Regioselective Synthesis of Poly-Substituted Pyrroles from Baylis-Hillman Adducts *via* the [3+1+*N*] Annulation Strategy

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Poly-substituted pyrrole derivatives were synthesized from Baylis-Hillman adducts *via* the following consecutive reactions comprised of (i) bromination of the Baylis-Hillman adduct, (ii) In-mediated Barbier reaction with aldehyde, (iii) PCC oxidation to α-methylene-γ-keto ester, (iv) reaction with amine to form enamine intermediate, (v) Michael type cyclization, and the final (vi) aerobic oxidation.

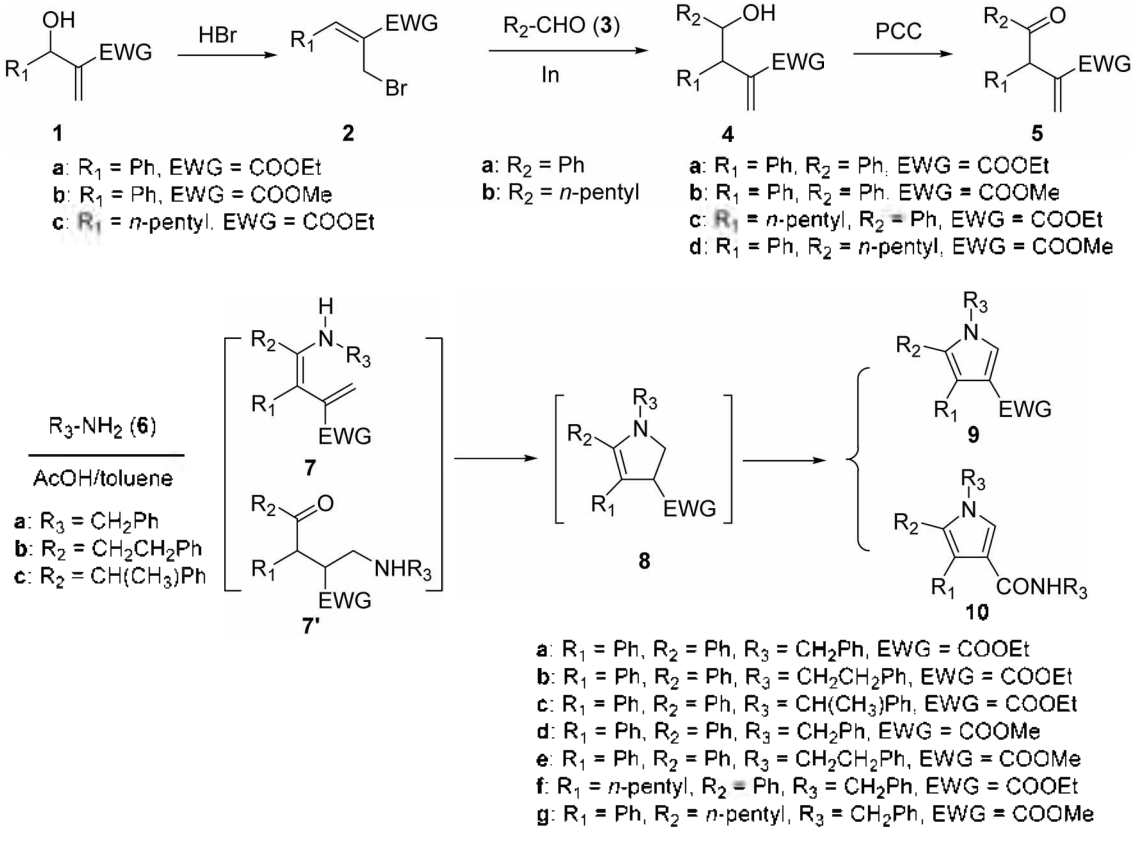
Key Words : Pyrroles, Baylis-Hillman adducts, Barbier reaction, PCC, Aerobic oxidation

Introduction

Suitably substituted pyrroles are the basic skeleton of many biologically important substances[1,2] and numerous methods for the synthesis of pyrrole derivatives have been investigated extensively.[1,2] The synthetic applicability of Baylis-Hillman adducts has also been reported in many papers.[3-5] However, the synthesis of pyrrole derivatives from Baylis-Hillman adducts has not been reported much.[4,5] Very recently, we reported the synthesis of 2,3,4-trisubstituted pyrroles starting from the rearranged *aza*-Baylis-Hillman adducts involving [3+*N*+1] *annulation*.[5a] We also developed another efficient synthetic method of poly-substituted pyrroles by using [3+(*N*+1)] *annulation*.[5b]

