Tetrahedron 66 (2010) 6047–6053

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Selective and efficient oxidative modifications of flavonoids with 2-iodoxybenzoic acid (IBX)

Maurizio Barontini [a], Roberta Bernini [a,*], Fernanda Crisante [a], Giancarlo Fabrizi [b]

[a] Dipartimento di Agrobiologia e Agrochimica, Università degli Studi della Tuscia, Via S. Camillo De Lellis snc, 01100 Viterbo, Italy
[b] Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi di Roma La Sapienza, P.le A. Moro 5, 00185 Roma, Italy

ARTICLE INFO

Article history:
Received 1 February 2010
Received in revised form 20 May 2010
Accepted 7 June 2010
Available online 15 June 2010

Dedicated to Professor Enrico Mincione on the occasion of his retirement

Keywords:
Catecholic flavonoids
Methoxylated flavones
Aromatic hydroxylation
Dehydrogenation reaction
2-Iodoxybenzoic acid (IBX)
IBX polystyrene

ABSTRACT

2-Iodoxybenzoic acid (IBX), a mild and efficient hypervalent iodine oxidant, has been utilised in different reaction conditions to perform several efficient oxidative modifications of flavonoids. Fine-tuning of the reaction conditions allowed remarkably selective modifications of these compounds. At room temperature, IBX proved to be an excellent reagent for a highly regioselective aromatic hydroxylation of monohydroxylated flavanones and flavones, generating the corresponding catecholic derivatives showing high antioxidant activity. At 90 °C, IBX efficiently dehydrogenated a large panel of methoxylated flavanones to their corresponding flavones exhibiting anticancer activity. IBX polystyrene has also been utilised to increase the recovery of highly polar compounds. Following the first oxidation, the reagent was recovered and reused in several runs without loss of efficiency and selectivity. The first example of an application of IBX polystyrene in a dehydrogenation reaction has been described.

1. Introduction

Flavonoids constitute one of the major groups of secondary metabolites and play important roles in plant development, reproduction and defence. Structurally, they have a common, basic C6–C3–C6 skeleton structure consisting of two aromatic rings (A and B) and a heterocyclic ring (C) containing one oxygen atom. More than 4,000 compounds have been isolated and characterised as a consequence of the wide variety of functional group substitutions into these three rings.[1] These compounds are important components of the human diet, being present in food (fruit, vegetables) and beverages (tea, wine).[2]

Many studies have shown that they are biologically active molecules exhibiting antiviral, *anti*-inflammatory, hepatoprotective, antioxidant, antithrombotic, vasodilating, antiviral and anticarcinogenic activities.[3] Recently, the majority of interest has focused on their antioxidant property, which is due to their ability to reduce free radical formation and to scavenge free radicals.[4] In view of this capability, they have attracted attention as potential therapeutic agents against free radical-mediated diseases. Various structure–activity relationship studies of flavonoids have pointed to the importance of the number and location of the phenolic groups present for effective radical scavenging activity.[5] A recent publication reported that the *ortho*-dihydroxyl (catechol) substitution is one of the essential features to increase this activity, while isolated monohydroxyl or *meta*-dihydroxyl substitutions do not have this effect.[6] Moreover, the catecholic group imparts appreciable activity when it is found on either ring A or ring B. For example, 7,8-dihydroxyflavone and 5,7,3′,4′-tetrahydroxyflavone (luteolin) are more active than the corresponding 7-hydroxyflavone and 5,7,4′-trihydroxyflavone (apigenin, Fig. 1).[6]

Although a number of methods are available for the synthesis of flavonoids, they are not ideal for the preparation of catecholic derivatives because the phenolic hydroxyl groups of the starting materials must be derivatized as esters or ethers and then cleaved for regeneration. This often results in only partial deprotection of the phenolic hydroxyl groups, which lowers the overall yield and complicates the product isolation procedure.[7] As an alternative, catecholic flavonoids could be prepared by an oxidative pathway from the corresponding phenol derivatives. The selective hydroxylation of aromatic compounds is amongst the most challenging chemical reactions in synthetic chemistry and has gained increasing attention in recent years, particularly because of the use of hydroxylated aromatics as precursors for pharmaceuticals. In

* Corresponding author. Tel.: +39 761 357452; fax: +39 761 357230; e-mail address: berninir@unitus.it (R. Bernini).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.06.014

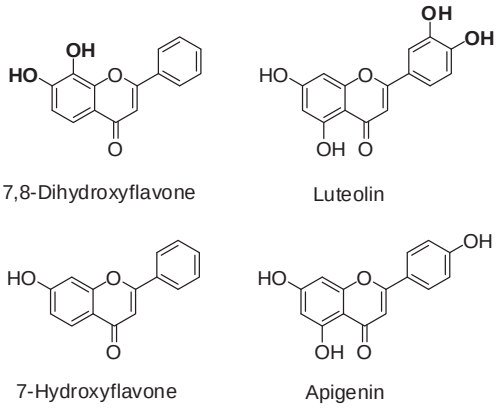


Figure 1. Some bioactive flavones.

flavonoid metabolism, cytochrome P450 monooxygenases catalyse the aromatic hydroxylation of large panels of derivatives.[8]

Our previous studies were concerned with the oxidative chemistry of flavonoids by the hydrogen peroxide/methyltrioxorhenium catalytic system for the generation of bioactive compounds; however, no catecholic derivatives were isolated.[9] Recently, Selenski and Pettus reported the synthesis of (±)-diinsininone, a biologically active compound having the flavanone skeleton.[10] A key step is the aromatic hydroxylation of 5,7,4′-trihydroxyflavanone (naringenin) to 5,7,3′,4′-tetrahydroxyflavanone (eriodictyol) performed with 1-hydroxy-1-oxo-1*H*-1λ^5-benz[*d*][1,2]iodoxol-3-one (2-iodoxybenzoic acid, IBX, Fig. 2), followed by reductive work-up of the resulting *ortho*-quinone with sodium dithionite ($Na_2S_2O_4$). This one-pot two step chemical process mimics the enzyme flavanone-3-hydrolase in flavan biosynthesis.[11]

