http://dx.doi.org/10.5012/bkcs.2012.33.5.1781

An Efficient Synthesis of Various γ-Substituted Butenolides from Morita-Baylis-Hillman Adducts

Jin Woo Lim, Ko Hoon Kim, Se Hee Kim, 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 February 1, 2012, Accepted February 15, 2012

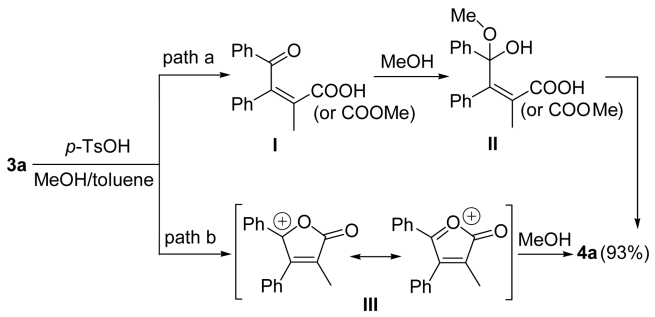
Key Words : γ-Substituted butenolides, Morita-Baylis-Hillman adducts, Indium, Zinc, Barbier reaction

Various butenolide moiety-containing natural substances are known to possess important biological activities.[1-3] Thus there have been reported numerous synthetic approaches for the butenolide scaffold.[2,3] Among the butenolides, γ-alkoxybutenolides have received a special attention due to their abundance in natural substances.[3] The synthesis of γ-alkoxybutenolides could be carried out from the corresponding γ-hydroxybutenolides most frequently.[4] The substitution of a hydroxyl group with an alkoxy moiety could be performed either under acidic[4a-c] or basic conditions.[4e]

Recently, we reported a facile synthetic protocol of γ-hydroxy-γ-substituted butenolides such as **3a**[5] starting from the Morita-Baylis-Hillman (MBH) bromide[6] *via* an indium-mediated Barbier type reaction with benzaldehyde and a subsequent base-mediated lactonization and concomitant aerobic oxidation process (vide infra, Scheme 1). In order to shed more light to our efficient synthetic protocol of γ-hydroxybutenolides,[5] we decided to examine the synthesis of various γ-substituted butenolides including γ-alkoxy or γ-alkylthio moieties, as shown in Scheme 1.

γ-Hydroxybutenolide **3a** was prepared according to our previous method from MBH bromide,[5] and the reaction of **3a** with methanol was examined in the presence of *p*-TsOH in toluene.[4] As expected, compound **4a** was obtained in good yield (93%). The reaction mechanism for the formation of γ-methoxybutenolide **4a** could be proposed as shown in Scheme 2. The first feasible route could be a consecutive acid-catalyzed ring-opening of **3a** to a γ-ketoacid (or its methyl ester) **I**, formation of a hemiketal intermediate **II**, and the final lactonization process to **4a** (path a). The second possibility could be an acid-catalyzed S_N1-type reaction involving a resonance-stabilized carbocation/*O*-acyloxonium ion intermediate **III** (path b).[7] Both pathways might contribute to some extents for the formation of **4a**.

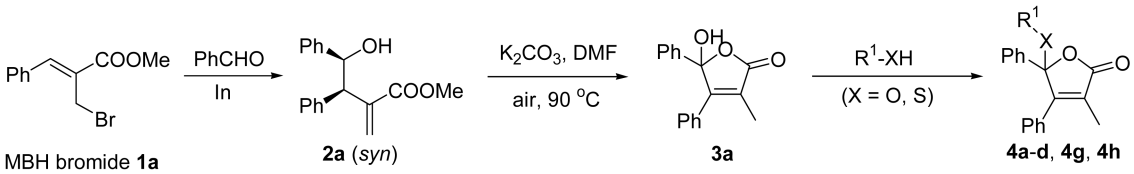
In order to check the possibility for the synthesis of **4a**



