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Research Article

A novel process for the preparation of [(R,S)/ (S,R)] and [(S,S)/ (R,R)] chroman epoxides, key intermediates in the synthesis of Nebivolol

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Abstract: A novel, cost effective, scalable process for the preparation of chroman epoxides starting from 4-fluorophenol is described. The highlights of the process are single step *O*-acylation, fries rearrangement, one pot synthesis of claisen condensation, cyclization, reduction, epoxidation with over all yield of 50.9% [(*R*,*S*)/(*S*,*R*)]-chroman epoxide-A is 33.9% and [(*S*,*S*)/(*R*,*R*)]-chroman epoxide-B is 17%.

Keywords: Nebivolol; Chroman epoxides; Hypertension; Synthesis; Reduction.

Introduction

The objective is to develop an industrially feasible process for the synthesis of chroman epoxides, which are key intermediates in the preparation[1-7] of nebivolol (**1**), a long acting, cardio-selective β_1-receptor antagonist without partial agonist activity and also used in treatment of hypertension[8].

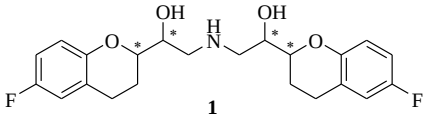

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Figure 1: Chemical structure of Nebivolol (**1**).

The common pathways[1,3,8,9-12] for the synthesis of chroman epoxides (**10**, **11**) relies on the preparation of chroman acid (**2**). These early reported procedures are suffering with critical problems such as number of isolations, low yields, cumbersome process, and harsh reaction conditions.

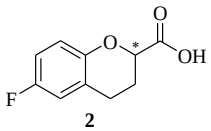

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Figure 2: Structure of chroman acid (**2**).

After comprehensive literature search, it is understanding that there is a need to develop a simple and convergent process for the preparation of chroman epoxides.

Materials and Methods

All the raw materials were procured from Merck laboratories, all the reagents and solvents were used without further purification.

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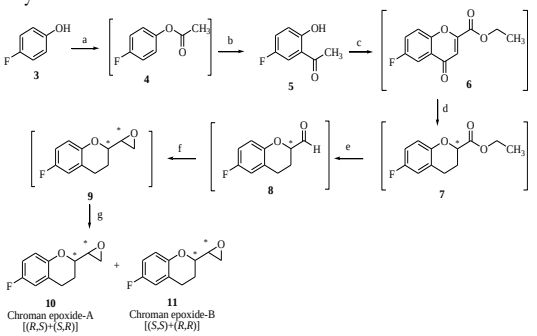
Results and Discussion

The present work describes the preparation of chroman epoxides (**10**, **11**) starting from commercially available 4-fluorophenol (**3**) as shown in **Scheme 1**. 4-Fluorophenol (**3**) on treatment with aluminum chloride and acetyl chloride at 50 °C temperature furnished *O*-acetyl ester (**4**), which is the prerequisite for fries rearrangement. The main problems associated with this process are incomplete *O*-acetylation and hydrolysis of **4**. To minimize these two problems, mole equivalents of acetyl chloride and $AlCl_3$ were optimized to a ratio of 1.5:2 respectively. After obtaining **4**, the reaction mass was heated to 130 °C to achieve 5-fluoro-2-hydroxy acetophenone (**5**), through fries rearrangement mechanism. The overall yield is 90% and it is much better than the previously reported yields of direct friedal craft acylation[12,13,14] of **3** to achieve **5**.



Scheme 1: *Reagents and conditions*: (a) CH_3COCl (b) $AlCl_3$, 130 °C, 1 h, 90% (c) (i) Diethyl oxalate, Sodium ethoxide, 80 °C, 2 h (ii) Ethanol, Conc. HCl, 25-30 °C, 15 h, 74% (d) CH_3COOH, Ethanol, 10% Pd/C, H_2, 25-30 °C, 15 h, 97% (e) Toluene, DIBAL-H, -70 °C, 15 min, 95% (f). DMSO, KOH, TMSOI, 10-15 °C, 15 min,

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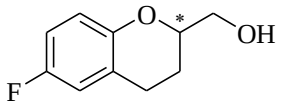
78% (g) Column chromatography, eluent: Ethyl acetate (3 to 10%) in hexanes.



