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**REGIOSELECTIVE INTRODUCTION OF SUBSTITUENTS TO THE
MESO-POSITION OF PYRROMETHENONE DERIVATIVE –
APPLICATION TO THE SYNTHESIS OF STERICALLY FIXED
PHYTOCHROME CHROMOPHORE ANCHORED TO THE C15
MESO-POSITION**

**Yudai Tanaka, Ryoji Iwamoto, Ryo Sakata, Takahiro Soeta, Kohei Endo,
Shuhei Fujinami, Katsuhiko Inomata, and Yutaka Ukaji***

Division of Material Chemistry, Graduate School of Natural Science and
Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan; e-mail
address: ukaji@staff.kanazawa-u.ac.jp

Abstract – Pyrromethenone derivatives corresponding to the CD-ring component of phycocyanobilin chromophore were regioselectively brominated with NBS at the *meso*-position retaining the stereochemistry of the olefinic carbon skeleton. Subsequent introduction of carbon-substituents to the brominated pyrromethenones was accomplished by treating with Grignard reagents to afford *meso*-alkylated (*E*)-isomers regardless of the stereochemistry of the starting brominated pyrromethenones. The resulting product was applied to the synthesis of a *meso*-anchored sterically fixed tetrapyrrole chromophore.

Phytochromes, one of the best-characterized photoreceptors, carry a covalently attached linear tetrapyrrole (bilin). Three different bilins are used as chromophores: land plants use phytochromobilin (PΦB), cyanobacteria use phycocyanobilin (PCB), and other bacteria use biliverdin (BV). Phytochromes play critical roles in various light-regulated processes, ranging from phototaxis and pigmentation in bacteria to seed germination, chloroplast development, shade avoidance, and flowering in higher plants, through the photoconversion between the red light-absorbing (Pr) and the far-red-light-absorbing (Pfr) forms.^{1,2}

The total syntheses of natural and unnatural bilin chromophores of phytochromes have been studied and the syntheses of phytochromobilin (PΦB), phycocyanobilin (PCB), modified PCBs, biliverdin (BV) and its analogs including sterically locked derivatives have been achieved by developing efficient methods for the preparation of each pyrrole ring and a new coupling reaction between them.² Toward sterically locked chromophores, both configurationally and conformationally locked ones were synthesized by cyclizing with an additional carbon chain between A and B rings and/or C and D rings.^{2,3} Very recently, we intensively studied regioselective oxidation of simple mono-pyrroles⁴ and successfully applied to the convergent synthesis of a sterically locked *5Z-anti-15E-anti-18Et-BV* derivative.⁵ In order to explore the detailed mechanism of photoconversion of phytochrome chromophores, synthesis of the chromophore sterically fixed at the *meso*-position, which can separately lock the configuration or conformation as can be seen in Figure 1, would be effective. For the synthesis of such *meso*-fixed chromophores, the regioselective oxidative functionalization at the *meso*-position of pyromethene derivatives accompanied with introduction of carbon skeleton followed by cyclization might be versatile and reliable strategy (Scheme 1). Herein we describe a regioselective introduction of substituents via regioselective bromination of the CD-ring component of chromophore and its application toward the synthesis of sterically fixed chromophores anchored to the C15 *meso*-position.