Results and Discussion

During the studies we imagined that we could synthesize 2,3,4-trisubstituted pyrroles by following the reaction sequence shown in Scheme 1 *via* the [3+1+*N*] *annulation* strategy. At the earliest stage of this project our synthetic rationale was the first construction of dihydropyrrole skele-



Scheme 1

Table 1. Synthesis of poly-substituted pyrroles

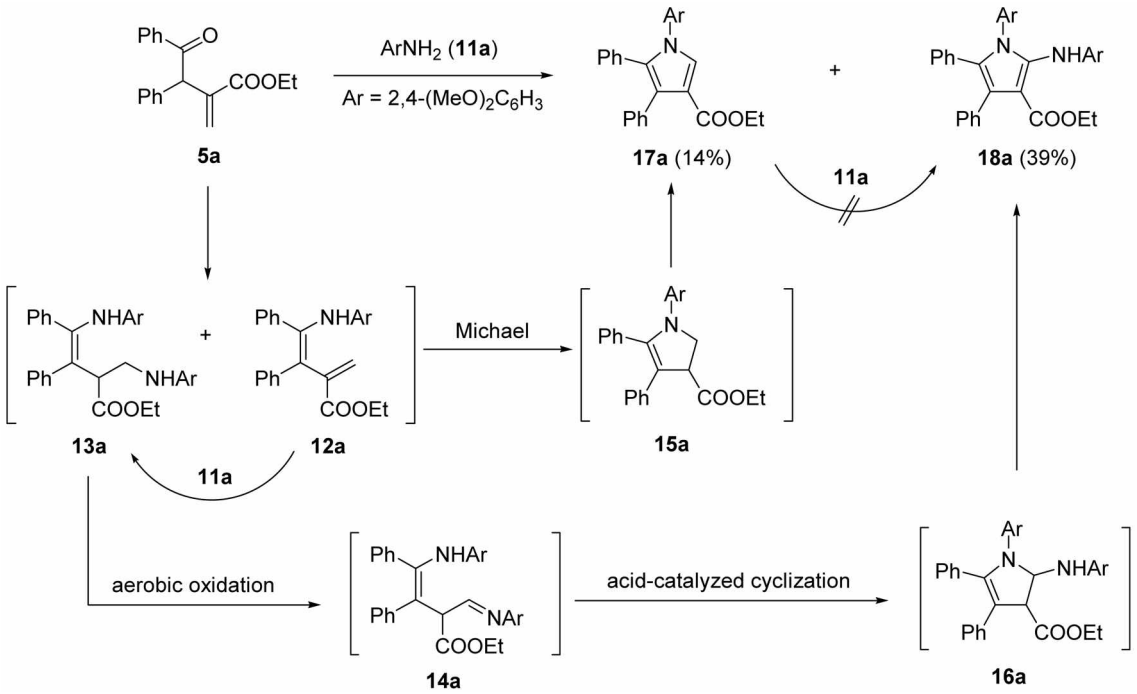
Entry	2+3	Compound **4** (%)[a]	Compound **5** (%)[b]	Compound **6**	Product **9** (%)[c]	Product **10** (%)[c]
1	**2a+3a**	**4a** (93)	**5a** (90)	**6a**	**9a** (50)	**10a** (5)
2				**6b**	**9b** (46)	**10b** (9)
3				**6c**	**9c** (47)	**10c** (2)
4	**2b+3a**	**4b** (91)	**5b** (88)	**6a**	**9d** (45)	**10a** (6)
5				**6b**	**9e** (40)	**10b** (11)
6	**2c+3a**	**4c** (83)	**5c** (85)	**6a**	**9f** (45)	**10f** (trace)[d]
7	**2b+3b**	**4d** (60)	**5d** (68)	**6a**	**9g** (40)	**10g** (trace)[d]

[a]Compound **2** (2.0 mmol), aldehyde **3** (1.5 equiv), In (1.1 equiv), aq THF, rt, 1-2 h. [b]Compound **4** (1.0 mmol), PCC (2.0 equiv), CH_2Cl_2, rt, 4 h. [c]Compound **5** (0.5 mmol), amine **6** (1.5 equiv), AcOH (1.0 equiv), toluene, 80-90 °C, 5-7 h. [d]Not isolated.

ton **8** and the second oxidation process to pyrrole **9**.

