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Note

The efficient total synthesis of bis-glycosyl apigenin from naringenin: a greener way

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ABSTRACT

An efficient total synthesis of 7-*O*-β-D-glucopyranosyl-4′-*O*-α-L-rhamnopyranosyl apigenin (**1**) was developed in only four steps from naringenin. Compared with our previously reported first total synthesis route (six steps and 19.6% overall yield), this new route contained two steps of highly regioselective glycosylation without any selective protection steps. 7,4′-di-*O*-β-D-glucopyranosyl apigenin (**2**) was also prepared efficiently by this method. The method is environmentally friendly, economical, and provides a greener method for flavonoid synthesis starting from an inexpensive flavanone.

Glycosylated flavonoids occur widely in human food and drinks, especially in fruits and vegetables,[1,2] and exhibit a broad spectrum of interesting biological activities,[3] such as activities against cancer, cardiovascular, and neurodegenerative diseases.[4,5] Flavonoids also contribute to the pigment of petal and plants, providing a colorful nature.[1]

The first total synthesis of 7-*O*-β-D-glucopyranosyl-4′-*O*-α-L-rhamnopyranosyl apigenin (**1**, Fig. 1) was recently reported by our group.[6] Because of its excellent inhibitory activity against hepatitis B virus replication and remarkable anti-stroke activity,[7,8] its preparation in large scale was needed for further pharmacology studies. During our process of research, a practical and much cheaper method was developed, which provided **1** from naringenin (an inexpensive flavanone) in four steps without any selective protection steps. Using the same method, 7,4′-di-*O*-β-D-glucopyranosyl apigenin (**2**) was prepared, which is an important pigment component contributing to the blue color of *Salvia Patens*' petals.[9] In addition, the route developed employed reagents and conditions that are both environmentally friendly and inexpensive.

Earlier work by Kondo and co-workers reported the direct glycosylation of naringenin.[9] Using these conditions, 7-*O*-glucosyl flavonoid **5** was obtained in moderate yield, but a large amount of Ag_2CO_3 (1.5 equiv) and quinoline were needed, which is not ideal for large-scale reactions. The phase transfer-catalyzed (PTC) method, which was successfully applied in flavonoid synthesis,[10,11] was also tried for this direct glycosylation, but in initial experiments, the yield was poor (Table 1, entries 1–3), due to the poor solubility of naringenin. However, in the case of Aliquat 336 ($CH_3(C_8H_{17})_3N^+Cl^-$), the yield and regioselectivity were better. Because naringenin in a mixture of $CHCl_3$ and water (entry 3) is a suspension, while naringenin could be readily dissolved in DMF–water (1:1), DMF was added to improve the solubility of naringenin. This change in solvent improved the reaction; using $CHCl_3$–DMF–water 1:1:1 (entry 6), 7-*O*-glucosyl flavonoid **5** was obtained in 47% yield. However, the hydrolysis of bromide **4** into compound **4a** still remained as a main side reaction.

Preliminary studies showed that by changing the number of equivalents of PTC from 0.5 to 0.1, the hydrolysis of bromide **4** was greatly decreased, while the glycosylation rate was not affected. However, the concentration of bromide **4** affected the glycosylation rate significantly. Further optimization of the number of equivalents of K_2CO_3 and Aliquat 336 led to a good result (entry 8), compound **5** was obtained in 71% yield. The hydrolysis of bromide **4** was greatly reduced with 0.1 equiv of PTC, which helped to maintain the concentration of bromide **4** and benefit the glycosylation reaction.