12

Figure 3: Chroman alcohol (**12**)

Compound **5** on claisen condensation with diethyl oxalate in presence of sodium ethoxide followed by cyclization results ketochromene ethyl ester (**6**). During the conversion of **5** to **6**, after completion of the condensation reaction, all work-up operations including neutralization of sodium ethoxide with aqueous HCl solution, distillation of solvent and cyclization, should be done at below 35°C to avoid the ester hydrolysis of **6**. Compound **6** on reduction with 10% Pd/C in a mixture of ethanol, acetic acid resulted chroman ethyl ester (**7**).

Coming to the work-up part of compound **7**, ethanol and acetic acid were distilled off from the reaction mass and crude mass was dissolved in toluene. After that, toluene layer was washed with aqueous sodium bicarbonate, followed by washing with water at 10-15 °C to remove residual acetic acid. Finally, the toluene layer was concentrated at atmospheric pressure till to get toluene solution of **7** with moisture content not more than 0.1% w/w. Because of the above operation **7** can be used directly in the next reduction reaction using DIBAL-H, to prepare chroman aldehyde (**8**).

After thorough literature survey, it is realized that the major yield loss of the processes[15,17, 18] used for the preparation of mixture of chroman epoxides [(*R*,*S*)/(*S*,*R*)] and [(*S*,*S*)/(*R*,*R*)] (**9**) was occurred during the synthesis **9** from **7**. The conversion of **7** to **8** was achieved by using DIBAL-H in toluene. At this stage for standardizing the reaction conditions, experiments were performed at different temperatures. After a detailed study (**Table 2**, S.No:1), the best condition identified is at -70 to -80°C. In reduction process, controlled the over reduced product chroman alcohol (**12**) by optimized the mole ratios of DIBAL-H and temperature of reaction.

In the present route, yield loss of the conversion of **7** to **8** was studied in detailed and better yields were reported by the direct conversion of **7** to **9** through **8**. Compound **8** was unstable as concentrated mass, even at cold conditions. Hence it is used as toluene solution and it does not polymerize in toluene solution up to two weeks under normal storage conditions.

Table 1: Effect of temperature on conversion of **6** to **7** using Pd/C.

S.No	Temperature (°C)	Reaction time (h)	Unreacted 6[a] (%)	Chroman acid (2)[b]	Chroman ethyl ester (7)[c]
1	10-15	30	2.80	0.21	96.40
2	25-30	13	0.21	0.28	98.6
3	35-40	8	0.11	4.57	94.80

a,b,c: Product percentages in HPLC monitoring

Table 2: Effect of temperature on conversion of **7** to **8** using DIBAL-H.

S.No.	Temperature (°C)	Unreacted 7[a] (%)	Chroman alcohol 12[b] (%)	chroman aldehyde (8)[c]
1	-70 to -80	ND	0.81	98.75
2	-50 to -60	ND	4.39	94.03
3	-45 to -55	1.11	4.57	93.91
4	-40 to -50	0.03	2.76	96.74
5	-20 to -30	0.05	6.16	93.28
6	0 to -5	8.81	54.37	6.68

a, b, c: product percentages in HPLC monitoring; ND: Not detected

Table 3: Effect of mole ratio of DIBAL-H in chroman aldehyde preparation at -70 to -80 °C.

S.No.	Mole ratio of DIBAL-H[a]	Unreacted 7[b] (%)	Chroman alcohol 12[c] (%)	chroman aldehyde (8)[d]
1	1.0	0.88	1.21	96.89
2	1.10	0.38	1.09	97.42
3	1.15	ND	0.81	98.75
4	1.20	0.08	2.89	96.42
5	1.25	ND	5.60	93.20

a: mole ratio with respect to chroman ethyl ester; b,c,d: product percentages in HPLC monitoring; ND: Not detected

Table 4: The results of effect of base in the chroman epoxides preparation.

S.No.	Base	Isomer 10[a] [(*R*,*S*)/(*S*,*R*)]	Isomer 11[b] [(*S*,*S*)/(*R*,*R*)]	Unreacted 8[c]
1	KOH	56.56	28.27	0.60
2	^{t}BuOK	43.33	23.65	1.08
3	NaH	22.38	10.50	0.70
4	K_2CO_3	6.56	3.66	19.73
5	Na_2CO_3	5.85	5.44	16.42
6	NaOH	39.72	18.42	ND
7	TEA	9.29	3.27	20.14
8	DIPEA	10.5	3.69	18.56

a,b,c: Conversions during reaction monitoring by HPLC; ND: Not detected; All the reactions were carried at 10-15 °C

Table 5: The effect of solvent in the preparation of epoxides.

