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Facile Synthesis of 5-Hydroxy-3-pyrrolin-2-ones from Morita-Baylis-Hillman Adducts

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An efficient synthetic method of various 5-hydroxy-3-pyrrolin-2-one derivatives has been developed starting from the MBH adducts. In addition, some synthetic applicability of the prepared 5-hydroxy-3-pyrrolin-2-ones was demonstrated including the synthesis of lactam-fused tetrahydroisoquinolines.

Key Words : 5-Hydroxy-3-pyrrolin-2-ones, Morita-Baylis-Hillman adducts, Hemiaminals

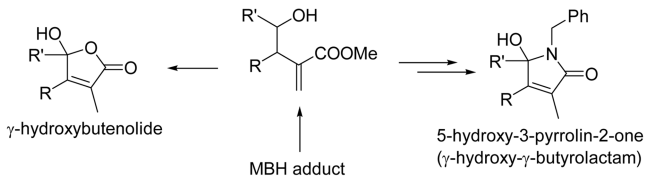
Introduction

Recently, we have reported the synthesis of γ-hydroxybutenolides from homoallylic alcohols which were prepared from the Morita-Baylis-Hillman (MBH) adducts.[1,2] As a continuous work we envisioned that 5-hydroxy-3-pyrrolin-2-ones (γ-hydroxy-γ-butyrolactams)[3-5] could also be prepared using the same homoallylic alcohol, as shown in Scheme 1. The 5-hydroxy-3-pyrrolin-2-one moiety was found in many biologically active compounds including oteromycin,[3d] UCS1025A,[3b] PI-091,[3e] and quinolactacin C.[3e] Thus, numerous approaches have been reported for the synthesis of 5-hydroxy-3-pyrrolin-2-ones,[3-5] and these compounds have also been used as useful synthetic intermediates in organic synthesis.[4d,f-h]