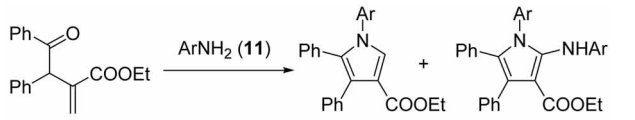
Thus we prepared starting material **5a** from Baylis-Hillman adduct **1a** according to the reported method: (i) bromination of Baylis-Hillman adduct **1a** to cinnamyl bromide **2a** (95%, HBr),[3,6] (ii) In-mediated Barbier reaction of **2a** and benzaldehyde (**3a**) to make **4a** (93%),[6] (iii) PCC oxidation of **4a** to α-methylene-γ-keto ester **5a** (90%). With this compound **5a** in our hand, we examined the reaction of **5a** and benzylamine (**6a**) under various conditions. Among the examined conditions the use of AcOH (1.0 equiv) in toluene was the best choice. Under the conditions we obtained **9a** (50%) and the corresponding amide derivative **10a** (5%). During the reaction progress we observed the presence of a small amount of dihydropyrrole intermediate **8a** which converted into the pyrrole **9a** (*vide infra*). We tried the synthesis of dihydropyrrole **8a**. When the reaction of **5a** and **6a** was carried out under strictly controlled nitrogen atmosphere (0.1 equiv of CF_3COOH, benzene, reflux, 24 h), we observed the formation of **8a** in appreciable amounts together with **9a** (14%) and remaining **5a** (32%). Compound **8a** was isolated in 35% yield by rapid column chromatography and identified the structure by ^1H and ^{13}C NMR spectra as correct.[7] However, this compound **8a** was oxidized rapidly, and converted to **9a** spontaneously. The conversion of **8a** into **9a** can be explained by aerobic oxidation.[8] Encouraged by the results we made other α-methylene-γ-keto esters **5b-d** and examined the reactions with some representative amines, benzylamine (**6a**), phenethyl amine (**6b**), and *sec*-phenethylamine (**6c**). The results are summarized in Table 1.

As shown in Table 1, we made 2,3,4-trisubstituted pyrroles **9a-g** in moderate yields (40-50%) and we observed some amide derivatives **10a-g** (trace-11%), which was isolated in most cases. The reaction mechanism for the formation of dihydropyrrole intermediate could be explained as in Scheme 1 involving the formation of enamine intermediate **7** and the following Michael type cyclization to **8**.[9,10] However, the mechanism involving the initial formation of Michael addition product **7'** and the following dehydrative cyclization to **8** cannot be excluded.



Scheme 2

Table 2. Reaction of **5a** and anilines **11**



5a **a**: Ar = 2,4-$(MeO)_2C_6H_3$ **17** **18**
b: Ar = 4-$MeOC_6H_4$
c: Ar = C_6H_5

Entry	Anilines	Conditions[a]	Products **17/18** (%)[b]
1	**11a** (3.0 equiv)	AcOH (0.5 equiv), 20 h	**17a/18a** (10/52)
2	**11a** (3.0 equiv)	AcOH (1.0 equiv), 20 h	**17a/18a** (14/39)
3	**11a** (3.0 equiv)	AcOH (2.0 equiv), 26 h	**17a/18a** (52/9)
4	**11a** (3.0 equiv)	AcOH (6.0 equiv), 24 h	**17a/18a** (58/9)
5	**11a** (2.0 equiv)	HCOOH (1.0 equiv), 48 h	**17a/18a** (5/26[c])
6	**11a** (2.0 equiv)	CF_3COOH (1.0 equiv), 48 h	**17a/18a** (7/7[d])
7	**11b** (3.0 equiv)	AcOH (2.0 equiv), 24 h	**17b/18b** (50/14)
8	**11c** (3.0 equiv)	AcOH (2.0 equiv), 48 h	**17c/18c** (37/11[e])

[a]Toluene was used as solvent, 80-90 °C. [b]Isolated yield of pure product. [c]Starting material **5a** was recovered in 23% yield. [d]Starting material **5a** was recovered in 21% and trifluoroacetamide derivative of **11a** was isolated in 10%. [e]In compound **18c** small amount of 17c was contaminated.

As a next trial, we examined the reaction of **5a** and aniline (**11c**) under the same conditions (1.0 equiv of AcOH in toluene). However, the reaction was sluggish and many compounds were observed on TLC (*vide infra*). Thus, we examined the reaction with electron-rich 2,4-dimethoxyaniline (**11a**). When we used 1.0 equiv of AcOH we isolated compound **17a** in only 14% yield (entry 2 in Table 2). From the reaction compound **18a** was isolated as the major product (39%) interestingly. The formation of **17a** and **18a** can be explained as in Scheme 2. Compound **17a** can be produced as for the compounds **9a-g** involving the intermediate enamine **12a** and dihydropyrrole **15a**. Whereas, compound **18a** might be formed *via* the sequential process: (i) Michael addition of **11a** to **12a** to form **13a**, (ii) aerobic oxidation to **14a**,[11] (iii) acid-catalyzed cyclization of **14a** to **16a** and the final (iv) aerobic oxidation.[8] In these respects, the yield and the ratio between **17a**/**18a** could be changed by modification of reaction conditions. Thus we examined the reaction of **5a** and **11a** in six different conditions (entries 1-6 in Table 2). Although combined yield of **17a** and **18a** was not changed much, the ratio between **17a**/**18a** was influenced by the amount of acetic acid, dramatically. Compound **17a** was obtained as the major (58%) with 6.0 equiv of AcOH (entry 4), whereas compound **18a** was the major (52%) with 0.5 equiv of AcOH (entry 1). The effect of AcOH on the ratio of **17a**/**18a** is not clear at this stage. The use of formic acid and CF_3COOH showed low yields of products (entries 5 and 6). The reaction with 4-methoxyaniline (**11b**) afforded **17b** (50%) and **18b** (14%) as in entry 7, similarly. The reaction with aniline (**11c**, *vide supra*) showed sluggish reactivity, however we obtained the corresponding pyrroles **17c** and **18c** after 48 h, albeit in low yields (entry 8).

