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# Oxidative Radical Cyclization–Cyclization Reaction Leading to 1*H*-Benzo[*f*]isoindole Derivatives

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**Abstract:** The synthesis of 1*H*-benzo[*f*]isoindole derivatives was achieved by the cascade radical cyclization–cyclization reaction of the active methine substrate having an allyl group and phenyl group as different two radical acceptors. This oxidative transformation proceeded by using iron(III) chloride $FeCl_3$ as a mild oxidant via the intramolecular radical addition to the allyl group followed by the second radical addition to the phenyl group.

**Keywords:** radical; cyclization; benzoisoindole; iron; oxidation

## 1. Introduction

Hexahydro-1*H*-benzo[*f*]isoindol-1-one and dihydro-1*H*-benzo[*f*]isoindol-1-one are the core structures in some natural products and the biologically active agents (Figure 1) [1–6]. Therefore, we felt attracted to the possibility of a new synthetic method based on the oxidative radical cyclization leading to γ-lactams, which was recently developed by our group [7].

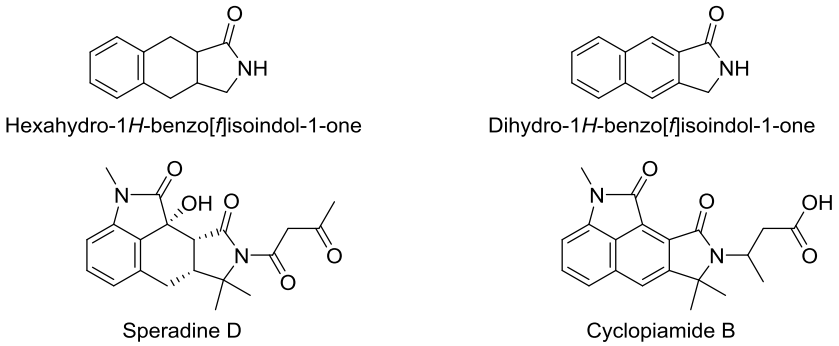
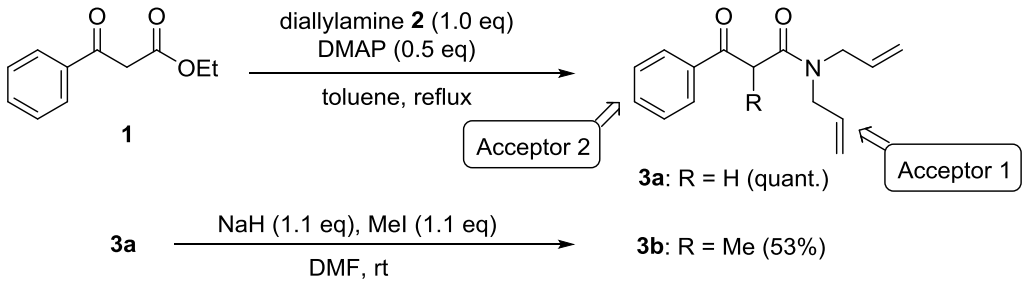



**Figure 1.** 1*H*-Benzo[*f*]isoindole derivatives.

The oxidative radical reactions have made great advances in synthetic chemistry mainly by using manganese (III) acetate $Mn(OAc)_3$ and cerium (IV) ammonium nitrate (CAN) [8,9]. However, less is known about the cascade oxidative radical cyclization–cyclization reactions of the active methylenes or methines having two radical acceptors [10–15]. Furthermore, these reported transformations are dependent on a toxic strong oxidant such as $Mn(OAc)_3$; thus, the replacement of heavy metal oxidant into the less toxic and mild electron transfer reagents is also a challenging task. We are interested in the cascade radical cyclization–cyclization reaction as a new strategy for constructing the 1*H*-benzo[*f*]isoindole structure. In this paper, we report the synthesis of 1*H*-benzo[*f*]isoindole derivatives *trans*-**4** and *cis*-**4** by the cascade transformation using iron(III) chloride $FeCl_3$ as a mild and environmentally benign oxidant [16–20].