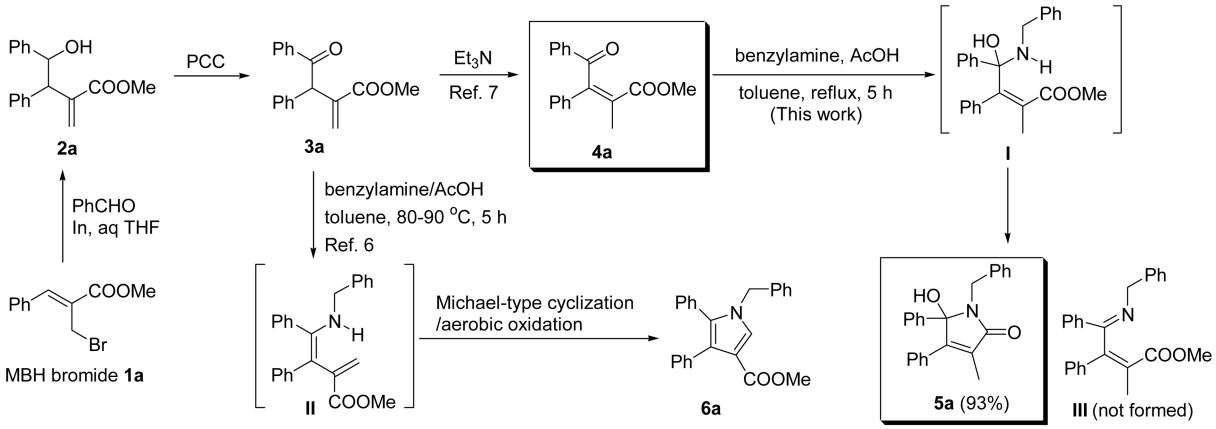
Results and Discussion

Previously, we have reported the synthesis of poly-substituted pyrrole **6a** by the reaction of benzylamine and α-methylene-γ-ketoester **3a**, prepared from MBH bromide **1a** *via* an indium-mediated Barbier reaction with benzaldehyde and a subsequent oxidation of the alcohol moiety with pyridinium chlorochromate (PCC).[6] Pyrrole **6a** was formed *via* the Michael-type cyclization of enamine intermediate **II** and a following aerobic oxidation, as shown in Scheme 2.[6] We thought that the formation of an enamine intermediate **II** might be an obstacle for the synthesis of 5-hydroxy-3-pyrrolin-2-one derivative **5a**. Thus, we examined the reaction of benzylamine and **4a**, prepared by double bond isomerization of **3a** with Et_3N.[7] We expected that a tetrahedral hemiaminal intermediate **I** could be cyclized to **5a** under mild acidic conditions instead of dehydration to the corresponding imine **III** or enamine **II**. To our delight, the reaction of **4a** and benzylamine in toluene in the presence of AcOH afforded **5a** in high yield (93%).

Encouraged by the successful synthesis of 5-hydroxy-3-pyrrolin-2-one **5a**, we examined the synthesis of various 5-hydroxy-3-pyrrolin-2-ones from three representative γ-keto-esters **4a-c**. The whole results are summarized in Table 1.

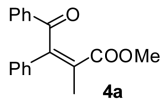
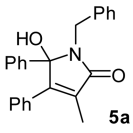
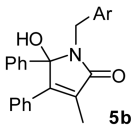
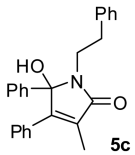
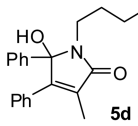
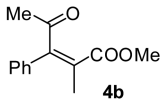
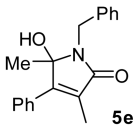
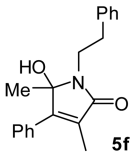
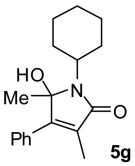
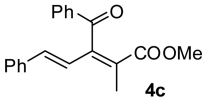
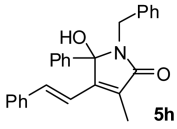


Scheme 1



Scheme 2

Table 1. Synthesis of 5-hydroxy-3-pyrrolin-2-one derivatives

Entry	Substrate	Conditions	Product (%)
1	 **4a**	benzylamine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 5 h	 **5a** (93)
2	**4a**	*p*-methoxybenzylamine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 5 h	 **5b** (84)[a]
3	**4a**	phenethylamine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 5 h	 **5c** (91)
4	**4a**	3-phenyl-1-propylamine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 5 h	 **5d** (90)
5	 **4b**	benzylamine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 3 h	 **5e** (87)
6	**4b**	phenethylmine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 3 h	 **5f** (70)[b]
7	**4b**	cyclohexylamine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 5 h	 **5g** (77)
8	 **4c**	benzylamine (2.0 equiv) AcOH (1.0 equiv) toluene, reflux, 5 h	 **5h** (79)

[a]Ar is *p*-methoxyphenyl. [b]Dehydration product **11** (see Scheme 4) was isolated in low yield (11%).

