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$BF_3{\cdot}OEt_2$ mediated regioselective deacetylation of polyacetoxyacetophenones and its application in the synthesis of natural products ☆

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ABSTRACT

We have developed an efficient method to regioselectively deacetylate polyacetoxyacetophenones using $BF_3{\cdot}OEt_2$ in excellent yields and demonstrated the application of the procedure in the synthesis of natural products.

1. Introduction

As a part of our ongoing interest in developing new and efficient antiparasitic agents, we recently reported the antimalarial activity of naturally occurring prenylated chalcones, the antileishmanial activity of natural chromenodihydrochalcones and synthetic chromenochalcones and chromanochalcones.[1] The general method for the synthesis of chromanochalcones involves: C-prenylation of 2,4-dihydroxyacetophenone (**1**), subsequent cyclization of the 3-C-prenyl unit with the C-4 hydroxyl of acetophenone **2** to provide the acetylchroman intermediate **3**.[2] The Claisen–Schmidt condensation[3] of **3** with a substituted benzaldehyde (Fig. 1) leads to

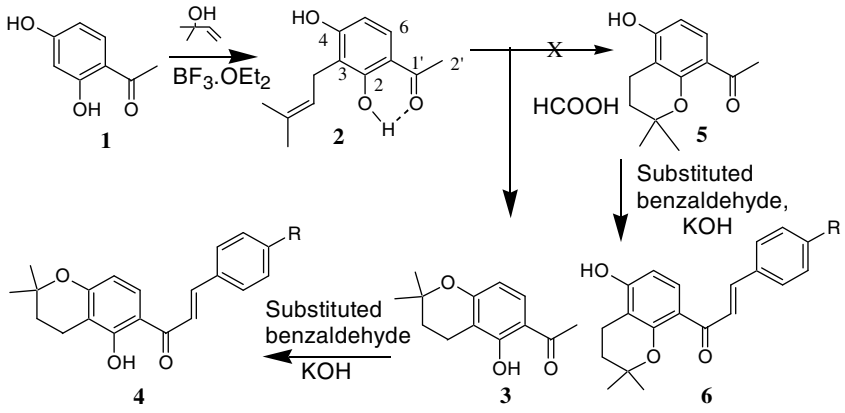

Figure 1. General method for the synthesis of chromanochalcones **4** and **6**.

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Table 1
Regioselective deacetylation using $BF_3{\cdot}OEt_2$

