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Convergent synthesis of mosloflavone, negletein and baicalein from crysin

Giuliana Righi [a], Roberto Antonioletti [a], Ilaria Proietti Silvestri [b], Nicola D'Antona [c], Daniela Lambusta [c], Paolo Bovicelli [d,*]

[a] C.N.R. Institute of Biomolecular Chemistry (ICB), Unity of Rome, c/o Department of Chemistry, Sapienza University of Rome, p.le A. Moro 5, I—00185 Rome, Italy
[b] Department of Chemistry, Sapienza University of Rome, p.le A. Moro 5, I—00185 Rome, Italy
[c] CNR ICB-Unity of Catania, V. P. Gaifani, 18—95126 Catania, Italy
[d] CNR ICB-Unity of Sassari, Traversa La Crucca 3—Baldanica I-07040 Sassari, Italy

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ABSTRACT

An expeditious synthesis of three polyoxygenated flavones: mosloflavone, negletein and baicalein, starting from crysin, an easily available flavone, by a bromination/methoxylation procedure is reported. The convergent synthesis exploits a base induced Wesley–Moser type rearrangement.

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1. Introduction

Flavonoids are molecules with antioxidant properties widely occurring in the plant kingdom. The specific properties of these molecules are due to the presence of aromatic moieties and of many oxygenated groups.[1] Methoxylated flavones exhibiting interesting biological activities have recently been isolated from plants.[2]

Despite the biological importance evidenced for this class of natural compounds, an extensive investigation into the activities of most of them is limited because of their scarce availability. Moreover, the synthesis and/or structural modification of these polyphones is often complex, low yielding and expensive.[3,4,5]

Because of the increasing interest in these molecules, methods for their synthesis and structural modification are the goals of several research groups.

Our interest in this field is to exploit our experience in the functionalisation of aromatic compounds to prepare natural and new flavonoids that are potentially useful as drugs or food preservatives.

Recently we reported a protocol for introducing oxygenated moieties into activated aromatic rings.[6] A selective bromination, followed by a methanolysis protocol, was performed on a series of natural compounds with the aim to improve their antioxidant properties.[7] Previously reported oxygenation methods of flavonoids, i.e., catalised hydrogen peroxide[8] or potassium persulfate[9] systems are directed to introduce hydroxyl groups in the skeleton and are usually low yielding.

In particular the methanolysis protocol, developed in our laboratories, is actually considered of general value and can be used as routine synthetic step. Also sensitive compounds, such as flavones are usually submitted to the process with success.[10]

Our protocol consists in mixing at room temperature NaOMe and CuBr in DMF, which is then added to the bromo-aromatic substrate in DMF at 120 °C and the methanolysis reaction occurs in few minutes. It is noteworthy that the bromo-aromatic substrates used do not need to be highly activated.

The process was used with success in the preparation of some rare flavones such as 3′-demethoxysudachitin, compound present in several plant extracts often used in traditional medicines and known to possess a number of biological activities.

At the present we are studying the scope and limitations of the method and the possibility to exploit it to synthesise a series of flavones.

2. Results and discussion

Initially in our protocol the bromination step was performed with a oxone/NaBr system, which produces a highly reactive electrophilic species, which is able to brominate activated aromatic systems, such as in the case of hydroxytyrosol[11] and bioactive biphenols syntheses,[12] already reported by us.

The method is not useful in the case of the A-ring of flavones, since its efficiency does not allow a descrimination between different highly activated sites, i.e., the C-6 and C-8-positions of crysin. For this reason we explored other brominating agents.

Tetrabutylamonium tribromide (TBATB) is reported in literature, as an efficient generator of HBr[13] but is also able to brominate double bonds, such as in the case of some chalcones.[14] This reagent showed to be very efficient in the selective bromination of crysin

* Corresponding author. Tel.: +39 06 490422; fax: +39 06 49913628.
E-mail address: paolo.bovicelli@cnr.it (P. Bovicelli).

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dimethyl ether in the 6-position, as already reported for a similar iodination reaction[15] (Scheme 1).

On the contrary, if one or the both hydroxyl groups were left unprotected a mixture of bromoderivatives were obtained in any condition. In the case of 7-methoxycrysin the reaction led to a mixture, which tended towards the 6,8-dibromo derivative with an excess of the reagent. Under mild conditions it was possible to obtain a mixture of two monobromo derivatives, inseparable by common chromatographic techniques.

