Synthesis of 6- or 8-Bromo Flavonoids by Regioselective Mono-Bromination and Deprotection Protocol from Flavonoid Alkyl Ethers

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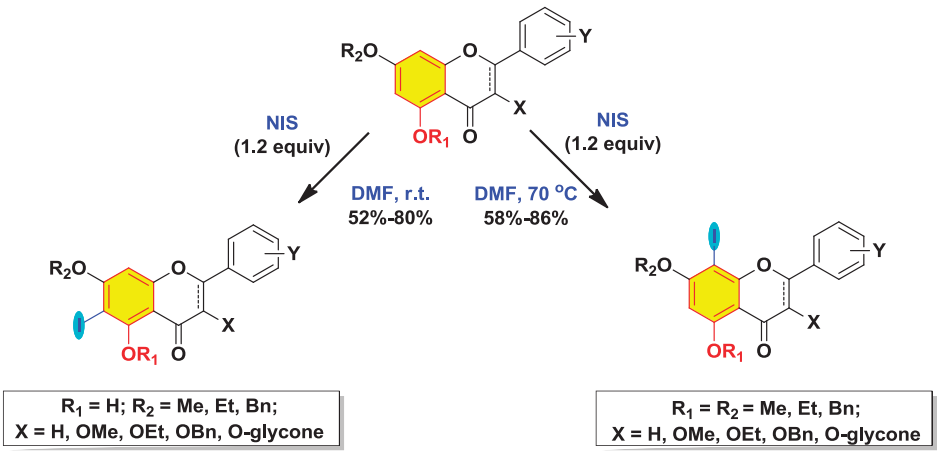
C-6 and C-8 monobromo flavonoids are important building blocks for the synthesis of flavonoid natural products and their derivatives. Bromination of suitably alkylated flavonoids with *N*-bromosuccinimide in dichloromethane (DCM), followed by deprotection with BCl_3, gives either a C-6 or a C-8 monobromo flavonoid in high yield and with high regioselectivity, depending on the protection pattern of the C-5 and C-7 OH groups. The mild and neutral conditions are particularly useful for the regioselective bromination of acid-labile substrates.

Keywords: Flavonoids, Regioselective, Bromination

Introduction

Flavonoids are polyphenolic secondary metabolites found in plants and various common food.[1] Many of them possess a broad range of pharmacological properties including anticancer, antiviral, antioxidant, and anti-inflammatory properties.[2] Among those, C-6 and C-8 alkyl or aryl substituted flavonoids are most common; they can be prepared from the corresponding halogen-substituted flavonoids by Suzuki coupling[3] or Ullmann coupling.[4] Recently, we developed a regioselective iodination method for flavonoids by *N*-iodosuccinimide (NIS) under neutral conditions (Scheme 1).[5] Although the *O*-alkylated mono-iodo flavonoids can be obtained in high yield, the subsequent dealkylation is always accompanied by deiodination. Moreover, it is well known that iodide is more susceptible to dehalogenation in the aforementioned coupling reactions, especially when a bulky substituent is located *ortho* to the halogen group, compared to the corresponding bromide. In 1985, Ichikawa achieved the transformations of quercetin and kaempferol to their 6-bromo and 6,8-dibromo derivatives by a mixture of HBr and H_2O_2 in methanol.[6] However, the strong acidic conditions limited their applications. In 2010 and 2014, Lewin[7] and Rocco[8] reported the bromination of quercetin and its derivatives with *N*-bromosuccinimide (NBS), respectively. However, a mixture of 6-bromo, 8-bromo, and 6,8-dibromo products was obtained under these conditions. This encouraged us to develop an efficient regioselective method to prepare bromo-substituted flavonoids. Herein we report a mild and regioselective monobromination of O-alkylated flavonoid derivatives using NBS as



Scheme 1. Regioselective iodination of flavonoids by NIS.

bromination reagent in DCM. By using this protocol, monobromo flavonoids can be prepared easily by regioselective bromination and subsequent dealkylation.