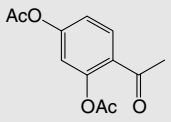
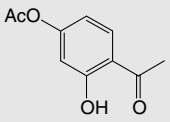
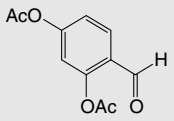
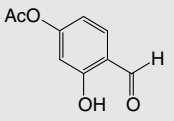
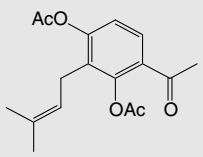
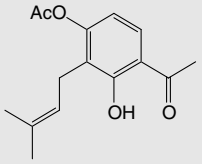
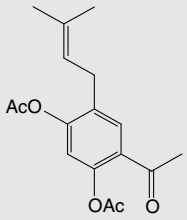
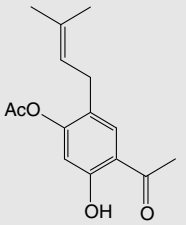
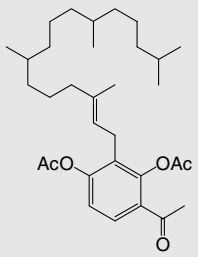
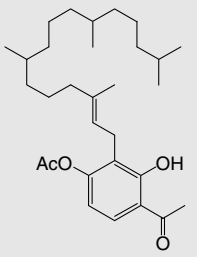
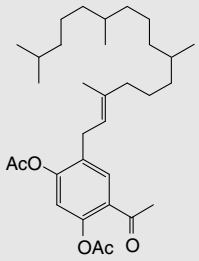
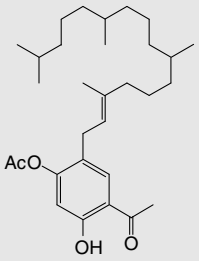
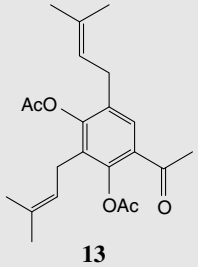
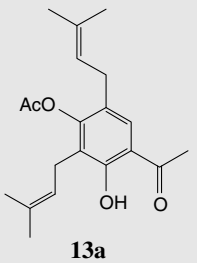
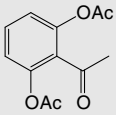
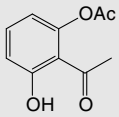
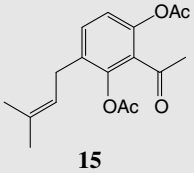
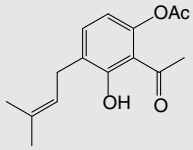
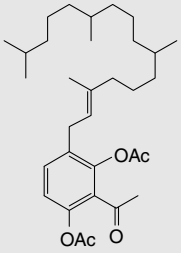
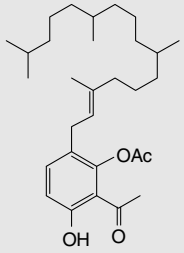
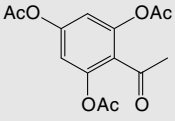
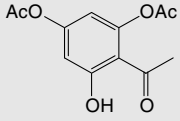
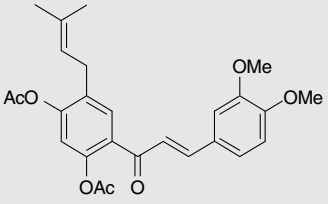
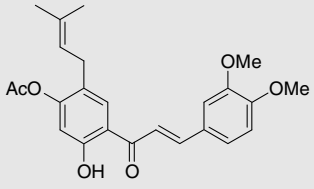
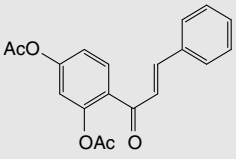
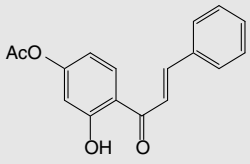
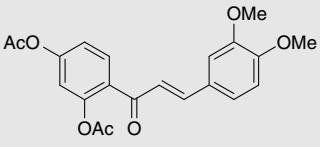
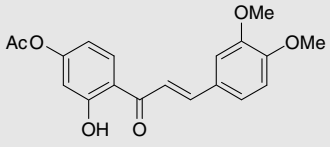
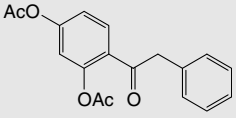
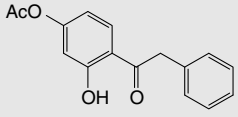
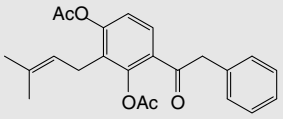
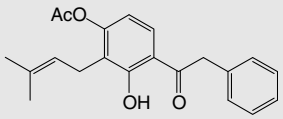
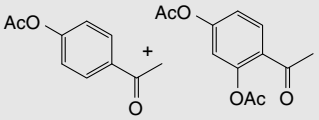
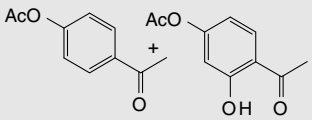
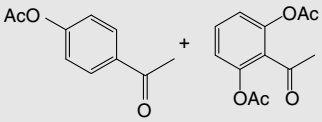
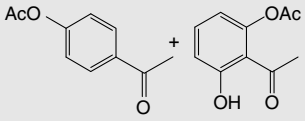
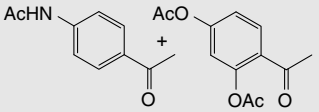
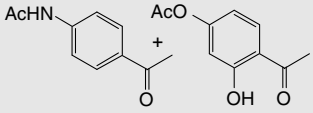
Entry	Substrate	Product	Yield[a] (%)
1	 **7**	 **7a**	93
2	 **8**	 **8a**	91
3	 **9**	 **9a**	95
4	 **10**	 **10a**	96
5	 **11**	 **11a**	90
6	 **12**	 **12a**	92
7	 **13**	 **13a**	89

Table 1 (*continued*)

