

## Facile Synthesis of 5-Alkylidene-1,5-dihydropyrrol-2-ones from Morita-Baylis-Hillman Adducts

Bo Ram Park, Cheol Hee Lim, Jin Woo Lim, and Jae Nyoung Kim\*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Korea

\*E-mail: kimjn@chonnam.ac.kr

Received December 5, 2011, Accepted December 27, 2011

**Key Words :** 5-Alkylidene-1,5-dihydropyrrol-2-ones, 5-Hydroxypyrrol-2(5H)-ones, Morita-Baylis-Hillman adducts,  $\gamma$ -Alkylidenebutenolides

5-Alkylidene-1,5-dihydropyrrol-2-ones have received a special attention due to their abundance in biologically important substances including pukeleimide,<sup>1a</sup> ampullicin,<sup>1b,c</sup> isoampullicin,<sup>1b,c</sup> pulchellactam,<sup>1d-f</sup> pandamarine,<sup>1b</sup> and holomycin,<sup>1a</sup> as shown in Figure 1. Thus numerous methods for the synthesis of 5-alkylidene-1,5-dihydropyrrol-2-ones have been reported;<sup>1,2</sup> however, a facile synthetic pathway to this class of compounds is highly required until now. In addition, various 5-hydroxypyrrol-2(5H)-one derivatives, the precursors of 5-alkylidene-1,5-dihydropyrrol-2-ones in this paper, have been known to possess interesting biological activities.<sup>3</sup>

Recently various cyclic compounds have been synthesized from Morita-Baylis-Hillman (MBH) adducts.<sup>4</sup> Among the cyclic compounds, syntheses of various lactam derivatives have received much attention by us<sup>5</sup> and other groups.<sup>6</sup> Very recently, we reported a facile synthesis of  $\gamma$ -alkylidenebutenolides (such as **1a**) from MBH bromides, as shown in Scheme 1.<sup>7</sup> As a continuous work, we decided to examine the synthesis of 5-alkylidene-1,5-dihydropyrrol-2-ones (such as **3a**) from the readily available  $\gamma$ -alkylidenebutenolides.<sup>7</sup>

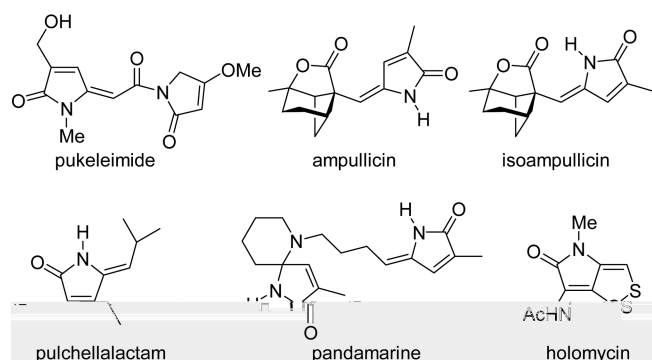
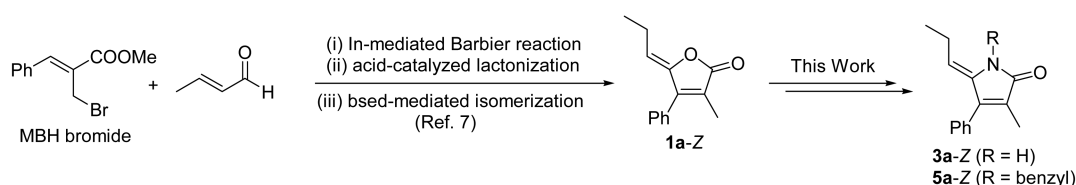


