Tetrahedron Letters 49 (2008) 6241–6244

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Synthesis of 1,5-dicarbonyl and related compounds from Baylis–Hillman adducts via Pd-mediated decarboxylative protonation protocol

Saravanan Gowrisankar, Ko Hoon Kim, Sung Hwan Kim, Jae Nyoung Kim *

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

ARTICLE INFO

*Article history:*
Received 22 July 2008
Revised 8 August 2008
Accepted 11 August 2008
Available online 19 August 2008

*Keywords:*
1,5-Dicarbonyls
Baylis–Hillman adducts
Palladium
Decarboxylative protonation

ABSTRACT

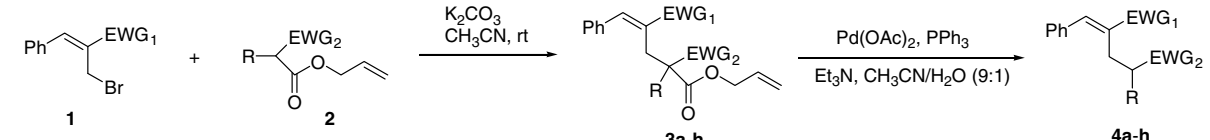
We prepared various 1,5-dicarbonyl and related compounds from Baylis–Hillman adducts by using a Pd-mediated decarboxylative protonation protocol.



Baylis–Hillman adducts have been used as effective precursors for the synthesis of various 1,5-dicarbonyl compounds.[1–4] Previous syntheses of these compounds from Baylis–Hillman adducts were carried out by using (carbethoxymethylene)triphenylphosphorane,[1] or via the Johnson–Claisen rearrangement with trialkyl orthoacetate.[2] However, these methods have some drawbacks including the limitations of substituents.[1,2] Due to the importance of 1,5-dicarbonyl and related moieties in both natural product chemistry and synthetic organic chemistry, a new and efficient synthetic approach is highly desirable.[1–3,5]

Baylis–Hillman acetates themselves can be used as effective substrates in the Pd-mediated reactions via the corresponding π-allylpalladium complex, and many papers using this concept have already been reported.[6] Palladium-assisted decarboxylative protonation and allylation of allyl esters have also been reported.[7,8] In a continuation of our studies on Pd-mediated reactions using the Baylis–Hillman adducts,[9] we theorized that various 1,5-dicarbonyl and related compounds could be synthesized easily from Baylis–Hillman adducts, as shown in Scheme 1, by using the Pd-mediated decarboxylative protonation as the key step.

Initially, we synthesized the starting material **3a** ($EWG_1$ = COOMe, $EWG_2$ = COOEt, R = H) from the reaction between the acetate of Baylis–Hillman adduct and allyl ethyl malonate (**2a**). However, **3a** was obtained as a mixture of *E*/*Z* (9:1). Thus, we used cinnamyl bromide **1a**, which can be synthesized as a pure *E* form by the treatment of Baylis–Hillman adduct with aqueous HBr,[10] and obtained **3a**-*E* in good yield (92%, vide infra, entry 1 in Table 2). With this compound **3a**, we examined the reaction conditions




**1a**: $EWG_1$ = COOMe
**1b**: $EWG_1$ = COOEt
**1c**: $EWG_1$ = $COCH_3$

**2a**: R = H, $EWG_2$ = COOEt
**2b**: R = H, $EWG_2$ = COOallyl
**2c**: R = $CH_2Ph$, $EWG_2$ = COOallyl
**2d**: R = H, $EWG_2$ = COMe
**2e**: R = H, $EWG_2$ = CN

**Scheme 1.**

* Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389.
*E-mail address:* kimjn@chonnam.ac.kr (J. N. Kim).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.08.051

**Table 1**
Optimization of reaction conditions for the conversion of **3a** to **4a**

| Entry | Conditions[a] | 4a (%) |
|---|---|---|
| 1 | HCOOH (1.2 equiv)/$Et_3N$ (1.2 equiv)/$CH_3CN$/reflux/1 h | 65 |
| 2 | HCOOH (1.2 equiv)/$Et_3N$ (1.2 equiv)/THF/60 °C/6 h | 50 |
| 3 | $Et_3N$ (1.2 equiv)/$CH_3CN$–$H_2O$ (9:1)/70 °C/2 h | 90 |
| 4 | $CH_3CN$–$H_2O$ (9:1)/70 °C/8 h | 67 |
| 5 | $Et_3N$ (1.2 equiv)/dry $CH_3CN$/60 °C/12 h | <5 |