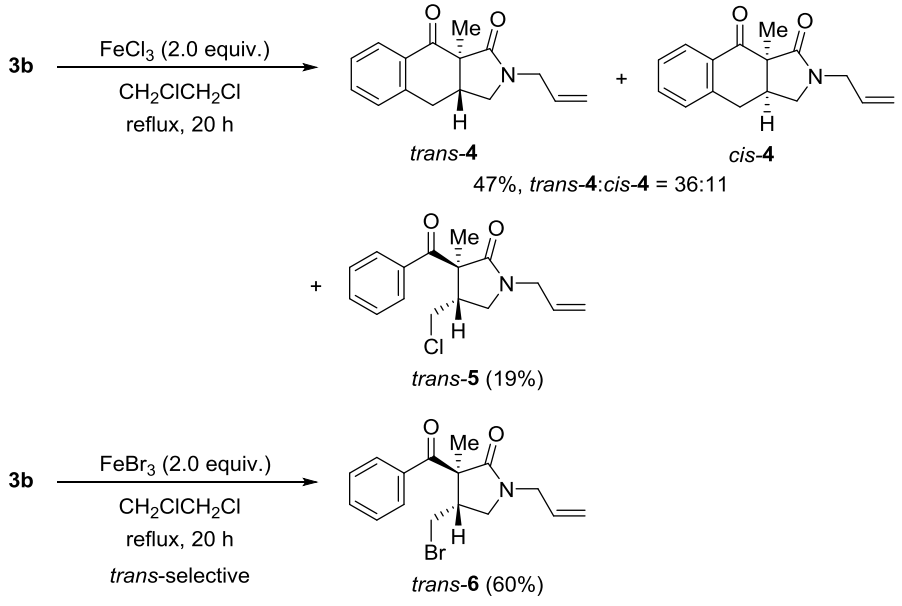
## 2. Results

At first, we prepared two substrates **3a** [21] and **3b** having an allyl group and a phenyl group as two different radical acceptors (Scheme 1). In the presence of *N*,*N*-dimethylaminopyridine (DMAP), treatment of ethyl benzoylacetate **1** with diallylamine **2** in toluene under reflux conditions afforded the desired methylene substrate **3a** in almost quantitative yield. Another methine substrate **3b** was obtained in 53% yield by α-methylation of substrate **3a** using NaH and MeI.




**Scheme 1.** Preparation of substrates **3a** and **3b**.

For the oxidative radical reactions, 2.0 equivalents of $FeCl_3$ were initially employed as a mild oxidant in $CH_2ClCH_2Cl$ under reflux conditions (Scheme 2). Although treatment of active methylene **3a** with $FeCl_3$ did not afford the desired product effectively, the $FeCl_3$-promoted cascade radical cyclization–cyclization reaction of α-methylated methine **3b** took place to afford the 1*H*-benzo[*f*]isoindole derivatives *trans*-**4** and *cis*-**4** in 47% combined yield and 36:11 *trans*/*cis*-selectivity, accompanied with a small amount of the mono-cyclized product *trans*-**5** (19% yield). In marked contrast to $FeCl_3$-promoted transformation, the use of $FeBr_3$ did not lead to the formation of 1*H*-benzo[*f*]isoindole derivatives. The mono-cyclized product *trans*-**6** was only obtained in 60% yield with high *trans*-selectivity. The excellent *trans*-selectivity of the mono-cyclized products *trans*-**5** and *trans*-**6** would be attributable to the steric effect in an initial radical intermediate. The relative stereochemistry of *trans*-**4** and *cis*-**4** was determined by NOESY experiments [22] and the stereochemistry of *trans*-**5** and *trans*-**6** was assumed on the basis of NOESY experiments and similarly based on our relative reaction [7].




**Scheme 2.** Oxidative radical cyclization of **3b**.

## 3. Discussion

In order to understand this transformation, the thermodynamic data were obtained by density functional calculation (Figure 2) [22]. These data indicate that the conversion of methine substrate **3b** into *trans*-**4** and $H_2$ is exothermic ($\Delta H = -17$ kJ/mol at 298.15 K). Totally, the change in Gibbs energy suggests that the transformation of **3b** into *trans*-**4** is favorable to proceed in view of thermodynamics ($\Delta G < 0$ kJ/mol at 298.15 K). Furthermore, the calculation data show that *cis*-**4** is more stable than *trans*-**4**.