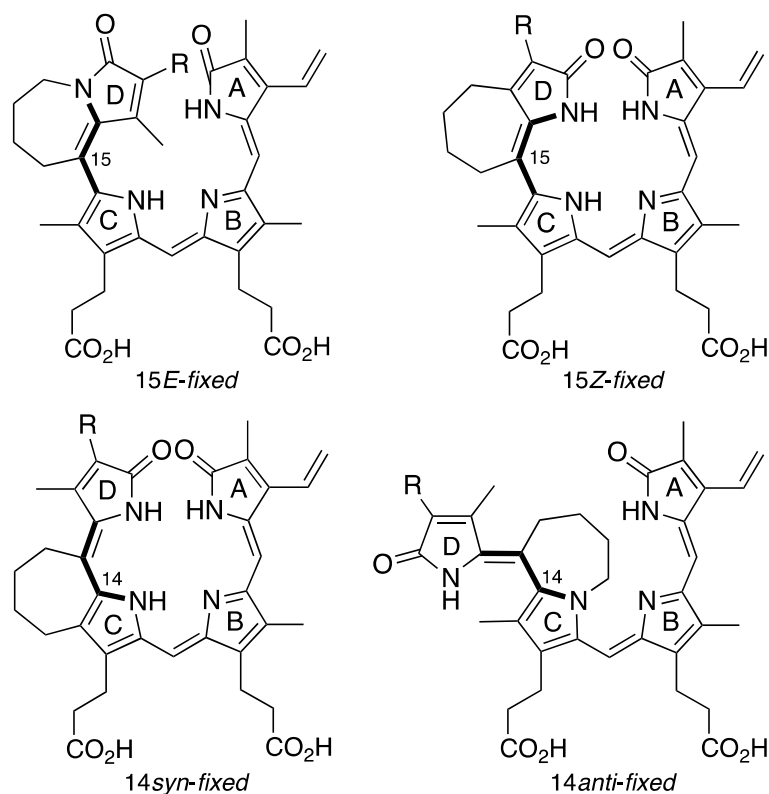
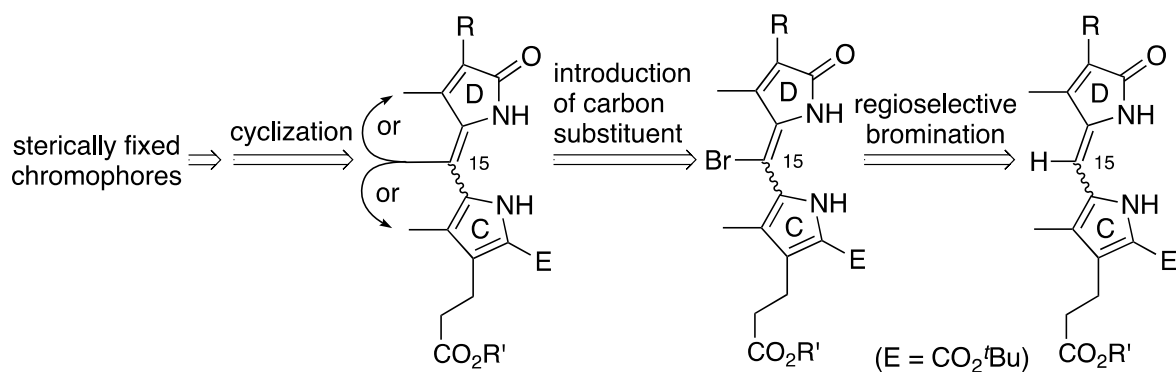
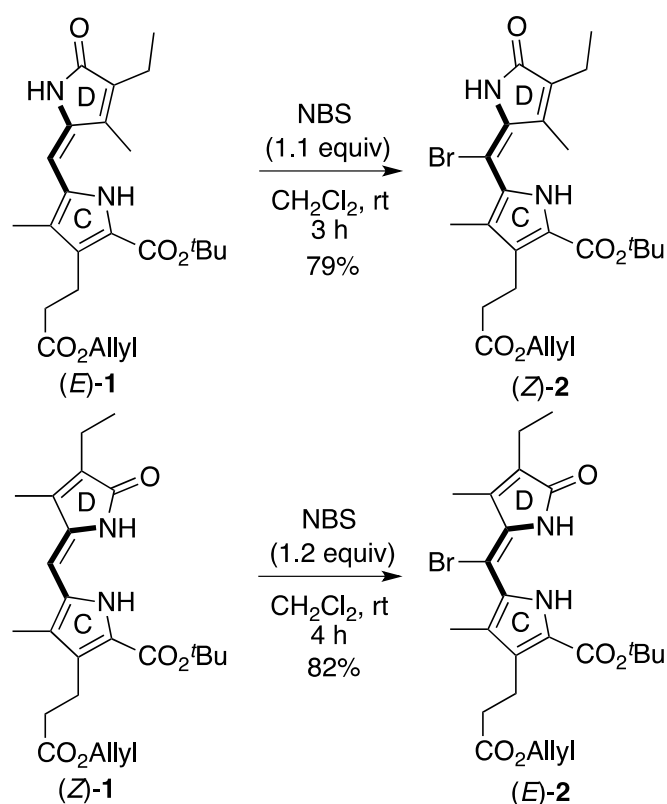


Figure 1. Examples of sterically fixed chromophores anchored to the C15 *meso*-position (R = Et or vinyl)



Scheme 1. Strategy for the synthesis of sterically fixed CD-ring components (R = Et or vinyl)

