Preparation and Properties of 1,1′-Disubstituted Trichotomine Derivatives with a Twisted C=C Bond

Hajime Irikawa,* Satoru Kanke, Kousuke Mito, Yasuhiro Kobayashi, Tomoko Akasaka, Tadashi Atsumi, Hirokazu Arimoto, and Yasuaki Okumura

Department of Chemistry, Faculty of Science, Shizuoka University, Ohya, Shizuoka 422

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Green trichotomine derivatives bearing alkyl groups on C^1 and $C^{1'}$ were prepared. In their absorption spectra, the λ_{max} shifted to longer wavelengths as the 1,1′-substituents became bulkier, and the bathochromism indicated twisting of the central C^2=$C^{2'}$ double bond. A 1,1′-dimethyltrichotomine derivative underwent autooxidation to give orange-red 1,11b-dihydroxylated and 1,11b-seco-dicarbonyl compounds, in which twisting of the central C^2=$C^{2'}$ double bond might be relieved by the decreasing steric interactions between the substituents on C^1 and the $C^{3'}$ carbonyl groups.

A blue pigment, trichotomine dimethyl ester (**1**), has an H-type chromophore similar to that of indigo **2a**.[1] Numerous indigo derivatives have been studied owing to their properties as dyes.[2] The X-ray analysis of **2a** showed that it had a planar structure, and that of *N*,*N*′-dimethylindigo **2b** (R = Me) indicated that the central C=C bond was twisted because of steric interactions between the *N*,*N*′-substituents and the carbonyl groups.[3] We also carried out the X-ray analysis of **1**, and clarified that **1** had a planar structure similar to that of **2a**.[4] In a previous paper, we reported the preparation and X-ray analysis of a 1,1′-bis(ethoxycarbonyl)trichotomine derivative, **3**, which had a twisted C^2=$C^{2'}$ double bond similar to that of **2b**.[5] It was also documented that the absorption spectra of *N*,*N*′-dialkylindigos **2b** and *N*,*N*′-diacylindigos **2c** showed bathochromic shifts as the substituents on the nitrogen atoms became bulkier, and that the bathochromism resulted from the twisting of the central C=C bond.[3,6] In this paper, we wish to report the preparation and properties of trichotomine derivatives, which have alkyl groups on C^1 and $C^{1'}$, and are anticipated to have twisted central C^2=$C^{2'}$ double bonds because of steric interactions between the 1-substituent and the $C^{3'}$-carbonyl group, and between the 1′-substituent and the C^3-carbonyl group.

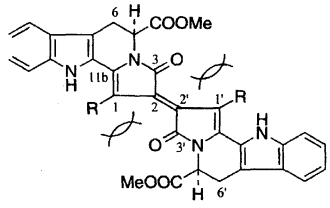
Results and Discussion

Preparation and Properties of 1,1′-Disubstituted Trichotomine Derivatives. 1,1′-Dimethyltrichotomine derivative **4** was prepared by a method similar to that reported in a previous paper.[5] L-Tryptophan methyl ester was condensed with methyl 3-methyl-4-oxobutanoate[7] to give a mixture of four isomers **5a**—**5d** (Chart 1), in which the stereochemistry of C^1 and C^{11b} was determined as follows. The low-field C^5-proton signals of **5a** (δ = 5.36) and **5c** (δ = 5.34) indicated β-orientations for the C^{11b}-protons in **5a** and **5c**.[8] The high-field C^5-proton signals of **5b** (δ = 4.06) and **5d** (δ = 4.07) suggested α-orientations for the C^{11b}-protons in **5b** and **5d**. The *cis*-relationships of the C^1-methyl group and the C^{11b}-proton in **5a** and **5b** were determined by the NOEs in the NOESY spectra of **5a** and **5b**. Isomer **5d** was easily separated by column chromatography and subjected to the following reactions. On treatment with *N*-bromosuccinimide (NBS), **5d** was dehydrogenated to give **6**, which underwent autooxidation in CH_2Cl_2 containing diisopropylamine (*i*-Pr_2NH) to afford a green compound (**4**). In a one-pot reaction, **4** was prepared from **5d** in a 9% yield along with a trace amount of **7**. In the absorption spectrum of **4**, the λ_{max} was observed at 715 nm, which was shifted to a longer wavelength by 57 nm relative to that of **1** (658 nm).[1] This trend is similar to that observed between indigo (**2a**, 604 nm) and *N*,*N*′-dimethylindigo (**2b**, R = Me, 655 nm) bearing a twisted central C=C bond.[3] Furthermore, **3** (R = COOEt, λ_{max} 690 nm) had a bent propeller structure and was twisted by 19° and tilted by 11°.[5] The 1,1′-methyl groups in **4** are as bulky as the 1,1′-ethoxycarbonyl groups in **3**. Therefore, these facts suggested that the C^2=$C^{2'}$ double bond of **4** was twisted because of steric interactions between the 1-methyl group and the 3′-carbonyl group, and between the 1′-methyl group and the 3-carbonyl group.