S.No.	Solvent	Isomer 10[a] [(*R,S*)/(*S,R*)]	Isomer 11[b] [(*S,S*)/(*R,R*)]	Unreacted 8[c]
1	DMSO/Toluene	56.56	28.27	0.60
2	DMSO/DCM	46.59	24.21	ND

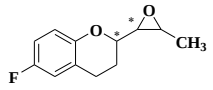
a,b,c: Conversions during reaction monitoring by HPLC; ND: Not detected

Table 6: The results of the study of reaction temperatures of **9**.

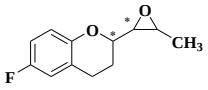
S.No.	Temperature (°C)	Isomer 10[a] [(*R,S*)/(*S,R*)]	Isomer 11[b] [(*S,S*)/(*R,R*)]	Unreacted 8[c]
1	10-15	56.56	28.27	0.60
2	25-30	54.59	27.46	0.96
3	40-45	43.85	25.65	1.2

a,b,c: Conversions during reaction monitoring by HPLC

Finally, the conversion of **8** to **9** was studied using different bases at various temperatures in different solvents and established a reaction condition that the condensation with trimethylsulfoxonium iodide and potassium hydroxide powder (**Table 4**, S.No:1) in a mixture of dimethyl sulfoxide and toluene (**Table 5**, S.No:1) at 10-15 °C to furnish **9**. During preparation of **9**, observed two new impurities in both the isomers A (**13**) and isomer B (**14**) at a level of 1.0%. These two new impurities were isolated by using column chromatography, characterized and established the structures as shown in **Figure 4**.



13
[(*R,S*)/(*S,R*)]-Chroman epoxides methyl impurity



14
[(*R,R*)/(*S,S*)]-Chroman epoxides methyl impurity

Figure 4: Structure of chroman epoxides methyl impurities (**13 & 14**).

With the above optimized set of reaction conditions for the synthesis of **10** and **11**starting from **2**, we next explored the above process for synthesizing the other possible positional isomers from fluoro phenols, and the results were summarized in **Table 7**.

Table 7: Different positional isomers of chroman epoxides.

S.No	Substitution	Hydroxy aceto phenone[a]	Keto Chromene ethyl ester[b]	Chroman ethyl ester[c]	Chroman aldehyde[d]	Chroman epoxide isomer A[e]	Chroman epoxide isomer B[f]
1	4-Fluoro	90	74	97	98.74	60.49	30.12
2	3-Fluoro	60	68	96	96.53	50.4	26.25
3	2-Fluoro	38.6	80	98	94.15	52.7	30
4	Desfluoro	40	82	95	95.2	63	37.5

a, e, f: Isolated yield; b, c, d: Conversions in HPLC monitoring.

Experimental section:

Preparation of 5-fluoro-2-hydroxy acetophenone (5):

Compound **3** (50 g, 0.446 mol) was added to acetyl chloride (52.56 g, 0.669 mol) with stirring at 25-30 °C. The reaction mass was heated to 60 °C and added aluminum chloride (119.1 g, 0.893 mol) in portion wise in about 1 h. The resulting mixture was heated to 130 °C for 2 h. After monitoring by TLC, the thick syrupy mass was added to precooled water (250 mL), affords **3** as a white solid (61.9 g, 90%).

^{1}H NMR ($CDCl_3$, δ *ppm*): 2.62 (s, 3H), 6.94-7.40 (m, 3H), 11.97 (s, 1H); $[MH]^-$ m/z: 153.1 (Actual mass: 154)

4-fluoro-2-hydroxy acetophenone (5a):

^{1}H NMR ($CDCl_3$, δ *ppm*): 2.60 (s, 3H), 6.95-7.76 (m, 3H), 12.58 (s, 1H); IR: 1864 cm^{-1}.

3-fluoro-2-hydroxy acetophenone (**5b)**:

^{1}H NMR ($CDCl_3$, δ *ppm*): 2.65 (s, 3H), 7.54-6.83 (m, 3H), 12.28 (s, 1H); $[MH]^-$ m/z: 152.9 (Actual mass: 154)

2-hydroxy acetophenone (**5c)**:

^{1}H NMR ($CDCl_3$, δ *ppm*): 2.63 (s, 3H), 6.88-7.74 (m, 4H), 12.25 (s, 1H); IR:1887 cm^{-1}.