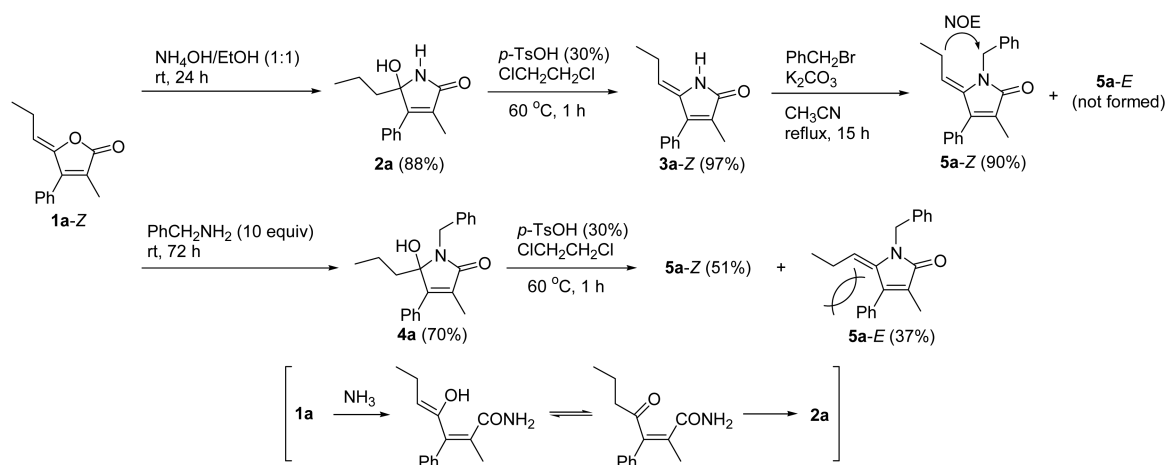
Figure 1

At the outset of our study, we examined the reaction of  $\gamma$ -propylidenebutenolide **1a**<sup>7</sup> with ammonia in ethanol at room temperature,<sup>8</sup> as shown in Scheme 2. As expected, 5-hydroxypyrrol-2(5H)-one **2a** was obtained in good yield (88%) by following the mechanism shown below in Scheme 2.<sup>8,9b</sup> Subsequent acid-catalyzed dehydration of **2a** produced 5-propylidene-1,5-dihydropyrrol-2-one (**3a**) in good yield (97%) in a highly stereoselective manner. As observed in a similar case<sup>8,9b</sup> and in our previous paper,<sup>7</sup> the *Z*-isomer was formed exclusively due to the unfavorable steric hindrance between the ethyl group of a propylidene moiety and the phenyl group at the 4-position. However, the reaction of **1a** and benzylamine afforded **4a** in moderate yield (70%) although excess amounts (10 equiv) of benzylamine were used. Moreover, an acid-catalyzed dehydration<sup>9</sup> of **4a** produced a mixture of *E/Z* isomers of *N*-benzyl-5-propylidene-1,5-dihydropyrrol-2-one (**5a**). The *Z*-isomer was formed as a major product (51%) along with appreciable amounts of *E*-isomer (37%). The stereochemistry of **5a-Z** was confirmed by NOE experiments. The ratio of *E/Z* stated that the unfavorable steric hindrance between the ethyl group of a propylidene moiety and the phenyl group at the 4-position is larger than that of the *N*-benzyl moiety. The *Z*-form of this compound could be synthesized more easily from **3a** and benzyl bromide in good yield (90%) in the presence of K<sub>2</sub>CO<sub>3</sub>. In the reaction we did not observe the formation of **5a-E** in any trace amount.

Encouraged by the successful results, we carried out the synthesis of 5-hydroxypyrrol-2(5H)-ones **2b-d** from  $\gamma$ -alkylidenebutenolides **1b-d**,<sup>7</sup> and the results are summarized in Table 1. The yields of **2b-d** were moderate to good (62–80%). For the synthesis of compound **2d**, we used THF as a co-solvent due to the limited solubility of **1d** in EtOH. These compounds were converted to 5-alkylidene-1,5-dihydro-



Scheme 1



Scheme 2

**Table 1.** Conversion of  $\gamma$ -alkylidenebutenolides to 5-alkylidene-1,5-dihydropyrrol-2-ones **3a-d**

| Entry | $\gamma$ -Alkylidenebutenolide <sup>a</sup> | 5-Hydroxypyrrol-2(5H)-one <sup>b</sup> | $\gamma$ -Alkylidenelactam <sup>c</sup> |
|-------|---------------------------------------------|----------------------------------------|-----------------------------------------|
| 1     |                                             |                                        |                                         |
| 2     |                                             |                                        |                                         |
| 3     |                                             |                                        |                                         |
| 4     |                                             |                                        |                                         |

