Synthesis of 2-Benzylidene-7a-alkyltetrahydropyrrolizine-3,5-diones Starting from Baylis-Hillman Adducts

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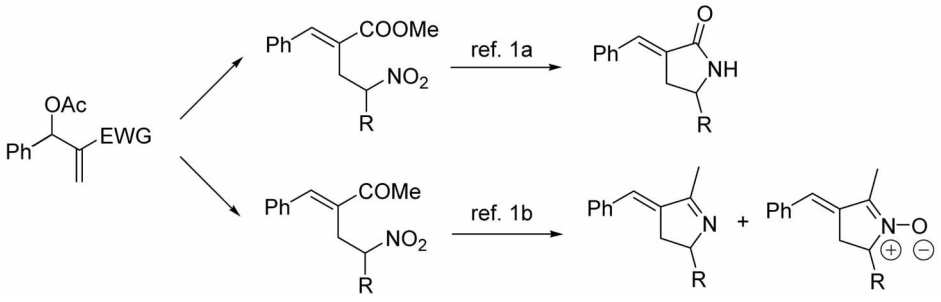
Recently, 3-alkylidenedihydropyrrol-2-ones[1a] and 3-alkylidenedihydropyrrole derivatives[1b] were synthesized starting from the Baylis-Hillman adducts of methyl acrylate and methyl vinyl ketone, respectively. These compounds were prepared by the reductive cyclization of nitroalkane derivatives, which were synthesized from the Baylis-Hillman acetate by the S_N2' reaction with primary nitroalkane,[1,2] as shown in Scheme 1.

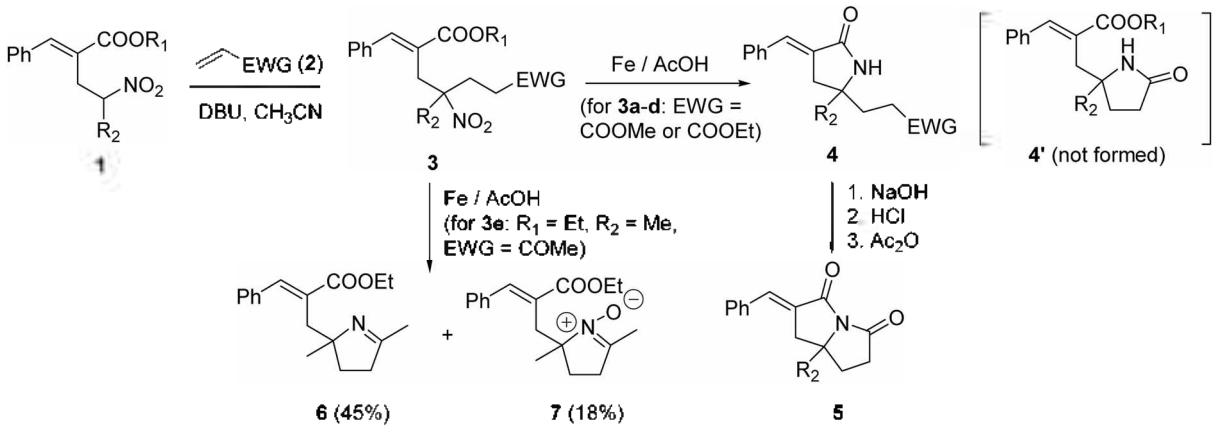
We reasoned that we could prepare tetrahydropyrrolizine-3,5-dione skeleton by using the same nitroalkane derivative **1** as the starting material as shown in Scheme 2. A variety of compounds with tetrahydropyrrolizine-3,5-dione backbone were known and have been synthesized.[3,4] The overall reaction pathway for the target compound involved sequential introduction of primary nitroalkane at the primary position of Baylis-Hillman adduct to make the starting material **1**,[1,2] Michael addition of **1** to appropriate Michael acceptor **2** to form **3**, reduction of the nitro group of **3** and concomitant cyclization to lactam compound **4**. From this lactam derivative **4** the desired tetrahydropyrrolizine-3,5-dione skeleton **5** could be synthesized.