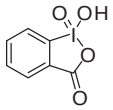


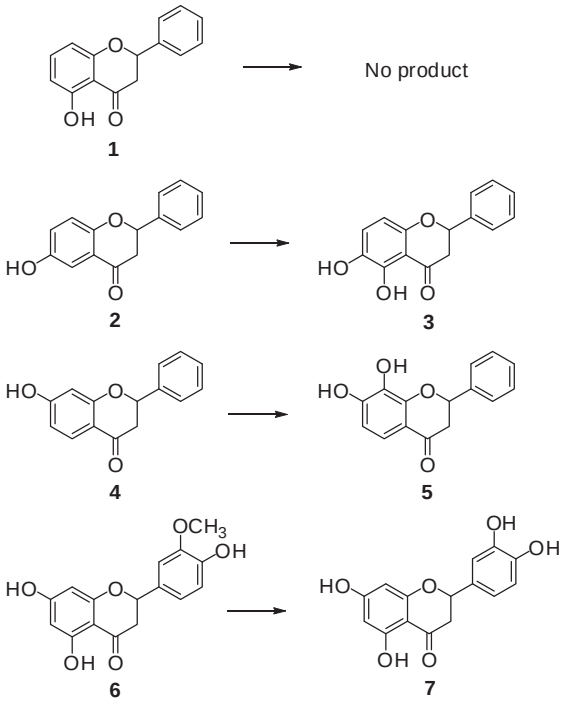
Figure 2. 2-Iodoxybenzoic acid (IBX).

IBX is a long-established reagent first prepared in 1893 by Hartman and Mayer,[12] but only after the development of an improved method for its synthesis [13] did it become a powerful reagent for several organic transformations.[14] Both the aromatic hydroxylation of phenols [15] and the oxidative demethylation of phenolic methyl aryl ethers [16] can be performed with high regioselectivity; catecholic compounds can be isolated in excellent yields and high purity. According to the previously reported ionic mechanism, the first step of the aromatic hydroxylation reaction of phenols is an intramolecular electrophilic aromatic substitution and the key intermediate is a λ^5-iodanyl complex between the iodine atom of IBX and the phenolic functionality of the substrate.[15,16]

This unique example of aromatic hydroxylation of flavonoid derivatives reported by Selenski and Pettus [10] as well as the experience of our own research group both in the oxidative chemistry of flavonoids [9] and in the preparation of naturally occurring catecholic compounds with IBX,[17] prompted us to exploit their utilisation in order to prepare a large panel of biologically active polyhydroxylated flavonoids.

2. Results and discussion

First, we applied the IBX-oxidative procedure to flavanones (Scheme 1). 5-Hydroxyflavanone **1** was solubilised in dimethyl sulfoxide, then IBX was added. The mixture was kept at room temperature under stirring for 24 h. Under these experimental



Scheme 1. Aromatic hydroxylation of flavanones **1**, **2**, **4** and **6**.

conditions, the substrate **1** was unreactive (Table 1, entry 1). A similar behaviour was observed heating the reaction mixture to 60 °C (Table 1, entry 2). This unexpected result may be explained by the establishment of the well-known hydrogen bond between the hydroxyl group in C-5 and the oxygen atom of the carbonyl group in

Table 1
Experimental data of oxidation depicted[a,b] in Scheme 1

Entry	Substrate	Product	*T* (°C)	Reaction time (h)[a]	Conv. (%)	Yields[c] (%)
1[a]	**1**	—	25	24	—	—
2[a]	**1**	—	60	24	—	—
3[a]	**2**	**3**	25	1	>98	95
4[a]	**4**	**5**	25	24	84	80
5[a]	**4**	**5**	60	24	88	84
6[a]	**6**	**7**	25	2	>98	70
7[b]	**6**	**7**	25	2	>98	95

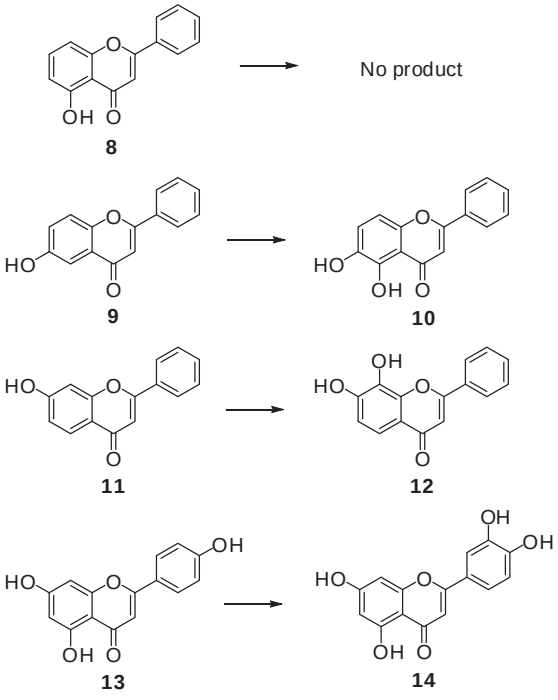
[a] Oxidant: IBX.
[b] Oxidant: IBX-polystyrene.
[c] Yields were given on the isolated product.

C-4 on 5-hydroxyflavanone **1**,[18] which evidently hindered the formation of the λ^5-iodanyl complex. On the basis of this possible explanation, we decided to try the IBX-oxidative procedure on flavanones having one or more hydroxyl groups in different positions on the A ring. The oxidation of 6-hydroxyflavanone **2** with IBX and the subsequent reduction with $Na_2S_2O_4$ in aqueous solution generated an oxidation product with quantitative conversion and yield after only 1 h (Table 1, entry 3). Spectroscopic data (^{1}H and ^{13}C NMR) and gas-mass spectrometry (GC-MS) analysis confirmed the structure of 5,6-dihydroxyflavanone **3**. Under similar experimental conditions, the oxidation of 7-hydroxyflavanone **4** proceeded with satisfactory conversion and yield to give a compound after a longer reaction time (Table 1, entries 4 and 5). By comparison of our spectroscopic data with data in the literature,[19] this compound was identified as 7,8-dihydroxyflavanone **5**.