Interestingly, in some cases (Table 1, entries 2 and 5), a small amount of 7,4′-di-*O*-β-D-glucosyl flavonoid **6** was produced at the early stage of reaction, which was isolated and confirmed by ^1H NMR spectroscopy. Our attempts to glycosylate compound **5** with bromide **4** under the above PTC conditions failed, proving that the 4′-hydroxy group of naringenin is much more inert than the 7-hydroxy group (Scheme 1). Based on this result, we thought that the formation of **6** did not proceed in a stepwise PTC glycosylation via compound **5**, but required the formation of di-anion (where the

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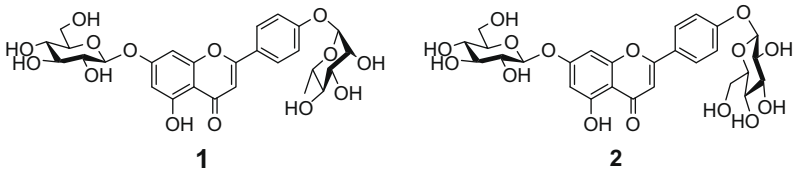


Figure 1. 7-*O*-β-D-Glucopyranosyl-4′-*O*-α-L-rhamnopyranosyl apigenin (**1**) and 7, 4′-di-*O*-β-D-glucopyranosyl apigenin (**2**).

Table 1
Study of selective direct glycosylation of naringenin[a]

Entry	K_2CO_3 (equiv)	PTC agent	Catalyst equiv	Solvent ratio[b]	Yield (%)	
					5	**6**
1	1.5	TBAB	0.1	1:1:0	Trace	—
2	1.5	TBAB	0.5	1:1:0	12.5%	7%
3	1.5	Aliquat336	0.5	1:1:0	23%	—
4	1.5	Aliquat336	0.5	20:20:1	31%	2%
5	1.5	Aliquat336	0.5	2:2:1	42%	4%
6	1.5	Aliquat336	0.5	1:1:1	47%	5%
7	2.5	Aliquat336	0.5	1:1:1	61%	5%
8	2	Aliquat336	0.1	1:1:1	71%	—

[a] The reactions were vigorously stirred at 40 °C for 24 h.
[b] Solvent ratio of H_2O–$CHCl_3$–DMF (v/v/v).

7,4′-hydroxyl groups are both deprotonated). Such a species would be more difficult to transfer into chloroform during the reaction. At the early stage of the reaction, dianion was formed under the high concentration of K_2CO_3. When an effective amount of PTC was used (0.5 equiv, entry 7), the dianion could be transferred into chloroform, where they reacted with bromide **4** directly to provide product **6**. When a smaller amount (0.1 equiv) of PTC was used (entry 8), the concentration of di-anion in $CHCl_3$ was reduced greatly, this reaction pathway was retarded.

Boron chelates were reported to improve the selectivity or reactivity of aryl substitution reaction.[12] Inspired by these reports, several Lewis acids were tried to investigate the metal chelating effect on glycosylation (Table 2). Unfortunately, none gave an improved result, and a lower yield was obtained. When K_2CO_3 was added, there was a white flocculent solid that formed after 6 h, which was carbonate, thus demonstrating that the Lewis acid hindered the base-promoted glycosylation reaction (see Scheme 2).

Compound **5** could be oxidized with DDQ or iodine–pyridine to compound **7** in good yield.[13] The iodine–pyridine method was used because of its mild conditions, better reproducibility, and easy work-up, which showed great advantage in our scale-up attempts.

The subsequent 4′-O-glycosylation has been reported to be difficult. The success of this kind of glycosylation has been achieved by using glucosyl fluorides with hindered base DTBMP and TMG.[9] Although the yield was good, the expensive donor and the reagents prompted us to find a cheaper glycosylation condition (see Scheme 3).

Table 2
Investigation of the metal chelating effect on glycosylation[a]

Entry	Lewis acid	Equiv	Yield (%)
1	—	—	61
2	$ZnCl_2$	1	33
3	$AlCl_3$	1	37
4	$Yb(OTf)_3$	0.8	36
5	$MgCl_2$	1	43
6	$B(OCH_3)_3$	1	42

[a] Reaction conditions: 2.5 equiv K_2CO_3, 0.5 equiv Aliquat 336, H_2O–$CHCl_3$–DMF 1:1:1, vigorously stirred at 40 °C for 24 h.