Experimental

Synthesis of Bromo-Flavonoid Alkyl Ethers. 6-Bromo-2-(3,4-dimethoxyphenyl)-5-hydroxy-3,7-dimethoxy-4*H*-chromen-4-one (2); 8-bromo-2-(3,4-dimethoxyphenyl)-5-hydroxy-3,7-dimethoxy-4*H*-chromen-4-one (3); and 6,8-dibromo-2-(3,4-dimethoxyphenyl)-5-hydroxy-3,7-dimethoxy-4*H*-chromen-4-one (4). NBS (196 mg, 1.1 mmol) was added in portions to **1** (358 mg, 1.0 mmol) in DCM (10 mL) at −40 °C over 5 min. The mixture was stirred for 6 h at −40 °C. After completion of the reaction, the mixture was concentrated to dryness under reduced pressure. The crude product was purified by column chromatography on silica (petroleum ether/ethyl acetate/dichloromethane 30:1:1) to afford compound **2** (223 mg, 51%) and compound **3** (109 mg, 25%) as yellow solids. Data for **2**: ^{1}H NMR (400 MHz, DMSO-d_6, δ): 13.42 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 7.17 (d, J = 8.8 Hz,1H), 7.06 (s, 1H), 3.99 (s, 3H), 3.87 (s, 6H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 56.0, 56.1, 56.8, 60.3, 90.6, 94.0, 106.4, 110.9, 111.3, 122.3, 122.6, 139.1, 148.9, 151.6, 155.7, 156.2, 158.2, 161.3, 178.2; LRMS (ESI) *m/z* 439 $[M + H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{19}H_{17}O_7Br$ $[M + H]^+$ 437.0230; found, 437.0226; m.p.: 180.9–182.0 °C.

Data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 12.79 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.91 (s, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.46 (s, 1H), 3.99 (s, 9H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 55.9, 56.0, 56.9, 60.1, 87.7, 95.6, 106.2, 111.0, 111.2, 122.8, 122.8, 138.9, 148.9, 151.7, 152.4, 155.8, 161.6, 178.6; LRMS (ESI) *m/z* 439 $[M + H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{19}H_{17}O_7Br$ $[M + H]^+$ 437.0230; found, 437.0228; m.p.: 218.8–219.0 °C.

NBS (196 mg, 1.1 mmol) was added in portions to **1** (358 mg, 1 mmol) in DMF (10 mL) at 0 °C over 5 min. The mixture was stirred for 6 h at 0 °C. After completion of the reaction, the mixture was diluted with DCM (50 mL) and washed with water (100 mL × 3). The organic phase was concentrated to dryness under reduced pressure, the crude product was purified by column chromatography on silica (petroleum ether/ethyl acetate/dichloromethane 30:1:1) to afford compound **2** (101 mg, 23%) and compound **4** (160 mg, 31%) as yellow solids. Data for **4**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 12.49 (s, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.87 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H) 4.00 (s, 3H), 3.98 (s, 6H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 55.9, 56.1, 60.1, 61.2, 95.1, 100.5, 108.9, 111.1, 111.1, 122.3, 122.9, 139.1, 148.9, 151.2, 152.0, 156.5, 157.8, 159.8, 178.2; LRMS (ESI) *m/z* 514 $[M + H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{19}H_{17}O_7Br_2$: $[M + H]^+$ 514.9336; found, 514.9320; m.p.: 199.0–200.6 °C.

8-Bromo-2-(3,4-dimethoxyphenyl)-3,5,7-trimethoxy-4*H*-chromen-4-one (15). NBS (178 mg, 1.0 mmol) was added to a stirred solution of **14** (372 mg, 1 mmol) in DCM (10 mL) at 25 °C. After the addition, the mixture was stirred for 2 h and then concentrated to dryness under reduced pressure, the crude product was purified by column chromatography on silica (petroleum ether/ethyl acetate 3:1) to afford compound **15** (433 mg, 96%) as a white solid. Data for **15**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.98 (d, J = 8.4 Hz, 1H), 7.97 (s, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.43 (s, 1H), 4.04 (s, 6H), 3.98 (s, 3H), 3.97 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 56.0, 56.1, 56.8, 60.2, 90.6, 93.9, 106.4, 110.9, 111.3, 122.3, 122.6, 139.1, 148.9, 151.6, 155.7, 156.2, 158.2, 161.3, 178.2; LRMS (ESI) *m/z* 453 $[M + H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{20}H_{20}O_7Br$ $[M + H]^+$ 451.0387; found, 451.0380; m.p.: 185.9–186.0 °C.

