δ = 20.6, 20.7, 28.4, 37.9, 51.0, 52.7, 89.7, 93.7, 122.1, 123.1, 128.1, 136.5, 141.2, 143.0, 167.9, 168.0, and 169.9. HRMS Found: *m/z* 401.0420. Calcd for $C_{17}H_{17}Cl_2NO_6$: M, 401.0431.

Formation of 19. A mixture of **15** (16 mg, 0.048 mmol), *t*-BuOCl (21 mg, 0.19 mmol), MeOH (0.1 ml), and CH_2Cl_2 (5 ml) was left at room temperature for 16 h, and worked up as described above to give **19** (13 mg, 68%).

Autoxidation of 15. 1) in $Cl_2CHCHCl_2$. A solution of **15** (20 mg, 60 μmol) in $Cl_2CHCHCl_2$ (20 ml) was stirred at 141—143 °C for 2 h under an oxygen atmosphere. The resulting blue solution was concentrated under reduced pressure. The residue was washed with MeOH and separated by column chromatography (SiO_2, MeOH–$CHCl_3$) to give **2** (20%) and **21** (28%) (as a mixture of amorphous powder, 9 mg) in a ratio of 2 : 3 (determined by ^1H NMR). The pigment **2** was identical with that reported previously by ^1H NMR and TLC comparisons.[7] ^{13}C NMR of **2**: δ = 20.6, 20.7, 28.4, 36.2, 98.3, 120.6, 123.8, 125.0, 130.0, 133.7, 141.5, 143.5, 144.0, 168.1, 168.2, and 169.1.

2) in *n*-BuOH. A solution of **15** (20 mg, 60 μmol) in *n*-BuOH (20 ml) was stirred at 91—96 °C for 24 h under oxygen atmosphere. The resulting blue solution was worked up as described above to give **2** (24%) and **21** (4%) (as a mixture, 5 mg) in a ratio of 6 : 1.

3) Without Solvent. Crystals of **15** (15 mg, 45 μmol) were heated at 170—177 °C for 15 min. The resulting pigments were purified as described above to give **2** (13%) and **21** (2%) (as a mixture, 2 mg) in a ratio of 6 : 1.

4) in Chlorobenzene. A solution of **15** (20 mg, 60 μmol) in chlorobenzene (5 ml) was refluxed for 30 min. The solution was concentrated under reduced pressure. The residue was crystallized

from MeOH–$CHCl_3$ to give **2** (18%) and **21** (26%) (as a mixture, 8 mg) in a ratio of 2 : 3.

Autoxidation of 19. 1) in $Cl_2CHCHCl_2$. A solution of **19** (30 mg, 75 μmol) in $Cl_2CHCHCl_2$ (20 ml) was refluxed for 10 min. To the solution was added hexane. The resulting precipitate was collected. Crystallization from MeOH–$CHCl_3$ gave **21** (as a powder, 5 mg, 21%): UV-vis ($CHCl_3$) 301 (ε 23600), 318 (23300), and 632 nm (23800); ^{1}H NMR δ = 2.31 (6H, s), 2.34 (3H, s), 2.35 (3H, s), 3.03 (4H, m), 3.82 (4H, m), 7.14 (1H, s), 7.16 (1H, s), 7.55 (1H, s), 7.62 (1H, s), and 8.39 (1H, s); ^{13}C NMR δ = 20.5, 20.6, 20.7, 20.8, 28.3, 29.4, 36.3, 36.4, 100.6, 103.7, 120.9, 123.4, 123.6, 123.8, 124.3, 124.5, 126.7, 134.1, 134.2, 135.2, 137.3, 141.0, 141.6, 143.3, 144.0, 145.9, 166.1, 167.3, 167.9, 168.0, 168.1, and 168.2; MS (SIMS) *m/z* 633 $(M+H)^+$. Found: C, 60.58; H, 3.84; N, 4.43%. Calcd for $C_{32}H_{25}ClN_2O_{10}$: C, 60.72; H, 3.98; N, 4.43%.

2) in Chlorobenzene. A solution of **19** (30 mg, 75 μmol) and chlorobenzene (8 ml) was refluxed for 30 min. To the blue solution was added hexane. The resulting precipitate was collected. Crystallization from MeOH–$CHCl_3$ gave **4** (as a powder, 13 mg, 52%): UV-vis ($CHCl_3$) 314 (ε 17800), 365 (11800), 677 (sh, 14500), and 719 nm (15100); ^{1}H NMR δ = 2.31 (3H×2, s), 2.33 (3H×2, s), 3.04 (2H×2, t, J = 6.2 Hz), 3.85 (2H×2, t, J = 6.2 Hz), 7.18 (1H×2, s), and 8.37 (1H×2, s); ^{13}C NMR δ = 20.6, 20.8, 29.2, 36.9, 106.9, 123.6, 123.8, 130.0, 135.7, 140.4, 141.1, 144.0, 163.1, 167.8, and 168.1. HRMS Found: *m/z* 667.0872. Calcd for $C_{32}H_{25}Cl_2N_2O_{10}$: M+H, 667.0886.

Formation of 2 from 4. A mixture of **4** (20 mg, 30 μmol), *n*-BuOH (20 ml), and $Cl_2CHCHCl_2$ (10 ml) was refluxed for 2 h. The solution was concentrated under reduced pressure. The residue was crystallized from MeOH–$CHCl_3$ to give **2** (3 mg, 17%), which was identical with the authentic **2** based on a ^{1}H NMR comparison.

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11) Twisting of the C^2=$C^{2'}$ double bond of **3** and **4** was also suggested by calculation of the dihedral angle of the C^1–C^2–$C^{2'}$–$C^{3'}$ using MOPAC PM3 (25° and 21°, respectively). Details will be presented elsewhere.

12) A similar 1,1-dichloro-10b-hydroxy compound was obtained by treatment of **17** with *t*-BuOCl in wet CH_2Cl_2 at room temperature for 9 h. ^{13}C NMR δ = 88.9 (C^{10b}) and 90.4 (C^1). HRMS Found: *m/z* 387.0265. Calcd for $C_{16}H_{15}Cl_2NO_6$: M, 387.0275.

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