

Synthesis of β,γ -Disubstituted α -Methylene- γ -butyrolactams Starting from the Baylis-Hillman Adducts

Ka Young Lee, Young Ju Lee,[†] 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

[†]Korea Basic Science Institute, Gwangju Branch, Gwangju 500-757, Korea

Received September 2, 2006

Key Words : α -Methylene- γ -butyrolactams, Baylis-Hillman adducts, Fe/AcOH

α -Methylene- γ -butyrolactam derivatives are biologically important compounds.¹⁻³ They exhibit less cytotoxic activity than the corresponding α -methylene- γ -butyrolactone compounds in some cases.^{1,2} However, the synthesis of these compounds was studied less extensively. In addition, many of the synthetic procedures showed the formation of undesired endocyclic unsaturated lactam during the synthesis of α -methylene compounds.¹ Recently, Yus and co-workers reported the indium-promoted synthesis of α -methylene- γ -butyrolactams from the reaction of 2-(bromomethyl)acrylic acid and aldimine.^{2a} In their paper they obtained γ -substituted- α -methylene- γ -butyrolactam derivatives in 18-49% yields as their *N*-substituted forms.^{2a}

We and other groups reported a number of papers on the synthesis of a variety of heterocyclic compounds starting from the Baylis-Hillman adducts.⁵ Basavaiah and co-workers published the synthesis of α -arylidene- γ -butyrolactam derivatives recently.^{3a} However, they did not examine the synthesis of α -methylene- γ -butyrolactam derivatives.^{3a} We presumed that we could synthesize α -methylene- γ -butyrolactams from the Baylis-Hillman adducts by following the Scheme 1.

Thus, we prepared starting material **3a** according to the method involving the DABCO salt concept, which was developed by us (Scheme 1).⁶ The reaction of the Baylis-Hillman adduct **1a** and HBr gave the cinnamyl bromide **2a** in good yield.⁷ The reaction of **2a** and DABCO in aqueous

THF gave the corresponding DABCO salt, which reacted with nitroethane to afford **3a**. The compound **3a** was obtained as a diastereomeric *syn/anti* mixture, which could be separated by column chromatography.⁶ However, it was impossible to assign their stereochemistry at the earliest stage. With the fast moving component (later it was found as **3a-anti**, *vide infra*) we obtained **4a-anti** in 78% yield under the reductive cyclization conditions of Fe/AcOH.^{3a,8} Similarly, we obtained **4a-syn** in 77% yield under the same conditions from the slow moving **3a-syn** component.

The structures of **4a-syn** and **4a-anti** could be assigned by NOE experiments. As shown in Figure 1, when we irradi-

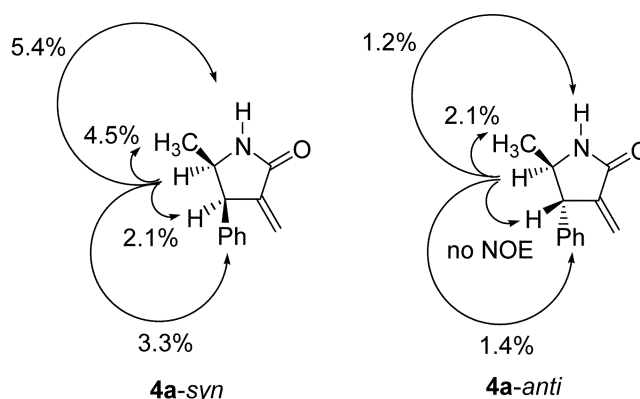
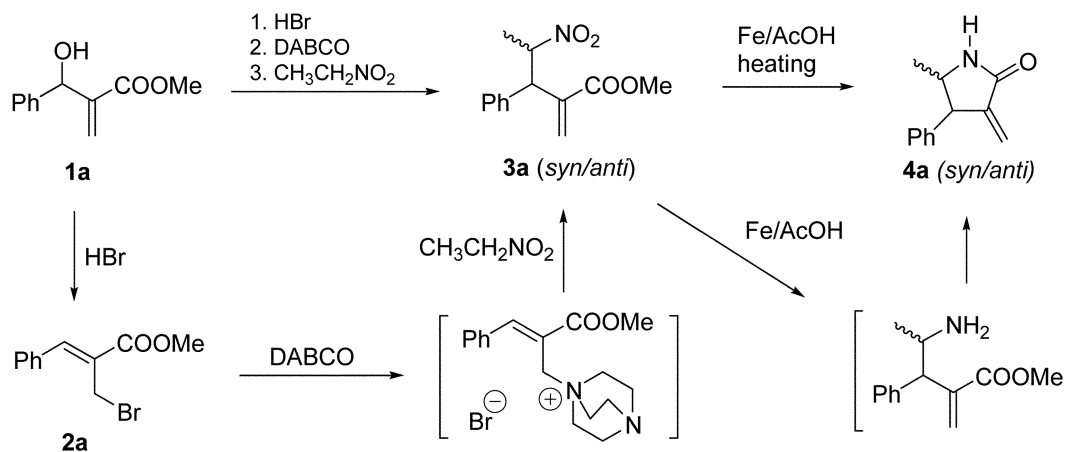


