Synthesis of Poly-substituted 2-Pyridones *via* [3+2+1] Annulation Protocol from Baylis-Hillman Adducts

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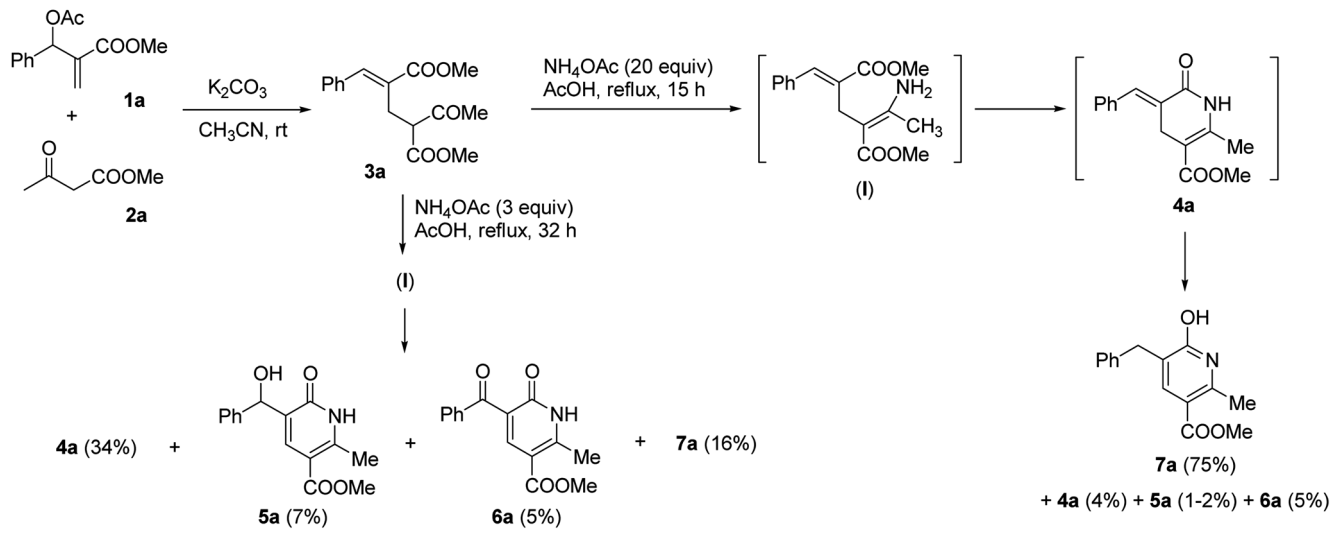
The synthesis of a substituted 2-pyridone ring is an area of continuing interest due to its abundance in many biologically important compounds containing this moiety.[1-3] Although numerous papers have been reported on the synthesis of this class of compounds,[1-3] development of a new and efficient synthetic procedure is still required.

Recently, we reported an efficient synthetic method for poly-substituted pyridines from the combination of Baylis-Hillman adducts (3 carbons), activated methylene compounds (2 carbons) and ammonium acetate (1 nitrogen) *via* [3+2+1] annulation protocol in good yields, regioselectively.[4] In the previous paper, we used Baylis-Hillman adducts derived from methyl vinyl ketone and obtained 2-methyl pyridine derivatives.[4] In continuation of our research, we intended to prepare the valuable poly-substituted 2-pyridones[1-3] by using the Baylis-Hillman adducts of methyl acrylate **1a** as shown in Scheme 1.

The starting material **3a** was synthesized from the reaction of Baylis-Hillman acetate **1a** and methyl acetoacetate (**2a**) in 77% yield.[5] The ester **3a** indeed produced 2-pyridone **7a**, albeit in low yield (16%), along with three other products, **4a** (34%), **5a** (7%) and **6a** (5%), when subjected to the conditions previously employed for the synthesis of pyridine derivatives (NH_4OAc (3.0 equiv)/AcOH/reflux).[4] Increasing the reaction temperature or varying the solvent (propionic or butyric acid) did not improve the results. The use of NH_4Cl or NH_4OH was also not effective.

