Chemistry of Natural Compounds, Vol. 47, No. 1, March, 2011 [Russian original No. 1, January–February, 2011]

SYNTHESIS OF FLUORINE-CONTAINING 3-HYDROXYFLAVANONES AND ISOFLAVONES

T. S. Khlebnikova,* Yu. A. Piven′, N. B. Khripach, and F. A. Lakhvich

UDC 547.814.5:547.539.1

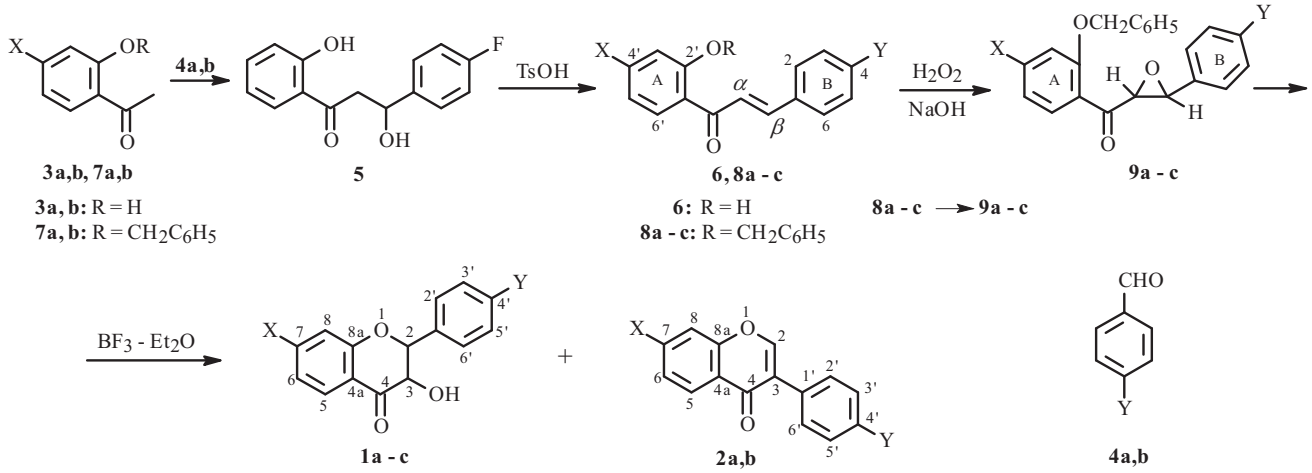
Fluorine-containing 3-hydroxyflavanones and isoflavones were synthesized by epoxidation of F-containing chalcones by hydrogen peroxide under basic conditions and subsequent intramolecular cyclization of the resulting epoxides using $BF_3{\cdot}Et_2O$. The ratio of products depended on the presence and position of the F atom.

Keywords: F-containing 3-hydroxyflavanones, isoflavones, chalcone epoxides.

Flavonoids include a large group of polyphenolic natural compounds that are widely distributed in higher plants and exhibit various types of biological activity [1]. Notable among them is 3-hydroxyflavanone, taxifolin (dihydroquercetin), which exhibits strong hepatoprotective activity [2] and is a powerful antioxidant [3] that is used to treat is chemic stroke, angina pectoris, and other cardiovascular diseases [3]. Genistein (5,7,4′-trihydroxyisoflavone) and diadzein (7,4′-dihydroxyisoflavone) are some of the most common and most studied isoflavonoids with broad spectra of biological activity (antioxidant, antitumor, estrogenic, and other types of physiological activity) [3, 4–8].

Selective introduction of F atoms or fluoroalkyl groups is a well-known technique for modifying the biological activity of various classes of natural compounds including steroids, nucleosides, antibiotics, prostaglandins, and others [9].

