A mild synthesis of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol]

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A new synthesis of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol (**1**) is described, with most reactions being carried out at room temperature and normal pressure, that will further contribute to the development of new scalable synthesis of the related drug substance of Nebivolol (overall yield: 33%).

Keywords: α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol], nebivolol, antihypertensive agent, synthesis

α,α'-[Iminobismethylene]bis[6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-methanol](**1**) has several isomers, in which (S,R,R,R)- is a known drug of Nebivolol. Nebivolol is a potent and selective β_1-adrenergic blocker, with potent antihypertensive activity. The selectivity of Nebivolol in β_1-adrenocepter antagonism was proved to be higher than that of clinically used atenolol, pindolol and propranolol.[1,2]

There are several methods for dealing with the synthesis of Nebivolol, among which the one filed in the patent EP334429 is most likely to be the practical and scalable one. However, the key intermediate epoxide in the reported method was prepared under harsh conditions with uncommon reagents with low overall yield.[3-6] Based on the method in EP334429, we disclose here a new and efficient total synthesis of **1** that used mostly conventional reaction conditions and reagents, which will further contribute to the development of new scalable synthesis of the related drug substance of Nebivolol.

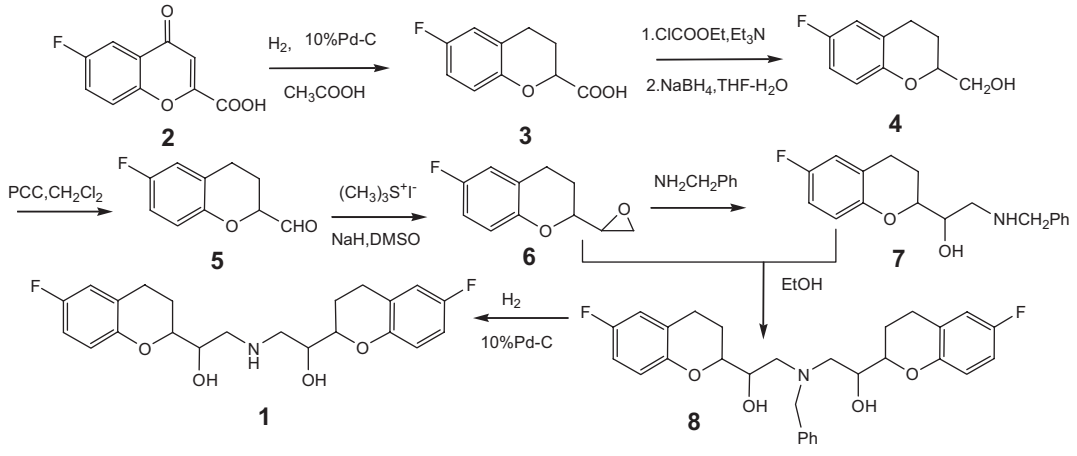
Results and discussion

In our new synthesis, **1** was prepared by the coupling reaction of the two segments: epoxide (**6**) and hydroxy amine (**7**) which itself was obtained via the nucleophilic opening of **6** with benzylamine. The key epoxide (**6**) was prepared from the aldehyde (**5**) with the requisite sulfur ylide as shown in Scheme 1. In the patent EP334429, the key intermediate **6** was also prepared from the corresponding acid (**3**) under very harsh (unconventional) conditions.

A facile, industrially feasible approach was searched to improve the route described in EP334429. We adopted the alcohol (**4**), which was prepared by the reduction of the mixed anhydride of **3** by $NaBH_4$ with a high yield of 90%.[7,8] Then, the aldehyde (**5**) was prepared by conventional oxidation of the alcohol (**4**) via PCC with additives in the yield of 78%;[9,10] these two steps were carried out at ambient temperature and normal pressure with 67% overall yield, which is higher than that of the method in EP334429 (58%).