In the case of crysin the dibromo derivative was already present at low conversion and then 6,8-dibromocrysin **7** was the only product obtainable in good yields.

N-Bromosuccinimide had a different behaviour with 5,7-dimethoxycrysin being able to brominate the C-8-position, but it failed to selectively functionalise flavones with free hydroxy groups (Scheme 1).

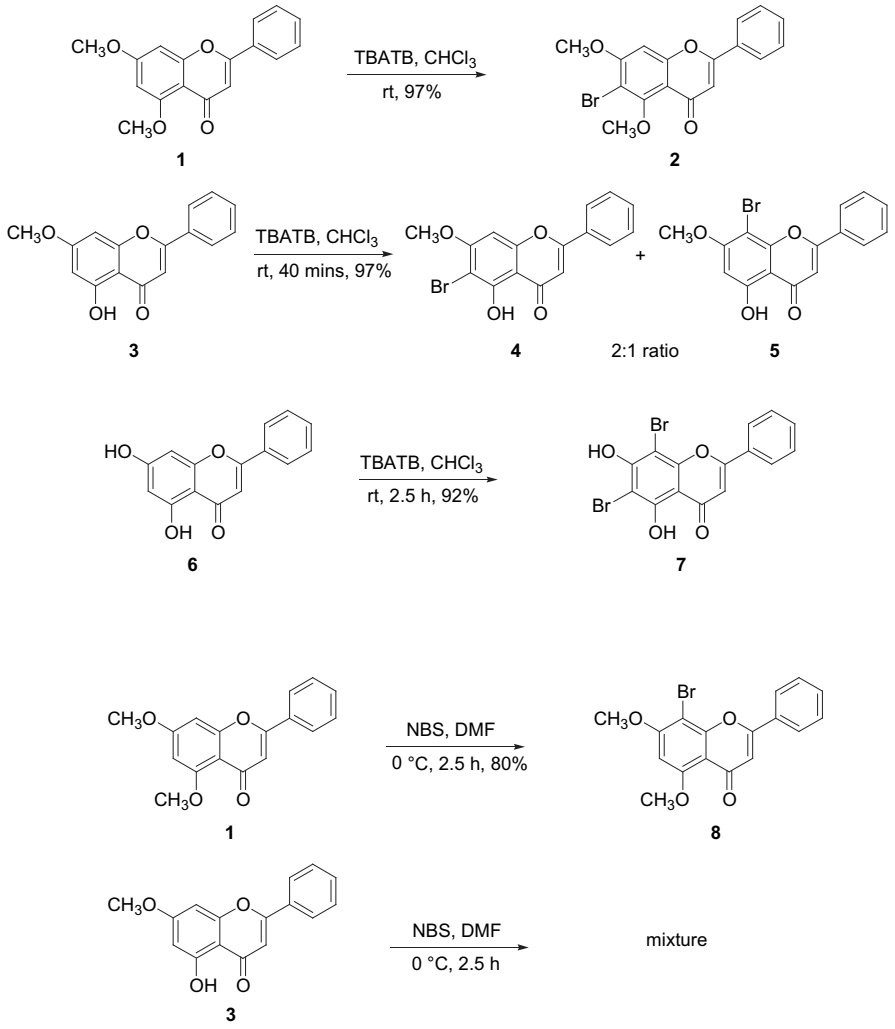
Surprisingly any attempt at methanolysis of **2** and **8** failed. Then, with the aim of exploiting our protocol to obtain polyoxygenated flavones, we purified the compounds obtained from bromination of **3** as acetyl derivatives.

Compounds **9** and **10** were submitted to the usual methanolysis step and **11** was obtained as the main product from the both substrates (Scheme 2). In the case of **9** the reaction occurred in few minutes, in the case of **10**, 5 h were required to converge an initial complex mixture towards the main product. This behaviour led us to hypothesise a process in which, after the preliminary deacetylation, a rearrangement occurred in which an open form of the ring C was involved (Scheme 3).

