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Syntheses of Biliverdin Derivatives Sterically Locked at the CD-Ring Components

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Total syntheses of biliverdin derivatives with a *Z-syn*, *Z-anti*, or *E-syn* CD-ring components were accomplished via new and efficient methods for the construction of sterically locked CD-ring components towards the elucidation of the stereochemistry of the chromophore in phytochromes.

Light is vital for photosynthesis, and it is also necessary for directing plant growth and development. The sensing of light in environmental conditions is essential for plants as vision is for animals. To fine-tune their development according to light intensity, direction, wavelength, and periodicity, they possess multiple light sensors. There are several light-sensing systems involved in these responses, such as the blue light sensitive system with cryptochrome[1a] or phototropin[1b] and the red light sensitive system with phytochrome.[1c] Phytochromes are chromoproteins that have either phytochromobilin (PΦB) or phytocyanobilin (PCB) as a chromophore, which is covalently bound to the protein by a thioether bond through an A-ring ethylidene side chain and responds to red and far-red light through a reversible interchange between *Z*- and *E*-forms at the C15 position of the chromophores (Fig. 1).[2] This double-bond photoisomerization converts the physiologically inactive red light absorbing P_r form into the active far-red light absorbing P_{fr} form and vice versa. The interchange between the P_r and P_{fr} forms is essential for light absorbing biological processes in the phytochrome chromophore function. Some bacterial phytochromes have biliverdin (BV) as a natural chromophore, and we have recently determined that BV covalently binds to the apoprotein of *Agrobacterium* phytochrome Agp1 via its A-ring vinyl side chain.[3]

During photoconversion, the chromophore also moves around the exocyclic single bonds. In principle, each single bond can adopt either a *syn* or *anti* conformation.[4] Vibrational spectroscopy provided indirect insight into the conformation of

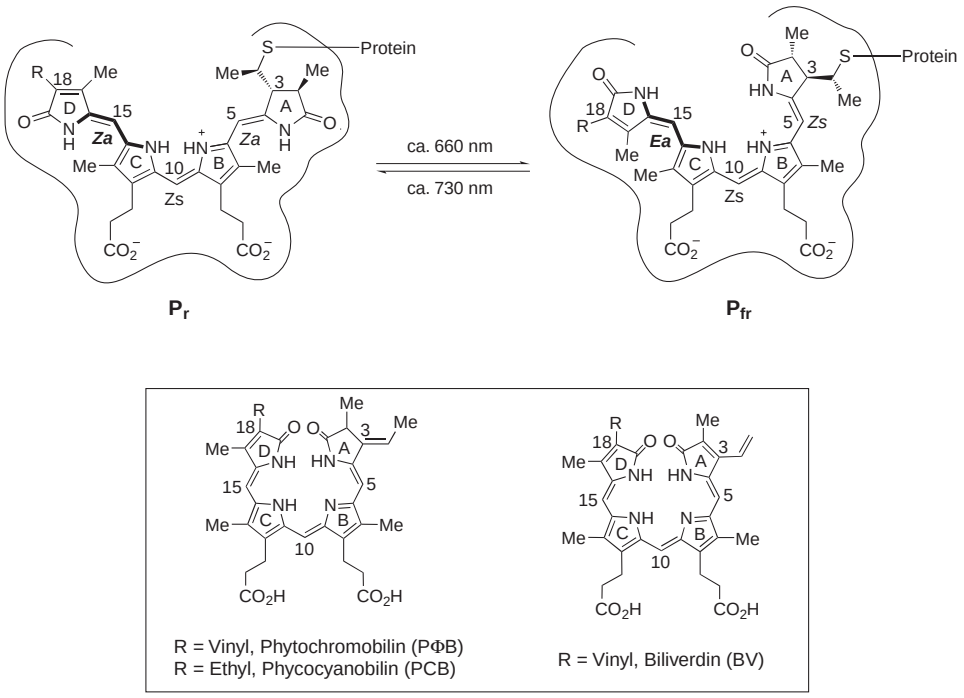

Fig. 1. Photoreversibility of phytochromes between P_r and P_{fr}, and the structure of phytochrome chromophores.

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the phytochrome chromophore in the P_r, P_{fr}, and intermediate states, but the data were ambiguous and have been interpreted in different ways.[2,5–7] For example, it was proposed that the formation of P_{fr} is accompanied by a *syn*/*anti* rotation around the C14–C15 single bond.[5] More recently, interpretation of resonance Raman spectra by density functional theory calculations proposed that the C14–C15 single bond is in an *anti* conformation throughout the entire photocycle and that the C5–C6 single bond rotates from *anti* to *syn* upon conversion from P_r to P_{fr} as shown in Fig. 1.[2]

To analyze the structure and function of the chromophore in phytochromes, we have studied on the total syntheses of natural and unnatural chromophores.[8–11] In this paper, we describe the syntheses of three different types of BV derivatives, in which the stereochemistry between the rings C and D are locked in *Z-syn*, *Z-anti*, and *E-syn* configuration and conformation,[12] respectively, to determine the stereochemistry of the chromophore at the C15 position of P_r and P_{fr} forms and the function of the reconstituted Agp1. The retro-synthetic analyses of the three chromophores are shown in Fig. 2.

Results and Discussion

Preparation of Allyl (*Z*)-3-(4-Methyl-5-{[4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene]methyl}-1*H*-pyrrol-3-yl)-propanoate (4). The AB-ring component **4** is common for all chromophores prepared herein. We previously reported that it can be readily prepared by cleavage of BV diallyl ester with thiobarbituric acid in methanol; however, unusable barbituric acid adducts were produced at the same time.[13c] Therefore, an alternative method was developed starting from 3-methyl-4-[2-(*p*-tolylthio)ethyl]-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one[8f] (**11**) as the A-ring precursor and *t*-butyl 3-(3-allyloxy-3-oxopropyl)-5-formyl-4-methyl-1*H*-pyrrole-2-carboxylate[8c] (**10a**), the latter of which is a precursor common to the B- and C-rings of BV, as shown in Scheme 1. Compounds **11** and **10a** were coupled according to the original Wittig-type coupling reaction[8b] in which tributylphosphine and 1,8-diazabicyclo[5.4.0]-

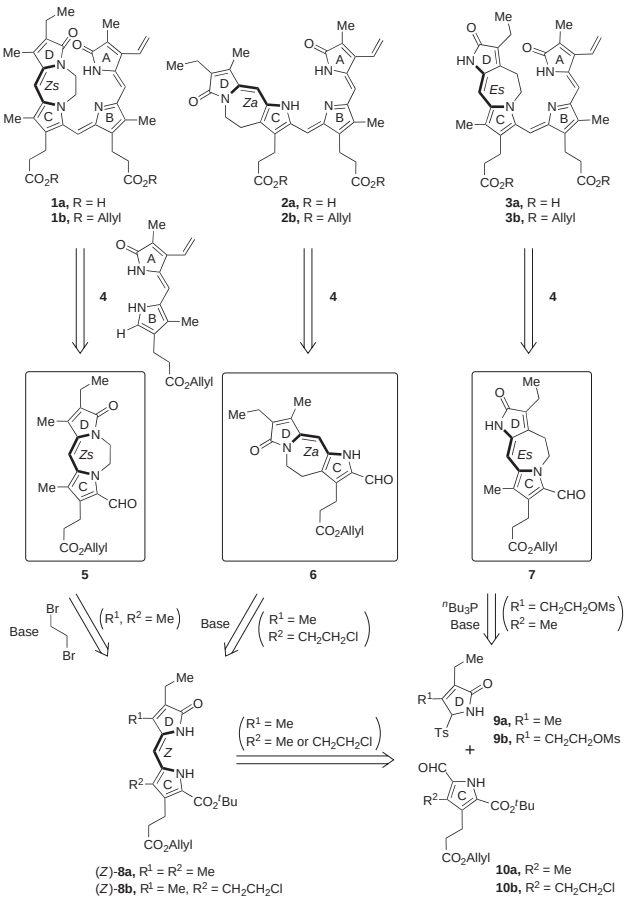
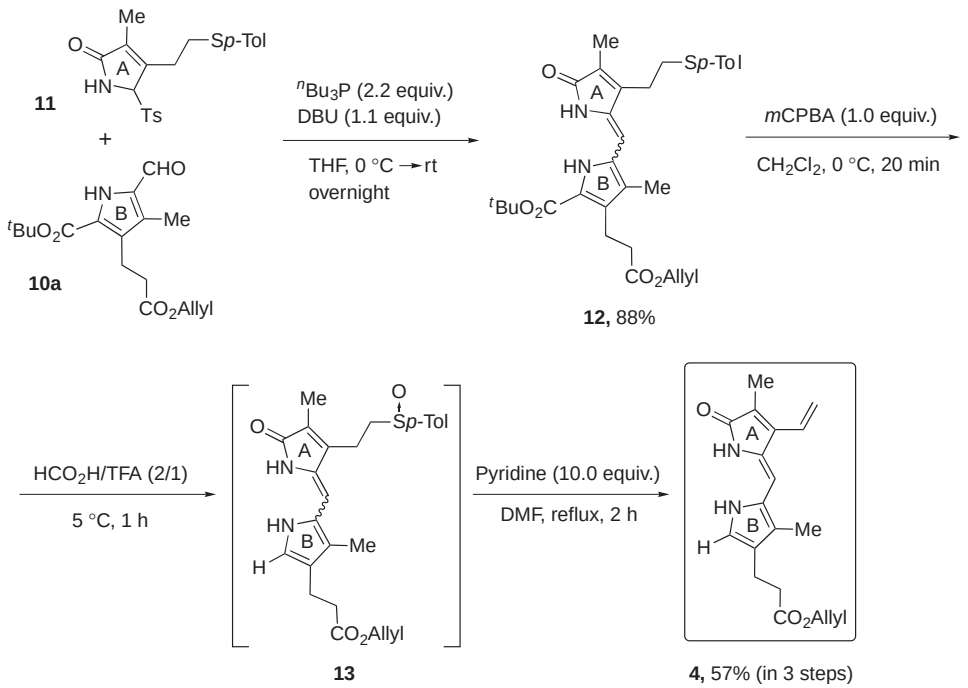
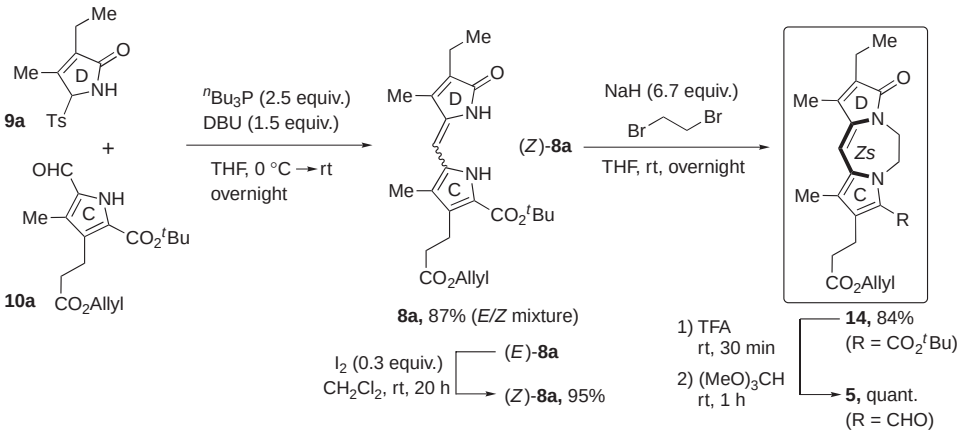