Figure 1



Scheme 1

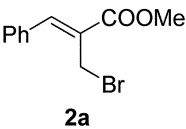
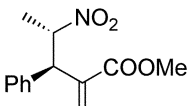
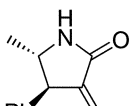
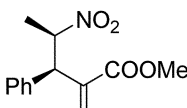
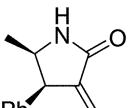
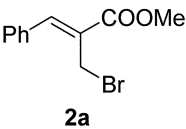
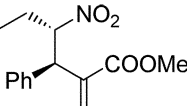
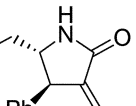
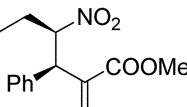
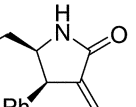
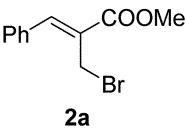
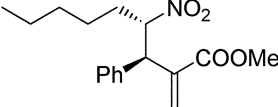
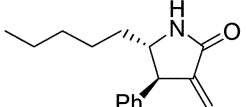
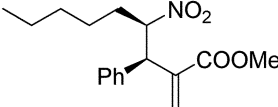
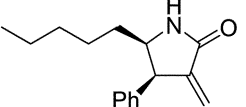
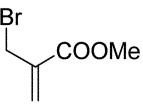
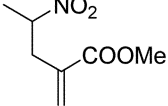
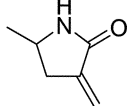
ated the proton at γ -position we observed 2.1% NOE for the β -proton of **4a-syn**, whereas no increment for **4a-anti**. From the results we assigned the fast moving component of **3a** as *anti* form and the slow moving component as *syn* form (see also entries 1 and 2 in Table 1).

With these successful results we examined the generality of the reactions with other entries as summarized in Table 1. We obtained similar results when we changed nitroethane into nitropropane (entries 3 and 4) or nitrohexane (entries 5 and 6). However, the separation of **3c-anti** and **3c-syn** was

impossible and we used the mixture for the synthesis of **4c**. Fortunately, we could isolate **4c-syn** in pure state in 62% yield. The corresponding **4c-anti** must be formed in the reaction mixture, but we did not obtain **4c-anti** in sufficient amount in analytically pure state. As shown in entry 7, use of **3d** afforded γ -mono-substituted lactam derivative **4d** in 81% yield.

In summary, we disclosed the efficient synthetic method for β,γ -disubstituted- α -methylene- γ -butyrolactams in moderate yields starting from the Baylis-Hillman adducts.

Table 1. Synthesis of α -methylene- γ -butyrolactams

Entry	Starting materials	Intermediates 3'	Products 4'
1	 2a	 3a-anti (33)	 4a-anti (78)
2		 3a-syn (49)	 4a-syn (77)
3	 2a	 3b-anti (15)	 4b-anti (67)
4		 3b-syn (65)	 4b-syn (76)
5	 2a	 3c-anti (ca. 14) ^c	 4c-anti (-) ^d
6		 3c-syn (ca. 55) ^c	 4c-syn (62) ^d
7	 2b	 3d (79) ^e	 4d (81)

^aConditions: (i) **2a** (1.0 mmol), aq THF, DABCO (2.0 equiv), rt, 20 min, (ii) nitroalkane (1.5 equiv), rt, 2 days. ^bConditions: **3** (1.0 equiv), Fe (10 equiv), AcOH, 90–100 °C, 12 h. ^cThe two compounds **3c-anti** and **3c-syn** were isolated (69%) as a mixture and the ratio was 1 : 4 (*anti*/*syn*) based on ¹H NMR. We used the mixture for the next reaction. ^dWe isolated **4c-syn** only in 62% yield in pure state. ^eConditions: **2b** (1.0 equiv), DMF, nitroethane (1.5 equiv), K₂CO₃ (2.0 equiv), rt, 2 h.