<sup>a</sup>Prepared according to Ref. 7. <sup>b</sup>Conditions: substrate **1** (1.0 mmol),  $\text{NH}_4\text{OH}/\text{EtOH}$  (1:1, 4.0 mL), rt, 24 h. <sup>c</sup>Conditions: substrate **2** (0.5 mmol),  $p\text{-TsOH}$  (0.3 equiv), 1,2-dichloroethane, 60 °C, 1 h. <sup>d</sup>THF was added as a co-solvent.

pyrrol-2-ones **3b-d** in excellent yields (91–96%) in the presence of  $p\text{-TsOH}$ .<sup>9</sup> In all entries, the corresponding *Z*-isomers were formed exclusively, as in the case of **3a** (vide supra).

As for the synthesis of **5a-Z** (vide supra, Scheme 2), *N*-benzylation reactions of **3c-Z** and **3d-Z** were carried out similarly, and compounds **5c-Z** and **5d-Z** were synthesized in good yields (89–92%), as shown in Scheme 3. The formation

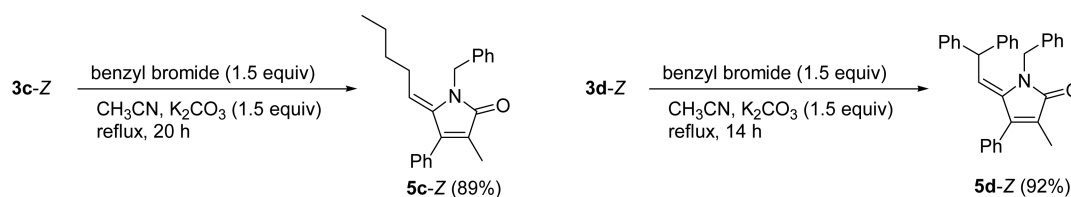
of the corresponding *E*-form was not observed in any trace amount due to a similar steric reason.

In summary, an expedient synthetic procedure of 5-alkylidene-1,5-dihydropyrrol-2-ones was disclosed from the corresponding  $\gamma$ -alkylidenebutenolides which were prepared from the Morita-Baylis-Hillman bromides. The reaction of  $\gamma$ -alkylidenebutenolides and ammonia and subsequent dehydration produced 5-alkylidene-1,5-dihydropyrrol-2-ones stereoselectively, and the stereochemistry was not changed during the benzylation to furnish a stereoselective synthetic protocol of *N*-benzyl-5-alkylidene-1,5-dihydropyrrol-2-ones.

## Experimental Section

**Typical Procedure for the Synthesis of 2a.** To a stirred solution of  $\gamma$ -alkylidenebutenolide **1a**<sup>7</sup> (214 mg, 1.0 mmol) in EtOH (2.0 mL) was added  $\text{NH}_4\text{OH}$  (28%, 2.0 mL), and the reaction mixture was stirred at room temperature for 24 h. After the aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc/ $\text{CH}_2\text{Cl}_2$ , 3:2:1), compound **2a** was obtained as a white solid, 203 mg (88%). Other compounds were synthesized similarly, and the spectroscopic data of **2a-d** are as follows.

**Compound 2a:** 88%; white solid, mp 164–166 °C; IR (KBr) 3375, 3214, 1708, 1666  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.79 (t,  $J = 7.5$  Hz, 3H), 1.05–1.17 (m, 1H), 1.25–1.41 (m, 1H), 1.59–1.71 (m, 1H), 1.79–1.89 (m, 1H), 1.81 (s, 3H), 4.66 (br s, OH), 7.34–7.44 (m, 3H), 7.61–7.65 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.47, 14.00, 16.63, 38.95, 90.29, 128.39, 128.54, 128.63, 128.78, 132.44, 154.19, 173.65; ESIMS  $m/z$  232 ( $\text{M}^+ + \text{H}$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{17}\text{NO}_2$ : C, 72.70; H, 7.41; N, 6.06. Found: C, 72.89; H,



Scheme 3

7.53; N, 5.97.