The conventional way to obtain the oxirane (**6**) from the corresponding aldehyde (**5**) is the epoxidation of the double bond, which was constructed using the Wittig reaction of **5**. We, however, preferred using the direct epoxidation reagent, trimethylsulfonium iodide, instead of trimethylsulfoxonium iodide in EP334429 to obtain **6** in quantitative yield.[11,12] Most reactions were done at room temperature and normal pressure with a higher yield (33% in total).

In conclusion, we have accomplished a new synthesis of **1** with efficient synthetic operations. Because commercially available (conventional) reagents were employed under mild conditions for the preparation of **6**, our new approach looks most attractive for scalable plant synthesis, provided that the purification can be carried out without chromatography. Although the starting materials used here were all racemic and the terminal product **1** is a mixture, the reactions can be done like those of EP334429 without any changes in the stereo structures.[7,8,10,12] It is thus practical for the synthesis of the optically pure compounds when starting with non-racemic compounds. The spectral data of **1** are in agreement with the reported values.



Scheme 1

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Experimental

General

Melting points were uncorrected. ^{1}H NMR spectra were obtained in $CDCl_3$ at Bruker AC-400. Chemical shifts are given in ppm, with respect to internal TMS, *J* values are quoted in Hz. IR spectra were obtained neat with a Nicolet NEXUS-670 spectrophotometer, only the most significant absorptions in cm^{-1} are indicated. Mass spectra were obtained on a Trace DSQ GC–MS spectrometer. DMSO, triethylamine and CH_2Cl_2 were distilled from CaH_2 and stored over molecular sieves (4 Å). THF were dried over sodium wires. Ethanol and methanol were dried over molecular sieves (3 Å).

6-Fluoro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid 2 was prepared according to the literature.[13-15]

6-Fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxylic acid **3**: To a solution of 6-fluoro-4-oxo-4*H*-1-benzopyran-2-carboxylic acid **2** (10 g, 48 mmol) in acetic acid (100 ml) were added palladium-on-charcoal catalyst 10% (0.5 g). The resulting suspension was put into an autoclave (0.25L) and hydrogenated at 2MPa and 70–80°C. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was poured into the cool water to precipitate a white solid. The crude product was filtered off, and recrystallised from toluene and dried *in vacuo* at 70°C, yielding 8.1 g (86%) of compound **3** as a colourless solid. M.p.129.2–130.3°C. IR(KBr): υ3186, 2945, 1735, 1490, 1210, 848 cm^{-1}. ^{1}H NMR($CDCl_3$): δ 10.08 (brs, –COOH), 6.75–6.88(m, 3H, Ar*H*), 4.74–4.77(q, *J* = 3.53 Hz, 1H, 2-C*H*), 2. 86–2.79 (2H, m, 3-C*H*2), 2.22–1.99(2H, m, 4-C*H*2). GC –MS(EI, 70Ev): *m/z* (%) = 197 (M^+ + H, 12), 196 (M^+, 100), 151(86). Anal Calcd for $C_{10}H_9FO_3$: C, 61.22; H, 4.62. Found C, 61.31; H, 4.65.

6-Fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol **4**: To a solution of **3** (6 g, 31 mmol) in THF (100 ml) were added under stirring, Et_3N (3.1 g, 31 mmol), and then ClCOOEt (3.3 g, 31 mmol) whilst being cooled in an ice bath. The resulting solution was then allowed to warm to room temperature with stirring for an additional 10 h. The resulting mixture was filtered off to remove the inorganic salts, and the residual liquid was transferred into a solution of $NaBH_4$ (3.8 g, 100 mmol) in H_2O/THF (100 ml, 1: 4) dropwisely, under adequate stirring. Resulting mixture was further stirred at ambient temperature for 5 h. To this mixture was then added 1N HCl to adjust the pH 7, followed by removal of THF under vacuum. The aqueous mixture was then extracted with ethyl acetate (3 × 150 ml), and the organic layer was washed with 10% NaOH, water and brine, dried over Na_2SO_4. The volatiles were concentrated to afford 5.0 g (90%) **4** as a colourless oil, which turned to a colourless solid after several days. M.p. 52.1–52.8°C. IR(film): υ3286, 2935, 2873, 2846, 1613, 1485, 1430, 1209 cm^{-1}. ^{1}H NMR($CDCl_3$): δ6.79–6.75(m, 3H, 5-*H*, 7-*H*, 8-*H*), 4.11–4.09 (m, 2H, 2-C*H*), 3.86–3.74 (m, 2H, 3-CH_2), 2.88–2.74 (m, 2H, 4-CH_2), 2.11–1.97(m, 1H, -CH_2-O*H*), 1.96–1.68 (m, 2H, CH_2-OH). GC-MS (EI, 70EV): *m/z*(%) = 183 (M^+ + H, 5), 182(M^+, 55), 151(100), 103(40). Anal Calcd for $C_{10}H_{11}FO_2$: C, 65.92; H, 6.08. Found C, 65.95; H, 6.11.