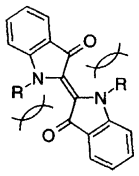
In order to introduce bulky substituents onto C^1 and $C^{1'}$, **1** was reacted with Eschenmoser's salt, CH_2=$N^+Me_2 \cdot I^-$, to give 1,1′-bis(dimethylaminomethyl) derivative **8** (R = CH_2NMe_2).

The λ_{max} of **8** was observed at 741 nm, and the bathochromic shift by 83 nm also indicated twisting of the C^2=$C^{2'}$ double bond of **8** similar to that of **3**. To make the 1,1′-substituents more bulky, **8** was treated with methyl iodide in acetone to give methiodide **9** (R = $CH_2N^+Me_3 \cdot I^-$), which was not stable in solution, and attempts to obtain a crystal suitable for X-ray analysis were unsuccessful.

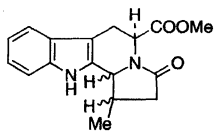
On stirring in MeOH and CH_2Cl_2 at room temperature for 6 d, **9** changed into bis(methoxymethyl) derivative **10a**, (R = CH_2OMe), in which the congestion around the C^2=$C^{2'}$



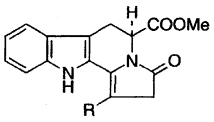
1 R = H
3 R = COOEt
4 R = Me
8 $R = CH_2NMe_2$
9 $R = CH_2N^+Me_3I^-$
10a - 10e $R = CH_2O$-Alkyl
Alkyl: **a** = Me
b = Et
c = *n*-Pr
d = *i*-Pr
e = *t*-Bu



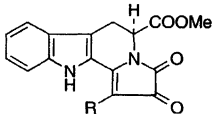
2a R = H
2b R = Alkyl
2c R = Acyl



5a $H^1 = \alpha$ $H^{11b} = \beta$
5b $H^1 = \beta$ $H^{11b} = \alpha$
5c $H^1 = \beta$ $H^{11b} = \beta$
5d $H^1 = \alpha$ $H^{11b} = \alpha$



6 R = Me
15 R = COOEt



7 R = Me
16 R = COOEt

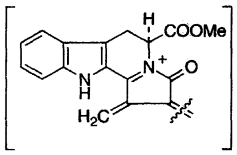


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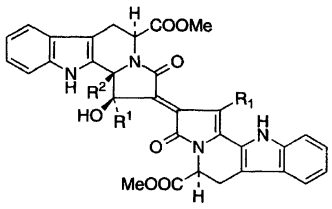
Chart 1.

double bond might be decreased by the small methoxymethyl groups. Formation of **10a** might be rationalized by addition of MeOH to a plausible intermediate such as **11**, which was generated by the Hoffmann-type elimination of Me_3N. Similarly, **9** reacted with EtOH, *n*-PrOH, *i*-PrOH, and *t*-BuOH to give corresponding 1,1′-bis(alkoxy) derivatives **10b**—**10e**, respectively. The absorption spectra of **10a**—**10e** showed λ_{max} at 725 (ε 54300), 728 (53300), 728 (55300), 732 (45900), and 739 (28300) nm, respectively. The λ_{max} shifted to longer wavelengths by 67 to 81 nm relative to that of **1** as the 1,1′-substituents became bulkier. The molar absorptivity ε of **10e** was smaller than those of **10a**—**10d**. The alkyl groups in the $C^{1,1'}$–CH_2O–alkyl moiety are separated by two atoms (an oxygen and a methylene carbon) from the $C^{1,1'}$ positions, and do not affect the electronic effects of the chromophore. Therefore, the absorption spectral characteristics observed in **10a**—**10e** are due to steric effects of the 1,1′-substituents, and indicate twisting of the $C^2=C^{2'}$ double bonds of **10a**—**10e**.

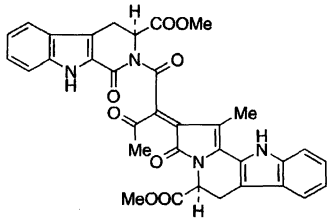
Next, we compared the IR and ^{13}C NMR spectra of **10a**—**10e**, and attempted to determine the spectroscopic properties of the twisted $C^2=C^{2'}$ double bond. But the 1,1′-substituents had little effect on the amido carbonyl and C=C streching bands, since they were observed in 1669 (**10a**)—1665 (**10e**) cm^{-1} and 1577 (**10a**)—1578 (**10e**) cm^{-1}, respectively.

The ^{13}C NMR (in acetone-d_6) signals of **10a**—**10e** were assigned using CH-COSY and COLOC experiments. The C^2 signals were observed at δ = 130.4 (**10a**)—129.4 (**10e**), and no distinctive spectroscopic characteristics of the twisted $C^2=C^{2'}$ double bond were found. The chemical shifts of other carbons were also identical within 1 ppm, except for the C^1–CH_2O–alkyl signals.

