Pergamon

Tetrahedron 56 (2000) 6339–6344

TETRAHEDRON

Enantioselective Total Synthesis of the Antihypertensive Agent (*S*,*R*,*R*,*R*)-Nebivolol☆

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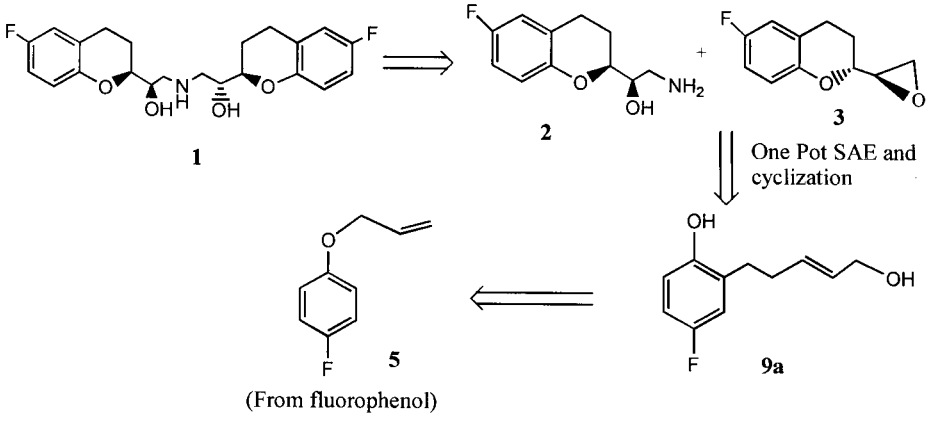
Received 6 April 2000; revised 30 May 2000; accepted 15 June 2000

Abstract—The total synthesis of (*S*,*R*,*R*,*R*)-Nebivolol, a hypertensive agent, is reported. Claisen rearrangement and a one-pot Sharpless asymmetric epoxidation, intramolecular epoxide opening with internal phenoxide anion to generate the chiral chromane are the key steps.

Nebivolol, **1**, is a potent and selective β_1-adrenergic blocker with antihypertensive activity.[1] The selectivity of **1** in β_1-adrenocepter antagonism was greater than that of clinically used atenolol, pindolol and propranolol.[2] (*S*,*R*,*R*,*R*)-Nebivolol was reported to be the most active isomer by the Janssen Research Foundation and the R. W. Johnson Pharmaceutical Research Institute.[3] The beneficial hemodynamic profile of racemic nebivolol has been mainly ascribed to the L-enantiomer,[3d] which is devoid of β-adrenoceptor blocking properties as therapeutic doses. It is interesting to note that D-nebivolol carries β-adrenoceptor blocking properties while in other β-adrenoceptor antagonists these properties are carried by the L-enantiomer.[3e] Our own interest in the total synthesis of clinically useful compounds, especially those containing amino functionality,[4] prompted us to take up the synthesis of this molecule. In this paper we disclose a stereo- and enantioselective total synthesis of (*S*,*R*,*R*,*R*)-Nebivolol. The general retrosynthetic analysis that was adopted is illustrated in Scheme 1.

According to this plan, the fragments **2** and **3** would be joined through nucleophilic opening of epoxide **3** with amine **2**. The fragments **2** and **3** would be obtained from a one-pot Sharpless asymmetric epoxidation (SAE), ring closure of appropriate allylalcohol **9a**. The allyl alcohol was in turn prepared from Clasien rearrangement of the requisite allylic ether **5**. Our synthesis began from commercially available *p*-fluorophenol **4**, which on treatment with acetone, K_2CO_3 and allylbromide under reflux conditions furnished *O*-allyl ether **5**, the prerequisite for Claisen



Scheme 1.

☆ IICT communication no. 4390.

Keywords: amine; chromanes; antihypertensive; epoxidation; coupling reaction.
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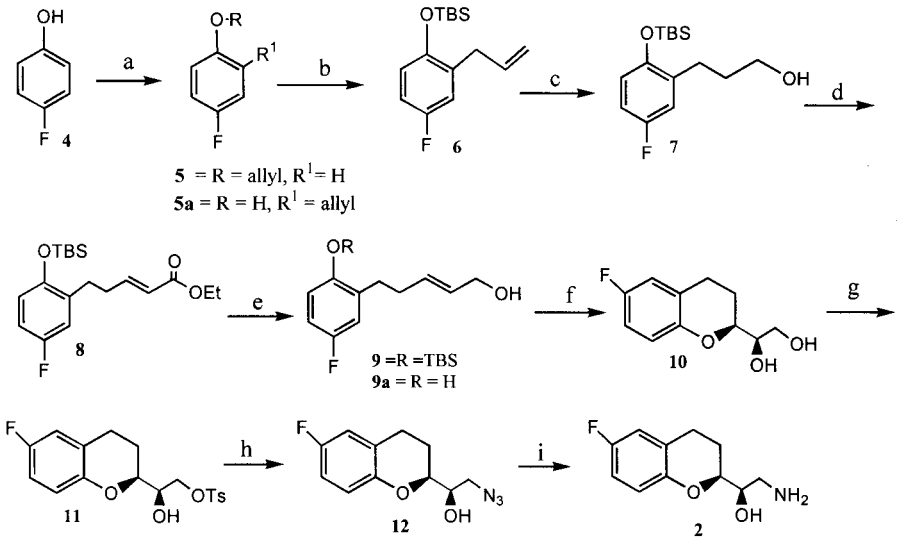
PII: S0040-4020(00)00572-X