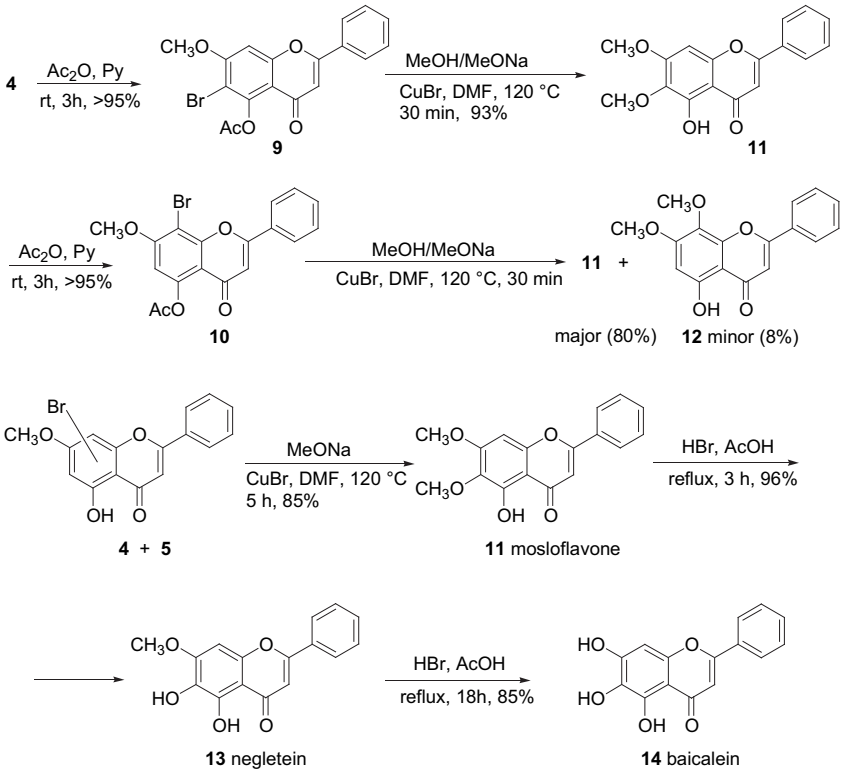
This rearrangement, known as Wesley–Moser, was previously reported[16,17] only in acidic media via an equilibrium of open–close forms leading to the more thermodynamically stable compound. In our case **11** was the preferred product. Mosloflavone **11** is a component of *Desmos chinensis*.[18] By progressive selective demethylation steps, two more natural products were produced: negletein **13**, component of *Centaurea clementei*,[19] and baicalein **14**, component of *Scutellaria baicalensis*.[20] The full process allows then a convergent synthesis of three natural compounds starting from the inexpensive crysin (Scheme 2).

Compound **13** was obtained despite the literature precedent for a similar reaction affording a different regioisomer as the reported product.[21]

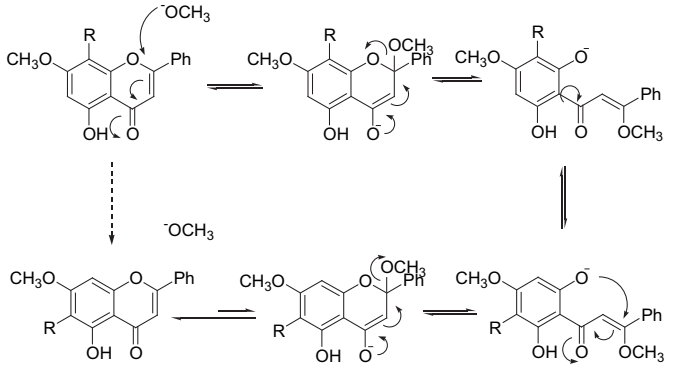
In the ^{13}C spectrum the methoxy group of **13** has a chemical shift of 56.3 ppm, value compatible with a methoxyl with almost one *ortho* position free of functional groups. Indeed a methoxy substituent on an aromatic system lies in the plane of the ring. In this conformation there is the maximum overlap between the lone pair of the oxygen and the π-orbitals of the aromatic ring. The methyl carbon is then shielded by the conjugated electrons and chemical shifts occur between 55.0 and 56.5 ppm. When the methoxy group is between bulky substituents, this conformation is disfavoured, the oxygen is not fully conjugated with the aromatic ring and the methoxy carbon deshielded to 59.5–63.6 ppm[22]



Scheme 1. Selective bromination of flavones.



Scheme 2. Convergent synthesis of mosloflavone, negletein and baicalein.



Scheme 3. Proposed mechanism for the Wesley–Moser type rearrangement in basic media.

3. Conclusions

By a simple strategy for oxy-functionalizing activated aromatic rings, crysin, an easily available flavone, was converted in higher oxygenated flavones, already known for their biological properties and likewise not easily available until now. Mosloflavone, negletein and baicalein were prepared in good amounts by a convergent procedure.