Entry	Substrate	Product	Yield[a] (%)
8	 **14**	 **14a**	87
9	 **15**	 **15a**	89
10	 **16**	 **16a**	83
11	 **17**	 **17a**	71
12	 **18**	 **18a**	85
13	 **19**	 **19a**	88
14	 **20**	 **20a**	90
15	 **21**	 **21a**	93

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Product	Yield[a] (%)
16	 **22**	 **22a**	90
17	 **23** **7**	 **23** **7a**	97/87
18	 **23** **14**	 **23** **14a**	98/96
19	 **24** **7**	 **24** **7a**	95/90

[a] Isolated yields

chromanochalcone **4**. Since the C-2-hydroxyl of **2** is in chelation with carbonyl (C-1′), the 3-*C*-prenyl unit cyclizes preferentially with the C-4 hydroxyl to give **3**. We wanted to synthesize the isomeric acetylchroman **5**, in which the C-3-prenyl is cyclized with the C-2 hydroxyl and to use **5** for the synthesis of chromanochalcone **6** (Fig. 1).

The synthesis of **7a**–**22a** (Table 1) is possible either by regioselective protection of the C-4 hydroxyl in the presence of a C-2 hydroxyl or by deprotection of the C-2 hydroxyl in presence of a C-4 hydroxyl of **7**–**22** (Table 1). To our knowledge there is no reagent currently available to achieve either task.

Several deacetylating agents such as Zn–MeOH,[4] $LiBH_4$,[4] *p*-TsOH–SiO_2–H_2O,[4] bis(tributyltin)oxide,[5] NaHTe,[6] borohydride exchange resin,[7] Al_2O_3/microwaves,[8] metal complexes,[9] enzymes,[10] metalloenzymes,[11] antibodies,[12] cyclodextrin[13] micelle-catalyzed saponification[14] and $[tBu_2SnOH(Cl)]_2$[15] are known in the literature, but none of these have been reported for regioselective deacetylation.

Parmar and co-workers[16] reported enzymatic regioselective deacetylation using lipase, which was derived from *Aspergillus carneus*. However, their method has several disadvantages such as laborious purification of the enzyme, long reaction time (8 days) and moderate yields (60–65%).

Recently, we utilized $BF_3{\cdot}OEt_2$ as a condensing agent in the synthesis of chalcones[17] and also as a regioselective cyclizing agent in the synthesis of chromanochalcones from prenylated chalcones in high yields.[18] Thus, we wanted to use the $BF_3{\cdot}OEt_2$ for regioselective deacetylation. It was anticipated that $BF_3{\cdot}OEt_2$ might preferentially form a complex with the C-2-hydroxyl and carbonyl (C-1′) of **7**, leading to deacetylation to give **7a** (Fig. 2).

To explore this possibility we carried out a deacetylation reaction on **7** using $BF_3{\cdot}OEt_2$. Delightfully, regioselective deacetylation occurred to give 4-acetoxy-2-hydroxyacetophenone (**7a**) in excellent yield.[19] To demonstrate the generality, the reaction was carried out under the same conditions on 2,4-diacetoxybenzaldehyde (**8**) and polyacetoxyacetophenones such as 2,4-diacetoxy-C-alkylated acetophenones **9**–**13**, 2,6-diacetoxyacetophenone (**14**), 2,6-diacetoxy-C-alkylated acetophenones **15** and **16**, 2,4,6-triacetoxyacetophenone (**17**), 2,4-diacetoxy-C-alkylated chalcone **18**, 2,4-diacetoxy chalcones **19** and **20** and 2,4-diacetoxy-2′-phenyl acetophenones **21** and **22**, and obtained the respective regioselective deacetylated products **8a**–**22a** in excellent yields in a short duration of time. It is also noteworthy to mention here that $BF_3{\cdot}OEt_2$ did not affect an aromatic ester **23** and amide **24**, when the chemoselective reaction was carried out in presence of **7** and **14** (Table 1, entries 17–19).

