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Palladium-catalyzed synthesis of benzo[*c*]pyrimido[1,6-*a*]azepine scaffold from Morita–Baylis–Hillman adducts: intramolecular 6-arylation of uracil nucleus

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ABSTRACT

Palladium-catalyzed intramolecular arylation at the C-6 position of uracil moiety was examined. Morita–Baylis–Hillman adducts bearing an uracil moiety at the primary position served an efficient way to a benzo[*c*]pyrimido[1,6-*a*]azepine scaffold.

Recently various tetracyclic fused indole derivatives have been synthesized via a palladium-catalyzed cyclization of indole-containing Morita–Baylis–Hillman adducts in our group.[1] As a continuous study, we were interested in the synthesis of benzoazepine derivatives[2] fused with a uracil moiety, because these compounds have a potential hepatitis C virus (HCV) NS5B polymerase inhibitory activity.[3]

The arylation of uracil ring was carried out most frequently by palladium-catalyzed cross-coupling reactions of 5-halouracils with arylboronic acids[4] or arylstannanes.[5] Very recently, a palladium-catalyzed direct arylation of uracil derivatives with aryl halides has been reported.[6,7] We also reported a regioselective palladium-catalyzed direct arylation of uracil derivatives.[8]

In these respects, we decided to check the feasibility of the Pd-catalyzed intramolecular arylation to the 6-position of uracil moiety in order to synthesize benzoazepine derivatives as shown in Scheme 1. The reaction of Morita–Baylis–Hillman acetate **1a** and uracil (**2a**) in the presence of K_2CO_3 in DMF afforded the starting material **3a** in a good yield (80%). However, a palladium-catalyzed cyclization of **3a** failed completely under various reaction conditions.[9] Literature survey revealed that a Pd-catalyzed C-arylation of free (N–H)-containing heterocycles is a difficult task.[6,10] Thus we decided to protect the N^3-position of **3a** with a benzyl group to prepare **4a** (94%). To our delight, a Pd-catalyzed cyclization of **4a** provided **5a** in a good yield (78%) in a short time (30 min) in the presence of $Pd(OAc)_2$, TBAB (tetrabutylammonium bromide) and KOAc in DMF.[1,7a,11]

Encouraged by the successful results, we prepared starting materials **4b–f** by the selective N^1-alkylation of uracil derivatives **2a–d** with Morita–Baylis–Hillman acetates **1a–c** and a subsequent N^3-protection with benzyl bromide, as shown in Table 1. All entries showed good to moderate yields (73–89% for the first cinnamylation at N^1-position, 79–96% for the second benzylation at N^3-position). During the preparation of **3a–f**, the corresponding *Z*-isomers were formed in trace amounts; however, we separated *E*-isomers of **3a–f** and used for the next benzylation. As uracil derivatives, we used uracil (**2a**), thymine (**2b**), 5-fluorouracil (**2c**), and 5-ethyluracil (**2d**). With these starting materials **4b–f** we examined the palladium-catalyzed cyclization, and the results are summarized in Table 1. 5-Substituted uracil derivatives **4b–d** with methyl, fluoro, and ethyl groups afforded the corresponding benzo[*c*]pyrimido[1,6-*a*]azepine derivatives **5b–d** in moderate yields (62–83%). Naphthalene derivative **4e** and dimethoxyphenyl derivative **4f** also produced the corresponding products **5e** and **5f** in reasonable yields (59–78%).