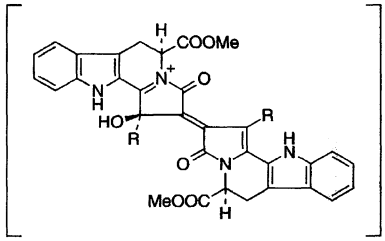
Autooxidation of 3 and 4. Attempts to obtain a crystal of **4** suitable for X-ray analysis were unsuccessful, since **4** was not stable in solution. On standing for several weeks in *t*-BuOH or CH_2Cl_2, **4** underwent autooxidation to give a complex mixture of products, from which two orange-red compounds, **12** (λ_{max} = 500 nm) and **13** (λ_{max} = 499 nm), were obtained (Chart 2). The ^1H and ^{13}C NMR spectra of **12** indicated that the two indole rings remained intact and **12** had an unsymmetrical structure. The ^1H NMR signals at δ = 5.74 and 7.48 were exchangeable with D_2O, and suggested the presence of two hydroxy groups on the quaternary C^1 (δ_C = 81.8) and C^{11b} (δ_C = 86.2). Two methyl carbon signals at δ_C = 13.7 ($C^{1'}$–Me) and at a low-field (δ_C = 22.2, C^1–Me)



12 R^1 = Me R^2 = OH
17 R^1 = COOEt R^2 = OBu^n
19 R^1 = COOEt R^2 = OMe



13



14 R = Me
18 R = COOEt

Chart 2.

supported the presence of one hydroxy group on C^1. The molecular ion peak in the FABMS spectrum of **12** was larger by 34 (OH×2) than that of **4**. So, the 1,11b-dihydroxylated structure **12** was in line with the spectral data. The orientation of the hydroxy group on C^{11b} was suggested to be β, since the ^{1}H NMR signal of C^5–H was observed at a low-field (δ = 5.18 or 5.64).[8] The C^1–methyl group was deduced to be α, since its ^{1}H NMR signal was observed at a high-field (δ = 1.17, 3H, s), and it seems to be shielded in the same way as the C^1–methyl group (δ = 0.74) in **5c**. On the other hand, in the FABMS spectrum of **13**, the molecular ion peak was larger by 32 (two oxygens) than that of **4**. The presence of the methyl ketone group in **13** was suggested from the ^{1}H NMR signal (δ = 2.26, 3H, s) and the ^{13}C NMR signal (δ = 194.4). So, the 1,11b-seco-dicarbonyl structure of **13** was in agreement with the spectral data. Usually, the 3-position of indoles undergoes autooxidation to give 3-hydroperoxy-3*H*-indoles.[9] It is also reported that **2b** (R = Me) is readily oxidizable in solution because of the high electron density at the central sp^2 carbon atoms, and *N*-methylisatin is the oxidation product.[3] In the case of **4**, the enamine-type C^1=C^{11b} double bond was more oxidizable than the C^2=$C^{2'}$ and C^{6a}=C^{11a} double bonds, and autooxidation of **4** might proceed via a C^1-hydroperoxylated intermediate, which changed into a C^1-hydroxylated compound such as **14** or into a compound having a dioxetane ring attached to the C^1–C^{11b} position. Compound **12** might be formed by addition of water to **14** from the less hindered side, and **13** might be obtained by cleavage of the C^1–C^{11b}–dioxetane ring.

Similar autooxidation was observed in the preparation of **3** under Iwadare's conditions used for the synthesis of **1**.[1] On heating in *n*-BuOH at 95—100 °C for 70 h under oxygen atmosphere, **15** underwent autooxidation to give **3**, **16**,[5] and orange compound **17** (λ_{max} = 485 nm). On stirring in a mixture of *i*-Pr_2NH, *n*-BuOH, and CH_2Cl_2, **3** afforded the same **17** (26%) as that obtained above. The ^{1}H and ^{13}C NMR spectra of **17** suggested an unsymmetrical structure and the presence of a hydroxy group (δ_H = 6.43) on C^1 (δ_C = 83.2) and a butoxy group (δ_C = 14.0, 19.5, 31.9, 64.3) on C^{11b} (δ_C = 89.1). In the FABMS spectrum of **17**, the molecular ion peak was not found, but the observed fragment ion peak at m/e 721 ($M^+ - OBu$) could be explained by a compound such as **18**, supporting the described structure of **17**. In the presence of MeOH, **3** was similarly oxidized to afford orange compound **19** (λ_{max} = 485 nm). In the COLOC spectrum of **19**, cross-peaks between the C^{11b} signal (δ_C = 89.4) and the H^5 (δ_H = 5.58) and the CH_3O (δ_H = 3.70) signals supported the presence of the methoxy group on C^{11b}. The FABMS spectrum of **19** also did not show the molecular ion peak. But, the observed fragment ion peak at *m/z* 721 was assigned to **18** mentioned above, and the fragmentation pattern of **19** was similar to that of **17**, supporting the described structure of **19**. The configurations of the ethoxycarbonyl groups on C^1 and the alkoxy groups on C^{11b} in **17** and **19** were assigned similarly. In the ^{1}H NMR spectra of **17** and **19**, the methyl signals were observed at a high-field (δ = 0.66, 3H, t, CH_3CH_2OOC–C_1). The spectra also indicated that the ethoxycarbonyl groups were on the α side, and shielded in the same way as the C^1–methyl group in **5c**. The β-orientation of the alkoxy groups were deduced from the low-field C^5-proton signals (δ = 5.24—5.58).[8] Autooxidation of **3** might proceed via intermediate **18**, which gives **17** and **19** by addition of *n*-BuOH and MeOH, respectively, from the less hindered β side.