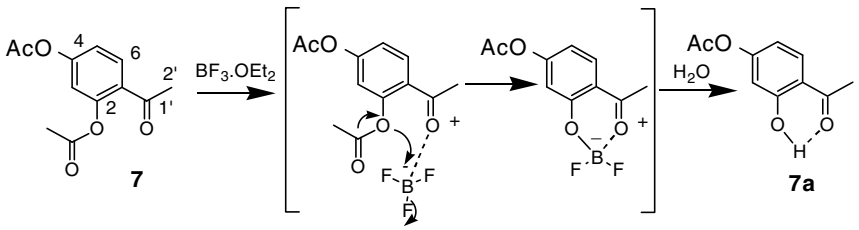


Figure 2. Possible reaction mechanism for the regioselective deacetylation of 2,4-diacetoxyacetophenone **7**.

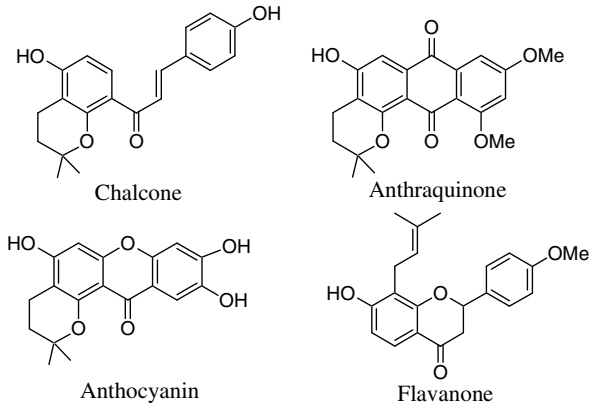


Figure 3. Natural products in which the chelated hydroxyl is engaged in chroman ring formation and flavanone formation.

Several biologically active natural products such as chalcones,[20] anthocyanins[21] and anthraquinones[22] have been reported in the literature, in which the chelated hydroxyl is involved in chroman ring formation (Fig. 3).

To show the application of this methodology in the synthesis of such natural products and their analogues, we employed $BF_3{\cdot}OEt_2$ for the regioselective deacetylation of C-alkylated (prenylated and phytylated) acetophenones **9 and 11** and subsequently the prenyl or phytyl group was subjected to cyclization with the C-2 hydroxyl to provide the desired acetyl chromans **25** and **27**. Chromans **25** and **27** were subjected to Claisen–Schmidt condensation (Scheme 1) with *p*-methoxybenzaldehyde to give chromanochalcones **26** and **28**.

Several prenylated flavanones have been reported from various terrestrial plants.[23] Prenylated chalcones are the main precursors for the biosynthesis of prenylated flavanones.

In the presence of HCOOH, the prenylated chalcone **29** will give chromanoflavone **30** via cyclization of the prenyl group with the C-4′ hydroxyl and of the chelated hydroxyl (C-2′) with the α,β-unsaturated double bond (Scheme 2). $BF_3{\cdot}OEt_2$ was employed to regioselectively deprotect the C-2 acetyl group of **18** to provide the free hydroxyl in **18a**, which was subsequently cyclized to give prenylated flavanone **31**.[24]

In summary, we have developed a method to regioselectively deacetylate the polyacetoxyacetophenones, aldehydes, C-alkylated acetophenones, chalcones and C-alkylated chalcones using $BF_3{\cdot}OEt_2$ for the first time. This method has several advantages such as regioselectivity, high yields, simple procedure, short reaction times and tolerates other functional groups such as amides and esters. The application of this method was also demonstrated in the synthesis of natural products such as chromanochalcones and prenylated flavanones.