The reaction mechanism could be proposed as shown in Scheme 2. An oxidative addition of C–Br bond of **4a** to Pd^0 produced an arylpalladium intermediate **I**. A subsequent 7-exo-carbopalladation of **I** to form **II**, and the following epimerization at C-5 position of the uracil moiety via a corresponding *O*-palladium intermediate **III** gave **IV**, which produced **5a** by a syn β-H elimination process.[12]

However, the Pd-catalyzed cyclization reaction with 5-nitrouracil derivative **4g** failed, as shown in Scheme 3. Expected compound **5g** was not formed in any trace amount. Instead, rearranged MBH acetate **6** was isolated in 62% along with many intractable side

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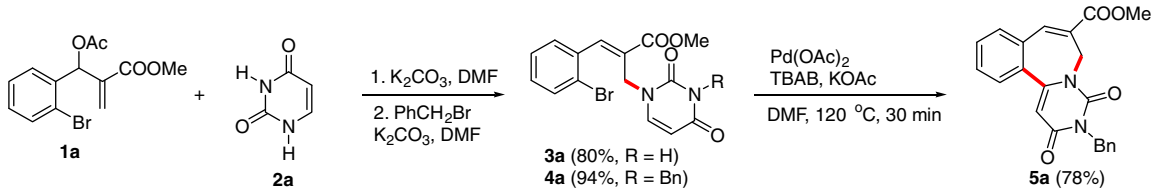
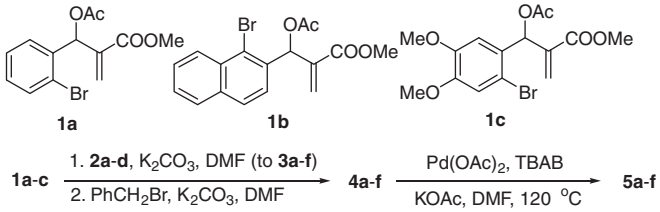
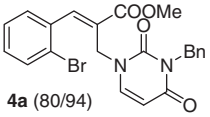
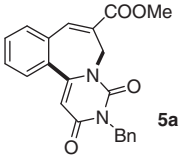
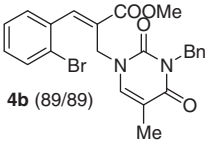
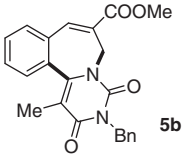
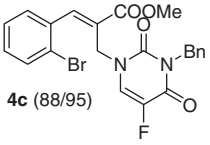
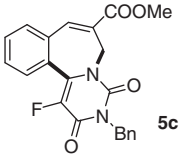
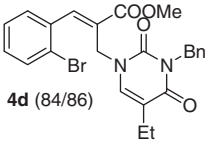
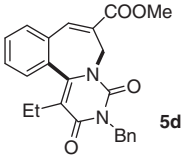
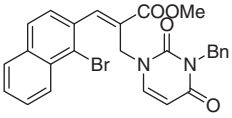
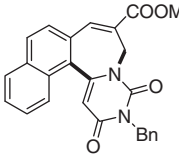
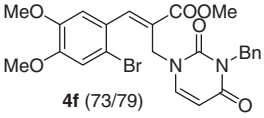
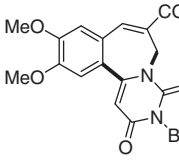


Scheme 1.

Table 1
Preparation of starting materials **4a–f** and Pd-catalyzed synthesis of **5a–f**

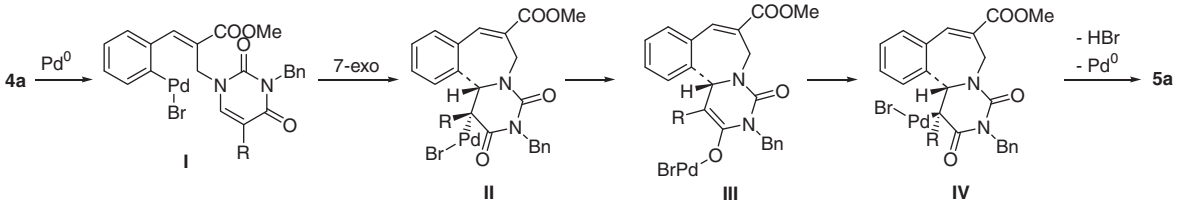


Entry	1+2	Substrate **4**[a] (%)	Product **5**[b] (%)
1	**1a+2a**	 **4a** (80/94)	 **5a** (78)
2	**1a+2b**	 **4b** (89/89)	 **5b** (83)
3	**1a+2c**	 **4c** (88/95)	 **5c** (62)
4	**1a+2d**	 **4d** (84/86)	 **5d** (79)
5	**1b+2a**	 **4e** (78/96)	 **5e** (78)
6	**1c+2a**	 **4f** (73/79)	 **5f** (59)