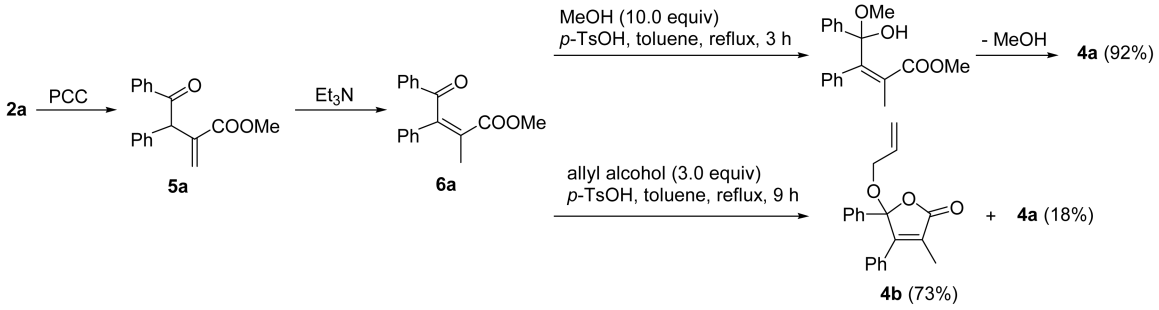
Scheme 2

from different starting materials, we prepared **5a** and **6a** from **2a** by PCC oxidation and Et_3N-mediated double bond isomerization,[5,8] as shown in Scheme 3. The reaction of **6a** and methanol in the presence of *p*-TsOH afforded **4a** in good yield (92%). The results stated that the first mechanism in Scheme 2 is a probable pathway. However, the synthesis of γ-substituted butenolides from **6a** has some drawbacks compared to the synthesis from **3a**. As an example, when we carried out the reaction of **6a** and allyl alcohol, both compounds **4a** and **4b** were formed together. Compound **4a** was formed to some extent (18%) by the methanol generated during the formation of **4b**. The reaction of **5a** and methanol did not produce **4a** in any trace amount. Thus, we concluded that the synthesis of γ-substituted butenolides could be performed more efficiently from γ-hydroxybutenolide **3a** than from **5a** or **6a**.

According to the above results, we decided to use γ-hydroxybutenolide **3a** as a starting material for the preparation of various γ-substituted butenolides. The reactions of **3a** with some representative alcohols and thiols were examined, and the results are summarized in Table 1. We carried out the reactions in refluxing toluene in short time (2-9 h). The reaction at lower temperature required somewhat

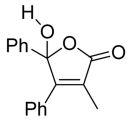
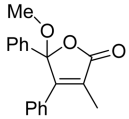
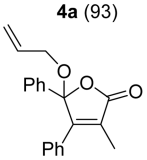
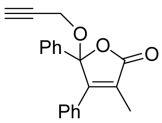
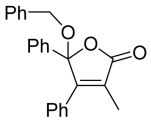
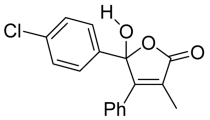
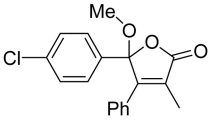
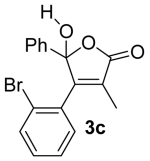
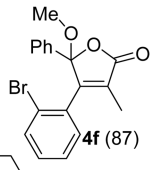
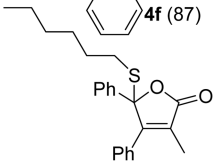
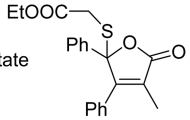


Scheme 1



Scheme 3

Table 1. Synthesis of various γ-substituted butenolides

Entry	Substrate	Conditions[a]	Product (%)
1	 **3a**	MeOH (10.0 equiv) 2 h	 **4a** (93)
2	**3a**	allyl alcohol (3.0 equiv) 2 h	 **4b** (90)
3	**3a**	propargyl alcohol (3.0 equiv) 9 h	 **4c** (86)
4	**3a**	benzyl alcohol (3.0 equiv) 9 h	 **4d** (87)
5	 **3b**	MeOH (10.0 equiv) 5 h	 **4e** (91)
6	 **3c**	MeOH (10.0 equiv) 3 h	 **4f** (87)
7	**3a**	hexanethiol (1.0 equiv) 2 h	 **4g** (82)
8	**3a**	ethyl mercaptoacetate (1.0 equiv) 2 h	 **4h** (70)