In summary, we disclosed an efficient synthetic method of poly-substituted pyrroles starting from the Baylis-Hillman adducts *via* the [3+1+*N*] *annulation* protocol. Further synthetic applications of this methodology are under progress actively in our group.

Experimental Section

General procedure. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in ppm relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejon, Korea. All reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230-400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

Typical procedure for the synthesis of starting material 4a. A mixture of cinnamyl bromide **2a** (538 mg, 2.0 mmol), benzaldehyde (**3a**, 318 mg, 3.0 mmol), and indium powder (253 mg, 2.2 mmol) in aqueous THF (1:1, 5 mL) was stirred at room temperature for 2 h. After the usual aqueous workup and column chromatographic purification (hexanes/EtOAc, 10:1) process, desired compound **4a** (551 mg, 93%) was obtained as colorless oil. Syntheses of compounds **4b-d** were carried out similarly and the representative spectroscopic data are as follows.

Compound **4a**: 93%; colorless oil; IR (film) 3498, 3030, 1714, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, J = 7.2 Hz, 3H), 2.11 (br s, 1H), 3.94-4.05 (m, 2H), 4.30 (d, J = 7.8 Hz, 1H), 5.26 (d, J = 7.8 Hz, 1H), 5.78 (s, 1H), 6.23 (s, 1H), 7.20-7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.92, 54.23, 60.73, 75.67, 126.53, 126.94, 127.10, 127.69, 128.16, 128.43, 129.18, 138.68, 141.29, 142.04, 166.45.

Compound **4b**: 91%; colorless oil; IR (film) 3503, 3030, 1717, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.30 (d, J = 3.6 Hz, 1H), 3.48 (s, 3H), 4.26 (d, J = 7.8 Hz, 1H), 5.16-5.20 (m, 1H), 5.74 (s, 1H), 6.18 (s, 1H), 7.16-7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 51.63, 54.03, 75.41, 126.69, 126.80, 126.90, 127.48, 127.69, 128.23, 129.06, 138.56, 140.93, 142.03, 166.78.

Compound **4c**: 83%; colorless oil; IR (film) 3461, 2931, 1713, 1151 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 6.6 Hz, 3H), 1.05-1.26 (m, 6H), 1.29 (t, J = 7.2 Hz, 3H), 1.50-1.66 (m, 2H), 2.83 (d, J = 3.0 Hz, 1H), 2.92-2.99 (m, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.84 (dd, J = 5.1 Hz and 3.0 Hz, 1H), 5.42 (s, 1H), 6.22 (s, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.97, 14.12, 22.45, 27.03, 27.34, 31.75, 49.37, 60.94, 76.44, 126.47, 126.76, 127.15, 127.91, 140.89, 142.65, 168.03.

Compound **4d**: 60%; colorless oil; IR (film) 3528, 2953, 1721, 1146 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, J = 7.5 Hz, 3H), 1.24-1.32 (m, 4H), 1.36-1.39 (m, 2H), 1.44-1.56 (m, 3H), 3.68 (s, 3H), 3.91 (d, J = 6.5 Hz, 1H), 4.13-

4.14 (m, 1H), 5.88 (s, 1H), 6.36 (s, 1H), 7.22-7.26 (m, 1H), 7.29-7.33 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.99, 22.58, 25.57, 31.71, 35.35, 51.94, 52.46, 72.74, 126.04, 127.03, 128.50, 129.27, 138.86, 141.71, 167.25.

Typical procedure for the synthesis of compound 5a. A mixture of **4a** (296 mg, 1.0 mmol) and PCC (430 mg, 2.0 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with CH_2Cl_2 and filtered through a pad of Celite. After removal of solvent under reduced pressure and column chromatographic purification (hexanes/EtOAc, 15:1) process, desired **5a** (265 mg, 90%) was obtained as a white solid. Syntheses of compounds **5b-d** were carried out similarly and the representative spectroscopic data are as follows.