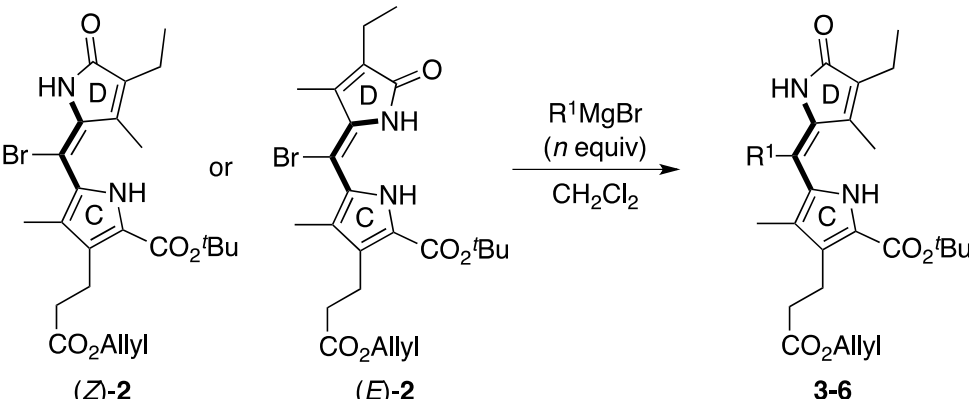
Firstly, as one of the (*E*)-CD-ring component (R = Et) of P□B chromophore, in conjunction with 18Et-BV chromophore, (*E*)-**1**^{3a} was chosen as a model compound and treated with NBS in CH₂Cl₂ at room temperature.⁶ Regioselectively brominated product at the *meso*-position, (*Z*)-**2**, was obtained in 79% yield.⁷ In the case of (*Z*)-**1**,^{3a} bromination with NBS also afforded regioselectively *meso*-brominated pyrromethenone derivative (*E*)-**2** in 82% yield.⁸



Next, the introduction of carbon substituents was investigated (Table 1). When (*Z*)-**2** was treated with 3 equiv of *n*-BuMgBr, *meso*-butylated pyrromethenone derivative **3** was obtained in 21% yield⁹ and 65% of unreacted (*Z*)-**2** was recovered (Entry 1). By increasing the amount of *n*-BuMgBr, the chemical yield was

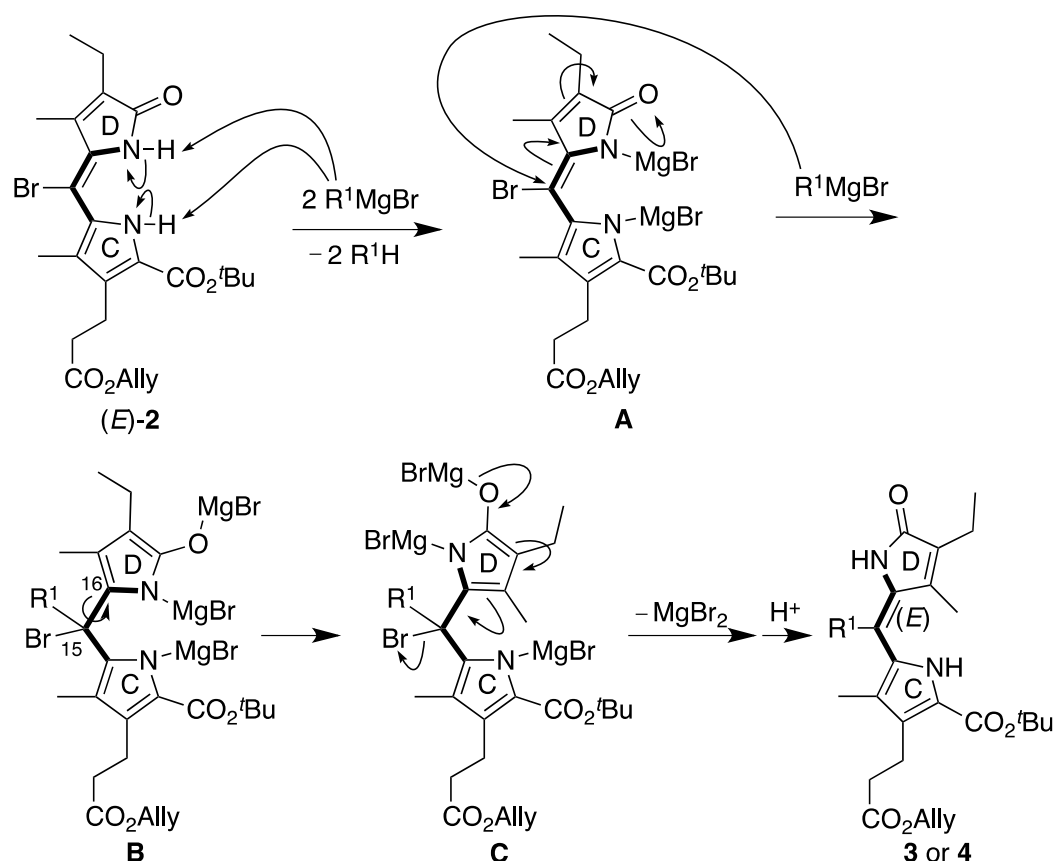
slightly improved (Entry 2). However, further increase of the Grignard reagent or reaction temperature resulted in giving considerable amount of by-products probably due to nucleophilic addition to an allyl ester moiety. It was found that the similar reaction using vinyl Grignard reagent proceeded more smoothly to give the vinylated product **4** in 75% yield (Entry 4).¹⁰ Propenyl Grignard reagent also afforded the *meso*-substituted pyrromethenone derivative **5** (Entry 6). In the case of 1-hexynyl Grignard reagent, which was generated *in situ* from 1-hexyne and *n*-BuMgBr, the introduction of sp-carbon was achieved to furnish **6** in 55% yield (Entry 7). In the reaction of (*E*)-**2** with *n*-BuMgBr and CH₂=CHMgBr, products **3** and **4** with *E* stereochemistries, which are same products as those from (*Z*)-**2**, were surprisingly produced, respectively (Entries 3 and 5).^{9,10} One possible elucidation of these phenomena is shown in Scheme 2. That is, electrostatic repulsion between two N-MgBr bonds in **B** induced rotation around the C15–C16 axis followed by elimination of a bromide anion via **C** to afford (*E*)-products, **3** or **4**.