Herein the synthesis of novel 3-hydroxyflavanones and isoflavones containing an F atom is investigated. For this, we studied a synthetic approach that included transformation of F-containing chalcone epoxides using $BF_3{\cdot}Et_2O$ as a Lewis acid [10]. This approach enabled both 3-hydroxyflavanones **1** and isoflavones **2** (mono- and di-F-substituted depending on the structures of the starting materials) to be obtained. The chalcones were prepared via condensation of the corresponding acetophenones and benzaldehydes under basic conditions. The starting material for constructing the F-substituted flavonoid ring A was 2-hydroxy-4-fluoroacetophenone; F-substituted ring B, 4-fluorobenzaldehyde.



1a, **2a**, **6**, **8a**, **9a**: X = H, Y = F; **1b**, **2b**, **6**, **8b**, **9b**: X = Y = F; **1c**, **8c**, **9c**: X = F, Y = NO_2; **3a**, **7a**: X = H; **3b**, **7b**: X = F; **4a**: Y = F; **4b**: Y = NO_2

Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, 220141, Minsk, ul. Akad. Kuprevicha, 5/2, e-mail: khlebnicova@iboch.bas-net.by. Translated from *Khimiya Prirodnykh Soedinenii*, No. 1, pp. 31–35, January–February, 2011. Original article submitted May 18, 2010.

TABLE 1. PMR and ^{13}C NMR Spectra of **1a**–**c** and **2a**, **2b**

C atom	1a	1b	1c	2a	2b
	δ_C, ppm, $^2J_{CF}$/Hz				
C-2	83.12	83.46	82.95	152.91	152.93
C-3	73.66	73.36	73.40	124.55	124.84
C-4	194.05	192.68	191.97	176.21	175.33
C-4a	118.44	115.40 (d, ^4J = 3)	115.44 (d, ^4J = 3)	124.49	121.41 (d, ^4J = 3)
C-5	127.39	129.93 (d, ^3J = 11)	130.18 (d, ^3J = 12)	126.42	129.83 (d, ^3J = 11)
C-6	122.27	110.88 (d, ^2J = 23)	111.35 (d, ^2J = 23)	125.36	114.26 (d, ^2J = 23)
C-7	137.05	168.12 (d, ^1J = 256)	168.33 (d, ^1J = 257)	133.75	164.72 (d, ^1J = 256)
C-8	118.11	105.12 (d, ^2J = 23)	105.35 (d, ^2J = 23)	118.09	104.70 (d, ^2J = 25)
C-8a	161.58	163.29 (d, ^3J = 12)	163.01 (d, ^3J = 13)	156.24	157.26 (d, ^3J = 13)
C-1′	132.21 (d, ^4J = 3)	131.81 (d, ^4J = 3)	143.06	127.78 (d, ^4J = 3)	127.59 (d, ^4J = 4)
C-2′, C-6′	129.35 (d, ^3J = 8)	129.37 (d, ^3J = 8)	128.36	130.70 (d, ^3J = 8)	130.74 (d, ^3J = 8)
C-3′, C-5′	115.70 (d, ^2J = 21)	115.74 (d, ^2J = 23)	123.89	115.51 (d, ^2J = 22)	115.60 (d, ^2J =22)
C-4′	163.20 (d, ^1J = 248)	163.25 (d, ^1J = 247)	148.54	162.78 (d, ^1J = 248)	162.94 (d, ^1J = 247)
H atom	δ_H, ppm, J/Hz				
H-2	5.13 (d, J = 12.5)	5.14 (d, J = 12.8)	5.27 (d, J = 12.2)	8.01 s	7.98 s
H-3	4.59 (dd, J = 12.5, 1.6)	4.56 (dd, J = 12.8, 1.6)	4.50 (dd, J = 12.2, 1.3)	–	–
H-5	7.93 (dd, J = 7.7, 1.6)	7.95 (dd, J = 8.6, 6.4)	7.98 (dd, J = 8.6, 6.4)	8.32 (dd, J = 8.3, 1.9)	8.33 m
H-6	7.13 m	6.85 (td, J = 8.3, 2.2)	6.98 (td, J = 8.4, 2.2)	7.45 (ddd, J = 8.0, 7.0, 0.9)	7.17 m
H-7	7.57 m	–	–	7.70 (ddd,J = 1.6, 7.0, 8.7)	–
H-8	7.05 (dd, J = 8.3, 1.6)	6.74 (dd, J = 9.6, 2.2)	6.79 (dd, J = 9.3, 2.2)	7.50 (d, J = 8.7)	7.18 m
H-2′, H-6′	7.56 m	7.55 m	8.32 m	7.56 m	7.54 m
H-3′, H-5′	7.17 m	7.16 m	7.78 m	7.14 m	7.14 m
O-H	3.70 (d, J = 1.6)	–	3.75 (d, J = 1.3)	–	–

