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Regioselective monobromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones using bromodimethylsulfonium bromide and synthesis of 8-bromoflavones and 7-bromoaurones

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7-Bromoaurones

ABSTRACT

A wide variety of monobrominated compounds **2a–l** have been prepared in good yields from (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1a–l**) through regioselective ring bromination using 1.5 equiv of bromodimethylsulfonium bromide (BDMS) at room temperature. Similarly, some of the 2′-hydroxychalcones can be converted directly into tribromides **3** or dibromides **4** by employing 4.0 equiv of BDMS under different reaction conditions which in turn can be transformed into 8-bromoflavones and 7-bromoaurones on treatment with 0.2 M ethanolic KOH solution. Mild reaction conditions, good yields and no chromatographic separation are some of the salient features of the present protocol.

2′-Hydroxychalcones are essential intermediates for biosynthesis of flavonoids in plants and many of them are found as such in nature.[1] In addition, they display a wide range of biological activities such as antitumoral,[2–4] anti-inflammatory,[5] antibacterial,[6] antiulcerogenic,[7] antioxidant,[6,8,9] antimalarial[10] and antileishmaniosis activities.[10,11] Link and Sorensen reported[12] that 2′,4′,6′,4-tetrahydroxychalcone is a key precursor for phlorizin (Fig 1) which is used for inhibition of the sodium/glucose cotransporters (SGLTs) and thereby lowering the blood glucose levels in diabetic animals. A few years ago, Rossi-Bergmann and co-workers have shown[11] that 2′-hydroxychalcone containing bromine atom in ring A of flavones moiety exhibits better antileishmanial activity as compared to 2′-hydroxychalcone itself. Moreover, these brominated compounds might be converted easily into 8-bromoflavones and 7-bromoaurones which are key building blocks for the synthesis of naturally occurring flavonoids such as vitexin, phlorizin, orientin, and cupressuflavone as shown in Figure 1. Therefore, the synthesis of brominated 2′-hydroxychalcones is highly desirable from biological point of view.

In the past few years, our research group[13] as well as others[14] have demonstrated that bromodimethylsulfonium bromide (BDMS) can serve as a useful brominating reagent and an effective catalyst in various organic transformations, which has been reviewed[15] in 2009. It is easier to handle as compared to hazardous molecular bromine. Recently we have further shown its usefulness in multicomponent reactions for the synthesis of heterocyclic compounds[16] as well as in carbohydrate chemistry.[17] Due to its unique reactivity and properties, we have perceived that it can be explored further for regioselective ring bromination over enone double bond of 2′-hydroxychalcones. Though numerous methods for bromination are known in the literature, the regioselective bromination in the aromatic ring remains a challenging task particularly for phenols and amines.[18] In this Letter, we wish to report regioselective mono bromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones as depicted in Scheme 1.

For the present study, the brominating reagent, bromodimethylsulfonium bromide (BDMS)[19] and (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones[11](**1**) were prepared by following the literature procedures. Subsequently, the substrate **1a**, (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (0.5 mmol), in 2 mL of dichloromethane (DCM) was treated with 1.0 equiv amount of BDMS at room temperature. The brominated compound **2a** was isolated in 67% yield within 5 min and it was characterized from ^{1}H and ^{13}C NMR spectra and elemental analysis. After getting the desired product, the reaction condition was optimized by carrying out the experiment with different amounts of BDMS under various solvent systems. The best result obtained in terms of yield, time and selectivity is mentioned in Table 1. It was noted that the best yield of the mono brominated