Preparation of ethyl 6-fluoro-4-oxo-4*H*-chromene-2-carboxylate (6):

To a solution of sodium ethoxide (127.89 g, 1.88 mol) in ethanol (800 mL) were added compound **5** (60 g, 0.389 mol) and diethyl oxalate (147.9 g, 1.013 mol) at 25-30 °C. The resulting mixture was refluxed for 2h, and monitored reaction till starting material was consumed completely. The reaction mixture was concentrated under vacuum at below 50°C resulted residue diluted with methylene chloride (300 mL) and DM Water (900 mL) then acidified with hydrochloric acid. Layers were separated out aqueous phase was extracted with methylene chloride (2×300 mL) combined organic layer was washed with DM water (250 mL), the methylene chloride was recovered from organic layer by vacuum distillation. Resulted residue was dissolved in ethanol (400 mL) added hydrochloric acid (210 mL) stirred for 15 h, monitored reaction progress till starting material was consumed completely. The reaction mixture concentrated completely under vacuum below 35 °C. The resulted residue was mixed with water (300 mL) and methylene chloride (150 mL) at below 35 °C.

The organic phase was separated and washed with aqueous sodium bicarbonate solution followed by water (120 mL). The organic phase was concentrated at below 35 °C to afford a white solid **7** (68.61 g, 74%).

^{1}H NMR (DMSO-d_6, δ *ppm*): 1.45 (t, J = 15 Hz, 3H), 4.47 (q, J = 6 Hz, 6 Hz, 2H), 7.11 (s, 1H), 7.48-7.85 (m, 3H); $[MH]^+$ m/z: 237 (Actual mass 236); IR: 1742, 1654, 1625 cm^{-1}.

Ethyl 7-fluoro-4-oxo-4*H*-chromene-2-carboxylate (**6a**):
^{1}H NMR (DMSO-d_6, δ *ppm*): 1.44 (t, J = 10 Hz, 3H), 4.48 (q, J = 7.5 Hz, 7 Hz, 2H), 7.14 (s, 1H), 7.38-7.97 (m, 3H); $[MH]^+$ m/z: 237 (Actual mass 236); IR: 1742, 1654, 1625 cm^{-1}; HPLC Purity: 93.65%.

Ethyl 8-fluoro-4-oxo-4*H*-chromene-2-carboxylate (**6b**):
^{1}H NMR (DMSO-d_6, δ *ppm*): 1.44 (t, J = 7.5 Hz, 3H), 4.47 (q, J = 7 Hz, 7.5 Hz, 2H), 7.10 (s, 1H), 7.16-8.23 (m, 3H); $[MH]^+$ m/z: 237 (Actual mass 236); IR: 1742, 1654, 1625 cm^{-1}; HPLC Purity: 99.24%.

Ethyl-4-oxo-4*H*-chromene-2-carboxylate (**6c**):
^{1}H NMR (DMSO-d_6, δ *ppm*): 1.44 (t, J = 7.5 Hz, 3H), 4.41 (q, J = 7.5 Hz, 7 Hz, 2H), 6.96 (s, 1H), 7.54-8.07 (m, 4H); $[MH]^+$ m/z: 219 (Actual mass 218); IR: 1742, 1654, 1625 cm^{-1}.

Preparation of chroman carboxylic acid ethyl ester (7):
To a solution of compound **6** (60 g, 0.253 mol) in a mixture of acetic acid (150 mL) and ethanol (1200 mL) at ambient temperature was hydrogenated with 10% palladium on charcoal (6 g, 50% wet) for 3 h. Monitored by HPLC till starting material consumed completely, there after catalyst was filtered off through celite bed. Concentrated the filtrate under vacuum at 40 °C, the concentrated mass was diluted with Toluene (300 mL) and washed with water fallowed by neutralized with aqueous sodium bicarbonate solution. Organic layer was separated and concentrated at atmospheric pressure till moister content attained to not more than 0.1% w/w. The solution contains compound **7**, have HPLC purity 97 %.

^{1}H NMR ($CDCl_3$, δ *ppm*): 1.29 (t, J = 9.5 Hz, 3H), 2.17 (m, 1H), 2.29 (m, 1H), 2.75 (m, 1H), 2.82 (m, 1H), 4.25 (q, J = 7.5 Hz, 7 Hz, 2H), 4.69 (t, J = 7.5 Hz, 1H), 6.73-6.89 (m, 3H); IR: 1753 cm^{-1}.