It is worth noting that the aromatic hydroxylation of 6-hydroxyflavanone **2** and 7-hydroxyflavanone **4** with IBX proceeded with full regioselectivity. As shown previously by Selenski

and Pettus,[10] this could be rationalised by the theory of Dewar,[20] which has been widely investigated in relation to several electrophilic aromatic substitution reactions, e.g., the bromination of phenols and indane derivatives[21] and the amino-methylation of bicyclic phenols.[22] According to Dewar, 1,2,4-trisubstitued benzenes, wherein an electron withdrawing and an electron donating substituent are *ortho* to each other and an electron donating substituent is at the 4-position, will yield the 1,2,3,4-monosubstition product. This phenomenon has been ascribed to the conjugation between the adjacent 1- and 2-substituent, which tends to increase the bond order of the annular bond. Then, starting with 6-hydroxyflavanone **2** and 7-hydroxyflavanone **4**, the presence of an hydroxyl group on the A ring (an electron donating group), a carbonyl group (an electron withdrawing substituent) and a pyranic oxygen (an electron donating substituent) in *ortho* position on the A ring directed the substitution to the carbon C-5 of compound **2** and C-8 for **4**. Finally, 5,7,4′-trihydroxy-3′methoxyflavanone **6** (hesperetin) was treated with IBX. A selective demethylation at the C-3′ position of the B ring resulted in the production of 5,7,3′,4′-tetrahydroxyflavanone **7** (eriodictyol)[23,24] in 70% yield (Table 1, entry 6). As already observed by us with other phenolic compounds,[17c,d] the demethylation reaction of phenolic methyl aryl ethers is quick and probably proceeded with the mechanism already reported in the literature.[16] No hydroxylation products on the aromatic ring A were observed.

On the basis of these satisfactory results, we extended the oxidative procedure to 5-hydroxyflavone **8**, 6-hydroxyflavone **9**, 7-hydroxyflavone **11** and 5,7,4′-trihydroxyflavone **13** (Scheme 2).



Scheme 2. Aromatic hydroxylation of flavones **8**, **9**, **11** and **13**.

We observed a similar trend to that of flavanones. 5-Hydroxyflavone **8** was also unreactive, even at high temperature (Table 2, entry 1); 6-hydroxyflavone **9** and 7-hydroxyflavone **11** selectively yielded the corresponding catecholic compounds 5,6-dihydroxyflavone **10** and 7,8-dihydroxyflavone **12** in quantitative yields (Table 2, entries 2 and 3). 7-Hydroxyflavone **11** was less reactive, requiring a high reaction temperature. A recent publication reported the oxidation of 5-hydroxyflavone with potassium persulfate to a trace amount of 5,6-dihydroxyflavone **10** (yield of 5%).[25] The *anti*-

Table 2
Experimental data of oxidation depicted[a,b] in Scheme 2

Entry	Substrate	Product	*T* (°C)	Reaction time (h)[a]	Conv. (%)	Yields[c] (%)
1[a]	**8**	—	80	24	—	—
2[a]	**9**	**10**	25	1	>98	>98
3[a]	**11**	**12**	80	24	>98	>98
4[a]	**13**	**14**	25	1	>98	72
5[b]	**13**	**14**	25	2	>98	95

[a] Oxidant: IBX.
[b] Oxidant: IBX-polystyrene.
[c] Yields were given on the isolated product.

HIV activities of compounds **10** and **12** have been extensively studied.[26] A selective *ortho*-hydroxylation of the B ring of compound **13** gave rise to 5,7,3′,4′-tetrahydroxyflavone **14** (luteolin) in 72% yield (Table 2, entry 4).

On the basis of our previous experience on the use of IBX polystyrene (Fig. 3) for the construction of catecholic compounds,[17d–f] we utilised this heterogeneous oxidant to increase the yield of eriodictyol **7** and luteolin **14** being the work-up favourable to the recovery of highly polar products. After the oxidation reaction, the polymer was recovered by simple filtration; compounds **7** and **14** were quantitatively isolated (Table 1, entry 7; Table 2, entry 5). Polymer-supported IBX was regenerated and reused for five runs without loss of efficiency and selectivity.

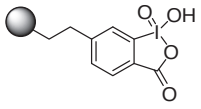
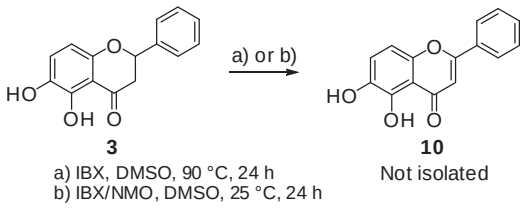


Figure 3. IBX polystyrene[27].

Finally, we exploited the ability of IBX to perform oxidations adjacent to carbonyl functionalities to obtain α,β-unsaturated carbonyl compounds in the presence of an excess of the reagent and under elevated temperatures. Mechanistic investigations demonstrated that these reactions were initiated by single-electron transfer from the substrate to IBX to form a radical cation, which reacted further to give the final products.[28] We then planned the dehydrogenation of the catecholic flavanones **3**, **5** and **7** in order to directly obtain the corresponding flavones **10**, **12** and **14**. As a model substrate, we utilised 5,6-dihydroxyflavanone **3** (Scheme 3). The substrate was solubilised in DMSO and an excess of IBX was added at high temperature. Unfortunately, the expected 5,6-dihydroxy-