[a] In all cases, $Pd(OAc)_2$ (5 mol %) and $PPh_3$ (10 mol %) were used.

for the selective Pd-mediated decarboxylative protonation. As shown in Table 1, the conditions comprised of $Pd(OAc)_2/PPh_3$/HCOOH/$Et_3N$ in $CH_3CN$ (entry 1) afforded **4a** in 65%. The reaction in THF was less effective (entry 2). When the reaction was carried out under aqueous $CH_3CN$ in the presence of $Et_3N$, the highest yield of **4a** (90%) was obtained (entry 3).[11] Although the role of $Et_3N$ is not clear at this stage, the reaction without $Et_3N$ gave diminished yield of product (67%, entry 4). The reaction in dry $CH_3CN$ was very sluggish as expected due to the absence of proton source (entry 5).

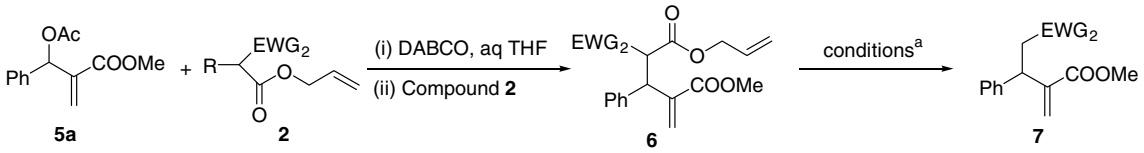
**Table 2**
Synthesis of 1,5-dicarbonyl and related compounds **4**

| Entry | **1** + **2** | **3** (%) | Time (h) | **4**[a] (%) |
|---|---|---|---|---|
| 1 | **1a** + **2a** | **3a** (92) | 2 | **4a** (90) |
| 2 | **1a** + **2b** | **3b** (86) | 6 | **4b** (88) |
| 3 | **1a** + **2c** | **3c** (78) | 6 | **4c** (89) |
| 4 | **1a** + **2d** | **3d** (85) | 5 | **4d** (86) |
| 5 | **1b** + **2a** | **3e** (89) | 3 | **4e** (88) |
| 6 | **1b** + **2b** | **3f** (87) | 4 | **4f** (91) |
| 7 | **1b** + **2e** | **3g** (71) | 2 | **4g** (66)[b] |
| 8 | **1c** + **2d** | **3h** (74) | 2 | **4h** (88) |

[a] Conditions: $Pd(OAc)_2$ (5 mol %), $PPh_3$ (10 mol %), $Et_3N$ (1.2 equiv), $CH_3CN$–$H_2O$ (9:1), 70 °C, 2–6 h.
[b] Decarboxylative allylation product was isolated in 16%.

Encouraged by the results, we prepared substrates **3b–h** from the reaction of cinnamyl bromides **1a–c** and allyl malonates **2a–e** in 71–89% yields. These compounds were subjected to the optimized conditions (entry 3 in Table 1) and we obtained good to excellent yields of products **4b–h** (66–91%), as summarized in Table 2. It is interesting to note that decarboxylation-allylation product was also isolated in 16% for the starting material **3g** (entry 7).[8]

**Table 3**
Synthesis of 1,5-dicarbonyl compounds **7**




| Entry | **5a** + **2** | **6** (%) | Time (h) | **7** (%) |
|---|---|---|---|---|
| 1 | **5a** + **2a** | **6a** (46) | 2 | **7a** (82) |
| 2 | **5a** + **2b** | **6b** (53) | 3 | **7b** (87) |
| 3 | **5a** + **2d** | **6c** (50) | 3 | **7c** (96) |

[a] Conditions: $Pd(OAc)_2$ (5 mol %), $PPh_3$ (10 mol %), $Et_3N$ (1.2 equiv), $CH_3CN$–$H_2O$ (9:1), 70 °C, 2–3 h.