6-Fluoro-3,4-dihydro-2H-1-benzopyran-2-carboxaldehyde **5**: A mixture of pyridinium chlorochromate (19.4 g, 96 mmol), 20.0 g of SiO_2 and 100 ml of dichloromethane was stirred. A solution of **4** (3.0 g, 16 mmol) in 25 ml of dichloromethane was transferred into the reaction mixture over 5 min, and the resulting mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was then diluted with 200 ml of diethyl ether, the solution was decanted, and the remaining black solid was thoroughly washed with three 100 ml portions of diethyl ether. The combined solution was concentrated by rotary evaporation at room temperature (80 mmHg) to give a crude product as a brown oil. Purification by column chromatography yields 2.3 g (78%) of **5** as a colourless oil. IR(film): υ2952, 2820, 1735, 1210 cm^{-1}. ^{1}H NMR($CDCl_3$) δ 9.81 (1H, s, -C*H*O), 6.91–6.73 (3H, m, 5-*H*, 7-*H*, 8-*H*), 4.48–4.45(q, *J* = 3.53 Hz, 1H, ArOC*H*), 2.88–2.72 (2H, m, 3-CH_2), δ2.25–2.18(1H, m, 4-CH_2), 2.08–1.99 (1H, m, 4-CH_2). GC-MS (EI, 70EV): *m/z*(%) = 149(100), 150(60), 151(6), 101(32), 75(15). Anal Calcd for $C_{10}H_9FO_2$: C, 66.66; H, 5.03, Found C, 66.58; H, 5.12.

6-Fluoro-3,4-dihydro-2-oxiranyl-2H-1-benzopyran **6**: A mixture of sodium hydride suspension (0.2 g, 8 mmol) and dimethyl sulfoxide (5 ml) was cooled in an ice-salt bath. A solution of trimethylsulfonium iodide (1.2 g, 5.6 mmol) in dimethyl sulfoxide (10 ml) was added during a period of 30 minutes and stirring was continued for 20 minutes. A solution of **5** (1.0 g, 5.6 mmol) in dimethyl sulfoxide (5 ml) was added dropwise and upon completion, The resulting mixture was allowed to warm to room temperature while continuing the stirring for an additional 1 h. The reaction mixture was poured into icy water and the product was extracted with hexane. The extract was washed three times with water, dried, filtered and evaporated, yielding 1.06 g (100%) of **6** as a pale yellow oil. Rf (30% ethyl acetate/hexane) 0.75; IR (film): υ3045, 2990, 1650, 1160, 1050, 960, 650 cm^{-1}. 1H NMR ($CDCl_3$): 6.82–6.73 (m, 3H, C_6H_3-F), 3.85–3.51 (m, 1H, CH_2-C*H*O), 3.14–3.11(m, 1H, C*H*O), 2.90–2.76 (m, 4H, CH_2-O, CH_2-C_6H_3), 2.17–2.11 (m, 1H, C*H*-CHO), 2.01–1.70 (m, 1H, C*H*-CHO). GC-MS (EI, 70EV): *m/z*(%) = 195(M^+ + H, 12), 194(M^+, 100), 151(82), 57(21). Anal Calcd for $C_{11}H_{11}FO_2$: C, 68.03; H, 5.71. Found C, 67.95; H, 6.62.