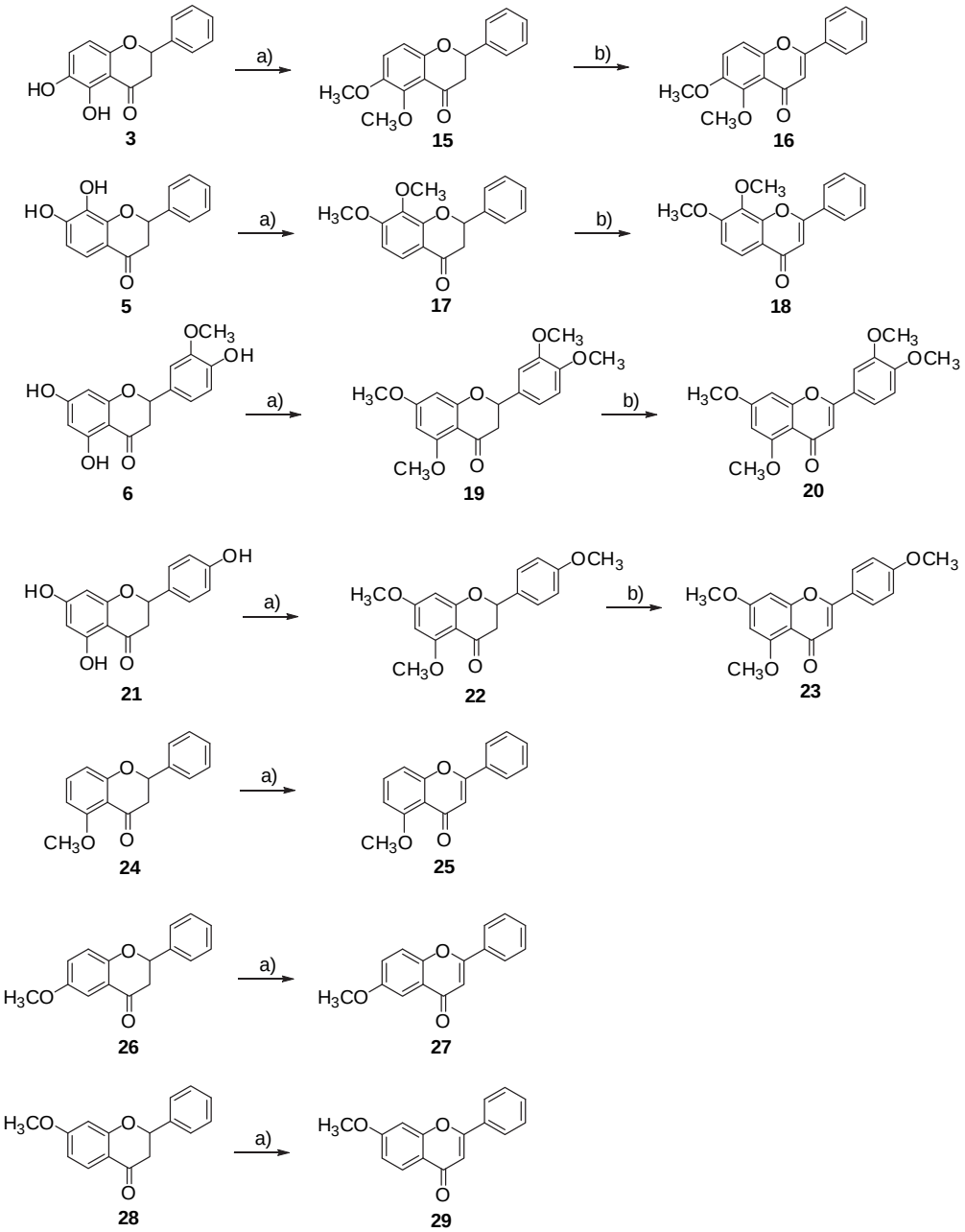
Scheme 3.

flavone **10** was not isolated from the complex reaction mixture. To exclude that this result was due to the instability of the catecholic compound in these harsh conditions, we tried the dehydrogenation reaction at room temperature by using *N*-methyl morpholine-*N*-oxide (NMO).[29] However, also under these experimental conditions, the desired product 5,6-dihydroxyflavone **10** could not be isolated.

On the basis of these results, we considered the protection of the phenolic groups of flavanones to be appropriate before performing the dehydrogenation reaction. The methylation reaction was chosen in order to obtain methoxylated flavones as final products, a class of biologically active flavonoids.[30] Recently, Walle and colleagues

reported that these compounds show in vivo cancer chemopreventive properties superior to the more common unmethoxylated derivatives [31] These effects are attributed to their high hepatic metabolic stability as well as high intestinal absorption in humans, which increase the oral bioavailability in vivo. 5,6-Dihydroxyflavanone **3** was firstly methylated under classical conditions with dimethyl sulfate in basic conditions to obtain 5,6-dimethoxyflavanone **15** (Scheme 4). This compound was solubilised in DMSO and treated with IBX at high temperature. After 24 h, the corresponding 5,6-dimethoxyflavone **16** was isolated in quantitative yield (Table 3, entry 1). This efficient procedure was successfully extended to 7,8-dimethoxyflavanone **17**, methylated hesperetin **19**, methylated naringenin **22** previously prepared by us and to commercially available 5-methoxyflavanone **24**, 6-methoxyflavanone **26** and 7-methoxyflavanone **28**. The corresponding methoxylated flavones **18**, **20**, **23**, **25**, **27** and **29** were isolated in satisfactory to excellent yields (Table 3, entries 3, 5, 7, 11 and 13).

Finally, we tested the efficiency and selectivity of IBX polystyrene as oxidant in the dehydrogenation reaction. After 24 h, the conversion of the substrate and the yield of the final product **16** were comparable to those obtained with homogeneous IBX (Table 3, compare entry 1 with entry 2). At the end of the reaction, IBX polystyrene was regenerated and reused. In this case, the efficiency and selectivity of the reagent persisted for only three runs, probably due to the high temperature of the reaction (90 °C). Similar results were obtained from methylated flavanones **17**, **19**, **21**, **22**, **24**, **26**, **28** obtaining flavones **18**, **20**, **23**, **25**, **27** and **29** (Table 3, entries 4, 6, 8, 10, 12 and 14). To the best of our knowledge, this is



a) K_2CO_3, $(CH_3)_2SO_4$, acetone, 25 °C, 24 h (Conv. and yields: >98%)
b) IBX, DMSO, 90 °C, 24 h (Conv. and yields: see **Table 3**)

Scheme 4. Dehydrogenation reaction of methylated flavonoids **15**, **17**, **19**, **22**, **25**, **27**, **29**.

Table 3
Dehydrogenation of methoxylated flavanones[b]

Entry	Substrate	Product	Conv. (%)	Yields[c] (%)
1[a]	**15**	**16**	>98	95
2[b]	**15**	**16**	95	92
3[a]	**17**	**18**	>98	>98
4[b]	**17**	**18**	95	95
5[a]	**19**	**20**	92	90
6[b]	**19**	**20**	90	88
7[a]	**22**	**23**	90	88
8[b]	**22**	**23**	92	90
9[a]	**24**	**25**	>98	>98
10[b]	**24**	**25**	92	92
11[a]	**26**	**27**	85	80
12[b]	**26**	**27**	84	80
13[a]	**28**	**29**	80	75
14[b]	**28**	**29**	78	78

[a] Oxidant: IBX.
[b] Oxidant: IBX-polystyrene.
[c] Yields were given on the isolated product.

the first example of an application of IBX polystyrene on the dehydrogenation reaction of carbonyl compounds.