The reaction of equivalent amounts of 2-hydroxyacetophenone (**3a**) and 4-fluorobenzaldehyde (**4a**) in the presence of KOH at 0°C for 72 h formed only β-hydroxy-4-fluorodihydrochalcone **5**, dehydration of which in refluxing benzene in the presence of *p*-toluenesulfonic acid produced *trans*-chalcone **6**. However, subsequent epoxidation of **6** formed a complicated product mixture. Therefore, the hydroxyl of 2-hydroxyacetophenones **3a** and **3b** was protected by refluxing with benzylchloride in EtOH in the presence of K_2CO_3 to produce 2-benzyloxyacetophenones **7a** and **7b** in good yields. Alkaline aldol condensation of benzylated 2-hydroxyacetophenones **7a** and **7b** and benzaldehydes **4a** and **4b** at 0°C produced *trans*-chalcones **8a-c** in 70–90% yields. Epoxidation of F-containing chalcones **8a**–**c** by H_2O_2 in the presence of NaOH (10%) gave the F-containing *trans*-epoxides of chalcones **9a**–**c** (52–90% yields). Then, these underwent cyclization by $BF_3 \cdot Et_2O$ to form 2,3-*trans*-3-hydroxyflavanones **1a**–**c** and rearrangement with subsequent cyclization to form isoflavones **2a** and **2b**, the ratio of which depended on the positions of the substituents. Thus, the yield of **1a** was 40% with an F atom in the 4-position of **9a**; of isoflavone **2a**, 6%. Introduction of an F atom in the 4′-position of **9b** gave **1b** (42%) and also increased the yield of **2b** (to 28%). Apparently the formation of only **1c** in 60% yield can be explained by the influence of the nitro group in the 4-position of epoxide **9c** ring B.

The structures of the synthesized **1**, **2**, and **5**–**9** were confirmed by IR, PMR, ^{13}C NMR, and ^{19}F NMR spectral data. Thus, the PMR spectrum of **5** showed resonances for two nonequivalent α-methylene protons at δ 3.43 ppm (dd, ^2J = 17.7 Hz, ^3J = 9.0 Hz) and 3.36 (dd, ^2J = 17.7 Hz, ^3J = 3.2 Hz), for a proton as a doublet at 5.36 (^3J = 9.0 Hz), and for a hydroxyl proton as a broad singlet at 3.32. According to the literature [11, 12], this confirmed that **5** was a β-hydroxychalcone. The presence of resonances for vinyl protons at 7.59 and 7.89 with SSCC 15.6 Hz and at 7.38–7.45 and 7.40–7.62 with SSCC 15.7–15.8 was indicative of the trans-configuration of **6** and benzylated chalcones **8a**–**c**, respectively. PMR spectra of trans-epoxides **9a**–**c** typically showed resonances for the epoxide ring at 3.96–4.03 and 4.23-4.39 with SSCC 1.7 [13] in addition to methylene resonances of the benzyl at 4.91–4.98 and 4.98–5.01 with geminal SSCC 10.9–12.0 because of the nonequivalent protons.

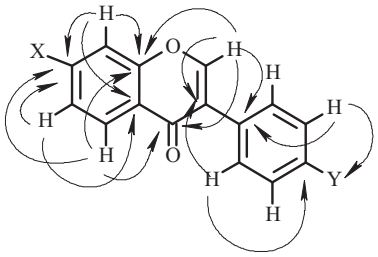


Fig. 1. Characteristic C—H correlations in HMBC spectra of **2a** and **2b**.