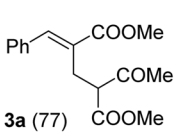
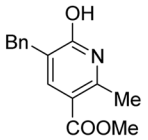
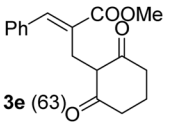
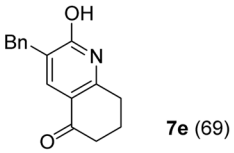
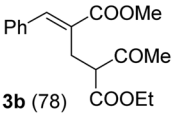
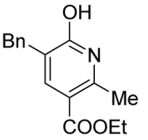
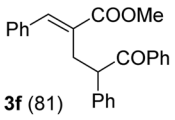
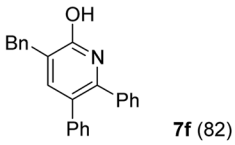
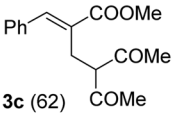
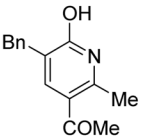
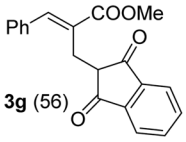
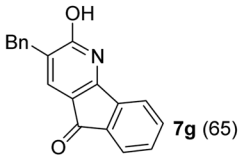
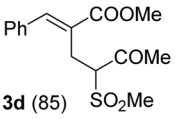
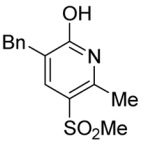
Fortunately, during the examinations we found that the use of excess amounts of NH_4OAc afforded good yield of **7a**. The reaction gave much better yield of **7a** (75%), while suppressing the formation of by-products **4a** (4%), **5a** (1-2%) and **6a** (5%), when **3a** was heated in AcOH with 20 equiv of NH_4OAc. The use of excess amounts of NH_4OAc might be beneficial for the isomerization of **4a** to **7a**,[6] although the reason is not clear at this stage. Encouraged by the results we prepared starting materials **3b-g** similarly from ethyl acetoacetate (**2b**), 2,4-pentanedione (**2c**), methanesulfonylacetone (**2d**), 1,3-cyclohexanedione (**2e**), deoxybenzoin (**2f**), and 1,3-indandione (**2g**) in 56-85% yields. The syntheses of **7b-g** were carried out by the same method for **7a** and the results are summarized in Table 1.

Various 2-pyridone derivatives **7b-g** were synthesized in 64-82% yields including bicyclic (entry 5) and tricyclic compound (entry 7). In all cases trace amounts of the corresponding benzylidene compounds, alcohols, and benzoyl derivatives were observed on TLC, but we didn't isolate them except entry 1 (*vide supra*, Scheme 1). The formation of alcohol **5a** and benzoyl derivative **6a** could be explained



Scheme 1

Table 1. Synthesis of various pyridin-2-ols[a]

Entry	Substrate (%)	Time (h)	Product (%)	Entry	Substrate (%)	Time (h)	Product (%)
1	 **3a** (77)	15	 **7a** (75)	5	 **3e** (63)	24	 **7e** (69)
2	 **3b** (78)	32	 **7b** (71)	6	 **3f** (81)	72	 **7f** (82)
3	 **3c** (62)	24	 **7c** (68)	7	 **3g** (56)	8	 **7g** (65)
4	 **3d** (85)	72	 **7d** (64)				

[a]Conditions: Substrate **3** (1.0 mmol), NH_4OAc (20 equiv), AcOH, reflux, 8-72 h.