7-Fluoro chroman ethyl ester 7a:
^{1}H NMR ($CDCl_3$, δ *ppm*): 1.26 (t, J = 7 Hz, 3H), 2.22 (m, 2H), 2.68 (m, 1H), 2.76 (m, 1H), 4.25 (q, J = 7 Hz, 7 Hz, 1H), 4.73 (m, 1H), 6.57-6.98 (m, 3H); $[MH+Na]^+$ m/z: 247 (Actual mass 224); IR: 1753 cm^{-1}.

8-Fluoro chroman ethyl ester 7b:
^{1}H NMR ($CDCl_3$, δ *ppm*): 1.27 (t, J = 7 Hz, 3H), 2.26 (m, 2H), 2.79 (m, 2H), 4.24 (m, 2H), 4.83 (t, J = 4.5 Hz, 1H), 6.75-6.94 (m, 3H); $[MH]^+$ m/z: 225 (Actual mass 224); IR: 1753 cm^{-1}.

Desfluoro chroman ethyl ester 7c:
^{1}H NMR ($CDCl_3$, δ *ppm*): 1.20 (t, J = 8 Hz, 3H), 2.06 (m, 1H), 2.15 (m, 1H), 2.61 (m, 1H), 2.78 (m, 1H), 4.15 (q, J = 7 Hz, 7 Hz, 2H), 4.87 (t, J = 6.5 Hz, 1H), 6.80-7.10 (m, 4H); $[MH]^+$ m/z: 207 (Actual mass 206); IR: 1753 cm^{-1}.

Preparation of chroman carboxaldehyde (8):
The toluene solution of compound **7** (55 g,0.245 mol) was cooled to -70 °C under nitrogen atmosphere was added DIBAL-H (188 mL, 0.280 mol, 1.5 molar solution in toluene) in about to 3 h. The mixture was stirred at -70 °C for 30 min, monitored by HPLC. The excess DIBAL-H was quenched with methanol (10.18 g, 0.318 mol) at -70 °C and poured into precooled aqueous hydrochloric acid (365 mL) at 0-25 °C in 45 min. Then resulting solution heated to 35 °C the layers were separated; organic layer was washed with brain solution (2×110 mL). Affords a toluene solution of compound **8** (HPLC purity: 98.74%).

^{1}H NMR ($CDCl_3$, δ *ppm*): 2.0-2.23 (m, 3H), 2.73-2.83 (m, 4H), 4.45 (t, J = 9 Hz, 1H), 6.74-6.90 (m, 5H), 9.80 (s, 1H).

Preparation of Chroman Epoxides (9):
To a suspension of trimethylsulfoxonium iodide (48.84 g, 0.222 mol) in dimethyl sulfoxide (160 mL) at 25-30 °C was added powdered KOH (15.2 g, 0.230 mol) stirred the contents until get a clear solution. There after cooled to 10-15 °C and added toluene solution of **8** at 10-15 °C in 30 min. Monitored the reaction progress by HPLC, reaction mixture was cooled to 0-5 °C and added precooled DM water (360 mL, 10-15 °C) at below 25 °C. The two-phase mixture stirred for 30 min, the aqueous phase was separated and extracted with toluene (90 mL). The combined organic phase was washed with DM water (110 mL) and brain solution (2×110 mL) and concentrated to afford crude product of **10** and **11** as oily mass (41.4 g, 86.9%). The **10** and **11** were separated by column chromatography (hexane/ethyl acetate 9.7:0.3) to afford **10** (24.84 g) as a colorless viscous oil, (hexane/ethyl acetate 9:1) to afford **11**(12 g) as a colorless viscous oil.

6-Fluoro chroman epoxide-A [(*R*,*S*)/(*S*,*R*)] (10): ^{1}H NMR ($CDCl_3$, δ *ppm*): 1.91 (m, 1H), 2.12 (m, 1H), 2.81 (m, 3H), 2.90 (m, 1H), 3.12 (t, J= 6Hz, 1H), 3.82 (m, 1H), 6.73-6.83 (m, 3H); IR: 1493, 1435 cm^{-1}.

6-Fluoro chroman epoxide-B [(*R*,*R*)/(*S*,*S*)] (11): ^{1}H NMR ($CDCl_3$, δ *ppm*): 1.93-2.04 (m, 2H),

2.78-2.88 (m, 4H), 3.17-3.20 (m, 1H), 3.83 (t,J = 7.8 Hz, 1H), 6.72-6.80 (m, 3H); IR: 1492, 1435 cm^{-1}.