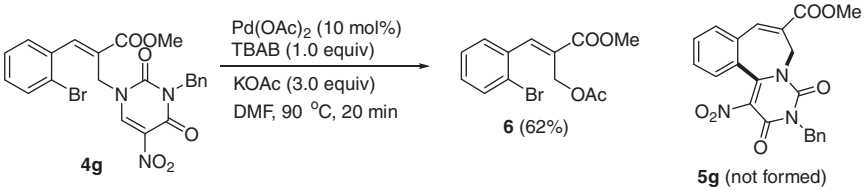
[a] Conditions: (i) **1** (1.0 mmol), **2** (1.5 equiv), K_2CO_3 (2.0 equiv), DMF, rt, 5 h (**3a–f**); (ii) **3** (0.8 mmol), $PhCH_2Br$ (1.5 equiv), K_2CO_3 (2.0 equiv), DMF, rt, 5 h (**4a–f**). Yields were noted in the parenthesis as follows (**3a–f**/**4a–f**).
[b] Conditions: **4** (0.5 mmol), $Pd(OAc)_2$ (10 mol %), TBAB (1.0 equiv), KOAc (3.0 equiv), DMF, 120 °C, 30 min (for **5a–e**) and 80 min (for **5f**).

products. Compound **6** could be formed via the nucleophilic displacement of 5-nitro-3-benzyluracil moiety with an acetate ion. Compound **5g** was not formed also when we use K_2CO_3 or Cs_2CO_3 instead of KOAc in order to suppress the formation of **6**.

Thus, we turned our attention to a functionalization at the 5-position of the uracil moiety of **5a**, in order to synthesize a variety of similar benzoazepine derivatives including a 5-nitro derivative **5g**. The results are summarized in Table 2. As shown in entry 1,

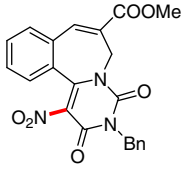
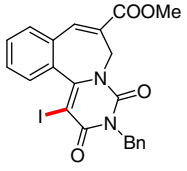
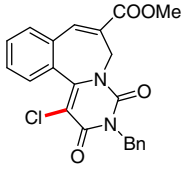
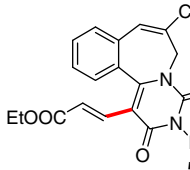
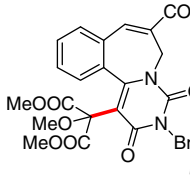


Scheme 2.



Scheme 3.

Table 2
Various functionalization at the 5-position of uracil moiety in **5a**

Entry	Conditions	Product **5** (%)
1	$Cu(NO_3)_2$ (2.0 equiv), Ac_2O, rt, 8 h	 **5g** (54)
2	I_2 (1.5 equiv), $Ce(NH_4)_2(NO_3)_6$ (1.0 equiv) CH_3CN, reflux, 10 h	 **5h** (80)
3	LiCl (1.2 equiv), $Ce(NH_4)_2(NO_3)_6$ (2.0 equiv) CH_3CN/AcOH, 80 °C, 1 h	 **5i** (70)
4	Ethyl acrylate (30 equiv), $Pd(TFA)_2$ (10 mol %) AgOAc (4.0 equiv), PivOH (6.0 equiv), 100 °C, 18 h	 **5j** (51)
5	Dimethyl malonate (6.0 equiv) $Ce(NH_4)_2(NO_3)_6$ (6.0 equiv) CH_3CN/MeOH (3:1), rt, 3 h	 **5k** (65)