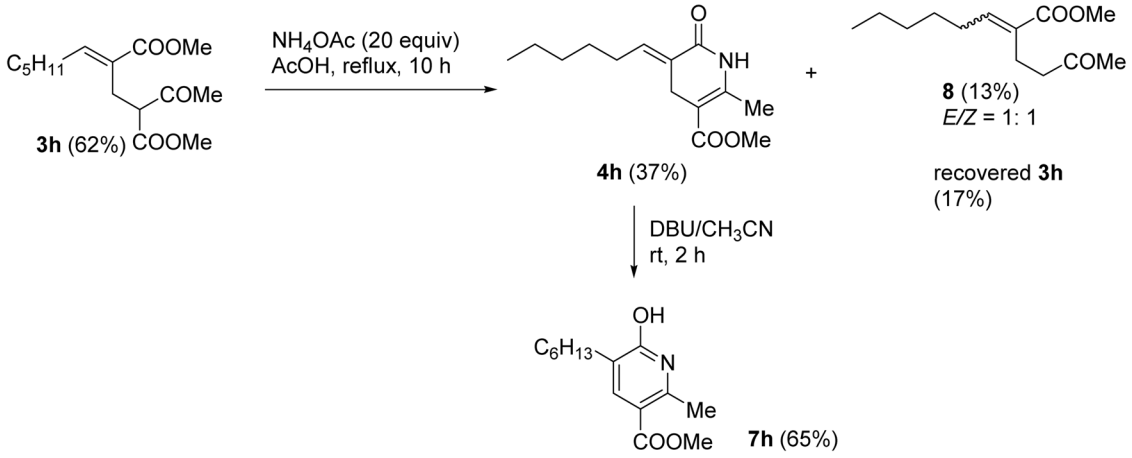
by the aerobic oxidation of **4a** tentatively.[7-9]

We obtained alkylidene derivative **4h** in low yield (37%) when we used **3h** as the starting material (Scheme 2). In addition, we isolated **8** (13%, *E/Z* mixture) and remaining starting material **3h** (17%). Isomerization of the double bond of **4h** was not effective under the reaction conditions. Although desired compound **7h** was observed in trace amounts on TLC, we could not isolate **7h** in pure form. Thus we made **7h** (65%) by treatment of **4h** with DBU (2.0 equiv) in CH_3CN at room temperature for 2 h by double bond isomerization.[6]

In summary, we disclosed an efficient synthetic method of poly-substituted 2-pyridones from the combination of Baylis-Hillman adducts (3 carbons), activated methylene compounds (2 carbons) and ammonium acetate (1 nitrogen) *via* [3+2+1] annulation protocol in good yields, in a highly regioselective fashion.

Experimental Section

Typical procedure for the synthesis of compound 3a.[5] To a stirred mixture of **1a** (234 mg, 1.0 mmol) and **2a** (128 mg, 1.1 mmol) in CH_3CN (5 mL) was added K_2CO_3 (152 mg, 1.1 mmol) and the resulting mixture was stirred at room temperature for 5 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 8:1) we obtained **3a** (224 mg, 77%) as colorless oil. Other compounds **3b**-**h** were synthesized similarly in 56-85% yields. The spectroscopic data of unknown compounds **3a**, **3b**, **3d**, **3f**, **3g**, and **3h** are as follows (The compounds



Scheme 2

3c[5f] and **3e**[5b] are known compounds).

Compound 3a. 77%; colorless oil; IR (film) 1744, 1715, 1436, 1260, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H), 3.04-3.25 (m, 2H), 3.56 (s, 3H), 3.82 (s, 3H), 3.81-3.86 (m, 1H), 7.29-7.42 (m, 5H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.42, 28.72, 52.07, 52.24, 58.06, 128.53, 128.65, 128.91, 129.00, 134.88, 141.86, 167.96, 169.63, 201.99; ESIMS *m/z* 289 (M^+-1).

Compound 3b. 78%; colorless oil; IR (film) 1738, 1716, 1436, 1260, 1097 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.14 (t, *J* = 7.2 Hz, 3H), 2.14 (s, 3H), 3.04-3.26 (m, 2H), 3.80-3.85 (m, 1H), 3.82 (s, 2H), 3.94-4.15 (m, 2H), 7.30-7.42 (m, 5H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.83, 25.40, 28.66, 52.06, 58.20, 61.36, 128.54, 128.65, 129.01, 129.07, 134.90, 141.74, 168.00, 169.24, 202.10; ESIMS *m/z* 303 (M^+-1).