Table 1. Substitution Reaction of (*Z*)-**2** and (*E*)-**2** with Grignard reagents



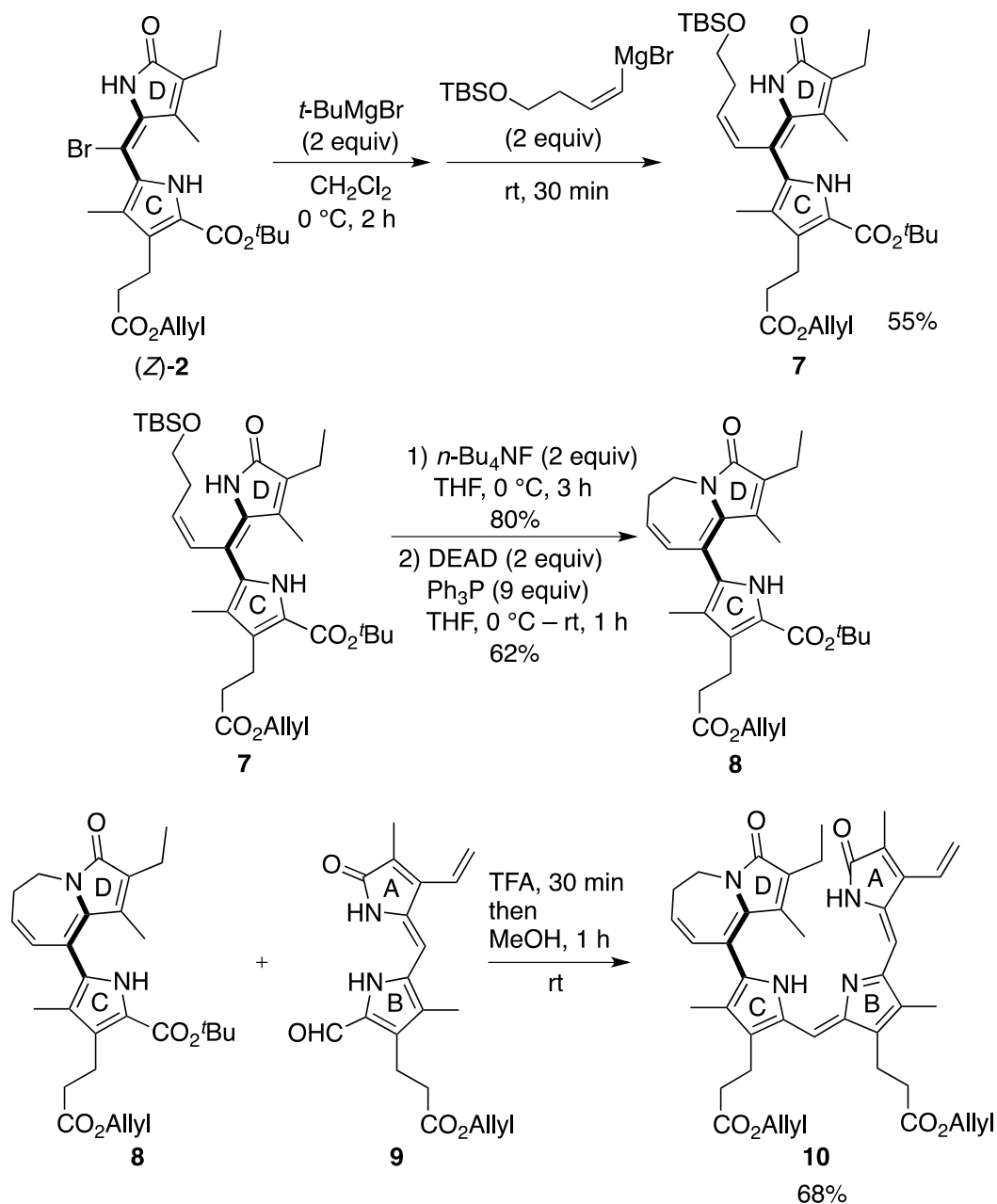
Entry	2	R ¹	<i>n</i>	Temp	Time	Product	Yield/%
1	<i>Z</i>	<i>n</i> -Bu	3	0 °C	2 h	3	21 ^{a)}
2	<i>Z</i>		5	0 °C	2 h		36 ^{a)}
3	<i>E</i>		5	0 °C	2 h		35
4	<i>Z</i>	CH ₂ =CH	4	rt	20 min	4	75 ^{a)}
5	<i>E</i>		4	rt	30 min		68
6	<i>Z</i>	MeCH=CH	4	rt	20 min	5	66 ^{b)}
7	<i>Z</i>	<i>n</i> -BuC≡C	5	0 °C	30 min	6	55 ^{a)}