**Compound 2b:** 62%; white solid, mp 140–142 °C; IR (KBr) 3335, 3263, 1702  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.83 (s, 3H), 1.93–2.04 (m, 1H), 2.15–2.25 (m, 1H), 2.45–2.55 (m, 1H), 2.67–2.77 (m, 1H), 4.71 (br s, OH), 6.99–7.02 (m, 2H), 7.09–7.21 (m, 3H), 7.34–7.43 (m, 3H), 7.62–7.65 (m, 2H), 7.79 (br s, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.54, 29.75, 38.62, 90.08, 125.87, 128.30, 128.32, 128.48, 128.55, 128.80, 128.94, 132.22, 141.15, 154.21, 173.79; ESIMS  $m/z$  294 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{19}\text{NO}_2$ : C, 77.79; H, 6.53; N, 4.77. Found: C, 77.71; H, 6.42; N, 4.56.

**Compound 2c:** 80%; white solid, mp 114–116 °C; IR (KBr) 3401, 3293, 2953, 1700, 1649  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.77 (t,  $J$  = 6.6 Hz, 3H), 1.05–1.20 (m, 5H), 1.25–1.34 (m, 1H), 1.62–1.72 (m, 1H), 1.80–1.90 (m, 1H), 1.82 (s, 3H), 4.80 (br s, OH), 7.33–7.44 (m, 3H), 7.58–7.64 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.46, 13.82, 22.31, 22.81, 31.53, 36.65, 90.35, 128.36, 128.54, 128.64, 128.75, 132.44, 154.15, 173.68; ESIMS  $m/z$  260 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{21}\text{NO}_2$ : C, 74.10; H, 8.16; N, 5.40. Found: C, 74.44; H, 8.37; N, 5.19.

**Compound 2d:** 75%; white solid, mp 106–108 °C; IR (KBr) 3313, 3301, 1699, 1493  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.76 (s, 3H), 2.50 (dd,  $J$  = 14.4 and 8.7 Hz, 1H), 2.62 (dd,  $J$  = 14.4 and 5.7 Hz, 1H), 4.04 (br s, OH), 4.15 (dd,  $J$  = 8.7 and 5.7 Hz, 1H), 5.90 (br s, NH), 7.04–7.24 (m, 10H), 7.32–7.38 (m, 3H), 7.45–7.51 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.60, 42.23, 46.27, 89.31, 126.28, 126.57, 127.41, 127.93, 128.35, 128.56, 128.58, 128.65, 128.76, 128.92, 132.10, 143.90, 144.64, 153.74, 172.36; ESIMS  $m/z$  370 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{23}\text{NO}_2$ : C, 81.27; H, 6.27; N, 3.79. Found: C, 81.06; H, 6.44; N, 3.68.

**Typical Procedure for the Synthesis of 3a-Z.** A stirred solution of compound **2a** (116 mg, 0.5 mmol) and *p*-TsOH (27 mg, 0.15 mmol) in 1,2-dichloroethane (1.0 mL) was heated to 60 °C for 1 h. After the aqueous extractive workup and column chromatographic purification process ( $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ , 20:1), compound **3a-Z** was obtained as a white solid, 103 mg (97%). Other compounds were synthesized similarly, and the spectroscopic data of **3a-d** are as follows.

**Compound 3a-Z:** 97%; white solid, mp 102–104 °C; IR (KBr) 3183, 1686  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.09 (t,  $J$  = 7.5 Hz, 3H), 1.95 (s, 3H), 2.29–2.39 (m, 2H), 5.12 (t,  $J$  = 7.8 Hz, 1H), 7.26–7.31 (m, 2H), 7.37–7.48 (m, 3H), 8.91 (br s, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.10, 13.94, 21.13, 116.62, 128.29, 128.33, 128.73, 129.44, 132.10, 137.12, 144.45, 172.20; ESIMS  $m/z$  214 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{NO}$ : C, 78.84; H, 7.09; N, 6.57. Found: C, 78.79; H, 7.35; N, 6.41.