The orientations of the C-2 and C-3 substituents of **1a**–**c** were established based on the SSCC $^3J_{2,3}$ = 12.1–12.8 Hz, which were characteristic of *trans*-diaxial coupled protons. The ^{19}F NMR spectra of **1a**, **1c**, **2a**, **5**, **6**, **8a**, **8c**, and **9a** gave an F resonance in the range from –97.3 to –113.6 ppm; for **1b**, **2b**, **8b**, and **9b**, for two F atoms in the range from –98.4 to –104.1 and –110.1 to –113.6.

Table 1 presents the NMR spectral data for **1a**–**c** and **2a**, **2b**. It can be seen that the positions and shapes of the resonances for C-1′–C-6′ of 4′-fluoro 3-hydroxyflavanones **1** and isoflavones **2** are practically independent of the structure of the other parts of the molecules. The location of the F atom in the 4′-position was confirmed by the $^2J_{C4',F}$ SSCC of 247–248 Hz. The SSCC $^3J_{CF}$, $^4J_{CF}$, and $^5J_{CF}$ were 20–23, 8, and 3-4, respectively, and agreed with the expected values. Resonances in the PMR and ^{13}C NMR spectra were fully assigned using two-dimensional spectroscopy (COSY, HSQC, HMBC, NOESY, J-resolved, TOCSY) included in the standard programs of the spectrometer. Quaternary C atoms were assigned by analyzing their through-space C–H couplings. Thus, a cross-peak for the C-4a resonance with those for H-6 and H-8; for C-8a with H-5, H-8, and H-2; and for C-7 with H-5, H-6, and H-8 appeared in the HMBC spectra of all studied compounds (Fig. 1). Splitting of the C-1′ resonance as the result of through-space coupling with F also argued in favor of the selected assignments for C-3 (cross peaks with H-2, H-2′, and H-6′) and C-1′ (cross peaks with H-2, H-3′, and H-5′).

Thus, F-containing 3-hydroxyflavanones and isoflavones were synthesized from the corresponding chalcone epoxides. Transformation by $BF_3 \cdot Et_2O$ of chalcone epoxides containing an F atom in the 4′ -position gave primarily 3-hydroxyflavanones whereas introduction of an F atom in the 4-position favored isomerization of the epoxide and increased the yield of the isoflavone. The presence of a nitro group in the 4-position formed only the 3-hydroxyflavanone.

EXPERIMENTAL

NMR spectra were taken in $CDCl_3$ on a Bruker Avance-500 spectrometer (if not indicated otherwise) using TMS as an internal standard for PMR (500 MHz) and ^{13}C NMR (125 MHz) spectra and CCl_3F for ^{19}F NMR (470 MHz). IR spectra were recorded in KBr disks on a Bomem Michelson 100 instrument. Melting points were determined on a Boetius block. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using Et_2O. Elemental analyses of all compounds agreed with those calculated.

Benzylation of Acetophenones 3a and 3b. A solution of acetophenone (**3a**, **3b**, 0.001 mol) and benzylchloride (0.006 mol) in Et_2O (30 mL) was treated with K_2CO_3 (0.006 mol) and refluxed for 6 h. The solvent was removed in a rotary evaporator. The solid was dissolved in $CHCl_3$ (30 mL), washed with H_2O (3 × 10 mL), and dried over $MgSO_4$. The solvent was removed in a rotary evaporator. The solid was purified by column chromatography (EtOAc:hexane) to afford **7a** and **7b**.

2-Benzyloxyacetophenone (7a): yield 92%, mp 38–40°C (EtOH), in agreement with the literature [14].

2-Benzyloxy-4-fluoroacetophenone (7b): yield 83%, mp 58–59°C (EtOH), $C_{15}H_{13}FO_2$.