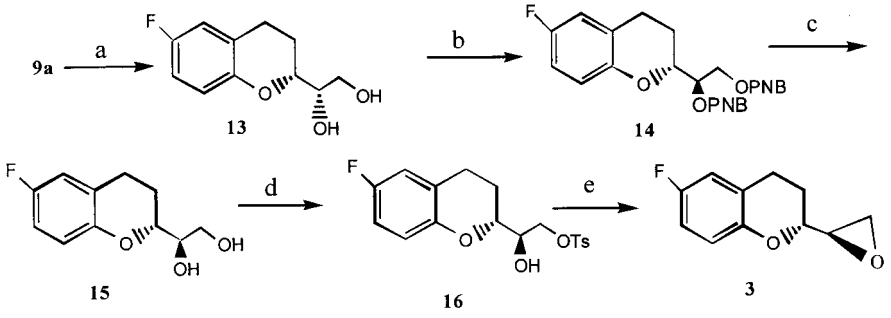


Scheme 2. (a) Allylbromide, K_2CO_3 (83%); (b) (i) heating, 210°C (76%), (ii) TBDMSCl, imidazole (84%); (c) $BH_3{\cdot}Me_2S$, H_2O_2, OH^- (75%); (d) Dess–Martin periodinane, followed by $PPh_3{=}CH\text{-}COOEt$ (72%); (e) (i) DIBAL (78%), (ii) TBAF in THF (80%); (f) (−)-DET, Ti(isopropoxide)$_4$, TBHP, −20°C, NaOH (65%); (g) TsCl, Py. (82%); (h) NaN_3, DMF (77%); (i) Pd/C in EtOH (81%).

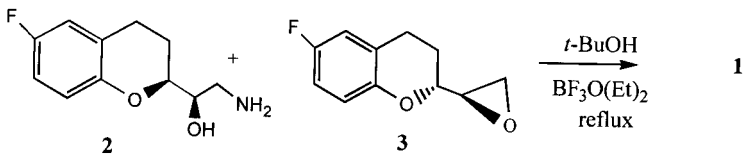
rearrangement[5] (Scheme 2). Thermal rearrangement of *O*-allyl ether **5** generated 2-allyl-4-fluoro phenol **5a**. Protection of the phenol group **6** was achieved with TBDMS-Cl and imidazole. Hydroboration of **6** ($BH_3{\cdot}Me_2S$, followed by H_2O_2) furnished primary alcohol **7**, which upon one pot oxidation with Dess–Martin periodinane and Wittig olefination with ethyltriphenylphosporane furnished α,β-unsaturated ester[6] **8**. DIBAL-H reduction of ester **8** produced the corresponding alcohol followed by desilylation (TBAF) to yield the allyl alcohol **9a** setting the stage for Sharpless asymmetric epoxidation. The two requisite chromanes **10** and **13** were obtained from **9a** in 'one pot' on treatment with (−)-DET and (+)-DET, respectively, followed by sodium hydroxide workup.[7] Chromane **10** on treatment with tosylchloride followed by NaN_3 in DMF gave the azido alcohol **12** (Scheme 2). Reduction of the azide to its corresponding amine **2** completed the synthesis of the left fragment of Nebivolol.

Similarly under Mitsunobu conditions (p-$NO_2C_6H_4COOH$, TPP and DEAD) chromane **13** furnished benzoate derivative[8] **14** with inversion at C_2. Standard deprotection of di-PNB ester **14** (NaOMe, MeOH) to diol **15**, monotosylation to **16** and base (NaOMe, CH_2Cl_2) to form epoxide **3** (Scheme 3). The total synthesis of **1** was completed by coupling the two fragments involving nucleophilic opening of epoxide **3** with hydroxy amine **2** followed by derivatizing the product as the hydrochloride salt (Scheme 4). The spectral data of **1** are in total agreement with the reported[9] values.

In conclusion, we present an efficient and convergent synthesis



Scheme 3. (a) (+)-DET, Ti (isopropoxide)$_4$, TBHP, −20°C, NaOH (65%); (b) p-$NO_2C_6H_4COOH$, DEAD, TPP (61%); (c) NaOMe (72%); (d) TsCl, Py. (75%); (e) NaOMe, in DCM (62%).



Scheme 4.

of (*S*,*R*,*R*,*R*)-Nebivolol in optically pure form. The commercial availability of Sharpless asymmetric epoxidation reagents and easy preparation of allylalcohols makes this approach most attractive for the synthesis of other possible isomers and analogues. The utilization of 'one-pot' reactions makes the synthesis quite efficient overall.

Experimental

General methods

Crude products were purified by column chromatography on silica gel (60–120 mesh). ^{1}H NMR spectra were obtained in $CDCl_3$ at 200 MHz. Chemical shifts are given in ppm, with respect to internal TMS, *J* values are quoted in Hz. Infrared spectra were obtained neat, only the most significant absorptions in cm^{-1} are indicated. DMSO, triethylamine and CH_2Cl_2 were distilled from CaH_2 and stored over molecular sieves. Benzene and THF were dried over sodium and benzophenone. All reactions were carried out under nitrogen atmosphere using dry glassware.