Under conditions similar to those used for autooxidation of **3** and **4**, trichotomine dimethyl ester **1** was stable. Therefore, congestion around the central C^2=$C^{2'}$ double bonds in **3** and **4** makes the C^1 = C^{11b} double bonds readily oxidizable, and formation of **12**, **13**, **17**, and **19** might indicate that twisting of the C^2=$C^{2'}$ double bonds in **3** and **4** is relieved by the decreasing steric interactions between the substituents on C^1 and the $C^{3'}$-carbonyl groups.

Experimental

All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AC300 (300 MHz, 75 MHz) in $CDCl_3$, unless otherwise stated, using TMS as an internal standard. ^{13}C NMR spectra in a CD_3COCD_3 solution were recorded using a solvent signal at δ = 29.8 as a reference. IR spectra were recorded on a Bruker IFS 66V. Absorption spectra were measured on a Shimadzu-UV-3100. Mass spectra were obtained on a JEOL-DX303.

Preparation of 5a—5d. A mixture of L-tryptophan methyl ester (4.36 g, 20 mmol), methyl 3-methyl-4-oxobutanoate (3.90 g, 30 mmol), trifluoroacetic acid (0.1 ml), and molecular sieves 4A (4 g) in dry benzene (100 ml) was refluxed for 2 h. The molecular sieves were then removed by filtration. To the filtrate was added trifluoroacetic acid (2 drops). The resulting mixture was refluxed for 45 h, washed with aqueous $NaHCO_3$, and with brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to leave an oil, which contained four isomers, **5a**—**5d**, in a ratio of 1.0 : 1.6 : 1.0 : 1.3 (determined by ^{1}H NMR). Separation by column chromatography (SiO_2, AcOEt–hexane) gave **5a**—**5d** (total amount 4.54 g, 76%).

5a: Mp 107—113 °C (AcOEt–hexane); ^{1}H NMR δ = 1.45 (3H, d, *J* = 6.1 Hz), 2.30—2.42 (2H, m), 2.63 (1H, m), 3.11 (1H, ddd, *J* = 15.8, 7.2, and 2.1 Hz), 3.43 (1H, d, *J* = 15.8 Hz), 3.63 (3H, s), 4.78 (1H, d, *J* = 8.6 Hz), 5.36 (1H, d, *J* = 7.2 Hz), 7.09—7.53 (4H, m), and 8.42 (1H, br s); ^{13}C NMR δ = 18.1, 23.7, 36.3, 39.9, 49.1, 52.5, 59.0, 105.7, 111.1, 118.4, 119.9, 122.4, 126.6, 132.0, 136.5, 171.2, and 173.3. Found: *m/z* 298.1319. Calcd for $C_{17}H_{18}N_2O_3$: M, 298.1317.

5b: Mp 223—225 °C (AcOEt–hexane); ^{1}H NMR δ = 1.37 (3H, d, *J* = 6.4 Hz), 2.15 (1H, dd, *J* = 15.7 and 5.3 Hz), 2.43—2.65 (2H, m), 2.98 (1H, dd, *J* = 15.6 and 4.6 Hz), 3.34 (1H, dd, *J* = 15.6 and 10.5 Hz), 3.76 (3H, s), 4.06 (1H, dd, *J* = 10.5 and 4.6 Hz), 4.56 (1H, br s), 7.05—7.47 (4H, m), and 9.21 (1H, br s); ^{13}C NMR δ = 19.7, 22.8, 32.9, 38.5, 52.1, 54.1, 62.8, 107.3, 111.0, 117.8, 119.4, 121.8, 126.1, 132.8, 136.3, 170.0, and 174.6. Found: *m/z* 298.1307. Calcd for $C_{17}H_{18}N_2O_3$: M, 298.1317.

5c: Mp 290—292 °C (AcOEt–hexane); ^{1}H NMR δ = 0.74 (3H, d, *J* = 6.9 Hz), 2.19 (1H, d, *J* = 15.8 Hz), 2.50—2.98 (2H, m), 3.08 (1H, ddd, *J* = 15.7, 7.1, and 2.2 Hz), 3.47 (1H, d, *J* = 15.7 Hz), 3.62 (3H, s), 5.28 (1H, d, *J* = 5.5 Hz), 5.34 (1H, d, *J* = 7.1 Hz), 7.10—7.56 (4H, m), and 8.29 (1H, br s); ^{13}C NMR δ = 15.5, 23.7, 31.6, 40.3, 49.4, 52.6, 56.4, 107.6, 111.0, 118.4, 119.8, 122.3, 126.7,

129.7, 136.6, 171.2, and 173.4. Found: *m/z* 298.1307. Calcd for $C_{17}H_{18}N_2O_3$: M, 298.1317.