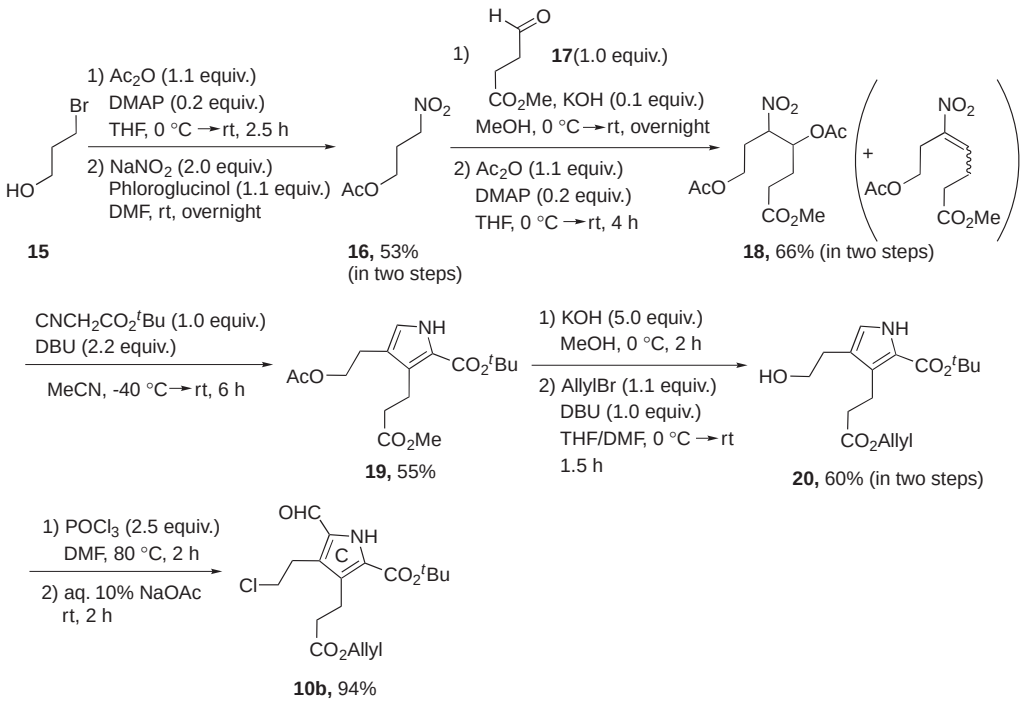
Fig. 2. Retrosynthetic analysis of the sterically locked chromophores **1**–**3**.



Scheme 1.



Scheme 2.

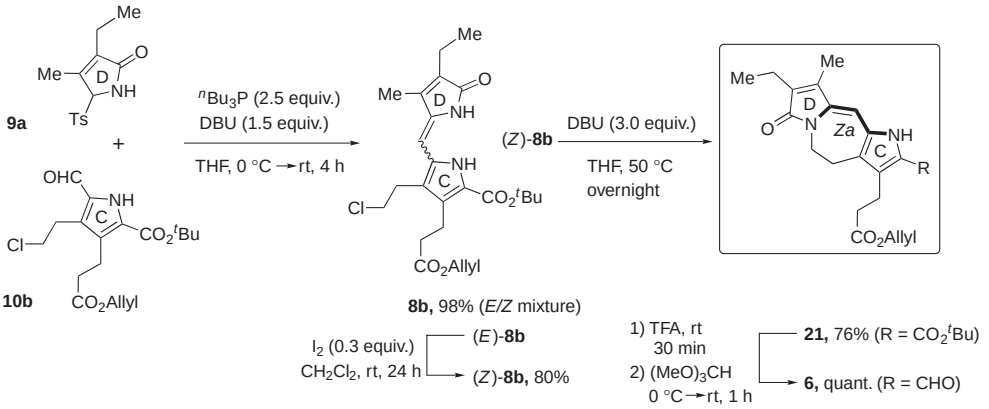


Scheme 3.

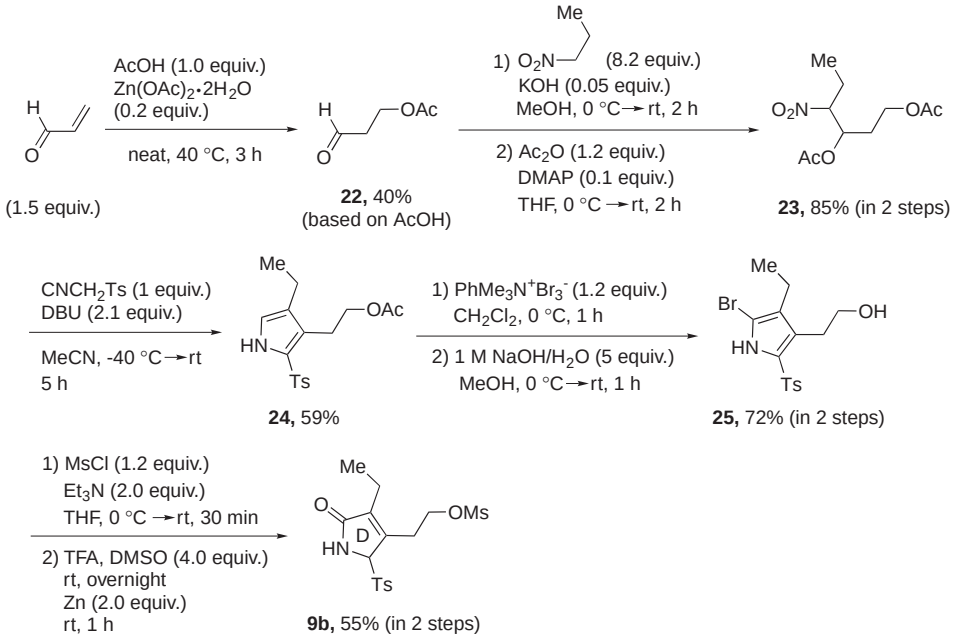
undec-7-ene (DBU) are used in THF to afford a mixture of *Z*- and *E*-isomers of the AB-ring precursor **12** bearing a *p*-tolylthioethyl side chain in 88% yield. Compound **12** was converted to the corresponding sulfoxide with *m*CPBA in CH_2Cl_2, followed by treatment with a mixture of formic acid and trifluoroacetic acid (TFA) at 5 °C to afford the decarboxylated dipyrrin-1(10*H*)-one intermediate **13**. The crude product **13** was refluxed in DMF in the presence of pyridine to afford the desired AB-ring component **4** as only *Z*-isomer in 57% yield in three steps from compound **12**.

Preparation of Allyl (*Z*)-3-(2-Ethyl-8-formyl-1,10-dimethyl-3-oxo-5,6-dihydro-3*H*-dipyrrolo[1,2-*d*:2′,1′-*g*][1,4]-diazepin-9-yl)propanoate (5). The sterically locked CD-ring component **5** bearing *Z-syn* configuration and conformation was prepared via our Wittig-type coupling reaction between 3-ethyl-4-methyl-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one[8b] (**9a**) and formylpyrrole **10a** in the presence of a mixture of tributylphosphine and DBU in THF to afford a mixture of coupling products (*Z*)- and (*E*)-**8a** in 87% yield (Scheme 2). The coupling product (*E*)-**8a** was readily converted to the corresponding isomer (*Z*)-**8a** by treatment with a catalytic amount of iodine in CH_2Cl_2 in 95% yield. Compound (*Z*)-**8a**, thus obtained, was then reacted with 1,2-dibromoethane in the presence of NaH in THF to afford the cyclized CD-ring component **14** in 84% yield. The *t*-butoxycarbonyl group of compound **14** was converted to a formyl group by treating with TFA followed by addition of trimethyl orthoformate $(MeO)_3CH$ at room temperature to give the formylated CD-ring component **5** in quantitative yield.

Preparation of *t*-Butyl 3-(3-Allyloxy-3-oxopropyl)-4-(2-chloroethyl)-5-formyl-1*H*-pyrrole-2-carboxylate (10b). The formylpyrrole derivative[11] **10b** was prepared starting from the commercially available 3-bromo-1-propanol (**15**) as shown in Scheme 3. Alcohol **15** was first acetylated using acetic



Scheme 4.