1-Allyloxy-4-fluoro-benzene (5). To a solution of *p*-fluorophenol **4** (30 g, 267 mmol) in acetone (250 mL) were added anhydrous K_2CO_3 (64.6 g, 468 mmol) and allyl bromide (38.8 g, 321 mmol). The resulting mixture was refluxed for 8 h, cooled to room temperature and poured into cold water (500 mL). The aqueous layer was extracted with three portions of ether (3×200 mL) and the combined organic layers is washed with 2 M sodium hydroxide solution (100 mL) and dried over anhydrous K_2CO_3. The solvents were removed under vacuum to afford allyl phenyl ether **5** (34 g, 83%) as a colorless oil. R_f (10% ethyl acetate/hexane) 0.95; IR (neat): 3100, 3045, 1650, 1500, 980 650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05–6.80 (m, 4H, C_6H_4F), 6.15–5.95 (m, 1H, CH_2–C*H*=CH), 5.45 (dd, 1H, *J*=14.0, 2.0 Hz, CH_2–CH=C*H*), 5.3 (dd, 1H, *J*=9.0, 1.0 Hz, C*H*=CH–CH_2), 4.5 (d, 2H, *J*=4.5 Hz, CH_2–CH=CH); EI MS *m*/*z*, 111 (M^+-41), 73, 57, 41; Anal Calcd for C_9H_9OF: C, 71.04; H, 5.96. Found C, 71.10; H, 6.05.

2-Allyl-4-fluoro-phenol (5a). Compound **5** (25 g, 164 mmol) was heated at 210°C for 6 h. After monitoring by TLC the reaction was cooled to room temperature and was then dissolved in 100 mL of 5 M NaOH solution and extracted with two portions (2×100 mL) of light petroleum ether (60–80°C) to remove small amounts of 2-methyl dihydrobenzofuran which forms as a by-product. The aqueous alkaline solution was carefully acidified with 2N hydrochloric acid under cooling. The aqueous layer was extracted with ether (300 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure to afford 2-allyl phenol **5a** (19 g, 76%) as a colorless oil. R_f (15% ethyl acetate/hexane) 0.75; IR (neat): 3345, 3045, 1650, 1360, 1200, 685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–6.65 (m, 3H, C_6H_3–F), 6.10–5.90 (m, 1H, CH_2–C*H*=CH_2), 5.15 (dt, 2H, *J*=8.6, 2.0 Hz CH_2=CH), 3.35 (d, 2H, *J*=7.5 Hz CH_2–CH=CH_2); EI MS *m*/*z* 111(M^+-41), 72, 57, 41; Anal Calcd for C_9H_9OF: C, 71. 04; H, 5.96. Found C, 71.10; H, 6.05.

2-Allyl-(1-*tert*-butyldimethylsilyloxy)-4-fluoro-benzene (6). To a solution of **5a** (18 g, 118 mmol) and imidazole (12 g, 177 mmol) in dry CH_2Cl_2 (150 mL) was slowly added *t*-butyldimethylsilyl chloride (19.5 g, 130 mmol) in CH_2Cl_2 (25 mL) at 0°C. The reaction mixture was stirred for 10 h at room temperature after which it was diluted with CH_2Cl_2 (100 mL). The organic layer was washed with water (2×100 mL), brine (100 mL) and dried over Na_2SO_4. The volatiles were removed under reduced pressure. The crude product was purified by column chromatography (hexane) to afford silyl ether **6** (26.5 g, 84%) as a colorless oil. R_f (5% ethyl acetate/hexane) 0.75; IR (neat): 3045, 3020, 2990, 1650, 1580, 1200, 650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–6.65 (m, 3H, C_6H_3–F), 6.05–5.85 (m, 1H, CH_2–C*H*=CH_2), 5.15 (d, 1H, *J*=1.5 Hz, CH_2=CH), 5.05 (dd, 1H, *J*=9.5, 1.5 Hz, CH_2=CH), 3.35 (d, 2H, *J*=8.5 Hz, CH_2–CH=CH), 1.05 (s, 9H, C(CH_3)$_3$), 0.2 (s, 6H, Si–2×CH_3); EI MS *m*/*z* 152 (M^+-115), 73, 57 41 Anal Calcd for $C_{15}H_{23}OFSi$: C, 67.62; H, 8.7. Found C, 67.75; H, 8.65.