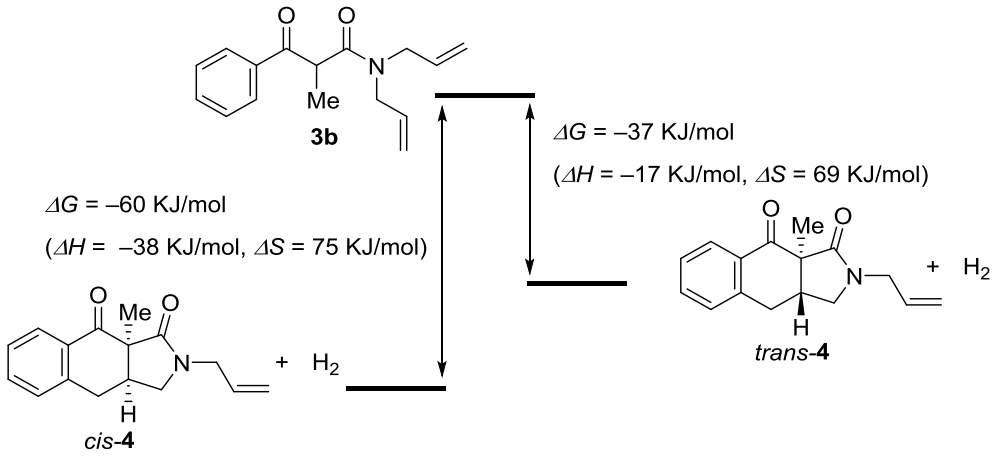



**Figure 2.** Calculation study.

This $FeCl_3$-promoted transformation starts from the single electron-transfer (SET) in the enolate-Fe(III) complex **A** to afford Radical **B** (Figure 3). The product *trans*-**4** would be formed via the 5-*exo*-*trig* cyclization of Radical **B**, the second cyclization of Radical **C** onto phenyl group, and the subsequent oxidation of Radical **D** with $FeCl_3$ affording the cation intermediate **E**. It should be noted that the *trans*/*cis*-selectivity of **4** is determined by the stereoselectivity of the first cyclization of Radical **B**. We presume that the reversibility in cyclization of the resonance-stabilized Radical **B** affording the unstable primary Radical **C** leads to the erosion of *trans*/*cis*-selectivity, because 1*H*-benzo[*f*]isoindole derivative *trans*-**4** is unstable as compared with *cis*-**4** (Figure 2).

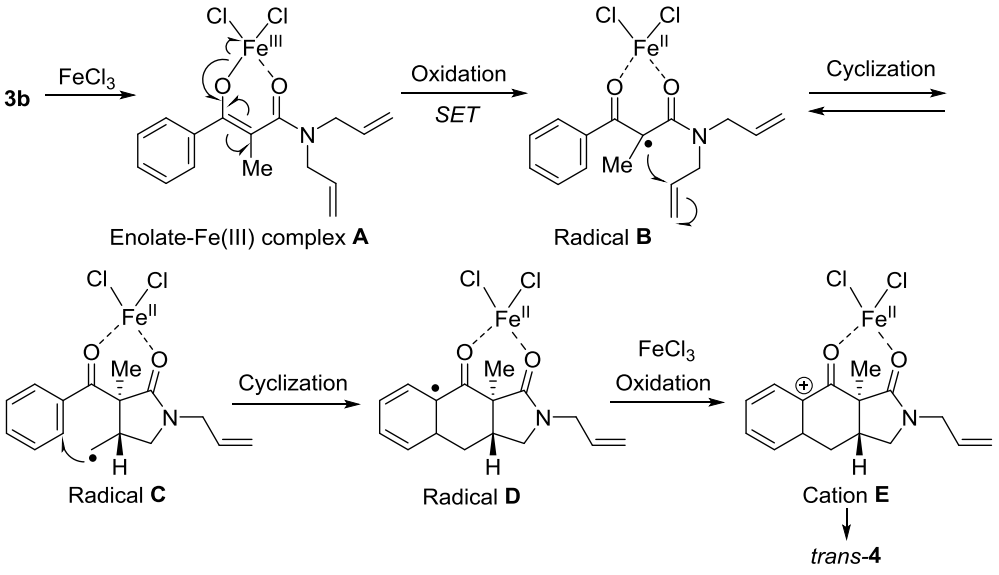



**Figure 3.** Possible reaction pathway.

In the case of $FeBr_3$-promoted transformation, the reversibility in cyclization of Radical **B** would be suppressed by the rapid trapping of Radical **B** with $FeBr_3$ leading to the predominant formation of the mono-cyclized product *trans*-**6**. We think that high *trans*-selectivity in $FeBr_3$-promoted mono-cyclization supports this hypothesis. Moreover, this result indicates that the second cyclization is not a Friedel–Crafts reaction. Consequently, the use of $FeCl_3$ as an oxidant is essential for the second radical cyclization of Radical **B**.

