# Chemoselective Suzuki–Miyaura Cross-Coupling Reactions of 6-Bromo-3-(trifluoromethylsulfonyloxy)flavone

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*Received: 14.01.2013; Accepted after revision: 26.02.2013*

**Abstract:** Arylated flavones were prepared by Suzuki–Miyaura reactions of 6-bromo-3-(trifluoro-sulfonyloxy)flavone. The reactions proceeded with very good chemoselectivity in favor of position 3.

**Key words:** catalysis, flavones, heterocycles, palladium, cross-coupling reactions

Flavones (2-arylchromones) constitute an important class of oxygen heterocycles which are widespread in various plants and agricultural products, including vegetables, seeds, nuts, and fruits.[1–4] Examples include apigenin and genistein which are found in *Apium graveolens* and *Soya hispida*, respectively (Figure 1).[5] Flavonoids received considerable attention in recent years because of their potential beneficial effects on human health. Flavonoids have been reported to exhibit various pharmacological activities, including vasodilating,[6] antiviral,[7] antioxidative,[8] antimicrobial,[9] DNA cleaving,[10] antiinflammatory,[11] antimutagenic,[12] antiallergic,[13] anticancer,[14] antiarthritic,[15] analgesic,[16] antidiabetic,[17] antiulcer,[18] antianginous,[19] antiosteoporotic,[20] antihepatotoxic,[21] antidiarrhoeal,[22] antifungal,[23] and various enzyme-inhibitory effects.[24]

Various synthetic protocols have been developed for the synthesis of flavones and isoflavones. Traditionally, flavones have been prepared by Baker–Venkataraman rearrangement,[25] by oxidative cyclization of 2-hydroxychalcones,[26] or by regioselective cyclization of *ortho*-alkynoylphenols.[27] Flavones have also been prepared by intramolecular Wittig reactions.[28] The easiest synthesis of 3-hydroxyflavones is the so-called Algar–Flynn–Ozamada reaction, that is, oxidative cyclization of 2-hydroxychalcones by alkaline hydrogenperoxide.[29]

Flavones and isoflavones are available by transition-metal-catalyzed cross-coupling reactions, such as the cyclization of 2-halophenols with terminal acetylenes and carbon monoxide[30] or by Suzuki–Miyaura cross-coupling reactions of halogenated chromones.[31] Flavones have been prepared by oxidative addition of arylboronic acids to chromones.[32] We have recently reported the synthesis of arylated flavones by regioselective Suzuki–Miyaura reactions of the bis(triflates) of 5,7- and 7,8-dihydroxyflavone.[33] Herein, we report a convenient approach to arylated flavones by what are, to the best of our knowledge, the first Suzuki–Miyaura cross-coupling reactions of 6-bromo-3-(trifluorosulfonyloxy)flavone. Surprisingly, the reactions proceed with very good chemoselectivity in favor of position 3.

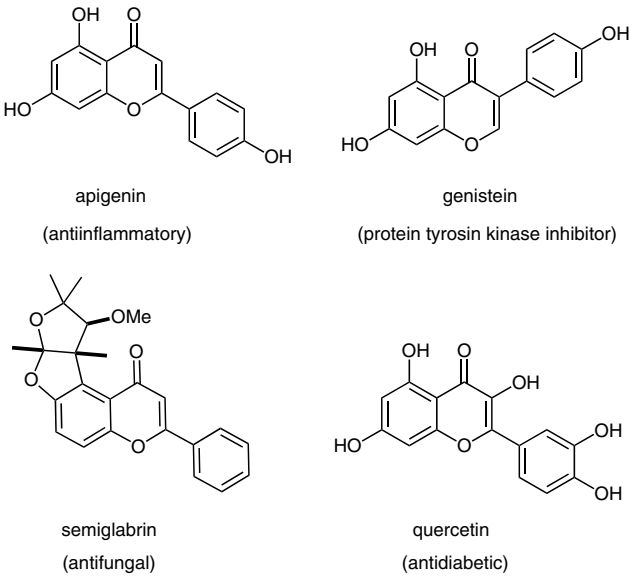
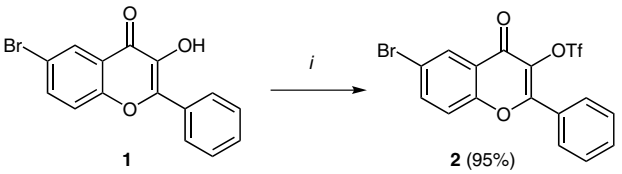