Compound 3d. 85%; colorless oil; IR (film) 1718, 1709, 1437, 1311, 1264, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3H), 2.76 (s, 3H), 3.26-3.30 (m, 2H), 3.84 (s, 3H), 4.32-4.36 (m, 1H), 7.35-7.47 (m, 5H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.04, 31.70, 37.53, 52.34, 72.28, 127.00, 128.83, 128.94, 129.16, 134.33, 143.04, 167.55, 200.93; ESIMS *m/z* 309 (M^+-1).

Compound 3f. 81%; white solid, mp 86-87 °C; IR (film) 1704, 1683, 1447, 1254, 1205, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.18-3.32 (m, 2H), 3,76 (s, 3H), 4.89-4.94 (m, 1H), 7.03-7.17 (m, 7H), 7.21-7.27 (m, 3H), 7.31-7.37 (m, 2H), 7.41-7.47 (m, 1H), 7.65 (s, 1H), 7.86-7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.91, 51.97, 52.15, 127.04, 128.09, 128.25, 128.42, 128.51, 128.65, 128.70, 128.76, 130.37, 132.77, 135.36, 136.47, 138.25, 141.71, 168.64, 199.27; ESIMS *m/z* 369 (M^+-1).

Compound 3g. 56%; yellow oil; IR (film) 1744, 1709, 1435, 1259, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.13 (d, *J* = 7.8 Hz, 2H), 3.45 (t, *J* = 7.8 Hz, 1H), 3.76 (s, 3H), 7.27-7.43 (m, 5H), 7.79-7.85 (m, 2H), 7.86 (s, 1H), 7.91-7.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.83, 51.82, 52.01, 123.20, 128.57, 128.59, 129.02, 129.23, 135.21, 135.54, 141.21, 141.99, 168.17, 199.44; ESIMS *m/z* 319 (M^+-1).

Compound 3h. 62%; colorless oil; IR (film) 1747, 1719, 1436, 1224, 1148 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87-0.92 (m, 3H), 1.24-1.46 (m, 6H), 2.19-2.26 (m, 2H), 2.42 (s, 3H), 2.73-2.90 (m, 2H), 3.70 (s, 3H), 3.74 (s, 3H), 3.80-3.85 (m, 1H), 6.87 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.91, 22.43, 25.40, 28.36, 28.60, 29.45, 31.48, 51.73, 52.31, 58.02, 127.60, 146.58, 167.62, 169.76, 202.45.

Typical procedure for the synthesis of compound 7a. A mixture of **3a** (145 mg, 0.5 mmol) and NH_4OAc (770 mg, 10 mmol) in AcOH (4 mL) was heated to reflux for 15 h. After the usual aqueous workup and column chromatographic purification process ($CHCl_3$/EtOAc, 8:1) we obtained **7a** (97 mg, 75%) as a white solid. Other compounds **7b**-**g** and **4h** were synthesized similarly (37-82%). Spectroscopic data of prepared compounds **7a**-**d**, **7f**, **7g**, **4a**, **5a**, **6a**, **4h**, **7h**, and **8** are as follows (The compound **7e**[3e] is known).

Compound 7a. 75%; white solid, mp 216-217 °C; IR (KBr) 3412, 1716, 1655, 1280, 1236, 1086 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.52 (s, 3H), 3.72 (s, 3H), 3.73 (s, 2H), 7.18-7.33 (m, 5H), 7.65 (s, 1H), 12.08 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 16.57, 32.93, 49.48, 103.92, 124.03, 126.20, 126.30, 126.73, 136.00, 137.81, 149.11, 160.67, 163.11; ESIMS *m/z* 256 (M^+-1). Anal Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.29; H, 5.77; N, 5.26.