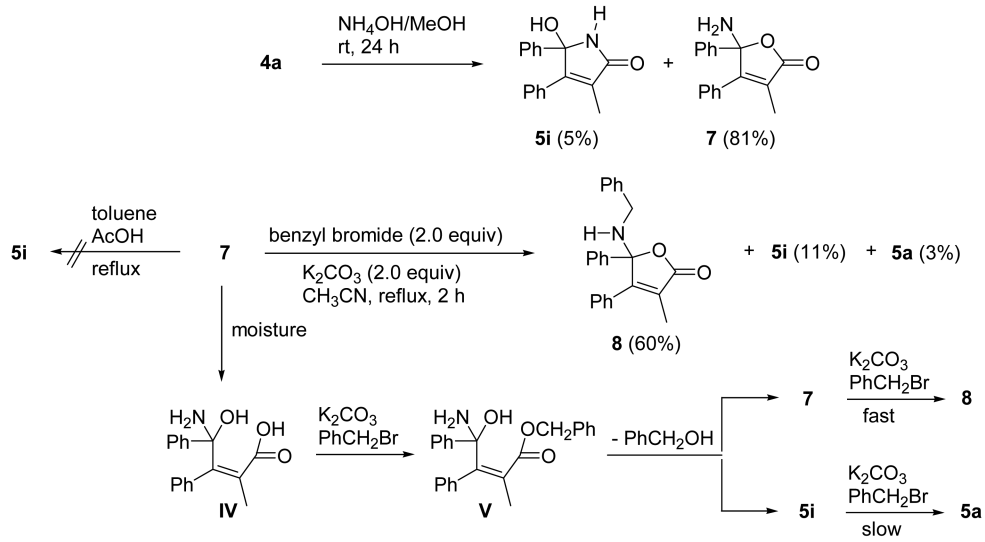
The key starting materials **4a-c** were prepared according to our previous papers[1,6,7] *via* a three-step procedure, namely (i) an indium-mediated Barbier reaction of the corresponding MBH bromide and an aldehyde to prepare a homoallylic alcohol **2**, PCC oxidation to α-methylene-γ-ketoester **3**, and a subsequent Et_3N-mediated isomerization of double bond to form **4**. The reactions of **4a-c** with various amine derivatives were examined including benzylamine, *p*-methoxybenzylamine, phenethylamine, 3-phenyl-1-propylamine, and cyclohexylamine.

As shown in Table 1, the reactions of **4a** and *p*-methoxybenzylamine (entry 2), phenethylamine (entry 3), and 3-phenyl-1-propylamine (entry 4) provided the corresponding 5-hydroxy-3-pyrrolin-2-ones **5b-d** in good yields (84-91%). However, the reaction of **4a** and cyclohexylamine did not afford the expected product in any trace amount, presumably due to the steric crowdedness during the formation of a hemiaminal intermediate (vide infra). The reactions of **4b** and benzylamine (entry 5) and phenethylamine (entry 6) gave **5e** and **5f** in good yields (70-87%). It is interesting to note that the reaction of **4b** and cyclohexylamine produced **5g** in good yield (77%), as shown in entry 7. The result stated that a steric hindrance could be a major reason for the failure in the reaction of **4a** and cyclohexylamine, as noted above. The reaction of a cinnamyl derivative **4c** and benzylamine (entry 8) also produced **5h** in good yield (79%). However, the reaction of **4c** and cyclohexylamine failed due to the same steric reason as in the case of **4a** (vide supra). Unfortunately, the reactions with aniline and **4a** or **4b** failed completely.

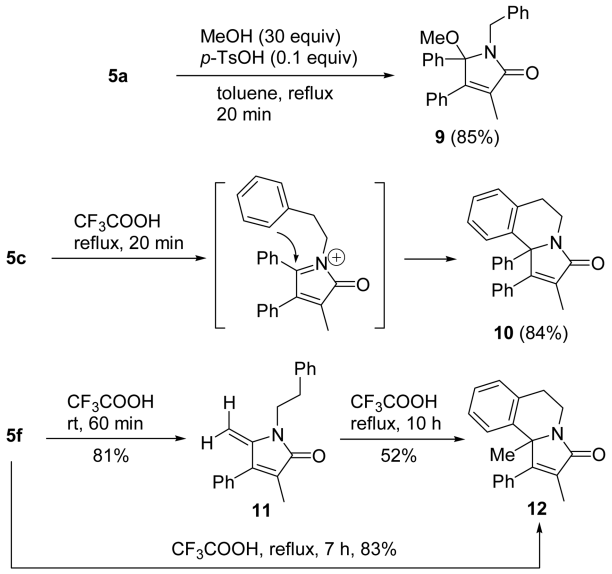
The preparation of *N*-unsubstituted lactam was examined using NH_4OAc under the same conditions (toluene, AcOH, reflux); however, we could not obtain the product **5i** in any trace amount. When we used NH_4OH in MeOH at room temperature, 5-aminolactone **7**[8] was obtained in good yield (81%) instead of the expected 5-hydroxylactam **5i**, as shown in Scheme 3. Compound **5i** was formed in only trace amount (5%). The reason for the selective formation of 5-aminolactone **7** is not clear at this stage. The benzylation of **7** was carried out in the presence of K_2CO_3 in acetonitrile, and we obtained the corresponding *N*-benzyl derivative **8** in moderate yield (60%) along with appreciable amounts of 5-hydroxylactam **5i** (11%) and a trace amount of its benzyl derivative **5a** (3%). The formations of **5i** and **5a** could be explained as follows: (i) ring-opening of **7** to a hemiaminal intermediate **IV** by a trace amount of moisture in the reaction mixture, *in-situ* formation of the corresponding benzyl ester **V**, a subsequent ring-closure to lactam **5i**, and the final *N*-benzylation to **5a**.[5c] In a separate experiment, we observed that the benzylation of **5i** to **5a** required a long time.