IR spectrum (KBr, ν, cm^{-1}): 1664 (C=O), 1606, 1265. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.57 (3H, s, Me), 5.14 (2H, s, CH_2), 6.73 (2H, m, H_{arom}), 7.36–7.45 (5H, m, H_{arom}), 7.83 (1H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 32.21, 71.20, 100.86 (d, ^2J = 26), 108.06 (d, ^2J = 21), 124.87, 127.8, 128.79, 128.65, 132.92 (d, ^3J = 11), 135.55, 159.97 (d, ^3J = 11), 166.26 (d, ^1J = 253), 198.11. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –103.91.

Condensation of Acetophenones 3a, 7a, 7b and Benzaldehydes 4a and 4b. A solution of acetophenone (**3a**, **7a**, **7b**, 2 mmol) and benzaldehyde (**4a**, **4b**, 2 mmol) in EtOH (10 mL) was stirred at room temperature and treated dropwise with KOH (3 mL, 3%). For **4a**, the mixture was held at 0°C for 72 h. The resulting precipitate was filtered off, washed with H_2O (3 mL), and dried in vacuo to afford *β*-hydroxydihydrochalcone **5** or chalcones **8a** and **8b**, respectively. For **4b**, the mixture

was stirred at room temperature under an Ar atmosphere for 18 h and treated with H_2O (10 mL). The resulting precipitate was filtered off and dried in vacuo to afford **8c**. Compounds **5** and **8a**–**c** were isolated as colorless crystalline compounds.

***β*-Hydroxy-4-fluorodihydrochalcone 5**: yield 63%, mp 107–109°C (EtOH), $C_{15}H_{13}FO_3$.

IR spectrum (KBr, ν, cm^{-1}): 1639 (C=O), 1604, 1512. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 3.32 (1H, br.s, OH), 3.34 (1H, dd, ^2J = 17.7, ^3J = 3.2), 3.42 (1H, dd, ^2J = 17.7, ^3J = 9.0), 5.36 (1H, d, ^3J = 9.0), 6.89 (1H, m, H_{arom}), 7.00 (1H, m, H_{arom}), 7.07 (2H, m, H_{arom}), 7.42 (2H, m, H_{arom}), 7.50 (1H, m, H_{arom}), 7.69 (1H, m, H_{arom}), 12.04 (1H, m, OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 47.27, 69.39, 115.64 (d, ^2J = 21), 118.86, 119.33, 128.59 (d, ^3J = 8), 130.14, 137.37, 138.58, 162.46 (d, ^1J = 246), 162.73, 205.45. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –114.78.

2′-Benzyloxy-4-fluorochalcone (8a): yield 90%, mp 108–110°C (EtOH), $C_{22}H_{17}FO_2$.

IR spectrum (KBr, ν, cm^{-1}): 1654 (C=O), 1599, 1583. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 5.16 (2H, s, CH_2), 6.98 (2H, t, ^3J = 8.6, H_{arom}), 7.07 (2H, m, H_{arom}), 7.32 (5H, m, H_{arom}), 7.42 (3H, m, H_{arom}), 7.42 (3H, m, H_{arom}), 7.43 (1H, d, ^3J = 15.7, H_{vinyl}), 7.58 (1H, d, ^3J = 15.7, H_{vinyl}), 7.76 (1H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 70.74, 112.87, 115.84 (d, ^2J = 22), 121.23, 127.07, 127.74, 128.16, 128.67, 129.12, 130.19 (d, ^3J = 9), 131.02, 131.40, 133.35, 136.18, 141.34, 157.64, 163.74 (d, ^1J = 251), 191.77. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –110.23.

2′-Benzyloxy-4,4′-difluorochalcone (8b): yield 89%, mp 101–104°C (EtOH), $C_{22}H_{16}F_2O_2$.