Compound 7b. 71%; white solid, mp 194-195 °C; IR (KBr) 3412, 1708, 1655, 1279, 1231, 1082 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.23 (t, *J* = 6.9 Hz, 3H), 2.50 (s, 3H), 3.71 (s, 2H), 4.17 (q, *J* = 6.9 Hz, 2H), 7.16-7.30 (m, 3H), 7.63 (s, 1H), 12.03 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 14.13, 18.51, 34.81, 60.07, 106.04, 125.98, 128.11, 128.26, 128.66, 138.02, 139.78, 150.93, 162.58, 164.67; ESIMS *m/z* 270 (M^+-1). Anal Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.56; H, 6.54; N, 5.02.

Compound 7c. 68%; white solid, mp 184-185 °C; IR (KBr) 3432, 1683, 1650, 1568, 1275, 1231 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.37 (s, 3H), 2.47 (s, 3H), 3.73 (s, 2H), 7.14-7.28 (m, 5H), 7.81 (s, 1H), 11.99 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.74, 29.86, 35.83, 115.33, 126.66, 128.20, 128.93, 129.34, 139.69, 140.70, 150.84, 162.96, 196.48; ESIMS *m/z* 240 (M^+-1). Anal Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.48; H, 6.03; N, 5.77.

Compound 7d. 64%; white solid, mp 266-267 °C; IR (KBr) 3412, 1652, 1605, 1302, 1159, 1131 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 2.51 (s, 3H), 3.12 (s, 3H), 3.72 (s, 2H), 7.16-7.32 (m, 5H), 7.51 (s, 1H), 12.26 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 17.94, 35.64, 44.92, 116.83, 126.86, 129.07, 129.50, 129.51, 136.61, 140.08, 149.69, 163.20; ESIMS *m/z* 276 (M^+-1). Anal Calcd for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.44; H, 5.53; N, 5.24.

Compound 7f. 82%; white solid, mp 272-273 °C; IR (KBr) 3415, 1652, 1644 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.82 (s, 2H), 6.97-7.00 (m, 2H), 7.13-7.37 (m, 13H), 7.35 (s, 1H), 11.77 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 35.97, 126.72, 127.13, 128.75, 128.88, 129.02, 129.41, 129.65, 130.10, 130.45, 138.85, 140.78, 141.40, 162.70, four carbons were overlapped; ESIMS *m/z* 336 (M^+-1). Anal Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.30; H, 5.88; N, 4.26.

Compound 7g. 65%; yellow solid, mp 347-348 °C; IR (KBr) 3407, 1714, 1634, 1616, 1576, 1406, 1140 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) d 3.75 (s, 2H), 7.18-7.33 (m, 5H), 7.37 (s, 1H), 7.46 (qd, *J* = 7.2 and 0.9 Hz, 1H), 7.50-7.52 (m, 1H), 7.60 (td, *J* = 7.2 and 1.5 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 13.22 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 35.58, 121.08, 122.81, 126.15, 128.37, 128.91, 130.35, 130.91, 131.60, 133.73, 134.03, 136.32, 139.46, 156.94, 163.51, 188.17; ESIMS *m/z* 286 (M^+-1). Anal Calcd for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N, 4.88. Found: C, 79.62; H, 4.38; N, 4.84.

Compound 4a. 34%; pale yellow solid, mp 142-143 °C; IR (KBr) 3420, 3207, 1715, 1633, 1614, 1368, 1236, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 3.75 (s,

3H), 3.77-3.78 (m, 2H), 7.35-7.51 (m, 5H), 7.56 (br s, 1H), 7.82 (t, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.07, 28.09, 51.40, 101.67, 125.62, 128.57, 129.02, 130.40, 135.06, 138.08, 143.95, 165.77, 167.34; ESIMS *m/z* 256 (M^+-1).

Compound 5a. 7%; pale yellow solid, mp 198-199 °C; IR (KBr) 3436, 1716, 1649, 1433, 1289, 1092 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.52 (s, 3H), 3.75 (s, 3H), 5.93 (s, 1H), 7.24-7.36 (m, 5H), 7.91 (s, 1H), 11.99 (s, 1H), 12.17 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 18.49, 18.63, 51.58, 51.66, 68.28, 82.03, 105.92, 126.49, 126.81, 126.86, 127.52, 127.92, 128.02, 128.28, 131.92, 135.44, 136.84, 138.53, 144.06, 151.48, 152.38, 161.40, 161.47, 165.07, 165.21; ESIMS *m/z* 272 (M^+-1).