**Figure 1** Some pharmacologically active flavone natural products

The reaction of 6-bromo-3-hydroxyflavone[34] (**1**) with triflic anhydride afforded triflate **2** in good yield (Scheme 1).[36]

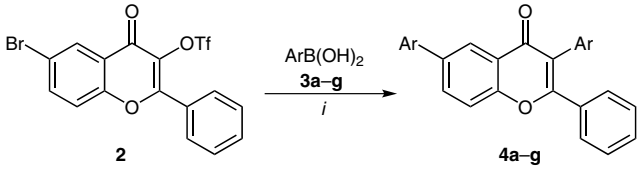



**Scheme 1** Synthesis of **2**. *Reagents and conditions*: (*i*) **1** (1.0 equiv), $Tf_2O$ (2.0 equiv), pyridine (5.0 equiv), $CH_2Cl_2$, 0–20 °C, 18 h.

The Suzuki–Miyaura reaction of **2** with arylboronic acids **3a**–**f** (2.3 equiv) afforded the 3,6-diarylflavones **4a**–**g** (Scheme 2, Table 1).[37,38] The best yields were obtained when $Pd(PPh_3)_4$ (6 mol%) and $K_3PO_4$ (3.0 equiv) were used as catalyst and base, respectively. The reactions were

*SYNLETT* 2013, 24, 0860–0864
Advanced online publication: 08.03.2013
DOI: 10.1055/s-0032-1318479; Art ID: ST-2013-D0046-L

carried out in dioxane (90 °C, 12 h). The highest yields were obtained for products **4a**,**b**, which are derived from electron-rich (highly nucleophilic) arylboronic acids **3a**,**b**. The yield dropped when the more sterically hindered *ortho*-substituted arylboronic acid **3c** was employed. The use of electron-poor arylboronic acids (products **4e**,**f**) also worked well, although the yields were slightly lower as compared to **4a**,**b**.



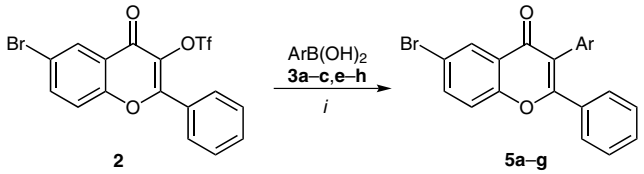

**Scheme 2** Synthesis of **4a**–**g**. *Reagents and conditions*: (*i*) **2** (1.0 equiv), $ArB(OH)_2$ (2.3 equiv), $Pd(PPh_3)_4$ (6 mol%), $K_3PO_4$ (3.0 equiv), dioxane, 90 °C, 12 h.

**Table 1** Synthesis of **4a**–**g**

| **3**, **4** | Ar | Yield of **4** (%)[a] |
|---|---|---|
| **a** | 4-$MeOC_6H_4$ | 90 |
| **b** | 4-$EtOC_6H_4$ | 95 |
| **c** | 2-$MeOC_6H_4$ | 78 |
| **d** | 4-$MeC_6H_4$ | 85 |
| **e** | 4-$ClC_6H_4$ | 75 |
| **f** | 3-$FC_6H_4$ | 83 |
| **g** | 4-$FC_6H_4$ | 73 |

[a] Yields of isolated compounds.

The Suzuki–Miyaura reaction of **2** with 1.1 equivalents of arylboronic acids **3a**–**c**,**e**–**h** gave the 3-aryl-6-bromoflavones **5a**–**g** (Scheme 3, Table 2).[39,40] The reactions proceeded with very good chemoselectivity in favor of position 3. During the optimization, it proved to be important to carry out the reaction at 65 °C instead of 90 °C. Higher temperatures result in the formation of considerable amounts of diarylated products. The use of a 9:1 mixture of toluene and MeOH proved to be important, as the use of dioxane resulted in the formation of mixtures. A relatively long reaction time (24 h) was necessary in order to achieve a complete conversion.