6-Bromo-2-(3,4-diethoxyphenyl)-3,7-diethoxy-5-hydroxy-4*H*-chromen-4-one (9) and 8-bromo-2-(3,4-diethoxyphenyl)-3,7-diethoxy-5-hydroxy-4*H*-chromen-4-one (10). NBS (196 mg, 1.1 mmol) was added in portions to **8** (414 mg, 1.0 mmol) in DCM (10 mL) at −40 °C over 5 min. The mixture was stirred for 6 h at −40 °C. After completion of the reaction, the mixture was concentrated to dryness under reduced pressure, the crude product was purified by column chromatography on silica (petroleum ether/ethyl acetate/dichloromethane 30:1:1) to afford compound **9** (281 mg, 57%) and compound **10** (59 mg, 12%) as yellow solids. Data for **9**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 13.45 (s, 1H), 7.74 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.49 (s, 1H), 4.16–4.21 (m, 6H), 4.08 (q, J = 7.2 Hz, 2H), 1.51 (m, 9H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.4, 14.7, 14.9, 15.6, 64.5, 64.9, 65.5, 68.7, 91.2, 94.2, 106.2, 112.2, 113.7, 122.2, 122.7, 137.9, 148.2, 151.4, 155.7, 156.6, 158.2, 160.7, 178.34; LRMS (ESI) *m/z* 493 $[M + H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{23}H_{26}O_7Br$ $[M + H]^+$ 493.0856; found, 493.0851; m.p.: 169.3–171.9 °C. Data for **10**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.95–7.97 (m, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.42 (s, 1H), 4.18–4.23 (m, 6H), 4.13 (q, J = 6.8 Hz, 2H), 1.50–1.54 (m, 9H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.5, 14.7, 14.8, 15.7, 64.5, 64.6, 65.5, 68.6, 87.9, 96.3, 106.1, 112.4, 113.3, 122.6, 122.9, 137.8, 148.2, 151.3, 152.5, 156.2, 161.0, 161.4, 178.8; LRMS (ESI) *m/z* 493 $[M + H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{23}H_{26}O_7Br$ $[M + H]^+$ 493.0856; found, 493.0849; m.p.: 172.4–173.2 °C.

8-Bromo-2-(3,4-diethoxyphenyl)-3,5,7-triethoxy-4*H*-chromen-4-one (17). NBS (178 mg, 1.0 mmol) was added to a stirred solution of **16** (442 mg, 1.0 mmol) in DCM (10 mL) at 25 °C. After completion of the reaction, the mixture was concentrated to dryness under reduced pressure, the crude product was purified by recrystallization in ethyl acetate to get a yellow solid **17** (505 mg, 97%). Data for **17**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.97 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.41 (s, 1H), 4.12–4.23 (m, 10H), 1.50–1.58 (m, 12H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 14.6, 14.7, 14.8, 15.7, 64.4, 64.5, 65.3, 65.6, 67.9, 76.8, 77.1, 77.4, 90.8, 94.1, 110.1, 112.4, 113.2, 122.1, 123.4, 139.8, 148.1, 150.6, 152.8, 154.1, 159.4, 159.7, 173.8; LRMS (ESI) *m/z* 521 $[M + H]^+$; HRMS

(ESI) *m/z*: Calcd for $C_{25}H_{30}O_7Br$ $[M+H]^+$ 521.1169; found, 521.1174; m.p.: 174.9–176.8 °C.

6-Bromo-2-(3,4-diisopropoxyphenyl)-5-hydroxy-3,7-diisopropoxy-4*H*-chromen-4-one (12). NBS (196 mg, 1.1 mmol) was added in portions to **11** (470 mg, 1.0 mmol) in DCM (10 mL) at −40 °C over 5 min. The mixture was stirred for 6 h at −40 °C. After completion of the reaction, the mixture was concentrated to dryness under reduced pressure, the crude product was purified by column chromatography on silica (petroleum ether/ethyl acetate 30:1) to afford compound **12** (411 mg, 75%) as a yellow solid. Data for **12**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 13.53 (s, 1H), 7.78 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.50 (s, 1H), 4.48–4.74 (m, 4H), 1.46 (d, J = 6.0 Hz, 6H), 1.38–1.41 (m, 12H), 1.21 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.9, 22.1, 22.3, 71.7, 72.5, 72.9, 75.1, 92.2, 95.0, 105.9, 115.6, 119.7, 123.3, 123.5, 136.6, 148.0, 151.9, 155.6, 156.9, 158.3, 159.8, 178.6; LRMS (ESI) *m/z* 549 $[M+H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{27}H_{33}O_7Br$ $[M+H]^+$ 549.1482; found, 549.1489; m.p.: 110.8–111.0 °C.

8-Bromo-2-(3,4-diisopropoxyphenyl)-3,5,7-triisopropoxy-4*H*-chromen-4-one (19). This compound was synthesized by following the same procedure for the synthesis of compound **17** by using **18** (512 mg, 1.0 mmol) as substrate to afford compound **19** (573 mg, 97%) as a yellow solid. Data for **19**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.99 (s, 1H), 7.95 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.42 (s, 1H), 4.50–4.83 (m, 5H), 1.38–1.47 (m, 24H), 1.21 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.9, 22.1, 22.2, 22.3, 22.4, 71.8, 72.4, 72.6, 73.8, 74.0, 93.1, 99.7, 111.5, 116.0, 118.4, 123.1, 124.3, 138.4, 148.2, 151.0, 153.5, 154.4, 158.4, 158.6, 173.9; LRMS (ESI) *m/z* 591 $[M+H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{30}H_{40}O_7Br$ $[M+H]^+$ 591.1952; found, 591.1926; m.p.: 124.4–124.6 °C.