nitration of **5a** under the influence of $Cu(NO_3)_2/Ac_2O$ afforded product **5g** in moderate yields (54%).[13] Iodination of **5a** with iodine in the presence of ammonium cerium nitrate (CAN) afforded **5h** (entry 2) in a good yield (80%).[14] Chlorination of **5a** was carried out to form **5i** (70%) by LiCl/CAN according to the reported method.[15] In addition, a palladium-catalyzed Fujiwara–Moritani reaction[16] of **5a** with ethyl acrylate afforded the corresponding compound **5j** in a reasonable yield (51%). As a last entry (entry 5), an introduction of a malonate moiety was performed according to the literature method to form **5k** in a moderate yield (65%).[17]

Although the yields were moderate in some entries (entries 1 and 4), we could prepare variously functionalized benzoazepine derivatives.

In summary, a palladium-catalyzed intramolecular arylation at the C-6 position of the uracil moiety was examined. Morita–Baylis–Hillman adducts bearing an uracil moiety at the primary position provided an efficient way to a novel benzo[*c*]pyrimido[1,6-*a*]azepine scaffold. In addition, various functionalizations of the synthesized benzoazepine derivative were successfully carried out. Further studies on the biological activities are underway and the results will be published in due course.

Acknowledgments

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8. Kim, K. H.; Lee, H. S.; Kim, J. N. *Tetrahedron Lett.* **2011**, *52*, 6228–6233. and further references cited therein.
9. The reactions of **3a** under the following conditions were all ineffective: (i) $Pd(OAc)_2$, TBAB, K_2CO_3, DMF, 120 °C;[1] (ii) $Pd(OAc)_2$, PPh_3, CuI, Cs_2CO_3, DMF, 150 °C;[6] (iii) $Pd(OAc)_2$, TBAB, KOAc, DMF, 120 °C;[7] (iv) $Pd(OAc)_2$, TBAC, PivOH, K_2CO_3, DMF, 130 °C;[8] (v) $Pd(OAc)_2$, PPh_3, PivOH, K_2CO_3, DMF, 130 °C.[8]
10. For the difficulty in the Pd-catalyzed C-arylation of free (N–H)-containing heterocycles including free (N–H)-indoles and pyrroles, see: Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476–1479. In addition, the failure of C-arylation of uracil derivatives was also noted in Ref. 6.
11. Typical procedure for the synthesis of **4a** and **5a**: A solution of MBH acetate (**1a**, 313 mg, 1.0 mmol), uracil (**2a**, 168 mg, 1.5 mmol), and K_2CO_3 (276 mg, 2.0 mmol) in DMF (2.0 mL) was stirred at room temperature for 5 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 1:2) compound **3a** was obtained as a white solid, 293 mg (80%). A solution of **3a** (292 mg, 0.8 mmol), benzyl bromide (205 mg, 1.2 mmol), and K_2CO_3 (221 mg, 1.6 mmol) in DMF (2.0 mL) was stirred at room temperature for 5 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 1:2) compound **4a** was obtained as colorless oil, 343 mg (94%). A mixture of compound **4a** (228 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 10 mol %), TBAB (161 mg, 0.5 mmol), and KOAc (147 mg, 1.5 mmol) in DMF (2.0 mL) was heated to 120 °C for 30 min. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 1:1) compound **5a** was obtained as a white solid, 146 mg (78%). Other compounds were synthesized similarly, and the selected spectroscopic data of **4a** and **5a**–**k** are as follows.