5d: Mp 192—194 °C (AcOEt–hexane); ^{1}H NMR δ = 1.06 (3H, d, J = 7.0 Hz), 2.07 (1H, dd, J = 16.5 and 4.3 Hz), 2.75 (1H, dd, J = 16.5 and 7.7 Hz), 2.89 (1H, m), 3.05 (1H, dd, J = 15.6 and 4.7 Hz), 3.31 (1H, dd, J = 15.6 and 10.1 Hz), 3.84 (3H, s), 4.07 (1H, dd, J = 10.1 and 4.7 Hz), 5.07 (1H, d, J = 6.3 Hz), 7.11—7.55 (4H, m), and 8.32 (1H, br s); ^{13}C NMR δ = 15.9, 23.6, 31.5, 39.3, 52.6, 54.5, 59.7, 109.8, 111.1, 118.3, 119.9, 122.5, 126.5, 130.1, 136.6, 170.4, and 174.4. Found: C, 68.53; H, 5.90; N, 9.48%. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39%.

Preparation of 6. To a solution of **5d** (150 mg, 0.50 mmol) in dry CH_2Cl_2 (10 ml) was added a solution of NBS (98 mg, 0.55 mmol) in dry CH_2Cl_2 (20 ml). The solution was stirred at room temperature for 1 h, washed with water, and with brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to leave a residue, which was crystallized from $CHCl_3$–hexane to give **6** (120 mg, 81%): Mp 264—267 °C (in a sealed tube); ^{1}H NMR δ = 2.11 (3H, s), 3.17 (1H, d, J = 24.2 Hz), 3.23 (1H, dd, J = 16.0 and 6.4 Hz), 3.34 (1H, d, J = 24.2 Hz), 3.62 (3H, s), 3.63 (1H, d, J = 16.0 Hz), 5.16 (1H, d, J = 6.4 Hz), 7.12—7.57 (4H, m), and 8.36 (1H, br s); ^{13}C NMR δ = 13.3, 23.6, 42.5, 50.1, 52.8, 106.4, 109.2, 111.3, 119.0, 120.4, 123.5, 125.9, 126.0, 126.5, 137.6, 170.9, and 176.0. Found: *m/z* 296.1140. Calcd for $C_{17}H_{16}N_2O_3$: M, 296.1162.

Oxidative Dimerization of 6. A solution of **6** (30 mg) and *i*-Pr_2NH (1 drop) in CH_2Cl_2 (10 ml) was stirred at room temperature for 30 h, and concentrated under reduced pressure. The residue was separated by column chromatography (SiO_2–$CHCl_3$), and crystallized from MeOH to give **4** (3 mg, 10%): Mp 226—228 °C; UV-vis ($CHCl_3$) 370 (ε 22800) and 715 nm (41500); IR ($CHCl_3$) 1738, 1667, and 1583 cm^{-1}; ^{1}H NMR δ = 2.48 (3H×2, s), 3.36 (1H×2, dd, J = 16.8 and 7.5 Hz), 3.60 (3H×2, s), 3.79 (1H×2, d, J = 16.8), 5.24 (1H×2, d, J = 7.5 Hz), 7.14—7.62 (4H×2, m), and 8.49 (1H×2, br s); ^{13}C NMR δ = 13.8, 24.3, 50.4, 53.0, 111.7, 112.1, 115.0, 119.7, 121.1, 125.4, 126.0, 126.3, 131.9, 134.2, 139.5, 167.7, and 170.9. Found: *m/z* 588.2000. Calcd for $C_{34}H_{28}N_4O_6$: M, 588.2009.

One-Pot Preparation of 4. A mixture of **5d** (298 mg, 1.0 mmol) and NBS (230 mg, 1.3 mmol) in dry CH_2Cl_2 (30 ml) was stirred at room temperature for 30 min. To the solution was added *i*-Pr_2NH (0.5 ml). The resulting solution was stirred at room temperature overnight, washed with water, and dried over Na_2SO_4. Evaporation of the solvent and separation by column chromatography (SiO_2–$CHCl_3$) gave **4** (27 mg, 9%) along with a small amount of **7** (as an oil, 0.5 mg, 0.2%). **7**: UV(MeOH) 349 (ε 19000) and 444 nm (15100); ^{1}H NMR δ = 2.18 (3H, s), 3.45 (1H, dd, J = 17.1 and 7.1 Hz), 3.65 (3H, s), 3.84 (1H, dd, J = 17.1 and 1.3 Hz), 5.23 (1H, dd, J = 7.1 and 1.3 Hz), 7.22—7.73 (4H, m), and 8.62 (1H, br s); ^{13}C NMR δ = 7.1, 24.0, 49.5, 53.2, 102.8, 112.2, 119.2, 120.8, 121.8, 123.6, 125.5, 127.7, 140.4, 149.8, 159.9, 169.8, and 183.3. Found: *m/z* 310.0945. Calcd for $C_{17}H_{14}N_2O_4$: M, 310.0953.