Thus, we prepared **1a** from the reaction of the corresponding Baylis-Hillman acetate and nitroethane as reported.[1,2] The next Michael addition reaction was carried out with methyl acrylate (**2a**) in the presence of DBU in CH_3CN to produce **3a**.[2] With this compound **3a** in our hands, we examined the reduction of nitro group under Fe/AcOH conditions and obtained **4a** (54%). We could not find the other possible lactam compound **4'** (Scheme 2). The next cyclization reaction of **4a** to the final compound **5a** was performed according to method already reported in a similar system,[3c] hydrolysis of the ester group and the following lactamization under the influence of acetic anhydride at refluxing temperature.

Encouraged by the successful results, we examined the

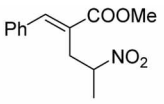
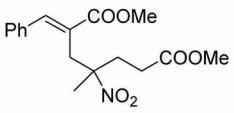
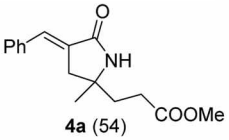
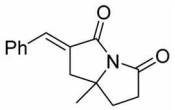
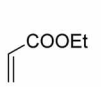
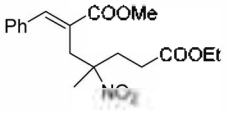
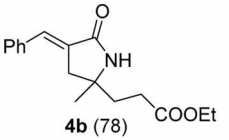
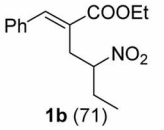
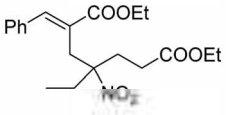
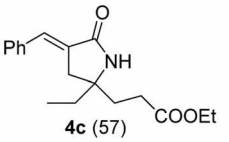
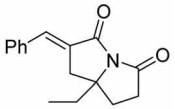
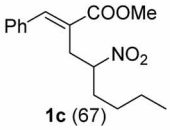
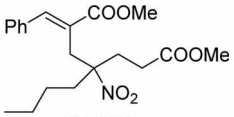
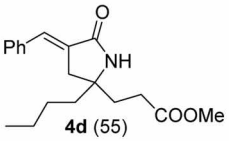
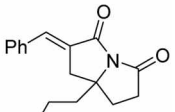
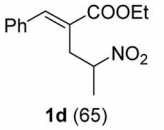
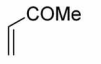
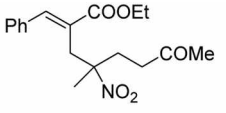


Scheme 1



Scheme 2

Table 1. Synthesis of 2-benzylidene-7a-alkyltetrahydropyrrolozine-3,5-diones

Entry	Substrate 1[a]	Michael acceptor 2	Intermediate 3[b]	Pyrrolidinone 4[c]	Pyrrolizine 5[d]
1	 **1a** (63)	 **2a**	 **3a** (85)	 **4a** (54)	 **5a** (63)
2	**1a**	 **2b**	 **3b** (78)	 **4b** (78)	**5a** (75)
3	 **1b** (71)	**2b**	 **3c** (82)	 **4c** (57)	 **5b** (74)
4	 **1c** (67)	**2a**	 **3d** (73)	 **4d** (55)	 **5c** (64)
5	 **1d** (65)	 **2c**	 **3e** (87)		

