Synthesis of Substituted Uracil Derivatives from the Acetates of the Baylis-Hillman Adducts

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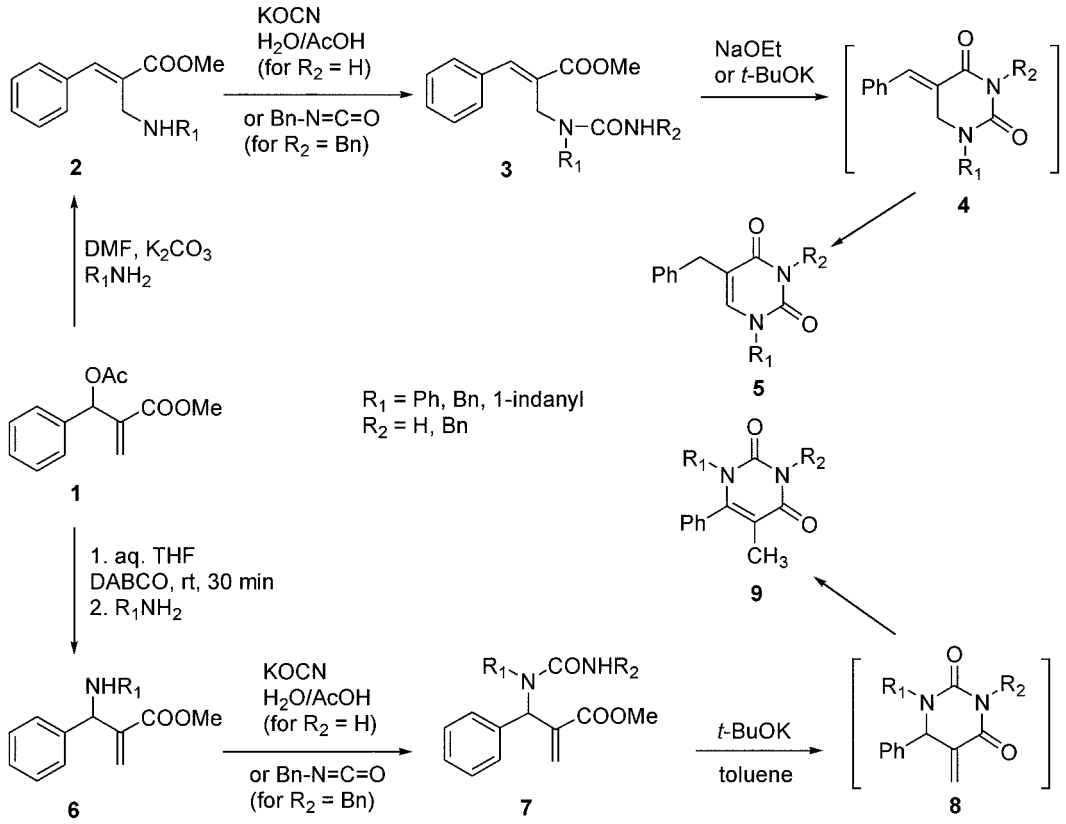
The Baylis-Hillman adducts have been used for the synthesis of a variety of carbocycles and heterocycles.[1-3] However, to the best of our knowledge, synthesis of pyrimidine-2,4-dione skeleton (simply as uracil ring) starting from the Baylis-Hillman adducts has not been published.

A broad spectrum of antiviral activity has been described for 5-substituted pyrimidine nucleosides.[4,5] Although many approaches for the synthesis of 5-substituted pyrimidine bases have been reported,[4,5] a new synthetic method of 5-substituted uracil derivatives are still of particular interest in terms of new drug development. Recently, Knochel and coworkers reported the synthesis of 5-benzyl substituted uracil derivatives from zincated thymine derivatives and aryl iodide in the presence of palladium reagent.[6] We described herein a novel synthesis of 5-substituted uracils from Baylis-Hillman adducts.