3-(2-*tert*-Butyldimethylsilyloxy-5-fluoro-phenyl)-1-propanol (7). To a cold solution of **6** (15 g, 52.8 mmol) in THF (100 mL) was added BH_3·DMS (26.4 mmol, 1 M solution in THF) and stirred for 1.5 h at 10°C and monitored by TLC till the starting material is consumed completely. The reaction mixture was cooled to 0°C, the excess boron reagent was quenched with 1 M NaOH (8 mL) and stirred for 30 min maintaining at 0°C. 30% H_2O_2 (92.4 mmol) was added at 0°C and stirred for 2 h. The reaction mixture was diluted with water (100 mL), and extracted with ethyl acetate (200 mL), the organic layers were combined and washed with brine (150 mL). The organic layer is separated, volatiles were removed under vacuum and the crude product thus obtained was purified by column chromatography (9:1 hexane/ethyl acetate) to afford **7** (12 g, 75%) as a colorless oil. R_f (15% ethyl acetate/hexane) 0.5; IR (neat): 3550, 3045, 2990, 1580, 1220, 1050, 650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–6.65 (m, 3H, C_6H_3–F) 3.60 (t, 2H, *J*=5.9 Hz, CH_2–OH) 2.65 (t, 2H, *J*=5.9 Hz, CH_2–C_6H_3–F) 1.80–1.75 (m, 2H, CH_2–CH_2–C_6H_3–F) 1.02 (s, 9H, C(CH_3)$_3$) 0.22 (s, 6H, Si–2×CH_3); EI MS *m*/*z* 266 [M^+-18], 97, 71, 57; Anal Calcd for $C_{15}H_{25}O_2FSi$: C, 63.34; H, 8.86. Found C, 63.50; H, 8.62.

Ethyl-5-(2-*tert*-butyldimethylsilyloxy-5-fluoro-phenyl)-2-pentenoate (8). To a stirred solution of **7** (5 g, 17.6 mmol) and benzoic acid (8.5 g, 70.4 mmol) in a mixture of dry CH_2Cl_2 (100 mL) and dry DMSO (20 mL), Dess–Martin periodinane (17.9 g, 42.2 mmol) was added. The reaction mixture turned to orange-brown color within seconds and started boiling. It was subsequently stirred for 30 min during which time it attained room temperature. At this temperature was added ethyltriphenylphosphorane (7 g, 21 mmol) and the reaction mixture was stirred for a further 10 h. It was quenched with solid $NaHCO_3$ (15 g). Ether (250 mL) was added and stirred for 15 min. The mixture was filtered and the organic layer was washed with water (100 mL) and brine (100 mL) to afford the crude product which was purified by column chromatography (hexane/ethyl acetate 95:5) to afford **8** (4.4 g, 72%) as a pale yellow oil. R_f (20% ethyl acetate/hexane) 0.7; IR (neat): 3030, 2990, 1720, 1600, 1580, 1220, 685 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ

7.10–6.65 (m, 4H, C_6H_3–F+enone–*H*), 5.80 (d, 1H, *J*=17 Hz, C*H*=CH), 4.25 (q, 2H, *J*=6.5 Hz, O–CH_2), 2.75 (t, 2H, *J*=7.8 Hz, CH_2–C_6H_3–F), 2.45 (dt, 2H, *J*=7.5, 2.0 Hz, CH_2–CH=CH), 1.35 (t, 3H, *J*=6.5 Hz, CH_3–CH_2), 1.05 (s, 9H, C(CH_3)$_3$), 0.25 (s, 6H, Si–2×CH_3); EI MS *m/z* 295 [M^+−57], 249, 221, 198, 167, 75, 57; Anal Calcd for $C_{19}H_{29}O_3FSi$: C, 64.74; H, 8.29. Found C, 64.85; H, 8.20.

5-(2-*tert*-Butyldimethylsilyloxy-5-fluoro-phenyl)-(*E*)-2-penten-1-ol (9). To a solution of **8** (7 g, 19.8 mmol) in dry CH_2Cl_2 (75 mL) at −10°C under nitrogen atmosphere was added DIBAL-H (49.7 mmol, 2 M solution in hexane). The mixture was stirred at 0°C for 30 min after which it was allowed to attain room temperature and stirred for a further 2 h subsequently. The excess DIBAL-H was quenched with methanol (2 mL) and poured into sodium potassium tartarate solution (10 g in 100 mL water) with vigorous stirring until the layers were separated. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate 8:2) to afford **9** (4.8 g, 78%) as a colorless oil. R_f (20% ethyl acetate/hexane) 0.65; IR (neat): 3500, 3045, 2990, 1600, 1550, 1200, 1050, 650 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 6.85–6.50 (m, 3H, C_6H_3–F), 5.80–5.50 (m, 2H, C*H*=C*H*), 4.05 (d, 2H, *J*=4.6 Hz, CH_2–OH), 2.65 (t, 2H, *J*=6.9 Hz, CH_2–Ph), 2.30 (m, 2H, CH_2–CH=CH), 1.0 (s, 9H, C(CH_3)$_3$), 0.20 (s, 6H, Si–2×CH_3); EI MS *m/z* 310, 199, 75, 41; Anal Calcd for $C_{17}H_{27}O_2FSi$: C, 65.75; H, 8.77. Found C, 65.60; H, 8.84.