The solvent showed remarkable influence on the glycosylation: the use of CH_2Cl_2 gave the best results. Addition of DMF or acetonitrile, which improves the solubility of compound **7**, did not increase the yield, due to the increased hydrolyzation of rhamnosyl bromide (Table 3, entry 5 and 6). Similar results were obtained when the equivalents of Aliquat 336 was raised to 1 equiv (entry 3). Interestingly, when the concentration of flavonoid **7** in CH_2Cl_2 was diluted to 0.05 mol/L, the yield improved remarkably (Table 3, entry 7). Global deprotection of compound **9** with sodium methoxide provided flavonoid **1** in 93% yield.

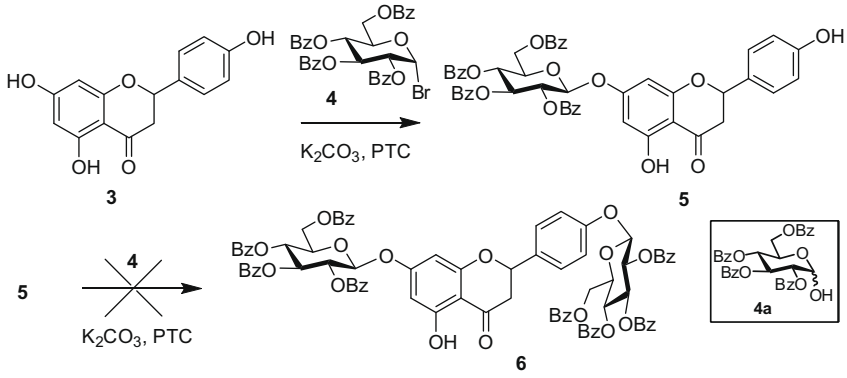
Using these optimized conditions, 4′-O-glycosylation of flavonoid **7** with tetrabenzoylglucosyl bromide proceeds smoothly and compound **10** was obtained in 55% yield. Next, **2** was obtained by the treatment with NaOMe. Although the yield of glycosylation was lower than that of the reported fluoride case,[9] the application of much more easily accessed glycosyl bromide donor make this an attractive synthetic route. These two synthetic cases demonstrated that glycosyl bromides can be suitable donors for flavonoid 4′-O-glycosylation, which has been reported to be difficult.

In conclusion, the synthesis of 7-*O*-β-D-glucopyranosyl-4′-*O*-α-L-rhamnopyranosyl apigenin **1** was accomplished in four steps and 30% overall yield from inexpensive naringenin. This new route contained two highly regioselective glycosylation steps without any selective protection step, and improved remarkably our previously reported first total synthesis of **1**[6] (six steps and 19.6% overall yield) and was easy to scale up. 7,4′-di-*O*-β-D-glucopyranosyl apigenin **2** was also prepared efficiently by this method. The method is environmentally friendly, economical, and provides a greener method for flavonoid synthesis starting from an inexpensive flavanone.