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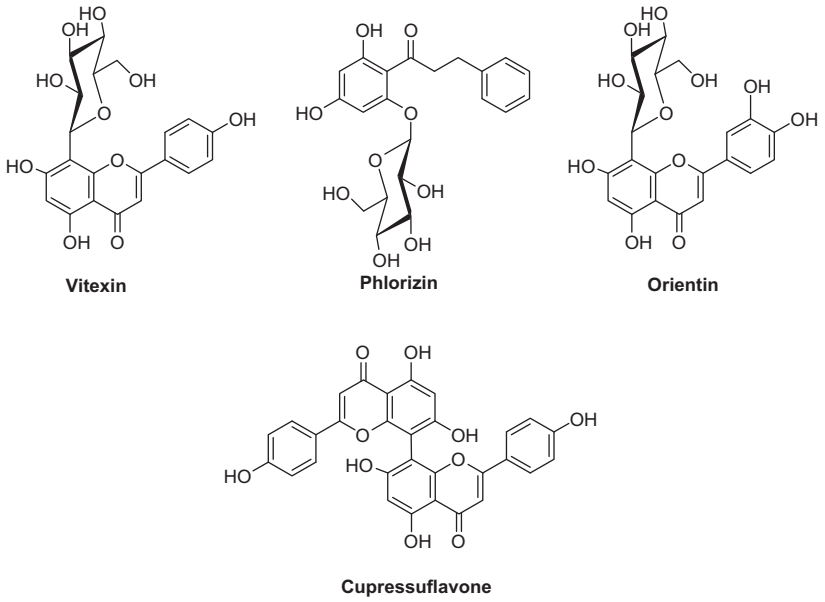
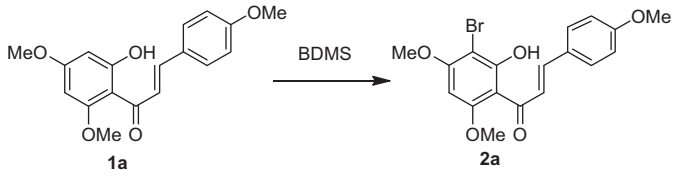


Figure 1. Some naturally occurring flavonoids.

Scheme 1. Synthesis of (*E*)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones using BDMS.

Table 1
Optimization of the reaction conditions[a]



S. No.	BDMS/equiv	Solvent	Time/min	Yield[b] (/%)
1	1.0	DCM	45	67
2	1.5	DCM	5	96
3	2.0	DCM	5	95
4	1.5	MeCN	10	81
5	1.5	EtOAc	5	86

[a] The reactions were carried out with 0.5 mmol of the substrate.
[b] Isolated yields.

product, (*E*)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**2a**) was obtained using 1.5 equiv of BDMS in dichloromethane.

After optimization, the reaction of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (**1b)** was carried out under identical reaction conditions and the product **2b** was isolated in 93% yield.

Encouraged by these successful results, a wide range of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**1c–l**) were also examined with 1.5 equiv amount of BDMS under similar reaction conditions[20] and the desired regioselective monobrominated products **2c–l** were obtained in excellent yields as shown in Table 2.

The products were characterized by usual spectroscopic methods and also by single crystal XRD data. The XRD data reveal that regioselective monobromination occurs at the position adjacent to the OH group as shown in Figure 2.[21]

It is a well-known fact that (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones are key starting materials for the synthesis of flavones and aurones. We conceived that 8-bromoflavones and 7-bromoaurones can be synthesized easily from (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones since there still exists a further possibility for bromination. Consequently, the scope and generality of the reaction were also examined with excess amount of BDMS. It was noted that compound **1a** on treatment with 4.0 equiv of BDMS in DCM provided the tribrominated product **3a** in 84% yield which was smoothly converted into 8-bromoflavone (**5a**) on treatment with 0.2 M ethanolic KOH solution as shown in Scheme 2. The structure was also confirmed by usual spectroscopic techniques and from single crystal XRD data. It is clear that the cyclization took place at the β-position with respect to carbonyl group. Likewise, other substrates **1b** and **1l** were also converted into desired 8-bromoflavone derivatives **5b** and **5l** by following the two-step procedure.[22]

It is well-established in the literature that the bromination of alkene can give methoxy brominated compound on treatment with molecular Br_2 in MeOH.[23] We thought that methoxy group can be incorporated at the β-position of the (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones if the reaction is carried out with DCM-MeOH system. Subsequently, the substrate **1a** was treated with 4 equiv of BDMS in DCM/MeOH (5:2) and the product **4a** was isolated in 80% yield. Then, the compound **4a** was further transformed into 7-bromoaurone (**6a)** on treatment with 0.2 M ethanolic KOH solution as depicted in Scheme 3. Likewise, the substrate **1b** was converted into the corresponding 7-bromoaurone derivative **6b** by performing the similar sequence of reactions.[24]