Experimental Section

Typical procedure for the synthesis of 3a and 4a: A solution of **2a** (508 mg, 2.0 mmol) and DABCO (448 mg, 4.0 mmol) in aq THF (5 mL) was stirred 20 min at room temperature. To the reaction mixture nitroethane (225 mg, 3.0 mmol) was added and the reaction mixture was stirred at room temperature for 2 days. After the usual aqueous extractive workup with ether and flash column chromatographic purification process (hexanes/ether, 8:1) we obtained **3a-anti** (165 mg, 33%, $R_f = 0.27$) and **3a-syn** (245 mg, 49%, $R_f = 0.22$). The next reductive cyclization of **3a-anti** to **4a-anti** is typical. A mixture of **3a-anti** (125 mg, 0.5 mmol) and Fe (280 mg, 5.0 mmol) in acetic acid (2 mL) was heated to 90–100 °C for 12 h. After the usual aqueous extractive workup with ether and flash column chromatographic purification process with ether we obtained **4a-anti** (73 mg, 78%, $R_f = 0.30$). Spectroscopic data of synthesized compounds **3a-d** and **4a-d** are as follows.

Compound 3a-anti: 33%; colorless oil; IR (film) 1722, 1551, 1265, 1153 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 1.40 (d, $J = 6.5$ Hz, 3H), 3.67 (s, 3H), 4.46 (d, $J = 11.5$ Hz, 1H), 5.21–5.27 (m, 1H), 5.91 (s, 1H), 6.34 (s, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 19.01, 51.03, 52.04, 85.01, 124.72, 127.83, 128.63, 128.87, 136.57, 139.37, 165.84.

Compound 3a-syn: 49%; colorless oil; IR (film) 1718, 1551, 1248, 1150 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 1.60 (d, $J = 6.5$ Hz, 3H), 3.71 (s, 3H), 4.39 (d, $J = 11.0$ Hz, 1H), 5.45–5.51 (m, 1H), 5.80 (s, 1H), 6.35 (s, 1H), 7.21–7.29 (m, 5H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 18.84, 52.18, 52.22, 85.53, 127.48, 127.71, 127.90, 128.66, 137.36, 139.09, 166.14.

Compound 3b-anti: 15%; colorless oil; IR (film) 1722, 1551, 1250, 1153 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 0.89 (t, $J = 7.5$ Hz, 3H), 1.55–1.62 (m, 1H), 1.74–1.82 (m, 1H), 3.67 (s, 3H), 4.48 (d, $J = 12.0$ Hz, 1H), 5.04–5.10 (m, 1H), 5.94 (s, 1H), 6.34 (s, 1H), 7.25–7.34 (m, 5H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 10.12, 26.08, 50.17, 52.08, 91.62, 124.93, 127.83, 128.65, 128.91, 136.85, 139.35, 165.90.

Compound 3b-syn: 65%; colorless oil; IR (film) 1720, 1552, 1252, 1151 cm^{-1} ; ^1H NMR (CDCl_3 , 500 MHz) δ 0.98 (t, $J = 7.5$ Hz, 3H), 1.89–1.95 (m, 2H), 3.69 (s, 3H), 4.40 (d, $J = 11.5$ Hz, 1H), 5.30–5.33 (m, 1H), 5.80 (s, 1H), 6.32 (s, 1H), 7.19–7.30 (m, 5H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 10.12, 25.95, 51.24, 52.06, 92.11, 127.27, 127.59, 127.89, 128.54, 137.35, 139.11, 166.05.

Compound 3c-anti: 14%; colorless oil; IR (film) 2951, 1718, 1551, 1252, 1150 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.81 (t, $J = 6.6$ Hz, 3H), 1.15–1.34 (m, 6H), 1.77–1.97 (m, 2H), 3.68 (s, 3H), 4.45 (d, $J = 11.7$ Hz, 1H), 5.10–5.19 (m, 1H), 5.93 (s, 1H), 6.32 (s, 1H), 7.18–7.35 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.79, 22.21, 25.31, 30.79, 32.60, 50.54, 52.11, 90.25, 125.07, 127.84, 128.67, 128.94, 136.93, 139.37, 165.92.