In conclusion, we have developed the $FeCl_3$-promoted oxidative radical cyclization–cyclization reaction for constructing the 1*H*-benzo[*f*]isoindole structure.

## 4. Experimental Section

### *4.1. General Information*

Melting points are uncorrected. $^1$H-NMR spectra were measured in $CDCl_3$ with TMS as an internal standard (0.00 ppm). $^{13}$C-NMR spectra were measured in $CDCl_3$ as an internal standard (77.0 ppm). For silica gel column chromatography, SiliCycle Inc. SiliaFlash F60 was used. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$, manufacturer of pharmaceutical, Kenilworth NJ, USA). The substrate **3a** is the known compound [21].

### *4.2. N,N-Diallyl-3-oxo-3-phenylpropanamide (**3a**)*

To a solution of diallylamine **2** (2.46 mL, 20 mmol) and *N*,*N*-dimethylaminopyridine (1.22 g, 10 mmol) in toluene (20 mL), ethyl benzoylacetate **1** (3.46 mL, 20 mmol) was added under argon atmosphere at room temperature. The stirred reaction mixture was heated at reflux for 15 h. The reaction mixture was diluted with water and then extracted with AcOEt. The organic phase was dried over $Na_2SO_4$ and then concentrated at reduced pressure. The purification of the residue by flash silica gel column chromatography (AcOEt/hexanes = 1:10 to 1:4) afforded the product **3a** [21] (4.87 g, quant.).

Colorless oil. IR (KBr) 3083, 2982, 1689, 1628, 1576, 1482 $cm^{-1}$. The presence of keto and enol isomers precluded a comprehensive assignment of all proton and carbon resonances. $^1$H-NMR ($CDCl_3$) δ 8.01 (6/5H, m), 7.75 (4/5H, m), 7.59 (3/5H, m), 7.50–7.38 (12/5H, m), 5.88–5.74 (10/5H, m), 5.73 (2/5H, s; enol form), 5.25-5.16 (20/5H, m), 4.10 (6/5H, s; keto form), 4.09–3.92 (22/5H, m). $^{13}$C-NMR ($CDCl_3$) δ 194.1, 172.3, 171.6, 167.1, 136.3, 134.9, 133.6, 133.1, 132.8, 132.6, 130.7, 128.7 (2C), 128.4, 125.9, 117.4, 117.1, 117.0, 85.1, 49.9, 49.3, 48.0, 45.6. HRMS ($ESI^+$) calcd for $C_{15}H_{17}NO_2Na$ ($M + Na^+$): 266.1152, Found: 266.1175.

### *4.3. N,N-Diallyl-2-methyl-3-oxo-3-phenylpropanamide (**3b**)*

After NaH (60% oil suspension, 181 mg, 4.5 mmol) was washed with hexanes twice under argon atmosphere at room temperature, DMF (10.3 mL) was added. To this stirring suspension, a solution of **3a** (1.00 g, 4.1 mmol) in DMF (10.3 mL) was added at 0 °C. After being stirred at the same temperature for 1 h, methyl iodide (0.28 mL, 4.5 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was diluted with saturated $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $Na_2SO_4$ and then concentrated at reduced pressure. The purification of the residue by flash silica gel column chromatography (AcOEt/hexanes = 1:2) afforded the product **3b** (558 mg, 53%).

Colorless crystals. Mp 51.5–52.5 °C (hexanes). IR (KBr) 2984, 2937, 1695, 1637, 1449, 1414 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 7.93 (2H, m), 7.56 (1H, m), 7.45 (2H, m), 5.79–5.66 (2H, m), 5.24-5.09 (4H, m), 4.44 (1H, q, *J* = 7.1 Hz), 4.15 (1H, dd, *J* = 15.1, 5.5 Hz), 3.85–3.79 (3H, m), 1.49 (3H, d, *J* = 7.1 Hz). $^{13}$C-NMR ($CDCl_3$) δ 197.0, 170.5, 135.6, 133.3, 132.6, 132.5, 128.7, 128.3, 117.4, 117.3, 49.2, 47.9, 46.7, 14.7. HRMS ($ESI^+$) calcd for $C_{16}H_{20}NO_2$ ($M + H^+$): 258.1489, Found: 258.1488.