Preparation of 8. A mixture of **1** (112 mg, 0.20 mmol) and Eschenmoser's salt (320 mg, 1.73 mmol) in dry CH_2Cl_2 (100 ml) was refluxed for 68 h. The mixture was washed with aqueous $NaHCO_3$, and with brine, and then dried over Na_2SO_4. The solvent was removed under reduced pressure to leave a residue, which was separated by column chromatography (SiO_2–$CHCl_3$) to give **8** (as an oil, 93 mg, 69%): UV-vis ($CHCl_3$) 373 (ε 21900) and 741 nm (52700); IR ($CHCl_3$) 1745, 1664, and 1577 cm^{-1}; ^{1}H NMR δ = 2.38 (6H×2, s), 3.37 (1H×2, dd, J = 17.1 and 7.1 Hz), 3.47 (1H×2, d, J = 14.9 Hz), 3.65 (3H×2, s), 3.73 (1H×2, d, J = 17.1 Hz), 4.02 (1H×2, d, J = 14.9 Hz), 5.24 (1H×2, d, J = 7.1 Hz), 7.08—7.60 (4H×2, m), and 12.63 (1H×2, br s); ^{13}C NMR δ = 24.0, 44.1, 50.1, 52.8, 56.7, 112.3, 113.9, 114.7, 119.8, 120.2, 124.8, 126.9, 127.0, 130.2, 135.5, 139.7, 168.8, and 170.8. Found: *m/z* 674.2875. Calcd for $C_{38}H_{38}N_6O_6$: M, 674.2853.

Preparation of the Methiodide 9. A solution of **8** (69 mg, 0.10 mmol) and CH_3I (1.37 g, 9.6 mmol) in dry acetone (8 ml) was left at room temperature for 11 d. Filtration of the resulting crystals gave **9** (85 mg, 87%): IR(Nujol) 1738, 1660, and 1538 cm^{-1}.

Without further purification, **9** was subjected to the next experiments.

Formation of the Alkoxymethyl Derivatives 10a—10e. **10a—10e** were prepared by stirring a mixture of the methiodide **9**, an appropriate alcohol, and CH_2Cl_2 at room temperature for 1 to 2 weeks. Typical procedure is as follows.

A mixture of **9** (30 mg), MeOH (1 ml), and CH_2Cl_2 (10 ml) was stirred at room temperature for 6 d, and concentrated under reduced pressure. The residue was separated by column chromatography (SiO_2–$CHCl_3$) to give **10a** (as an oil, 13 mg, 65%): UV-vis ($CHCl_3$) 371 (ε 24500) and 725 nm (54300); IR ($CHCl_3$) 1745, 1669, and 1577 cm^{-1}; ^{1}H NMR (CH_3COCD_3) δ = 3.39 (3H×2, s), 3.40 (1H×2, m), 3.63 (3H×2, s), 3.74 (1H×2, d, J = 17.1 Hz), 4.89 (2H×2, AB-q, J = 14.1 Hz), 5.25 (1H×2, d, J = 7.1 Hz), 7.07—7.65 (4H×2, m), and 10.36 (1H×2, br s); ^{13}C NMR (CD_3COCD_3) δ = 24.3 (C_6), 50.9 (C_5), 53.0 (*Me*OOC), 57.0 (*Me*OCH_2), 68.2 (*C*H_2OMe), 113.2 (C_{10}), 113.7 (C_1), 115.8 (C_{6a}), 120.4 (C_7), 121.2 (C_8), 126.0 (C_9), 126.1 (C_{11a}), 127.1 (C_{6b}), 130.4 (C_2), 136.5 (C_{11b}), 140.7 (C_{10a}), 168.8 (C_3), and 171.4 (*C*OOMe). Found: *m/z* 648.2252. Calcd for $C_{36}H_{32}N_4O_8$: M, 648.2220.

10b (as an oil, yield 40%): UV-vis ($CHCl_3$) 372 (ε 24500) and 728 nm (53300); IR ($CHCl_3$) 1743, 1668, and 1577 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ = 1.20 (3H×2, t, J = 7.0 Hz), 3.30—3.90 (4H×2, m), 3.64 (3H×2, s), 4.92 (2H×2, AB-q, J = 14.3 Hz), 5.27 (1H×2, d, J = 6.5 Hz), 7.10—7.70 (4H×2, m), and 10.52 (1H×2 br s); ^{13}C NMR (CD_3COCD_3) δ = 15.5, 24.4, 51.0, 53.0, 65.3, 66.4, 113.0, 114.2, 115.7, 120.5, 121.3, 126.1, 126.2, 127.1, 130.3, 136.5, 140.6, 168.7, and 171.4. Found: *m/z* 676.2541. Calcd for $C_{38}H_{36}N_4O_8$: M, 676.2533.

10c (as an oil, 41%): UV-vis ($CHCl_3$) 372 (ε 25900) and 728 nm (55300); IR ($CHCl_3$) 1743, 1668, and 1578 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ = 0.88 (3H×2, t, J = 7.4 Hz), 1.60 (2H×2, m), 3.41—3.62 (3H×2, m), 3.64 (3H×2, s), 3.79 (1H×2, d, J = 17.2 Hz), 4.94 (2H×2, AB-q, J = 14.0 Hz), 5.28 (1H×2, d, J = 7.3 Hz), 7.10—7.70 (4H×2, m), and 10.48 (1H×2, br s); ^{13}C NMR (CD_3COCD_3) δ = 11.0, 23.5, 24.5, 51.0, 53.0, 66.5, 71.7, 113.0, 114.2, 115.7, 120.5, 121.3, 126.1, 126.2, 127.2, 130.4, 136.5, 140.6, 168.7, and 171.4. Found: *m/z* 704.2759. Calcd for $C_{40}H_{40}N_4O_8$: M, 704.2846.