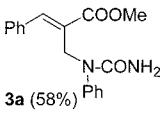
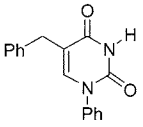
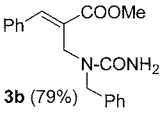
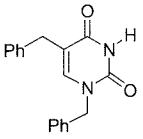
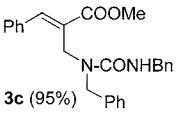
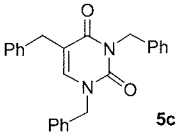
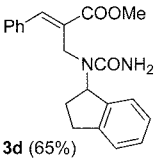
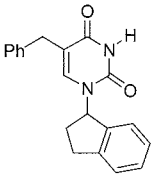
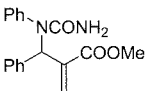
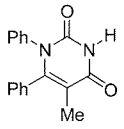
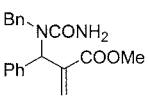
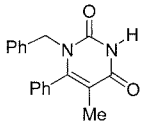
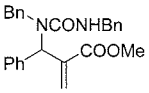
During the investigations on the Baylis-Hillman chemistry[2,7] we presumed that we could prepare 5-substituted uracils by following Scheme 1. Introduction of amine at the Baylis-Hillman acetate **1** could afford **2** and **6** depending upon the reaction conditions (vide infra).[7] Synthesis of urea derivatives was carried out by using KOCN or benzyl isocyanate to form **3** and **7**, and the following cyclization of the urea derivatives with alkoxide base would give the pyrimidine-2,4-dione skeletons **5** and **9**. We expected that the corresponding intermediates with *exo*-double bond, **4** and **8**, could be converted easily into the *endo* form, **5** and **9**, during the reaction.

Synthesis of *N*-substituted cinnamylamine derivatives **2** was carried out from the reaction of **1** and amine compounds in DMF in the presence of K_2CO_3 in moderate yields. The *N*-substituted urea derivatives, **3a**, **3b** and **3d**, were prepared



Scheme 1

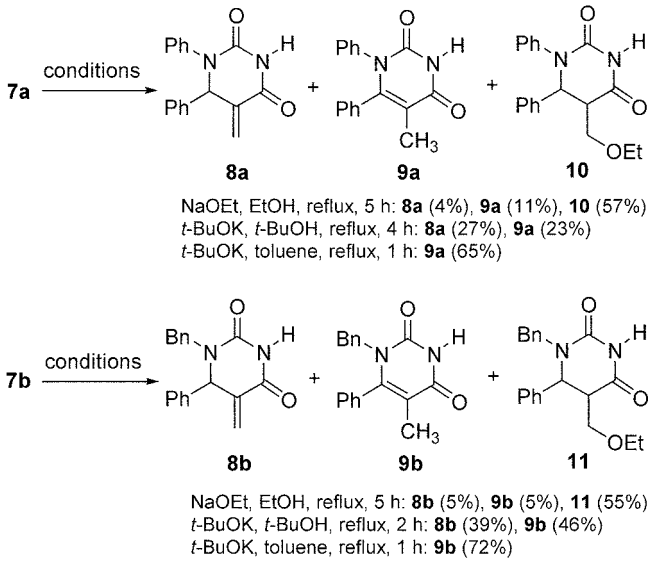
Table 1. Synthesis of substituted uracil derivatives **5a-d** and **9a-b**