3. Conclusions

This paper has described some useful and efficient applications of IBX to the oxidative chemistry of flavonoids to obtain bioactive compounds in high yields. Fine-tuning of the reaction conditions allowed remarkably selective modifications of these compounds. Under controlled conditions (IBX: 1.2 equiv, room temperature), a regioselective aromatic hydroxylation of a large panel of flavanones and flavones generated the corresponding *ortho*-dihydroxylated flavonoids with powerful antioxidant properties. In the presence of an excess of oxidant and under elevated temperatures, an efficient dehydrogenation reaction of methoxylated flavanones generated the corresponding flavones with anticancer properties. IBX polystyrene showed similar efficiency and selectivity in the oxidation reactions in comparison to homogeneous IBX, allowing the quantitative isolation of high polar compounds. This is the first example of a dehydrogenation reaction performed by this heterogeneous oxidant to be reported.

4. Experimental

4.1. General

Hydroxylated flavonoids **1**, **2**, **4**, **6**, **8**, **9**, **11**, **13** and **14** and methoxylated flavonoids **24**, **26** and **28** were commercially supplied (Aldrich, Apin Chemicals). All chemicals used were of analytical grade. Homogeneous IBX was prepared in our laboratory as described in the literature.[13] IBX polystyrene was purchased from Novabiochem (loading factor=1.1 mmol/gram). Silica gel 60 F_{254} plates and silica gel 60 were obtained from Merck. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker 200 MHz spectrometer using $CDCl_3$ and CD_3OD as solvents. All chemical shifts are expressed in parts per million (δ scale) and coupling constants in hertz. GC–MS analysis was performed on a Shimatzu VG 70/250S apparatus equipped with a CP-SIL 8 CB-MS column (25 m, 0.25 mm and 0.25 mm film thickness). The analyses were performed using an isothermal temperature profile of 100 °C for 2 min, followed by a 10 °C/min temperature gradient for 15 min until 280 °C. The injector temperature was 280 °C.

4.2. General procedure for the aromatic hydroxylation of flavanones and flavones

Oxidation with homogeneous IBX. To a solution of substrate (1.0 mmol) solubilised in DMSO (10 mL) was added IBX (1.2 equiv), which was then stirred at room temperature or 60 °C for 1–24 h depending on the substrate. During the reaction, a chromatic change from yellow to brown was observed. At the end, H_2O (10 mL) and an excess of $Na_2S_2O_4$ were added and the solution was left under stirring until it became yellow. Ethyl acetate was added to the mixture, then it was treated with pH 8.5 buffer solution to remove *o*-iodobenzoic acid. The aqueous phase was extracted with ethyl acetate. The organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. After evaporation of the solvent, the catecholic flavonoids were isolated by chromatographic purification on silica gel (230–400 mesh).

Oxidation with IBX polystyrene. The substrate (1.0 mmol) was solubilised in DMSO (10 mL) at room temperature under magnetic stirring and then commercial polymer-supported IBX (3.0 mmol) was added. When the substrate disappeared, the polymer was recovered by simple filtration and the remaining solution was treated with water (10 mL) and an excess of $Na_2S_2O_4$. The products were extracted with ethyl acetate. The organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. After evaporation of the solvent, catecholic compounds were isolated. Polymer-supported IBX was regenerated by treating the filtered resin with a solution of tetrabutylammonium oxone and methanesulfonic acid according to the procedure reported by us previously.[17d,e]

*4.2.1. 5,6-Dihydroxyflavanone (**3**).* Yellow solid (243 mg; yield: 95%). Mp 154–155 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.86 (dd, 1H, J_1=3.2 and J_2=17.3 Hz), 3.11 (dd, 1H, J_1=12.9 and J_2=17.3), 5.39 (dd, 1H, J_1=3.1 and J_2=12.9), 6.44 (d, 1H, J=8.8 Hz), 7.08 (d, 1H, J=8.8 Hz), 7.36–7.47 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.0, 79.3, 106.9, 108.0, 123.5, 126.1, 126.1, 128.8, 128.9, 138.3, 138.4, 147.5, 154.2, 198.7. *m*/*z* 256 (M^+, 25), 152 (100), 124 (12). Anal. Calcd for $C_{15}H_{12}O_4$ (256.25): C, 70.31; H, 4.72; O, 24.97. Found: C, 70.37; H, 4.69; O, 24.94.

*4.2.2. 7,8-Dihydroxyflavanone (**5**).* Yellow solid (205 mg. Yield: 80%). Mp 162–164 °C (lit.[32] 164–166 °C). Spectroscopic data were according to the literature.[19]

*4.2.3. 5,7,3′,4′-Tetrahydroxyflavanone (**7**) (eriodictyol).* Yellow oil (288 mg; yield: >98%). Mp 282–284 °C (lit.[32] 281–282 °C). Spectroscopic data were according to the authentic commercial sample.

*4.2.4. 5,6-Dihydroxyflavone (**10**).* Yellow solid (254 mg. Yield: >98%). Mp 189–191 °C (lit.[25] 193–195 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.96 (d, 1H, J=8.9 Hz), 7.27 (d, 1H, J=8.9 Hz), 7.45–7.54 (m, 3H), 7.89 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 105.1, 106.8, 110.8, 121.4, 126.4, 129.1, 131.4, 132.0, 140.1, 145.4, 149.6, 165.1, 183.7. *m*/*z* 256 (M^+, 20), 152 (100), 124 (4). Anal. Calcd for $C_{15}H_{10}O_4$ (254.24): C, 70.87; H, 3.96; O, 25.17. Found: C, 70.79; H, 4.01; O, 25.20.