Compound 3c-syn: 55%; colorless oil; IR (film) 2953, 1722, 1551, 1252, 1153 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.23–1.34 (m, 6H), 1.77–1.97 (m, 2H), 3.73 (s, 3H), 4.37 (d, $J = 11.1$ Hz, 1H), 5.37 (td, $J =$

11.1 and 3.0 Hz, 1H), 5.80 (s, 1H), 6.35 (s, 1H), 7.18–7.35 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.86, 22.30, 25.45, 30.92, 32.66, 51.68, 52.26, 90.89, 127.20, 127.79, 128.06, 128.71, 137.35, 139.42, 166.20.

Compound 3d: 79%; colorless oil; IR (film) 2951, 1722, 1551, 1308, 1163 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.56 (d, $J = 6.9$ Hz, 3H), 2.76 (dd, $J = 14.1$ and 5.1 Hz, 1H), 2.90 (dd, $J = 14.1$ and 9.0 Hz, 1H), 3.79 (s, 3H), 4.80–4.92 (m, 1H), 5.67 (s, 1H), 6.27 (s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 19.24, 37.93, 52.18, 82.36, 129.38, 134.63, 166.42.

Compound 4a-anti: 78%; white solid, mp 112–113 °C; IR (film) 3219, 2964, 1701, 1659, 1427 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.33 (d, $J = 6.3$ Hz, 3H), 3.55–3.60 (m, 1H), 3.67–3.76 (m, 1H), 5.11 (d, $J = 3.0$ Hz, 1H), 6.09 (d, $J = 3.0$ Hz, 1H), 7.20–7.39 (m, 5H), 7.62 (br s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 21.00, 54.32, 56.43, 117.41, 127.29, 128.39, 128.80, 140.60, 145.12, 170.00; LCMS m/z 187 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.89; H, 7.21; N, 7.35.

Compound 4a-syn: 77%; white solid, mp 129–130 °C; IR (film) 3188, 2926, 1693, 1653, 1435 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.82 (d, $J = 6.3$ Hz, 3H), 4.01–4.11 (m, 1H), 4.31–4.36 (m, 1H), 5.32 (d, $J = 2.7$ Hz, 1H), 6.23 (d, $J = 2.7$ Hz, 1H), 7.17–7.37 (m, 5H), 7.56 (br s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 19.50, 49.12, 51.72, 118.56, 127.23, 128.40, 129.46, 138.51, 143.21, 170.61; LCMS m/z 187 (M^+). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.77; H, 7.13; N, 7.42.

Compound 4b-anti: 67%; white solid, mp 122–123 °C; IR (film) 3198, 2922, 1697, 1659 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.95 (t, $J = 7.5$ Hz, 3H), 1.54–1.79 (m, 2H), 3.52–3.59 (m, 1H), 3.65–3.70 (m, 1H), 5.13 (d, $J = 3.0$ Hz, 1H), 6.12 (d, $J = 3.0$ Hz, 1H), 6.57 (br s, 1H), 7.19–7.38 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 10.04, 28.79, 51.82, 61.85, 118.07, 127.24, 128.23, 128.86, 141.67, 144.72, 169.57; LCMS m/z 201 (M^+).

Compound 4b-syn: 76%; white solid, mp 120–121 °C; IR (film) 3182, 2972, 1695, 1659, 1456 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.82 (t, $J = 7.5$ Hz, 3H), 0.96–1.16 (m, 2H), 3.74–3.82 (m, 1H), 4.31–4.36 (m, 1H), 5.30 (d, $J = 2.7$ Hz, 1H), 6.20 (d, $J = 2.7$ Hz, 1H), 7.19–7.36 (m, 5H), 8.32 (br s, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 10.67, 26.64, 49.01, 58.06, 117.87, 127.12, 128.28, 129.46, 138.62, 143.65, 171.00; LCMS m/z 201 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{15}\text{NO}$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.73; H, 7.70; N, 6.84.

Compound 4c-syn: 62%; white solid, mp 118–119 °C; IR (film) 3203, 2930, 1701, 1655, 1456 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 0.79 (t, $J = 7.2$ Hz, 3H), 0.85–1.27 (m, 8H), 3.79–3.87 (m, 1H), 4.30–4.35 (m, 1H), 5.30 (d, $J = 2.7$ Hz, 1H), 6.20 (d, $J = 2.7$ Hz, 1H), 7.17–7.36 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 13.85, 22.36, 25.91, 31.48, 33.43, 49.21, 56.32, 118.17, 127.23, 128.37, 129.51, 138.59, 143.40, 170.59; LCMS m/z 243 (M^+).