6-Bromo-5-hydroxy-7-isopropoxy-2-phenyl-4*H*-chromen-4-one (23). This compound was synthesized by following the same procedure for the synthesis of compound **12** by using **22** (296 mg, 1.0 mmol) as substrate. Purification of the crude product by column chromatography on silica (petroleum ether/ethyl acetate/dichloromethane 30:1:1) gave compound **23** (318 mg, 85%) as a yellow solid. Data for **23**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 13.48 (s, 1H), 7.90 (d, J = 6.4 Hz, 2H), 7.53–7.55 (m, 3H), 6.72 (s, 1H), 6.57 (s, 1H), 4.69–4.75 (m, 1H), 1.48 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.9, 72.6, 92.5, 95.9, 105.8, 105.9, 126.4, 129.2, 131.2, 132.0, 156.8, 158.6, 160.3, 164.2, 181.9; LRMS (ESI) *m/z* 375 $[M+H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{18}H_{16}O_4Br$ $[M+H]^+$ 375.0226; found, 375.0227; m.p.: 170.2–170.8 °C.

8-Bromo-5,7-diisopropoxy-2-phenyl-4*H*-chromen-4-one (26). This compound was synthesized by following the same procedure for the synthesis of compound **17** by using **25** (338 mg, 1.0 mmol) as substrate to afford compound **26** (380 mg, 91%) as a yellow solid. Data for **26**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.00–8.02 (m, 2H), 7.51–7.53 (m, 3H), 6.71 (s, 1H), 6.50 (s, 1H), 4.66–4.75 (m, 1H), 4.55–4.64 (m, 1H), 1.46 (d, J = 6.0 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.9, 22.0, 72.6, 73.7, 93.4, 99.8. 108.2, 111.3, 126.3, 129.0, 131.3, 131.4, 155.6, 158.5, 158.9, 160.8, 177.1; LRMS (ESI) *m/z* 417 $[M+H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{21}H_{22}O_4Br$ $[M+H]^+$ 417.0690; found, 417.0684; m.p.: 115.5–115.7 °C.

6-Bromo-5-hydroxy-7-isopropoxy-3-(4-isopropoxyphenyl)-4*H*-chromen-4-one (29). This compound was synthesized by following the same procedure for the synthesis of compound **12** by using **28** (354 mg, 1.0 mmol) as substrate. Purification of the crude product by column chromatography on silica (petroleum ether/ethyl acetate 20:1) gave compound **29** (307 mg, 71%) as a yellow solid. Data for **29**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 13.62 (s, 1H), 7.89 (s, 1H), 7.43 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.46 (s, 1H), 4.68 (m, 1H), 4.58 (m, 1H), 1.45 (d, J = 6.0 Hz, 6H), 1.35 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.8, 22.0, 69.9, 72.6, 92.2, 95.7, 106.3, 115.9, 122.3, 123.8, 130.1, 152.7, 156.8, 158.3, 158.9, 160.2, 180.3; LRMS (ESI) *m/z* 433 $[M+H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{21}H_{21}O_5BrNa$ $[M+Na]^+$ 455.0465; found, 455.0478; m.p.: 148.8–149.0 °C.

8-Bromo-5,7-diisopropoxy-3-(4-isopropoxyphenyl)-4*H*-chromen-4-one (32). This compound was synthesized by following the same procedure for the synthesis of compound **17** by using **31** (396 mg, 1.0 mmol) as substrate to afford compound **32** (394 mg, 83%) as a white solid. Data for **32**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.84 (s, 1H), 7.43 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.49 (s, 1H), 4.52–4.73 (m, 3H), 1.43–1.46 (m, 12H), 1.34 (d, J = 6.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.9, 22.0, 22.1, 69.9, 72.6, 73.1, 92.6, 99.2, 111.9, 115.8, 123.8, 125.9, 130.5, 150.1, 155.8, 157.9, 158.7, 159.0, 175.1; LRMS (ESI) *m/z* 475 $[M+H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{24}H_{28}BrO_5$ $[M+H]^+$ 475.1115; found, 475.1107; m.p.: 95.5–96.6 °C.