*4.2.5. 7,8-Dihydroxyflavone (**12**).* Yellow solid (254 mg; yield: >98%). Mp 248–250 °C (lit.[33] 250–251 °C). Spectroscopic data were according to the literature.[34]

*4.2.6. 5,7,3′,4′-Tetrahydroxyflavone (**14**) (luteolin).* Yellow solid (206 mg; yield: 72%). Mp 325–328 °C (lit.[35] 328–330 °C). Spectroscopic data were according to the literature.[36]

4.3. General procedure for the methylation of flavanones

The substrate (1.0 mmol) was solubilised in acetone (10 mL) at room temperature. Then, potassium carbonate (1.5 mmol per hydroxyl group) and dimethyl sulfate (6 mmol per hydroxyl group) were added. The reaction was monitored by TLC. When the

substrate disappeared (24 h), the acetone was evaporated under reduced pressure. The mixture was neutralised by 1 M HCl and the product was extracted with ethyl acetate (3×10 mL). The organic layers were washed with a saturated solution of NaCl and dried over dry Na_2SO_4. The product was obtained pure in quantitative yield.

*4.3.1. 5,6-Dimethoxyflavanone (**15**).* Yellow solid (270 mg; yield: 95%). Mp 140–142 °C (lit.[37] 142–144 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.81 (dd, 1H, J_1=16.7 and J_2=3.2 Hz), 3.02 (dd, 1H, J_1=16.7 and J_2=12.9 Hz), 3.79 (s, 3H), 3.88 (s, 3H), 5.36 (dd, 1H, J_1=3.2 and J_2=12.9 Hz), 6.76 (d, 1H, J=9.0 Hz), 7.10 (d, 1H, J=9.0 Hz), 7.31–7.46 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 46.2, 57.2, 60.4, 79.0, 112.8, 116.0, 121.2, 126.1, 128.7, 128.8, 138.8, 147.7, 149.7, 156.1, 190.9. *m*/*z* 284 (M^+, 36.5), 180 (100), 165 (84), 137 (39), 109 (12). Anal. Calcd for $C_{17}H_{16}O_4$ (284.31): C, 71.82; H, 5.67; O, 22.51. Found: C, 71.90; H, 5.72; O, 22.38.

*4.3.2. 7,8-Dimethoxyflavanone (**17**).* Yellow solid (284 mg; yield: >98%). Mp 112–115 °C (lit.[38] 114 °C). Spectroscopic data were according to the literature.[38]

*4.3.3. 5,7,3′,4′-Tetramethoxyflavanone (**19**) (methylated hesperetin).* Yellow oil (327 mg; yield: 95%). Spectroscopic data were according to the literature.[9a,b]

*4.3.4. 5,7,3′-Trimethoxyflavanone (**22**) (methylated naringenin).* Yellow oil (314 mg; yield: >98%). Spectroscopic data were according to the literature.[9a,b]

4.4. General procedure for the dehydrogenation of methylated flavanones

Dehydrogenation with homogeneous IBX. To a solution of substrate (1.0 mmol) solubilised in DMSO (10 mL) was added IBX (2.0 equiv), which was then stirred at 90 °C for 24 h. At the end, ethyl acetate was added to the mixture, then it was treated with a solution of $NaHCO_3$. The aqueous phase was extracted with ethyl acetate. The organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. After evaporation of the solvent, the corresponding flavones were isolated by chromatographic purification on silica gel (230–400 mesh).

Dehydrogenation with homogeneous IBX and NMO. IBX (1.2 mmol) and NMO (1.2 mmol) were added to DMSO (2.5 mL) and stirred at room temperature until complete dissolution (15–60 min). Then, the substrate was added (1.0 mmol), the mixture was stirred and the reaction was monitored by TLC. The mixture was diluted with a solution of $NaHCO_3$ and extracted with diethyl ether. The organic extracts were evaporated and dried over Na_2SO_4. Finally, the organic phase was concentrated and the product was purified by a chromatographic column of silica gel.

Dehydrogenation with polymer-supported IBX. The substrate (1.0 mmol) was solubilised in DMSO (10 mL) at 90 °C under magnetic stirring, then commercial polymer-supported IBX (3.0 mmol) was added. When the substrate disappeared, the polymer was recovered by simple filtration. The products were extracted with ethyl acetate. The organic phases were washed with a saturated solution of NaCl and dried over Na_2SO_4. After evaporation of the solvent, the corresponding flavones were isolated. Polymer-supported IBX was regenerated by treating the filtered resin with a solution of tetrabutylammonium oxone and methanesulphonic acid according to the procedure reported by us previously.[17d,e]

*4.4.1. 5,6-Dimethoxyflavone (**16**).* Yellow solid (268 mg; yield: 95%). Mp 192–194 °C (lit.[39] 196 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.92 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 6.70 (1H, s, H-3), 7.46–7.54 (5H, m, H-7,8,3′,4′,5′), 7.86–7.91 (2H, m, H-2′,6′). ^{13}C NMR (50 MHz, $CDCl_3$): δ 57.2, 61.9, 108.0, 113.4, 117.2, 119.1, 126.1, 129.0, 131.4, 133.8, 147.9, 150.0, 151.6, 161.6, 178.1. *m*/*z*: 282 (M^+, 33), 267 (100), 239 (29), 165 (21), 133 (43), 102 (35), 77 (40). Anal. Calcd for $C_{17}H_{14}O_4$ (282.29): C, 72.33; H, 5.00; O, 22.67. Found: C, 72.40; H, 5.08; O, 22.52.

*4.4.2. 7,8-Dimethoxyflavone (**18**).* Yellow solid (282 mg; yield: >98%). Mp 145–147 °C (lit.[40] 147–148 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.99 (s, 3H), 4.00 (s, 3H), 6.77 (s, 1H), 7.04 (d, 1H, J=9.0 Hz), 7.51–7.54 (m, 3H), 7.93–7.98 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.5, 61.6, 106.9, 109.9, 118.6, 121.0, 126.2, 129.1, 131.5, 131.9, 137.0, 150.6, 156.7, 163.0, 178.1. *m*/*z* 282 (M^+, 100), 267 (33), 239 (17), 165 (53), 137 (59), 109 (37), 66 (30). Anal. Calcd for $C_{17}H_{14}O_4$ (282.29): C, 72.33; H, 5.00; O, 22.67. Found: C, 72.38; H, 5.08; O, 22.54.