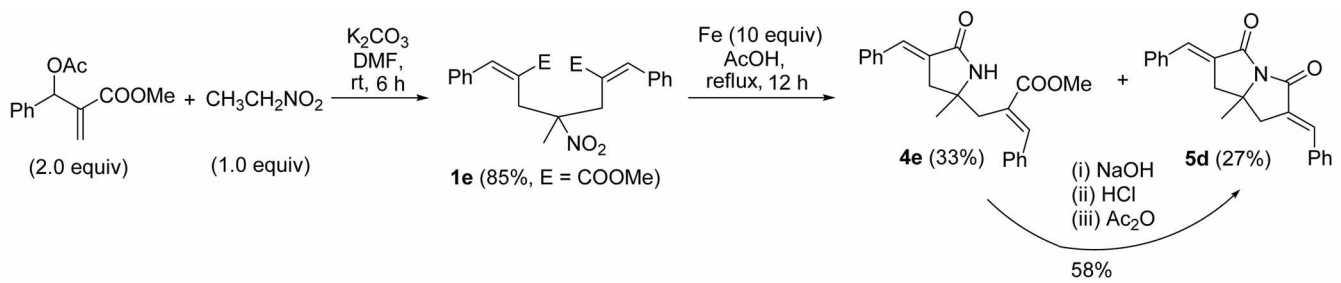
[a]The starting materials **1a-d** were prepared according to ref. 1 and 2. [b]Conditions: **1** (1.0 equiv), **2** (1.5 equiv), DBU (1.0 equiv), CH_3CN, rt, 30-60 min. [c]Conditions: **3** (1.0 equiv), Fe (10 equiv), AcOH, reflux, 2-9 h. [d]Conditions: (i) **4** (1.0 equiv), NaOH (3.0 equiv), aq EtOH, (ii) H_3O^+, (iii) Ac_2O, 110 °C, 2 h.

reactions with nitroalkane derivatives **1b-d** and Michael acceptors **2** including ethyl acrylate (**2b**) and methyl vinyl ketone (**2c**). The results are summarized in Table 1. The starting materials **1a-d** were prepared in 63-71% yields from the reaction of the corresponding Baylis-Hillman acetate and appropriate nitroalkanes under the influence of K_2CO_3 in DMF at room temperature.[1,2] The next Michael reaction was carried out with the aid of DBU in CH_3CN at room temperature in short time to produce **3a-e** in high yields (73-87%). The reductive cyclization of **3a-d** was carried out with Fe/AcOH under refluxing conditions and we obtained the desired compounds **4a-d** in 54-78% isolated yields. These compounds were transformed to **5a-c** in 63-75% yields (entries 1-4). As expected from the results of our previous paper,[1b] we obtained **6** (45%) and **7** (18%) from the reaction of **3e** under the same reductive cyclization conditions (entry 5 in Table 1 and Scheme 2).

Scheme 2

As shown in Scheme 3, we could also prepare symmetric bis-benzylidene compound **5d**. The required starting material **1e** was synthesized directly in 85% yield from the reaction Baylis-Hillman acetate and nitroethane in a 2 : 1 ratio. From the reaction of **1e** we isolated **4e** (33%) together with the final bis-benzylidene derivative **5d** (27%). The lactam **4e** could be converted into **5d** by following the same reaction conditions in 58% yield.

In summary, we disclosed the synthesis of 2-benzylidene-7a-alkyl-tetrahydropyrrolizine-3,5-dione derivatives starting from the Baylis-Hillman adducts. The synthetic method was straightforward and the synthetic applications toward some important alkaloid backbone are actively underway.



Scheme 3

Experimental Section

Synthesis of 3a (Typical procedure): To a stirred solution of **1a** (498 mg, 2.0 mmol) and methyl acrylate (**2a**, 258 mg, 3.0 mmol) in CH_3CN (5 mL) was added DBU (304 mg, 2.0 mmol) and stirred at room temperature for 30 min. After the usual aqueous extractive workup with ether and column chromatographic purification process (hexanes/ether, 5 : 1) we obtained **3a** as a colorless oil, 570 mg (85%). The other compounds **3b-e** were synthesized analogously and the spectroscopic data are as follows.

Compound **3a**: colorless oil; IR (CH_2Cl_2) 1739, 1543, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.84-1.94 (m, 1H), 2.03-2.22 (m, 2H), 2.27-2.37 (m, 1H), 3.25 (d, J = 14.7 Hz, 1H), 3.38 (d, J = 14.7 Hz, 1H), 3.63 (s, 3H), 3.79 (s, 3H), 7.26-7.29 (m, 2H), 7.31-7.44 (m, 3H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.43, 28.63, 33.95, 35.47, 51.78, 52.19, 89.96, 127.60, 128.41, 128.67, 128.77, 134.98, 143.92, 168.04, 172.41.