2″,2‴,3″,3‴,4″,4‴-Hexa-*O*-acetyl-8-bromo-3′,4′,5,7-tetra-*O*-methylrutin (35). This compound was synthesized by following the same procedure for the synthesis of compound **17** by using **34** (918 mg, 1.0 mmol) as substrate to afford compound **35** (918 mg, 92%) as a white solid. Data for **35**: ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.97 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.43 (s, 1H), 5.91 (d, J = 8.0 Hz, 1H), 5.22–5.33 (m, 2H), 5.03–5.11 (m, 3H), 4.92 (t, J = 10.0 Hz, 1H), 4.51 (s, 1H), 4.05 (s, 6H), 4.02 (s, 3H), 3.97 (s, 3H), 3.71–3.75 (m, 1H), 3.59–3.66 (m, 2H), 3.44 (dd, J = 11.6 Hz, 4.8 Hz, 1H), 2.09 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H), 1.03 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 17.2, 20.7, 20.8, 20.9, 55.9, 56.1, 56.6, 56.7, 60.4, 66.6, 66.6, 68.8, 69.4, 69.5, 70.8, 71.6, 72.7, 73.0, 90.6, 91.8, 97.8, 98.6, 109.7, 110.9, 111.7, 122.7, 122.9, 135.5, 148.5, 151.2, 154.1, 154.1, 160.2, 160.6, 169.7, 169.7, 169.9, 170.0, 170.1, 172.8; LRMS (ESI) *m/z* 997 $[M+H]^+$; HRMS (ESI) *m/z*: Calcd for $C_{43}H_{50}O_{22}Br$ $[M+H]^+$ 997.1972; found, 997.1944; m.p.: 103.1–103.3 °C.

Synthesis of Bromo-Flavonoids. 6-Bromo-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one (20).

Boron tri-chloride (10 mL, 10 mmol, 1 M solution in hexane) was added to a stirred solution of **12** (550 mg, 1.0 mmol) in anhydrous DCM (20 mL) at −20 °C for 30 min. After addition, the reaction mixture was heated to reflux for 2 h. Then the reaction was cooled to room temperature, excess methanol was added drop wise at −10 °C with stirring for 10 min and then concentrated under reduced pressure. The crude product was purified by recrystallization in DCM to get compound **20** (377 mg, 99%) as a yellow solid. Data for **20**: ^{1}H NMR (400 MHz, DMSO-d_6, δ): 13.39 (s, 1H), 11.65 (s, 1H), 9.62 (s, 1H), 9.53 (s, 1H), 9.32 (s, 1H), 7.68(s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.63 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 92.5, 94.0, 103.8, 115.6, 116.1, 120.6, 122.2, 136.2, 145.6, 147.9, 148.4, 154.9, 157.8, 160.5, 175.9.

8-Bromo-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4*H*-chromen-4-one (21). This compound was synthesized by following the same procedure for the synthesis of compound **20** by using **19** (590 mg, 1.0 mmol) as substrate to afford compound **21** (377 mg, 99%) as an orange solid. Data for **21**: ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.45 (s, 1H), 11.61 (s, 1H), 9.62 (s, 2H), 7.83 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 6.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 86.4, 98.7, 104.2, 115.7, 116.2, 120.5, 122.4, 136.4, 145.6, 147.5, 148.5, 152.6, 159.9, 161.0, 176.1.

6-Bromo-5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one (24). Boron tri-chloride (5.0 mL, 5.0 mmol, 1 M solution in hexane) was added to a stirred solution of **23** (375 mg, 1.0 mmol) in anhydrous DCM (20 mL) at −20 °C for 30 min. After addition, the reaction mixture was heated to reflux for 2 h. Then the reaction was cooled to room temperature, excess methanol was added dropwise at −10 °C with stirring for 10 min and then concentrated under reduced pressure. The crude product was purified by recrystallization in DCM to get compound **24** (330 mg, 99%) as a white solid. Data for **24**: ^{1}H NMR (400 MHz, DMSO-d_6, δ): 13.73 (s, 1H), 11.84 (s, 1H), 8.10–8.11 (m, 2H), 7.57–7.64 (m, 3H), 7.08 (s, 1H), 6.75 (s, 1H).

8-Bromo-5,7-dihydroxy-2-phenyl-4*H*-chromen-4-one (27). This compound was synthesized by following the same procedure for the synthesis of compound **24** by using **26** (417 mg, 1.0 mmol) as substrate to afford compound **27** (330 mg, 99%) as a yellow solid. Data for **27**: ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.84 (s, 1H), 11.75 (s, 1H), 8.14 (m, 2H), 7.60–7.65 (m, 3H), 7.12 (s, 1H), 6.45 (s, 1H).

6-Bromo-5,7-dihydroxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (30). This compound was synthesized by following the same procedure for the synthesis of compound **20** by using **29** (433 mg, 1.0 mmol) as substrate to afford compound **30** (345 mg, 99%) as a white solid. Data for **30**: ^{1}H NMR (400 MHz, DMSO-d_6, δ): 13.84 (s, 1H), 11.77 (s, 1H), 9.61 (s, 1H), 8.40 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 6.62 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 93.4, 94.2, 105.2, 115.6, 121.4, 122.7, 130.7, 154.8, 156.5, 158.0, 159.1, 161.1, 180.4.