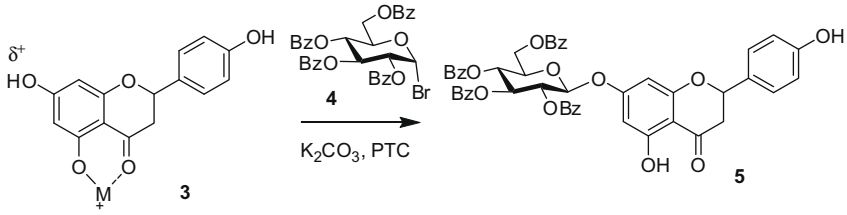
1. Experimental section

1.1. General methods

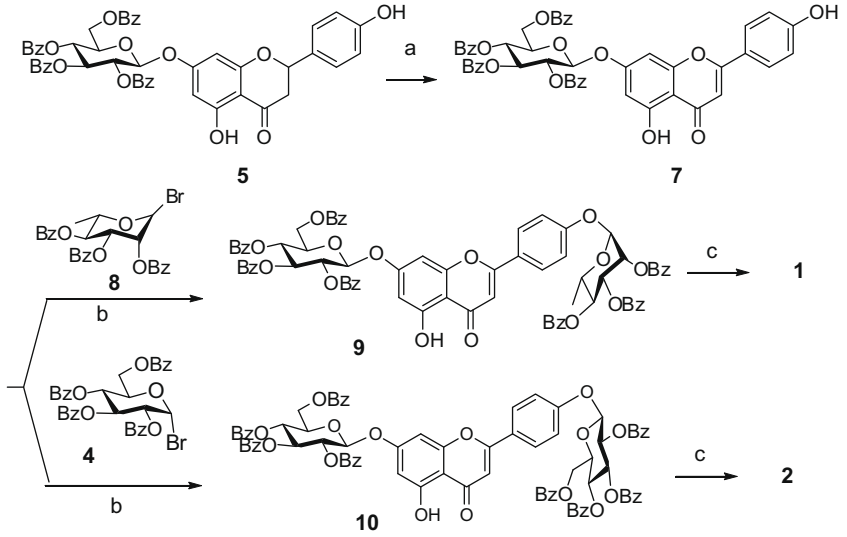
Reagents and solvents were reagent grade and used without further purification. Methylene dichloride was distilled from calcium hydride. All reactions involving air or moisture sensitive reagents or intermediates were performed under a nitrogen or



Scheme 1. Reagents and conditions: K_2CO_3, PTC, H_2O–DMF–$CHCl_3$, 40 °C, 24 h.



Scheme 2. Reagents and conditions: Lewis acid, Aliquat 336, H_2O–DMF–$CHCl_3$, then K_2CO_3, 40 °C, 24 h.



Scheme 3. Reagents and conditions: (a) I_2, py, 90 °C, 4 h, 90%; (b) K_2CO_3, Aliquat 336, H_2O–CH_2Cl_2, 40 °C, 24 h, for **9**: 52%, for **10**: 55%; (c) $NaOCH_3$, for **1**: 93%, for **2**: 91%.

Table 3
Study of 4′-O-rhamnosylation of flavonoid **7**[a]

Entry	Base (equiv)	PTC agent	Catalyst equiv	Solvent	Yield (%)
1	K_2CO_3 (2)	Aliquat336	0.2	$CHCl_3$	13
2	K_2CO_3 (2)	TBAB	0.2	$CHCl_3$	Trace
3	NaOH (2)	Aliquat336	1	$CHCl_3$	Trace
4	K_2CO_3 (2)	Aliquat336	0.2	CH_2Cl_2	25
5	K_2CO_3 (2)	Aliquat336	0.2	CH_2Cl_2/DMF[b]	Trace
6	K_2CO_3 (2)	Aliquat336	0.2	CH_2Cl_2/CH_3CN[b]	18
7	K_2CO_3 (2)	Aliquat336	0.2	CH_2Cl_2[c]	52
8	K_2CO_3 (2)	Aliquat336	0.2	CH_2Cl_2[d]	31

[a] Unless indicated, the reactions were vigorously stirred at 40 °C for 24 h, the concentration of flavonoid **7** in chloroform was 0.1 M.
[b] Solvent ratio is CH_2Cl_2–X 2:1 (v/v).
[c] The concentration of flavonoid **7** in CH_2Cl_2 was 0.05 M.
[d] The concentration of flavonoid **7** in CH_2Cl_2 was 0.025 M.

argon atmosphere. Flash chromatography was performed on Qingdao Haiyang silica gel (300−400 mesh). Analytical TLC was performed using 0.25 mm EM Silica Gel 60 F_{250} plates that were visualized by irradiation (254 nm) or by staining with H_2SO_4–CH_3OH solution. ^1H and ^{13}C NMR spectra were obtained using 300 MHz Bruker AM300 and 400 MHz Varian instruments. Elemental analysis was performed on a Foss-Heraeus Vario EL instrument. Mass spectra (ESI) were performed on Shimadzu LCMS-2010EV. High resolution mass spectra (MALDI/DHB) were performed on IonSpec 4.7 Tesla FTMS from Varian.