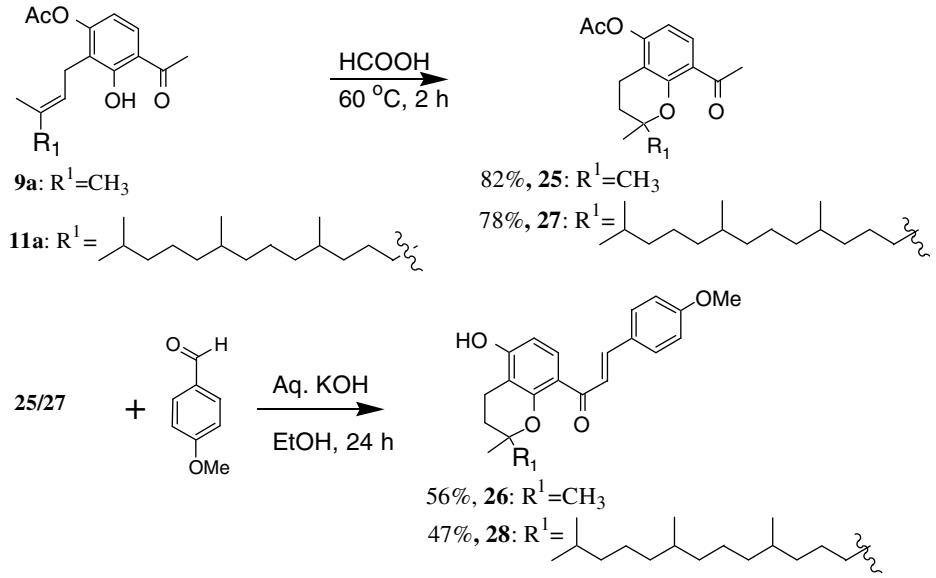
2. Experimental

2.1. Representative procedure for the preparation of 4-acetoxy-2-hydroxy-3-prenyl acetophenone (9a)

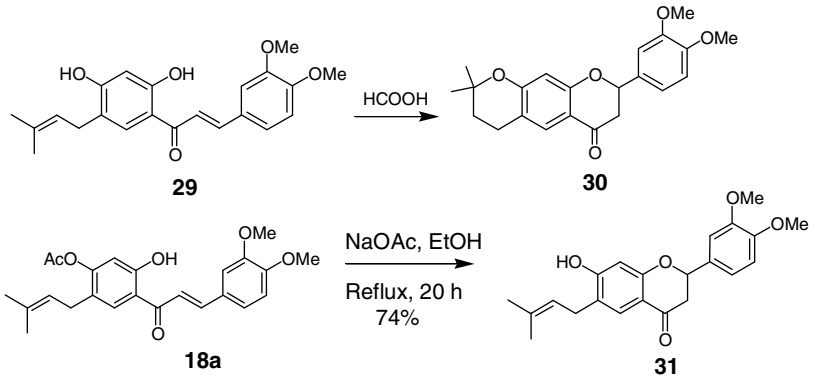
To a stirred solution of **9** (500 mg, 1.6 mmol) in 1,4-dioxane (10 mL) was added gradually $BF_3{\cdot}OEt_2$ (0.31 mL, 2.5 mmol) at room temperature. The resultant solution was stirred for 3 h at 50 °C. After cooling to room temperature and dilution with diethyl ether (100 mL), the solution was washed with water (3 × 30 mL) to decompose the $BF_3{\cdot}OEt_2$ complex. The organic solution obtained after extraction was dried over anhyd Na_2SO_4 and filtered, the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using hexane–ethyl acetate (95:5) as a mobile phase to afford compound **9a** (385 mg, 95%); mp: 65–67 °C; IR (KBr) 2923, 1764, 1635, 1417, 1368, 1199, 1047, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.82 (s, 1H, chelated-OH), 7.64 (d, J = 8.72 Hz, 1H), 6.65 (d, J = 8.72 Hz, 1H), 5.14 (t, J = 6.96 Hz, 1H), 3.32 (d, J = 6.96 Hz, 2H), 2.62 (s, 3H), 2.95 (s, 3H), 1.77 (s, 3H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.1, 168.9, 162.6, 154.8, 132.7, 129.1, 121.3, 121.2, 117.6, 113.6, 26.9, 25.9, 22.9, 21.2, 18.1; MS (ESI) m/z 263.4 $(M+H)^+$.

2.2. Representative procedure for the preparation of acetic acid 8-acetyl 2,2-dimethyl-chroman-5-yl ester (25)

A stirred solution of **9a** (250 mg, 0.95 mmol) in formic acid (20 mL) was heated on an oil bath at 60 °C for 2 h. After the reaction mixture was cooled to room temperature, water (50 mL) was added and the reaction mixture was extracted with diethyl ether (3 × 25 mL). The organic solution obtained after extraction



Scheme 1. Synthesis of chromanochalcones **26** and **28**.