7-Fluoro chroman epoxide-A (**10a**): ^1H NMR ($CDCl_3$, δ *ppm*): 1.86-1.94 (m, 1H), 2.12-2.18 (m, 1H), 2.77-2.80 (m, 3H), 2.89-2.91 (m, 1H), 3.11-3.13 (m, 1H), 3.84-3.88 (m, 1H), 6.53-7.00 (m, 3H); IR: 1351,1336 cm^{-1}.

7-Fluoro chroman epoxide-B (**11a**): ^1H NMR ($CDCl_3$, δ *ppm*): 1.88-1.96 (m, 1H), 2.03-2.08 (m, 1H), 2.78-2.82 (m, 3H), 2.86-2.88 (m, 1H), 3.17-3.20 (m, 1H), 3.85-3.89 (m, 1H), 6.55-6.98 (m, 3H); IR: 1360,1337 cm^{-1}.

8-Fluoro chroman epoxide-A (**10b**): ^1H NMR ($CDCl_3$, δ *ppm*): 1.92-1.98 (m, 1H), 2.16-2.21(m, 1H), 2.81-2.86 (m, 3H), 2.91-2.93 (m, 1H), 3.16-3.18 (m, 1H), 3.83-3.87 (m, 1H), 6.74-6.92 (m, 3H); IR: 1407 cm^{-1}.

8-Fluoro chroman epoxide-B (**11b**): ^1H NMR ($CDCl_3$, δ *ppm*): 1.91-2.00 (m, 1H), 2.04-2.11(m, 1H), 2.83-2.88 (m, 4H), 3.23-3.25 (m, 1H), 4.01-4.02 (m, 1H), 6.72-6.90 (m, 3H); IR: 1555 cm^{-1}.

Desfluoro chroman epoxide-A (**10c**): ^1H NMR ($CDCl_3$, δ *ppm*): 1.70-1.78 (m, 1H), 1.99-2.03 (m, 1H), 2.72-2.84 (m, 4H), 3.16-3.18 (m, 1H), 3.94-3.96 (m, 1H), 6.75-7.07 (m, 4H); IR: 1406 cm^{-1}.

Desfluoro chroman epoxide-B (**11c**): ^1H NMR ($CDCl_3$, δ *ppm*): 1.76-1.84 (m, 1H), 1.99-2.03 (m, 1H), 2.71-2.84 (m, 4H), 3.16-3.18 (m, 1H), 3.74-3.77 (m, 1H), 6.76-7.07 (m, 4H); IR: 1793 cm^{-1}.

Chroman epoxides methyl impurity [(*R,S*)/(*S,R*)](13): ^1H NMR ($CDCl_3$, δ *ppm*): 1.38-1.39 (d, J =5 Hz, 3H), 1.85-1.90 (m, 1H), 2.10-2.14 (m, 1H), 2.78-2.85 (m, 3H), 3.06-3.08 (m, 1H), 3.79-3.83 (m, 1H), 6.74-6.79 (m, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ *ppm*): 17.4, 24.1, 24.2, 53.6, 59.9, 75.5, 77.0, 114.0, 115.3, 117.5.

Chroman epoxides methyl impurity [(*R,R*)/(*S,S*)](14): ^1H NMR ($CDCl_3$, δ *ppm*): 1.37-1.38 (d, J = 5.5 Hz, 3H), 1.86-1.93 (m, 1H), 2.00-2.17 (m, 1H), 2.76-2.85 (m, 2H), 2.91-2.92 (m, 1H), 3.08-3.11 (m, 1H), 3.87-3.90 (m, 1H), 6.72-6.78 (m, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, δ *ppm*): 17.4, 24.1, 24.5, 51.2, 60.6, 75.3, 77.0, 114.0, 115.1, 117.7.

Conclusion

Here we disclosed cost effective, simple and novel route for the preparation of chroman epoxides starting from 4-fluorophenol without generation of chroman acid intermediate. The process includes fries rearrangement, claisen condensation, cyclization, reduction, epoxidation with over all yield of 50.9% [(*R*,*S*)/(*S*,*R*)]-chroman epoxide-A is 33.9% and [(*S*, *S*)/(*R*, *R*)]-chroman epoxide-B is 17%.

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