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Base-catalyzed domino reaction toward 3-benzylidenecyclohexenes: DBU-promoted sequential Michael, aldol, dehydration, and dealkoxycarbonylation

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Abstract—3-Benzylidenecyclohexene derivatives were prepared starting from the Baylis–Hillman adducts by using DBU-promoted domino process involving Michael, aldol, dehydration, and dealkoxycarbonylation.

Practical and efficient construction of highly functionalized and diversified molecules from readily available starting materials is a great challenge and highly desirable.[1,2] Domino processes have received much attention because they address fundamental principles of synthetic efficiency and reaction processing.[1,2] The significant feature of domino process is the formation of complex molecules starting from simple substrates in two or more steps, which occur in succession in the same pot without isolation of intermediates.[1,2]

During the chemical transformations of Baylis–Hillman adducts[3] we found an efficient domino process for the formation of 3-benzylidenecyclohexenes, serendipitously. Much effort has been devoted to the synthesis of suitably substituted cyclohexene derivatives due to their usefulness as synthetic intermediates.[4,5] In these contexts, we wish to report herein the results of novel domino reaction to 3-benzylidenecyclohexene derivatives.

As shown in Scheme 1, we used the malonate derivatives **2** as starting materials. Compounds **2** were easily synthesized from the reaction of diethyl (or dimethyl-) malonate and the acetate of the Baylis–Hillman adduct of alkyl vinyl ketone in a S_N2' manner.[6] The reaction of **2** and Michael acceptor **3** in CH_3CN under the influence of DBU afforded the cyclohexene derivatives **7** directly via the domino process. The reaction definitively involved the sequential Michael addition of **2** to the appropriate Michael acceptor **3** to give **4**, intramolecular aldol-type cyclization to **5**, dehydration to **6**, and DBU-promoted dealkoxycarbonylation to **7**.[6c,7] All the reactions proceeded under the influence of DBU sequentially in good yields in one pot experiment. The use of K_2CO_3/DMF, Cs_2CO_3/CH_3CN, or lesser amounts of DBU showed slow and incomplete reaction.

As an example, the reaction of **2a** and methyl vinyl ketone (**3a**) in CH_3CN in the presence of DBU (2 equiv) at refluxing temperature (1 h) gave **7a** in 84% yield.[8] The reaction mechanism could be suggested as shown in Scheme 1. However, we are not aware of the exact stage of dealkoxycarbonylation reaction. At the earliest stage of this experiment, we isolated one of the possible diastereomers of the aldol product **5a** in 43% yield.[9] The results implied that the dealkoxycarbonylation might occur at the final stage as shown in Scheme 1.[10] Usually dealkoxycarbonylation required drastic conditions such as DMAP/*p*-xylene/reflux/2–6 days.[6c] It is very interesting to note that the dealkoxycarbonylation of **6a** occurred under such relatively mild conditions (DBU, CH_3CN, reflux, 1 h).[6c,7,10]

Encouraged by the results we synthesized some cyclohexene derivatives **7b–i** analogously and the results are summarized in Table 1. As shown in Table 1, ethyl vinyl ketone (**3b**), methyl acrylate (**3c**), ethyl acrylate (**3d**), and acrylonitrile (**3e**) could be used as the Michael acceptor

Keywords: Domino reaction; 3-Benzylidenecyclohexenes; Baylis–Hillman adducts; Dealkoxycarbonylation.
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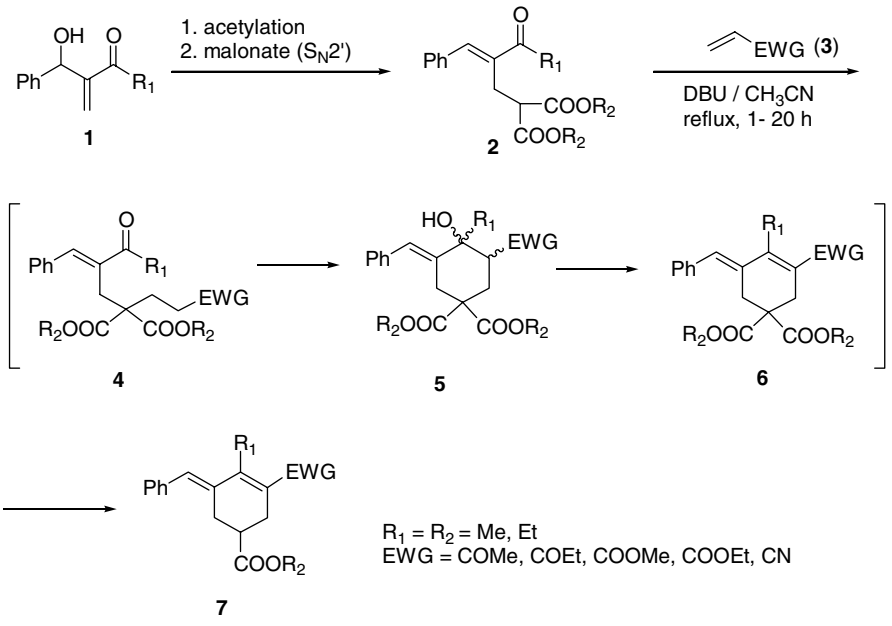