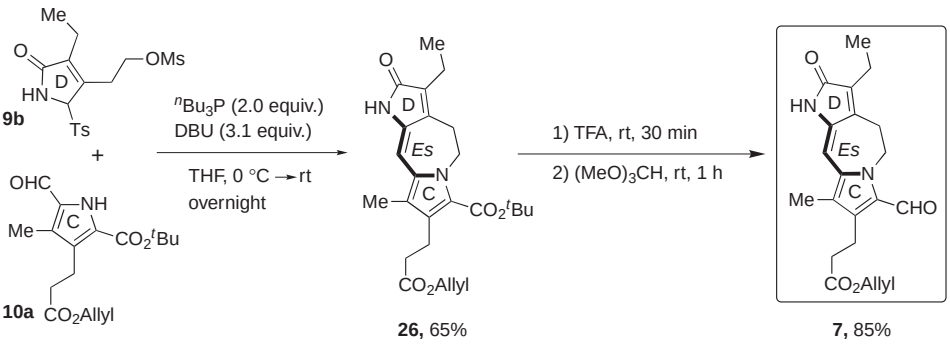


Scheme 5.

anhydride in the presence of catalytic amount of 4-(dimethylamino)pyridine (DMAP) in THF, followed by nitration with sodium nitrite in the presence of phloroglucinol in DMF to give 3-nitropropyl acetate (**16**) in 53% yield in two steps. Compound **16** was coupled with the oxo-ester **17** in a manner similar to our previous preparation of the B- and C-rings,[8c,g] followed by acetylation of the resulting nitro-alcohol to give the nitro-acetate **18** which was contaminated with the corresponding nitro-olefin. When compound **18** was treated with *t*-butyl isocyanoacetate and DBU according to Barton's method[14] in acetonitrile, the pyrrole derivative **19** was obtained in 55% yield. Hydrolysis of compound **19** with KOH in MeOH, followed by allylation with allyl bromide in the presence of DBU in THF/DMF afforded the pyrrole **20** in 60% yield. When compound **20** was formylated by Vilsmeier reaction to give the formylated product in situ, chlorination of the hydroxy group proceeded simultaneously to afford the formylpyrrole **10b** bearing 2-chloroethyl group in 94% yield.

Preparation of Allyl (*Z*)-3-(8-Ethyl-2-formyl-9-methyl-7-oxo-1,4,5,7-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-3-yl)-propanoate (6). As shown in Scheme 4, compounds **9a** and **10b** were coupled according to the Wittig-type reaction developed in our laboratory using tributylphosphine in the presence of DBU in THF to afford the CD-ring precursor **8b** as a mixture of *E*- and *Z*-isomers in 98% yield. We found that compound (*E*)-**8b** should be converted to the *Z*-isomer by treating with a catalytic amount of iodine in CH_2Cl_2 prior to the cyclization. Compound (*Z*)-**8b** was cyclized at 50 °C in the presence of DBU in THF affording the desired product **21** in 76% yield. Subsequent formylation was accomplished by treating with $(MeO)_3CH$ in TFA to give the formylated CD-ring component **6** in quantitative yield.

Preparation of 3-Ethyl-4-[2-(mesyloxy)ethyl]-5-tosyl-1,5-dihydro-2*H*-pyrrol-2-one (9b). The 5-tosylpyrrolinone derivative **9b** was prepared starting from propenal as shown in Scheme 5. Treatment of propenal with acetic acid in the presence of catalytic amount of zinc diacetate afforded 3-oxopropyl acetate (**22**) in 40% yield.[15] Compound **22** was then coupled with 1-nitropropane according to Henry reaction in the presence of catalytic amount of KOH in MeOH. The resulting



Scheme 6.

Table 1. Construction of the Biliverdin Derivatives with the Sterically Locked CD-Ring Components

CD-Ring Component —**4**, H_2SO_4 (2.0 equiv.), MeOH, rt, 1 h→ Sterically Locked BV Diallyl Ester

Sterically Locked BV Diallyl Ester —$[Pd(PPh_3)_4]$ (0.2 equiv.), NaTs (2.0 equiv.), THF/MeOH, rt, 10 min→ Sterically Locked BV

CD-ring component	Sterically locked BV diallyl ester/%	Sterically locked BV/%
5	**1b**, 69	**1a**, 80
6	**2b**, 87	**2a**, 90
7	**3b**, 45	**3a**, 42

nitro-alcohol was then acetylated using acetic anhydride in the presence of catalytic amount of DMAP in THF to give the nitro-diacetate **23** in 85% yield in two steps. Compound **23** was reacted under Barton's method conditions, i.e., tosylmethyl isocyanide (TosMIC) in the presence of DBU, to afford tosylpyrrole derivative **24** in 59% yield. Compound **24** was then brominated with trimethylphenylammonium tribromide ($PhMe_3N^+Br_3^-$) in CH_2Cl_2, followed by hydrolysis of the acetoxy group with 1 M (= 1 mol dm^{-1}) aq NaOH in MeOH to give compound **25** in 72% yield in two steps. Mesylation and subsequent redox-type reaction[8a,i] using DMSO and zinc in TFA afforded the 5-tosylpyrrolinone derivative **9b** in 55% yield in two steps.

Preparation of Allyl (*E*)-3-(3-Ethyl-7-formyl-9-methyl-2-oxo-1,2,4,5-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-8-yl)-propanoate (7). As shown in Scheme 6, compounds **9b** and **10a** were coupled by a Wittig-type reaction with tributylphosphine in the presence of DBU in THF to afford directly the cyclized CD-ring component **26** as *E-syn* isomer in 65% yield. Formylation reaction was carried out by treating with TFA and subsequent addition of $(MeO)_3CH$ to give the formylated CD-ring component **7** in 85% yield.

Construction of the Biliverdin Derivatives as 15*Z-syn*, 15*Z-anti*, and 15*E-syn* Chromophores in Free Acid Forms. Coupling reactions between the CD-ring components **5**, **6**, and **7**, prepared above, with the AB-ring component **4** were carried out in methanol under acidic conditions to afford the sterically locked BV diallyl ester derivatives **1b**, **2b**, and **3b** in 69, 87, and 45% yields, respectively (Table 1).

Finally, the carboxylate groups were deprotected via a Pd^0-catalyzed reaction using sodium *p*-toluenesulfinate (NaTs) as a nucleophile in THF/MeOH to give the desired chromophores **1a**, **2a**, and **3a** in 80, 90, and 42% yields, respectively, in free acid forms.

Chromophores **1a**, **2a**, and **3a** were attached to the Agp1 apoprotein to determine the stereochemistry of CD-ring component of BV in Agp1. It was found that compound **2a**, which is a BV derivative having 15*Za* configuration and conformation, forms a covalent bond with Agp1 apoprotein, and the absorption spectrum corresponding to P_r form was observed. Furthermore, size exclusion chromatograph of Agp1-M15 (the *N*-terminal 504 amino acids of Agp1) apoprotein adduct with compound **2a** and the autophosphorylation of the Agp1 adduct with compound **2a** showed that the stereochemistry of CD-ring moiety of P_r form of natural Agp1 is 15*Za*.[16] Recently, we also prepared another derivative of the chromophore in which the stereochemistry of the CD-ring moiety is fixed to 15*Ea*.[17] This 15*Ea* chromophore was also attached to the Agp1 apoprotein, and the adduct was found to be the P_{fr} form of Agp1.[16] From these results, sterically locked chromophores will open new avenues of investigation concerning the stereochemistry and function of phytochrome chromophores both in vitro and in vivo.

Experimental

^{1}H NMR spectra were recorded on JEOL JNM-GX Lambda 400 and 300 NMR spectrometers. Chemical shifts are reported in δ-scale relative to TMS ($\delta = 0$) as an internal standard. The IR spectra were measured on a JASCO FT/IR-230 spectrometer, and the MS spectra were recorded by using Hitachi M-80 and JEOL SX-102A mass spectrometers. All solvents were distilled and stored over drying agents. THF was freshly distilled from sodium diphenylketyl. Thin-layer chromatography (TLC) and flash column chromatography were performed using Merck's silica gel 60 PF_{254} (Art. 7749) and Cica-Merck's silica gel 60 (No. 9385-5B), respectively. Commercially available reagents were used without further purification, unless otherwise noted.

***t*-Butyl 3-(3-Allyloxy-3-oxopropyl)-4-methyl-5-({4-methyl-5-oxo-3-[2-(*p*-tolylthio)ethyl]-1*H*-pyrrol-2(5*H*)-ylidene}methyl)-1*H*-pyrrole-2-carboxylate (12).** To a mixed solution of 5-tosylpyrrolinone[8e] **11** (2.0 g, 5 mmol) and formylpyrrole[8b] **10a** (1.6 g, 5 mmol) in THF (30 mL) was added ^{n}Bu$_3$P (2.7 mL, 11 mmol) dropwise at 0 °C under N_2, followed by dropwise addition of DBU (0.82 g, 5.5 mmol) in THF (2 mL). The reaction mixture was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with both a saturated aqueous solution of NH_4Cl and brine, and

then dried over $MgSO_4$. The solvent was evaporated, and the product was separated by flash column chromatography (SiO_2, hexane/EtOAc = 4/1, v/v) to give compound **12** (2.42 g, 88%) as a yellow solid of the mixture of (*Z*)- (60%) and (*E*)-isomers (28%). Mp 177.5–178.0 °C (from EtOAc/hexane). IR (KBr) 3330, 3122, 2974, 1735, 1695, 1656, 1450, 1365, 1273, 1157, 1132, 987, 847, 810, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (*Z*)-isomer: δ 1.56 (s, 9H), 1.93 (s, 3H), 2.00 (s, 3H), 2.34 (s, 3H), 2.54 (t, J = 8.1 Hz, 2H), 2.79 (t, J = 7.9 Hz, 2H), 2.82 (t, J = 8.3 Hz, 2H), 3.08 (t, J = 8.3 Hz, 2H), 4.59 (d, J = 5.7 Hz, 2H), 5.23 (dd, J = 10.4, 1.3 Hz, 1H), 5.31 (dd, J = 17.2, 1.3 Hz, 1H), 5.79 (s, 1H), 5.92 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 9.48 (brs, 1H), 9.52 (brs, 1H); (*E*)-isomer: δ 1.57 (s, 9H), 1.82 (s, 3H), 1.96 (s, 3H), 2.29 (s, 3H), 2.55 (t, J = 8.0 Hz, 2H), 2.55–2.65 (m, 4H), 3.00 (t, J = 8.0 Hz, 2H), 4.59 (d, J = 5.7 Hz, 2H), 5.23 (d, J = 10.5 Hz, 1H), 5.31 (dd, J = 17.2, 1.3 Hz, 1H), 5.92 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 6.11 (s, 1H), 7.03 (d, J = 8.2 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 8.20 (brs, 1H), 8.98 (brs, 1H). Found: C, 67.62; H, 6.93; N, 4.82%. Calcd for $C_{31}H_{38}N_2O_5S$: C, 67.61; H, 6.95; N, 5.09%.