IR spectrum (KBr, ν, cm^{-1}): 1649 (C=O), 1600, 1587. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 5.14 (2H, s, CH_2), 6.79 (2H, m, H_{arom}), 6.97 (2H, m, H_{arom}), 7.28 (2H, m, H_{arom}), 7.35 (3H, m, H_{arom}), 7.45 (3H, m, H_{arom}), 7.45 (1H, d, ^3J = 15.8, H_{arom}), 7.62 (1H, d, ^3J = 15.8, H_{vinyl}), 7.85 (1H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 71.16, 100.78 (d, ^2J = 26), 108.28 (d, ^2J = 22), 115.86 (d, ^2J = 22), 125.15, 126.72, 127.25, 127.86, 128.48, 128.82, 130.21 (d, ^3J = 9), 133.30 (d, ^3J = 11), 135.42, 141.44, 159.44 (d, ^3J = 11), 163.77 (d, ^1J = 251), 166.07 (d, ^1J = 253), 189.85. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –104.11, –110.12.

2′-Benzyloxy-4-nitro-4′-fluorochalcone (8c): yield 71%, mp 178–180°C (EtOH), $C_{22}H_{16}FNO_4$.

IR spectrum (KBr, ν, cm^{-1}): 1653 (C=O), 1606, 1587. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 5.14 (2H, s, CH_2), 6.83 (2H, m, H_{arom}), 7.31 (2H, m, H_{arom}), 7.31 (1H, m, H_{arom}), 7.38 (1H, d, ^3J = 15.6, H_{vinyl}), 7.40 (1H, d, ^3J = 15.6, H_{vinyl}), 7.46 (2H, m, H_{arom}), 7.63 (2H, m, H_{arom}), 7.92 (1H, m, H_{arom}), 8.08 (2H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 71.41, 100.76 (d, ^2J = 26), 108.57 (d, ^2J = 22), 123.95, 124.40, 128.24, 128.69, 128.80, 128.95, 130.71, 133.73 (d, ^3J = 11), 135.15, 139.00, 141.50, 148.15, 159.88 (d, ^3J = 11), 166.55 (d, ^1J = 254), 188.87. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –102.75.

Dehydration of *β*-Hydroxy-4-fluorodihydrochalcone (5). A solution of **5** (0.52 g, 2 mmol) in benzene (30 mL) was refluxed with a Dean—Stark trap in the presence of a catalytic amount of *p*-toluenesulfonic acid for 7 h, washed with H_2O, and dried over $MgSO_4$. The solvent was removed in a rotary evaporator. The solid was purified by column chromatography (EtOAc:hexane) to afford **6** (0.48 g, 88%) as a yellow crystalline compound, mp 115–117°C (Et_2O:hexane), $C_{15}H_{11}FO_2$.

IR spectrum (KBr, ν, cm^{-1}): 1639 (C=O), 1581, 1508. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 6.95 (1H, m, H_{arom}), 7.04 (1H, m, H_{arom}), 7.14 (2H, m, H_{arom}), 7.51 (2H, m, H_{arom}), 7.59 (1H, d, ^3J = 15.6, H_{vinyl}), 7.67 (2H, m, H_{arom}), 7.89 (1H, d, ^3J = 15.6, H_{vinyl}), 7.91 (1H, m, H_{arom}), 12.79 (1H, s, OH). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 116.40 (d, ^2J = 22), 118.63, 119.02, 119.96, 120.09, 129.74, 130.76 (d, ^3J = 8), 131.03, 136.62, 144.28, 163.75, 164.42 (d, ^1J = 252), 193.08. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –108.53.

Epoxidation of F-Containing Chalcones 8a-c. A solution of **8a-c** (1 mmol) in acetone (10 mL) and MeOH (2 mL) was stirred at room temperature, treated with NaOH solution (0.3 mL, 10%), treated dropwise with H_2O_2 solution (1 mL, 30%), and refluxed for 1.5–6 h (TLC monitoring). The organic solvents were removed in a rotary evaporator. The residue was dissolved in $CHCl_3$ (30 mL), washed with H_2O (2 × 10 mL), and dried over $MgSO_4$. The $CHCl_3$ was removed in a rotary evaporator to afford chalcone epoxides **9a-c** as colorless crystalline compounds.

2′-Benzyloxy-4-fluorochalcone epoxide (9a): yield 90%, mp 112–115°C (Et_2O), $C_{22}H_{17}FO_3$.