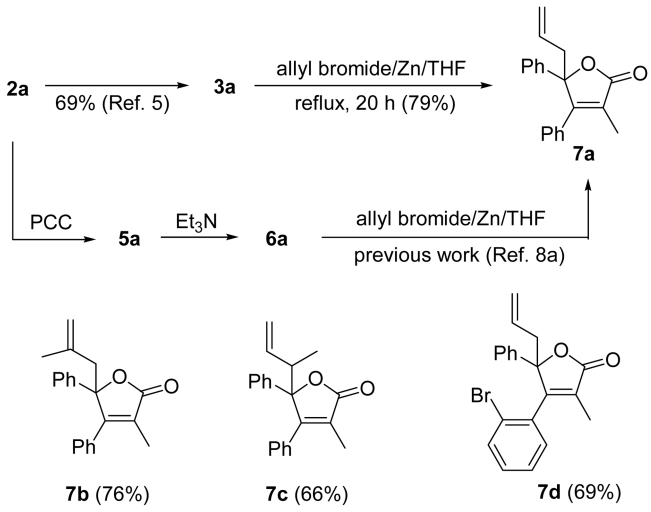
[a]Reaction conditions: *p*-TsOH (10 mol %), toluene, reflux.

longer reaction time for the completion.

As shown in Table 1, the reactions of **3a** with allyl alcohol (entry 2), propargyl alcohol (entry 3), and benzyl alcohol (entry 4) afforded **4b-d** in good yields (86-90%). Besides **3a** the reactions of other γ-hydroxybutenolides **3b** and **3c** with methanol also gave the corresponding γ-methoxy derivatives **4e** and **4f** in good yields (87-91%). Similarly, thiol derivatives such as *n*-hexanethiol and ethyl mercaptoacetate afforded the corresponding γ-thioalkyl derivatives **4g** and **4h** in 82 and 70% yield, respectively. For the last two entries, we used 1.0 equiv of the thiol in order to reduce the appalling odor during the experiments.

γ-Alkenyl-substituted butenolides have also received much attention.[2,8a] Thus, as an extension, we examined the synthesis of γ-allylbutenolide **7a** by the reaction of **3a** and allyl bromide in the presence of zinc dust, as shown in Scheme 4. Actually, compound **7a** has been synthesized from **2a** in a three-step procedure (*via* **5a** and **6a**) very recently in our group.[8a] We thought compound **7a** could also be synthesized from **2a** in a two-step procedure *via* **3a**. As expected, compound **7a** was synthesized from **3a** in a moderate yield (79%). Similarly, various γ-alkenylbutenolides **7b-d** were synthesized by the reactions of **3a** with methallyl bromide or crotyl bromide and **3c** with allyl bromide under the zinc-mediated Barbier type reaction conditions.

In summary, we disclosed an efficient synthesis of various



Scheme 4

γ-substituted butenolides from the corresponding γ-hydroxybutenolides, which were prepared from Morita-Baylis-Hillman adducts *via* a consecutive bromination, indium-mediated Barbier type reaction, and K_2CO_3-mediated concomitant lactonization/aerobic oxidation.

Experimental Section

Preparation of Starting Materials. Compounds **3a-c** were prepared according to the reported procedure,[5] and the spectroscopic data of unknown compound **3c** are as follows.

Compound 3c: 43%; pale yellow solid, mp 146-148 °C; IR (KBr) 3368, 1737, 1335, 1238 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.71 (s, 3H), 7.14-7.72 (m, 9H), 8.42 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 10.01, 106.23, 122.43, 125.82, 126.43, 127.30, 128.04, 128.88, 129.76, 130.94, 131.28, 132.68, 137.06, 157.94, 171.60; ESIMS *m/z* 367 [M^++Na], 369 [M^++Na+2]. Anal. Calcd for $C_{17}H_{13}BrO_3$: C, 59.15; H, 3.80. Found: C, 59.36; H, 3.64.

Typical Procedure for the Synthesis of 4a. A stirred mixture of compound **3a** (80 mg, 0.3 mmol) and MeOH (96 mg, 3.0 mmol) in toluene (1.0 mL) was added *p*-TsOH (5.7 mg, 10 mol %), and the reaction mixture was heated to reflux for 2 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 12:1) compound **4a** was obtained as a white solid, 190 mg (93%). Other compounds **4b-h** were synthesized similarly and the spectroscopic data are as follows.