Allyl (*Z*)-3-{4-Methyl-5-[(4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-1*H*-pyrrol-3-yl}propanoate (4). To a solution of compound **12** (2.42 g, 4.4 mmol) in CH_2Cl_2 (20 mL), a solution of *m*CPBA (70% purity, 1.085 g, 4.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C, and the mixture was allowed to stir for 20 min. The reaction mixture was quenched by the addition of a saturated aqueous solution of $NaHSO_3$, and then, the organic solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, and dried over $MgSO_4$. The solvent was evaporated, and the solid residue was dissolved in a mixture of formic acid and TFA (2/1, v/v, 9 mL/mmol) and allowed to stir at 5 °C for 1 h. The reaction mixture was treated with solid Na_2CO_3 and was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was evaporated, and the residual mixture was dissolved in DMF (20 mL) under N_2. After addition of pyridine (3 mL, 44 mmol), the mixture was refluxed for 2 h with stirring. The reaction mixture was partitioned between EtOAc/Et_2O and water, and the organic layer was successively washed with 1 M HCl, a saturated aqueous solution of $NaHCO_3$ and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to afford compound **4** as a yellow solid (850 mg) in 57% yield in three steps. Mp 151–153 °C (from EtOAc/hexane). IR (KBr) 3336, 3154, 2920, 1738, 1657, 1638, 1442, 1418, 1377, 1339, 1262, 1171, 984, 926, 808, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.95 (s, 3H), 2.09 (s, 3H), 2.59 (t, J = 7.7 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 4.60, (d, J = 5.6 Hz, 2H), 5.23 (d, J = 10.5 Hz, 1H), 5.31 (d, J = 17.1 Hz, 1H), 5.56 (d, J = 17.5 Hz, 1H), 5.58 (d, J = 11.5 Hz, 1H), 5.92 (ddt, J = 17.1, 10.5, 5.6 Hz, 1H), 6.18 (s, 1H), 6.59 (dd, J = 17.6, 11.7 Hz, 1H), 6.77 (brd, J = 1.7 Hz, 1H), 10.53 (s, 1H), 11.34 (s, 1H). Found: C, 69.90; H, 6.71; N, 8.56%. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58%.

***t*-Butyl 3-(3-Allyloxy-3-oxopropyl)-5-[(4-ethyl-3-methyl-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-4-methyl-1*H*-pyrrole-2-carboxylate (8a).** To a mixed solution of 5-tosylpyrrolinone **9a**[8b] (313 mg, 1.1 mmol) and formylpyrrole **10a**[8a] (300 mg, 0.9 mmol) in THF (18 mL) was added $^nBu_3P$ (0.6 mL, 2.3 mmol) dropwise at 0 °C under N_2, followed by dropwise addition of DBU (213 mg, 1.4 mmol) in THF (2.0 mL). The reaction mixture was allowed to stir at room temperature overnight. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of NH_4Cl and with brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 4/1, v/v) to afford compound **8a** (349 mg, 87%) as a yellow solid [a mixture of (*Z*)- (27%) and (*E*)-isomers (60%)]. IR (KBr) 3329, 3130, 2969, 2927, 2871, 1739, 1696, 1657, 1453, 1368, 1275, 1265, 1136, 779, 720 cm^{-1}. The (*Z*)- and (*E*)-isomers were further separated by repeating the flash column chromatography with a longer column under the same conditions. ^1H NMR ($CDCl_3$, 300 MHz) (*Z*)-**8a**: δ 1.09 (t, J = 7.5 Hz, 3H), 1.56 (s, 9H), 2.08 (s, 3H), 2.10 (s, 3H), 2.42 (q, J = 7.4 Hz, 2H), 2.54 (t, J = 8.1 Hz, 2H), 3.02 (t, J = 8.1 Hz, 2H), 4.59 (d, J = 5.9 Hz, 2H), 5.23 (d, J = 10.5 Hz, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.91 (ddt, J = 17.2, 10.5, 5.9 Hz, 1H), 5.93 (s, 1H), 8.95 (s, 1H), 9.40 (s, 1H); (*E*)-**8a**: δ 1.08 (t, J = 7.5 Hz, 3H), 1.56 (s, 9H), 1.87 (s, 3H), 1.99 (s, 3H), 2.35 (q, J = 7.5 Hz, 2H), 2.56 (t, J = 7.9 Hz, 2H), 3.02 (t, J = 8.0 Hz, 2H), 4.58 (d, J = 5.7 Hz, 2H), 5.23 (d, J = 10.5 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.91 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 6.17 (s, 1H), 8.63 (s, 1H), 9.05 (s, 1H). (*E*)-**8a** (210 mg, 0.5 mmol) was treated with a catalytic amount of iodine (41 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) for 20 h at room temperature. The solvent was evaporated, and the residue was partitioned between EtOAc and water. The organic layer was successively washed with a saturated aqueous solution of $NaHSO_3$, a solution of $NaHCO_3$, and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SO_2, hexane/EtOAc = 4/1, v/v) to give (*Z*)-**8a** (200 mg) in 95% yield. Mp 164–166 °C (from EtOAc/hexane). Found: C, 67.16; H, 7.49; N, 6.48%. Calcd for $C_{24}H_{32}N_2O_5$: C, 67.27; H, 7.53; N, 6.54%.

***t*-Butyl (*Z*)-9-(3-Allyloxy-3-oxopropyl)-2-ethyl-1,10-dimethyl-3-oxo-5,6-dihydro-3*H*-dipyrrolo[1,2-*d*:2′,1′-*g*][1,4]diazepine-8-carboxylate (14).** To a suspension of NaH (34 mg, 60% in mineral oil, 0.8 mmol) in THF (1 mL) was added a catalytic amount of 18-crown-6 (32 mg, 0.12 mmol), suspended in THF (1 mL), and a solution of compound (*Z*)-**8a** (52 mg, 0.12 mmol) in THF (2 mL), followed by the addition of 1,2-dibromoethane (3 mL). The mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to afford compound **14** (46 mg, 84%) as a yellow solid. Mp 70–71 °C (from EtOAc/hexane). IR (neat) 2976, 2933, 1738, 1691, 1458, 1425, 1396, 1370, 1345, 1294, 1243, 1167, 1128, 1047, 1002, 959, 849, 773 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (t, J = 7.6 Hz, 3H), 1.58 (s, 9H), 2.09 (s, 3H), 2.13 (s, 3H), 2.39 (q, J = 7.6 Hz, 2H), 2.53 (t, J = 8.1 Hz, 2H), 3.00 (t, J = 8.1 Hz, 2H), 4.59 (d, J = 5.9 Hz, 2H), 5.23 (dd, J = 10.2, 1.7 Hz, 1H), 5.30 (dd, J = 17.3, 1.7 Hz, 1H), 5.93 (ddt, J = 17.3, 10.2, 5.9 Hz, 1H), 5.99 (s, 1H). The protons of the ethylene bridge were not observed clearly. Found: C, 68.58; H, 7.47; N, 6.08%. Calcd for $C_{26}H_{34}N_2O_5$: C, 68.70; H, 7.54; N, 6.16%.

Allyl (*Z*)-3-(2-Ethyl-8-formyl-1,10-dimethyl-3-oxo-5,6-dihydro-3*H*-dipyrrolo[1,2-*d*:2′,1′-*g*][1,4]diazepin-9-yl)propanoate (5). A solution of compound **14** (46 mg, 0.1 mmol) in TFA (1 mL) was allowed to stir for 30 min at room temperature under N_2. Then, $(CH_3O)_3CH$ (0.5 mL) was added dropwise. After stirring for 1 h at room temperature, the reaction mixture was

quenched by adding water and extracted with EtOAc, and then, the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to give compound **5** as a yellow solid in quantitative yield (38 mg). Mp 88–89 °C (from EtOAc/hexane). IR (KBr) 2970, 2932, 2874, 1735, 1689, 1639, 1427, 1369, 1339, 1285, 1242, 1161, 1062, 840, 774, 722 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, J = 7.7 Hz, 3H), 2.11 (s, 3H), 2.14 (s, 3H), 2.40 (q, J = 7.5 Hz, 2H), 2.58 (t, J = 7.6 Hz, 2H), 3.03 (t, J = 7.6 Hz, 2H), 4.02 (br, 2H), 4.58 (d, J = 5.7 Hz, 2H), 5.23 (d, J = 10.5 Hz, 1H), 5.29 (d, J = 17.2 Hz, 1H), 5.91 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 5.98 (s, 1H), 9.70 (s, 1H). The protons of the ethylene bridge were not observed clearly. Found: C, 68.97; H, 6.73; N, 7.27%. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32%.