Compound **5a**: 90%; white solid, mp 51-53 °C; IR (film) 2981, 1713, 1684, 1137 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (t, J = 7.2 Hz, 3H), 4.12-4.22 (m, 2H), 5.26 (s, 1H), 5.89 (s, 1H), 6.48 (s, 1H), 7.21-7.38 (m, 7H), 7.42-7.48 (m, 7H), 7.96-8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.88, 55.21, 60.96, 127.54, 128.22, 128.37, 128.70, 128.95, 129.42, 132.78, 135.50, 136.22, 140.48, 166.34, 197.36.

Compound **5b**: 88%; white solid, mp 73-75 °C; IR (film) 2951, 1716, 1682, 1139 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, 3H), 5.28 (s, 1H), 5.88 (s, 1H), 6.47 (s, 1H), 7.24-7.40 (m, 7H), 7.45-7.50 (m, 1H), 7.95-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.15, 55.32, 127.66, 128.50, 128.65, 128.84, 129.06, 129.52, 132.91, 135.60, 136.27, 140.16, 167.01, 197.42.

Compound **5c**: 85%; colorless oil; IR (film) 2957, 2931, 1713, 1687, 1221 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83-0.88 (m, 3H), 1.25-1.33 (m, 9H), 1.64-1.71 (m, 1H), 1.92-2.00 (m, 1H), 4.19-4.26 (m, 2H), 4.68 (t, J = 7.2 Hz, 1H), 5.71 (s, 1H), 6.36 (s, 1H), 7.41-7.47 (m, 2H), 7.51-7.56 (m, 1H), 7.99-8.03 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.89, 14.02, 22.34, 27.26, 31.72, 32.46, 46.83, 61.13, 126.71, 128.50 (2C), 132.88, 136.63, 139.29, 166.49, 199.97.

Compound **5d**: 68%; colorless oil; IR (film) 2954, 2931, 1716, 1633, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, J = 7.2 Hz, 3H), 1.14-1.28 (m, 4H), 1.49-1.60 (m, 2H), 2.39-2.63 (m, 2H), 3.76 (s, 3H), 4.98 (s, 1H), 5.24 (s, 1H), 6.38 (s, 1H), 7.16-7.20 (m, 2H), 7.27-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.79, 22.28, 23.38, 31.07, 42.27, 52.04, 59.73, 127.71, 128.00, 128.94, 129.58, 135.05, 139.61, 167.10, 207.85.

Typical procedure for the synthesis of compounds 9a and 10a. A mixture of g-keto ester **5a** (147 mg, 0.5 mmol) and benzylamine (**6a**, 81 mg, 0.75 mmol) in AcOH (30 mg, 0.5 mmol) and toluene (0.5 mL) was heated to 80-90 °C for 5 h. After removal of solvent under reduced pressure and column chromatographic purification (hexanes/EtOAc, 4:1) process, desired pyrrole **9a** (96 mg, 50%) and amide compound **10a** (11 mg, 5%) was obtained. The other entries were carried out similarly and the spectroscopic data of **9a-g** and **10a-c** are as follows.

Compound **9a**: 50%; yellow solid, mp 116-117 °C; IR (film) 2979, 1713, 1520, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, J = 7.2 Hz, 3H), 4.15 (q, J = 7.2 Hz, 2H), 5.00 (s, 2H), 6.99-7.29 (m, 15H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.16, 51.19, 59.40, 114.15, 124.50, 125.95, 126.91, 127.05, 127.38, 127.70, 127.73, 128.11, 128.70, 130.87, 131.14, 131.18, 133.33, 134.63, 137.17, 164.61; ESIMS m/z 382 (M^++1). Anal. Calcd for $C_{26}H_{23}NO_2$: C, 86.86; H, 6.08; N, 3.67. Found: C, 86.99; H, 6.43; N, 3.31.

Compound **10a**: 5%; yellow gum; IR (film) 3419, 3062, 1647, 1534 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.38 (d, J = 5.7 Hz, 2H), 5.00 (s, 2H), 5.67 (t, J = 5.7 Hz, 1H), 7.00-7.35 (m, 20H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.28, 51.27, 118.12, 121.31, 126.16, 126.98, 127.02, 127.11, 127.43, 127.70, 127.72, 128.09, 128.36 (2C), 128.70, 130.98, 131.00, 131.12, 132.91, 134.58, 137.20, 138.30, 164.62; ESIMS m/z 443 (M^++1).