Compound 4a: 93%; white solid, mp 70-72 °C; IR (KBr) 1763, 1450, 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 3.42 (s, 3H), 7.25-7.41 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.28, 51.23, 108.99, 126.15, 126.69, 128.31, 128.44, 128.56, 129.08, 129.69, 130.56, 136.31, 156.23, 172.05; ESIMS *m/z* 303 [M^++Na]. Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.34; H, 5.93.

Compound 4b: 90%; white solid, mp 84-86 °C; IR (KBr) 1754, 1449, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.11 (s, 3H), 4.03-4.12 (m, 1H), 4.13-4.22 (m, 1H), 5.17-5.25 (m, 1H), 5.29-5.40 (m, 1H), 5.90-6.05 (m, 1H), 7.24-7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.21, 65.08, 108.65, 117.19, 126.13, 126.41, 128.30, 128.46, 128.52, 129.09, 129.65, 130.53, 133.34, 136.28, 156.75, 171.98; ESIMS *m/z* 329 [M^++Na]. Anal. Calcd for $C_{20}H_{18}O_3$: C, 78.41; H, 5.92. Found: C, 78.66; H, 5.79.

Compound 4c: 86%; pale yellow solid, mp 68-70 °C; IR (KBr) 3292, 2132, 1757, 1449, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09 (s, 3H), 2.47 (t, *J* = 2.4 Hz, 1H), 4.28 (d, *J* = 2.4 Hz, 2H), 7.23-7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.18, 52.73, 74.97, 78.57, 108.51, 126.24, 126.49, 128.43, 128.54, 128.61, 129.34, 129.75, 130.32, 135.38, 156.77, 171.68; ESIMS *m/z* 327 [M^++Na]. Anal. Calcd for $C_{20}H_{16}O_3$: C, 78.93; H, 5.30. Found: C, 78.89; H, 5.62.

Compound 4d: 87%; colorless oil; IR (film) 1764, 1449, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H), 4.56 (d, *J* = 11.1 Hz, 1H), 4.69 (d, *J* = 11.1 Hz, 1H), 7.20-7.49 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.35, 66.03, 108.71, 126.22, 126.56, 127.77, 127.87, 128.38, 128.42, 128.55, 128.58, 129.17, 129.74, 130.55, 136.35, 136.73, 156.70, 172.01; ESIMS *m/z* 379 [M^++Na]. Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found: C, 80.57; H, 5.98.

Compound 4e: 91%; pale yellow oil; IR (film) 1766, 1492, 1243 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 3.41 (s, 3H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 9.0 Hz, 2H), 7.31-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.30, 51.22, 108.42, 126.91, 127.64, 128.36, 128.56, 128.69, 129.89, 130.27, 135.03, 135.09, 155.80, 171.76; ESIMS *m/z* 337 [M^++Na], 339 [M^++Na+2]. Anal. Calcd for $C_{18}H_{15}ClO_3$: C, 68.68; H, 4.80. Found: C, 68.97; H, 4.94.

Compound 4f: 87%; pale yellow oil; IR (film) 1773, 1233 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80 (s, 3H), 3.42 (s, 3H), 7.16-7.54 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.02, 52.42, 108.57, 123.44, 126.49, 126.86, 128.33, 129.17, 129.89, 130.42, 131.46, 132.72, 132.74, 134.39, 157.47, 171.98; ESIMS *m/z* 381 [M^++Na], 383 [M^++Na+2]. Anal. Calcd for $C_{18}H_{15}BrO_3$: C, 60.18; H, 4.21. Found: C, 60.34; H, 4.31.

Compound 4g: 82%; pale yellow oil; IR (film) 2955, 2927, 1766, 1445, 1333, 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.15-1.39 (m, 6H), 1.51-1.64 (m, 2H), 1.90 (s, 3H), 2.40-2.52 (m, 1H), 2.55-2.65 (m, 1H), 7.09-7.15 (m, 2H), 7.20-7.41 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.78, 13.95, 22.40, 28.61, 28.65, 30.24, 31.23, 97.01, 125.42, 126.47, 128.31 (2C), 128.55, 128.74, 129.36, 131.02, 136.15, 161.59, 172.45; ESIMS *m/z* 389 [M^++Na]. Anal. Calcd for $C_{23}H_{26}O_2S$: C, 75.37; H, 7.15. Found: C, 75.26; H, 7.41.