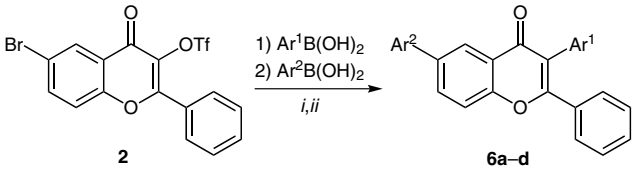

**Scheme 3** Synthesis of **5a**–**g**. *Reagents and conditions*: (*i*) **2** (1.0 equiv), $ArB(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (3 mol%), $K_3PO_4$ (1.5 equiv), toluene–MeOH (9:1), 65 °C, 24 h.

**Table 2** Synthesis of **5a**–**g**

| **3** | **5** | Ar | Yield of **5** (%)[a] |
|---|---|---|---|
| **a** | **a** | 4-$MeOC_6H_4$ | 82 |
| **b** | **b** | 4-$EtOC_6H_4$ | 90 |
| **c** | **c** | 2-$MeOC_6H_4$ | 71 |
| **e** | **d** | 4-$ClC_6H_4$ | 68 |
| **f** | **e** | 3-$FC_6H_4$ | 85 |
| **g** | **f** | 4-$FC_6H_4$ | 90 |
| **h** | **g** | 4-$F_3CC_6H_4$ | 78 |

[a] Yields of isolated compounds.

The one-pot Suzuki–Miyaura reaction of **2** with two different arylboronic acids (sequential addition) afforded the 3,6-diarylflavones **6a**–**d** (Scheme 4, Table 3).[41,42] During the optimization, it proved again to be important to carry out the first step of the one-pot reaction at 65 °C. A relatively long reaction time (36 h) was again necessary in order to induce a complete conversion.




**Scheme 4** Synthesis of **6a**–**d**. *Reagents and conditions*: (*i*) **2** (1.0 equiv), $Ar^1B(OH)_2$ (1.0 equiv), $Pd(PPh_3)_4$ (3 mol%), $K_3PO_4$ (1.5 equiv), toluene–MeOH (4:1), 65 °C, 36 h; (*ii*) $Ar^2B(OH)_2$ (1.3 equiv), $K_3PO_4$ (1.5 equiv), $Pd(PPh_3)_4$ (6 mol%), 105 °C, 12 h.

**Table 3** Synthesis of **6a**–**d**

| **3**, **4** | **6** | $Ar^1$ | $Ar^2$ | Yield of **6** (%)[a] |
|---|---|---|---|---|
| **b**,**g** | **a** | 4-$EtOC_6H_4$ | 4-$FC_6H_4$ | 76 |
| **g**,**b** | **b** | 4-$FC_6H_4$ | 4-$EtOC_6H_4$ | 84 |
| **b**,**k** | **c** | 4-$EtOC_6H_4$ | 3-$MeC_6H_4$ | 91 |
| **g**,**e** | **d** | 4-$FC_6H_4$ | 4-$ClC_6H_4$ | 70 |

[a] Yields of isolated compounds.

It is noteworthy that 2,3-diarylflavones have been reported recently to comprise a new class of selective COX-2 inhibitors.[43]

In general, Pd-catalyzed cross-coupling reactions of polyhalogenated substrates or of bis(triflates) proceed more rapidly at the sterically less hindered and more electron-deficient position.[44] In case of Suzuki–Miyaura reactions, bromides usually react faster than triflates, due to the formation of a stable boron–bromide bond.[45] Surprisingly, the Suzuki–Miyaura reactions of **2** proceeded by chemoselective attack onto the triflate group. We have report-

ed earlier that the Suzuki–Miyaura reaction of 6-bromo-4-(trifluoromethylsulfonyloxy)coumarin also proceeded at the triflate group first.[46] However, in that case, position 4 is highly electron deficient, while position 3 of the current substrate **2** is less electron deficient, due to the electron-donating effect of the flavones' oxygen atom. In case of the current substrate **2**, the higher reactivity of position 3, which is more sterically hindered than position 6, might be explained by a catalyst directing effect of the neighboring carbonyl group.

## Acknowledgment

Financial support by the DAAD (scholarships for O.A.A.) and by the State of Mecklenburg-Vorpommern is gratefully acknowledged. The project is implemented through the New Hungary Development Plan, co-financed by the European Social Fund and the European Regional Development Fund. The project was also funded by the EFRE program of the EU.