Entry	conditions[a]	**3** and **7** (%)	conditions[b]	**5** and **9** (%)
1	**2a**, KOCN aq. AcOH rt, 1 h	 **3a** (58%)	NaOEt, EtOH reflux, 2 h	 **5a** (70)
2	**2b**, KOCN aq. AcOH rt, 3 h	 **3b** (79%)	NaOEt, EtOH reflux, 1 h	 **5b** (80)
3	**2b**, BnNCO toluene rt, 12 h	 **3c** (95%)	*t*-BuOK, *t*-BuOH reflux, 1 h	 **5c** (60)
4	**2c**, KOCN aq. AcOH rt, 60 h[c]	 **3d** (65%)	*t*-BuOK, *t*-BuOH reflux, 10 h	 **5d** (71)
5	**6a**, KOCN aq. AcOH rt, 7 h	 **7a** (81%)	*t*-BuOK, toluene reflux, 1 h	 **9a** (65)
6	**6b**, KOCN aq. AcOH rt, 7 h	 **7b** (70%)	*t*-BuOK, toluene reflux, 1 h	 **9b** (72)
7	**6b**, BnNCO toluene rt, 12 h	 **7c** (82%)	*t*-BuOK, toluene reflux, 5 h	**5c** (50)

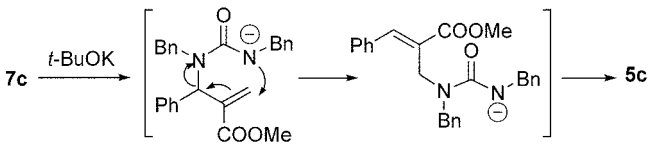
[a]KOCN (2 equiv) and BnNCO (2 equiv) were used. [b]NaOEt (2 equiv) and *t*-BuOK (1.2 equiv) were used. [c]The reaction was carried out by slow addition of excess amounts of aq. KOCN (4 equiv).

from the reaction of the corresponding cinnamylamine compounds **2** with KOCN (2 equiv) in aqueous acetic acid in moderate yields at room temperature. *N*,*N*-Disubstituted urea derivative **3c** was synthesized from the reaction of **2b** and benzyl isocyanate. With these urea compounds **3a-d** in our hands, we examined various conditions for the effective cyclization toward 5-substituted uracil skeleton. Among them the use of NaOEt or *t*-BuOK was found to be the best choice. As shown in Table 1, **3a-d** was converted into the desired uracils **5a-d** in short time with NaOEt or *t*-BuOK in moderate yields.

In order to prepare 5,6-disubstituted uracils **9**, we introduced some amine molecules at the secondary position of the Baylis-Hillman adduct according to the well-known protocol involving the use of DABCO salt concept[7] to make **6a** and **6b**. Corresponding urea derivatives **7a-c** was



Scheme 2



Scheme 3

prepared as before (vide supra). However, the use of NaOEt in the cyclization stage to the desired **9** caused some problems. In the reaction mixture of **7a**/NaOEt/EtOH, we found the formation of variable amounts of **8a**, **9a**, and **10** (Scheme 2). The compound **10** might be generated by the Michael type addition of ethanol at the *exo*-methylene double bond of **8a**. Thus, we changed the base as a non-nucleophilic *t*-BuOK. However, the use of *t*-BuOK in *t*-BuOH also did not produce the desired **9a** in high yield. Appreciable amounts of **8a** (27%) were isolated together with **9a** (23%). The effective synthesis of **9a** was finally achieved when we used *t*-BuOK in toluene at refluxing temperature (Scheme 2 and entry 5 in Table 1). Similarly, the use of NaOEt/EtOH or *t*-BuOK/*t*-BuOH did not give high yield of **9b** from **7b** as shown in Scheme 2. Fortunately, the use of *t*-BuOK in toluene gave **9b** in good yield (entry 6 in Table 1).

It is interesting to note that the reaction of **7c**/*t*-BuOK in toluene afforded **5c** in moderate yield, unexpectedly, instead of the expected 5,6-disubstituted uracil derivative. The plausible reaction mechanism is depicted in Scheme 3. The urea moiety of **7c** rearranged to the primary position to give the thermodynamically more stable form. Then the following cyclization gave **5c**.

In summary, we disclosed facile synthesis of a variety of 5-substituted and 5,6-disubstituted uracil derivatives starting from the acetates of the Baylis-Hillman adducts. We think that this method could be used successfully for the synthesis of biologically active nucleoside derivatives.