4. Experimental

4.1. General

NMR spectra were recorded on a VARIAN Mercury 3000 instrument (^{1}H, 300 MHz; ^{13}C, 75 MHz). Chemical shifts were calculated from the residual solvent signals of δ_H 2.04 ppm and δ_C 206.0 ppm in acetone-d_6, δ_H 7.24 ppm and δ_C 77.0 ppm in chloroform-d, δ_H 2.49 ppm and δ_C 39.5 in dimethyl sulfoxide-d_6. Melting points were measured on a Mettler FP80 instrument and were uncorrected. HRMS were performed on a Q-TOF MICRO spectrometer (Micromass, now Waters, Manchester, UK) equipped with an ESI source. All chromatographic purifications were performed on silica gel (100–200 mesh from E. Merck, Germany). Thin layer chromatography (TLC) was performed on precoated silica gel 60 F_{254} aluminium sheets (Merck Italia) and spots were visualised under UV torch. Organic solvents used for the chemical synthesis and for chromatography acquired from Merck Italia were of analytical grade.

*4.1.1. 5,7-Dimethoxyflavone (**1**).* To a solution of crysin (1 g, 3.94 mmol) in acetone (30 mL), K_2CO_3 (1.63 g, 11.8 mmol) and $(CH_3O)_2SO_2$ (1.99 g, 15.8 mmol) were added. The mixture was stirred for 6 h at 60 °C and monitored by TLC. After completion of the reaction the mixture was quenched with NH_4OH (5 mL of 10% sol in water) and acetone was removed under vacuum. The residue was dissolved in a small amount of ethyl acetate and HCl 2 M was added until the mixture was acidic. The mixture was extracted with ethyl acetate (3×30 mL) and the combined organic layers were washed with brine (30 mL) and dried over anhydrous sodium sulfate. The solvent was removed to obtain **1** (1.08 g, 3.82 mmol, 97% yield) as a yellow powder. Analytical data were in agreement with those reported in literature,[23,24] mp 201–202 °C (lit. 201.7 °C). ^{1}H NMR (chloroform-d_1) δ (ppm): 7.86 (2H, m, Ar-H), 7.49 (3H, m, Ar-H), 6.67 (1H, s, C^3-H), 6.56 (1H, d, J=2.2 Hz, C^8-H), 6.37 (1H, d, J=2.2 Hz, C^6-H), 3.49 (3H, s, CH_3O), 3.90 (3H, s, CH_3O).

*4.1.2. 6-Bromo-5,7-dimethoxyflavone (**2**).* To a solution of **1** (500 mg, 1.77 mmol) in chloroform (7 mL) TBATB (753 mg, 1.77 mmol) was added in one portion. After stirring for 1.5 h at rt the mixture was

diluted with water (14 mL) and extracted with ethyl acetate (3×14 mL). The extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Compound **2** (620 mg, 1.72 mmol) was obtained as yellow gummy liquid. IR $\nu_{(max)}$ ($CHCl_3$) 1640, 1350, 1165 cm^{-1}. ^1H NMR (chloroform-d_1) δ (ppm): 7.90 (2H, dd, J=2.1, 8.0 Hz), 7.45 (3H, m), 6.73 (1H, s), 6.41 (1H, s), 3.97 (3H, s), 3.95 (3H, s). ^{13}C NMR (chloroform-d_1) δ (ppm): 177.0, 161.0, 160.5, 160.2, 154.9, 131.5, 130.5, 128.8, 126.0, 108.9, 107.3, 96.7, 92.4, 58.9, 56.7. HRMS: calcd for $C_{17}H_{13}BrO_4Na^+$ (M+Na^+) 382.9895; found 382.9885.

*4.1.3. 5-Hydroxy-7-methoxyflavone (**3**).* Compound **3** was prepared via the same procedure as for **1** stopping the reaction after 1.5 h. Analytical data were in agreement with those reported in literature,[24] mp 166–168 °C (lit. 166.6). ^1H NMR (chloroform-d_1) δ (ppm): 12.72 (1H, s, C^5-OH), 7.88–7.91 (2H, m, $C^{2'}$-H, $C^{6'}$-H), 7.55–7.53 (3H, m, $C^{3'}$-H, $C^{4'}$-H, $C^{5'}$-H), 6.64 (1H, s, C^3-H), 6.50 (1H, d, J=2 Hz), 6.38 (1H, d, J=2 Hz), 3.88 (3H, s, CH_3O).