**Compound 3b-Z:** 91%; white solid, mp 160–162 °C; IR (KBr) 3190, 1682  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.94 (s, 3H), 3.72 (d,  $J$  = 8.1 Hz, 2H), 5.33 (t,  $J$  = 8.1 Hz, 1H), 7.16–7.31 (m, 7H), 7.33–7.45 (m, 3H), 9.79 (br s, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.12, 33.91, 113.25, 126.34, 128.32, 128.35, 128.55, 128.61, 129.22, 129.42, 131.92, 138.18, 139.46, 144.55, 172.76; ESIMS  $m/z$  276 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{17}\text{NO}$ : C, 82.88; H, 6.22; N, 5.09.

Found: C, 82.57; H, 6.03; N, 4.97.

**Compound 3c-Z:** 96%; white solid, mp 125–127 °C; IR (KBr) 3183, 2957, 1690, 1361  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.91 (t,  $J$  = 7.2 Hz, 3H), 1.31–1.50 (m, 4H), 1.95 (s, 3H), 2.33 (dt,  $J$  = 7.8 and 7.2 Hz, 2H), 5.14 (t,  $J$  = 7.8 Hz, 1H), 7.26–7.31 (m, 2H), 7.36–7.48 (m, 3H), 9.17 (br s, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.06, 13.84, 22.37, 27.47, 31.50, 115.35, 128.24, 128.31, 128.68, 129.44, 132.16, 137.69, 144.30, 172.29; ESIMS  $m/z$  242 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}$ : C, 79.63; H, 7.94; N, 5.80. Found: C, 79.91; H, 8.08; N, 5.83.

**Compound 3d-Z:** 93%; white solid, mp 207–209 °C; IR (KBr) 3175, 3028, 1680  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.95 (s, 3H), 5.24 (d,  $J$  = 9.9 Hz, 1H), 5.62 (d,  $J$  = 9.9 Hz, 1H), 7.16–7.33 (m, 12H), 7.39–7.48 (m, 3H), 9.22 (br s, NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.15, 49.13, 115.95, 126.69, 128.25, 128.42, 128.46, 128.68, 129.38, 129.42, 131.86, 137.82, 143.15, 144.72, 172.39; ESIMS  $m/z$  352 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{25}\text{H}_{21}\text{NO}$ : C, 85.44; H, 6.02; N, 3.99. Found: C, 85.78; H, 6.32; N, 3.85.

**Typical Procedure for the Synthesis of 5a-Z.** A stirred solution of compound **3a** (85 mg, 0.4 mmol), benzyl bromide (103 mg, 0.6 mmol), and  $\text{K}_2\text{CO}_3$  (83 mg, 0.6 mmol) in  $\text{CH}_3\text{CN}$  (1.0 mL) was heated to reflux for 15 h. After the aqueous extractive workup and column chromatographic purification process (hexanes/ $\text{EtOAc}/\text{CH}_2\text{Cl}_2$ , 6:1:1), compound **5a-Z** was obtained as colorless oil, 109 mg (90%). Other compounds **5c-Z** and **5d-Z** were synthesized similarly, and the spectroscopic data including **4a** are as follows.

**Compound 5a-Z:** 90%; colorless oil; IR (film) 2964, 1691, 1439  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.78 (t,  $J$  = 7.5 Hz, 3H), 1.96 (s, 3H), 2.15–2.25 (m, 2H), 4.96 (t,  $J$  = 8.1 Hz, 1H), 5.13 (s, 2H), 7.13–7.17 (m, 2H), 7.20–7.35 (m, 5H), 7.36–7.48 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.53, 14.47, 20.40, 44.74, 118.18, 125.82, 126.81, 126.88, 128.22, 128.24, 128.59, 129.72, 132.41, 137.78, 138.31, 145.62, 171.43; ESIMS  $m/z$  304 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{21}\text{NO}$ : C, 83.13; H, 6.98; N, 4.62. Found: C, 83.23; H, 7.12; N, 4.46.