Allyl 3-{(*Z*)-2-{[(*Z*)-2-(3-Allyloxy-3-oxopropyl)-9-ethyl-1,10-dimethyl-8-oxo-5,6-dihydro-8*H*-dipyrrolo[1,2-*d*:2′,1′-*g*][1,4]diazepin-3-yl]methylene}-4-methyl-5-[(*Z*)-(4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-2*H*-pyrrol-3-yl}propanoate (1b). To a mixed solution of compounds **5** (38 mg, 0.1 mmol) and **4** (33 mg, 0.1 mmol) in MeOH (4 mL), a solution of H_2SO_4 (20 mg, 0.2 mmol) in MeOH (1 mL) was added dropwise at room temperature under N_2, and the mixture was allowed to stir for 1 h. The reaction mixture was quenched by addition of a buffer solution (pH 7.0) and partitioned between EtOAc and water. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the blue residue was separated by thin layer chromatography (SiO_2, hexane/$CHCl_3$/MeOH = 7/4/0.5, v/v/v) to afford compound **1b** as a blue solid (47 mg, 69%). Mp 63–65 °C (from EtOAc/hexane). IR (KBr) 3536, 2965, 1733, 1698, 1675, 1589, 1456, 1414, 1357, 1317, 1269, 1201, 1160, 1104, 986, 961, 932 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, J = 7.3 Hz, 3H), 2.05 (s, 3H), 2.09 (s, 3H), 2.14 (s, 3H), 2.18 (s, 3H), 2.39 (q, J = 7.6 Hz, 2H), 2.53 (t, J = 8.1 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 3.79–4.24 (br, 2H), 4.52 (d, J = 5.6 Hz, 2H), 4.57 (d, J = 5.6 Hz, 2H), 5.18 (dd, J = 10.3, 1.2 Hz, 1H), 5.20 (dd, J = 10.2, 1.5 Hz, 1H), 5.23 (dd, J = 16.8, 1.4 Hz, 1H), 5.27 (dd, J = 17.3, 1.5 Hz, 1H), 5.66 (d, J = 11.5 Hz, 1H), 5.70 (d, J = 18.8 Hz, 1H), 5.85 (ddt, J = 16.7, 10.8, 5.6 Hz, 1H), 5.88 (ddt, J = 16.1, 11.0, 5.6 Hz, 1H), 6.03 (s, 2H), 6.62 (dd, J = 17.9, 11.5 Hz, 1H), 6.94 (s, 1H), 10.49 (brs, 1H). The protons of the ethylene bridge were not observed clearly. Found: C, 71.24; H, 6.68; N, 8.08%. Calcd for $C_{41}H_{46}N_4O_6$: C, 71.28; H, 6.71; N, 8.11%.

3-{(*Z*)-2-{[(*Z*)-2-(2-Carboxyethyl)-9-ethyl-1,10-dimethyl-8-oxo-5,6-dihydro-8*H*-dipyrrolo[1,2-*d*:2′,1′-*g*][1,4]diazepin-3-yl]-methylene}-4-methyl-5-[(*Z*)-(4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-2*H*-pyrrol-3-yl}propanoic Acid (1a). To a mixed solution of **1b** (38 mg, 0.05 mmol) and $[Pd(PPh_3)_4]$ (13 mg, 0.011 mmol) in THF (1.4 mL), a solution of NaTs (20 mg, 0.11 mmol) in MeOH (1.4 mL) was added at room temperature under N_2. After stirring for 10 min, the solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, $CHCl_3$/MeOH/AcOH = 200/15/1, v/v/v). The solvent of the blue fraction was evaporated, and the resulting solid residue was recrystallized from $CHCl_3$/hexane to afford compound **1a** as a blue solid (24 mg, 80%). Decomposed above 270 °C. IR (KBr) 3537, 3265, 3022, 2944, 2293, 2253, 1931, 1443, 1375, 1230, 1038, 919, 759, 668 cm^{-1}; ^1H NMR (C_5D_5N, 400 MHz) δ 1.03 (t, J = 7.6 Hz, 3H), 1.90 (s, 3H), 1.98 (s, 3H), 2.11 (s, 3H), 2.16 (s, 3H), 2.33 (q, J = 7.6 Hz, 2H), 2.85 (t, J = 7.3 Hz, 2H), 2.91 (t, J = 7.3 Hz, 2H), 3.24 (t, J = 7.3 Hz, 2H), 3.34 (t, J = 7.3 Hz, 2H), 4.52 (br, 2H), 4.84 (br, 2H), 5.56 (d, J = 11.7 Hz, 1H), 5.63 (d, J = 17.8 Hz, 1H), 5.99 (s, 1H), 6.26 (s, 1H), 6.68 (dd, J = 17.8, 11.5 Hz, 1H), 7.62 (s, 1H). Protons of $CO_2\underline{H}$ and N$\underline{H}$ were not observed clearly. UV–vis (MeOH) λ_{max} 383 (ε = 39850), 639 (ε = 18650) nm. HRMS (FAB) ($M^+ + 1$), Found: m/z 611.2876. Calcd for $C_{35}H_{39}N_4O_6$: 611.2869.

3-Nitropropyl Acetate (16). To a mixed solution of DMAP (1.952 g, 16 mmol) and 3-bromopropan-1-ol **15** (11.12 g, 80 mmol) in THF (40 mL) was added Ac_2O (9.7 mL, 88 mmol) dropwise under N_2 at 0 °C. After stirring for 30 min at 0 °C and 2.5 h at room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic extract was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, and dried over $MgSO_4$. The solvent was evaporated to give the acetylated product (12.742 g, 88%) as a colorless oil, which was used for the next reaction without further purification. IR (neat) 2966, 2902, 1741, 1439, 1387, 1366, 1238, 1037 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.06 (s, 3H), 2.18 (quint, J = 6.2 Hz, 2H), 3.47 (t, J = 6.5 Hz, 2H), 4.20 (t, J = 6.1 Hz, 2H) ppm. The resulting 3-bromopropyl acetate (12.62 g, 70 mmol) was treated with $NaNO_2$ (9.62 g, 140 mmol) and phloroglucinol (12.472 g, 77 mmol) under N_2 in DMF (100 mL), and the mixture was allowed to stir overnight at room temperature. The mixture was then partitioned between EtOAc/Et_2O and water, and the organic extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the product was purified by flash column chromatography (SiO_2, hexane/EtOAc = 2/1, v/v) to give compound **16** as an oil in 60% yield (6.174 g); IR (neat) 2253, 1740, 1556, 1363, 1223 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.07 (s, 3H), 2.36 (quint, J = 6.6 Hz, 2H), 4.19 (t, J = 6.1 Hz, 2H), 4.50 (t, J = 6.8 Hz, 2H). HRMS (TOF) ($M^+ + 1$), Found: m/z 148.0641. Calcd for $C_5H_{10}NO_4$: 148.0610.

***t*-Butyl 4-(2-Acetoxyethyl)-3-(3-methoxy-3-oxopropyl)-1*H*-pyrrole-2-carboxylate (19).** To a mixture of methyl 4-oxobutanoate **17** (2.32 g, 20 mmol) and compound **16** (2.94 g, 20 mmol), a solution of KOH (131 mg, 2 mmol) in MeOH (3 mL) was added dropwise at 0 °C, and the mixture was allowed to stir overnight at room temperature. After evaporation of the solvent, the residue was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, and dried over $MgSO_4$. The solvent was evaporated to give the nitro-alcohol as a crude product. This product was mixed with DMAP (488 mg, 4 mmol) in THF (15 mL) at 0 °C, and Ac_2O (2.1 mL, 22 mmol) was added dropwise with stirring at room temperature. After stirring for 4 h, the mixture was quenched by MeOH (2 mL) for 15 min. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc and water. The organic extract was washed with both a saturated aqueous solution of $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated, and the product was isolated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to give a mixture of diastereomers of compound **18** (4.03 g, ca. 66% yield) contaminated with the corresponding nitro-olefin as an oil.

To a solution of *t*-butyl isocyanoacetate (1.27 g, 9 mmol) in MeCN (10 mL) at −40 °C under N_2, DBU (2.95 mL, 19.8 mmol) was added, followed by dropwise addition of compound **18** (2.748 g, 9 mmol) in MeCN (5 mL). After stirring for 6 h at room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The extract was successively washed with a saturated aqueous solution of $NaHSO_3$, a solution of $NaHCO_3$, and brine, and then dried over

$MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 4/1, v/v) to give compound **19** (1.69 g, 55%) as an oil. IR (neat) 3320, 2977, 2936, 1737, 1720, 1684, 1455, 1408, 1368, 1243, 1135, 1050, 933 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.57 (s, 9H), 2.05 (s, 3H), 2.53 (t, J = 8.2 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 3.01 (t, J = 8.1 Hz, 2H), 3.67 (s, 3H), 4.18 (t, J = 7.1 Hz, 2H), 6.71 (d, J = 2.9 Hz, 1H), 9.10 (brs, 1H). HRMS (TOF) ($M^+ + 1$), Found: m/z 340.1775. Calcd for $C_{17}H_{26}NO_6$: 340.1760.

***t*-Butyl 3-(3-Allyloxy-3-oxopropyl)-4-(2-hydroxyethyl)-1*H*-pyrrole-2-carboxylate (20).** To a solution of compound **19** (1.565 g, 4.6 mmol) in MeOH (20 mL), a 3 M KOH solution in MeOH (7.7 mL, 23 mmol) was added dropwise at 0 °C. After stirring for 2 h, the solvent was evaporated. The residue was acidified (pH 3–4) with 1 M HCl and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated to afford a crude product. To a solution of the product in THF/DMF (20/10 mL), DBU (0.7 mL, 4.6 mmol) was added dropwise at 0 °C under N_2, followed by dropwise addition of allyl bromide (0.44 mL, 5.1 mmol), and the mixture was allowed to stir for 1.5 h at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. The residue that was obtained by evaporating the solvent was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to afford compound **20** (0.89 g, 60% in two steps) as an oil. IR (neat) 3346, 2978, 2935, 1738, 1714, 1407, 1223, 1172, 1133, 1051, 933 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.57 (s, 9H), 2.58 (t, J = 8.1 Hz, 2H), 2.71 (t, J = 6.5 Hz, 2H), 3.02 (t, J = 8.1 Hz, 2H), 3.75 (t, J = 6.5 Hz, 2H), 4.58 (dt, J = 5.7, 1.3 Hz, 2H), 5.22 (dq, J = 10.5, 1.5 Hz, 1H), 5.29 (dq, J = 17.2, 1.5 Hz, 1H), 5.91 (ddt, J = 17.2, 10.5, 5.7 Hz, 1H), 6.73 (d, J = 2.9 Hz, 1H), 9.34 (brs, 1H). HRMS (TOF) ($M^+ + 1$), Found: m/z 324.1835. Calcd for $C_{17}H_{26}NO_5$: 324.1811.