All the products were fully characterized from IR, ^{1}H, and ^{13}C NMR spectra as well as by their elemental analysis. The structures of 8-bromoflavone and 7-bromoaurone were further confirmed by X-ray crystallography studies as shown in Fig 3a and 3b.[21]

Table 2
Regioselective bromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones by employing bromodimethylsulfonium bromide[a]

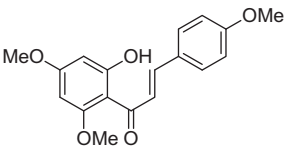
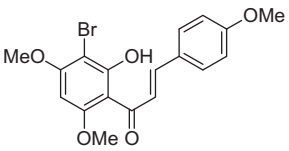
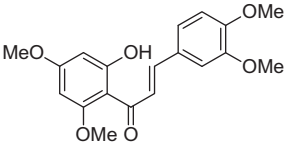
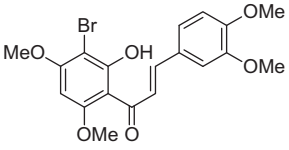
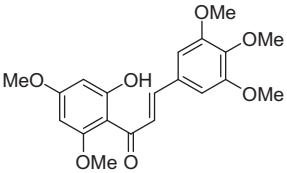
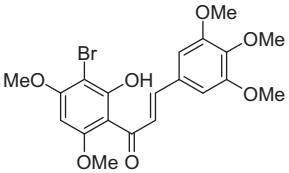
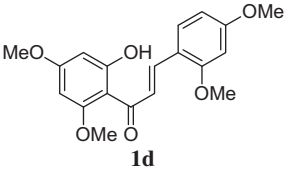
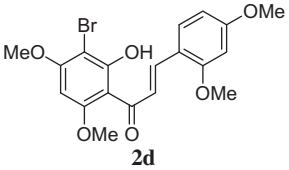
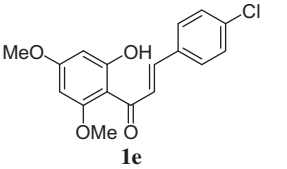
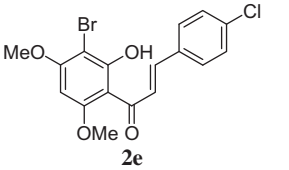
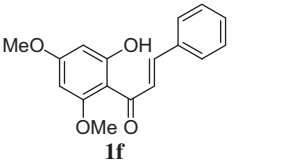
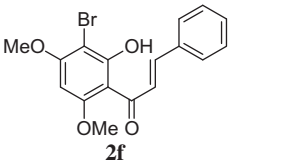
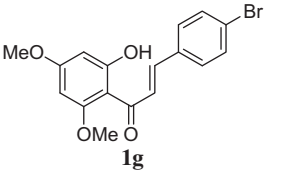
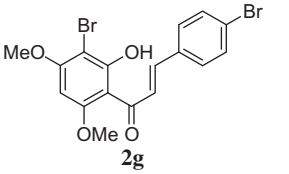
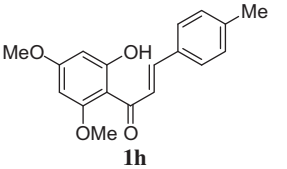
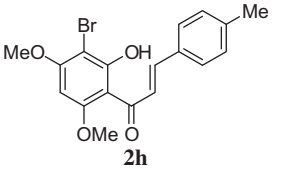
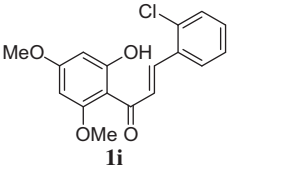
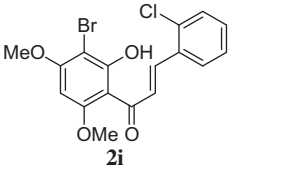
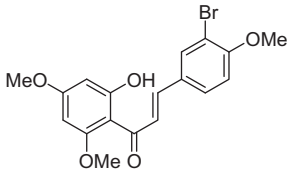
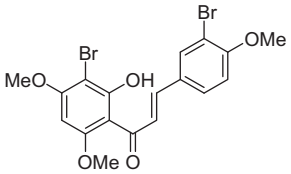
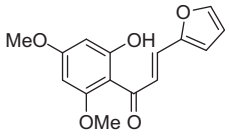
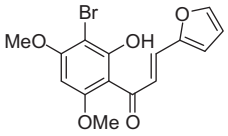
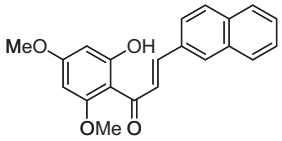
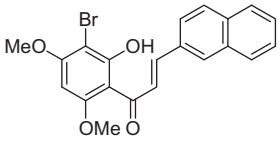
Entry	Substrate (1)	Product (2)	Yield[b] (%)
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	93
3	 **1c**	 **2c**	98
4	 **1d**	 **2d**	94
5	 **1e**	 **2e**	90
6	 **1f**	 **2f**	87
7	 **1g**	 **2g**	85
8	 **1h**	 **2h**	94
9	 **1i**	 **2i**	97