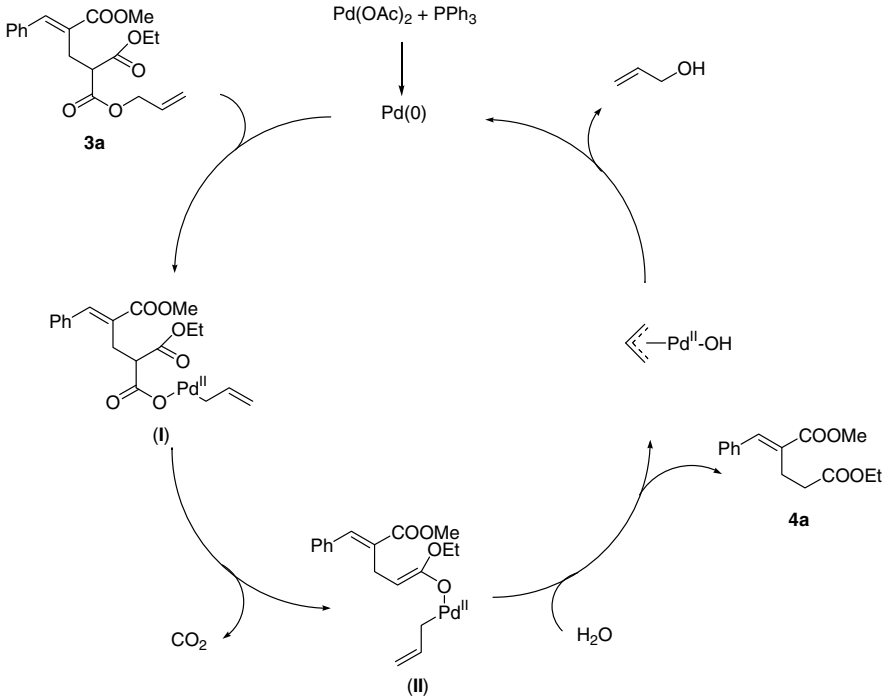
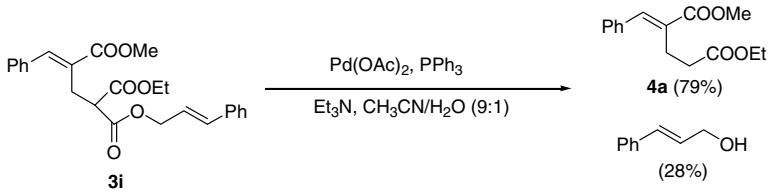
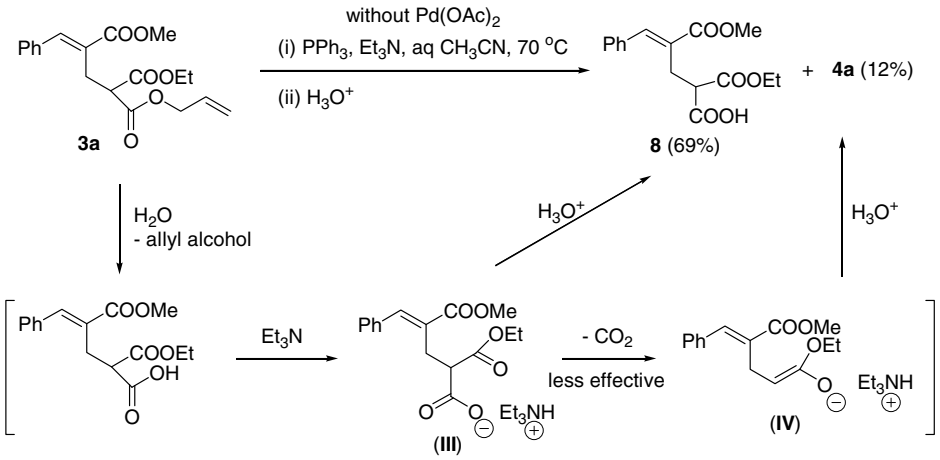



**Figure 1.** Postulated mechanism.




**Scheme 2.**




**Scheme 3.**

Introduction of allyl malonates at the secondary position of the Baylis–Hillman adducts was carried out according to the reported conditions involving the use of DABCO in aqueous THF.[12] Actually, we prepared three compounds **6a–c** in moderate yields (46–53%) and then examined the Pd-mediated decarboxylative protonation reaction (Table 3). As expected 1,5-dicarbonyl compounds **7a–c** were obtained similarly in good yields (82–96%).

The reaction mechanism for the conversion of **3a** into **4a** can be postulated as shown in Figure 1. Oxidative addition of Pd(0) to **3a** affords the Pd-carboxylate (**I**), which is converted to Pd-enolate (**II**) after decarboxylation.[7a] The Pd-enolate reacts with water to give product **4a** and the π-allylpalladium complex, which regenerates Pd(0) and liberates allyl alcohol.[7a] The detection of liberated allyl alcohol was somewhat difficult, thus we made the cinnamyl derivative **3i** and carried out decarboxylative protonation under the same conditions (Scheme 2). We did not observe the formation of β-methyl styrene. Instead, we isolated cinnamyl alcohol (28%), cinnamyl acetate (7%), and product **4a** (79%). The low yield of cinnamyl alcohol must be due to the instability of cinnamyl alcohol itself under the reaction conditions. The mechanism of HCOOH/$Et_3N$ system (entries 1 and 2 in Table 1) might involve the liberation of propene instead of allyl alcohol.[7b–e]