Experimental Section

Synthesis of starting materials: The starting materials **2a-c** were synthesized from the acetate of the Baylis-Hillman adduct **1** and aniline, benzylamine, and 1-amino-indan, respectively, in DMF in the presence of K_2CO_3 according to the literature method.[3,7] Synthesis of **6a** and **6b** was carried out according to the reported method using the corresponding DABCO salt of **1** and aniline or benzylamine in aq. THF.[3,7] These starting materials **2a-c**, **6a**, and **6b** were used for the synthesis of urea derivatives **3a-d** and **7a-c**. Synthesis of mono-substituted ureas (**3a**, **3b**, **3d**, **7a**, **7b**) was carried out with KOCN (2 equiv) in aq. AcOH at room temperature. *N*,*N*-Disubstituted urea derivatives (**3c** and **7c**) were synthesized easily from **2b** and **6b** with benzyl isocyanate (2 equiv) in toluene. The spectroscopic data of prepared starting urea derivatives **3a-d** and **7a-c** are as follows.

3a: 58%; white solid, mp 134-135 °C; IR (CH_2Cl_2) 3487, 1716, 1670, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 4.49 (br s, 2H), 4.89 (s, 2H), 6.97-7.35 (m, 10H), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 44.21, 52.26, 128.21, 128.55, 128.60, 129.01, 129.04, 129.51, 129.77, 134.70, 140.66, 143.49, 157.73, 168.30.

3b: 79%; white solid, mp 148-149 °C; IR (CH_2Cl_2) 3437, 1701, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 4.21 (s, 2H), 4.29 (s, 2H), 5.18 (br s, 2H), 6.77-6.81 (m, 2H), 7.05-7.37 (m, 8H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 42.31, 48.45, 52.40, 126.81, 127.60, 128.09, 128.68, 128.89, 128.98, 129.11, 134.09, 137.42, 143.08, 159.96, 168.61.

3c: 95%; clear oil; IR (CH_2Cl_2) 3359, 1712, 1647, 1531 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.27 (s, 2H), 4.29 (s, 2H), 4.38 (d, J = 5.4 Hz, 2H), 5.93 (t, J = 5.4 Hz, 1H, NH), 6.83-6.88 (m, 2H), 7.06-7.35 (m, 13H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 42.33, 45.24, 49.26, 52.56, 127.03, 127.12, 127.77, 127.98, 128.37, 128.59, 128.89, 129.18, 129.37, 129.62, 134.28, 138.14, 139.97, 142.85, 159.10, 168.79.

3d: 65%; clear oil; IR (CH_2Cl_2) 3479, 1709, 1666, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87-2.04 (m, 1H), 2.14-2.26 (m, 1H), 2.64 (t, J = 7.5 Hz, 2H), 3.85 (s, 3H), 4.41 (d, J = 15.6 Hz, 1H), 4.65 (d, J = 15.6 Hz, 1H), 4.94 (s, 2H), 5.35 (t, J = 7.8 Hz, 1H), 6.95-7.33 (m, 9H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.92, 30.12, 42.77, 52.39, 61.57, 124.34, 125.25, 126.55, 127.80, 128.45, 129.01, 129.50, 130.41, 134.16, 141.50, 141.92, 142.90, 160.64, 168.75.

7a: 81%; white solid, mp 110-111 °C; IR (CH_2Cl_2) 3487, 1724, 1674, 1593 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 4.47 (s, 2H), 5.66 (s, 1H), 6.39 (s, 1H), 6.46 (s, 1H), 7.08-7.28 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 52.16, 62.69, 127.50, 127.62, 128.23, 128.39, 129.23, 129.57, 130.19, 138.42, 140.69, 140.72, 157.60, 167.09.

7b: 70%; white solid, mp 142-143 °C; IR (CH_2Cl_2) 3386, 1720, 1666, 1597 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.58 (s, 3H), 4.34 (d, J = 16.5 Hz, 1H), 4.68 (d, J = 16.5 Hz, 1H), 4.95 (s, 2H), 5.63 (s, 1H), 6.41 (s, 2H), 7.02-7.29 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 48.74, 52.14, 60.19, 126.99, 127.15, 127.92, 127.97, 128.44, 128.47, 128.74, 137.70, 137.73, 139.98, 159.94, 166.66.