Table 2 (*continued*)

Entry	Substrate (1)	Product (2)	Yield[b] (%)
10	 **1j**	 **2j**	82
11	 **1k**	 **2k**	95
12	 **1l**	 **2l**	85

[a] The reaction was carried out with 0.5 mmol of the substrate in each case using 1.5 equiv amount of BDMS in DCM.
[b] Isolated yields.

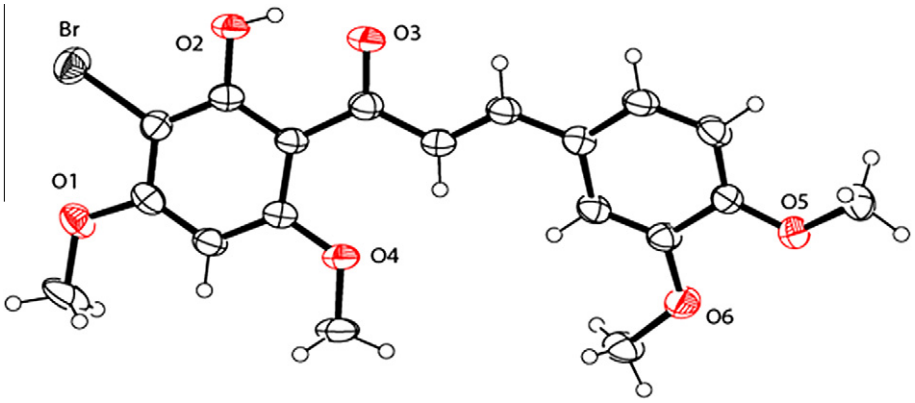
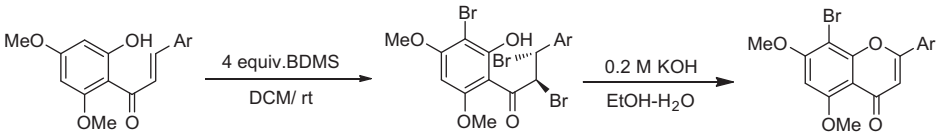


Figure 2. X-ray crystal structure of (*E*)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (**2b**).



5a: Ar= 4-Methoxyphenyl
5b: Ar= 3,4-Dimethoxyphenyl
5l: Ar= Napthyl

Scheme 2. Synthesis of 8-bromoflavones.

In conclusion, we have achieved regioselective monobromination of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones using BDMS under mild reaction conditions. In addition, 8-bromoflavones and 7-bromoaurones were also synthesized by employing excess amount of BDMS followed by base catalyzed cyclization using ethanolic KOH solution. The 7-bromoaurone and 8-bromoflavone can be utilized for the synthesis of vitexin, bisflavones, and aureusidin which is under progress and will be reported in due course of time.