Scheme 1.

Table 1. Synthesis of benzylidene cyclohexene derivatives **7**

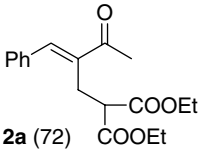
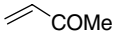
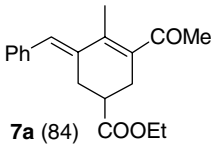
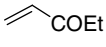
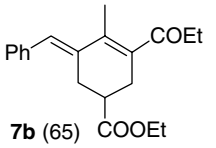
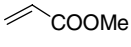
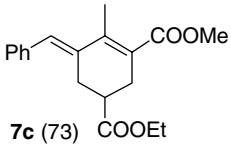
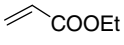
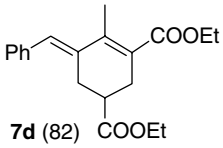
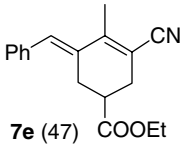
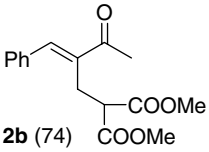
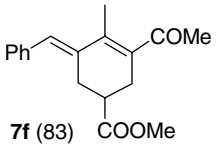
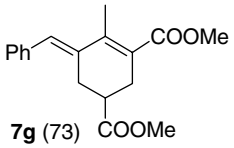
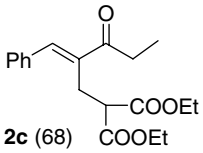
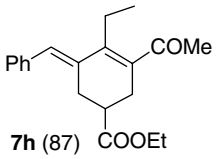
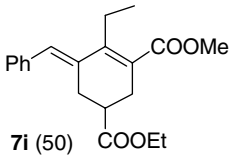
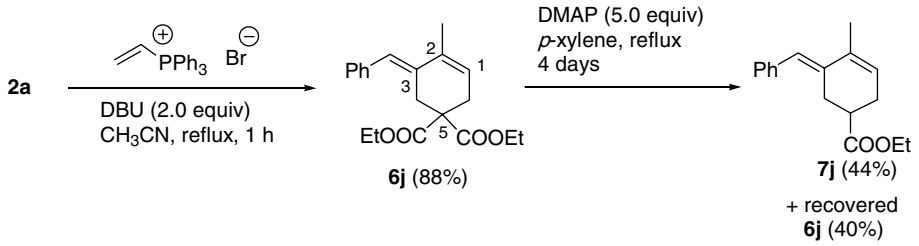
Entry	Compound **2** (%)	Compound **3**[a]	Conditions	Product **7** (%)
1	 **2a** (72)	 **3a**	DBU (2 equiv), CH_3CN, reflux, 1 h	 **7a** (84)
2	**2a**	 **3b**	DBU (2 equiv), CH_3CN, reflux, 3 h	 **7b** (65)
3	**2a**	 **3c**	DBU (2 equiv), CH_3CN, reflux, 20 h	 **7c** (73)
4	**2a**	 **3d**	DBU (2 equiv), CH_3CN, reflux, 20 h	 **7d** (82)
5	**2a**	 **3e**	DBU (2 equiv), CH_3CN, reflux, 16 h	 **7e** (47)
6	 **2b** (74)	**3a**	DBU (2 equiv), CH_3CN, reflux, 1 h	 **7f** (83)

Table 1 (*continued*)

Entry	Compound **2** (%)	Compound **3**[a]	Conditions	Product **7** (%)
7	**2b**	**3c**	DBU (2 equiv), CH_3CN, reflux, 20 h	 **7g** (73)
8	 **2c** (68)	**3a**	DBU (2 equiv), CH_3CN, reflux, 1 h	 **7h** (87)
9	**2c**	**3c**	DBU (2 equiv), CH_3CN, reflux, 8 h	 **7i** (50)

[a] Activated alkene was used in 2.0 equiv.