6-Fluoro-3,4-dihydro-α-[[(phenylmethyl)amino]methyl]-2H-1-benzopyran-2-methanol **7**: A solution of **6** (0.5 g, 2.6 mmol), benzenemethanamine(1.67 g, 15.6 mmol) and methanol (10 ml) was stirred overnight at room temperature. The reaction mixture was evaporated and concentrated on a rotary evaporator, the residue was diluted with hexane (25 ml). The precipitated product was filtered off and crystallised from ethanol. The product was filtered off and dried, yielding 0.71 g (92%) of **7** as a white solid. M.p. 115.3–117.0°C; IR (KBr): υ3500, 3100, 3020, 2990, 1650, 1250, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$): 7.36–7.26 (m, 5H, C_6H_5-), 6.79–6.69 (m, 3H, C_6H_3-F), 3.90–3.74 (m, 4H, C*H*-OH, C*H*O, ArCH_2-NH), 3.01–2.97 (t, 2H, *J* = 3.57 Hz, CH_2-C_6H_3-F), 2.88–2.74 (m, 2H, NH-CH_2-CHOH), 2.30–2.08(m, 1H, C*H*-CHO), 1.96–1.76 (m, 1H, C*H*-CHO). Anal Calcd for $C_{18}H_{20}FO_2N$: C, 71.74; H, 6.69; N, 4.65. Found C, 71.95; H, 6.72; N, 4.32.

α,α'-[[(Phenylmethyl)imino]bismethylene]bis-[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] **8**: A solution of **7** (0.5 g, 1.7 mmol), 6(0.32 g 1.7 mmol) and 10 ml ethanol was stirred for 4 hours at reflux temperature. The reaction mixture was evaporated, the residue was purified by column chromatography over silica gel using a mixture of petrol ether and ethyl acetate (50 : 10 by volume) as eluent, yielding 0.69 g (82%) of **8** as a colourless oil. IR(film) υ3350, 3173, 2950, 1495, 1450 cm^{-1}. ^{1}H NMR ($CDCl_3$): 7.33–7.25(m, 5H, C_6H_5-CH_2N), 6.77–6.64 (m, 6H, C_6H_3-F), 4.15–3.85 (m, 4H, C*H*-OH-C*H*O), 3.74–3.64 (m, 2H, N-CH_2Ar), 3.17–2.83 (m, 4H, CHOH-CH_2-NH-), 2.80–2.60 (m, 4H, CH_2-C_6H_3-F), 2.14–1.70 (m, 4H, -CHO-CH_2-CH_2). Anal Calcd for $C_{29}H_{31}F_2NO_4$: C, 70.29; H, 6.31; N, 2.83. Found C, 70.45; H, 6.37, N, 2.43.

α,α'-[Iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] **1**: A mixture of **8** (0.2 g, 0.39 mmol) and 10 ml 2-methoxyethanol was hydrogenated at normal pressure and at room temperature with palladium-on-charcoal catalyst 10% (0.1 g). After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated under vacuum and extracted with ethylacetate (20 ml) and dried over Na_2SO_4. The residue was purified by column chromatography over silica gel using a mixture of petrol ether and ethyl acetate (50 : 10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 0.107 g (65%) of **1** as a colourless oil. IR (film) υ3382, 3052, 2927, 1494, 1434 cm$^{-1.}$ ^{1}H NMR ($CDCl_3$): 8.18(s, 1H, CH_2-N*H*-CH_2), 6.76–6.69 (m, 6H, C_6H_3-F), 3.94–3.80 (m, 4H, C*H*-OH-C*H*O), 3.70–3.35 (m, 4H, CH_2-NH-), 2.83–2.77 (m, 4H, CH_2-C_6H_3-F), 2.24–1.70 (m, 4H, CHO-CH_2-CH_2). Anal Calcd for $C_{22}H_{25}F_2NO_4$: C, 65.17; H, 6.22; N, 3.45. Found C, 65.46; H, 6.35; N, 3.23.

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