Scheme 2. Synthesis of prenylated flavanone **31**.

was dried over anhyd Na_2SO_4 and filtered, the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using hexane–ethyl acetate (95:5) as a mobile phase to afford compound **25** (205 mg, 82%); IR (neat) 2977, 2931, 1766, 1672, 1591, 1421, 1367, 1203, 1162, 1046, 908 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, J = 8.55 Hz, 1H), 6.66 (d, J = 8.55 Hz, 1H), 2.63 (t, J = 6.51 Hz, 2H), 2.61 (s, 3H), 2.33 (s, 3H), 1.84 (t, J = 6.51 Hz, 2H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3, 168.8, 155.3, 152.8, 129.1, 126.2, 115.2, 113.4, 75.8, 32.3, 31.6, 27.1 (2C), 21.1, 17.8; MS (ESI) m/z 263.0 $(M+H)^+$; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ $(M+H)^+$: 263.12833, found. 263.12770.

2.3. Representative procedure for the preparation of 1-(5-hydroxy 2,2-dimethyl-chroman-8-yl)-3-(4-methoxy-phenyl) propenone (26)

To a solution of **25** (150 mg, 0.57 mmol) and KOH (200 mg dissolved in 5 mL of aqueous ethanol) was added *p*-methoxybenzaldehyde (117 mg, 0.85 mmol). The mixture was kept at room temperature for 24 h. The resultant mixture was quenched in ice-cold water and acidified with 1 N HCl. The crude product was filtered under suction and extracted with ethyl acetate (3 × 25 mL). The combined extract was washed with water (2 × 10 mL). The organic layer obtained after extraction was dried over anhyd Na_2SO_4 and filtered, the solvent was evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography using hexane–ethyl acetate (90:10) solvent system to afford compound **26** (110 mg, 56%); mp: 184–186 °C; IR (KBr) 3019, 2928, 2854, 1641, 1592, 1512, 1440, 1244, 1217, 1172, 1071, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.32 (d, J = 15.15 Hz, 1H), 7.69 (m, 3H), 7.36 (d, J = 15.15 Hz, 1H), 7.01 (d, J = 8.73 Hz, 2H), 6.73 (s, 1H, ArOH), 6.50 (d, J = 9.21 Hz, 1H), 3.91 (s, 3H), 2.80 (t, J = 6.72 Hz, 2H), 1.86 (t, J = 6.72 Hz, 2H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 192.0, 161.1, 159.9, 155.4, 140.9, 129.6, 129.5 (2C), 127.9, 125.3, 120.2, 114.1 (2C), 108.5, 106.4, 74.8, 54.8, 31.4, 26.3 (2C), 16.7; MS (ESI) m/z 339.0 $(M+H)^+$; HRMS (ESI) calcd for $C_{21}H_{23}O_4$ $(M+H)^+$: 339.15963, found. 339.15763.

2.4. Preparation of 2-(3,4-dimethoxy-phenyl)-7-hydroxy-6-(3-methyl-but-2-enyl)-chroman-4-one (31)

To a stirred solution of **18a** (100 mg, 0.24 mmol) in EtOH (5 mL/mmol) were added NaOAc (80 mg, 0.97 mmol) and H_2O (3 drops). The reaction mixture was heated to reflux for 20 h and then allowed to cool to room temperature. The mixture was diluted with H_2O and extracted with Et_2O. The combined organic phases were washed with brine, dried over anhyd Na_2SO_4 and filtered; the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using hexane–ethyl acetate (90:10) solvent system to afford flavanone **31** (66 mg, 74%); mp: 136–138 °C; IR (KBr) 3021, 2973, 2930, 1669, 1609, 1516, 1459, 1374, 1217, 1033, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.69 (s, 1H), 6.99 (m, 2H), 6.90 (s, 1H), 6.47 (s, 1H), 5.34 (m, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.31 (d, J = 7.01 Hz, 2H), 3.05 (dd, J = 3.82, 16.99 Hz, 1H), 2.82 (m, 1H), 1.75 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 191.7, 162.5, 162.4, 149.8, 149.7, 135.5, 131.8, 128.8, 122.7, 121.7, 119.3, 114.9, 111.5, 109.8, 104.0, 80.2, 56.4 (2C), 44.7, 30.1, 26.3, 18.3; MS (ESI) m/z 369.2 $(M+H)^+$; HRMS (ESI) calcd for $C_{22}H_{25}O_5$ $(M+H)^+$: 369.17020, found. 369.17185.

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Supplementary data

Spectral data of all the synthetic compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.020.

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