Scheme 2.

successfully. Short reaction time was sufficient to complete the reaction for the cases of alkyl vinyl ketones **3a** and **3b**. For acrylates **3c** and **3d**, relatively long reaction time was required to obtain the products in reasonable yields. In addition, moderate yield of product **7e** was obtained for acrylonitrile (**3e**) presumably due to low acidity of the α-proton nearby the –CN group.[3a]

In summary, we disclosed an efficient domino process for the synthesis of highly functionalized cyclohexene derivatives in good yields starting from the easily available Baylis–Hillman adducts. Further transformations of these compounds to more valuable compounds are actively in progress .

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References and notes

1. For some examples of domino process in the Baylis–Hillman chemistry, see: (a) Habib-Zahmani, H.; Hacini, S.; Bories, C.; Faure, R.; Rodriguez, J. *Synthesis* **2005**, 2151; (b) Wang, W.; Yu, M. *Tetrahedron Lett.* **2004**, *45*, 7141; (c) Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413; (d) Reiser, U.; Jauch, J. *Synlett* **2001**, 90; (e) Mix, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 2015.
2. (a) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vogtle, F., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 39–64; (b) Tejedor, D.; Gonzalez-Cruz, D.; Garcia-Tellado, F.; Marrero-Tellado, J. J.; Rodriguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390; (c) Langer, P.; Holtz, E.; Karime, I.; Saleh, N. N. R. *J. Org. Chem.* **2001**, *66*, 6057; (d) Bhar, S. S.; Ramana, M. M. V. *J. Org. Chem.* **2004**, *69*, 8935; (e) Molander, G. A.; Huerou, Y. L.; Brown, G. A. *J. Org. Chem.* **2001**, *66*, 4511; (f) Bose, G.; Nguyen, V. T. H.; Ullah, E.; Lahiri, S.; Gorls, H.; Langer, P. *J. Org. Chem.* **2004**, *69*, 9128.
3. For our recent publications on the chemical transformations of Baylis–Hillman adducts, see: (a) Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 8799; (b) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859; (c) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387; (d) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493; (e) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481, and further references cited therein.
4. For the synthesis of highly functionalized cyclohexenes and their synthetic applications, see: (a) Kanemasa, S.; Sakoh, H.; Wada, E.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3312; (b) Kurosawa, H.; Kajimaru, H.; Ogoshi,

S.; Yoneda, H.; Miki, K.; Kasai, N.; Murai, S.; Ikeda, I. *J. Am. Chem. Soc.* **1992**, *114*, 8417; (c) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763; (d) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2002**, *124*, 4178; (e) Garcia-Gomez, G.; Moreto, J. M. *Chem. Eur. J.* **2001**, *7*, 1503; (f) Organ, M. G.; Winkle, D. D.; Huffmann, J. *J. Org. Chem.* **1997**, *62*, 5254; (g) Dauben, W. G.; Hart, D. J.; Ipaktschi, J.; Kozikowski, A. P. *Tetrahedron Lett.* **1973**, 4425.

5. Keller-Schierlein, W.; Widmer, J.; Maurer, B. *Helv. Chim. Acta* **1972**, *55*, 198.
6. For the introduction of malonates to Baylis–Hillman adducts: (a) Im, Y. J.; Lee, C. G.; Kim, H. R.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 2987; (b) Im, Y. J.; Lee, K. Y.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2002**, *43*, 4675; (c) Im, Y. J.; Kim, J. M.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 1361.
7. For the references of dealkoxycarbonylation, see: (a) Taber, D. F.; Amedio, J. C., Jr.; Gulino, F. *J. Org. Chem.* **1989**, *54*, 3474; (b) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618; (c) Miles, D. H.; Huang, B.-S. *J. Org. Chem.* **1976**, *41*, 208; (d) Huang, B.-S.; Parish, E. J.; Miles, D. H. *J. Org. Chem.* **1974**, *39*, 2647.
8. Typical procedure for the synthesis of 3-benzylidenecyclohexene **7a**: The synthesis of **2a–c** was carried out as reported in 68–74% yields.[6] A stirred mixture of **2a** (318 mg, 1.0 mmol), methyl vinyl ketone **3a** (140 mg, 2.0 mmol), and DBU (304 mg, 2.0 mmol) in CH_3CN (3 mL) was heated to reflux for 1 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 8:1) we obtained **7a** as clear oil, 251 mg (84%). The other cyclohexenes **7b–h** were synthesized analogously and the spectroscopic data are as follows.