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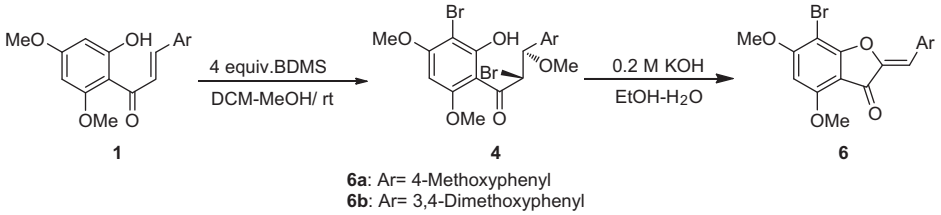

Scheme 3. Synthesis of 7-bromoaurones.

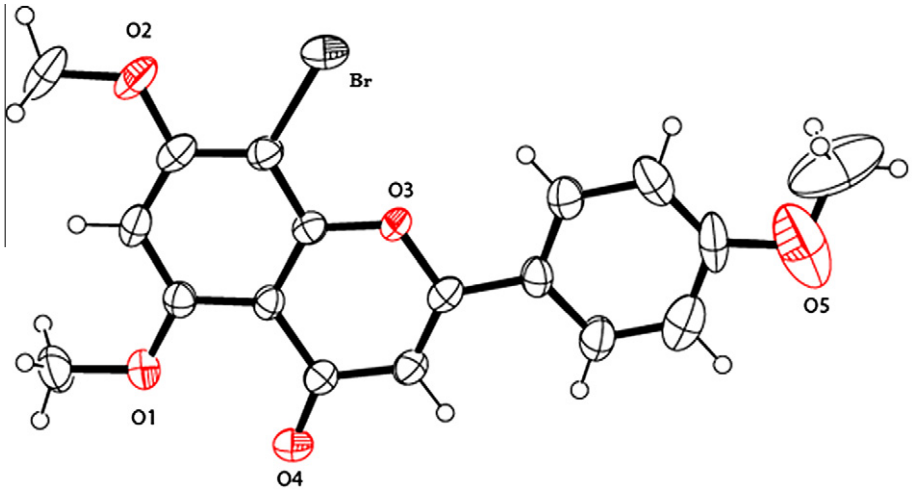

Figure 3a. X-ray crystal structure of 8-bromoflavone **5a**.

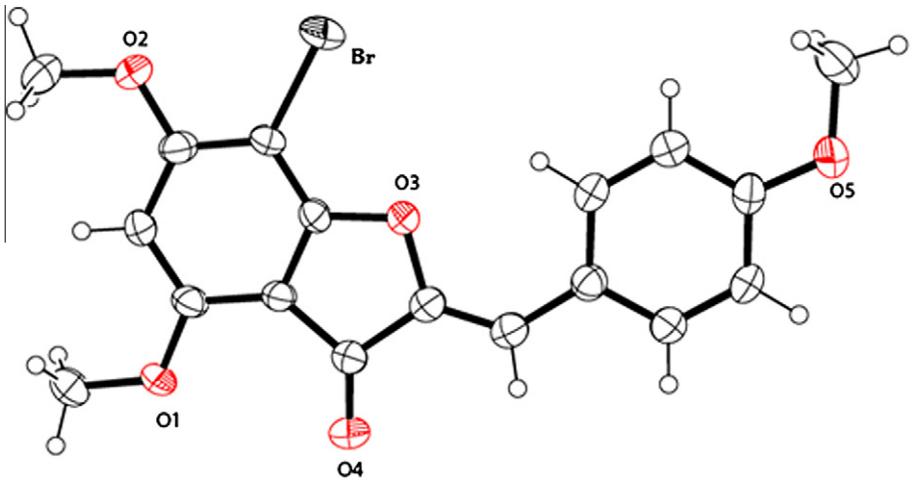

Figure 3b. X-ray crystal structure of 7-bromoaurone **6a**.

ing laboratory facilities and DST-FIST for financial support for creating single crystal XRD facility in the Department of Chemistry. We are thankful to the referees for their valuable comments and suggestions.

Supplementary data

Supplementary data (compounds **2b**, **5a** and **6a**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.122.