**Compound 5c-Z:** 89%; colorless oil; IR (film) 2957, 2925, 1694, 1441  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  0.71 (t,  $J$  = 7.2 Hz, 3H), 1.04–1.14 (m, 4H), 1.96 (s, 3H), 2.17 (dt,  $J$  = 7.8 and 7.2 Hz, 2H), 4.98 (t,  $J$  = 7.8 Hz, 1H), 5.14 (s, 2H), 7.12–7.17 (m, 2H), 7.19–7.37 (m, 5H), 7.38–7.47 (m, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.47, 13.61, 22.16, 26.71, 32.14, 44.71, 116.89, 125.76, 126.62, 126.82, 128.16, 128.18, 128.53, 129.65, 132.39, 138.03, 138.26, 145.56, 171.39; ESIMS  $m/z$  332 ( $\text{M}^+\text{H}$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{25}\text{NO}$ : C, 83.34; H, 7.60; N, 4.23. Found: C, 83.39; H, 7.85; N, 4.32.

**Compound 5d-Z:** 92%; yellow solid, mp 96–98 °C; IR (KBr) 3027, 1695, 1444  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  1.99 (s, 3H), 5.03 (s, 2H), 5.05 (d,  $J$  = 10.8 Hz, 1H), 5.44 (d,  $J$  = 10.8 Hz, 1H), 6.75–6.79 (m, 4H), 7.08–7.24 (m, 9H), 7.26–7.46 (m, 7H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  9.64, 44.64, 47.60, 117.12, 125.58, 126.50, 127.23, 127.68, 127.76, 128.37, 128.39, 128.59, 129.02, 129.65, 132.06,

138.18, 138.41, 143.85, 145.78, 171.50; ESIMS  $m/z$  442 ( $M^+ + H$ ). Anal. Calcd for  $C_{32}H_{27}NO$ : C, 87.04; H, 6.16; N, 3.17. Found: C, 86.89; H, 6.47; N, 3.04.

**Compound 4a:** 70%; white solid, mp 144–146 °C; IR (KBr) 3324, 2959, 1675, 1436  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  0.25 (t,  $J = 7.2$  Hz, 3H), 0.37–0.49 (m, 1H), 0.55–0.66 (m, 1H), 1.53–1.70 (m, 2H), 1.90 (s, 3H), 3.55 (br s, OH), 4.42 (d,  $J = 15.0$  Hz, 1H), 4.76 (d,  $J = 15.0$  Hz, 1H), 7.20–7.46 (m, 8H), 7.57–7.62 (m, 2H);  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  9.91, 13.10, 16.03, 36.51, 42.05, 93.46, 127.33, 128.39, 128.41, 128.55, 128.73, 128.75, 129.71, 132.29, 138.35, 151.52, 171.36; ESIMS  $m/z$  322 ( $M^+ + H$ ). Anal. Calcd for  $C_{21}H_{23}NO_2$ : C, 78.47; H, 7.21; N, 4.36. Found: C, 78.75; H, 7.39; N, 4.18.

**Typical Procedure for the Synthesis of 5a-E.** A stirred solution of compound 4a (96 mg, 0.3 mmol) and *p*-TsOH (16 mg, 30 mol %) in 1,2-dichloroethane (1.0 mL) was heated to 60 °C for 1 h. After the aqueous extractive workup and column chromatographic purification process ( $CH_2Cl_2$ ), compound 5a-E was obtained as colorless oil, 34 mg (37%), along with 5a-Z (46 mg, 51%). The spectroscopic data of 5a-E are as follows.

**Compound 5a-E:** 37%; colorless oil; IR (film) 2964, 1688, 1411  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 300 MHz)  $\delta$  0.71 (t,  $J = 7.5$  Hz, 3H), 1.63–1.73 (m, 2H), 1.85 (s, 3H), 4.90 (s, 2H), 5.27 (t,  $J = 8.4$  Hz, 1H), 7.21–7.27 (m, 5H), 7.29–7.35 (m, 2H), 7.36–7.44 (m, 3H);  $^{13}C$  NMR ( $CDCl_3$ , 75 MHz)  $\delta$  9.14, 14.66, 20.37, 42.74, 118.12, 126.95, 127.05, 128.10, 128.38, 128.53, 128.61, 131.45, 134.67, 137.05, 137.79, 142.70, 169.40; ESIMS  $m/z$  304 ( $M^+ + H$ ). Anal. Calcd for  $C_{21}H_{21}NO$ : C, 83.13; H, 6.98; N, 4.62. Found: C, 83.01; H, 7.17; N, 4.45.

**Acknowledgments.** This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government (2011-0002570). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

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