Compound 4h: 70%; pale yellow oil; IR (film) 1768, 1734, 1276, 1134 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, *J* = 7.2 Hz, 3H), 1.92 (s, 3H), 3.31 (d, *J* = 15.0 Hz, 1H), 3.40 (d, *J* = 15.0 Hz, 1H), 4.01-4.25 (m, 2H), 7.11-7.17 (m, 2H), 7.23-7.45 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.89, 13.92, 32.70, 61.81, 96.22, 126.27, 126.44, 128.42, 128.46, 128.59, 129.09, 129.55, 130.54, 135.37, 160.63, 168.99, 171.78; ESIMS *m/z* 391 [M^++Na]. Anal. Calcd for $C_{21}H_{20}O_4S$: C, 68.46; H, 5.47. Found: C, 68.69; H, 5.56.

Typical Procedure for the Synthesis of 7a. To a stirred solution of **3a** (80 mg, 0.3 mmol) and allyl bromide (91 mg, 0.75 mmol) in THF (1.0 mL) was added Zn dust (98 mg, 1.5 mmol), and the reaction mixture was heated to reflux for 20 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 7:1) compound **7a** was obtained as a white solid, 87 mg (79%). Other compounds **7b-d** were synthesized similarly, and the spectroscopic data of prepared compounds were same with the reported.[8a]

Acknowledgments. This study was financially supported by Chonnam National University, 2011. Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

References and Notes

1. For selected leading references on butenolide-containing substances,

see: (a) Carter, N. B.; Nadany, A. E.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2324-2342. (b) Takahashi, S.; Maeda, K.; Hirota, S.; Nakata, T. *Org. Lett*. **1999**, *1*, 2025-2028. (c) Sorg, A.; Blank, F.; Bruckner, R. *Synlett* **2005**, 1286-1290. (d) Chia, Y.-C.; Chang, F.-R.; Wu, Y.-C. *Tetrahedron Lett*. **1999**, *40*, 7513-7514. (e) Koseki, K.; Ebata, T.; Kadokura, T.; Kawakami, H.; Ono, M.; Matsushita, H. *Tetrahedron* **1993**, *49*, 5961-5968. (f) Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc*. **2006**, *128*, 11332-11333. (g) Park, B. R.; Kim, K. H.; Lim, J. W.; Kim, J. N. *Tetrahedron Lett*. **2012**, *53*, 36-40.