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(34) 6-Bromo-3-hydroxyflavone (**1**) was prepared by the reaction of the corresponding 2′-hydroxychalcone with ethanolic alkaline hydrogenperoxide solution,[29] the product was obtained after recrystallization (EtOH) in 56% yield; mp 189–191 °C, lit.[35a]; mp 180–181 °C, lit.[35a]; mp 183–184 °C.
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(36) **Synthesis of 6-Bromo-4-oxo-2-phenyl-4*H*-chromen-3-yl Trifluoromethanesulfonate (2)**
$Tf_2O$ (0.53 mL, 3.20 mmol) was added at 0 °C to a solution of **1** (0.5 g, 1.58 mmol) and pyridine (0.64 mL, 7.88 mmol) in $CH_2Cl_2$ (15 mL). The reaction mixture was stirred at r.t. under argon atmosphere for 18 h. To the reaction mixture was added toluene (10 mL), and the solution was

 

concentrated in vacuo. The residue was purified by chromatography (EtOAc–heptanes) without aqueous workup to yield **2** as a white solid (0.674 g, 95%); mp 160–162 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, 1 H, *J* = 8.9 Hz, ArH), 7.48–7.60 (m, 3 H, ArH), 7.77–7.81 (m, 3 H, ArH), 8.35 (d, 1 H, *J* = 2.5 Hz, ArH). $^{19}$F NMR (282.4 MHz, $CDCl_3$): δ = –73.7. $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 118.20 (q, $J_{C,F}$ = 320.9, $CF_3$), 119.7 (C), 120.2 (CH), 124.8, 128.1 (C), 128.2 (2 CH), 129.0, 132.7 (CH), 133.8 (C), 137.8 (CH), 154.2, 159.2 (C), 170.0 (CO). IR (KBr): ν = 3083, 3070, 2928 (w), 1651, 1620 (s), 1604, 1538, 1496, 1461, 1451 (m), 1425 (s), 1367 (m), 1335, 1321, 1292, 1269, 1250, 1232 (w), 1212, 1201, 1170, 1139, 1120 (s), 1078, 1060, 1033 (w), 990 (m), 975, 932, 912, 894 (w), 856, 827, 804 (s), 784 (w), 767, 764 (s), 711 (m), 693, 678, 661 (s), 646 (m), 619 (s), 571, 559, 545, 529 (m) cm$^{-1}$. GC–MS (EI, 70 eV): *m/z* (%) = 450 (13) [M, $^{81}$Br]$^+$, 448 (13) [M, $^{79}$Br]$^+$, 319 (12), 318 (59), 317 (35), 316 (59), 315 (53), 290 (19), 289 (100), 287 (95), 261 (17), 259 (12). HRMS (EI, 70 eV): *m/z* calcd for $C_{16}H_8BrF_3O_5S$ [M, $^{79}$Br]$^+$: 447.92224; found: 447.92265; *m/z* calcd. for $C_{16}H_8BrF_3O_5S$ [M, $^{81}$Br]$^+$: 449.92020; found: 449.92043.

(37) **General Procedure for the Synthesis of 4a–g**
A 1,4-dioxane solution of **2** (0.11 mmol), arylboronic acid (2.3 equiv), $K_3PO_4$ (3.0 equiv), and $Pd(PPh_3)_4$ (6 mol%) was heated at 90 °C for 12 h under argon atmosphere. After cooling to 20 °C, $H_2O$ was added, and the reaction mixture was extracted with $CH_2Cl_2$ (3 × 25 mL). Organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–heptanes).