*4.1.4. 6-Bromo-5-hydroxy-7-methoxyflavone (**4**) and 8-bromo-5-hydroxy-7-methoxyflavone (**5**).* To a solution of **3** (500 mg, 1.86 mmol) in chloroform (7 mL), TBATB (793 mg, 1.86 mmol) was added in one portion. The mixture was left stirring at rt for 2 h, then worked up as for **2**. A 2:1 mixture of **4** and **5** (626 mg, 1.80 mmol) was obtained as yellow powder. The two isomers were inseparable by common techniques and were characterised as the acetate after chromatography on silica gel (hexane/ethyl acetate 8:2). The mixture was stirred overnight with a 1:1 solution of pyridine and acetic anhydride (6 mL). The mixture was poured in cold water (20 mL) and extracted with ethyl acetate (3×5 mL). The organic layers were washed with a 2 M solution of HCl in water (2×5 mL) and a saturated solution of $NaHCO_3$ (3×5 mL). Evaporation of the solvent under reduced pressure gave a 2:1 mixture of **9** and **10** in almost quantitative yield. Compound **9** (65% yield from **3**), R_f 0.36. IR $\nu_{(max)}$ ($CHCl_3$) 1715, 1650, 1350, 1165 cm^{-1}. ^1H NMR (chloroform-d_1) δ (ppm): 7.81 (2H, dd, J=2.2, 8.0 Hz, $C^{2'}$-H, $C^{6'}$-H), 7.54–7.48 (3H, m, $C^{3'}$-H, $C^{4'}$-H, $C^{5'}$-H), 6.91 (1H, s), 6.61 (1H, s), 4.01 (3H, s, CH_3O), 2.49 (3H, s, CH_3COO). ^{13}C NMR (chloroform-d_1) δ (ppm): 175.6, 168.3, 162.0, 160.0, 157.5, 148.0, 131.6, 131.2, 129.0, 126.1, 112.2, 108.5, 105.7, 98.0, 57.0, 20.9. HRMS: calcd for $C_{18}H_{13}BrO_5Na^+$ (M+Na^+) 410.9844; found 411.9839. Compound **10** (32% yield from **3**), R_f 0.33. IR $\nu_{(max)}$ ($CHCl_3$) 1715, 1645, 1350, 1160 cm^{-1}. ^1H NMR (chloroform-d_1) δ (ppm): 7.98 (2H, dd, J=2.2, 8.0 Hz, $C^{2'}$-H, $C^{6'}$-H), 7.51–7.55 (3H, m, $C^{3'}$-H, $C^{4'}$-H, $C^{5'}$-H), 6.68 (1H, s), 6.66 (1H, s), 4.01 (3H, s, CH_3O), 2.45 (3H, s, CH_3COO). ^{13}C NMR (chloroform-d_1) δ (ppm): 176.3, 169.4, 162.2, 160.0, 154.7, 149.9, 131.8, 131.0, 129.1, 126.4, 111.9, 107.7, 104.3, 97.5, 57.0, 21.1. HRMS: calcd for $C_{18}H_{12}BrO_5Na^+$ (M+Na^+) 410.9844; found 410.9848.

*4.1.5. 6,8-Dibromo-5,7-dihydroxyflavone (**7**).* To a solution of **6** (500 mg, 1.97 mmol) in chloroform (7 mL), TBATB (1.67 g, 3.94 mmol) was added in one portion. After 2.5 h under stirring at rt the mixture was diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL) to give pure **7** (746 mg, 1.8 mmol, 92% yield) as a pale yellow oil. Analytical data were in agreement with the literature.[25] ^1H NMR (aceton-d_6) δ (ppm): 13.71 (1H, s, C^5-OH), 8.12–8.09 (2H, m, $C^{2'}$-H, $C^{6'}$-H), 7.62–7.59 (3H, m, $C^{3'}$-H, $C^{4'}$-H, $C^{5'}$-H), 7.03 (1H, s, C^3-H).