a) Unreacted (*Z*)-**2** was recovered in 65% (Entry 1), 35% (Entry 2), 16% (Entry 4), and 10% (Entry 7), respectively. b) A mixture of (*E*)- and (*Z*)-isomers were obtained.



Scheme 2. A plausible pathway from (E)-2 to 3 or 4

To synthesize sterically fixed CD-ring components anchored to the *meso*-position, introduction of a substituent bearing an ω -leaving group was examined. Based on the results shown in Table 1, the Grignard reagent as an sp^2 carbon nucleophile was chosen. That is, the reaction of (Z)-2 with (Z)-TBSOCH₂CH₂CH=CHMgBr¹¹ was examined. The reactivity of the Grignard reagent was rather low and a substituted product 7 was obtained in 43% yield by the use of 9 equiv of the Grignard reagent. Thus, initial deprotonation of two amino protons was performed with a simpler Grignard reagent as shown in Scheme 3. When (Z)-2 was successively treated with 2 equiv of *t*-BuMgBr and 2 equiv of (Z)-TBSOCH₂CH₂CH=CHMgBr, the *meso*-substituted product 7 was obtained in 55% yield. A 15*E*-fixed CD-ring component 8 was obtained by the deprotection of silyl group followed by the Mitsunobu reaction. The coupling reaction between the C/D- and A/B-ring components (8 and 9¹²) was carried out under acidic conditions to afford the sterically fixed 18Et-BV diallyl ester derivative 10 bearing the 15*E*-fixed C/D-ring component in 68% yield.¹³

Scheme 3. Synthesis of 15*E*-fixed 18Et-BV derivative **10**

As described above, the regioselective bromination of the CD-ring component of bilin chromophore at the *meso*-position was achieved with NBS to give the corresponding bromo-substituted CD-ring component. Further substitution reaction of the resulting *meso*-brominated pyrromethenone derivative with the Grignard reagent was realized to afford carbon homologated pyrroles, which was successfully applied to the synthesis 15*E*-fixed 18Et-BV derivative. The present method provides a promising strategy for the synthesis of various types of sterically fixed chromophores anchored to the *meso*-position.