8-Bromo-5,7-dihydroxy-3-(4-hydroxyphenyl)-4*H*-chromen-4-one (33). This compound was synthesized by following the same procedure for the synthesis of compound **20** by using **32** (476 mg, 1.0 mmol) as substrate to afford compound **33** (345 mg, 99%) as a white solid. Data for **33**: ^{1}H NMR (400 MHz, DMSO-d_6, δ): 13.01 (s, 1H), 11.72 (s, 1H), 9.62 (s, 1H), 8.49 (s, 1H), 7.40 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.45 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 86.5, 99.5, 105.8, 115.6, 121.3, 123.0, 130.7, 154.4, 154.6, 158.1, 161.2, 161.5, 180.7; LRMS (ESI) *m/z* 371 $[M + Na]^+$; HRMS (ESI) *m/z*: Calcd for $C_{15}H_9O_5BrNa$ $[M + Na]^+$ 370.9526; found, 370.9512; m.p.: 227.6–227.8 °C.

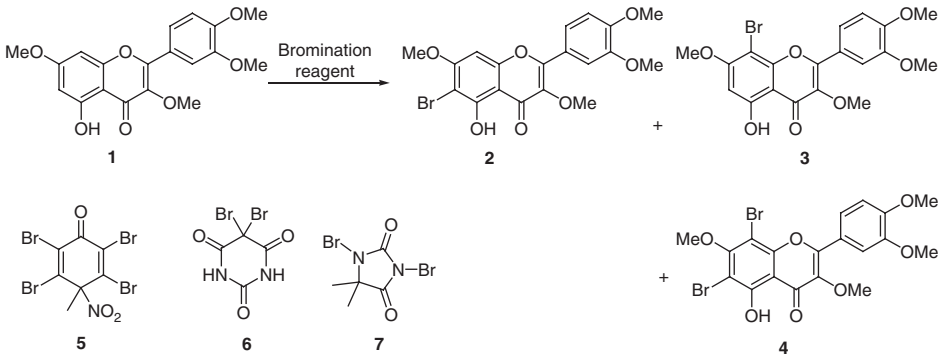
Results and Discussion

Initially, we tried the bromination on the tetramethyl-protected quercetin **1** substrate by using NBS as bromination reagent in DMF at 0 °C. Unlike the iodination by NIS,[5] we got the 6-bromo product **2** and 6,8-dibromo product **4** (Table 1, entry 1). We envisioned that the strong electrophilicity of NBS compared to NIS diminished the selectivity. Carrying out the reaction at − 20 °C in CH_2Cl_2 (DCM), proved effective in blocking the formation of the dibromide by-product. However, the 8-bromo derivative **3** was afforded in 26 % yield (Table 1, entry 2). Other bromination reagents such as 2,3,5,6-tetrabromo-4-methyl-4-nitrocyclohexa-2,5-dienone, which is reported as a mild nitration[9] or bromination agent,[10] 5,5-dibromobarbituric acid,[11] and 1,3-dibromo-5,5-dimethylhydantoin[12] were tested (Table 1, entries 3–5). All of them afforded the mono-bromo products **2** and **3**. When the reaction was carried out at −40 °C by using NBS, the yield of compound **2** improved slightly (Table 1, entry 6). Further decreasing the reaction temperature to − 78 °C did not affect the yield and regioselectivity of the reaction (Table 1, entry 7). It is worth mentioning that compounds **2–4** are not easy to separate and the solubilities of these three compounds are not good which leads to the loss of the compounds during column separation.

To improve regioselectivity, bulkier substituents such as ethyl and isopropyl were employed to protect the corresponding phenolic –OH groups. As expected, the regioselectivity and the yield of the 6-bromo product improved under the optimized conditions (Scheme 2). It is noteworthy that the solubilities of the products were greatly increased when isopropyl was used, which makes it much easier to separate the regioisomers on a column.

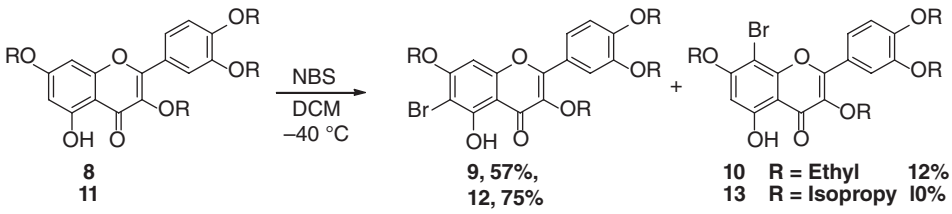
Based on our previous work on regioselective iodination by NIS,[5] the pentamethyl-protected quercetin **14** is expected to be less reactive compared with the corresponding tetramethyl-protected substrate **1** because of its steric effect and the absence of H-bonding between the halogenating reagent and phenolic –OH group of the substrate. Therefore, the bromination of compound **14** was initially carried out at 25 °C with NBS in DCM. To our delight, only the 8-bromo derivative **15** was obtained with 96% yield (Table 2, entry 1). When the reaction was carried out at 0 °C, conversion was