1.2. 7-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-naringenin (5)

A solution of naringenin (19 g, 70 mmol) and K_2CO_3 (20 g, 144 mmol) in DMF (700 mL), H_2O (700 mL), was mixed with aliquat 336 (3 g, 7 mmol) and bromide **4** (72.5 g, 110 mmol) in $CHCl_3$ (700 mL). The mixture was stirred vigorously at 45 °C for 24 h, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (hexane–EtOAc 3:1, R_f = 0.26) to obtain **5** (43.7 g, 70%) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 2.76 (1H, m), 3.04 (1H, m), 4.40 (1H, m), 4.53 (1H, dd, J = 6.4, 12.0 Hz), 4.73 (1H, m), 5.27 (1H, m), 5.54 (1H, dd, J = 7.6, 11.2 Hz), 5.79 (2H, m), 6.02 (1H, t, J = 9.2 Hz), 6.15 (1H, m), 6.27 (1H, m), 6.90 (2H, m), 7.39 (14H, m), 7.97 (8H, m). ^{13}C NMR (100 MHz, $CDCl_3$): 42.8, 43.2, 63.1, 69.2, 71.4, 72.6, 72.9, 78.9, 96.3, 96.4, 97.2, 97.9, 98.0, 104.3, 115.7, 127.7, 127.9, 128.3–133.5 (m, Ar), 156.6, 162.8, 162.9, 163.9, 164.0, 164.3, 164.4, 165.0, 165.2, 165.8, 166.2, 196.4, 196.5. ESI-MS (*m/z*): 873.12 $[M+Na]^+$, 889.10 $[M+K]^+$.

1.3. 7-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-apigenin (7)

A solution of **5** (13.5 g, 16.2 mmol), and iodine (4 g, 16 mmol) in pyridine (140 mL) was heated to 90 °C for 4 h. The mixture was cooled and poured into cold water. The precipitate was separated and the mixture was extracted with EtOAc. The combined organic phases were washed with saturated sodium thiosulfate and water, successively. Then, the organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (hexane–THF 3:2, R_f = 0.25) to obtain compound **7** (12.1 g, 88%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.46 (1H, dd, J = 2.4, 6.8 Hz), 4.53 (1H, dd, J = 6.0, 6.4 Hz), 4.78 (1H, dd, J = 2.4, 9.6 Hz), 5.58 (1H, d, 7.6 Hz), 5.81 (2H, m), 6.03 (1H, t, J = 9.2 Hz), 6.53 (3H, m), 6.95 (1H, s), 6.97 (2H, s), 7.36 (8H, m), 7.51 (4H, m), 7.69 (2H, d, J = 8.4 Hz), 7.91 (2H, d, J = 7.6 Hz), 7.99 (6H, m), 12.73 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 63.0, 69.3, 71.6, 72.7, 73.0, 95.6, 98.2, 99.8, 104.1, 106.8, 116.2 (2C), 123.0, 128.4, 128.5, 128.6, 128.9–133.6 (m, Ar), 157.2, 159.8, 161.9, 162.3, 164.6, 165.1, 165.2, 165.8, 166.2, 182.4. ESI-MS (*m/z*): 871.18 [M+Na]+, 849.20 $[M+H]^+$.

1.4. 7-*O*-(2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl)-4′-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl) apigenin (9)

A solution of K_2CO_3 (1.38 g, 10 mmol) in H_2O (100 mL), was mixed with acceptor **5** (4.2 g, 5 mmol), Aliquat 336 (0.4 g, 1 mmol) and bromide **4** (5.4 g, 10 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred vigorously at 45 °C for 24 h, the organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were combined, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (hexane–THF–CH_2Cl_2 3:1:1, R_f = 0.19) to obtain **9** (3.4 g, 52%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.42 (3H, CH_3), 4.34 (1H, m), 4.53 (3H, m), 4.80 (1H, d, J = 11.6 Hz), 5.66 (1H, d, J = 7.2 Hz), 5.86 (4H, m), 6.02 (2H, m), 6.35 (1H, m), 6.62 (2H, m), 7.19–8.26 (39H, Ar), 12.71 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 17.6, 63.0, 68.0, 69.3, 69.6, 70.4, 71.4, 71.5, 72.6, 73.0, 95.7, 98.2, 99.9, 100.1, 105.0, 105.9, 106.9, 116.9, 122.5, 125.4, 127.7, 128.2–133.9 (m, Ar), 158.8, 161.9, 162.1, 162.4, 162.4, 163.4, 163.8, 164.5, 164.9, 165.2, 165.5, 165.6, 166.0, 182.30. ESI-MS (*m/z*): 1329.27 $[M+Na]^+$, 1345.28 $[M+K]^+$, 1307.26 $[M+H]^+$.