Compound **3b**: colorless oil; IR (CH_2Cl_2) 1732, 1543, 1442 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 7.2 Hz, 3H), 1.35 (s, 3H), 1.84-1.94 (m, 1H), 2.02-2.21 (m, 2H), 2.27-2.37 (m, 1H), 3.25 (d, J = 14.7 Hz, 1H), 3.38 (d, J = 14.7 Hz, 1H), 3.79 (s, 3H), 4.08 (q, J = 7.2 Hz, 2H), 7.27-7.30 (m, 2H), 7.31-7.43 (m, 3H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.08, 21.39, 28.88, 33.96, 35.52, 52.17, 60.66, 89.99, 127.61, 128.41, 128.65, 128.76, 134.97, 143.87, 168.03, 171.95.

Compound **3c**: colorless oil; IR (CH_2Cl_2) 1736, 1711, 1541, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.62 (t, J = 7.5 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.68-1.77 (m, 1H), 1.82-1.92 (m, 1H), 1.96-2.23 (m, 4H), 3.26 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 4.23 (q, J = 7.2 Hz, 2H), 7.26-7.43 (m, 5H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.91, 13.98, 14.09, 28.15, 28.67, 29.19, 32.19, 60.57, 61.36, 93.24, 128.23, 128.38, 128.45, 128.70, 135.13, 143.13, 167.63, 171.99.

Compound **3d**: colorless oil; IR (CH_2Cl_2) 1739, 1720, 1541, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, J = 7.2 Hz, 3H), 0.81-0.94 (m, 2H), 1.12 (quintet, J = 7.2 Hz, 2H), 1.57-1.67 (m, 1H), 1.73-1.84 (m, 1H), 1.96-2.11 (m, 3H), 2.16-2.25 (m, 1H), 3.27 (d, J = 2.1 Hz, 2H), 3.64 (s, 3H), 3.77 (s, 3H), 7.27-7.43 (m, 5H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.60, 22.64, 25.60, 28.50, 29.84, 32.59, 34.92, 51.75, 52.16, 92.85, 127.92, 128.39, 128.58, 128.75, 135.05, 143.38, 168.11, 172.45.

Compound **3e**: colorless oil; IR (CH_2Cl_2) 1716, 1541, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.33 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H), 1.79-1.97 (m, 1H), 2.04 (s, 3H), 2.10-2.27 (m, 3H), 3.26 (d, J = 14.7 Hz, 1H), 3.38 (d, J = 14.7 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 7.27-7.43 (m, 5H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.99, 21.79, 29.79, 32.65, 35.05, 37.83, 61.37, 90.12, 128.07, 128.41, 128.53, 128.75, 135.13, 143.45, 167.58, 206.15.

Synthesis of 4a (Typical procedure): A mixture of **3a** (503 mg, 1.5 mmol) and Fe (840 mg, 15 mmol) in AcOH (4 mL) was heated to reflux for 2 h. After the usual aqueous extractive workup with EtOAc and column chromatographic purification process (hexanes/EtOAc, 1 : 1) we obtained **4a** as a white solid, 222 mg (54%). The other compounds **4b-d** were synthesized analogously and the spectroscopic data are as follows.

Compound **4a**: white solid, mp 118-119 °C; IR (CH_2Cl_2) 3213, 1736, 1693, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 3H), 1.88-2.08 (m, 2H), 2.29-2.44 (m, 2H), 2.87 (dd, J = 17.4 and 2.7 Hz, 1H), 2.98 (dd, J = 17.4 and 2.7 Hz, 1H), 3.64 (s, 3H), 7.27-7.51 (m 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.75, 29.01, 37.05, 39.70, 51.81, 56.19, 128.69 (2C), 129.60, 130.57, 131.16, 135.50, 170.87, 173.59; LCMS *m/z* 273 (M^+).