5-(5-Fluoro-2-hydroxy-phenyl)-*E*-2-penten-1-ol (9a). To a stirred solution of **9** (5 g, 16 mmol) in THF (50 mL) at 0°C was added TBAF (8 mmol, 1 M solution in THF). The reaction mixture was allowed to warm to room temperature and stirred for a further 3 h. The excess TBAF was quenched with saturated NH_4Cl solution (50 mL) and the reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (100 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude product thus obtained was purified by column chromatography (hexane/ethyl acetate 7.5:2.5) to afford **9a** (2.5 g, 80%) as a colorless viscous oil. R_f (30% ethyl acetate/hexane) 0.35; IR (neat): 3500, 3350, 3045, 2990, 1650, 1465, 1200, 650 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.72–6.50 (m, 3H, C_6H_3–F), 5.70–5.45 (m, 2H, C*H*=C*H*), 3.95 (d, 2H, *J*=4.6 Hz, CH_2–OH), 2.55 (t, 2H, *J*=7.0 Hz, CH_2–C_6H_3), 2.25 (m, 2H, CH_2–CH=CH); EI MS *m/z* 195, 75, 41; Anal Calcd for $C_{11}H_{13}O_2F$: C, 67.33; H, 6.68; Found C, 67.45; H, 6.52.

1-[6-Fluoro-(2*S*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol (10). To a stirred suspension of activated powdered 4 Å molecular sieves (5 g) in dry CH_2Cl_2 (50 mL) at −20°C under nitrogen atmosphere was added (+)-DET (2.3 g, 11.2 mmol) in CH_2Cl_2 (15 mL), titanium tetraisopropoxide (3.4 g, 12.3 mmol) and TBHP (40 mmol) sequentially. After 20 min the resulting mixture was treated with allyl alcohol **9a** (2 g, 10.2 mmol) in CH_2Cl_2 (20 mL) over a period of 20 min and maintained at the same temperature for 4 h. The reaction mixture was subsequently allowed to warm to 0°C and poured into freshly prepared solution of ferrous sulphate (3.2 g) and tartaric acid (1 g) in water (20 mL) maintained at 0°C. The two-phase mixture was stirred for 30 min, the aqueous phase was separated and extracted with CH_2Cl_2 (50 mL). The combined organic phases were treated with a pre-cooled solution of 30% NaOH in saturated brine (30 mL). The two-phase mixture was stirred for 1 h at the same temperature. The aqueous layer was separated and extracted with CH_2Cl_2 (2×50 mL). The organic extracts were dried over Na_2SO_4 and concentrated to afford the crude product, which was purified by column chromatography (hexane/ethyl acetate 7:3) to afford **10** (1.4 g, 65%) as a semisolid. R_f (30% ethyl acetate/hexane) 0.3; IR (neat): 3550, 3050, 2990, 1650, 1200, 1050, 960 cm^{-1}; $[\alpha]_D^{25}$=+71.8 (*c* 1 MeOH); ^1H NMR (200 MHz, $CDCl_3$): δ 6.82–6.65 (m, 3H, C_6H_3F), 4.0–3.65 (m, 4H, OC*H*, C*H*–OH, CH_2–OH), 2.90–2.70 (m, 2H, CH_2–C_6H_3–F), 2.30–2.15 (m, 1H C*H*–CHO), 1.90–1.75 (m, 1H, C*H*–CHO); EI MS *m/z* 212, 151, 125, 57 Anal Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17. Found C, 62.30; H, 6.27.

6-Fluoro-2-[1-hydroxy-2-(4-methylphenylsulfonyloxy)-(1*R*)-ethyl]-(2*S*)-3*H*,4*H*-chromene (11). To a solution of compound **10** (1.2 g, 5.6 mmol) in dry CH_2Cl_2 (15 mL) containing dry pyridine (1 mL) at 0°C under nitrogen atmosphere was added tosyl chloride (1.2 g, 6.2 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 10 h at room temperature. It was washed with saturated $CuSO_4$ solution (20 mL) and extracted with CH_2Cl_2 (50 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 1:9) to afford **11** (1.7 g, 82%) as a pale yellow solid. Mp (102–104°C); R_f (30% ethyl acetate/hexane) 0.45; IR (KBr): 3500, 3045, 2990, 1650, 1500, 1160, 1050, 650 cm^{-1}; $[\alpha]_D^{25}$=+54.4 (*c* 1 $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, 2H, *J*=8.0 Hz, C_6H_4–CH_3), 7.35 (d, 2H, *J*=8.0 Hz, C_6H_4–CH_3), 6.80–6.50 (m, 3H, C_6H_3–F) 4.35 (dd, 1H, *J*=10.0, 2.0 Hz, C*H*–OTs), 4.20 (dd, 1H, *J*=10.0, 4.2 Hz, C*H*–OTs), 3.95–3.80 (m, 2H, OC*H*, C*H*–OH), 2.85–2.70 (m, 2H, CH_2–C_6H_3–F), 2.48 (s, 3H CH_3–C_6H_4), 2.25–2.15 (m, 1H, C*H*–CHO) 1.85–1.65 (m, 1H, C*H*–CHO); EI MS *m/z* 366, 151, 91; Anal Calcd for $C_{18}H_{19}FO_5S$: C, 59.01; H, 5.23; Found C, 58.94; H, 5.15.