IR spectrum (KBr, ν, cm^{-1}): 1660 (C=O), 1597, 1514. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 3.98 (1H, d, ^3J = 1.6, $H_{epoxide}$), 4.23 (1H, d, ^3J = 1.6, $H_{epoxide}$), 4.98 (1H, d, ^2J = 12.0, CH_2), 5.01 (1H, d, ^2J = 12.0, CH_2), 6.93 (2H, m, H_{arom}), 7.04 (2H, m, H_{arom}), 7.13 (4H, m, H_{arom}), 7.24 (3H, m, H_{arom}), 7.50 (1H, m, H_{arom}), 7.84 (1H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 59.37, 63.23, 70.83, 112.89, 115.58 (d, ^2J = 22), 121.32, 126.39, 127.44, 127.52, 128.33, 128.68, 131.02, 131.77, 134.86, 135.38, 158.61, 162.90 (d, ^1J = 247), 194.97. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –113.35.

2′-Benzyloxy-4,4′-difluorochalcone epoxide (9b): yield 52%, mp 114–117°C (Et_2O), $C_{22}H_{16}F_2O_3$.

IR spectrum (KBr, ν, cm^{-1}): 1668 (C=O), 1600, 1514. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 3.96 (1H, d, ^3J = 1.6, $H_{epoxide}$), 4.39 (1H, d, ^3J = 1.6, $H_{epoxide}$), 4.94 (1H, d, ^2J = 11.5, CH_2), 4.98 (1H, d, ^2J = 11.5, CH_2), 6.75 (2H, m, H_{arom}), 6.93

(2H, m, H_{arom}), 7.12 (4H, m, H_{arom}), 7.26 (3H, m, H_{arom}), 7.90 (1H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 71.16, 100.78 (d, ^2J = 26), 108.28 (d, ^2J = 22), 115.86 (d, ^2J = 22), 125.15, 126.72, 127.25, 127.86, 128.48, 128.82, 130.21 (d, ^3J = 9), 133.30 (d, ^3J = 11), 135.42, 141.44, 159.44 (d, ^3J = 11), 163.77 (d, ^1J = 251), 166.07 (d, ^1J = 253), 189.85. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –104.11, –110.12.

2′-Benzyloxy-4-nitro-4′-fluorochalcone epoxide (9c): yield 67%, mp 170–173°C (Et_2O), $C_{22}H_{16}FNO_5$.

IR spectrum (KBr, ν, cm^{-1}): 1674 (C=O), 1605, 1523. PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 4.03 (1H, d, ^3J = 1.6, $H_{epoxide}$), 4.39 (1H, d, ^3J = 1.6, $H_{epoxide}$), 4.91 (1H, d, ^2J = 10.8, CH_2), 4.97 (1H, d, ^2J = 10.8, CH_2), (2H, m, H_{arom}), 7.17 (7H, m, H_{arom}), 7.95 (1H, m, H_{arom}), 8.03 (2H, m, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm, J_{CF}/Hz): 58.54, 63.02, 71.57, 100.86 (d, ^2J = 26), 108.91 (d, ^2J = 22), 123.82, 126.32, 127.98, 128.77, 133.60 (d, ^3J = 11), 134.23, 143.15, 147.93, 151.90, 160.60 (d, ^3J = 11), 167.15 (d, ^1J = 256). ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –100.67.

Transformation of Chalcone Epoxides 9a-c by $BF_3 \cdot Et_2O$. A solution of F-containing epoxide **9a-c** (1 mmol) in benzene (15 mL) was stirred, treated with $BF_3 \cdot Et_2O$ (0.5 mL) at room temperature, stirred for 30 min, treated with Et_2O (50 mL), washed with H_2O (3 × 15 mL), and extracted with NaOH solution (5%, 3 × 15 mL). The organic layer was dried over $MgSO_4$. The solvent was removed in a rotary evaporator. The solid was chromatographed over a column (EtOAc:hexane) to afford **1a-c** in 40, 42, and 60% yields, respectively. The alkaline solution was acidified with dilute HCl (1:10) and extracted with Et_2O. The extract was dried over $MgSO_4$. The solvent was removed. The solid was chromatographed over a column (EtOAc:hexane) to afford **2a** and **2b** in 6 and 28% yields, respectively. Isoflavone **2c** was not isolated.