7c: 82%; yellow oil; IR (CH_2Cl_2) 3437, 3363, 1724, 1643, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.57 (s, 3H), 4.32 (d, J = 16.7 Hz, 1H), 4.35 (d, J = 5.3 Hz, 2H), 4.73 (d, J = 16.7 Hz, 1H), 4.87 (t, J = 5.3 Hz, 1H), 5.63 (s, 1H), 6.42 (s, 1H), 6.48 (s, 1H), 7.01-7.30 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 45.03, 48.68, 52.17, 60.21, 127.05, 127.10, 127.23, 127.28, 127.81, 127.92, 128.48, 128.53, 128.55, 128.81, 137.99, 138.05, 139.30, 140.26, 158.39, 166.77.

Typical procedure for the synthesis of uracil derivative 5a: To a stirred solution of **3a** (310 mg, 1 mmol) in ethanol (1 mL) was added a solution of NaOEt (21% solution in EtOH, 650 mg, 2 mmol) and the reaction mixture was heated to reflux for 2 h. After the usual workup and column chromatographic purification (hexanes/EtOAc, 3 : 1) process, we obtained the desired compound **5a** as a white solid, 195 mg (70%). Synthesis of other uracil derivatives was carried out similarly and the spectroscopic data of prepared uracil derivatives **5a-d**, **9a** and **9b** are as follows.

5a: 70%; white solid, mp 129-130 °C; IR (CH_2Cl_2) 3186, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 2H), 6.96 (t, J = 0.9 Hz, 1H), 7.19-7.46 (m, 10H), 9.26 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.63, 115.59, 126.45, 126.93, 128.86, 128.94, 129.16, 129.71, 138.25, 138.74, 141.68, 150.30, 163.79; Mass (70 eV) *m*/*z* (rel. intensity) 51 (100), 65 (23), 77 (73), 130 (70), 206 (35), 278 (M^+, 17).

5b: 80%; white solid, mp 170-171 °C; IR (CH_2Cl_2) 3209, 1693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.61 (s, 2H), 4.82 (s, 2H), 6.73 (t, J = 1.2 Hz, 1H), 7.14-7.38 (m, 10H), 9.10 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 32.65, 51.40, 115.52, 126.88, 128.12, 128.62, 128.88, 129.12, 129.26, 135.51, 138.29, 141.02, 151.09, 163.65; Mass (70 eV) *m*/*z* (rel. intensity) 65 (33), 76, (17), 91 (100), 115 (13), 201 (15), 292 (M^+, 15).

5c: 60%; clear oil; IR (CH_2Cl_2) 1701, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (s, 2H), 4.81 (s, 2H), 5.14 (s, 2H), 6.72 (t, J = 1.2 Hz, 1H), 7.13-7.50 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 33.38, 44.94, 52.41, 114.65, 126.79, 127.74, 128.00, 128.49, 128.56, 128.82, 129.12, 129.18, 129.26, 135.66, 137.12, 138.37, 139.19, 151.68, 163.20; Mass (70 eV) *m*/*z* (rel. intensity) 65 (15), 91 (100), 248 (10), 291 (27), 382 (M^+, 15).

5d: 71%; white solid, mp 200-201 °C; IR (CH_2Cl_2) 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81-1.94 (m, 1H), 2.58-2.70 (m, 1H), 2.91 (t, J = 7.2 Hz, 2H), 3.53 (s, 2H), 6.14 (t, J = 7.2 Hz, 1H), 6.47 (s, 1H), 7.04-7.32 (m, 9H), 9.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.10, 32.57 (two carbon by ^1H-^{13}C COSY), 60.47, 115.13, 124.42, 125.24, 126.40, 127.34, 128.46, 128.63, 128.91, 138.00, 138.18, 139.30, 144.05, 151.30, 163.23.