In order to show the synthetic applicability of prepared compounds, we examined the syntheses of 5-alkoxy-3-pyrrolin-2-one derivative **9**[9] and lactam-fused isoquinoline derivatives **10** and **12**.[10] As shown in Scheme 4, the reaction of **5a** and MeOH in the presence of a catalytic amount of *p*-TsOH in refluxing toluene afforded compound **9** in good yield (85%). The cyclization reaction of **5c** was carried out in CF_3COOH in short time, and a pyrrolo[2,1-*a*]isoquinolin-3-one derivative **10** was obtained in good yield (84%) *via* the well-known *N*-acyliminium ion cyclization mechanism.[10] Similarly, compound **12** was obtained in good yield (83%) from **5f** under the similar reaction conditions. However, the reaction of **5f** at room temperature produced a dehydration product **11** (vide supra, entry 6 in Table 1) in 81%. This compound **11** was cyclized to **12** at refluxing temperature in moderate yield (52%). The reaction of *N*-benzyl derivative **5a** under the same conditions did not produce the corresponding cyclized product.

In summary, we disclosed an efficient synthesis of various 5-hydroxy-3-pyrrolin-2-one derivatives starting from the MBH adducts. In addition, some synthetic applicability of



Scheme 3



Scheme 4

the prepared 5-hydroxy-3-pyrrolin-2-ones was demonstrated including the synthesis of lactam-fused tetrahydroisoquinolines.

Experimental Section

The starting materials **4a-c** were prepared as reported previously.[7]

Typical Procedure for the Synthesis of 5a. A stirred mixture of **4a** (140 mg, 0.5 mmol), benzyl amine (107 mg, 1.0 mmol), acetic acid (30 mg, 0.5 mmol) in toluene (2.0 mL) was heated to reflux for 5 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 5:1:1), product **5a** was obtained as a pale yellow solid, 165 mg (93%). Other compounds were synthesized similarly, and the spectroscopic data of **5a-h** are as follows.

Compound 5a: 93%; pale yellow solid, mp 128-130 °C; IR (KBr) 3310, 1677, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3H), 2.81 (br s, 1H), 3.98 (d, J = 15.0 Hz, 1H), 4.68 (d, J = 15.0 Hz, 1H), 7.17-7.35 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.23, 43.03, 93.08, 126.28, 127.03, 128.15, 128.24, 128.29, 128.41, 128.59, 128.63, 128.66, 129.49, 131.76, 137.09, 138.18, 153.29, 171.00; ESIMS *m/z* 378 (M^++Na). Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 80.94; H, 6.17; N, 3.89.

