An Efficient Synthesis of Various $\gamma$-Substituted Butenolides from Morita-Baylis-Hillman Adducts

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Various butenolide moiety-containing natural substances are known to possess important biological activities. $^{1,2}$ Thus there have been reported numerous synthetic approaches for the butenolide scaffold. $^{2,3}$ Among the butenolides, $\gamma$-alkoxybutenolides have received a special attention due to their abundance in natural substances. $^{3}$ The synthesis of $\gamma$-alkoxybutenolides could be carried out from the corresponding $\gamma$-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 $\gamma$-hydroxy-$\gamma$-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 $\gamma$-hydroxybutenolides, $^5$ we decided to examine the synthesis of various $\gamma$-substituted butenolides including $\gamma$-alkoxy or $\gamma$-alkylthio moieties, as shown in Scheme 1.

$\gamma$-Hydroxybutenolide 3a was prepared according to our previous method from MBH bromide, $^7$ 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 $\gamma$-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 $\gamma$-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 from different starting materials, we prepared 5a and 6a from 2a by PCC oxidation and Et$_3$N-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 $\gamma$-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 $\gamma$-substituted butenolides could be performed more efficiently from $\gamma$-hydroxybutenolide 3a than from 5a or 6a.

According to the above results, we decided to use $\gamma$-hydroxybutenolide 3a as a starting material for the preparation of various $\gamma$-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
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. Therefore, 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. 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 crotol bromide and 3c with allyl bromide under the zinc-mediated Barbier type reaction conditions.

In summary, we disclosed an efficient synthesis of various...
γ-substituted butenolides from the corresponding γ-hydroxybutenolides, which were prepared from Morita-Baylis-Hillman adducts via a consecutive bromination, iodination-mediated Barbier type reaction, and K₂CO₃-mediated concomitant lactonization/aerobic oxidation.

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

**Compound 3c**: 4%; pale yellow solid, mp 146-148 °C; IR (KBr) 3368, 1737, 1335, 1238 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.71 (s, 3H), 7.14-7.22 (m, 9H), 8.42 (br s, 1H); ¹³C NMR (CDCl₃, 75 MHz) δ 10.18, 52.73, 74.97, 78.57, 108.51, 126.24, 126.49, 128.43, 128.54, 128.61, 129.75, 130.32, 135.38, 156.77, 171.68; ESIMS m/z 367 [M+Na]⁺. Anal. Caled for C₁₃H₁₃BrO₃: C, 75.30; H, 7.15. Found: C, 75.26; H, 7.59.

Typical Procedure for the Synthesis of 4a. A stirred mixture of compound 3a (80 mg, 0.3 mmol) and MeOH (96 mg, 3 mol mol⁻¹) 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 (CDCl₃, 300 MHz) δ 2.14 (s, 3H), 3.42 (s, 3H), 7.25-7.41 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ 10.28, 51.03, 108.88, 126.15, 126.69, 128.31, 128.44, 128.56, 129.08, 129.69, 130.36, 136.31, 156.23, 172.05; ESIMS m/z 303 [M+Na]⁺. Anal. Caled for C₁₃H₁₂O₃: C, 77.12; H, 5.75. Found: C, 75.36; H, 3.64.

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, 12:1) 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.**

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