(38) **3,6-Bis(4-methoxyphenyl)-2-phenyl-4*H*-chromen-4-one (4a)**
Starting with **2** (50 mg, 0.11 mmol), (4-methoxyphenyl)boronic acid (39 mg, 0.26 mmol), $K_3PO_4$ (70 mg, 0.33 mmol), and $Pd(PPh_3)_4$ (8 mg, 6 mol%), **4a** was prepared as a white solid (48 mg, 90%); mp 181–183 °C. Reaction temperature: 90 °C for 12 h. $^1$H NMR (250 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, $OCH_3$), 3.79 (s, 3 H, $OCH_3$), 6.77 (d, 2 H, *J* = 8.8 Hz, ArH), 6.94 (d, 2 H, *J* = 8.8 Hz, ArH), 7.08 (d, 2 H, *J* = 8.8 Hz, ArH), 7.18–7.28 (m, 3 H, ArH), 7.34–7.38 (m, 2 H, ArH), 7.49 (d, 1 H, *J* = 8.7 Hz, ArH), 7.55 (d, 2 H, *J* = 8.8 Hz, ArH), 7.82 (dd, 1 H, *J* = 8.8, 2.4 Hz, ArH), 8.37 (d, 1 H, *J* = 2.3 Hz, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 55.2, 55.4, ($OCH_3$), 113.9, 114.4, 118.4, (CH), 122.4 (C), 123.0 (CH), 123.6 125.0 (C), 128.1, 128.3, 129.6, 129.9 (CH), 132.1 (C), 132.2, 132.4 (CH), 133.5, 137.8, 155.1, 159.0, 159.5, 161.2 (C), 177.7 (CO). IR (KBr): ν = 3060, 3035, 2954, 2929, 2834 (w), 1633, 1605 (s), 1580, 1563 (m), 1557 (s), 1538 (w), 1511 (m), 1494 (w), 1479, 1446, 1439, 1410 (s), 1291, 1282, 1268 (m), 1244, 1229, 1179 (s), 1149, 1122, 1106, 1079, 1055 (w), 1031, 1018 (m), 1005, 973 (w), 928 (m), 916, 905, 848 (w), 835 (m), 813 (s), 797, 770 (m), 732, 709 (w), 689 (m), 673, 661, 652, 639, 624, 584, 579, 563 (w), 585, 539 (m) cm$^{-1}$. GC–MS (EI, 70 eV): *m/z* (%) = 434 (76) [M]$^+$, 433 (100) [M – H]$^+$, 418 (4), 390 (6), 311 (24), 226 (4). HRMS (EI, 70 eV): *m/z* calcd for $C_{29}H_{22}O_4$ [M]$^+$: 434.15126; found: 434.14966; *m/z* calcd for $C_{29}H_{21}O_4$ [M – H]$^+$: 433.14344; found: 433.14334.

(39) **General Procedure for the One-Pot Synthesis of 5a–g**
A toluene–MeOH (9:1) solution of **2** (0.11 mmol), arylboronic acid (1.1 equiv), $K_3PO_4$ (1.5 equiv), and $Pd(PPh_3)_4$ (3 mol%) was heated at 65 °C for 24 h under argon atmosphere. After cooling to 20 °C, $H_2O$ was added, and the reaction mixture was extracted with $CH_2Cl_2$ (3 × 25 mL). The organic layers were dried over $Na_2SO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc–heptanes).

(40) **6-Bromo-3-(4-methoxyphenyl)-2-phenyl-4*H*-chromen-4-one (5a)**
Starting with **2** (50 mg, 0.11 mmol), **5a** was prepared as a white solid (37 mg, 82%), mp 237–238 °C. Reaction temperature: 65 °C for 24 h. $^1$H NMR (300 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, $OCH_3$), 6.77 (d, 2 H, *J* = 8.9 Hz, ArH), 7.06 (d, 2 H, *J* = 8.9 Hz, ArH), 7.19–7.37 (m, 6 H, ArH), 7.70 (dd, 1 H, *J* = 8.9, 2.5 Hz, ArH), 8.33 (d, 1 H, *J* = 2.5 Hz, ArH). $^{13}$C NMR (62.9 MHz, $CDCl_3$): δ = 55.2 ($OCH_3$), 113.9 (CH), 118.3 (C), 119.9 (CH), 122.6, 124.4, 124.8 (C), 128.2, 128.9, 129.5, 130.1, 132.3 (CH), 133.1 (C), 136.5 (CH), 154.8, 159.1, 161.4 (C), 176.3 (CO). IR (KBr): ν = 3081, 3059, 3015, 2928, 2850, 2832 (w), 1635, 1604 (s), 1574, 1563 (w), 1556 (s), 1510 (w), 1466, 1455, 1444 (m), 1426, 1361 (s), 1288, 1270 (m), 1232, 1219, 1177 (s), 1146, 1121, 1107, 1061, 1048 (w), 1027, 1000 (s), 976, 960 (w), 928 (m), 906, 896, 841 (w), 824, 815 (s), 794 (w), 777 (s), 728 (w), 701, 696, 676, 666, 653, 648 (m), 640, 619, 610, 551 (w), 540, 530 (m) cm$^{-1}$. GC–MS (EI, 70 eV): *m/z* (%) = 408 (67) [M, $^{81}$Br]$^+$, 407 (100) [M – H, $^{81}$Br]$^+$, 406 (69) [M, $^{79}$Br]$^+$, 405 (84) [M – H, $^{79}$Br]$^+$, 364 (5), 362 (5), 327 (7), 283 (6), 255 (6), 226 (5), 208 (22). HRMS (ESI-TOF/MS): *m/z* calcd. for $C_{22}H_{16}BrO_3$ [M + H, $^{79}$Br]$^+$: 407.02773; found: 407.0270; *m/z* calcd for $C_{22}H_{16}BrO_3$ [M + H, $^{81}$Br]$^+$: 409.02597; found: 409.02509.