Compound 5b: 84%; white solid, mp 136-137 °C; IR (KBr) 3421, 1668, 1435 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.05 (s, 3H), 3.03 (br s, 1H), 3.72 (s, 3H), 3.92 (d, J = 15.0 Hz, 1H), 4.61 (d, J = 15.0 Hz, 1H), 6.70 (d, J = 8.7 Hz, 2H), 7.14 (d, J = 8.7 Hz, 2H) 7.22-7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.21, 42.45, 55.21, 93.09, 113.60, 126.30, 128.14, 128.27, 128.42, 128.55, 128.65, 129.55, 130.17, 130.41, 131.83, 137.28, 153.16, 158.54, 170.86; ESIMS *m/z* 408 (M^++Na). Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.98; H, 6.32; N, 3.54.

Compound 5c: 91%; pale yellow solid, mp 158-160 °C; IR (KBr) 3213, 1668, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.06 (s, 3H), 2.43-2.52 (m, 1H), 2.88-2.98 (m, 1H), 3.03 (br s, 1H), 3.11-3.21 (m, 1H), 3.52-3.61 (m, 1H), 7.04-7.08 (m, 2H), 7.13-7.33 (m, 11H), 7.36-7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.21, 34.60, 41.35, 92.54, 126.11, 126.28, 128.19, 128.39, 128.42, 128.51, 128.60, 128.67, 128.77, 129.64, 131.81, 137.42, 139.37, 152.96, 171.05; ESIMS *m/z* 392 (M^++Na). Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.03; H, 6.51; N, 3.73.

Compound 5d: 90%; white solid, mp 142-144 °C; IR (KBr) 3314, 1677, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55-1.65 (m, 1H), 1.72-1.82 (m, 1H), 2.03 (s, 3H), 2.49 (t, J = 7.8 Hz, 2H), 2.97-3.06 (m, 1H), 3.23 (br s, 1H), 3.35-3.45 (m, 1H), 7.03-7.05 (m, 2H), 7.09-7.32 (m, 11H), 7.36-7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.22, 29.93, 33.38, 39.23, 92.69, 125.66, 126.11, 128.19 (2C), 128.23, 128.30, 128.45, 128.57, 128.66, 129.68, 131.83, 137.44,

141.64, 152.85, 171.13; ESIMS *m/z* 406 (M^++Na). Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.22; H, 6.54; N, 3.48.

Compound 5e: 87%; pale yellow solid, mp 158-159 °C; IR (KBr) 3211, 1667, 1449 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (s, 3H), 1.90 (s, 3H), 3.62 (br s, 1H), 4.48 (d, *J* = 15.3 Hz, 1H), 4.84 (d, *J* = 15.3 Hz, 1H), 7.23-7.43 (m, 8H), 7.60 (d, *J* = 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.91, 23.49, 41.88, 90.72, 127.17, 127.86, 128.44, 128.49 (2C), 128.57, 128.75, 132.19, 138.65, 153.29, 170.82; ESIMS *m/z* 316 (M^++Na). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.98; H, 6.81; N, 4.49.

Compound 5f: 70%; white solid, mp 134-135 °C; IR (KBr) 3209, 1666, 1449 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.92 (s, 3H), 2.46 (br s, 1H), 2.87-2.97 (m, 1H), 3.09-3.19 (m, 1H), 3.47-3.58 (m, 1H), 3.64-3.74 (m, 1H), 7.21-7.32 (m, 5H), 7.37-7.44 (m, 3H), 7.54-7.57 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.80, 22.65, 35.00, 40.70, 90.28, 126.43, 128.45, 128.55 (2C), 128.71, 128.90, 129.07, 132.32, 139.38, 152.45, 170.37; ESIMS *m/z* 330 (M^++Na). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.43; H, 6.92; N, 4.53.