1.5. 7,4′-Di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-apigenin (10)

The procedure was the same as that for flavonoid **9**, yielding **10** (1.9 g, 55%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.53 (4H, m), 4.75 (2H, m), 5.54 (1H, d), 5.64 (1H, d, J = 7.6 Hz), 5.80 (4H, m), 6.05 (2H, m), 6.48 (1H, s), 6.57 (2H, s), 7.09 (2H, d, J = 8.8 Hz), 7.44 (26H, m), 7.98 (16H, m). ^{13}C NMR (100 MHz, $CDCl_3$): 63.0, 69.3, 69.6, 71.7, 72.6, 72.9, 73.0, 95.6, 98.2, 98.8, 99.8, 105.0, 106.9, 117.4, 125.8, 127.9, 128.3, 128.4–133.5 (m, Ar), 157.2, 159.4, 162.0, 162.5, 163.7, 165.0, 165.2, 165.3, 165.7 (2 C), 165.8, 166.0, 182.3. ESI-MS (*m/z*):1449.31 $[M+Na]^+$, 1427.31 $[M+K]^+$.

1.6. 7-*O*-β-D-Glucopyranosyl-4′-*O*-α-L-rhamnopyranosyl apigenin (1)

A solution of **9** (6.5 g, 5 mmol) in CH_2Cl_2 (100 mL) and MeOH (200 mL) with NaOMe (1 g, 20 mmol) was stirred for 4 h at rt. The mixture was quenched by adding methanolic HCl (2 M) to pH 6–7, and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel (CH_2Cl_2–CH_3OH 3:1) to give **1** (2.7 g, 93%). ^1H NMR (400 MHz, C_6D_6N): δ 8.07 (d, 2H, J = 8.8 Hz), 7.45 (d, 2H, J = 8.8 Hz), 7.23 (d, 1H, J = 1.6 Hz), 7.07 (s, 1H), 6.96 (d, 1H, J = 2 Hz), 6.22 (s, 1H), 5.92 (d, 1H, J = 7.7 Hz), 4.74 (m, 2H), 4.36 (m, 8H), 1.67 (d, 3H, J = 6.2 Hz). ^{13}C NMR (100 MHz, C_6D_6N): δ 183.2, 164.8, 164.5, 160.5, 158.3, 159.6, 129.1, 129.1, 125.1, 117.7, 117.7, 106.9, 105.3, 102.0, 101.2, 100.0, 96.0, 79.3, 78.4, 74.9, 73.8, 73.7, 72.5, 71.8, 71.5, 62.6, 18.9. ESI-MS (*m/z*): 601.1 $[M+Na]^+$, 613.1 $[M+Cl]^-$, HR-MS: *m/z* calcd for $C_{27}H_{31}O_{14}$: 579.1714, found: 579.1708.

1.7. 7,4′-Di-*O*-β-D-glucopyranosyl apigenin 2

The procedure was the same as that for **1**, giving **2** (2.9 g, 91%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.53 (4H, m), 4.75 (2H, m), 5.54 (1H, d), 5.64 (1H, d, J = 7.6 Hz), 5.80 (4H, m), 6.05 (2H, m), 6.48 (1H, s), 6.57 (2H, s), 7.09 (2H, d, J = 8.8 Hz), 7.44 (26 H, m), 7.98 (16H, m). ^{13}C NMR (100 MHz, $CDCl_3$): 63.0, 69.3, 69.6, 71.7, 72.6, 72.9, 73.0, 95.6, 98.2, 98.8, 99.8, 105.0, 106.9, 117.4, 125.8, 127.9, 128.3, 128.4–133.5 (m, Ar), 157.2, 159.4, 162.0, 162.5, 163.7, 165.0, 165.2, 165.3, 165.7 (2C), 165.8, 166.0, 182.3. ESI-MS (*m/z*):1449.31 $[M+Na]^+$, 1427.31 $[M+K]^+$.

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