Table 1. Bromination of compound **1** under different conditions.[a]



Entry	Reagent	Solvent	Temperature (°C)	Yield[b] (%)		
				2	**3**	**4**
1	NBS	DMF	0	23	0	31
2	NBS	DCM	–20	47	26	0
3	**5**	DCM	–20	41	25	0
4	**6**	DCM	–20	33	31	0
5	**7**[c]	DCM	–20	36	41	0
6	NBS	DCM	–40	51	25	0
7	NBS	DCM	–78	49	26	0

[a] Reaction conditions: **1** (1.0 mmol), bromination reagent (1.1 mmol), in DMF (10 mL) or DCM (10 mL).
[b] Isolated yield after purification by silica gel chromatography.
[c] **1** (1.0 mmol) and **7** (0.5 mmol) were used.



Scheme 2. Regioselective bromination of compounds **8** and **11**.

incomplete, which led to a drop in yield (Table 2, entry 2). For this substrate, other reagents such as **5–7** effected smooth bromination to give desired product in good yield (Table 2, entries 3–5). When ethyl or isopropyl groups were used as protecting groups, the mono-bromination yield was increased to 97 % (Table 2, entries 6 and 7).

With the bromo-quercetin derivatives **12** and **19** in hand, we tried the deprotection of the phenolic –OH groups with BCl_3 in DCM. Unlike the demethylation of **2** and **15** with BBr_3, the reaction was quite clean and the desired products **20** and **21** were obtained in nearly quantitative yields (Scheme 3).

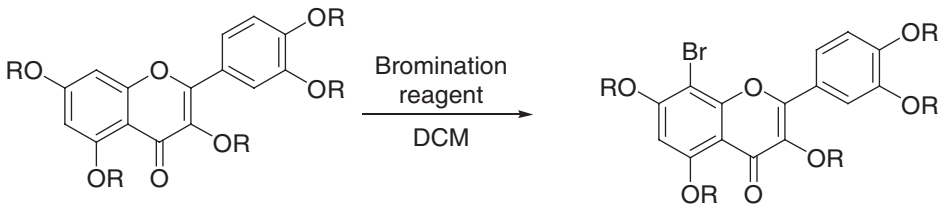
To further explore the scope and generality of this reaction, other flavonoids such as chrysin (Table 3, entries 1 and 2) and genistein (Table 3, entries 3 and 4) were converted into their isopropyl ethers and subjected to bromination with NBS/DCM under the optimized conditions. In all cases, completely regioselective brominations were achieved by alternating the pattern of phenolic –OH protection and good to high yields were obtained for the desired mono-bromo products, which were de-isopropylated with BCl_3 in nearly quantitative yields (Table 3).

Finally, this bromination protocol was applied to a rutin derivative containing an acid-labile glycosidic bond **34**. Due to its almost neutral conditions, the corresponding monobromide **35** was obtained as a single product in 92% yield (Scheme 4).

Conclusion

In summary, an efficient method was developed to prepare C-6 or C-8 mono-bromo flavonoids regioselectively, by bromination and subsequent dealkylation. The bromination can be conveniently directed to either the C-6 or C-8 position by

Table 2. Bromination of compounds **14–18** under different conditions.[a]