Compound 4d: 81%; white solid, mp 74–75 °C; IR (film) 3240, 2966, 1697, 1659, 1440 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.26 (d, $J = 6.3$ Hz, 3H), 2.32–2.42 (m, 1H), 2.95–3.05 (m, 1H), 3.75–3.86 (m, 1H), 5.33 (t, $J = 2.4$ Hz, 1H),

5.96 (t, $J = 2.4$ Hz, 1H), 7.74 (br s, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 22.91, 34.78, 46.99, 115.61, 139.97, 170.75.

Acknowledgments. This study was financially supported by Chonnam National University (2005). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and Notes

- For the biological activities of α -methylene- γ -butyrolactam derivatives, see: (a) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem.* **2005**, *48*, 3516. (b) Qiao, L.; Wang, S.; George, C.; Lewin, N. E.; Blumberg, P. M.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 6629. (c) Murata, K.; Kaneko, S.; Kitazume, T. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2685. (d) Belaud, C.; Roussakis, C.; Letourneux, Y.; El Alami, N.; Villieras, J. *Synth. Commun.* **1985**, *15*, 1233.
- For the synthesis of α -methylene- γ -butyrolactam derivatives, see: (a) Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376, and further references cited therein. (b) Nyzam, V.; Belaud, C.; Zammattio, F.; Villieras, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1835. (c) Lee, E.; Kang, T. S. *Bull. Korean Chem. Soc.* **1993**, *14*, 431. (d) Dembele, Y. A.; Belaud, C.; Villieras, J. *Tetrahedron: Asymmetry* **1992**, *3*, 511. (e) Blaszczyk, E.; Krawczyk, H.; Janecki, T. *Synlett* **2004**, 2685. (f) Chataigner, I.; Zammattio, F.; Lebreton, J.; Villieras, J. *Synlett* **1998**, 275. (g) El Alami, N.; Belaud, C.; Villieras, J. *Tetrahedron Lett.* **1987**, *28*, 59. (h) Patra, R.; Maiti, S. B.; Chatterjee, A. *Tetrahedron Lett.* **1991**, *32*, 1363. (i) El Alami, N.; Belaud, C.; Villieras, J. *Synth. Commun.* **1988**, *18*, 2073. (j) Tanaka, K.; Yoda, H.; Kaji, A. *Synthesis* **1985**, 84.
- For the synthesis of α -arylidene- γ -butyrolactam derivatives, see: (a) Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621. (b) Beji, F.; Lebreton, J.; Villieras, J.; Amri, H. *Tetrahedron* **2001**, *57*, 9959.
- For the isomerization of *exo*-methylene moiety during the preparation of α -methylene- γ -butyrolactams, see: (a) Tamchompoo, B.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1987**, *28*, 6675. (b) Henin, F.; Muzart, J.; Pete, J.-P. *Tetrahedron Lett.* **1986**, *27*, 6339. (c) Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058.
- For our recent publications on Baylis-Hillman chemistry, see: (a) Lee, M. J.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1355. (b) Lee, M. J.; Park, D. Y.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 1833. (c) Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 8799. (d) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859. (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387. (f) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493. (g) Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 3128. (h) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3463. (i) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2006**, *62*, 4052. (j) Gowrisankar, S.; Lee, C. G.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 6949. (k) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627. (l) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481, and further references cited therein.
- For the synthesis of starting materials, see: Kim, J. M.; Im, Y. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 657. Assignment of the structures of **3a-syn** and **3a-anti** was impossible due to similar coupling constant between the two protons at the 3- and 4-position of **3a**. Thus, the structures of **3a-syn** and **3a-anti** were assigned based on the assignment of the product **4a-syn** and **4a-anti** (see text).
- For the synthesis of Baylis-Hillman bromides, see: (a) Lee, M. J.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 140. (b) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 319. (c) Lee, K. Y.; Kim, S. C.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 977. (d) Lee, K. Y.; Seo, J.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3913. (e) Basavaiah, D.; Hyma, R. S.; Padmaja, K.; Krishnamacharyulu, M. *Tetrahedron* **1999**, *55*, 6971.
- (a) Lee, M. J.; Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1281. (b) Lee, H. S.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, in print.