   Compound **7a**: 84%; a colorless oil; IR (film) 2924, 1732, 1685, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, $J = 7.2$ Hz, 3H), 2.05 (s, 3H), 2.34 (s, 3H), 2.59–2.64 (m, 4H), 3.02–3.09 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 6.81 (s, 1H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.09, 16.00, 29.08, 29.74, 29.86, 39.32, 60.64, 126.93, 128.18, 128.77, 129.26, 134.05, 135.93, 136.28, 137.22, 174.33, 205.18; ESIMS (*m*/*z*) 299.2 (M^++H).

   Compound **7b**: 65%; a colorless oil; IR (film) 2978, 1732, 1689, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, $J = 7.2$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H), 1.98 (s, 3H), 2.52–2.68 (m, 6H), 3.04–3.09 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 6.76 (s, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.87, 14.09, 16.02, 29.05, 29.72, 35.22, 39.32, 60.62, 126.84, 128.02, 128.16, 129.23, 132.45, 135.74, 136.66, 137.25, 174.34, 208.95; ESIMS (*m*/*z*) 313.1 (M^++H).

   Compound **7c**: 73%; a colorless oil; IR (film) 2951, 1732, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, $J = 7.2$ Hz, 3H), 2.22 (s, 3H), 2.54–2.78 (m, 4H), 3.04–3.09 (m, 1H), 3.78 (s, 3H), 4.11 (q, $J = 7.2$ Hz, 2H), 6.88 (s, 1H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10, 16.29, 29.02, 30.09, 39.32, 51.61, 60.55, 127.02, 127.04, 128.18, 129.29, 129.44, 136.30, 137.16, 139.85, 169.57, 174.38; ESIMS (*m*/*z*) 315.1 (M^++H).

   Compound **7d**: 82%; a colorless oil; IR (film) 2981, 1732, 1716, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.33 (t, $J = 7.2$ Hz, 3H), 2.21 (s, 3H), 2.49–2.78 (m, 4H), 3.04–3.10 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 4.25 (q, $J = 7.2$ Hz, 2H), 6.86 (s, 1H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 14.09, 14.23, 16.24, 29.05, 30.09, 39.36, 60.52, 60.54, 126.97, 127.50, 128.17, 129.14, 129.29, 136.32, 137.20, 139.03, 169.28, 174.45; ESIMS (*m*/*z*) 329.2 (M^++H).

   Compound **7e**: 47%; a colorless oil; IR (film) 2202, 1732, 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, $J = 7.5$ Hz, 3H), 2.30 (s, 3H), 2.63–2.69 (m, 4H), 3.01–3.08 (m, 1H), 4.12 (q, $J = 7.5$ Hz, 2H), 6.90 (s, 1H), 7.26–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07, 18.60, 28.56, 30.17, 38.68, 60.90, 107.77, 119.35, 127.74, 128.36, 129.39, 131.64, 133.74, 136.07, 148.33, 173.31; ESIMS (*m*/*z*) 282.1 (M^++H).

   Compound **7f**: 83%; a colorless oil; IR (film) 2951, 1736, 1682, 1200 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.05 (s, 3H), 2.34 (s, 3H), 2.52–2.69 (m, 4H), 3.09 (dd, $J = 13.5$ and 1.8 Hz, 1H), 3.67 (s, 3H), 6.82 (s, 1H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.01, 29.14, 29.77, 29.86, 39.26, 51.86, 126.97, 128.22, 128.90, 129.26, 134.19, 135.90, 136.18, 137.20, 174.78, 205.06; ESIMS (*m*/*z*) 285.1 (M^++H).