Compound **9b**: 46%; yellow solid, mp 78-80 °C; IR (film) 2979, 1713, 1521, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, J = 7.2 Hz, 3H), 2.86 (t, J = 7.8 Hz, 2H), 4.01 (t, J = 7.8 Hz, 2H), 4.16 (q, J = 7.2 Hz, 2H), 6.89-6.92 (m, 2H), 6.99-7.05 (m, 2H), 7.10-7.27 (m, 1H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.19, 37.72, 49.14, 59.34, 113.70, 124.43, 125.90, 126.73, 127.03, 127.70, 128.17 (2C), 128.57, 128.58, 130.85, 131.05, 131.35, 132.88, 134.69, 137.54, 164.64; LCMS m/z 396 (M^++1).

Compound **10b**: 9%; yellow solid; IR (film) 3421, 2927, 1643, 1535 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.62 (t, J = 7.2 Hz, 2H), 2.88 (t, J = 7.8 Hz, 2H), 3.43-3.50 (m, 2H), 4.01 (t, J = 7.8 Hz, 2H), 5.40 (t, J = 5.7 Hz, 1H), 6.89-6.99 (m, 6H), 7.06-7.25 (m, 14H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 35.31, 37.80, 40.38, 49.02, 117.85, 120.97, 125.20, 126.13, 126.69, 126.92, 127.61, 128.08, 128.24, 128.41, 128.54, 128.55, 128.61, 130.84, 130.87, 131.22, 132.54, 134.58, 137.66, 139.03, 164.77; LCMS m/z 471 (M^++1).

Compound **9c**: 47%; yellow solid, mp 97-99 °C; IR (film) 2980, 1714, 1519, 1214 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, J = 7.2 Hz, 3H), 1.79 (d, J = 7.2 Hz, 3H), 4.16 (q, J = 7.2 Hz, 2H), 5.26 (q, J = 7.2 Hz, 1H), 7.00-7.29 (m, 15H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.18, 22.20, 55.37, 59.43, 114.05, 124.12, 124.31, 125.86, 125.90, 126.99, 127.49, 127.78, 128.05, 128.63, 130.86, 131.38, 131.42, 133.47, 134.69, 142.27, 164.83.

Compound **10c**: 2%; yellow solid; IR (film) 3413, 3061, 1683, 1532 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (d, J = 6.6 Hz, 3H), 1.77 (d, J = 6.9 Hz, 3H), 5.04-5.16 (m, 1H), 5.23 (q, J = 6.9 Hz, 1H), 5.64 (d, J = 8.4 Hz, 1H), 6.95-7.28 (m, 20H), 7.63 (s, 1H).

Compound **9d**: 45%; white solid, mp 127-129 °C; IR (film) 3029, 1716, 1520, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.68 (s, 3H), 5.01 (s, 2H), 7.00-7.34 (m, 15H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.74, 51.23, 113.64, 124.56, 126.03, 126.98, 127.14, 127.46, 127.75, 127.79, 128.15, 128.74, 130.81, 131.14, 131.17, 133.44, 134.47, 137.09, 164.94.

Compound **9e**: 40%; yellow solid, mp 106-107 °C; IR (film) 2946, 1716, 1223, 1122 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.86 (t, J = 7.8 Hz, 2H), 3.69 (s, 3H), 4.03 (t, J = 7.8 Hz, 2H), 6.89-6.92 (m, 2H), 7.00-7.03 (m, 2H), 7.13-7.27

(m, 11H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.71, 49.17, 50.74, 113.21, 124.49, 125.98, 126.76, 126.82, 127.11, 127.75, 128.20, 128.59 (2C), 130.80, 131.07, 131.31, 132.99, 134.54, 137.51, 165.00.

Compound **9f**: 45%; yellow oil; IR (film) 2954, 2929, 1705, 1237 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 6.6 Hz, 3H), 1.17-1.28 (m, 4H), 1.33 (t, J = 7.2 Hz, 3H), 1.45-1.55 (m, 2H), 2.54-2.59 (m. 2H), 4.27 (q, J = 7.2 Hz, 2H), 4.89 (s, 2H), 6.89-6.92 (m, 2H), 7.14-7.38 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.02, 14.47, 22.39, 25.28, 31.41, 31.87, 51.08, 59.25, 113.75, 124.45, 126.82, 127.05, 127.52, 127.88, 128.24, 128.58, 130.99, 131.65, 132.79, 137.48, 165.17; LCMS *m/z* 376 (M^++1).

Compound **9g**: 40%; yellow oil; IR (film) 2957, 2929, 1713, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, J = 6.6 Hz, 3H), 1.08-1.15 (m, 4H), 1.26-1.39 (m, 2H), 2.38-2.43 (m, 2H), 3.63 (s, 3H), 5.08 (s, 2H), 7.08-7.11 (m, 2H), 7.24-7.38 (m, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.82, 22.07, 24.13, 29.96, 31.36, 50.60, 51.02, 113.15, 123.85, 126.25, 126.68, 126.74, 127.46, 127.85, 128.89, 130.40, 132.74, 135.59, 137.02, 165.06.