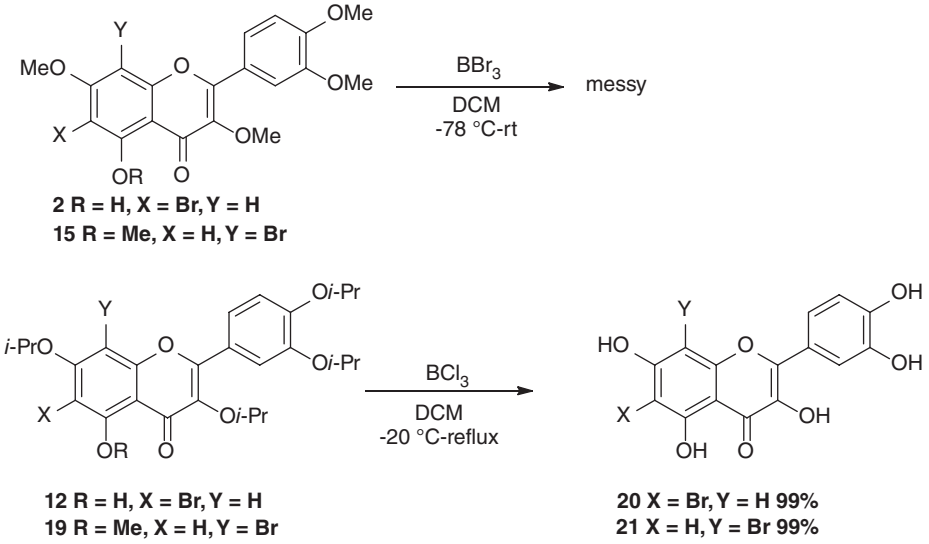


14
16
18

15 R = Methyl
17 R = Ethyl
19 R = Isopropyl

Entry	Reagent	Substrate	Temperature (°C)	Product	Yield (%)[b]
1	NBS	**14**	25	**15**	96
2	NBS	**14**	0	**15**	85
3	**5**	**14**	25	**15**	78
4	**6**	**14**	25	**15**	82
5	**7**[c]	**14**	25	**15**	93
6	NBS	**16**	25	**17**	97
7	NBS	**18**	25	**19**	97

[a] Reaction conditions: **1** (1.0 mmol), bromination reagent (1.0 mmol), in DCM (10 mL).
[b] Isolated yield after purification by silica gel chromatography.
[c] **7** (0.5 mmol) was used.



Scheme 3. Dealkylation of mono-bromo flavonoids.

alternating the protection pattern on the C-5 and C-7 ─OH groups with high regioselectivity. Thus, 5,7-*O*-diisopropylated flavonoids can be brominated with NBS/DCM to give the 8-bromo derivatives exclusively, whereas isopropyl ethers of flavonoids bearing a free ─OH group at C-5 yield 6-bromo regioisomers as the major products. The mild and neutral conditions of this protocol were found to be applicable to substrates containing an acid-labile glycosidic bond.

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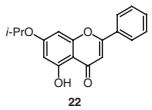
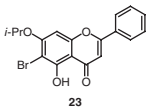
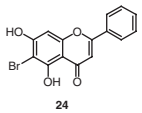
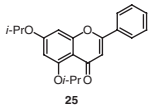
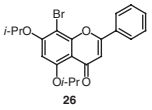
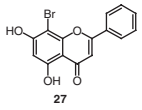
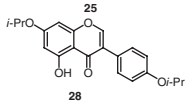
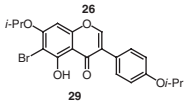
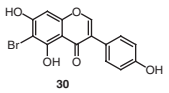
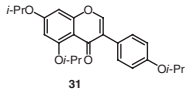
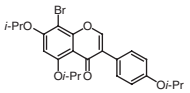
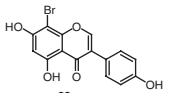
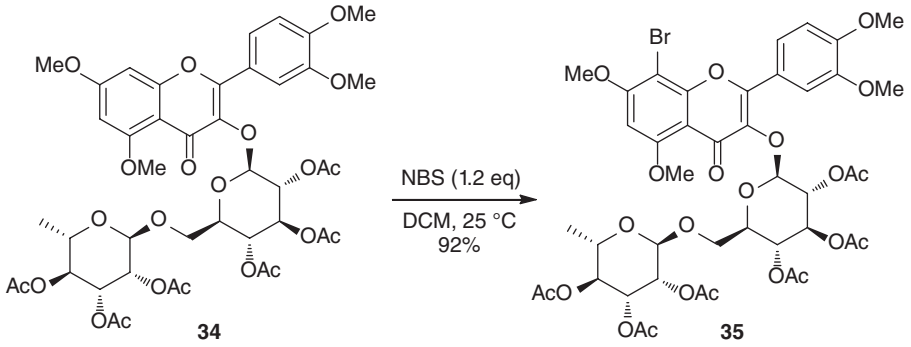
Supporting Information. Additional supporting information is available in the online version of this article.

Table 3. Bromination of protected flavonoid derivatives.

Entry	Substrates	Method[a]	Iodinated products	Yield[b] (%)	Deprotected product[c]	Yield[b] (%)
1	 **22**	A	 **23**	85	 **24**	99
2	 **25**	B	 **26**	91	 **27**	99
3	 **28**	A	 **29**	61	 **30**	99
4	 **31**	B	 **32**	83	 **33**	99

[a] Method A: reactions were performed with substrate (1.0 mmol) and NBS (1.1 mmol) in DCM at −40 °C; method B: reactions were performed with substrate (1.0 mmol) and NBS (1.0 mmol) in DCM at room temperature.
[b] Isolated yield after chromatography.
[c] Deprotection: reactions were performed with substrate (1.0 mmol) and BCl_3 (10 mmol) in anhydrous DCM at −20 °C.



Scheme 4. Regioselective bromination of rutin derivative **34**.

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