3-Hydroxy-4′-fluoroflavanone (1a): yield 40%, mp 149–133°C (Et_2O:hexane), $C_{15}H_{11}FO_3$. IR spectrum (KBr, ν, cm^{-1}): 1697 (C=O), 1606, 1577. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –112.52.

3-Hydroxy-7,4′-difluoroflavanone (1b): yield 42%, mp 97–100°C (Et_2O:hexane), $C_{15}H_{10}F_2O_3$. IR spectrum (KBr, ν, cm^{-1}): 1695 (C=O), 1615, 1591. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –98.46, –112.20.

3-Hydroxy-4′-nitro-7-fluoroflavanone (1c): yield 60%, mp 153–156°C (Et_2O:hexane), $C_{15}H_{10}FNO_5$. IR spectrum (KBr, ν, cm^{-1}): 1695 (C=O), 1612, 1591. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –97.83.

4′-Fluoroisoflavone (2a): yield 6%, mp 188–190°C (Et_2O:hexane), which agreed with the literature [15], $C_{15}H_9FO_2$. IR spectrum (KBr, ν, cm^{-1}): 1639 (C=O), 1604, 1573. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –113.92.

7,4′-Difluoroisoflavone (2b): yield 28%, mp 225–227°C (Et_2O:hexane), $C_{15}H_8F_2O_2$. IR spectrum (KBr, ν, cm^{-1}): 1643 (C=O), 1620, 1604. ^{19}F NMR spectrum ($CDCl_3$, δ, ppm): –102.96, –113.59.

REFERENCES

1. O. M. Andersen and K. R. Markham (eds.), *Flavonoids: Chemistry, Biochemistry and Application*, CRC Press, Boca Raton, 2006.
2. L. Cavallini and G. Luchetti, *Gazz. Med. Ital.*, **125**, 365 (1976).
3. Yu. A. Vladimirov, E. V. Proskurina, E. M. Demin, N. S. Matveeva, O. B. Lyubitskii, A. A. Novikov, D. Yu. Izmailov, A. N. Osipov, V. P. Tikhonov, and V. E. Kagan, *Biokhimiya (Moscow)*, **74**, 372 (2009).
4. P. G. Pietta, *J. Nat. Prod.*, **63**, 1035 (2000).
5. R. A. Dixon and D. Ferreira, *Phytochemistry*, **60**, 205 (2002).
6. G. Peterson and S. Barnes, *Biochem. Biophys. Res. Commun.*, **179**, 661 (1991).
7. R. K. Rishi, *Indian J. Pharm.*, **34**, 311 (2002).
8. C. Duffi, K. Perez, and A. Partridge, *Ca Cancer J. Clin.*, **57**, 260 (2007).
9. P. Kirsh, *Modern Fluoroorganic Chemistry*, Wiley-VCH Verlag GmbH, Weinheim, 2004.
10. S. C. Bhara, A. C. Jain, and T. R. Seshadri, *Tetrahedron*, **21**, 963 (1965).
11. J. A. N. Augustyn, B. C. B. Bezuidenhoudt, A. Swanepoel, and D. Ferreira, *Tetrahedron*, **46**, 4429 (1990).
12. R. J. J. Nel, H. Van Resnburg, P. S. Van Heerden, J. Coetzee, and D. Ferreira, *Tetrahedron*, **55**, 9727 (1999).
13. J. A. N. Augustyn, B. C. B. Bezuidenhodt, and D. Ferreira, *Tetrahedron*, **46**, 2651 (1990).
14. P. J. Wagner, M. A. Meador, and B.-S. Park, *J. Am. Chem. Soc.*, **112**, 5199 (1990).
15. Y. Hoshino, N. Miyaura, and A. Suzuki, *Bull. Chem. Soc. Jpn.*, **61**, 3008 (1988).