Synthesis of compounds 17 and 18. Syntheses of compounds **17a-c** and **18a-c** were carried out similarly for the synthesis of compound **9**, and the spectroscopic data of **17a-c** and **18a-c** are as follows.

Compound **17a**: 58% (entry 4 in Table 2); yellow solid, mp 138-140 °C; IR (film) 2926, 1716, 1521, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, J = 7.2 Hz, 3H), 3.51 (s, 3H), 3.79 (s, 3H), 4.17 (q, J = 7.2 Hz, 2H), 6.37-6.43 (m, 2H), 6.85-6.88 (m, 2H), 6.98-7.28 (m, 9H), 7.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.24, 55.39, 55.47, 59.37, 99.31, 104.07, 114.44, 121.74, 123.75, 126.05, 126.60, 127.16, 127.36, 129.10, 129.32, 130.28, 131.17, 131.70, 133.84, 134.92, 155.23, 160.51, 164.69; ESIMS *m/z* 428 (M^++1). Anal. Calcd for $C_{27}H_{25}NO_4$: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.92; H, 5.78; N, 3.03.

Compound **18a**: 52% (entry 1 in Table 2); yellow solid, mp 150-152 °C; IR (film) 3392, 2937, 1705, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.2 Hz, 3H), 3.48 (s, 3H), 3.68 (s, 3H), 3.69 (s, 3H), 3.74 (s, 3H), 4.02 (q, J = 7.2 Hz, 2H), 6.15-6.24 (m, 3H), 6.28 (d, J = 2.7 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 6.84-6.99 (m, 7H), 7.11-7.21 (m, 3H), 7.24-7.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.80, 55.07, 55.31, 55.51, 55.57, 59.09, 98.56, 98.68, 102.11, 103.38, 103.90, 117.94, 119.08, 122.04, 125.72, 126.23, 126.92, 127.11, 127.37, 128.88, 130.24, 130.68, 131.29, 131.96, 135.75, 140.99, 150.19, 154.62, 155.65, 160.37, 165.56; ESIMS *m/z* 579 (M^++1). Anal. Calcd for $C_{35}H_{34}N_2O_6$: C, 72.65; H, 5.92; N, 4.84. Found: C, 72.28; H, 5.68; N, 4.97.

Compound **17b**: 50%; yellow solid, mp 147-149 °C; IR (film) 2980, 1716, 1516, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18 (t, J = 7.0 Hz, 3H), 3.78 (s, 3H), 4.18 (q, J = 7.0 Hz, 2H), 6.80 (d, J = 9.0 Hz, 2H), 6.87-6.89 (m, 2H), 7.04-7.09 (m, 5H), 7.18-7.25 (m, 5H), 7.60 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.20, 55.40, 59.49, 114.08, 114.82, 124.94, 126.22, 126.87, 127.02, 127.21, 127.70, 128.48, 130.93, 131.07 (2C), 132.49, 132.61, 134.72, 158.61, 164.56.

Compound **18b**: 14%; yellow solid, mp 113-115 °C; IR (film) 3319, 2951, 1709, 1512 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, J = 7.0 Hz, 3H), 3.67 (s, 3H), 3.69 (s, 3H), 4.06 (q, J = 7.0 Hz, 2H), 6.56 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 6.68 (d, J = 9.0 Hz, 2H), 6.85-6.87 (m, 2H), 6.90 (d, J = 9.0 Hz, 2H), 6.97-7.01 (m, 3H), 7.16-7.26 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.86, 55.24, 55.48, 59.27, 101.56, 113.45, 113.88, 121.21, 122.21, 125.91, 126.51, 126.98, 127.41, 128.30, 129.41, 129.81, 131.22, 131.35, 131.36, 135.55, 137.42, 142.61, 154.92, 158.40, 166.17.

Compound **17c**: 37%; white solid, mp 139-141 °C; IR (film) 3128, 1693, 1520, 1227 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.19 (t, J = 7.0 Hz, 3H), 4.18 (q, J = 7.0 Hz, 2H), 6.87-6.89 (m, 2H), 7.04-7.13 (m, 5H), 7.19-7.32 (m, 8H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.21, 59.55, 115.25, 125.30, 125.84, 126.30, 126.97, 127.24, 127.33, 127.74, 128.36, 128.98, 129.08, 130.91, 131.00, 131.08, 134.62, 139.45, 164.51; LCMS *m/z* 368 (M^++1).

Compound **18c**: 11%; yellow oil; IR (film) 3333, 3060, 1705, 1498 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.96 (t, J = 7.0 Hz, 3H), 4.04 (q, J = 7.0 Hz, 2H), 6.68-7.28 (m, 21H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.80, 59.43, 103.90, 117.62, 120.90, 122.90, 126.07, 126.71, 127.06, 127.39, 127.47, 128.16, 128.33, 128.47, 128.56, 131.20, 131.23, 131.34, 135.28, 136.88, 139.55, 144.48, 165.70.