***t*-Butyl 3-(3-Allyloxy-3-oxopropyl)-4-(2-chloroethyl)-5-formyl-1*H*-pyrrole-2-carboxylate (10b).** To DMF (8 mL) was added $POCl_3$ (0.26 mL, 2.8 mmol) dropwise, and the mixture was stirred for 10 min at 0 °C and for additional 10 min at room temperature. A solution of compound **20** (362 mg, 1.12 mmol) in DMF (8 mL) was then added dropwise at 0 °C and the mixture was stirred for 10 min at 0 °C and 2 h at 80 °C. The reaction mixture was quenched by addition of a 10% aqueous NaOAc and stirred for 2 h at room temperature. The mixture was partitioned between EtOAc and water, and the organic extract was washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the product was purified by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to give compound **10b** (393 mg, 94%) as an oil. IR (neat) 3284, 2978, 2359, 1735, 1705, 1667, 1458, 1369, 1272, 1158, 1078, 932, 844 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.59 (s, 9H), 2.63 (t, J = 7.8 Hz, 2H), 3.02 (t, J = 7.7 Hz, 2H), 3.24 (t, J = 6.8 Hz, 2H), 3.67 (t, J = 6.9 Hz, 2H), 4.58 (dt, J = 5.6, 1.5 Hz, 2H), 5.23 (dq, J = 10.3, 1.2 Hz, 1H), 5.30 (dq, J = 17.3, 1.4 Hz, 1H), 5.90 (ddt, J = 17.3, 10.5, 5.6 Hz, 1H), 9.67 (brs, 1H), 9.77 (s, 1H). HRMS (TOF) ($M^+ + 1$), Found: m/z 370.1501 (^{35}Cl), 372.1491 (^{37}Cl). Calcd for $C_{18}H_{25}{}^{35}ClNO_5$: 370.1421, $C_{18}H_{25}{}^{37}ClNO_5$: 372.1392.

***t*-Butyl 3-(3-Allyloxy-3-oxopropyl)-4-(2-chloroethyl)-5-[(4-ethyl-3-methyl-5-oxo-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-1*H*-pyrrole-2-carboxylate (8b).** To a mixed solution of 5-tosylpyrrolinone **9a** (125 mg, 0.44 mmol) and formylpyrrole **10b** (138 mg, 0.37 mmol) in THF (8 mL), $^nBu_3P$ (0.23 mL, 0.93 mmol) was added dropwise at 0 °C under N_2, followed by dropwise addition of a solution of DBU (83 mg, 0.56 mmol) in THF (2 mL). The reaction mixture was allowed to stir for 4 h at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of NH_4Cl and with brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 4/1, v/v) to give **8b** as a yellow solid mixture (175 mg, 98%) of (*Z*)- (14%) and (*E*)-isomers (84%). IR (KBr) 3335, 2974, 2931, 1733, 1693, 1654, 1450, 1392, 1368, 1281, 1162, 1136, 1080, 987, 847, 779, 717, 685 cm^{-1}. The (*Z*)- and (*E*)-isomers were further separated by repeating the flash column chromatography with a longer column under the same conditions. ^1H NMR ($CDCl_3$, 400 MHz) (*E*)-**8b**: δ 1.07 (t, J = 7.6 Hz, 3H), 1.54 (s, 9H), 2.11 (s, 3H), 2.44 (q, J = 7.6 Hz, 2H), 2.59 (t, J = 7.6 Hz, 2H), 3.00 (t, J = 7.6 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 3.45 (t, J = 7.6 Hz, 2H), 4.58 (d, J = 5.6 Hz, 2H), 5.22 (dd, J = 10.5, 1.2 Hz, 1H), 5.30 (dd, J = 17.1, 1.5 Hz, 1H), 5.91 (ddt, J = 16.9, 10.0, 5.6 Hz, 1H), 5.94 (s, 1H), 10.04 (s, 1H), 10.33 (s, 1H). (*Z*)-**8b**: δ 1.07 (t, J = 7.6 Hz, 3H), 1.56 (s, 9H), 1.78 (s, 3H), 2.33 (q, J = 7.6 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2H), 2.91 (t, J = 7.5 Hz, 2H), 3.01 (t, J = 8.0 Hz, 2H), 3.53 (t, J = 7.5 Hz, 2H), 4.59 (dt, J = 5.9, 1.4 Hz, 2H), 5.23 (dq, J = 10.5, 1.2 Hz, 1H), 5.31 (dq, J = 17.1, 1.4 Hz, 1H), 5.92 (ddt, J = 17.3, 10.2, 5.9 Hz, 1H), 6.20 (s, 1H), 9.08 (s, 1H), 9.56 (s, 1H). Compound (*E*)-**8b** was converted to its isomer (*Z*)-**8b** as follows: A mixed solution of compound (*E*)-**8b** (26 mg, 0.05 mmol) and iodine (5 mg, 0.015 mmol) in CH_2Cl_2 (3 mL) was stirred for 24 h at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with both a saturated aqueous solution of $NaHSO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 4/1, v/v) to give compound (*Z*)-**8b** in 80% yield (21 mg). Mp 137–138 °C (from EtOAc/hexane). Found: C, 62.90; H, 6.97; N, 5.81%. Calcd for $C_{25}H_{33}ClN_2O_5$: C, 62.95; H, 6.97; N, 5.87%.

***t*-Butyl (*Z*)-3-(3-Allyloxy-3-oxopropyl)-8-ethyl-9-methyl-7-oxo-1,4,5,7-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepine-2-carboxylate (21).** To a solution of compound (*Z*)-**8b** (490 mg, 1.0 mmol) in THF (20 mL), DBU (0.46 mL, 3.0 mmol) was added under N_2, and the mixture was allowed to stir at 50 °C overnight. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 4/1, v/v) to give the product **21** in 76% yield (335 mg) as a yellow solid. Mp 73–75 °C (from EtOAc/hexane). IR (KBr) 3261, 2974, 2933, 1736, 1656, 1559, 1450, 1367, 1327, 1283, 1166, 1135, 1094, 993 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, J = 7.6 Hz, 3H), 1.60 (s, 9H), 2.05 (s, 3H), 2.39 (q, J = 7.6 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H), 2.87 (brt, J = 4.6 Hz, 2H), 3.04 (t, J = 7.8 Hz, 2H), 3.94 (br, 2H), 4.59 (d, J = 5.6 Hz, 2H), 5.22 (dd, J = 10.5, 1.2 Hz, 1H), 5.30 (dd, J = 17.1, 1.5 Hz, 1H), 5.91 (ddt, J = 17.1, 10.4, 5.6 Hz, 1H), 6.12 (s, 1H), 10.10 (s, 1H). Found: C, 68.09; H, 7.24; N, 6.32%. Calcd for $C_{25}H_{32}N_2O_5$: C, 68.16; H, 7.32; N, 6.36%.

Allyl (*Z*)-3-(8-Ethyl-2-formyl-9-methyl-7-oxo-1,4,5,7-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-3-yl)propanoate (6). After treating compound **21** (270 mg, 0.61 mmol) in TFA (6 mL) at room temperature for 30 min under N_2, $(CH_3O)_3CH$ (3 mL) was added dropwise at 0 °C, and the mixture was allowed to stir at

room temperature for 1 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with both a saturated aqueous solution of $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to give compound **6** in quantitative yield (221 mg) as a yellow solid. Mp 97–99 °C (from EtOAc/hexane). IR (KBr) 3249, 2925, 2875, 1739, 1695, 1612, 1453, 1411, 1388, 1327, 1184, 1142, 964, 936, 853, 836, 778, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (t, J = 7.5 Hz, 3H), 2.10 (s, 3H), 2.40 (q, J = 7.5 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.86 (brt, 2H), 3.07 (t, J = 7.3 Hz, 2H), 3.94 (br, 2H), 4.56 (d, J = 5.7 Hz, 2H), 5.22 (dd, J = 10.4, 1.4 Hz, 1H), 5.28 (dd, J = 17.2, 1.4 Hz, 1H), 5.88 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 6.30 (s, 1H), 9.59 (s, 1H), 11.07 (s, 1H). Found: C, 68.38; H, 6.51; N, 7.54%. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60%.

Allyl 3-{(*Z*)-2-[(*Z*)-{3-(3-Allyloxy-3-oxopropyl)-4-methyl-5-[(*Z*)-(4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-2*H*-pyrrol-2-ylidene}methyl]-8-ethyl-9-methyl-7-oxo-1,4,5,7-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-3-yl}propanoate (2b). To a mixed solution of compounds **6** (135 mg, 0.36 mmol) and **4** (100 mg, 0.31 mmol) in MeOH (13 mL), a solution of H_2SO_4 (60 mg, 0.62 mmol) in MeOH (2 mL) was added dropwise at room temperature under N_2. After stirring for 1 h, the reaction mixture was quenched with a buffer solution (pH 7.0) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the blue residue was separated by thin layer chromatography (SiO_2, hexane/$CHCl_3$/MeOH = 7/4/0.5, v/v/v) to afford compound **2b** in 87% yield (181 mg) as a blue solid. Mp 181–183 °C (from CH_2Cl_2/hexane); IR (KBr) 3444, 2925, 1730, 1686, 1589, 1456, 1415, 1274, 1177, 1098, 960, 916, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, J = 7.6 Hz, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.21 (s, 3H), 2.40 (q, J = 7.6 Hz, 2H), 2.58 (t, J = 7.6 Hz, 4H), 2.87 (brt, J = 5.1 Hz, 2H), 2.92 (t, J = 7.7 Hz, 2H), 2.96 (t, J = 7.6 Hz, 2H), 3.94 (br, 2H), 4.56 (d, J = 5.6 Hz, 2H), 4.57 (d, J = 5.7 Hz, 2H), 5.20 (d, J = 10.4 Hz, 2H), 5.26 (dd, J = 17.2, 1.5 Hz, 1H), 5.28 (dd, J = 17.2, 1.5 Hz, 1H), 5.68 (d, J = 10.8 Hz, 1H), 5.71 (d, J = 17.5 Hz, 1H), 5.87 (ddt, J = 17.2, 10.4, 5.6 Hz, 1H), 5.89 (ddt, J = 17.2, 10.4, 5.7 Hz, 1H), 6.07 (s, 1H), 6.28 (s, 1H), 6.64 (dd, J = 17.5, 10.8 Hz, 1H), 6.81 (s, 1H). N<u>H</u> protons were not observed clearly. Found: C, 70.95; H, 6.51; N, 8.23%. Calcd for $C_{40}H_{44}N_4O_6$: C, 70.99; H, 6.55; N, 8.28%.