Compound 5g: 77%; white solid, mp 120-121 °C; IR (KBr) 3407, 1665, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21-1.35 (m, 2H), 1.44 (s, 3H), 1.66-1.70 (m, 4H), 1.82-1.85 (m, 2H), 1.91 (s, 3H), 2.21-2.41 (m, 2H), 2.43 (br s, 1H), 3.39 (tt, *J* = 12.0 and 4.2 Hz, 1H), 7.37-7.45 (m, 3H), 7.55-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.67, 22.63, 25.21, 26.42 (2C), 30.36, 30.77, 52.01, 90.92, 128.43, 128.54, 128.57, 130.34, 132.59, 150.95, 169.36; ESIMS *m/z* 308 (M^++Na). Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.92; H, 7.94; N, 4.67.

Compound 5h: 79%; white solid, mp 166-168 °C; IR (KBr) 3396, 1668, 1438, 1405 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.13 (s, 3H), 2.70 (br s, 1H), 3.94 (d, *J* = 15.0 Hz, 1H), 4.63 (d, *J* = 15.0 Hz, 1H), 6.75 (d, *J* = 16.5 Hz, 1H), 6.84 (d, *J* = 16.5 Hz, 1H), 7.18-7.41 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.13, 42.68, 91.81, 116.89, 125.85, 126.82, 126.97, 128.21, 128.38, 128.52 (2C), 128.61, 128.65, 129.65, 136.31, 136.46, 137.96, 138.44, 150.24, 170.49; ESIMS *m/z* 404 (M^++Na). Anal. Calcd for $C_{26}H_{23}NO_2$: C, 81.86; H, 6.08; N, 3.67. Found: C, 81.83; H, 6.36; N, 3.59.

Synthesis of 7. A solution of **4a** (140 mg, 0.5 mmol) and ammonia (28% aqueous solution, 560 mg, 9.2 mmol) in MeOH (2.0 mL) was stirred at room temperature for 24 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 5:1:1), compound **7** was obtained as a pale yellow solid (107 mg, 81%) along with **5i** (6 mg, 5%) as a white solid. The spectroscopic data of **7** and **5i**[11] are as follows.

Compound 7: 81%; pale yellow solid, mp 160-161 °C; IR (KBr) 3391, 3308, 1733, 1656, 1335 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.00 (s, 3H), 2.62 (br s, 2H), 7.26-7.34 (m, 8H), 7.40-7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.12, 98.99, 125.35, 126.11, 128.25, 128.39, 128.57, 128.81, 129.28, 131.25, 137.69, 160.12, 173.03; ESIMS *m/z* 288 (M^++Na). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.13; H, 5.86; N, 5.01.

Compound 5i:[11] 5%; white solid, mp 178-180 °C; IR (KBr) 3327, 3197, 1682, 1448 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ 1.97 (s, 3H), 5.74 (br s, 1H), 7.03 (br s, 1H), 7.21-7.29 (m, 8H), 7.43-7.47 (m, 2H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ 9.53, 89.29, 125.73, 127.86, 127.88, 128.06, 128.10, 128.29, 128.59, 132.08, 139.50, 155.48, 173.28; ESIMS *m/z* 288 (M^++Na).

Synthesis of 8. A solution of **7** (80 mg, 0.3 mmol), benzyl bromide (103 mg, 0.6 mmol), and K_2CO_3 (83 mg, 0.6 mmol) in CH_3CN (1.0 mL) was heated to reflux for 2 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 9:8:1), compound **8** was obtained as a white solid (64 mg, 60%) along with **5i** (9 mg, 11%) and **5a** (3 mg, 3%). The spectroscopic data of **8** are as follows.

Compound 8: 60%; white solid, mp 156-157 °C; IR (KBr) 3183, 1709, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.18 (s, 3H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 6.14 (br s, 1H), 7.25-7.33 (m, 13H), 7.51-7.54 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.24, 64.30, 92.96, 125.88, 127.48, 127.58, 128.37 (2C), 128.46, 128.48, 128.51, 128.95, 131.12, 131.74, 137.76, 138.89, 152.03, 172.86; ESIMS *m/z* 378 (M^++Na). Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.19; H, 6.25; N, 3.69.