Compound **4b**: white solid, mp 116-118 °C; IR (CH_2Cl_2) 3209, 1732, 1693, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 6.9 Hz, 3H), 1.38 (s, 3H), 1.90-2.00 (m, 2H), 2.32-2.40 (m, 2H), 2.87 (dd, J = 17.7 and 2.7 Hz, 1H), 2.99 (dd, J = 17.7 and 2.7 Hz, 1H), 4.10 (q, J = 6.9 Hz, 2H), 7.11 (br s, 1H), 7.27-7.48 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.10, 28.70, 29.28, 37.05, 39.69, 56.24, 60.66, 128.66 (2C), 129.58, 130.72, 131.04, 135.52, 170.94, 173.15.

Compound **4c**: colorless oil; IR (CH_2Cl_2) 3197, 1732, 1693, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.94 (t, J = 7.5 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H), 1.66 (q, J = 7.5 Hz, 2H), 1.87-2.08 (m, 2H), 2.25-2.42 (m, 2H), 2.88 (s, 2H), 4.09 (q, J = 7.2 Hz, 2H), 7.28-7.50 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 7.90, 14.07, 28.87, 33.62, 34.73, 36.91, 59.14, 60.59, 128.60, 128.63, 129.58, 130.64, 130.88, 135.51, 171.37, 173.23.

Compound **4d**: white solid, mp 120-122 °C; IR (CH_2Cl_2) 3201, 1736, 1693, 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 6.6 Hz, 3H), 1.23-1.37 (m, 4H), 1.57-1.63 (m, 2H), 1.89-2.09 (m, 2H), 2.30-2.38 (m, 2H), 2.90 (s, 2H), 3.64 (s, 3H), 6.58 (br s, 1H), 7.26-7.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.93, 22.93, 25.70, 28.64, 35.10, 37.52, 41.06, 51.82, 58.69, 128.69 (2C), 129.65, 130.58, 130.90, 135.53, 171.02, 173.69.

Synthesis of 5a (Typical procedure): To a stirred mixture of **4a** (273 mg, 1.0 mmol) in aqueous ethanol was added NaOH solution and stirred at room temperature for 3 h. The reaction mixture was poured into cold HCl solution and extracted with EtOAc. After removal of solvent the crude reaction mixture was dissolved in acetic anhydride (2 mL) and heated to 110 °C for 2 h. After the usual aqueous extractive workup with CH_2Cl_2 and column chromatographic purification process (hexanes/EtOAc, 1 : 1) we obtained **5a** as a white solid, 152 mg (63%). Compounds **5b** and **5c** were prepared analogously and the spectroscopic data are as follows.

Compound **5a**: white solid, mp 211-213 °C; IR (CH_2Cl_2) 1766, 1689, 1647, 1327 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 3H), 2.04-2.28 (m, 2H), 2.63-2.92 (m, 2H), 3.01 (d, J = 16.5 Hz, 1H), 3.12 (d, J = 16.5 Hz, 1H), 7.40-7.46 (m, 5H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.23, 34.72, 35.38, 41.77, 63.78, 128.85, 129.70, 129.98, 131.64, 134.67, 136.96, 164.75, 171.74; LCMS *m/z* 241 (M^+).

Compound **5b**: white solid, mp 188-190 °C; IR (CH_2Cl_2)

1766, 1685, 1647, 1296 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, J = 7.5 Hz, 3H), 1.71 (qd, J = 7.5 and 2.7 Hz, 2H), 2.05-2.17 (m, 1H), 2.29-2.36 (m, 1H), 2.68-2.71 (m, 1H), 2.78-2.85 (m, 1H), 2.92 (dd, J = 16.5 and 3.3 Hz, 1H), 3.17 (dd, J = 16.5 and 1.8 Hz, 1H), 7.37-7.50 (m, 5H), 7.56 (dd, J = 3.3 Hz and 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 8.46, 32.93, 33.48, 34.65, 39.32, 66.55, 128.87, 129.66, 130.02, 131.79, 134.72, 136.22, 165.37, 172.38; LCMS *m/z* 255 (M^+).