3-{(*Z*)-2-[(*Z*)-{3-(2-Carboxyethyl)-4-methyl-5-[(*Z*)-(4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-2*H*-pyrrol-2-ylidene}methyl]-8-ethyl-9-methyl-7-oxo-1,4,5,7-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-3-yl}propanoic Acid (2a). To a mixed solution of compound **2b** (50 mg, 0.074 mmol) and [$Pd(PPh_3)_4$] (17 mg, 0.015 mmol) in THF (1.9 mL), a solution of NaTs (27 mg, 0.155 mmol) in MeOH (1.9 mL) was added under N_2 at room temperature. After stirring for 10 min, the solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, $CHCl_3$/MeOH/AcOH = 200/15/1, v/v/v). The blue fraction was evaporated, and the resulting solid residue was recrystallized from $CHCl_3$/hexane to afford free acid **2a** in 90% yield (40 mg) as a blue solid. Decomposed above 300 °C; IR (KBr) 3400, 3232, 2968, 2933, 1702, 1601, 1458, 1416, 1292, 1094, 954, 890, 839 cm^{-1}; ^1H NMR (C_5D_5N, 400 MHz) δ 1.11 (t, J = 7.5 Hz, 3H), 2.10 (s, 3H), 2.13 (s, 3H), 2.35 (s, 3H), 2.40 (q, J = 7.5 Hz, 2H), 2.83 (t, J = 7.1 Hz, 2H), 2.85–2.90 (m, 4H), 3.14 (t, J = 7.1 Hz, 2H), 3.20 (t, J = 7.1 Hz, 2H), 4.01 (br, 2H), 5.61 (dd, J = 11.7, 1.2 Hz, 1H), 5.70 (dd, J = 17.8, 1.2 Hz, 1H), 6.31 (s, 1H), 6.61 (s, 1H), 6.76 (dd, J = 17.8, 11.5 Hz, 1H), 7.57 (s, 1H). N<u>H</u> and CO_2<u>H</u> protons were not observed clearly; UV–vis (MeOH) λ_{max} 385 (ε = 23355), 645 (ε = 17729) nm; HRMS (FAB) ($M^+ + 1$), Found: m/z 597.2706. Calcd for $C_{34}H_{37}N_4O_6$: 597.2713.

3-Oxopropyl Acetate (22).[15] To a dispersion of $Zn(OAc)_2 \cdot 2H_2O$ (2.2 g, 10 mmol) in AcOH (3.0 mL, 50 mmol) was added propenal (5.0 mL, 75 mmol) dropwise at 40 °C under N_2, and the mixture was allowed to stir for 3 h. After filtration through celite and washing the solid with EtOAc, the filtrate was partitioned between EtOAc and water. Then, the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was evaporated to give compound **22** in 40% yield (2.3 g, a colorless oil), which was used for the next step without further purification. IR (neat) 3062, 2968, 2938, 2853, 2738, 1738, 1650, 1431, 1358, 1367, 1241, 1135, 1050, 956, 864, 793, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.00 (s, 3H), 2.70 (dt, J = 6.1, 1.5 Hz, 2H), 4.53 (t, J = 6.1 Hz, 2H), 9.73 (t, J = 1.5 Hz, 1H). HRMS (FAB) ($M^+ + 1$), Found: m/z 117.0554. Calcd for $C_5H_9O_3$: 117.0552.

3-(2-Acetoxyethyl)-4-ethyl-2-tosylpyrrole (24). To a mixture of compound **22** (1.263 g, 10.8 mmol) and 1-nitropropane (8.0 mL, 89 mmol) was added 0.5 mL of 1 M KOH (0.5 mmol) in MeOH at 0 °C. The reaction mixture was stirred for 2 h at room temperature. The mixture was quenched with 1 M HCl (0.5 mL), and the solvent was evaporated. The residue was partitioned between EtOAc and water, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and then brine, and dried over Na_2SO_4. The solvent was evaporated to give the crude nitro-alcohol as an oil. To a mixed solution of the resulting nitro-alcohol (2.09 g, 10.2 mmol) and DMAP (124 mg, 1.02 mmol) in THF (8.0 mL) was added dropwise acetic anhydride (1.1 mL, 12.2 mmol) at 0 °C under N_2. After stirring for 2 h at room temperature, the mixture was quenched with MeOH (1.7 mL), and then, the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water, and the organic layer was washed with both a saturated aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was evaporated to give 4-nitrohexane-1,3-diyl diacetate (**23**) as an oil in 85% yield (2.28 g) in two steps as a mixture of diastereomers. IR (neat) 2977, 2941, 1746, 1555, 1459, 1373, 1225, 1097, 1048, 948, 809, 732 cm^{-1}. HRMS (FAB) ($M^+ + 1$), Found: m/z 248.1140. Calcd for $C_{10}H_{18}NO_6$: 248.1134.

To a mixed solution of nitro-diacetate **23** (3.64 g, 14.7 mmol) and TosMIC (2.866 g, 14.7 mmol) in MeCN (30 mL) under N_2, DBU (4.6 mL, 30.9 mmol) was added dropwise at −40 °C, and then, the mixture was allowed to stir for 5 h at room temperature. The mixture was quenched with aqueous NH_4Cl, and then, the solvent was removed under reduced pressure. The residue was partitioned between EtOAc and water, and the organic layer was successively washed with 6 M HCl, a saturated aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was evaporated, and the product **24** was isolated by flash column chromatography (SiO_2, hexane/EtOAc = 4/1, v/v) as an oil in 59% yield (2.47 g); IR (neat) 3323, 2965, 2934, 2876, 1738, 1596, 1548, 1494, 1455, 1383, 1365, 1316, 1302, 1241, 1175, 1140, 1108, 1088, 1067, 1041, 975, 934, 911, 813, 706, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.15 (t, J = 7.6 Hz, 3H), 2.02 (s, 3H), 2.38 (s, 3H), 2.41 (q, J = 7.6 Hz, 2H), 2.93 (t, J = 7.8 Hz, 2H), 4.06 (t, J = 7.8 Hz, 2H), 6.74 (d, J = 2.9 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.77 (d, J = 8.5 Hz, 2H), 9.37 (brs, 1H). HRMS (FAB) ($M^+ + 1$), Found: m/z 336.1272. Calcd for $C_{17}H_{22}NO_4S$: 336.1270.

2-Bromo-3-ethyl-4-(2-hydroxyethyl)-5-tosylpyrrole (25). To a solution of the tosylpyrrole **24** (2.466 g, 7.35 mmol) in CH_2Cl_2 (45 mL), a trimethylphenylammonium tribromide (3.3 g, 8.82 mmol) was added portionwise at 0 °C, and the mixture was allowed to stir for 1 h. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of $NaHSO_3$, $NaHCO_3$, and brine, and then dried over Na_2SO_4. The solvent was evaporated, and the product was separated by flash column chromatography (SiO_2, EtOAc/hexane = 3/1, v/v) to give the brominated compound in 85% yield (3.71 g) as a solid. Mp 108–109 °C (from EtOAc/hexane); IR (neat) 3208, 2961, 2929, 2895, 2868, 2360, 1715, 1596, 1547, 1455, 1375, 1321, 1294, 1268, 1207, 1184, 1163, 1139, 1118, 1093, 1065, 1030, 969, 946, 916, 813, 719, 685, 670 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, $J = 7.6$ Hz, 3H), 2.03 (s, 3H), 2.39 (q, $J = 7.6$ Hz, 2H), 2.41 (s, 3H), 2.93 (t, $J = 7.4$ Hz, 2H), 4.06 (t, $J = 7.4$ Hz, 2H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.79 (d, $J = 8.3$ Hz, 2H), 9.29 (brs, 1H). Found: C, 49.21; H, 4.88; N, 3.38%. Calcd for $C_{17}H_{20}BrNO_4S$: C, 49.28; H, 4.87; N, 3.38%. To a solution of the resulting brominated compound (1.9 g, 4.59 mmol) in MeOH (5 mL) was added 1 M NaOH (23 mL, 23 mmol) dropwise at 0 °C under N_2. After stirring for 1 h at room temperature, the mixture was neutralized with 1 M HCl, and the solvent was removed under reduced pressure. The organic residue was dissolved in EtOAc and washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to give compound **25** in 85% yield (1.38 g) (72% in two steps) as a solid. Mp 204–205 °C (from EtOAc/THF/hexane); IR (KBr) 3451, 3079, 3010, 2966, 2890, 2703, 1735, 1596, 1550, 1479, 1455, 1374, 1300, 1259, 1227, 1196, 1161, 1135, 1091, 1062, 1036, 1015, 987, 837, 813, 788, 764, 705, 684, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, $J = 7.6$ Hz, 3H), 1.78 (brs, 1H), 2.38 (q, $J = 7.6$ Hz, 2H), 2.41 (s, 3H), 2.86 (t, $J = 6.7$ Hz, 2H), 3.72 (t, $J = 6.7$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.78 (d, $J = 8.4$ Hz, 2H), 9.17 (brs, 1H). Found: C, 48.47; H, 4.95; N, 3.70%. Calcd for $C_{15}H_{18}BrNO_3S$: C, 48.40; H, 4.87; N, 3.76%.