10d (as a oil, 18%): UV-vis ($CHCl_3$) 373 (ε 22000), and 732 nm (45900); IR ($CHCl_3$) 1742, 1667, and 1578 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ = 1.11 (3H×2, d, J = 6.1 Hz), 1.19 (3H×2, d, J = 6.1 Hz), 3.39 (1H×2, dd, J = 17.1 and 7.2 Hz), 3.62 (3H×2, s), 3.72—3.85 (2H×2, m), 4.94 (2H×2, AB-q, J = 14.4 Hz), 5.23 (1H×2, d, J = 7.2 Hz), 7.08—7.68 (4H×2, m), and 10.50 (1H×2, br s); ^{13}C NMR (CD_3COCD_3) δ = 21.7, 22.9, 24.4, 50.9, 52.9, 63.5, 70.5, 113.0, 115.0, 115.7, 120.5, 121.3, 126.0, 126.3, 127.2, 130.3, 136.6, 140.6, 169.0, and 171.5. Found: *m/z* 704.2906. Calcd for $C_{40}H_{40}N_4O_8$: M, 704.2846.

10e (as an oil, 10%): UV-vis ($CHCl_3$) 374 (ε 13300) and 739 nm (28300); IR ($CHCl_3$) 1741, 1665, and 1578 cm^{-1}; ^{1}H NMR (CD_3COCD_3) δ = 1.31 (9H×2, s), 3.47 (1H×2, dd, J = 17.3 and 7.3 Hz), 3.64 (3H×2, s) 3.83 (1H×2, d, J = 17.3 Hz), 4.92 (2H×2, AB-q, J = 15.1 Hz), 5.29 (1H×2, d, J = 7.3 Hz), 7.10—7.71 (4H×2,

m), and 10.78 (1H×2, br s); ^{13}C NMR (CD_3COCD_3) δ = 24.3, 28.1, 50.9, 53.0, 59.4, 76.1, 112.8, 115.5, 117.3, 120.6, 121.3, 126.0, 126.5, 127.3, 129.4, 136.2, 140.4, 169.2, and 171.4. Found: *m/z* 732.3207. Calcd for $C_{42}H_{44}N_4O_8$: M, 732.3159.

Autooxidation of 4. A solution of **4** (20 mg) in *t*-BuOH (5 ml) was allowed to stand at room temperature for 3 months, and concentrated to give a residue, which contained complex products along with **4**. The residue was dissolved in CH_2Cl_2 (10 ml) and left at room temperature for 1 week. The resulting orange solution did not contain **4**, and was evaporated to give an oil, which was separated by column chromatography (SiO_2, MeOH : $CHCl_3$ = 1 : 50) and PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 40) to yield **12** (as an oil, 2 mg, 10%) and **13** (as an oil, 1 mg, 5%).

12: UV-vis (MeOH) 319 (ε 14100) and 500 nm (10800); ^{1}H NMR δ = 1.17 (3H, s), 2.56 (3H, s), 3.14 (1H, dd, *J* = 16.2 and 7.0 Hz), 3.35 (1H, dd, *J* = 16.2 and 7.0 Hz), 3.53 (1H, d, *J* = 16.2 Hz), 3.67 (3H, s), 3.70—3.80 (1H), 3.76 (3H, s), 5.18 (1H, d, *J* = 7.0 Hz), 5.64 (1H, d, *J* = 7.0 Hz), 5.74 (1H, s, exchangeable with D_2O), 7.13—7.65 (8H, m), 7.48 (1H, s, exchangeable with D_2O), 8.51 (1H, br s), and 8.74 (1H, br s); ^{13}C NMR δ = 13.7, 22.2, 23.7, 24.3, 50.0, 50.2, 53.2, 53.3, 81.8, 86.2, 106.9, 107.0, 111.7, 111.8, 114.2, 118.9, 119.7, 119.9, 121.1, 123.2, 125.1, 125.4, 125.6, 125.7, 130.2, 133.5, 135.8, 136.7, 138.9, 145.5, 166.0, 170.1, 171.1, and 173.2. Found: *m/z* 622.2015. Calcd for $C_{34}H_{30}N_4O_8$: M, 622.2064.

13: UV-vis (MeOH) 315 (ε 20800) and 499 nm (9000); ^{1}H NMR δ = 2.26 (3H, s), 2.56 (3H, s), 3.20 (1H, dd, *J* = 16.3 and 7.3 Hz), 3.28 (3H, s), 3.60—3.75 (3H, m), 3.71 (3H, s), 5.00 (1H, d, *J* = 7.3 Hz), 6.00 (1H, dd, *J* = 6.0 and 2.5 Hz), 7.12—7.70 (8H, m), 8.39 (1H, br s), and 8.87 (1H, br s); ^{13}C NMR δ = 13.3, 22.9, 23.9, 29.9, 49.8, 52.6, 53.1, 56.2, 105.6, 111.6, 112.6, 114.9, 119.6, 121.0, 121.1, 121.2, 121.8, 124.7, 125.0, 125.4, 125.8, 127.1, 134.2, 135.4, 137.2, 138.6, 138.9, 168.0, 169.6, 170.1, 171.0, and 194.4. Found: *m/z* 621.2003. Calcd for $C_{34}H_{29}N_4O_8$: M+H, 621.1985.