### *4.4. 2-Allyl-9a-methyl-2,3,3a,9a-tetrahydro-1H-benzo[f]isoindole-1,9(4H)-dione (**4**) and trans-1-Allyl-3-benzoyl-4-(chloromethyl)-3-methylpyrrolidin-2-one (trans-**5**)*

The stirred suspension of $FeCl_3$ (127 mg, 1.0 mmol) and substrate **3b** (129 mg, 0.50 mmol) in $CH_2ClCH_2Cl$ (5.0 mL) was heated at reflux under argon atmosphere for 20 h. The reaction mixture was diluted with saturated $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $Na_2SO_4$ and then concentrated at reduced pressure. Rough purification of the residue by flash silica gel column chromatography (AcOEt/hexanes = 1:2) afforded the products as a mixture of two isomers. Second purification by preparative TLC (AcOEt/benzene = 1:4) afforded **4** as the isolated *trans*-**4** (46 mg, 36%), *cis*-**4** (14 mg, 11%), and *trans*-**5** (28 mg, 19%).

*trans*-**4**: Colorless oil. IR (KBr) 2930, 2872, 1716, 1677, 1600, 1489, 1415 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 8.08 (1H, br dd, *J* = 7.6, 1.4 Hz), 7.47 (1H, br td, *J* = 7.6, 1.4 Hz), 7.34 (1H, br t, *J* = 7.6 Hz), 7.25 (1H, br d, *J* = 7.6 Hz), 5.71 (1H, m), 5.22–5.17 (2H, m), 3.97 (1H, ddt, *J* = 15.1, 6.4, 1.4 Hz), 3.88 (1H, ddt, *J* = 15.1, 6.4, 1.4 Hz), 3.36 (1H, dd, *J* = 9.6, 6.9 Hz), 3.25 (1H, dd, *J* = 10.6, 9.6 Hz), 3.08 (1H, dd, *J* = 16.5, 12.4 Hz), 3.01 (1H, dd, *J* = 16.5, 4.6 Hz), 2.79 (1H, m), 1.28 (3H, s). $^{13}$C-NMR ($CDCl_3$) δ 194.3, 172.3, 141.0, 133.1, 132.3, 132.0, 129.0, 128.8, 127.2, 118.3, 50.1, 46.2, 45.1, 39.8, 28.1, 12.9. HRMS ($ESI^+$) calcd for $C_{16}H_{18}NO_2$ [M + $H^+$]: 256.1332, Found: 256.1326.

*cis*-**4**: Colorless oil. IR (KBr) 2929, 1704, 1600, 1489, 1451, 1441, 1420 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 7.99 (1H, br dd, *J* = 7.6, 1.4 Hz), 7.52 (1H, br td, *J* = 7.6, 1.4 Hz), 7.34 (1H, br t, *J* = 7.6 Hz), 7.24 (1H, br d, *J* = 7.6 Hz), 5.62 (1H, m), 5.11 (1H, dd, *J* = 10.1, 1.4 Hz), 5.05 (1H, dd, *J* = 17.4 , 1.4 Hz), 3.95 (1H, ddt, *J* = 15.6, 6.0, 1.4 Hz), 3.78 (1H, ddt, *J* = 15.6, 6.4, 1.4 Hz), 3.37 (1H, dd, *J* = 9.6, 7.8 Hz), 3.26 (1H, dd, *J* = 16.5, 5.0 Hz), 2.96 (1H, dd, *J* = 9.6, 8.5 Hz), 2.88 (1H, dd, *J* = 16.5, 3.7 Hz), 2.80 (1H, m), 1.54 (3H, s). $^{13}$C-NMR ($CDCl_3$) δ 193.4, 171.4, 140.3, 134.1, 132.9, 132.1, 129.1, 128.2, 127.3, 118.2, 55.1, 47.9, 45.7, 38.9, 27.8, 20.5. HRMS ($ESI^+$) calcd for $C_{16}H_{18}NO_2$ [M + $H^+$]: 256.1332, Found: 256.1343.