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20. *General method for the regioselective synthesis of (E)-1-(3′-bromo-2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (**2**)*: To a well stirred solution of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-ones (0.5 mmol) in 3 mL of DCM was added BDMS (0.167 g, 0.75 mmol) at room temperature. The reaction was complete instantaneously and the excess bromine was destroyed with 10% sodium metabisulphite solution. The reaction mixture was extracted with DCM (2 × 15 mL), washed with water, and dried over anhydrous sodium sulfate. After removal of solvent in rotary evaporator, the pure product was obtained as yellow solid. *Compound **2a***: Yellow solid, mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (s, 3H), 3.99 (s, 3H) , 4.00 (s, 3H), 6.08 (s, 1H), 6.94 (d, 2H, J = 8.8 Hz), 7.57 (d, 2H, J = 8.8 Hz), 7.76 (d, 1H, J = 15.6 Hz), 7.84 (d, 1H, J = 15.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 56.3, 56.5, 87.3, 92.1, 107.1, 114.6 (2C), 124.7, 128.2, 130.5 (2C), 143.7, 161.8, 161.9, 162.4, 163.4, 192.8; IR ν_{max}(KBr): cm^{-1} 1622, 1551, 1219, 1171; Anal. Calcd for $C_{18}H_{17}BrO_5$: C, 54.98; H, 4.36%; found C, 54.72; H, 4.27%. Compound **2b:** Yellow solid, mp 200–201 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H), 3.94 (s, 3H), 3.98 (s, 3H), 3.99 (s, 3H), 6.05 (s, 1H), 6.90 (d, 1H, J = 8.4 Hz), 7.11 (d, 1H, J = 2.0 Hz), 7.21 (dd, 1H, J = 1.6, 8.0 Hz), 7.73 (d, 1H, J = 15.2 Hz), 7.80 (d, 1H, J = 15.6 Hz); ^{13}C NMR (100 MHz, DMSO): δ 55.5, 55.7, 56.6, 56.8, 88.9, 90.6, 106.7, 110.9, 111.8, 123.2, 124.5, 127.5, 143.9, 149.0, 151.4, 161.3, 161.5, 161.9, 192.3; IR ν_{max} (KBr): cm^{-1} 1627, 1557, 1518, 1261, 1218; Anal. Calcd for $C_{19}H_{19}BrO_6$: C, 53.92; H, 4.52; found C, 53.75; H, 4.48%. *Compound **2k***: Yellow solid, mp 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 3H), 4.00 (s, 3H) , 6.07 (s, 1H), 6.52 (dd, 1H, J = 2.0 Hz, 3.2 Hz), 6.70 (d, 1H, J = 3.2 Hz), 7.53 (d, 1H, J = 1.6 Hz), 7.62 (d, 1H, J = 15.6 Hz), 7.76 (d, 1H, J = 15.2 Hz); ^{13}C NMR (100 MHz, DMSO): δ 56.9, 57.1, 89.2, 90.6, 106.7, 113.7, 118.1, 123.6, 130.5, 146.9, 151.4, 161.8, 162.1, 162.3, 191.9; IR ν_{max} (KBr): cm^{-1} 1633, 1604, 1424, 1317, 1225, 1136; Anal. Calcd for $C_{15}H_{13}BrO_5$: C, 51.01; H, 3.71%; found C, 50.95; H, 3.62%.
21. Complete crystallographic data of **2b**, **5a,** and **6a** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 810812, 810814 and 810813, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).
22. *Typical procedure for the preparation of tribromides (**3**) and synthesis of 8-bromoflavones (**5**)*: To a well stirred solution of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (0.5 mmol) in 5 mL of DCM was added BDMS (0.444 g, 2 mmol) at room temperature. The reaction was complete within 10 min. Then, it was quenched by adding 10% sodium metabisulphite solution and the reaction mixture was extracted with DCM (2 × 15 mL), washed with water, and dried over anhydrous sodium sulfate to obtain the tribromo derivatives **3**. The pure tribromide was obtained after recrystallization in DCM-hexane. Then the tribrominated compounds **3** on treatment with 0.2 M KOH (0.5 mL) in EtOH/H_2O (4:1) yielded 8-bromoflavones after usual work-up procedure. *Compound **5a***: Pale yellow solid, mp 239–240 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 4.03 (s, 3H) , 4.05 (s, 3H), 6.46 (s, 1H), 6.64 (s, 1H), 7.03 (d, 2H, J = 8.8 Hz), 7.96 (d, 2H, J = 9.