Autooxidation of 15. Oxygen was bubbled through a solution of **15** (30 mg) in *n*-BuOH (50 ml) kept at 95—100 °C for 70 h. The solution was concentrated under reduced pressure to give an oil, which was separated by PTLC (SiO_2, MeOH : $CHCl_3$ = 1 : 50) to yield **3** (2 mg, 7%), **16**[5] (6 mg, 19%), and **17** (as an oil, 2 mg, 6%). **17**: UV-vis (MeOH) 224 (ε 50100), 274 (14000), 350 (14500), and 485 nm (24600); ^{1}H NMR δ = 0.66 (3H, t, *J* = 7.2 Hz), 0.93 (3H, t, *J* = 7.2 Hz), 1.36—1.68 (4H, m), 1.42 (3H, t, *J* = 7.2 Hz), 2.88 (1H, dd, *J* = 15.6 and 7.5 Hz), 3.44 (1H, dd, *J* = 17.7 and 7.5 Hz), 3.58 (2H, q, *J* = 7.2 Hz), 3.61 (1H, d, *J* = 15.6 Hz), 3.69 (3H, s), 3.72 (3H, s), 3.78 (1H, d, *J* = 17.7 Hz), 3.94 (2H, m), 4.41 (2H, q, *J* = 7.2 Hz), 5.24 (1H, d, *J* = 7.5 Hz), 5.56 (1H, d, *J* = 7.5 Hz), 6.43 (1H, s, exchangeable with D_2O), 7.05—7.65 (8H, m), 8.53 (1H, br s), and 10.96 (1H, br s); ^{13}C NMR δ = 13.5, 14.1, 19.5, 21.7, 23.5, 31.9, 49.8, 50.3, 52.6, 53.4, 61.4, 62.5, 64.3, 83.2, 89.1, 101.4, 108.6, 111.8, 112.8, 117.6, 119.0, 119.7, 120.3, 121.1, 123.1, 123.2, 125.2, 125.4, 127.2, 128.1, 128.7, 136.6, 139.4, 141.5, 141.9, 166.0, 166.1, 168.1, 169.7, 169.8, and 170.2. Found: *m/z* 721.2151. Calcd for $C_{38}H_{33}N_4O_{11}$: M − OBu, 721.2146.

Autooxidation of 3. A mixture of **3** (30 mg), *i*-Pr_2NH (2 ml), *n*-BuOH (4 ml), and CH_2Cl_2 (4 ml) was stirred at room temperature for 5 d, and concentrated under reduced pressure. The residue was separated by column chromatography (SiO_2, $CHCl_3$ or AcOEt : hexane = 1 : 1) to give **17** (as an oil, 9 mg, 26%), which was identical with that obtained above by TLC and ^{1}H NMR comparisons.

Formation of 19. A mixture of **3** (30 mg), *i*-Pr_2NH (2 ml), MeOH (4 ml), and CH_2Cl_2 (4 ml) was sirred at room temperature for 4 d, and worked up as described above to give **19** (as an oil, 5 mg, 16%): UV-vis (MeOH) 223 (ε 58700), 274 (19800), 349 (15900), and 485 nm (25700); ^{1}H NMR δ = 0.66 (3H, t, *J* = 7.2 Hz), 1.43 (3H, t, *J* = 7.2 Hz), 2.91 (1H, dd, *J* = 15.7 and 6.7 Hz), 3.44 (1H, dd, *J* = 17.4 and 7.5 Hz), 3.61 (2H, q, *J* = 7.2 Hz), 3.63 (1H, d, *J* = 15.7 Hz), 3.66 (3H, s), 3.70 (3H, s), 3.71 (3H, s), 3.79 (1H, d, *J* = 17.4 Hz), 4.41 (2H, q, *J* = 7.2 Hz), 5.25 (1H, d, *J* = 7.5 Hz), 5.58 (1H, d, *J* = 6.7 Hz), 6.52 (1H, s, exchangeable with D_2O), 7.06—7.63 (8H, m), 8.60 (1H, br s), and 10.95 (1H, br s); ^{13}C NMR δ = 13.5, 14.0, 21.8, 23.5, 49.8, 50.4, 52.4, 52.5, 53.5, 61.5, 62.6, 83.0, 89.4, 101.8, 108.9, 111.8, 112.8, 117.8, 119.0, 119.8, 120.3, 121.1, 123.1, 123.3, 125.2, 125.3, 127.3, 127.6, 128.9, 136.7, 139.4, 140.9, 142.1, 166.0, 166.1, 167.8, 169.7, 169.9, and 170.2. Found: *m/z* 721.2213. Calcd for $C_{38}H_{33}N_4O_{11}$: M − OMe, 721.2146.

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