*trans*-**5:** Colorless oil. IR (KBr) 2980, 2933, 1697, 1645, 1490, 1444 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 7.86 (2H, br d, *J* = 7.4 Hz), 7.52 (1H, m), 7.42 (2H, br t, *J* = 7.6 Hz), 5.78 (1H, m), 5.33–5.22 (2H, m), 4.06 (1H, br dd, *J* = 14.6, 6.4 Hz), 3.95 (1H, br dd, *J* = 14.6, 6.4 Hz), 3.70 (1H, dd, *J* = 10.1, 7.8 Hz), 3.57 (1H, dd, *J* = 11.0, 6.0 Hz), 3.47 (1H, dd, *J* = 11.0, 8.7 Hz), 3.35 (1H, m), 3.18 (1H, dd, *J* = 10.1, 8.3 Hz), 1.45 (3H, s). $^{13}$C-NMR ($CDCl_3$) δ 198.6, 173.9, 135.7, 132.4, 131.5, 128.9, 128.5, 119.2, 59.1, 48.4, 45.6, 42.7, 42.4, 14.8. HRMS ($ESI^+$) calcd for $C_{16}H_{18}{}^{35}ClNO_2Na$ [M + $Na^+$]: 314.0918, Found: 314.0924; calcd for $C_{16}H_{18}{}^{37}ClNO_2Na$ (M + 2 + $Na^+$): 316.0894, Found: 316.0902.

### *4.5. trans-1-Allyl-3-benzoyl-4-(bromomethyl)-3-methylpyrrolidin-2-one (trans-**6**)*

The stirred suspension of $FeBr_3$ (296 mg, 1.0 mmol) and substrate **3b** (129 mg, 0.50 mmol) in $CH_2ClCH_2Cl$ (5.0 mL) was heated at reflux under argon atmosphere for 20 h. The reaction mixture was diluted with saturated $NaHCO_3$ and then extracted with AcOEt. The organic phase was dried over $Na_2SO_4$ and then concentrated at reduced pressure. Purification of the residue by preparative TLC (AcOEt/hexanes = 1:2) afforded *trans*-**6** (100 mg, 60%).

Colorless crystals. Mp 71.5–72 °C (AcOEt–hexane). IR (KBr) 2925, 2853, 1733, 1697, 1445 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 7.86 (2H, br dd, *J* = 8.2, 1.4 Hz), 7.52 (1H, m), 7.41 (2H, br t, *J* = 7.8 Hz), 5.79 (1H, m), 5.31–5.26 (2H, m), 4.05 (1H, br dd, *J* = 14.6, 6.4 Hz), 3.95 (1H, br dd, *J* = 14.6, 6.4 Hz), 3.72 (1H, dd, *J* = 10.1, 7.3 Hz), 3.44–3.36 (2H, m), 3.29 (1H, m), 3.16 (1H, dd, *J* = 10.1, 7.8 Hz), 1.43 (3H, s). $^{13}$C-NMR ($CDCl_3$) δ 198.4, 174.0, 135.6, 132.5, 131.4, 129.0, 128.4, 119.2, 59.7, 49.5, 45.6, 42.4, 30.3, 14.7. HRMS ($ESI^+$) calcd for $C_{16}H_{18}{}^{79}BrNO_2Na$ [M + $Na^+$]: 358.0413, Found: 358.0423; calcd for $C_{16}H_{18}{}^{81}BrNO_2Na$ (M + $Na^+$): 360.0393, Found: 360.0407.

**Supplementary Materials:** The following are available online at http://www.mdpi.com/1422-8599/2017/1/M929. Details of the calculation study: Table S1: Gibbs free energy, enthalpy, and entropy at 298.15 K; Table S2: Change in Gibbs free energy, enthalpy, and entropy, HMQC, HMBC, and NOESY experiments of products *trans*-**4**, *cis*-**4**, *trans*-**5** and *trans*-**6**, and $^1$H- and $^{13}$C-NMR spectra of Compounds **3a**, **3b**, *trans*-**4**, *cis*-**4**, *trans*-**5**, and *trans*-**6**.

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**Author Contributions:** E. Yoshioka performed experiments and analyzed the data. H. Miyabe contributed to design of the study and manuscript writing.

**Conflicts of Interest:** The authors declare no conflict of interest.

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22. See: Supplementary Material.