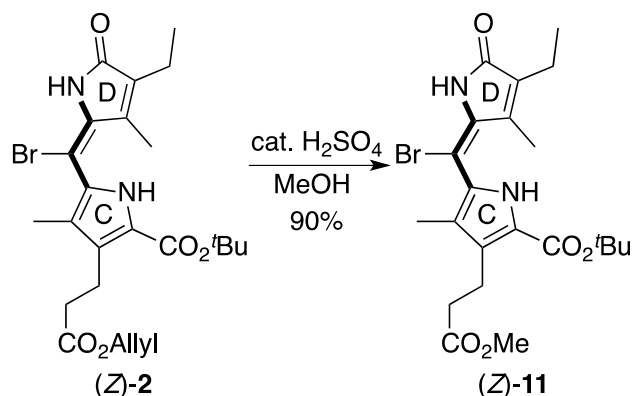
ACKNOWLEDGEMENTS

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- (Z)-**2**: Mp 105–107 °C (recrystallized from AcOEt/hexane); ¹H NMR (CDCl₃, 400 MHz): δ = 1.05 (t,

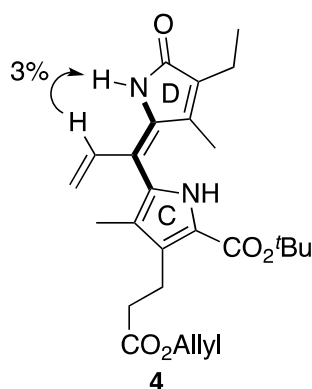
3H, $J = 7.8$ Hz), 1.49 (s, 3H), 1.56 (s, 9H), 1.97 (s, 3H), 2.27 (q, 2H, $J = 7.8$ Hz), 2.56 (t, 2H, $J = 8.2$ Hz), 3.00 (t, 2H, $J = 8.2$ Hz), 4.57 (d, 2H, $J = 6.0$ Hz), 5.23 (dd, 1H, $J = 10.6, 1.4$ Hz), 5.31 (dd, 1H, $J = 17.4, 1.4$ Hz), 5.91 (ddt, 1H, $J = 17.4, 10.6, 6.0$ Hz), 7.56 (br, 1H), 9.48 (br, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 9.2, 11.6, 13.0, 16.6, 20.8, 28.2, 35.0, 64.9, 81.0, 102.2, 117.9, 120.4, 120.6, 126.9, 128.5, 132.1, 137.7, 138.3, 140.5, 161.0, 171.8, 172.6$; IR (KBr) 3288, 2970, 2932, 2871, 1747, 1699, 1664, 1457, 1368, 1270, 1156, 1130 cm^{-1} ; HRMS (ESI-TOF): m/z calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_5^{79}\text{BrNa}$: 529.1314: $[M+\text{Na}]^+$; found: 529.1310, m/z calcd for $\text{C}_{24}\text{H}_{31}\text{N}_2\text{O}_5^{81}\text{BrNa}$: 531.1294: $[M+\text{Na}]^+$; found: 531.1288. Compound (*Z*)-**2** was converted to the corresponding methyl ester (*Z*)-**11**, whose structure was unambiguously determined by X-ray crystallographic analysis. (*Z*)-**11**: Crystal data: $\text{C}_{22}\text{H}_{29}\text{N}_2\text{O}_5\text{Br}$, $M_r = 481.39$, triclinic, $P1$, $a = 9.682(1)$, $b = 10.284(1)$, $c = 12.295(1)$ Å, $V = 1118.3(2)$ Å³, $\alpha = 67.333(5)^\circ$, $\beta = 85.501(8)^\circ$, $\gamma = 82.047(7)^\circ$, $Z = 2$. $D_{\text{calcd}} = 1.429$ g cm^{-3} . $R = 0.052$ ($R_w = 0.068$) for 3986 reflections with $I > 3.00\sigma(I)$ and 271 variable parameters. Crystallographic data for (*Z*)-**11** have been deposited with Cambridge Crystallographic Data Centre as supplementary publication No. CCDC 1011727. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html.