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References and Notes

1. For the synthesis and biological activities of pyrrole derivatives, see: (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264-287. (b) Gupton, J. T. *Top. Heterocycl. Chem.* **2006**, *2*, 53-92. (c) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213-7256. (d) Knight, D. W.; Sharland, C. M. *Synlett* **2004**, 119-121. (e) Knight, D. W.; Sharland, C. M. *Synlett* **2003**, 2258-2260. (f) Magnus, N. A.; Staszak, M. A.; Udodong, U. E.; Wepsiec, J. P. *Org. Proc. Res. Dev.* **2006**, *10*, 899-904. (g) Cohnen, E.; Dewald, R. *Synthesis* **1987**, 566-568. (h) Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1246-1251 and further references cited therein. (i) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090-2095.
2. For the synthesis and biological activities of pyrrole-containing compounds, see: (a) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379-9382. (b) Su, S.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744-7745. (c) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468-469. (d) Pandey, P. S.; Rao, T. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 129-131.
3. For the general review on Baylis-Hillman chemistry, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811-891. (b) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627-645. (c) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481-1490. (d) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511-4574 and further references cited therein.
4. For the synthesis of pyrroles from Baylis-Hillman adducts, see: (a) Declerck, V.; Ribiere, P.; Martinez, J.; Lamaty, F. *J. Org.*

Chem. **2004**, *69*, 8372-8381. (b) Shi, M.; Xu, Y.-M. *Eur. J. Org. Chem.* **2002**, 696-701. (c) Roy, A. K.; Pathak, R.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Synthesis* **2006**, 1021-1027. (d) Singh, V.; Kanojiya, S.; Batra, S. *Tetrahedron* **2006**, *62*, 10100-10110.

5. (a) Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2007**, *48*, 4119-4122. (b) Kim, S. J.; Kim, H. S.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 1605-1608.
6. For some leading references on the Barbier reaction, see: (a) Kabalka, G. W.; Venkataiah, B.; Chen, C. *Tetrahedron Lett.* **2006**, *47*, 4187-4189. (b) Lee, A. S.-Y.; Chang, Y.-T.; Wang, S.-H.; Chu, S.-F. *Tetrahedron Lett.* **2002**, *43*, 8489-8492. (c) Lee, K. Y.; Park, D. Y.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 1489-1492. (d) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333-5338. (e) Paquette, L. A.; Mendez-Andino, J. *Tetrahedron Lett.* **1999**, *40*, 4301-4304.
7. Although compound **8** was unstable, but we isolated this compound by rapid column chromatographic purification process and confirmed the structure as follows: 35%; yellow oil; IR (film) 3029, 1731, 1496, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (t, J = 7.2 Hz, 3H), 3.48 (t, J = 10.8 Hz, 1H), 3.60 (dd, J = 10.8 Hz and 6.0 Hz, 1H), 3.84 (d, J = 14.7 Hz, 1H), 4.01 (d, J = 14.7 Hz, 1H), 3.99-4.19 (m, 3H), 6.92-6.99 (m, 3H), 7.03-7.08 (m, 2H), 7.21-7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.02, 50.48, 54.76 (2C), 60.61, 110.44, 124.60, 126.99, 127.20, 127.71, 127.76, 128.38, 128.41, 128.71, 129.57, 133.36, 136.12, 138.77, 150.19, 174.39.
8. Aerobic oxidation of dihydropyrroles to pyrrole, see: Shim, Y. K.; Youn, J. I.; Chun, J. S.; Park, T. H.; Kim, M. H.; Kim, W. J. *Synthesis* **1990**, 753-754.
9. For the Michael addition of enamine intermediate, see: Panunzio, M.; Lentini, M. A.; Campana, E.; Martelli, G.; Tamanini, E.; Vicennati, P. *Synth. Commun.* **2004**, *34*, 345-359.
10. Some examples on the synthesis of pyrrole derivatives involving enamine intermediate, see: (a) Demir, A. S.; Aybey, A.; Kayalar, M. *ARKIVOC* **2005** (xv) 105-116. (b) Demir, A. S.; Emrullahoglu, M. *Tetrahedron* **2005**, *61*, 10482-10489. (c) Prior, A. M.; Robinson, R. S. *Tetrahedron Lett.* **2008**, *49*, 411-414.
11. (a) Witkop, B. *J. Am. Chem. Soc.* **1956**, *78*, 2873-2882. (b) Malhotra, S. K.; Hostynek, J. J.; Lundin, A. F. *J. Am. Chem. Soc.* **1968**, *90*, 6565-6566.