*4.4.3. 5,7,3′,4′-Tetramethoxyflavone (**20**) (methylated luteolin).* Yellow oil (281 mg; yield: 90%). Mp 190–194 °C (lit.[41] 193 °C). Spectroscopic data were according to the literature.[41]

*4.4.4. 5,7,3′-Trimethoxyflavone (**23**) (methylated apigenin).* Yellow solid (275 mg; yield: 88%). Mp 154–156 °C (lit.[41] 157 °C). Spectroscopic data were according to the literature.[41]

*4.4.5. 5-Methoxyflavone (**25**).* White solid (252 mg; yield: >98%). Mp 130–134 °C (lit.[42] 131 °C). Spectroscopic data were according to the authentic commercial sample.

*4.4.6. 6-Methoxyflavone (**27**).* White solid (202 mg; yield: 80%). Mp 164 °C (lit.[43] 161–163 °C). Spectroscopic data were according to the authentic commercial sample.

*4.4.7. 7-Methoxyflavone (**29**).* White solid (189 mg; yield: 75%). Mp 109–110 °C (lit.[44] 110 °C). Spectroscopic data were according to the authentic commercial sample.

Acknowledgements

The authors are grateful to Dr. Gianfranco Provenzano for the preparation of some samples. The University of Tuscia and Ministero della Ricerca Scientifica e Tecnologica are acknowledged for their financial support.

References and notes

1. *The Handbook of Natural Flavonoids*; Eds.; Harborne, J.B.; Baxter, H., John Wiley: New York, NY *The Flavonoids: Advances in Research*; Harborne, J. B., Mabry, T. J., Eds.; Chapman and Hall: London, 1982.
2. (a) Herrmann, K. *J. Food Technol.* **1976**, *11*, 433–448; (b) Singleton, V. L. *Adv. Food Res.* **1981**, *27*, 149–242.
3. See for example: (a) Harborne, T. B. *The Flavonoids: Advances in Research since*; Chapman and Hall: London, 1986; (b) Middleton, E. J.; Kandaswami, C.; Theoharides, T. C. *Pharmacol. Rev.* **2000**, *52*, 673–751; (c) Yang, C. S.; Prabhu, S.; Landau, J. *Drug Metab. Rev.* **2001**, *33*, 237–253; (d) Haghiac, M.; Walle, T. *Nutr. Cancer* **2005**, *53*, 220–231.
4. (a) Chewn, Z. Y.; Chan, P. T.; Ho, K. Y.; Fung, K. P.; Wang, J. *Chem. Phys. Lipids* **1996**, *79*, 157–163; (b) Rice-Evans, C. A.; Miller, N. J.; Paganga, G. *Free Radical Biol. Med.* **1996**, *20*, 933–956 Van Acker, S.A; (c) Van der Ber, D. J.; Tromp, M. N.; Griffioen, D. H.; Van Bennekon, W. P.; Van der Vijgh, W. J.; Bast, A. *Free Radical Biol. Med.* **1996**, *20*, 331–342; (d) Edenharder, R.; Grnhage, D. *Mutat. Res.* **2003**, *540*, 1–18.
5. Foti, M.; Piattelli, M.; Baratta, G. *J. Agric. Food Chem.* **1996**, *44*, 497–501.
6. Seyourn, A.; Asres, K.; Kamdeel El-Fiky, F. *Phytochemistry* **2006**, *67*, 2058–2070.
7. (a) Robinson, R.; Venkataraman, K. *J. Chem. Soc.* **1926**, 2336–2344; (b) Allan, J.; Robinson, R. *J. Chem. Soc., Trans.* **1924**, *125*, 2192–2195; (c) Baker, W. *J. Chem. Soc.* **1933**, 1381–1394; (d) Hoshino, Y.; Takeno, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1919–1920; (e) Saxena, S.; Mereddy, J.; Grover, S. *Synthesis* **1985**, 697–671; (f) Varma, R.; Saini, R.; Kumar, D. *J. Chem. Res.* **1998**, 348–349; (g) Ganguly, A.; Kaur, S.; Mahata, P.; Biswas, D.; Pramanik, B.; Chan, T. *Tetrahedron Lett.* **2005**, *46*, 4119–4121 and references therein; (h) Kabalba, G.; Mereddy, A. *Tetrahedron Lett.* **2005**, *46*, 6315–6318.
8. (a) Ayabe, S.-I.; Akashi, T. *Phytochem. Rev.* **2006**, *5*, 271–282; (b) Ullrich, R.; Hofrichter, M. *Cell. Mol. Life Sci.* **2007**, *64*, 271–293; (c) Urlacher, V. B. Handbook