Compound **4a**: 94%; colorless oil; IR (film) 1710, 1663, 1449, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.77 (s, 3H), 4.68 (s, 2H), 5.02 (s, 2H), 5.60 (d, J = 8.1 Hz, 1H), 7.05 (d, J = 8.1 Hz, 1H), 7.15–7.30 (m, 6H), 7.42 (d, J = 8.1 Hz, 2H), 7.58 (d, J = 7.2 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 44.05, 45.00, 52.44, 101.24, 123.17, 127.32, 127.36, 127.82, 128.13, 128.96, 129.56, 130.39, 132.69, 134.54, 136.66, 141.68, 143.98, 151.05, 162.61, 166.24; ESIMS m/z 455 (M^++H), 457 (M^++H+2). Anal. Calcd. For $C_{22}H_{19}BrN_2O_4$: C, 58.04; H, 4.21; N, 6.15. Found: C, 58.33; H, 4.42; N, 6.08.
Compound **5a**: 78%; white solid, mp 118–120 °C; IR (KBr) 1718, 1658, 1460, 1433 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.45 (d, J = 13.5 Hz, 1H), 3.89 (s, 3H), 5.08 (d, J = 13.5 Hz, 1H), 5.24 (d, J = 13.5 Hz, 1H), 5.79 (s, 1H), 6.01 (d, J = 13.5 Hz, 1H), 7.23–7.34 (m, 3H), 7.45 (d, J = 7.5 Hz, 1H), 7.50–7.62 (m, 4H), 7.69 (d, J = 7.5 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.20, 44.62, 52.66, 102.64, 127.59, 128.30, 129.29, 129.74, 130.36, 130.77, 130.87, 132.26, 133.38, 134.39, 136.73, 142.00, 150.52, 152.20, 161.97, 165.22; ESIMS m/z 375 (M^++H). Anal. Calcd. For $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.37; H, 4.93; N, 7.37.
Compound **5b**: 83%; white solid, mp 100–102 °C; IR (KBr) 1718, 1697, 1643, 1459, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80 (s, 3H), 3.37 (d, J = 14.4 Hz, 1H), 3.88 (s, 3H), 5.13 (d, J = 13.5 Hz, 1H), 5.27 (d, J = 13.5 Hz, 1H), 6.02 (d, J = 14.4 Hz, 1H), 7.23–7.34 (m, 3H), 7.44–7.58 (m, 6H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.24, 40.18, 44.87, 52.55, 109.58, 127.50, 128.24, 128.66, 129.39, 129.66, 130.00, 131.89, 132.12, 132.80, 135.65, 136.90, 141.82, 146.69, 149.91, 163.34, 165.28; ESIMS m/z 389 (M^++H). Anal. Calcd. For $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.34; H, 5.02; N, 7.12.
Compound **5c**: 62%; white solid, mp 146–148 °C; IR (KBr) 1719, 1660, 1275, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.42 (d, J = 14.1 Hz, 1H), 3.89 (s, 3H), 5.10 (d, J = 13.5 Hz, 1H), 5.28 (d, J = 13.5 Hz, 1H), 6.02 (d, J = 14.1 Hz, 1H), 7.25–7.35 (m, 3H), 7.48–7.62 (m, 5H), 7.69–7.74 (m, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.20, 45.19, 52.66, 127.02 (d, J_{C-F} = 3.5 Hz), 127.88, 128.38, 129.48, 129.56, 130.71, 130.94, 131.91 (d, J_{C-F} = 7.5 Hz), 132.17, 135.17, 136.17 (d, J_{C-F} = 29.3 Hz), 136.10, 137.59 (d, J_{C-F} = 223.2 Hz), 141.92, 148.52, 156.86 (d, J_{C-F} = 26.3 Hz), 165.11; ESIMS m/z 393 (M^++H). Anal. Calcd. For $C_{22}H_{17}FN_2O_4$: C, 67.34; H, 4.37; N, 7.14. Found: C, 67.55; H, 4.39; N, 7.02.