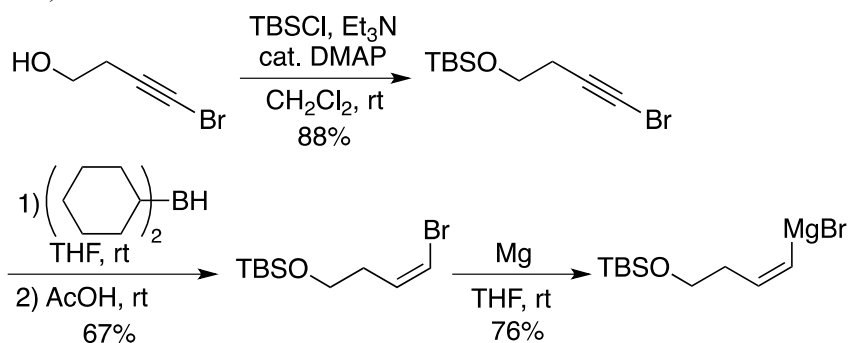
8. (*E*)-**2**: Mp 119–121 °C (recrystallized from AcOEt/hexane); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 1.01$ (t, 3H, $J = 7.6$ Hz), 1.45 (s, 3H), 1.51 (s, 9H), 1.95 (s, 3H), 2.23 (q, 2H, $J = 7.6$ Hz), 2.52 (t, 2H, $J = 7.8$ Hz), 2.98 (t, 2H, $J = 7.8$ Hz), 4.55 (d, 2H, $J = 6.0$ Hz), 5.20 (dd, 1H, $J = 10.6, 1.4$ Hz), 5.28 (dd, 1H, $J = 17.2, 1.4$ Hz), 5.88 (ddt, 1H, $J = 17.2, 10.6, 6.0$ Hz), 7.70 (br, 1H), 10.0 (br, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 9.2, 10.7, 12.9, 16.8, 20.8, 28.2, 35.1, 65.0, 81.7, 94.9, 118.2, 121.4, 121.8, 127.1, 128.2, 132.1, 137.9, 139.3, 141.4, 160.9, 170.3, 172.5$; IR (KBr) 3289, 2970, 2931, 2871, 1747, 1699, 1665, 1457, 1368, 1270, 1156, 1130 cm^{-1} ; HRMS (FAB⁺): m/z calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5^{79}\text{Br}$: 507.1495: $[M+\text{H}]^+$; found: 507.1487, m/z calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5^{81}\text{Br}$: 509.1474: $[M+\text{H}]^+$; found: 509.1477.
9. The ^1H and ^{13}C NMR spectra of the butylated compounds obtained from (*Z*)-**2** and (*E*)-**2** were identical each other. **3**: Mp 137–140 °C (recrystallized from AcOEt/hexane); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 0.80$ (t, 3H, $J = 6.4$ Hz), 0.97 (t, 3H, $J = 7.3$ Hz), 1.24–1.32 (m, 4H), 1.34 (s, 3H), 1.49 (s, 9H), 1.83 (s, 3H), 2.21 (q, 2H, $J = 7.3$ Hz), 2.36 (t, 2H, $J = 6.8$ Hz), 2.49 (t, 2H, $J = 7.8$ Hz), 2.95 (t, 2H, $J = 7.8$ Hz), 4.51 (d, 2H, $J = 5.5$ Hz), 5.16 (d, 1H, $J = 10.5$ Hz), 5.24 (d, 1H, $J = 16.9$ Hz), 5.84

(ddt, 1H, $J = 16.9, 10.5, 5.5$ Hz), 8.67 (br, 1H), 8.88 (br, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 9.3, 10.9, 13.2, 13.9, 16.7, 20.9, 22.8, 28.4, 30.5, 34.5, 35.3, 65.0, 81.1, 116.0, 118.2, 119.3, 119.7, 128.4, 130.3, 132.2, 136.3, 138.3, 140.1, 161.1, 171.9, 172.7$; IR (KBr) 3301, 2963, 2929, 2871, 1735, 1687, 1659, 1450, 1368, 1272, 1166, 1132 cm^{-1} ; HRMS (FAB^+): m/z calcd for $\text{C}_{28}\text{H}_{41}\text{N}_2\text{O}_5$: 485.3015: $[\text{M}+\text{H}]^+$; found: 485.3013. The stereochemistry of **3** was assumed to be *E* based on the stereochemistry of **4** shown in ref. 10.