2-Azido-1-[6-fluoro-(2*S*)-3*H*,4*H*-2-chromenyl]-(1*R*)-ethan-1-ol (12). To a solution of **11** (1.25 g, 3.4 mmol) in dry DMF (15 mL) was added sodium azide (1.05 g, 17 mmol) and stirred for 10 h at 80°C. The reaction mixture was cooled to room temperature and diluted with water (20 mL), the resulting mixture was extracted with ether (2×25 mL), washed with water (25 mL) and brine (25 mL) and dried with Na_2SO_4 and concentrated. The crude product was purified by column chromatography (hexane/ethyl acetate 8:2) to afford azide **12** (0.625 g, 77%) as a syrup. R_f (30% ethyl acetate/hexane) 0.65; IR (neat): 3550, 3045, 2990, 2140 1650, 1180, 650 cm^{-1}; $[\alpha]_D^{25}$=+50.2 (*c* 1 $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 6.70–6.52 (m, 3H, C_6H_3–F), 3.85–3.65 (m, 2H, C*H*–O, CHOH), 3.45 (d, 2H, *J*=4.5 Hz, CH_2–N_3), 2.75–2.65 (m, 2H, CH_2–C_6H_3–F), 2.25–2.0 (m, 1H, C*H*–CHO), 1.85–1.65 (m, 1H, C*H*–CHO); EI MS *m/z*

M^+ 237, 151, 125, 109, 57. Anal Calcd for $C_{11}H_{12}FN_3O_2$: C, 55.69; H, 5.10. Found C, 55.74; H, 5.05.

2-Amino-1-[6-fluoro-(2*S*)-3*H*,4*H*-2-chromenyl]-(1*R*)-ethan-1-ol (2). To a solution of **12** (0.250 mg, 1.05 mmol) in dry methanol (5 mL) at room temperature was added 10% Pd–charcoal (10 mg) and stirred under an atmosphere of hydrogen. After 8 h the reaction mixture was filtered through a funnel and the filtrates were concentrated under vacuum to afford **2** (0.180 g, 81%). The compound was dissolved in dry ether and dry HCl gas was passed through the solution to form the hydrochloride salt of compound **2** (0.155 g, 75% yield); mp 60–63°C; R_f (10% MeOH/$CHCl_3$) 0.3; IR (KBr): 3550, 3500,3100, 3020, 2990, 1650, 1250, 650 cm^{-1}; $[\alpha]_D^{25}$=+0.40 (*c* 1 MeOH); ^{1}H NMR (200 MHz, D_2O): δ 7.05–6.90 (m, 3H, C_6H_3–F), 4.25–4.05 (m, 2H, *CH*–OH, *CH*O), 3.55 (dd, 1H, *J*=12.3, 2.3 Hz, C*H*–NH_2), 3.17 (dd, 1H, *J*=12.3, 6.0 Hz, *CH*–NH_2), 3.05–2.85 (t, 2H, *J*= 7.0 Hz, CH_2–C_6H_3–F), 2.35–2.20 (m, 1H, *CH*–CHO), 2.0–1.85 (m, 1H, *CH*–CHO); EI MS *m/z* M^+ 211, 194, 176, 151, 126, 60, 57; Anal Calcd for $C_{11}H_{14}FNO_2$: C, 62.55; H, 6.68. Found C, 62.42; H, 6.50.

1-[6-Fluoro-(2*R*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*S*)-1,2-ethanediol (13). This compound was prepared from **9a** according to the procedure mentioned in the preparation of compound **10**, where instead of (+)-DET, (−)-DET was employed (65% yield). R_f (30% ethyl acetate/hexane) 0.3; IR (neat): 3550, 3045, 2990, 1650, 1100, 1050, 650 cm^{-1}; $[\alpha]_D^{25}$=−70.45 (*c* 1 MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–6.65 (m, 3H, C_6H_3–F), 4.0–3.65 (m, 4H, C*H*–O, C*H*–OH, CH_2–OH), 2.85–2.70 (m, 2H, CH_2–C_6H_3–F), 2.30–2.15 (m, 1H, CH_2–CHO), 1.90–1.70 (m, 1H, *CH*–CHO); EI MS *m/z* 212, 151, 125, 57; Anal Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17. Found C, 62.30; H, 6.15.

2-(1,2-Di-(4-nitrophenylcarbonyloxy)-(1*R*)-ethyl-6-fluoro-(2*R*)-3*H*,4*H*-chromene (14). To a solution of diethyldiazadicarboxylate (7.3 g, 42 mmol) in THF (50 mL) was added triphenyl phosphine (11.5 g, 42 mmol) in THF (50 mL) at −20°C followed by addition of a solution of **13** (1.5 g, 7 mmol) in THF (20 mL) and *p*-nitro benzoic acid (7 g, 42 mmol) in THF (15 mL). The resulting solution was stirred for 5 h at −20°C and then allowed to warm to room temperature while continuing the stirring for an additional 1 h. The solvent was removed under vacuum, ether was added to the residue to precipitate the triphenylphosphine-oxide, which was removed by filtration. The solvent from the resulting filtrate was removed under vacuum, the crude product was purified by column chromatography (hexane/ethyl acetate 95: 5) to afford **14** (2.2 g, 61%) as a syrup. R_f (25% ethyl acetate/hexane) 0.55; IR (neat): 3050, 2990, 1720, 1650, 1425, 1100, 960 cm^{-1}; $[\alpha]_D^{25}$=−45.80 (*c* 1 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 8.35–8.15 (2d, 4H, 2×$NO_2C_6H_4$–CO), 6.80–6.70 (m, 3H, C_6H_3–F), 4.50–4.20 (m, 3H, CH_2O, C*H*–OCO), 3.75–3.60 (m, 1H, C*H*O), 2.90–2.70 (m, 2H, CH_2–C_6H_3–F), 2.25–2.0 (m, 1H, C*H*–CHO), 1.95–1.80 (m, 1H, C*H*–CHO); Anal Calcd for $C_{25}H_{19}FN_2O_9$: C, 58.83; H, 3.75 Found C, 58.65; H, 3.80.