Compound **5c**: white solid, mp 146-148 °C; IR (CH_2Cl_2) 1766, 1693, 1647, 1284 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.6 Hz, 3H), 1.25-1.35 (m, 4H), 1.64-1.67 (m, 2H), 2.09-2.17 (m, 1H), 2.29-2.35 (m, 1H), 2.61-2.70 (m, 1H), 2.78-2.88 (m, 1H), 2.93 (dd, J = 16.8 and 3.0 Hz, 1H), 3.17 (dd, J = 16.8 and 1.5 Hz, 1H), 7.37-7.46 (m, 5H), 7.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.83, 22.86, 26.02, 33.97, 34.65, 39.88, 40.21, 66.19, 128.85, 129.63, 130.02, 131.78, 134.73, 136.15, 165.31, 172.35; LCMS *m/z* 283 (M^+).

Synthesis of compounds 1e, 4e, and 5d: Compound **1e** was prepared from the reaction of Baylis-Hillman acetate (2.0 equiv) and nitroethane (1.0 equiv) according to the previous method in 85% yield.[1,2] Reduction of **1e** was carried out according to the same procedure for the synthesis of **4a** and we obtained **4e** (33%) and **5d** (27%). The compound **4e** could be converted into **5d** in 58% yield by following the same protocol for the synthesis of **5a**. The spectroscopic data of **1e**, **4e**, and **5d** are as follows.

Compound **1e**: colorless oil; IR (CH_2Cl_2) 1716, 1543, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (s, 3H), 3.23 (s, 4H), 3.73 (s, 6H), 7.11-7.41 (m, 10H), 7.79 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.58, 35.42, 52.07, 90.72, 127.75, 128.54, 128.61, 128.68, 134.95, 143.53, 168.11.

Compound **4e**: white solid, mp 75-77 °C; IR (CH_2Cl_2) 3221, 1695, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 3H), 2.56 (dd, J = 17.4 and 2.7 Hz, 1H), 2.80 (dd, J = 17.4 and 2.7 Hz, 1H), 2.99 (s, 2H), 3.74 (s, 3H), 5.86 (br s, 1H), 7.11-7.47 (m, 11H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.61, 37.06, 39.55, 52.40, 57.71, 128.44 (2C), 128.51, 128.55, 128.76, 129.02, 129.52, 130.40, 130.74, 135.58, 135.60, 142.72, 169.25, 170.24.

Compound **5d**: white solid, mp 238-240 °C; IR (CH_2Cl_2) 1751, 1643, 1319 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 3.12 (d, J = 16.2 Hz, 2H), 3.22 (d, J = 16.2 Hz, 2H), 7.26-7.50 (m, 10H), 7.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.77, 41.51, 61.45, 128.87, 129.71, 129.98, 131.48, 134.75, 136.84, 165.23; LCMS *m/z* 329 (M^+).

Synthesis of compounds 6 and 7: We prepared compound **6** (45%) and **7** (18%) from **3e** according to the same procedure for the synthesis of **4a** and the spectroscopic data are as follows.

Compound **6**: colorless oil; IR (CH_2Cl_2) 2962, 1709, 1651, 1450, 1373 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.40-1.50 (m, 1H), 1.73-1.82 (m, 1H), 1.88 (s, 3H), 2.35-2.41 (m, 2H), 2.90 (d, J = 13.5 Hz, 1H), 2.98 (d, J = 13.5 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 7.26-7.47 (m, 5H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.20, 19.45, 27.60, 34.52, 36.85, 39.03, 60.81, 76.78, 127.94, 128.31, 129.16, 131.72, 136.07, 139.79, 169.66, 172.54.

Compound **7**: colorless oil; IR (CH_2Cl_2) 2966, 1705, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.67-1.77 (m, 1H), 1.93 (s, 3H), 2.07-2.16 (m, 1H), 2.39-2.44 (m, 2H), 3.03 (d, J = 13.8 Hz, 1H), 3.39 (d, J = 13.8 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 7.28-7.50 (m, 5H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.01, 14.21, 23.89, 29.52, 30.32, 32.89, 61.12, 76.82, 128.55, 128.65, 129.21, 129.35, 135.30, 141.92, 142.96, 168.70.

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References and Notes

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