   Compound **7g**: 73%; a colorless oil; IR (film) 2951, 1736, 1716, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H), 2.48–2.79 (m, 4H), 3.09 (d, $J = 12.6$ Hz, 1H), 3.65 (s, 3H), 3.78 (s, 3H), 6.89 (s, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.24, 29.02, 30.04, 39.19, 51.58, 51.74, 126.92, 127.01, 128.17, 129.25, 129.52, 136.21, 137.10, 139.93, 169.45, 174.78; ESIMS (*m*/*z*) 301.1 (M^++H).

   Compound **7h**: 87%; a colorless oil; IR (film) 2974, 1732, 1685, 1180 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, $J = 7.2$ Hz, 3H), 1.21 (t, $J = 7.2$ Hz, 3H), 2.34 (s, 3H), 2.48 (q, $J = 7.2$ Hz, 2H), 2.54–2.66 (m, 4H), 3.02–3.09 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 6.84 (s, 1H), 7.21–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.08, 14.97, 22.36, 29.21, 29.69, 29.71, 39.22, 60.62, 126.89, 128.16, 128.46, 129.26, 133.72, 135.51, 137.26, 139.87, 174.32, 204.85; ESIMS (*m*/*z*) 313.2 (M^++H).

   Compound **7i**: 50%; a colorless oil; IR (film) 2978, 1732, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, $J = 6.9$ Hz, 3H), 1.20 (t, $J = 6.9$ Hz, 3H), 2.48–2.78 (m, 6H), 3.06 (d, $J = 11.7$ Hz, 1H), 3.78 (s, 3H), 4.10 (q, $J = 6.9$ Hz, 2H), 6.92 (s, 1H), 7.22–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10, 14.66, 22.74, 29.12, 30.05, 39.24, 51.57, 60.53, 126.24, 127.00, 128.17, 129.13, 129.32, 134.25, 137.21, 145.96, 169.25, 174.41; ESIMS (*m*/*z*) 329.2 (M^++H).
9. ^1H NMR data of aldol product **5a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, $J = 7.2$ Hz, 3H), 1.20 (t, $J = 7.2$ Hz, 3H), 1.42 (s, 3H), 2.00 (dd, $J = 13.8$ and 13.2 Hz, 1H), 2.33 (s, 3H), 2.45–2.53 (m, 1H), 2.62 (dd, $J = 14.4$ and 1.8 Hz, 1H), 2.93 (s, OH, 1H), 3.14 (dd, $J = 13.2$ and 3.9 Hz, 1H), 3.56–3.70 (m, 2H), 3.95–4.05 (m, 1H), 4.05–4.22 (m, 2H), 6.86 (s, 1H), 7.18–7.34 (m, 5H).
10. The use of vinyltriphenylphosphonium bromide as the Michael acceptor in the reaction with **2a** under the same reaction conditions produced **6j** instead of **7j** in 88% yield (Scheme 2). The results stated that the electron withdrawing substituent at the 1-position of **6** facilitated the dealkoxycarbonylation presumably due to the disfavored steric interactions between the EWG and one of the ester moieties at the 5-position of **6**.[6c,7] Actually, compound **6j** was completely inert under DBU/CH_3CN/refluxing conditions for 3 h. However, compound **6j** could be converted into **7j** under more drastic conditions (5.0 equiv of DMAP, *p*-xylene, reflux, 4 days) in 44% yield (recovered **6j**: 40%).[6c,7] The spectroscopic data of **6j** and **7j** are as follows. Compound **6j**: 88%; a colorless oil; IR (film) 2981, 1732, 1246, 1184 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, $J = 7.2$ Hz, 6H), 1.91 (s, 3H), 2.70–2.72 (m, 2H), 3.12 (s, 2H), 4.04–4.16 (m, 4H), 5.69–5.72 (m, 1H), 6.55 (s, 1H), 7.17–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.86, 19.88, 31.59, 31.72, 54.16, 61.30, 124.57, 125.62, 126.37, 128.07, 129.07, 133.25, 133.91, 137.52, 171.00.

Compound **7j**: 44%; a colorless oil; IR (film) 2927, 1732, 1176 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.94 (s, 3H), 2.38–2.44 (m, 2H), 2.56–2.62 (m, 2H), 3.00–3.08 (m, 1H), 4.10 (q, $J = 7.2$ Hz, 2H), 5.76 (t, $J = 3.6$ Hz, 1H), 6.51 (s, 1H), 7.17–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.15, 20.10, 28.65, 29.25, 40.06, 60.37, 124.38, 126.32, 126.38, 128.09, 129.25, 133.48, 136.09, 137.69, 175.19.