Compound **5d**: 79%; white solid, mp 128–130 °C; IR (KBr) 1720, 1697, 1645, 1454, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J = 7.2 Hz, 3H), 2.03–2.39 (m, 2H), 3.35 (d, J = 14.1 Hz, 1H), 3.87 (s, 3H), 5.10 (d, J = 13.5 Hz, 1H), 5.29 (d, J = 13.5 Hz, 1H), 6.01 (d, J = 14.1 Hz, 1H), 7.23–7.34 (m, 3H), 7.44–7.58 (m, 6H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.75, 21.20, 40.22, 44.74, 52.55, 115.58, 127.47, 128.26, 128.72, 129.38, 129.55, 130.00, 130.82, 132.28, 133.00, 135.65, 136.99, 141.73, 146.83, 149.88, 162.79, 165.30; ESIMS m/z 403 (M^++H). Anal. Calcd. For $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.38; H, 5.82; N, 6.93.
Compound **5e**: 78%; white solid, mp 164–166 °C; IR (KBr) 1718, 1656, 1450, 1262 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.51 (d, J = 14.4 Hz, 1H), 3.91 (s, 3H), 5.12 (d, J = 13.8 Hz, 1H), 5.29 (d, J = 13.8 Hz, 1H), 5.81 (s, 1H), 6.05 (d, J = 14.4 Hz, 1H), 7.26–7.37 (m, 3H), 7.45 (d, J = 8.4 Hz, 1H), 7.50–7.62 (m, 4H), 7.89 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H), 8.29 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.70, 44.62, 52.66, 105.52, 126.19, 126.60, 127.62, 127.87, 128.33 (2C), 129.41, 130.64, 131.03, 131.27, 133.05, 133.24, 133.96, 136.72, 142.03, 148.47, 150.75, 161.55, 165.14 (one carbon was overlapped); ESIMS m/z 425 (M^++H). Anal. Calcd. For $C_{26}H_{20}N_2O_4$: C, 73.57; H, 4.75; N, 6.60. Found: C, 73.81; H, 4.78; N, 6.43.
Compound **5f**: 59%; white solid, mp 198–200 °C; IR (KBr) 1714, 1656, 1518, 1454, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.45 (d, J = 14.4 Hz, 1H), 3.88 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 5.08 (d, J = 13.8 Hz, 1H), 5.24 (d, J = 13.8 Hz, 1H), 5.77 (s, 1H), 6.01 (d, J = 14.4 Hz, 1H), 6.88 (s, 1H), 7.13 (s, 1H), 7.21–7.35 (m, 3H), 7.54 (d, J = 8.1 Hz, 2H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.45, 44.58, 52.54, 56.13, 56.20, 101.45, 111.95, 112.65, 126.73, 127.53, 128.05, 128.28, 129.20, 130.49, 136.78, 141.94, 150.38, 150.55, 150.94, 152.02, 162.13, 165.31; ESIMS m/z 435 (M^++H). Anal. Calcd. For $C_{24}H_{22}N_2O_6$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.41; H, 5.37; N, 6.23.
Compound **5g**: 54%; white solid, mp 208–210 °C; IR (KBr) 1726, 1669, 1528, 1465, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.37 (d, J = 14.4 Hz, 1H), 3.91 (s, 3H), 5.09 (d, J = 13.5 Hz, 1H), 5.29 (d, J = 13.5 Hz, 1H), 6.08 (d, J = 14.4 Hz, 1H), 7.30–7.37 (m, 3H), 7.47–7.70 (m, 6H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.66, 45.79, 52.86, 127.97, 128.23, 128.54, 128.91, 129.89, 130.38, 130.46, 130.81, 132.41, 132.80, 135.20, 135.45, 141.63, 147.42, 148.23, 154.98, 164.65; ESIMS m/z 420 (M^++H). Anal. Calcd. For $C_{22}H_{17}N_3O_6$: C, 63.01; H, 4.09; N, 10.02. Found: C, 63.33; H, 4.29; N, 9.89.
Compound **5h**: 80%; white solid, mp 218–220 °C; IR (KBr) 1718, 1649, 1579, 1447, 1430 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.40 (d, J = 14.4 Hz, 1H), 3.88 (s,