The reaction of **3a** using $PPh_3/Et_3N$/aqueous $CH_3CN$/70 °C/5 h also produced **4a**, albeit in lower yield (12%), even in the absence of $Pd(OAc)_2$ (Scheme 3). In the reaction, carboxylic acid **8** was isolated in 69% yield. The results demonstrate that hydrolysis of allyl ester can occur in part without the aid of Pd catalyst, but the subsequent decarboxylation of triethylammonium carboxylate (**III**) to triethylammonium enolate (**IV**) is somewhat difficult.

In summary, we disclose an efficient protocol for the synthesis of various 1,5-dicarbonyl and related compounds from Baylis–Hillman adducts by using the sequential introduction of allyl malonates followed by a Pd-mediated decarboxylative protonation strategy.

## Acknowledgments

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, KRF-2007-313-C00417). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

## References and notes

1. For the synthesis of 1,5-dicarbonyl compounds from Baylis–Hillman adducts by using phosphorous ylide, see: (a) Murthy, A. S. K.; Rambabu, C.; Vijeender, K.; Bhusan, P. B.; Chandrasekhar, S. *Synlett* **2007**, 494–496; (b) Im, Y. J.; Na, J. E.; Kim, J. N. *Bull. Korean Chem. Soc.* **2003**, *24*, 511–513; (c) Im, Y. J.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1361–1362; (d) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V. *J. Mol. Catal. A: Chem.* **2007**, *274*, 105–108.
2. For the synthesis of 1,5-dicarbonyl compounds from Baylis–Hillman adducts via the Johnson–Claisen rearrangement, see: (a) Das, B.; Majoy, A.; Banerjee, J. *Tetrahedron Lett.* **2006**, *47*, 7619–7623; (b) Basavaiah, D.; Pandiaraju, S. *Tetrahedron Lett.* **1995**, *36*, 757–758.
3. For the synthesis of 1,5-dicarbonyl compounds from Baylis–Hillman adducts using different approach, see: Garrido, N. M.; Garcia, M.; Diez, D.; Sanchez, M. R.; Sanz, F.; Urones, J. G. *Org. Lett.* **2008**, *10*, 1687–1690.
4. For the general review on Baylis–Hillman reaction, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp 201–350; (c) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062; (d) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627–645; (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490; (f) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511–4574 and further references cited therein.
5. (a) Gillingham, D. G.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 3860–3864; (b) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1998**, *63*, 4572–4573; (c) Fleming, K. N.; Taylor, R. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1728–1730; (d) Nicolaou, K. C.; Harrison, S. T. *J. Am. Chem. Soc.* **2007**, *129*, 429–440; (e) Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 6186–6187; (f) Dias, L. C.; de Sousa, M. A. *Tetrahedron Lett.* **2003**, *44*, 5625–5628; (g) Zheng, Y.; Avery, M. A. *Tetrahedron* **2004**, *60*, 2091–2095.
6. For the Pd-mediated reactions of Baylis–Hillman acetates, see: (a) Kabalka, G. W.; Dong, G.; Venkataiah, B.; Chen, C. *J. Org. Chem.* **2005**, *70*, 9207–9210; (b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807–5809; (c) Reddy, C. R.; Kiranmai, N.; Babu, G. S. K.; Sarma, G. D.; Jagadeesh, B.;

Chandrasekhar, S. *Tetrahedron Lett.* **2007**, *48*, 215–218; (d) Ranu, B. C.; Chattopadhyay, K.; Jana, R. *Tetrahedron Lett.* **2007**, *48*, 3847–3850; (e) Park, J. B.; Ko, S. H.; Kim, B. G.; Hong, W. P.; Lee, K.-J. *Bull. Korean Chem. Soc.* **2004**, *25*, 27–28; (f) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927–930; (g) Trost, B. M.; Brennan, M. K. *Org. Lett.* **2007**, *9*, 3961–3964 and further references cited therein.