10. The ^1H and ^{13}C NMR spectra of the vinylated compounds obtained from (*Z*)-**2** and (*E*)-**2** were identical each other. **4**: Mp 154–156 °C (recrystallized from AcOEt/hexane); ^1H NMR (CDCl_3 , 400 MHz): $\delta = 1.05$ (t, 3H, $J = 7.3$ Hz), 1.38 (s, 3H), 1.57 (s, 9H), 1.85 (s, 3H), 2.31 (q, 2H, $J = 7.3$ Hz), 2.58 (t, 2H, $J = 7.8$ Hz), 3.05 (t, 2H, $J = 7.8$ Hz), 4.58 (d, 2H, $J = 6.0$ Hz), 4.97 (d, 1H, $J = 16.5$ Hz), 5.23 (d, 1H, $J = 10.5$ Hz), 5.32 (d, 1H, $J = 16.5$ Hz), 5.35 (d, 1H, $J = 10.6$ Hz), 5.92 (ddt, 1H, $J = 16.5, 10.5, 6.0$ Hz), 6.86 (dd, 1H, $J = 16.5, 10.6$ Hz), 8.87 (br, 1H), 8.95 (br, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): $\delta = 9.0, 10.7, 13.2, 16.8, 20.9, 28.4, 35.4, 65.0, 81.1, 113.6, 118.2, 120.0, 120.2, 120.4, 126.6, 128.5, 132.2, 132.3, 137.0, 138.8, 140.6, 161.0, 171.7, 172.7$; IR (KBr) 3296, 2970, 2934, 2877, 1746, 1683, 1664, 1454, 1368, 1274, 1256, 1160, 1129 cm^{-1} ; HRMS (FAB^+): m/z calcd for $\text{C}_{26}\text{H}_{35}\text{N}_2\text{O}_5$: 455.2546: $[\text{M}+\text{H}]^+$; found: 455.2543. The stereochemistry of the vinyl-substituted pyrromethenone derivative **4** in a CDCl_3 solution was determined to be *E* by NOE measurement as shown below.



11. (*Z*)- $\text{TBSOCH}_2\text{CH}_2\text{CH}=\text{CHMgBr}$ was prepared from (*Z*)- $\text{TBSOCH}_2\text{CH}_2\text{CH}=\text{CHBr}$, which was available from $\text{HOCH}_2\text{CH}_2\text{C}\equiv\text{CBr}$ ¹⁴ according to the procedure similar to the synthesis of (*Z*)- $\text{TBSOCH}_2(\text{CH}_2)_3\text{CH}=\text{CHBr}$.¹⁵



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13. **10**: An oil; ^1H NMR (CDCl_3 , 400 MHz): δ = 0.98 (t, 3H, J = 7.3 Hz), 1.42 (s, 3H), 1.97 (s, 3H), 2.01 (br, 1H), 2.04 (s, 3H), 2.06 (s, 3H), 2.27 (q, 2H, J = 7.3 Hz), 2.28 (br, 1H), 2.57–3.62 (m, 6H), 2.91–3.00 (m, 4H), 3.91–3.97 (m, 1H), 4.07–4.14 (m, 1H), 4.55–4.59 (m, 4H), 5.21 (d, 2H, J = 10.5 Hz), 5.28 (d, 2H, J = 17.4 Hz), 5.65 (d, 1H, J = 11.4 Hz), 5.66 (d, 1H, J = 17.9 Hz), 5.89 (ddt, 2H, J = 17.4, 10.5, 6.0 Hz), 6.01 (s, 1H), 6.09 (d, 1H, J = 11.9 Hz), 6.16 (dt, 1H, J = 11.9, 5.0 Hz), 6.60 (dd, 1H, J = 17.9, 11.4 Hz), 6.88 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz): δ = 9.5, 9.75, 9.77, 11.2, 13.1, 17.3, 19.9, 20.0, 31.3, 35.3, 35.4, 40.5, 65.27, 65.30, 98.1, 111.1, 116.3, 118.3, 118.4, 121.6, 122.6, 126.2, 127.5, 129.1, 129.9, 132.02, 132.05, 132.3, 133.1, 135.4, 135.7, 139.4, 139.5, 139.8, 141.9, 142.6, 143.6, 148.6, 164.6, 169.3, 170.9, 172.30, 172.35; IR (neat) 3355, 2925, 2853, 1736, 1691, 1599, 1456, 1156, 1091, 961, 931, 756 cm^{-1} ; UV/Vis (MeOH): λ_{max} 333 (ϵ_{max} = 11,540), 582 (ϵ_{max} = 6,232) nm; HRMS (FAB $^+$): m/z calcd for $\text{C}_{43}\text{H}_{49}\text{N}_4\text{O}_6$: 717.3652: $[\text{M}+\text{H}]^+$; found: 717.3650.
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