3-Ethyl-4-[2-(mesyloxy)ethyl]-2-oxo-5-tosyl-1,5-dihydro-2*H*-pyrrole (9b). To a solution of the brominated tosylpyrrole **25** (1.37 g, 3.9 mmol) in THF (10 mL) at 0 °C, Et_3N (1.1 mL, 7.8 mmol) was added under N_2, followed by addition of $MeSO_2Cl$ (0.36 g, 4.7 mmol) in THF (2 mL), and the mixture was allowed to stir at room temperature for 30 min. The solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to give the mesylated product in 85% yield (1.48 g) as a solid, which was used for the next reaction without further purification. IR (KBr) 3276, 3024, 2964, 2940, 2869, 1594, 1550, 1490, 1455, 1382, 1343, 1319, 1292, 1256, 1204, 1169, 1138, 1119, 1092, 1059, 1014, 980, 948, 859, 817, 782, 770, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.17 (t, $J = 7.5$ Hz, 3H), 2.39 (q, $J = 7.5$ Hz, 2H), 2.42 (s, 3H), 2.95 (s, 3H), 3.04 (t, $J = 7.5$ Hz, 2H), 4.27 (t, $J = 7.5$ Hz, 2H), 7.32 (d, $J = 8.3$ Hz, 2H), 7.78 (d, $J = 8.4$ Hz, 2H), 9.31 (brs, 1H). The resulting product (1.03 g, 2.3 mmol) was dissolved in TFA (10 mL) at room temperature under N_2. After stirring for 15 min, DMSO (0.65 mL, 9.2 mmol) was added dropwise, and the mixture was allowed to stir overnight. Zn (0.3 g, 4.7 mmol) was then added portionwise, and the reaction mixture was stirred for 1 h. The TFA was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 2/1, v/v) to give compound **9b** in 65% yield (1.03 g) (55% in two steps) as a white solid. Mp 140–141 °C (from EtOAc/hexane); IR (KBr) 3196, 3081, 2969, 1703, 1596, 1460, 1354, 1317, 1259, 1176, 1131, 1080, 990, 975, 906, 830, 721, 668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.66 (t, $J = 7.6$ Hz, 3H), 2.06 (dq, $J = 14.8$, 7.6 Hz, 1H), 2.11 (dq, $J = 14.8$, 7.6 Hz, 1H), 2.40 (s, 3H), 3.00 (s, 3H), 3.07 (dt, $J = 15.4$, 4.9 Hz, 1H), 3.11 (dt, $J = 15.4$, 4.9 Hz, 1H), 4.41 (dt, $J = 9.8$, 5.4 Hz, 1H), 4.51 (dt, $J = 9.8$, 4.9 Hz, 1H), 5.22 (s, 1H), 6.48 (brs, 1H), 7.30 (d, $J = 8.2$ Hz, 2H), 7.64 (d, $J = 8.2$ Hz, 2H). Found: C, 49.35; H, 5.50; N, 3.58%. Calcd for $C_{16}H_{21}NO_6S_2$: C, 49.60; H, 5.46; N, 3.61%.

***t*-Butyl (*E*)-8-(3-Allyloxy-3-oxopropyl)-3-ethyl-9-methyl-2-oxo-1,2,4,5-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepine-7-carboxylate (26).** To a mixed solution of 5-tosylpyrrolinone **9b** (25 mg, 0.08 mmol) and formylpyrrole **10a** (40 mg, 0.1 mmol) in THF (10 mL), a solution of $^nBu_3P$ (32 mg, 0.16 mmol) in THF (1 mL) was added dropwise at 0 °C under N_2, followed by dropwise addition of DBU (37 mg, 0.25 mmol) in THF (2 mL). After stirring overnight at room temperature, the solvent was removed under reduced pressure, and the residue was partitioned between EtOAc and water. The organic layer was washed with both a saturated aqueous solution of NH_4Cl and brine, and then dried over Na_2SO_4. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to afford compound **26** as a yellow solid in 65% yield (20 mg). Mp 180–181 °C (from EtOAc/hexane); IR (KBr) 3213, 2973, 2933, 2553, 1736, 1682, 1538, 1481, 1455, 1414, 1396, 1368, 1348, 1284, 1250, 1176, 1129, 1082, 1055, 987, 956, 855, 817, 773, 735, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, $J = 7.7$ Hz, 3H), 1.58 (s, 9H), 2.06 (s, 3H), 2.38 (q, $J = 7.1$ Hz, 2H), 2.52 (t, $J = 7.9$ Hz, 2H), 2.98 (t, $J = 8.8$ Hz, 2H), 4.59 (d, $J = 5.8$ Hz, 2H), 5.26 (d, $J = 10.2$ Hz, 1H), 5.30 (d, $J = 17.3$ Hz, 1H), 5.91 (ddt, $J = 17.3$, 10.2, 5.8 Hz, 1H), 6.28 (s, 1H), 9.12 (brs, 1H). The protons of the bridged ethylene were not observed clearly. HRMS (FAB) ($M^+ + 1$), Found: m/z 441.2383. Calcd for $C_{25}H_{33}N_2O_5$: 441.2389.

Allyl (*E*)-3-(3-Ethyl-7-formyl-9-methyl-2-oxo-1,2,4,5-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-8-yl)propanoate (7). A solution of compound **26** (20 mg, 0.043 mmol) in TFA (0.43 mL) was allowed to stir at room temperature under N_2 for 30 min. Then, $(CH_3O)_3CH$ (0.22 mL) was added dropwise, and the mixture was allowed to stir at room temperature for 1 h. The reaction mixture was quenched by water and extracted with EtOAc, and then, the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and with brine, and dried over Na_2SO_4. The solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, hexane/EtOAc = 3/1, v/v) to afford compound **7** as a yellow solid in 85% yield (16 mg). Mp 175–176 °C (from EtOAc/hexane). IR (KBr) 3019, 2361, 1728, 1688, 1639, 1502, 1457, 1421, 1381, 1342, 1325, 1302, 1278, 1161, 1050, 983, 850, 734, 719, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (t, $J = 7.6$ Hz, 3H), 2.08 (s, 3H), 2.39 (q, $J = 7.6$ Hz, 2H), 2.57 (t, $J = 7.7$ Hz, 2H), 2.90 (brs, 2H), 3.03 (t, $J = 7.7$ Hz, 2H), 4.58 (d, $J = 5.9$ Hz, 2H), 5.24 (dd, $J = 10.5$, 1.3 Hz, 1H), 5.29 (dd, $J = 17.2$, 1.3 Hz, 1H), 5.90 (ddt, $J = 17.2$, 10.5, 5.9 Hz, 1H), 6.18 (s, 1H), 8.00 (brs, 1H), 9.71 (s, 1H). The protons of the ethylene bridge were not observed clearly. Found: C, 68.20; H, 6.53; N,

7.47%. Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60%.

Allyl 3-{(*Z*)-2-({(*E*)-8-(3-Allyloxy-3-oxopropyl)-3-ethyl-9-methyl-2-oxo-1,2,4,5-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-7-yl}methylene)-4-methyl-5-[(*Z*)-(4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-2*H*-pyrrol-3-yl}propanoate (3b). To a mixed solution of compounds **4** (180 mg, 0.6 mmol) and **7** (110 mg, 0.3 mmol) in MeOH (13 mL), a solution of H_2SO_4 (59 mg, 0.6 mmol) in MeOH (2 mL) was added dropwise at room temperature under N_2. After stirring for 1 h, the reaction mixture was quenched by a buffer solution (pH 7.0) and extracted by EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the blue residue was separated by thin layer chromatography (hexane/$CHCl_3$/MeOH = 7/4/0.5, v/v/v) to give compound **3b** as a greenish blue solid in 45% yield (20 mg). Decomposed above 200 °C (from EtOAc/hexane). IR (KBr) 3224, 2933, 1734, 1698, 1676, 1584, 1508, 1419, 1348, 1272, 1227, 1158, 984, 958, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07 (t, J = 7.6 Hz, 3H), 2.06 (s, 3H), 2.10 (s, 3H), 2.13 (s, 3H), 2.36 (q, J = 7.3 Hz, 2H), 2.52 (t, J = 7.8 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H), 2.97 (t, J = 7.8 Hz, 2H), 2.98 (t, J = 7.8 Hz, 2H), 3.12 (m, 2H), 4.52 (d, J = 5.6 Hz, 2H), 4.56 (d, J = 5.6 Hz, 2H), 5.18–5.30 (m, 4H), 5.68 (d, J = 11.7 Hz, 1H), 5.71 (d, J = 17.0 Hz, 1H), 5.78–5.94 (m, 1H), 6.07 (s, 1H), 6.16 (s, 1H), 6.54 (dd, J = 18.0, 11.7 Hz, 1H), 6.92 (s, 1H), 7.14 (s, 1H). One N<u>H</u> and bridged ethylene protons were not appeared clearly. HRMS (FAB) ($M^+ + 1$), Found: m/z 677.3334. Calcd for $C_{40}H_{45}N_4O_6$: 677.3339.

3-{(*Z*)-2-({(*E*)-8-(3-Carboxyethyl)-3-ethyl-9-methyl-2-oxo-1,2,4,5-tetrahydrodipyrrolo[1,2-*a*:2′,3′-*d*]azepin-7-yl}methylene)-4-methyl-5-[(*Z*)-(4-methyl-5-oxo-3-vinyl-1*H*-pyrrol-2(5*H*)-ylidene)methyl]-2*H*-pyrrol-3-yl}propanoic acid (3a). To a mixed solution of compound **3b** (20 mg, 0.03 mmol) and [Pd(PPh_3)$_4$] (7 mg, 0.006 mmol) in THF (1.3 mL), a solution of NaTs (11 mg, 0.06 mmol) in MeOH (1.3 mL) was added at room temperature under N_2. After stirring for 10 min, the solvent was evaporated, and the residue was separated by flash column chromatography (SiO_2, $CHCl_3$/MeOH/AcOH = 200/15/1, v/v/v). The greenish blue fraction was concentrated, and the resulting solid was recrystallized from $CHCl_3$/hexane to afford free acid **3a** in 42% yield (7 mg) as a greenish blue solid. Decomposed above 250 °C; IR (KBr) 3418, 2934, 1732, 1697, 1585, 1435, 1272, 1158, 1101, 959, 692 cm^{-1}; ^1H NMR (C_5D_5N, 400 MHz) δ 1.11 (t, J = 7.3 Hz, 3H), 2.06 (s, 6H), 2.19 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.97 (t, J = 7.6 Hz, 2H), 3.32 (t, J = 7.3 Hz, 4H), 3.43 (br, 2H), 5.60 (d, J = 11.5 Hz, 1H), 5.73 (d, J = 17.8 Hz, 1H), 6.36 (s, 1H), 6.38 (s, 1H), 6.78 (dd, J = 18.0, 11.2 Hz, 1H), 7.62 (s, 1H), 11.14 (br, 1H). Protons of CO_2<u>H</u>, one N<u>H</u>, and bridged ethylene were not appeared clearly. UV–vis (MeOH) λ_{max} 388 (ε = 28675), 648 (ε = 13100) nm; HRMS (FAB) ($M^+ + 1$), Found: m/z 597.2718. Calcd for $C_{34}H_{37}N_4O_6$: 597.2713.

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