2. For some examples of γ-alkyl- and γ-alkenylbutenolides, see: (a) Cui, H.-L.; Huang, J.-R.; Lei, J.; Wang, Z.-F.; Chen, S.; Wu, L.; Chen, Y.-C. *Org. Lett*. **2010**, *12*, 720-723. (b) Jiang, Y.-Q.; Shi, Y.-L.; Shi, M. *J. Am. Chem. Soc*. **2008**, *130*, 7202-7203. (c) Cho, C.-W.; Krische, M. J. *Angew. Chem. Int. Ed*. **2004**, *43*, 6689-6691. (d) van Oeveren, A.; Feringa, B. L. *J. Org. Chem*. **1996**, *61*, 2920-2921 and further references cited therein. (e) Ma, S.; Lu, L.; Lu, P. *J. Org. Chem*. **2005**, *70*, 1063-1065. (f) Arlt, A.; Koert, U. *Synthesis* **2010**, 917-922. (g) Wu, Y.; Yao, W.; Pan, L.; Zhang, Y.; Ma, C. *Org. Lett*. **2010**, *12*, 640-643. (h) Rosso, G. B.; Pilli, R. A. *Tetrahedron Lett*. **2006**, *47*, 185-188. (i) Virolleaud, M.-A.; Piva, O. *Synlett* **2004**, 2087-2090. (j) Zhang, J.; Blazecka, P. G.; Berven, H.; Belmont, D. *Tetrahedron Lett*. **2003**, *44*, 5579-5582. (k) For the synthesis of β-alkenylbutenolides, see: Ma, S.; Yu, Z. *J. Org. Chem*. **2003**, *68*, 6149-6152.
3. For some selected examples on the biologically important butenolides bearing an γ-alkoxy or γ-alkylthio moieties, see: (a) Kornsakulkarn, J.; Thongpanchang, C.; Chainoy, R.; Choowong, W.; Nithithanasilp, S.; Thongpanchang, T. *J. Nat. Prod*. **2010**, *73*, 759-762. (b) Mansoor, T. A.; Hong, J.; Lee, C.-O.; Sim, C. J.; Im, K. S.; Lee, D. S.; Jung, J. H. *J. Nat. Prod*. **2004**, *67*, 721-724. (c) Kim, M.-R.; Jung, H.-J.; Min, B.-S.; Oh, S.-R.; Kim, C.-S.; Ahn, K.-S.; Kang, W.-S.; Lee, H.-K. *Phytochemistry* **2002**, *59*, 861-865. (d) Fei, D.-Q.; Li, S.-G.; Liu, C.-M.; Wu, G.; Gao, K. *J. Nat. Prod*. **2007**, *70*, 241-245. (e) Schuffler, A.; Liermann, J. C.; Opatz, T.; Anke, T. *ChemBioChem*. **2011**, *12*, 148-154. (f) Schuffler, A.; Kautz, D.; Liermann, J. C.; Opatz, T.; Anke, T. *J. Antibiot.* **2009**, *62*, 119-121. (g) Lhullier, C.; Falkenberg, M.; Ioannou, E.; Quesada, A.; Papazafiri, P.; Horta, P. A.; Schenkel, E. P.; Vagias, C.; Roussis, V. *J. Nat. Prod*. **2010**, *73*, 27-32. (h) Wang, H.; Wang, Y.; Wang, W.; Fu, P.; Liu, P.; Zhu, W. *J. Nat. Prod*. **2011**, *74*, 2014-2018. (i) Black, C.; Grimm, E.; Wang, Z.; Leger, S. PCT Int. Appl. 1996, WO 96/36623 (*Chem. Abstr*. **1997**, 126, 89250).
4. For the conversion of γ-hydroxybutenolides into γ-alkoxy or γ-alkylthio derivatives, see: (a) Gassama, A.; Ernenwein, C.; Hoffmann, N. *ChemSusChem*. **2009**, *2*, 1130-1137. (b) Kurbangalieva, A. R.; Devyatova, N. F.; Bogdanov, A. V.; Berdnikov, E. A.; Mannafov, T. G.; Krivolapov, D. B.; Litvinov, I. A.; Chmutova, G. A. *Phosphorous, Sulfur, and Silicon* **2007**, *182*, 607-630. (c) Hauser, F. M.; Hewawasam, P.; Baghdanov, V. M. *J. Org. Chem*. **1988**, *53*, 223-224. (d) Feringa, B. L.; Lange, B. D. *Tetrahedron* **1988**, *44*, 7213-7222. (e) Shiraki, R.; Sumino, A.; Tadano, K.-I.; Ogawa, S. *J. Org. Chem*. **1996**, *61*, 2845-2852.
5. Kim, K. H.; Lee, H. S.; Kim, S. H.; Lee, K. Y.; Lee, J.-E.; Kim, J. N. *Bull. Korean Chem. Soc*. **2009**, *30*, 1012-1020.
6. For the general reviews on Morita-Baylis-Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891. (b) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447-5674. (c) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511-4574. (d) Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1-48. (e) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem*. **2002**, *6*, 627-645. (f) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2005**, *26*, 1481-1490. (g) Gowrisankar, S.; Lee, H. S.; Kim, S. H.; Lee, K. Y.; Kim, J. N. *Tetrahedron* **2009**, 65, 8769-8780.
7. For the *O*-acyloxonium ion intermediate, see: Barili, P. L.; Scartoni, V. *J. Heterocyclic Chem*. **1985**, *22*, 1199-1202.
8. For the synthesis of γ-keto ester derivatives, see: (a) Lim, J. W.; Kim, K. H.; Park, B. R.; Kim, J. N. *Tetrahedron Lett*. **2011**, *52*, 6545-6549. (b) Kim, J. M.; Lee, S.; Kim, S. H.; Lee, H. S.; Kim, J. N. *Bull. Korean Chem. Soc*. **2008**, *29*, 2215-2220.