Compound 6a. 5%; white solid, mp 234-235 °C; IR (KBr) 3415, 1722, 1663, 1652, 1600, 1256, 1198, 1082 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.62 (s, 3H), 3.76 (s, 3H), 7.49 (t, J = 7.2 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.75 (d, J = 7.2 Hz, 2H), 8.10 (s, 1H), 12.56 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 19.11, 51.80, 106.23, 125.66, 128.43, 129.13, 133.12, 137.02, 143.07, 157.32, 160.31, 164.49, 193.38; ESIMS *m/z* 270 (M^+-1).

Compound 4h. 37%; white solid, mp 157-158 °C; IR (KBr) 3412, 3199, 1712, 1638, 1365, 1225, 1087 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88-0.92 (m, 3H), 1.30-1.36 (m, 4H), 1.45-1.55 (m, 2H), 2.14-2.22 (m, 2H), 2.34 (s, 3H), 3.36-3.38 (m, 2H), 3.75 (s, 3H), 6.90-6.97 (m, 1H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.91, 18.87, 22.43, 26.13, 27.83, 28.33, 31.53, 51.22, 101.65, 125.39, 142.82, 144.65, 165.45, 167.52; ESIMS *m/z* 250 (M^+-1).

Compound 7h. 65%; white solid, mp 105-106 °C; IR (KBr) 3436, 1722, 1663, 1239, 1084 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87-0.91 (m, 3H), 1.26-1.40 (m, 6H), 1.55-1.62 (m, 2H), 2.51 (t, J = 7.5 Hz, 2H), 2.70 (s, 3H), 3.85 (s, 3H), 7.82 (s, 1H), 12.76 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.07, 19.33, 22.55, 28.26, 29.01, 29.54, 31.64, 51.69, 108.22, 129.57, 138.77, 150.02, 165.20, 165.78; ESIMS *m/z* 250 (M^+-1). Anal Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.88; H, 8.30; N, 5.46.

Compound 8. 13% (*E/Z*, 1:1); colorless oil; IR (KBr) 2928, 2857, 1717, 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.9 Hz, 1.5H), 0.89 (t, J = 6.9 Hz, 1.5H), 1.26-1.46 (m, 6H), 2.13 (s, 1.5H), 2.14 (s, 1.5H), 2.19 (q, J = 7.5 Hz, 1H), 2.41 (q, J = 7.5 Hz, 1H), 2.48-2.62 (m, 4H), 3.73 (s, 1.5H), 3.74 (s, 1.5H), 5.97 (t, J = 7.5 Hz, 0.5H), 6.79 (t, J = 7.5 Hz, 0.5H).

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References and Notes

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6. Conversion of **4a** into **7a** could be carried out more effectively with the aid of DBU. As an example, treatment of **4a** with DBU (2.0 equiv) in CH_3CN at room temperature in 2 h afforded **7a** in 85% yield.
7. Compound **4a** was easily oxidized to **6a** with PCC (pyridinium chlorochromate) in 75% yield (2.0 equiv of PCC, CH_2Cl_2, rt, 2 h). Alcohol derivative **5a** was also oxidized into **6a** in 81% yield under the same conditions. The final compound **7a** was reluctant to the PCC oxidation conditions. In addition, the air oxidation of **4a** to **6a** occurred slowly without PCC.[8] For the similar results using PCC oxidation process, see: Kim, S. J.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 1069-1072 and further references cited therein.
8. Compound **4a** was slowly converted into **6a** presumably *via* air oxidation process. TLC monitoring of a solution of **4a** in CH_2Cl_2 at room temperature for 15 days showed almost complete conversion of **4a** into **6a**, and indeed we isolated **6a** in 90% yield.
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