(41) **General Procedure for the One-Pot Synthesis of 6a–d**
A toluene–MeOH (9:1) solution of **2** (0.17 mmol), $Ar^1B(OH)_2$ (1.0 equiv), $K_3PO_4$ (1.5 equiv), and $Pd(PPh_3)_4$ (3 mol%) was heated at 65 °C for 36 h under argon atmosphere. After cooling to 20 °C, $Ar^2B(OH)_2$ (1.3 equiv), $Pd(PPh_3)_4$ (6 mol%), and MeOH (0.2 mL) were added, and the reaction mixture was heated at 105 °C for further 12 h. The reaction mixture was cooled again to 20 °C, $H_2O$ was added, and the reaction mixture was extracted with $CH_2Cl_2$ (3 × 25 mL).The combined organic layers were dried over $Na_2SO_4$, filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc–heptanes).

(42) **3-(4-Ethoxyphenyl)-2-phenyl-6-(*m*-tolyl)-4*H*-chromen-4-one (6c)**
Starting with **2** (75 mg, 0.17 mmol), (4-ethoxyphenyl)boronic acid as $Ar^1B(OH)_2$ (29 mg, 0.17 mmol), $K_3PO_4$ (53 mg, 0.26 mmol), $Pd(PPh_3)_4$ (6 mg, 3 mol%), and (3-methylphenyl)boronic acid as $Ar^2B(OH)_2$ (30 mg, 0.22 mmol), **6c** was prepared as a light yellow highly viscous oil (66 mg, 91%). Reaction temperature: 65 °C for 36 h, then 105 °C for 12 h. $^1$H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.0 Hz, $CH_3$), 2.36 (s, 3 H, $CH_3$), 3.95 (q, 2 H, *J* = 7.0 Hz, $OCH_2$), 6.75 (d, 2 H, *J* = 8.8 Hz, ArH), 7.07 (d, 2 H, *J* = 8.8 Hz, ArH), 7.11–7.31 (m, 5 H, ArH), 7.34–7.43 (m, 4 H, ArH), 7.50 (d, 1 H, *J* = 8.7 Hz, ArH), 7.84 (dd, 1 H, *J* = 8.7, 2.3 Hz, ArH), 8.41 (d, 1 H, *J* = 2.3 Hz, ArH). $^{13}$C NMR (75.5 MHz, $CDCl_3$): δ = 14.9, 21.6 ($CH_3$), 63.4 ($OCH_2$), 114.4, 118.4 (CH), 122.5, 123.6 (C), 124.1, 124.3 (CH), 124.8 (C), 128.0, 128.1, 128.5, 128.9, 129.6, 129.9, 132.4, 132.6 (CH), 133.5, 138.3, 138.7, 139.5, 155.4, 158.5, 161.2 (C), 177.7 (CO). IR (KBr): ν = 3055, 3034, 2975, 2922, 2871 (w), 1636, 1606 (s), 1558 (m), 1510 (s), 1494 (w), 1474 (s), 1444 (m), 1405, 1393 (w), 1361 (s), 1285, 1270 (w), 1224, 1174 (s), 1143, 1114, 1094, 1076 (w), 1041, 1029 (m), 1012, 1000, 933, 919, 845 (w), 825, 782, 769, 729, 718, 692 (s), 665 (w), 643, 631 (m), 597, 564, 531 (w) cm$^{-1}$. GC–MS (EI, 70 eV): *m/z* (%) = 432 (79) [M]$^+$, 431 (100) [M – H]$^+$, 403 (18), 375 (5), 222 (10). HRMS (EI, 70

eV): *m/z* calcd for $C_{30}H_{24}O_3$ $[M]^+$: 432.17200; found: 432.17124.

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