1-[6-Fluoro-(2*R*)-3*H*,4*H*-dihydro-2*H*-2-chromenyl]-(1*R*)-1,2-ethanediol (15). To a cold solution of **14** (2 g, 3.9 mmol) in dry methanol (15 mL) was added freshly prepared NaOMe (0.62 g, 11.7 mmol) in methanol. The reaction mixture was stirred for 3 h at room temperature. The solvent was removed under vacuum. The reaction mass was diluted with CH_2Cl_2 (25 mL) and quenched with saturated NH_4Cl solution (25 mL). The organic layer was washed with water and brine, dried over Na_2SO_4 and the volatiles were removed under vacuum to afford the crude product which was purified by column chromatography (hexane/ethyl acetate 7:3) to afford **15** (0.6 g, 72%) as a syrup. R_f (30% ethyl acetate/hexane) 0.3; IR (neat): 3500, 3045, 2990, 1650, 1500, 1200, 650 cm^{-1}; $[\alpha]_D^{25}$=65.80 (*c* 1 MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.85–6.70 (m, 3H, C_6H_3–F), 4.0–3.80 (m, 2H, C*H*–OH, C*H*O), 3.75 (dd, 1H, *J*=9.0, 3.0 Hz, C*H*–OH), 3.65 (dd, 1H, *J*=9.0, 3.0 Hz, C*H*–OH), 2.90–2.80 (m, 2H, CH_2–C_6H_3–F), 2.35–2.20 (m, 1H, C*H*–CHO), 1.95–1.8 (m, 1H, C*H*–CHO); EI MS *m/z* 212, 151, 125, 57; Anal Calcd for $C_{11}H_{13}FO_3$: C, 62.26; H, 6.17. Found C, 62.15; H, 6.25.

6-Fluoro-2-[1-hydroxy-2-(4-methylphenylsulfonyloxy)-(1*R*)-ethyl]-(2*R*)-3*H*,4*H*-chromene (16). This compound was prepared from **15** according to the procedure mentioned in the preparation of compound **11** to afford **16** (75%) as a pale yellow solid. Mp (102–105°C); R_f (30% ethyl acetate/hexane) 0.45; IR (KBr): 3500, 2990, 1650, 1100, 960 cm^{-1}; $[\alpha]_D^{25}$=+52.40 (*c* 1 MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, 2H, *J*=8.0 Hz, C_6H_4–CH_3), 7.35 (d, 2H, *J*=8.0 Hz, C_6H_4–CH_3), 6.75–6.55 (m, 3H, C_6H_3–F), 4.32 (dd, 1H, *J*=10.0, 2.0 Hz, C*H*–OTs), 4.20 (dd, 1H, *J*=10.0, 3.2 Hz, C*H*–OTs), 3.90–3.80 (m, 2H, OC*H*, C*H*–OH), 2.85–2.75 (m, 2H, CH_2–C_6H_3–F), 2.45 (s, 3H, C_6H_4–CH_3), 2.25–2.15 (m, 1H, C*H*–CHO), 1.85–1.70 (m, 1H, C*H*–CHO); EI MS *m/z* M^+ 366, 151, 91; Anal Calcd for $C_{18}H_{19}FO_5S$: C, 59.01; H, 5.23; Found C, 58.85; H, 5.05.

6-Fluoro-2-[(2*R*)-oxiran-2-yl]-(2*R*)-3*H*,4*H*-chromane (3). To a cold solution of **16** (0.5 g, 1.36 mmol) in CH_2Cl_2 (20 mL) was added freshly prepared NaOMe (0.144 g, 2.7 mmol). The reaction mixture was stirred for 6 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and quenched with saturated NH_4Cl solution (10 mL). The organic layer was washed with water and brine, extracted with CH_2Cl_2 (50 mL), dried Na_2SO_4. The volatiles were removed under reduced pressure. The crude product was purified by column chromatography (hexane/ethyl acetate 95:5) to afford **3** (0.165 g, 62%) as a colorless liquid. R_f (30% ethyl acetate/hexane) 0.75; IR (neat): 3045, 2990, 1650, 1160, 1050, 960, 650 cm^{-1}; $[\alpha]_D^{25}$=+73.30 (*c* 0.5 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 6.80–6.65 (m, 3H, C_6H_3–F), 3.80–3.65 (m, 1H, CH_2–C*H*O), 3.10–3.02 (m, 1H, C*H*O), 2.90–2.70 (m, 4H, CH_2–O, CH_2–C_6H_3), 2.20–2.05 (m, 1H, C*H*–CHO), 2.0–1.80 (m, 1H, C*H*–CHO); EI MS *m/z* 194, 151, 149, 96, 57; Anal Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found C, 67.95; H, 6.62.