Synthesis of 9. A solution of **5a** (107 mg, 0.3 mmol), MeOH (290 mg, 9.0 mmol), and *p*-TsOH (6 mg, 10 mol %) in toluene (1.0 mL) was heated to reflux for 20 min. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O/CH_2Cl_2, 4:1:1), compound **9** was obtained as a white solid (94 mg, 85%). The spectroscopic data of **9** are as follows.

Compound 9: 85%; white solid, mp 114-116 °C; IR (KBr) 1692, 1441, 1395, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.22 (s, 3H), 2.82 (s, 3H), 3.89 (d, *J* = 14.7 Hz, 1H), 4.53 (d, *J* = 14.7 Hz, 1H), 7.15-7.26 (m, 13H), 7.37-7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.57, 43.07, 49.76, 96.99, 126.41, 126.93, 127.92, 128.20, 128.25 (2C), 128.30, 128.59, 129.33, 131.83, 131.86, 137.48 (2C), 149.32, 171.24; ESIMS *m/z* 392 (M^++Na). Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.02; H, 6.59; N, 3.76.

Synthesis of 10. A solution of **5c** (112 mg, 0.3 mmol) in CF_3COOH (1.0 mL) was heated to reflux for 20 min. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/Et_2O/CH_2Cl_2, 5:1:1), compound **10** was obtained as a white solid (89 mg, 84%). Compounds **11** and **12** were synthesized from **5f** similarly, and the spectroscopic data of **10**-**12** are as follows.

Compound 10: 84%; white solid, mp 204-207 °C; IR (KBr) 1692, 1447, 1413 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.94 (s, 3H), 2.67-2.74 (m, 1H), 2.97-3.16 (m, 2H), 4.25-4.31 (m, 1H), 6.70-6.73 (m, 3H), 6.91-6.97 (m, 1H), 7.09-7.13 (m, 2H), 7.18-7.34 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.07, 29.10, 34.96, 71.73, 125.10, 127.36, 127.85, 128.14, 128.27, 128.30, 128.41, 128.49, 128.85, 129.75, 131.32, 134.63, 134.81, 135.05, 139.45, 156.09, 170.75;

ESIMS *m/z* 374 (M^++Na). Anal. Calcd for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.27; H, 6.33; N, 3.65.

Compound 11: 81%; white solid, mp 129-130 °C; IR (KBr) 1692, 1441, 1395, 1350 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.97 (s, 3H), 2.91-2.96 (m, 2H), 3.86-3.92 (m, 2H), 4.68 (d, *J* = 1.5 Hz, 1H), 4.83 (d, *J* = 1.5 Hz, 1H), 7.20-7.34 (m, 7H), 7.38-7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.38, 34.96, 41.09, 94.34, 126.49, 128.39, 128.41, 128.52, 128.81, 129.37, 129.65, 131.80, 138.69, 142.71, 145.32, 169.98; ESIMS *m/z* 312 (M^++Na). Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.29; H, 6.82; N, 4.85.

Compound 12: 83%; white solid, mp 118-120 °C; IR (KBr) 1678, 1442, 1377 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.68 (s, 3H), 1.77 (s, 3H), 2.72 (dd, *J* = 15.9 and 3.0 Hz, 1H), 3.06 (ddd, *J* = 15.9, 12.3 and 6.0 Hz, 1H), 3.24 (td, *J* = 12.3 and 3.6 Hz, 1H), 4.52-4.58 (m, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.88-6.93 (m, 1H), 7.09-7.14 (m, 4H), 7.42-7.46 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 9.44, 27.15, 30.37, 35.54, 66.29, 125.50, 126.64, 127.56, 128.19, 128.42, 129.08, 129.51, 130.78, 133.48, 134.56, 137.27, 157.94, 171.18; ESIMS *m/z* 312 (M^++Na). Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 83.37; H, 6.96; N, 4.78.

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