*4.1.6. 8-Bromo-5,7-dimethoxyflavone (**8**).* To a solution of **1** (200 mg, 0.71 mmol) in DMF (5 mL), NBS (132 mg, 0.71 mmol) was added in one portion. The mixture was left to stir for 2.5 h then quenched with a cold 2 M solution of HCl (5 mL) and extracted with ethyl acetate (3×10 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Compound **8** (149 mg, 0.57 mmol, 80% yield) was obtained as yellow oil. ^1H NMR (acetone-d_6) δ (ppm): 7.96 (2H, dd, J=2.2, 8.0 Hz), 7.47 (3H, m), 6.71 (1H, s), 6.41 (1H, s), 3.98 (3H, s), 3.96 (3H, s). ^{13}C NMR (chloroform-d_1) δ (ppm): 177.4, 162.7, 160.8, 160.3, 160.2, 131.4, 131.0, 128.9, 126.1, 109.6, 108.1, 92.2, 90.9, 56.5, 56.4. HRMS: calcd for $C_{17}H_{13}BrO_4$ 382.9895; found 382.9853.

*4.1.7. 6,7-Dimethoxy-5-hydroxyflavone (mosloflavone, **11**).* To a suspension of CuBr (104 mg, 0.73 mmol) in DMF (2.2 mL) a 25% solution of sodium methoxide in methanol (6.63 mL, 29.15 mmol) was added at rt and left under stirring until a bright blue colour appeared (about 1 h). The mixture was added to a solution of **9** (354 mg, 0.91 mmol) in DMF (3 mL) at 120 °C in 2 mL portions. The mixture was left stirring for 40 min, then cooled to rt, quenched with a cold 2 M solution of HCl in water (13 mL) and extracted with ethyl acetate (3×20 mL). The extracts were washed with brine (3×10 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Compound **11** (254 mg, 0.85 mmol, 93.4% yield) was obtained as yellow powdered. Compound **11** was also obtained by the same procedure starting from the mixture of **4** and **5** leaving stirring for 5 h to allow the Wessley–Moser rearrangement to occur. In this case from 454 mg (1.31 mmol) of mixture 333 mg (1.11 mmol) of **11** was obtained after chromatography on silica gel (hexane/ethyl acetate 8:2). Data agreed with those reported in literature,[26] mp 159–160 (lit. 159–160), ^1H NMR (chloroform-d_1) δ (ppm): 12.67 (1H, s, C^5-OH), 7.87–7.84 (2H, m, $C^{2'}$-H, $C^{6'}$-H), 7.55–7.53 (3H, m, $C^{3'}$-H, $C^{4'}$-H, $C^{5'}$-H), 6.64 (1H, s), 6.54 (1H, s), 3.95 (3H, s, CH_3O), 3.91 (3H, s, CH_3O).

*4.1.8. 5-Hydroxy-7,8-dimehtoxyflavone (**12**).* The same procedure as for **11** was used starting from **10** (300 mg, 0.77 mmol). The mixture was left stirring for 5 h to allow the Wessely–Moser rearrangement and worked up as usual. After chromatography (hexane/ethyl acetate 8:2) **11** (185 mg, 0.62 mmol, 80.5% yield) and **12** (19 mg, 0.06 mmol, 8% yield) were obtained as a gummy liquid. ^{13}C NMR, δ (ppm): 182.7, 163.9, 158.7, 157.6, 149.5, 131.9, 131.4, 129.1, 126.3, 105.3, 105.0, 95.9, 61.6, 56.3. Other data agreed with those reported in literature.[26]

*4.1.9. 5,6-Dihydroxy-7-methoxyflavone (negletein, **13**).* A solution of **11** (283 mg, 0.95 mmol) in acetic acid (15.3 mL) and hydrobromidic acid (7.6 mL, 47% in water) was refluxed for 3 h, and then the solution was cooled to rt and poured into ice. The resulting precipitate was filtered washing with water and dried in oven (60 °C) overnight. Compound **13** (260 mg, 0.91 mmol, 96% yield) was obtained as yellow powder. ^{13}C NMR, δ (ppm): 182.7, 164.3, 153.1, 150.8, 145.8, 131.9, 129.8, 129.2, 126.5, 126.4, 105.8, 105.6, 90.6, 56.6. Other data agreed with those reported in literature.[27]

*4.1.10. 5,6,7-Trihydroxyflavone (baicalein, **14**).* A solution of **13** (260 mg, 0.91 mmol) in acetic acid (14 mL) and hydrobromidic acid (7 mL, 47% in water) was heated to reflux for 18 h, and then the solution was cooled to rt and poured into ice. The resulting precipitate was filtered washing with water and dried in oven (60 °C) overnight. Compound **14** (207 mg, 0.77 mmol, 85% yield) was obtained as yellow powder and data were identical to that of an original sample from Sigma–Aldrich Co.

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