(+)-(*S*,*R*,*R*,*R*)-α,α^1-Imino-bis-(methylene)-bis-(6-fluoro-3,4-dihydro-2*H*,1-benzo-pyran-2-methanol)hydrochloride (3·HCl) (1). Amine **2** (*S*,*R*) (65 mg, 0.3 mmol) was dissolved in dry *t*-butanol (5 mL) and epoxide **3** (60 mg, 0.3 mmol), and catalytic amount of $BF_3{\cdot}O(Et)_2$ were added to the reaction mixture. The resulting mixture was refluxed for 4 h. The solvent was removed under vacuum and washed with water, brine and extracted with ethylacetate

(20 mL) and dried over Na_2SO_4. The volatiles were concentrated to afford a yellowish oil. The crude product was dissolved in dry DCM and dry HCl gas was passed through the solution to form the hydrochloride salt of compound **1** (0.025 g, 20%) as a white solid. R_f (10:1 CH_2Cl_2/MeOH) 0.26; IR (KBr) 3350, 3173, 2950, 1495, 1450 cm^{-1}. $[\alpha]_D^{25}=+0.038$ (c 0.02 MeOH); lit. +0.040 (c=0.0027); ^1H NMR (200 MHz, $CDCl_3$): 6.84–6.72 (m, 6H, C_6H_3–F), 4.15–3.85 (m, 4H, C*H*–OH–C*H*O), 3.42–3.15 (m, 4H, CH_2–NH–), 2.95–2.72 (m, 4H, CH_2–C_6H_3–F), 2.25–2.15 (m, 1H, C*H*–CHO), 2.20–1.80 (m, 2H, C*H*–CHO), 1.70–1.68 (m, 1H, C*H*–CH_2); HRMS calcd for $C_{22}H_{25}F_4NO_4$ (M+1)=406.1831, found 406.1833.

Acknowledgements

We thank Dr J. S. Yadav, Head, Organic Division—I, IICT, for helpful discussions and CSIR (New Delhi) for financial assistance to M. V. R.

References

1. (a) De Cree, J.; Geukens, H.; Leempoels, J.; Verhaegen, H. *Drug Dev. Res.* **1986**, *8*, 109–117. (b) De Cree, J.; Geukens, H.; Cobo, C.; Verhaegen, H. *Angiology* **1987**, *38*, 440–447. (c) Van de Water, A.; Janssen, W.; Van Nueten, J.; Xhonneux, R.; De Cree, J.; Verhaegen, H.; Reneman, R. S.; Janssen, P. A. J. *J. Cradiovasc. Pharmacol.* **1988**, *11*, 552–563.

2. Howe, R.; McLoughlin, B. J.; Rao, B. S.; Smith, L. H.; Chodnekar, M. S. *J. Med. Chem.* **1969**, *12*, 452–458.

3. (a) Van de Water, A.; Xhonneux, R. S.; Janssen, P. A. J. *Eur. J. Pharm.* **1988**, *156*, 95–103. (b) Xhonneux, R. S.; Wouters, L.; Reneman, R. S.; Janssen, P. A. J. *Eur. J. Pharm.* **1990**, *181*, 261–265. (c) Bowden, C. R.; Marchione, C. S. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 599–605. (d) Rahn, K. H. Hemodynamic effects of the optical isomers of betareceptor blocking agents, *Eur. Heart J. 4* (Suppl. D) 27. (e) Van de Water, A.; Xhonneux, R. S.; Reneman, R. S.; Janssen, P. A. J. Cardio vascular effects of D,L-nebivolol and its enanatiomers a comparison with those atenolol, *Eur. J. Pharm.* **1988**, *156*, 95.

4. (a) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071. (b) Chandrasekhar, S.; Mohapatra, S. *Tetrahedron Lett.* **1998**, *39*, 6415. (c) Chandrasekhar, S.; Mohapatra, S.; Yadav, J. S. *Tetrahedron* **1999**, *55*, 4763.

5. (a) Adams, R. *J. Am. Chem. Soc.* **1919**, *41*, 648. (b) Lauer, L. *J. Am. Chem. Soc.* **1939**, *61*, 1939. (c) Tarbell, D. S. *Org. React.* **1944**, *2*, 1–48.

6. Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376–9378.

7. (a) Hosokawa, T.; Kono, T.; Shinohara, T.; Murahashi. S. I. *J. Organomet. Chem.* **1989**, *370*, C13. (b) Corey, E. J.; Ha, D. C. *Tetrahedron Lett.* **1988**, *29*, 3171. (c) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (d) Katsuki, T.; Martin, V. S. Asymmetric Sharpless epoxidation of allylalcohols, *Org. React.* **1996**, *48*, 1–300.

8. (a) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017. (b) Loibner, H.; Zbiral, E. *Helv. Chem. Acta* **1977**, *60*, 417. (c) During the Mitsunobu reaction 15% epoxide formation is noticed, which is eliminated by column chromatography. ^1H NMR data, specific rotation and comparing with the final product after coupling with left-hand fragment confirm the inversion.

9. (a) Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340. (b) Synthesis and pharmacolgical properties: Van Lommen, G.; De Bruyn, M.; Schroven, M. *J. Pharm. Belg.* **1990**, *45*, 355.