7. For the Pd-mediated decarboxylative protonation, see: (a) Marinescu, S. C.; Nishimata, T.; Mohr, J. T.; Stoltz, B. M. *Org. Lett.* **2008**, *10*, 1039–1042; (b) Tsuji, J.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1985**, *50*, 3416–3417; (c) Ragoussis, V.; Giannikopoulos, A. *Tetrahedron Lett.* **2006**, *47*, 683–687; (d) Mandai, T.; Imaji, M.; Takada, H.; Kawata, M.; Nokami, J.; Tsuji, J. *J. Org. Chem.* **1989**, *54*, 5395; (e) Tsuji, J. *Pure Appl. Chem.* **1986**, *58*, 869–878.
8. For some examples on decarboxylative allylation, see: (a) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138–4139; (b) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995; (c) You, S.-L.; Dai, L.-X. *Angew. Chem., Int. Ed.* **2006**, *45*, 5246–5248; (d) Imao, D.; Itoi, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 1652–1658; (e) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248–7251; (f) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927; (g) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977–4980; (h) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14860–14861.
9. For our recent contributions on Pd-mediated reactions with Baylis–Hillman adducts, see: (a) Gowrisankar, S.; Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 1670–1673; (b) Kim, J. M.; Kim, K. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 3248–3251; (c) Lee, H. S.; Kim, S. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 1773–1776; (d) Gowrisankar, S.; Lee, H. S.; Lee, K. Y.; Lee, J.-E.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 8619–8622.
10. For the synthesis of cinnamyl bromide derivatives in a stereoselective manner, see: (a) Fernandes, L.; Bortoluzzi, A. J.; Sa, M. M. *Tetrahedron* **2004**, *60*, 9983–9989; (b) Das, B.; Banerjee, J.; Ravindranath, N. *Tetrahedron* **2004**, *60*, 8357–8361; (c) Sa, M. M.; Ramos, M. D.; Fernandes, L. *Tetrahedron* **2006**, *62*, 11652–11656; (d) Deng, J.; Hu, X.-P.; Huang, J.-D.; Yu, S.-B.; Wang, D.-Y.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2015–2017; (e) Buchholz, R.; Hoffmann, H.; Martin, R. *Helv. Chim. Acta* **1991**, *74*, 1213–1220; (f) Mazdiyasni, H.; Konopacki, D. B.; Dickman, D. A.; Zydowsky, T. M. *Tetrahedron Lett.* **1993**, *34*, 435–438.
11. Typical experimental procedure for the synthesis of **4a**: To a stirred solution of **3a** (346 mg, 1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), $PPh_3$ (26 mg, 0.1 mmol) in $CH_3CN$–$H_2O$ (3 mL, 9:1) was added $Et_3N$ (122 mg, 1.2 mmol), and the reaction mixture was heated to 70 °C for 2 h. After usual aqueous workup and column chromatographic purification process (hexanes/ether, 95:5), compound **4a** was isolated as colorless oil, 236 mg (90%). Other compounds were synthesized similarly and the representative spectroscopic data of **4a**, **4d**, and **7a** are as follows.
Compound **4a**:[2a] 90%, colorless oil; IR (film) 1710, 1635, 1254 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.24 (t, $J$ = 7.0 Hz, 3H), 2.55 (t, $J$ = 8.0 Hz, 2H), 2.88 (t, $J$ = 8.0 Hz, 2H), 3.83 (s, 3H), 4.11 (q, $J$ = 7.0 Hz, 2H), 7.32–7.42 (m, 5H), 7.74 (s, 1H).
Compound **4d**: 86%, colorless oil; IR (film) 1713, 1634, 1254 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 2.14 (s, 3H), 2.65–2.71 (m, 2H), 2.77–2.84 (m, 2H), 3.82 (s, 3H), 7.21–7.42 (m, 5H), 7.72 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 21.80, 29.68, 42.67, 51.98, 128.57 (2C), 129.02, 131.42, 135.20, 140.06, 168.34, 207.54.
Compound **7a**: 82%, colorless oil; IR (film) 1723, 1634, 1142 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.53 (t, $J$ = 7.0 Hz, 3H), 2.74–2.83 (m, 1H), 2.87–2.95 (m, 1H), 3.67 (s, 3H), 4.06 (q, $J$ = 7.0 Hz, 2H), 4.41 (t, $J$ = 8.1 Hz, 1H), 5.66 (s, 1H), 6.32 (s, 1H), 7.16–7.31 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.04, 39.58, 42.68, 51.86, 60.44, 124.49, 126.78, 127.76, 128.41, 141.14, 142.36, 166.70, 171.36.
12. For the regioselective introduction of nucleophiles at the secondary positions of Baylis–Hillman adducts by using the DABCO salt concept, see: (a) Kim, J. N.; Kim, J. M.; Lee, K. Y.; Gowrisankar, S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1733; (b) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481 and further references citied therein.