of Green Chemistry. In *Biocatalysis*; Crabtree, R. H., Ed.; Wiley-VCH: Weinheim, 2009; Vol. 3.
9. (a) Bernini, R.; Mincione, E.; Cortese, M.; Aliotta, G.; Oliva, A.; Saladino, R. *Tetrahedron Lett.* **2001**, *42*, 5401–5404; (b) Bernini, R.; Mincione, E.; Cortese, M.; Saladino, R.; Gualandi, G.; Belfiore, M. C. *Tetrahedron Lett.* **2003**, *44*, 4823–4825; (c) Bernini, R.; Mincione, E.; Provenzano, G.; Fabrizi, G. *Tetrahedron Lett.* **2005**, *46*, 2993–2996; (d) Bernini, R.; Mincione, E.; Provenzano, G.; Fabrizi, G.; Tempesta, S.; Pasqualetti, M. *Tetrahedron* **2008**, *64*, 7561–7566.
10. Selenski, C.; Pettus, T. R. R. *Tetrahedron* **2006**, *62*, 5298–5307.
11. Marles, M. A. S.; Ray, H.; Gruber, M. Y. *Phytochemistry* **2003**, *64*, 367–383.
12. Hartman, C.; Mayer, V. *Chem. Ber.* **1893**, *26*, 1727–1732.
13. Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
14. (a) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178; (b) Varvaglosis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: London, 1997; (c) *Encyclopedia of Reagents for Organic Synthesis*; Nicolau, K. C., Montagnon, T., Baran, P. S., Eds.; John Wiley: London, 2003; (d) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, *2*, 121–145; (e) Ladziata, U.; Zhadankin, V. V. *Arkivoc* **2006**, *IX*, 26–58 and references therein.
15. (a) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285–288; (b) Huang, Y.; Zhang, J.; Pettus, T. R. R. *Org. Lett.* **2005**, *7*, 5841–5844.
16. (a) Ozanne, A.; Pouysegu, L.; Depernet, D.; Francois, B.; Quideau, S. *Org. Lett.* **2003**, *5*, 2903–2906; (b) Quideau, S.; Pouysegu, L.; Deffieux, D.; Ozanne, A.; Gagnepain, J.; Fabre, I.; Oxoby, M. *Arkivoc* **2003**, *vi*, 106–119; (c) Quideau, S.; Pouysegu, L.; Gagnepain, J. *Molecules* **2005**, *10*, 201–216; (d) Quideau, S.; Pouysegu, L.; Deffieux, D. *Synlett* **2008**, 467–495.
17. (a) Bernini, R.; Mincione, E.; Barontini, M.; Crisante, F. *J. Agric. Food Chem.* **2008**, *56*, 8897–8904; (b) Bernini, R.; Barontini, M.; Spatafora, C. *Molecules* **2009**, *14*, 4669–4681; (c) Bernini, R.; Barontini, M.; Mosesso, P.; Pepe, G.; Willför, S. M.; Sjöholm, R. E. C.; Eklund, P. C.; Saladino, R. *Org. Biomol. Chem.* **2009**, *7*, 2367–2377; (d) Bernini, R.; Mincione, E.; Crisante, F.; Barontini, M.; Fabrizi, G. *Tetrahedron Lett.* **2009**, *50*, 1307–1310; (e) Bernini, R.; Crisante, F.; Barontini, M.; Fabrizi, G. *Synthesis* **2009**, *22*, 3838–3842; (f) Bernini, R.; Barontini, M.; Crisante, F.; Ginnasi, M. C.; Saladino, R. *Tetrahedron Lett.* **2009**, *50*, 6519–6521.
18. Exarchou, V.; Troganis, A.; Gerothanassis, I. P.; Tsimidou, M.; Boskou, D. *Tetrahedron* **2002**, *58*, 7423–7429 and references therein.
19. Hahm, E.-R.; Park, S.; Yang, C.-H. *Nat. Prod. Res.* **2003**, *17*, 431–436.
20. Dewar, M. J. S. *J. Chem. Soc.* **1949**, 463–468.
21. Nilsson, J. L. G.; Selander, H.; Sievertsson, H.; Skanberg, I.; Svensson, K. G. *Acta Chem. Scand.* **1971**, *25*, 94–100.
22. Lange, J.; Hoogeveen, S.; Veerman, W.; Wals, H. *Heterocycles* **2000**, *53*, 197–204.
23. Yun, B. S.; Lee, I. K.; Kim, J. P.; Chung, S. H.; Shim, G. S.; Yoo, I. D. *Arch. Pharm. Res.* **2000**, *23*, 147–150.
24. Areias, F. M.; Rego, A. C.; Oliveira, C. R.; Seabra, R. M. *Biochem. Pharmacol.* **2001**, *62*, 111–118.
25. Gao, H.; Nishioka, T.; Kawabata, J.; Kasi, T. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 369–375.
26. Zhang, Y. *Jiegou Huaxue* **2005**, *24*, 462–466.
27. (a) Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4395–4397; (b) Reed, N. N.; Delgado, M.; Hereford, K.; Clapham, B.; Janda, K. D. *Bioorg. Med. Chem.* **2002**, *12*, 2047–2049.
28. Nicolau, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.
29. Nicolau, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993–996.
30. (a) Van Zanden, J. J.; Wortelboer, H. M.; Bijlsma, S.; Punt, A.; Usta, M.; Van Bladeren, P. J.; Rietjens, I. M. C. M.; Cnubben, N. H. P. *Biochem. Pharmacol.* **2005**, *69*, 699–708; (b) Taleb-Contini, S. H.; Kanashiro, A.; Kabeya, L. M.; Polizello, A. C. M.; Lucisano-Valim, Y. M.; Oliveira, D. C. R. *Phytotherapy Res.* **2006**, *20*, 573–575.
31. (a) Wen, X.; Walle, T. *Drug Metab. Dispos.* **2006**, *34*, 1786–1792; (b) Walle, T. *Semin. Cancer Biol.* **2007**, *17*, 354–362; (c) Walle, T.; Ta, N.; Kawamori, T.; Wen, X.; Tsuji, P. A.; Walle, U. K. *Biochem. Pharmacol.* **2007**, *73*, 1288–1296; (d) Tsuji, P. A.; Walle, T. *Carcinogenesis* **2006**, *27*, 1579–1585.
32. Hattori, M.; Shu, Y.-Z.; El-Sedwy, A. I.; Namba, T. *J. Nat. Prod.* **1988**, *51*, 874–878.
33. Cushman, M. *Tetrahedron Lett.* **1990**, *31*, 6497–6500.
34. March, R. *Magn. Reson. Chem.* **2008**, *46*, 680–682.
35. Li, Y.-L. *Molecules* **2008**, *13*, 1931–1941.
36. (a) Christophoridou, S.; Dais, P.; Tseng, L.-H.; Spraul, M. *J. Agric. Food Chem.* **2005**, *53*, 4667–4679; (b) Flamini, G.; Antognoli, E.; Morelli, I. *Phytochemistry* **2001**, 559–564.
37. Rajagopalan, S.; Row, L.; Ramachandra, L.; Seshadri, T. R. *Proceeding-Indian Acad. Sci., Sect. A* **1946**, *23A*, 97–101.
38. Lee, J. I.; Jung, M. G. *Bull. Korean Chem. Soc.* **2005**, *26*, 2044–2046.
39. Baker, W. *J. Chem. Soc.* **1939**, *59*, 956–961.
40. Ashihara, Y. *Bull. Chem. Soc. Japan* **1977**, *50*, 3298–3301.
41. Sutthanut, K.; Sripanidkulchai, B.; Yenjai, C.; Jay, M. *J. Chromatogr., A* **2007**, *1143*, 227–233.
42. Looker, J. H. *J. Org. Chem.* **1962**, *27*, 381–389.
43. Lee, J. I. *Bull. Korean Chem. Soc.* **2005**, *26*, 1461–1463.
44. Virkar, V.; Shah, R. J. *J. Univ. Bombay* **1942**, *11*, 140–144.