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 56.7 (2C), 91.2, 92.2, 106.9, 109.9, 114.6 (2C), 117.8, 123.5, 128.1 (2C), 160.3, 160.5, 161.0, 162.4, 177.5; IR ν_{max} (KBr): cm^{-1} 1639, 1593, 1341; Anal. Calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86%; found C, 55.18; H, 3.81%. *Compound **5b***: Pale yellow solid, mp 229–230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (s, 3H), 3.94 (s, 3H) , 3.98 (s, 3H), 3.99 (s, 3H), 6.05 (s, 1H), 6.90 (s, 1H), 7.21 (dd, 1H, J = 1.6, 8.0 Hz), 7.73 (d, 1H, J = 15.2 Hz), 7.80 (d, 1H, J = 15.6 Hz); IR ν_{max} (KBr): cm^{-1} 1610, 1516, 1219, 1111; Anal. Calcd for $C_{19}H_{17}BrO_6$: C, 54.17; H, 4.07%; found C, 54.11; H, 4.01%. *Compound **5l***: Pale yellow solid, mp 315–316 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (s, 3H), 4.06 (s, 3H) , 6.48 (s, 1H), 6.86 (s, 1H), 7.57–7.59 (m, 2H), 7.96–8.01 (m, 4H), 8.60 (s, 1H); IR ν_{max} (KBr): cm^{-1} 1641, 1592, 1324, 1212; Anal. Calcd for $C_{21}H_{15}BrO_4$: C, 61.33; H, 3.68%; found C, 61.27; H, 3.61%.
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24. *Typical procedure for the preparation of dibromides (**4**) and synthesis of 7-bromoaurones (**6**)*: To a well stirred solution of (*E*)-1-(2′-hydroxy-4′,6′-dimethoxyphenyl)-3-aryl-2-propen-1-one (0.5 mmol) in DCM/MeOH (5:2), BDMS (0.444 g, 2 mmol) was added at room temperature. The reaction was over within 10 min and it was quenched by adding 10% sodium metabisulfite solution. The reaction mixture was extracted with DCM (2 × 15 mL), washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated in rotary evaporator and the crude product recrystallized in DCM-hexane mixture to get the pure brominated product **4**. The dibrominated product **4** on treatment with 0.2 M KOH (0.5 mL) in EtOH/H_2O (4:1) afforded 7-bromoaurones. *Compound **6a***: Pale yellow solid, mp 250–251 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H), 4.05 (s, 6H) , 6.21 (s, 1H), 6.84 (s, 1H), 7.01 (d, 2H, J = 8.4 Hz), 7.92 (d, 2H, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.6, 56.7, 57.2, 85.4, 90.8, 106.6, 112.5, 114.7 (2C), 125.2, 133.5 (2C), 146.6, 159.0, 161.1, 163.9, 164.2, 180.6; IR ν_{max} (KBr): cm^{-1} 1598, 1513, 1173, 1102; Anal. Calcd for $C_{18}H_{15}BrO_5$: C, 55.26; H, 3.86%; found C, 55.19; H, 3.78%. *Compound **6b***: Pale yellow solid, mp 207–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92 (s, 3H), 4.01 (s, 9H) , 6.18 (s, 1H), 6.80 (s, 1H), 6.90 (d, 1H, J = 8.4 Hz), 7.31 (dd, 1H, J = 1.6, 8.4 Hz), 7.81 (d, 1H, J = 1.6 Hz); ^{13}C NMR (100 MHz, DMSO): δ 55.5, 55.7, 56.6, 56.8, 88.9, 90.6, 106.7, 110.9, 111.8, 123.2, 124.5, 127.5, 143.9, 149.0, 151.4, 161.3, 161.5, 161.9, 192.3; IR ν_{max} (KBr): cm^{-1} 1609, 1517, 1247, 1111; Anal. Calcd for $C_{19}H_{17}BrO_6$: C, 54.17; H, 4.07%; found C, 54.11; H, 4.01%.