3H), 5.17 (d, J = 13.5 Hz, 1H), 5.30 (d, J = 13.5 Hz, 1H), 6.08 (d, J = 14.4 Hz, 1H), 7.26–7.35 (m, 3H), 7.44–7.62 (m, 5H), 7.84 (d, J = 7.8 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.77, 46.56, 52.66, 109.68, 127.84, 128.36, 128.74, 129.38, 129.72, 131.03, 132.93, 133.40, 134.60, 135.02, 136.30, 141.75, 149.72, 152.59, 160.14, 165.01; ESIMS m/z 523 (M^++Na). Anal. Calcd. For $C_{22}H_{17}IN_2O_4$: C, 52.82; H, 3.43; N, 5.60. Found: C, 52.95; H, 3.71; N, 5.73.

Compound **5i**: 70%; white solid, mp 198–200 °C; IR (KBr) 1720, 1657, 1452, 1433 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.39 (d, J = 14.4 Hz, 1H), 3.88 (s, 3H), 5.14 (d, J = 13.5 Hz, 1H), 5.30 (d, J = 13.5 Hz, 1H), 6.03 (d, J = 14.4 Hz, 1H), 7.25–7.35 (m, 3H), 7.46–7.62 (m, 5H), 7.80 (d, J = 7.8 Hz, 1H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.01, 45.91, 52.67, 109.07, 127.88, 128.37, 128.75, 129.70, 129.81, 130.28, 130.87, 132.56, 132.64, 135.41, 136.16, 141.82, 147.19, 148.97, 159.05, 165.00; ESIMS m/z 431 (M^++Na), 433 (M^++2+Na). Anal. Calcd. For $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.70; H, 4.42; N, 6.81.

Compound **5j**: 51%; white solid, mp 150–152 °C; IR (KBr) 1719, 1657, 1459, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J = 7.2 Hz, 3H), 3.39 (d, J = 14.1 Hz, 1H), 3.89 (s, 3H), 4.05–4.20 (m, 2H), 5.15 (d, J = 13.5 Hz, 1H), 5.29 (d, J = 13.5 Hz, 1H), 6.08 (d, J = 14.1 Hz, 1H), 6.79 (d, J = 15.6 Hz, 1H), 7.12 (d, J = 15.6 Hz, 1H), 7.24–7.36 (m, 3H), 7.47–7.67 (m, 6H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.16, 40.51, 45.03, 52.68, 60.06, 108.42, 120.87, 127.75, 128.36, 128.84, 129.52, 129.81, 130.76, 131.36, 133.00, 133.42, 135.99, 136.48, 137.22, 141.73, 149.07, 152.39, 160.85, 164.93, 167.88; ESIMS m/z 473 (M^++H). Anal. Calcd. For $C_{27}H_{24}N_2O_6$: C, 68.63; H, 5.12; N, 5.93. Found: C, 68.74; H, 5.03; N, 5.68.

Compound **5k**: 65%; white solid, mp 126–128 °C; IR (KBr) 1744, 1721, 1649, 1455, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.19 (s, 3H), 3.30 (d, J = 14.4 Hz, 1H), 3.61 (s, 3H), 3.65 (s, 3H), 3.89 (s, 3H), 5.07 (d, J = 13.8 Hz, 1H), 5.25 (d, J = 13.8 Hz, 1H), 6.04 (d, J = 14.4 Hz, 1H), 7.24–7.34 (m, 3H), 7.43–7.65 (m, 6H), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.24, 45.23, 52.57, 53.02, 53.10, 53.47, 83.57, 109.60, 127.68, 128.27, 128.84 (2C), 129.33, 130.75, 131.43, 131.93, 133.24, 136.22, 141.75, 149.14, 153.93, 162.44, 164.91, 166.28, 167.51 (one carbon was overlapped); ESIMS m/z 557 (M^++Na). Anal. Calcd. For $C_{28}H_{26}N_2O_9$: C, 62.92; H, 4.90; N, 5.24. Found: C, 63.10; H, 4.96; N, 5.15.

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