9a: 65%; white solid, mp 249-250 °C; IR (CH_2Cl_2) 1693 cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 1.73 (s, 3H), 6.99-7.20 (m, 10H), 10.78 (br s, 1H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 11.92, 109.04, 127.81, 127.89, 128.36, 128.42, 128.58, 129.23, 132.48, 137.00, 150.81, 150.91, 164.16.

9b: 72%, white solid, mp 172-173 °C; IR (CH_2Cl_2) 3182, 1682, 1466 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (s, 3H), 4.82 (s, 2H), 6.81-6.97 (m, 4H), 7.17-7.44 (m, 6H), 9.46 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.30, 48.96, 110.39, 127.01, 127.63,

128.45, 128.60, 128.98, 129.72, 132.49, 136.84, 151.78, 152.10, 164.12; Mass (70 eV) *m*/*z* (rel. intensity) 65 (11), 91 (100), 115 (9), 292 (M^+, 26).

Spectroscopic data of the intermediate *exo*-methylene compounds **8a** and **8b**, and the Michael-addition products **10** and **11** are as follows.

8a: 27%; clear oil; IR (CH_2Cl_2) 3213, 1701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52 (s, 1H), 5.77 (s, 1H), 6.43 (s, 1H), 7.17-7.38 (m, 10H), 8.33 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 66.29, 125.75, 126.16, 126.23, 127.33, 128.73, 129.35, 129.42, 136.01, 138.90, 140.44, 151.62, 162.91; Mass (70 eV) *m*/*z* (rel. intensity) 51 (16), 77 (37), 138 (56), 206 (73), 278 (M^+, 100).

8b: 39%; white solid, mp 189-190 °C; IR (CH_2Cl_2) 1705, 1670, 1485, 1227 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (d, J = 15.0 Hz, 1H), 5.02 (s, 1H), 5.47 (d, J = 15.0 Hz, 1H), 5.57 (s, 1H), 6.36 (s, 1H), 7.18-7.41 (m, 10H), 8.45 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 48.37, 61.28, 126.32, 126.50, 128.13, 128.26, 128.86, 129.07, 129.61, 135.79, 136.04, 138.84, 152.57, 162.67; Mass (70 eV) *m*/*z* (rel. intensity) 65 (20), 91 (100), 116 (84), 188 (48), 292 (M^+, 26).

10: 57%; clear oil; ^1H NMR ($CDCl_3$) δ 1.24 (t, J = 6.9 Hz, 3H), 3.12-3.17 (m, 1H), 3.54-3.70 (m, 2H), 3.77-3.81 (m, 1H), 3.89-3.95 (m, 1H), 5.18 (d, J = 1.8 Hz, 1H), 7.22-7.38 (m, 10H), 8.37 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.22, 50.59, 61.98, 67.06, 68.55, 126.21, 126.36, 127.23, 128.45, 129.26, 129.34, 138.82, 140.98, 151.75, 169.53; Mass (70 eV) *m*/*z* (rel. intensity) 55 (41), 77 (100), 91 (49), 119 (36), 180 (25), 324 (M^+, 1).

11: 55%; clear oil; IR (CH_2Cl_2) 3217, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (t, J = 6.9 Hz, 3H), 2.84-3.02 (m, 2H), 3.17-3.37 (m, 2H), 3.50 (dd, J = 8.7 and 4.2 Hz, 1H), 3.63 (d, J = 14.7 Hz, 1H), 4.69 (d, J = 1.5 Hz, 1H), 5.49 (d, J = 14.4 Hz, 1H), 7.17-7.40 (m, 10H), 9.03 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.96, 48.90, 50.48, 56.50, 66.58, 67.92, 126.25, 128.07, 128.45, 128.77, 129.09, 129.39, 136.59, 138.28, 152.98, 169.32.

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References and Notes

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